A contemporary examination of screening for peripheral arterial disease for the purpose of cardiovascular risk assessment

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Abstract

Peripheral Arterial Disease (PAD) is a marker of systemic atherosclerosis and is associated with a three to six fold increased risk of death from cardiovascular causes. Furthermore, it is typically asymptomatic and under-diagnosed; this has resulted in escalating calls for the instigation of primary care PAD screening via ankle brachial index (ABI) measurement. The concept of PAD screening is, however, contentious with significant ambiguity relating to its feasibility and efficacy. Hence, the aim of the research detailed within this thesis was to provide a contemporary and comprehensive investigation of PAD screening within the primary care setting. This was achieved via four inter-related studies:

1. PIPETTE Study (n=368) – a prospective observational study involving a trial of a proposed PAD screening strategy investigated (i) how PAD screening should be targeted and (ii) if individuals found to have PAD benefited from their diagnosis.
2. IVAM study (n=12) – a study designed to (i) validate PAD diagnoses in the PIPETTE study and (ii) function as a pilot study for future research investigating the accuracy of ABI measurement in primary and secondary care.
3. DUAL study (n=727 measurements) – a comparative study of the traditional method used for ABI measurement (Doppler ultrasound) versus automated ABI equipment.
4. GP survey – an all-Wales general practice survey regarding the current utility of the ABI within this setting.

Key Conclusions:
Results enabled identification of a screening target population which would result in a highly efficient PAD screening strategy. However, if the Doppler ABI continues to be utilised as the screening tool of choice, then prior to the formal implementation of PAD screening, there is a need for a robust ABI training programme with standardised methodology in order to optimise accuracy and consistency of results.

An automated ABI device demonstrated potential to address feasibility issues associated with PAD screening with the ABI via a reduced need for operator skill and significantly reduced screening time. However, further refinement of the device is required to improve its diagnostic accuracy.

The value of PAD screening, from a cardiovascular perspective, has been shown to be questionable, as a current cardiovascular risk assessment algorithm (QRISK2) also identified high risk in a large majority of individuals found to have PAD.
Acknowledgements

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This thesis would not have been possible without the help and support I received from many people.

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Conflict of Interest Statement: Huntleigh Healthcare part sponsored and supported the research reported within this thesis via provision of equipment and technical support; they did not however, have any role in study design and implementation, nor in the analysis of results and formation of conclusions.
Author’s Declaration

I declare that the work in this thesis was carried out in accordance with the regulations of the University of South Wales/Prifysgol De Cymru. The work is original except where acknowledged or indicated by special reference within the text. No part of this thesis has been submitted for any other degree.

Any views expressed are the views of the author and in no way represent those of the University of South Wales/Prifysgol De Cymru.

This dissertation has not been presented to any other University for examination in the United Kingdom or overseas.

Signed:

Date:
Publications arising from this thesis


Titles of proposed future publications

Prevalence of abnormal ABI in a targeted general practice population.

Comparison of an automated pneumoplethymographic ABI device with the traditional Doppler ultrasound method for peripheral arterial disease diagnosis.

Non-invasive diagnosis of peripheral arterial disease.

Undiagnosed symptomatic peripheral arterial disease: why do patients not present to their GPs?

Primary care management of peripheral arterial disease.

Considerations for undertaking research within a primary care setting.

Awards relating to this thesis

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Cwm Taf University Health Board Research & Development conference, November 2013: 3rd prize for oral presentation of the PIPETTE study.

University of South Wales, Annual Postgraduate Researchers’ presentation day, May 2013: 1st prize for poster presentation of the PIPETTE study.*

KESS Pecha Kucha Research Presentation, May 2013: 1st prize for oral presentation of the PIPETTE study.

* publications and poster included in appendices
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>ABI</td>
<td>Ankle brachial Index</td>
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<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
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<tr>
<td>AD</td>
<td>Automated ABI device</td>
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<tr>
<td>AGATHA</td>
<td>A Global Atherothrombosis Assessment</td>
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<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>ARAPACIS</td>
<td>Ankle-brachial Index Prevalence Assessment: Collaborative Italian Study</td>
</tr>
<tr>
<td>BHS</td>
<td>British Hypertension Society</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CAC</td>
<td>Coronary artery calcium</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>CTA</td>
<td>Computed tomography angiography</td>
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<tr>
<td>CV</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>CVA</td>
<td>Cardiovascular accident</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>CWDU</td>
<td>Continuous wave Doppler ultrasound</td>
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<tr>
<td>DH</td>
<td>Department of Health</td>
</tr>
<tr>
<td>DP</td>
<td>Dorsalis pedis</td>
</tr>
<tr>
<td>DSA</td>
<td>Digital subtraction angiography</td>
</tr>
<tr>
<td>DW</td>
<td>Doppler waveform</td>
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<tr>
<td>ECQ</td>
<td>Edinburgh Claudication Questionnaire</td>
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<tr>
<td>EMIS</td>
<td>Egton Medical Information Systems Limited</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>FN</td>
<td>False negative</td>
</tr>
<tr>
<td>FP</td>
<td>False positive</td>
</tr>
<tr>
<td>FRS</td>
<td>Framingham risk score</td>
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<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>HDL</td>
<td>High-density lipoprotein</td>
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<tr>
<td>IMT</td>
<td>Intima media thickness</td>
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<tr>
<td>LDL</td>
<td>Low-density lipoprotein</td>
</tr>
<tr>
<td>LR</td>
<td>Likelihood ratio</td>
</tr>
</tbody>
</table>
MAC: Medial artery calcification
MESA: Multi-Ethnic Study of Atherosclerosis
MI: Myocardial Infarction
NHS: National Health Service
NICE: National Institute for Health and Care Excellence
NNS: Number needed to screen
NPV: Negative predictive value
PAD: Peripheral arterial disease
PPV: Positive predictive value
PT: Posterior Tibial
PVW: Pulse volume waveform
QOL: Quality of life
QRISK: Qresearch cardiovascular risk algorithm
RA: Rheumatoid arthritis
REACH: Reduction of Atherothrombosis for Continued Health registry
SIGN: Scottish Intercollegiate Guidelines Network
SVT: Society of Vascular Technology
TASC: Trans-Atlantic Inter-Society Consensus
TIA: Transient ischaemic attack
TN: True negative
TP: True positive
VC: Vascular calcinosis
WHS: Welsh Health Survey
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Part 1 - Background and Statement of Problem
Chapter 1: Introduction

1.0 Cardiovascular Disease: a definition

Cardiovascular disease (CVD) is defined as any abnormal condition characterized by dysfunction of the heart and blood vessels (Hall, 2011). It is an umbrella term which broadly incorporates six groups as described by the World Health Organisation (WHO, 2014) (Figure 1.1).

1.1 Atherosclerosis

Atherosclerosis is the primary causative factor in the development of coronary heart disease (CHD), cerebrovascular disease (CBVD) and peripheral arterial disease (PAD); it is defined as: a disease of the large and intermediate–sized arteries in which fatty lesions, called atheromatous plaques, develop on the inside surfaces of the arterial walls.

The atherosclerotic process is complex (Figure 1.2) and can be divided into four stages (Muir, 2009).

**Lesion initiation:** Injury to the endothelium is caused by hypertension, hyperlipidaemia, inflammation or oxidative stress. Such damage increases the expression of adhesion molecules on endothelial cells and decreases their ability to release nitric oxide and other substances that help prevent adhesion of macromolecules, platelets and monocytes to the endothelium.

**Fatty streak formation:** following damage to the endothelium, circulating monocytes begin and lipids (mostly low density lipoproteins - LDLs) begin to accumulate at the site of injury. Monocytes migrate through the endothelium into the intimal layer of the arterial wall and are transformed into macrophages, which then ingest and oxidise the accumulated lipoproteins, giving the macrophages...
a foam-like appearance. These macrophage foam cells then aggregate on the blood vessel and form a visible fatty streak.

**Fibro proliferative atheroma origination:** over time the fatty streaks grow larger and coalesce, and the surrounding fibrous and smooth muscle tissues proliferate to form larger and larger plaques, known as atheromas. Inflammation occurs as cells and molecules accumulate.

**Advanced lesion:** the fibroproliferative atheroma develops into an advanced lesion, which is highly cellular, containing endothelial and smooth muscle cells, inflammatory cells and a lipid core. It is covered with a fibrous cap. Over time, the plaques accumulate and grow and bulge into the lumen of the artery, reducing blood flow and sometimes completely occluding the vessel. Furthermore, the fibrous cap is vulnerable to ulceration and once this occurs, the underlying plaque is exposed to the bloodstream, with resultant thrombus or embolus formation (Garcia, 2009).

Figure 1.2: Development of atherosclerosis (Hall, 2011)
1.2 Cardiovascular Disease: a global perspective

Cardiovascular disease remains the leading cause of global mortality and was responsible for the loss of 17.3 million lives in 2008 (WHO, 2011). Its incidence has continued to increase in low and middle income countries over the last thirty years; although several high income countries have successfully employed various strategies leading to its decline (Murray et al., 2013).

However, a recent systematic review has demonstrated that the prevalence of peripheral arterial disease (PAD), a branch of CVD, is actually increasing globally, regardless of country income level (Table 1.1) (Fowkes et al., 2013). This trend can be attributed to an ageing world population and it is evident that the increase is particularly striking among older age groups. For all age groups over 79 years, the increase from 2000 to 2010 was consistently greater than 35%.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>People living with PAD in year 2000 (thousands)</th>
<th>People living with PAD in year 2010 (thousands)</th>
<th>Rate of Change (2000-2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High Income Countries</td>
<td>Low &amp; Middle Income Countries</td>
<td>Worldwide</td>
</tr>
<tr>
<td>25-29 years</td>
<td>2311</td>
<td>10756</td>
<td>13068</td>
</tr>
<tr>
<td>30-34 years</td>
<td>2803</td>
<td>11469</td>
<td>14272</td>
</tr>
<tr>
<td>35-39 years</td>
<td>3486</td>
<td>11247</td>
<td>14733</td>
</tr>
<tr>
<td>40-44 years</td>
<td>4071</td>
<td>11138</td>
<td>15209</td>
</tr>
<tr>
<td>45-49 years</td>
<td>4528</td>
<td>11408</td>
<td>15936</td>
</tr>
<tr>
<td>50-54 years</td>
<td>4907</td>
<td>9902</td>
<td>14808</td>
</tr>
<tr>
<td>55-59 years</td>
<td>4530</td>
<td>9111</td>
<td>13641</td>
</tr>
<tr>
<td>60-64 years</td>
<td>5342</td>
<td>9074</td>
<td>14416</td>
</tr>
<tr>
<td>65-69 years</td>
<td>5287</td>
<td>8416</td>
<td>13704</td>
</tr>
<tr>
<td>70-74 years</td>
<td>5594</td>
<td>6953</td>
<td>12547</td>
</tr>
<tr>
<td>75-79 years</td>
<td>4808</td>
<td>4960</td>
<td>9768</td>
</tr>
<tr>
<td>80-84 years</td>
<td>3107</td>
<td>3015</td>
<td>6123</td>
</tr>
<tr>
<td>85-89 years</td>
<td>2246</td>
<td>1411</td>
<td>3658</td>
</tr>
<tr>
<td>≥90 years</td>
<td>1174</td>
<td>544</td>
<td>1717</td>
</tr>
<tr>
<td>Total</td>
<td>54195</td>
<td>109405</td>
<td>163600</td>
</tr>
</tbody>
</table>

Table 1.1 Estimated number of people living with peripheral arterial disease in high-income countries, low-income and middle-income countries, and worldwide in years 2000-2010 (Fowkes et al., 2013)

PAD has been noted to be a neglected aspect of CVD and this is despite it being the third leading cause of atherosclerotic cardiovascular morbidity, following coronary artery disease (Wood, 2013).
therefore represents a major public health challenge which warrants concerted research efforts and strategies in order to achieve optimal treatment and prevention of this disease.

1.3 Peripheral Arterial Disease: a definition

Peripheral arterial disease (PAD) is an umbrella term for a number of disorders which affect arterial beds exclusive of the coronary and cerebral arteries (Hirsch et al., 2006). It includes diseases of the abdominal aorta, renal and mesenteric arteries, and lower extremity arteries, with atherosclerosis being the most common aetiology. Non-atherosclerotic causes of PAD and PAD-like symptoms include popliteal artery entrapment syndrome, cystic adventitial disease, endofibrosis of the iliac arteries and fibromuscular dysplasia (Weinberg and Jaff, 2012); these are not the focus of this research. For the purpose of this thesis, PAD refers to the partial or complete atherosclerotic obstruction of the distal aorta and/or leg arteries which results in restricted blood flow to the legs (Figure 1.3).

**Figure 1.3: Diagrammatic representation of Peripheral Arterial Disease**
(Source: National Heart, Lung and Blood Institute, 2011)
1.4 Consequences of PAD

Consequences of PAD are three-fold (Figure 1.4). It is a chronic, slowly developing condition and depending on the degree of narrowing of the arteries, a plethora of symptoms may occur. The Rutherford classification (Rutherford et al., 1997) categorises PAD into four grades:

Grade 0 – Asymptomatic: Tendera et al. (2011) report that up to two thirds of PAD patients in the community are, in fact, typically asymptomatic.

Grade I – Intermittent claudication: this is the most common symptomatic presentation with reported prevalence varying from 1.6% to 12% (Hiatt, 2001). It is characterised by pain in the calves which increases on walking and typically resolves quickly at rest.

Grade II – Ischaemic rest pain: pain is present at rest, usually in the foot, and patients often complain of permanent coldness in the feet.

Grade III – Ulcers and gangrene: these indicate severe ischaemia; they are usually extremely painful and may necessitate amputation. Norgren et al. (2007) report the annual incidence of major amputations to be between 120 and 500 per million in the general population. The prognosis for such patients is poor; two years following an amputation, 30% are dead, 15% have had a contralateral amputation, 15% have had an above knee amputation and only 40% have full mobility.

![Figure 1.4: Consequences of Peripheral Arterial Disease](image)

1. Both symptomatic and asymptomatic PAD have been shown to be powerful and independent predictors of CAD and CBVD
2. Pain, ↓QoL, ↓mobility, ulcers, the need for surgery and possibly amputation
3. Restricts walking - lack of exercise may mean further ↑risk of CVD, cognitive decline, osteoporosis and cancer (Golomb et al., 2006)
Such symptoms obviously equate to considerable suffering for those who endure PAD, with detrimental repercussions on ability to continue with day to day activities and reduced quality of life. Furthermore, Golomb et al. (2006) noted that decreased mobility is likely to result in insufficient exercise which may serve to further increase risk of cardiovascular disease, and also increase the likelihood of cognitive decline (Sofi et al., 2011), osteoporosis (Suzuki, 2011) and cancer (Winzer et al., 2011).

A further, and perhaps the most eminent consequence of PAD, stems from the fact that it is a manifestation of systemic atherosclerosis and therefore a powerful predictor of coronary artery disease (CAD) and cerebrovascular disease (CBVD) (Tendera et al., 2011); this has resulted in it being the subject of significant research attention in the past two decades. PAD, symptomatic or not, has been associated with a three to six-fold increased risk of death from cardiovascular causes in multiple longitudinal studies (Fowkes et al., 2008). Furthermore, this increased risk is independent of, and in addition to, that expected by concomitant traditional cardiovascular (CV) risk factors (Heald et al., 2006) (this is discussed in greater detail in Section 2.3). Evidence regarding this association is sufficiently robust that major national and international guidelines now recommend the same strategy of cardiovascular risk modification for persons with PAD as for those with CAD (ACC/AHA, 2011; ESC, 2011; NICE, 2012a).

PAD can be detected and quantified by several non-invasive tests (section 2.1.2) but is most commonly diagnosed by means of the ankle brachial index (ABI). This is a measure of the blood pressure in the arteries supplying the legs relative to central aortic pressure, which is approximated by measuring the blood pressure in the arms. An ABI of ≤0.9 is considered diagnostic of PAD, and this is based on this cut-off point being shown, in several clinical trials, to be up to 95% sensitive in detecting angiogram positive disease and approximately 99% specific in identifying healthy subjects (Fowkes, 1988). The test procedure itself is commonly reported to be simple, quick and reproducible, which is amenable for use in non-specialist settings such as primary care (Kohlman-Trigoboff, 2013).

### 1.5 Under-diagnosis of PAD

Despite its association with severe health risk, the under-diagnosis of PAD is well documented (Hirsch et al., 2006). This may be partly attributed to the fact that up to two thirds of PAD patients are asymptomatic (Tendera et al., 2011). Poor awareness of the prevalence, natural history and prognostic significance of PAD on behalf of both the public and medical communities is also likely to be a contributing factor (Haigh et al., 2013). A surprising finding in population screening studies is
that between 10% and 50% of patients with intermittent claudication have never consulted a doctor about their symptoms (Norgren et al., 2007).

1.6 A call to PAD screening

<table>
<thead>
<tr>
<th>WHO Criteria</th>
<th>Current Peripheral Arterial Disease Position</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Condition</strong></td>
<td></td>
</tr>
<tr>
<td>An important health problem</td>
<td>Up to two thirds of PAD patients in the community are, in fact, typically asymptomatic (Tendera et al., 2011). PAD, symptomatic or not, has been associated with a three to six-fold increased risk of death from cardiovascular causes in multiple longitudinal studies (Fowkes et al., 2008).</td>
</tr>
<tr>
<td>A recognisable latent or early symptomatic stage</td>
<td></td>
</tr>
<tr>
<td>Natural history of the condition, including development from latent to declared disease should be adequately understood.</td>
<td></td>
</tr>
<tr>
<td><strong>Test</strong></td>
<td></td>
</tr>
<tr>
<td>A suitable test or examination which is acceptable to the population.</td>
<td>The ABI is considered the cornerstone of non-invasive assessment and diagnosis of PAD which is amenable for use in the primary care setting. However, it is not without its limitations (see Section 2.9.3). No studies have assessed patient perspective of the ABI as a screening test.</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
</tr>
<tr>
<td>An accepted treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.</td>
<td>All guidelines concur that patients with asymptomatic or symptomatic PAD require stringent secondary cardiovascular preventive strategies (see Table 2.4). Limited data exists on the impact of early intervention on asymptomatic PAD patients (Section 2.4).</td>
</tr>
<tr>
<td>An agreed policy on who to treat as patients.</td>
<td>An ABI of &lt; or ≤0.9 is considered diagnostic of PAD.</td>
</tr>
<tr>
<td><strong>Programme</strong></td>
<td></td>
</tr>
<tr>
<td>Evidence from high quality Randomised Control Trials that screening is effective in reducing mortality or morbidity.</td>
<td>None available</td>
</tr>
<tr>
<td>Adequate staffing and facilities for diagnosis and treatment available.</td>
<td>Limited data is available to indicate whether knowledge and skills for PAD screening/ABI measurement already exists within primary care, or if a training/education programme would be necessary.</td>
</tr>
<tr>
<td>Cost effective.</td>
<td>There have been no direct studies relating to the cost-effectiveness of PAD screening.</td>
</tr>
</tbody>
</table>

Table 1.2: The WHO principles of screening applied to peripheral arterial disease.

Based on current evidence discussed this far, it can be seen that PAD meets several of the key criteria, as set out by the World Health Organisation, which must be fulfilled prior to the instigation of a formalised screening programme (Wilson and Jungner, 1968) (Table 1.2). PAD is clearly an important health problem with a recognisable asymptomatic stage; there appears to be a suitable test for its diagnosis and subsequent treatment recommendations are in place. However, screening for PAD is a contentious concept for the reasons outlined below.
Firstly, there is uncertainty regarding the value of PAD screening. A review of national and international guidelines reveals that screening is not universally advocated and this may be attributed to a lack of randomised control trials of PAD screening versus no screening. Existing research also suggests that patients may have little to gain from a PAD diagnosis as management of cardiovascular risk factors in patients with PAD in the primary care setting is generally poor and less than optimal.

Secondly, despite extensive investigation of the epidemiology of PAD, there is no consensus regarding how a PAD screening strategy should be targeted. Furthermore, although existing literature is unanimous that PAD screening should come under the remit of primary healthcare, it is unclear if necessary skills for ABI measurement and PAD screening exist within this setting. The Scottish Intercollegiate Guidelines Network (SIGN) states that “there is a pool of expertise for measuring the ABI of patients in the community” (SIGN, 2006, p.13) but this statement is not substantiated and existing research regarding this issue has produced varying results.

Further uncertainty relates to the practicality of PAD screening; current research findings are mixed with some authors arguing that it is simple and quick and can easily be undertaken in general practice, whilst others report it to be considerably time consuming. Additionally, there appear to have been no studies which have investigated the patient perspective of ABI measurement and PAD screening, which of course should be a critical consideration prior to the development of any screening strategy.

A final consideration relating to PAD screening concerns recent technological advances involving the development of automated ABI devices. Such devices could potentially simplify the process of ABI measurement/PAD screening, making it less time consuming and more practical for use in the primary care setting. This potentially makes PAD screening a much more viable option. Existing research in this field, which has focussed primarily on automated ABI devices utilising oscillometric technology, has proven inconclusive.

Hence, the fundamental aim of the research presented within this thesis, is to address the ambiguities outlined above, via a contemporary and comprehensive investigation of PAD screening.
Chapter 2: Critical Review of Literature

2.0 Methods used to search, identify and extract evidence from the literature


The broad scope of this project made it necessary to read extensively on a considerably wide range of PAD related topics. This, combined with the fact that PAD has been a highly active research topic for several decades, resulting in tens of thousands of published papers dating back to 1938, meant that for pragmatic reasons, it was necessary to restrict the data search to the last 30 years. However, older papers that were referred to in the reviewed literature and considered pivotal or specifically relevant to this thesis, were subsequently sought out and obtained. Searches were further restricted to papers written in English.

Key word and combinations of keywords included, but were not limited to, the following areas:

**Disease**: peripheral arterial disease, peripheral arterial occlusive disease, peripheral vascular disease, lower extremity arterial occlusive disease, atherosclerosis obliterans, intermittent claudication, rest pain, chronic limb ischaemia.

**Diagnosis**: ankle brachial index, ankle brachial pressure index, ankle arm index, the Windsor Index, pulse volume recording, pulse volume waveforms, Doppler ultrasound, continuous wave Doppler ultrasound, oscillometric, pneumoplethysmography, photoplethysmography, angiography, arteriography, Duplex ultrasound, Edinburgh claudication questionnaire, pulse palpation, clinical examination, screening tools.

**Epidemiology**: epidemiology, research design, epidemiological study characteristics, epidemiological methods, incidence, prevalence.

**Screening**: primary care, secondary care, cardiovascular risk, cardiovascular risk tools, cardiovascular assessment.
**Treatment:** guidelines, aspirin, anti-platelets, clopidogrel, cardiovascular risk, statins, lipid lowering, exercise, smoking, smoking cessation, hypertension, anti-hypertensives, blood pressure, diet.

**Miscellaneous:** Guidelines, quality of life, treatment, risk factors.

As the surgical and endovascular treatment of PAD were not a focus of this project the following search terms were excluded:

**Excluded search terms:** Surgery, surgical, endovascular, intravascular, stent, bypass, angioplasty.

No restriction was placed on study type as both qualitative and quantitative study methodologies were considered relevant to this project. Review papers, commentaries, conference abstracts etc. were also included in order to gain further information regarding current perspectives of PAD screening.

Relevant papers were downloaded and printed to allow review and cataloguing of evidence. The final search date for papers and literature reviewed within this thesis was 01/05/14.

Other forms of information retrieval included reviews of bibliographies, reference lists, reference books, research texts as well as literature from key government reports. Personal communication was made with a number of study authors in order to clarify study details and results where necessary.
Literature Review

2.1 PAD Diagnosis

2.1.1 Gold Standard for PAD diagnosis

The gold standard for diagnosis of PAD is angiography. Radio-opaque dye is injected via a percutaneous femoral artery puncture, prior to x-ray based imaging to allow visualisation of the arterial tree. Digital subtraction techniques (Digital Subtraction Angiography: DSA) provide superior definition of the vascular tree; this technique "subtracts" the bones and other organs so only the vessels filled with contrast agent can be seen. Angiography however, has several associated risks which can be attributed to its invasive nature, including bleeding, infection and vessel disruption (NICE, 2012). As a result, computed tomography angiography (CTA) has, in recent years, been increasingly used as reference standard (Collins et al., 2007); however both DSA and CTA carry risks associated with the use of ionising radiation and contrast agents which can cause nephrotoxicity (Collins et al., 2007).

2.1.2 Non-invasive PAD diagnosis

Fortunately, PAD can also be diagnosed non-invasively via several different methods including: ankle brachial index measurement, clinical examination, history taking, Doppler waveform analysis, pulse volume waveform analysis, Duplex ultrasound scanning and the toe brachial index. An overview of the underlying principles and technology associated with each of these diagnostic methods is provided below.

2.1.2.1 Ankle brachial index

The ankle-brachial index (ABI) is the most widely used non-invasive diagnostic modality utilised to identify PAD; indeed it is considered the cornerstone of PAD assessment. It is calculated by dividing the systolic blood pressure at the ankle by the systolic brachial blood pressure; an ABI of ≤0.9 is considered diagnostic of PAD. The ABI is universally advocated as the screening tool of choice in current PAD guidance (ACC/AHA, 2005; SIGN, 2006; TASC, 2007; SVT, 2010, ESC, 2012, NICE, 2012a). Furthermore, current epidemiological definition of PAD is based on the presence of ABI ≤ 0.9. The ankle brachial index is a primary focus of the research reported within this thesis and as such, it is discussed in detail in section 2.2.
2.1.2.2 Clinical Examination

According to Au et al. (2013), the foundation of any PAD assessment should be always based on careful history taking combined with clinical examination as a fundamental first step. Detailed examination of the legs can provide valuable information regarding the state of the peripheral circulation (Marston, 2011). Dillavou and Kahn (2003) recommend that physical examination should include palpation and documentation of femoral, popliteal and pedal pulses, and auscultation for femoral and carotid bruits. Legs should also be inspected for signs of chronic ischaemia, including pallor, cyanosis and non-healing wounds. Trophic ischaemia related changes such as hair loss, smooth shiny skin and thickened nails may also be present.

Khan et al. (2006) conducted a meta-analysis of 17 studies which investigated the diagnostic performance of the clinical examination for PAD. The presence of a femoral bruit was the most positive clinical finding to diagnose PAD in asymptomatic patients (positive likelihood ratio [+LR]: 4.8, 95% CI 2.4 to 9.5). Other valuable clinical findings included claudication (+LR: 3.3, 95% CI 2.3 to 4.8) and reduced or absent pulse (+LR: 3.1, 95% CI 1.4 to 6.6). In patients complaining of leg pain that corresponded with intermittent claudication, the presence of cool skin was the most diagnostic positive finding (+LR: 5.9, 95% CI 4.1 to 8.6).

A more recent, large scale study by Cournot et al. (2007) corroborated the findings of Khan et al. (2006). Cournot and colleagues examined the accuracy of physical examination to identify PAD in 2736 asymptomatic individuals, aged 20-90, with no history of cardiovascular disease. They also found that the presence of a femoral bruit provided information on the presence of both ABI<0.9 (+LR: 2.90, 95% CI 1.63 to 5.16) and femoral plaque (+LR: 3.23, 95% CI 2.22 to 4.71) as identified by Duplex ultrasound. Similarly, the absence of both pedal pulses also provided information on the presence of ABI<0.9 (+LR: 3.57, 95% CI 1.96 to 6.60). However, in this study all clinical examinations were undertaken by the same trained physician and therefore offers no information with regard to how differing professionals, with differing levels of training and experience would perform in this task.

Armstrong et al., (2010) hold that most clinicians have the necessary expertise to undertake clinical examination for PAD and furthermore state, that any clinician, physician or nurse, can be reliably trained to do this. There is however, a dearth of evidence to support this view. McGee and Boyko (1998) investigated observer variation in assessment of pedal arteries by pulse palpation. A series of 5 controls and 33 claudicants had their dorsalis pedis (DP) and posterior tibial (PT) pulses examined by a consultant, registrar, senior house officer and nurse. In the control group, whilst there was no disagreement with regard to DP pulses, observers disagreed on the presence or absence of PT pulses in 30% of limbs. In the claudicants group, observers agreed on only 67% of DP pulses and 53% of PT pulses.
pulses. The authors concluded that pedal pulse palpation in patients with arterial disease is subject to substantial observer error. Factors such as the presence of oedema may make pulse palpation difficult and in addition, the dorsalis pedis pulse may be congenitally absent in around 3% of people (Chavatzas, 1974) which further complicates this clinical assessment procedure.

2.1.2.3 History taking to identify intermittent claudication

As discussed in section 1.4, intermittent claudication (IC) is the most common symptomatic presentation of PAD. IC arises during activity when the blood and oxygen demand of the working skeletal muscle exceeds supply (Olson and Treat-Jacobsen, 2004). It manifests itself as cramping pains which occur most commonly in the calf muscles but also in the thighs and buttocks; the pain location depends on the location of the arterial blockage (Olin, 1993). Classic claudication is defined by the World Health Organisation as “calf pain that occurs during exercise and ceases within 10 minutes of rest” (Rose, 1962).

Research has suggested that patients with PAD and symptoms of IC may not spontaneously offer a classic exertional history of leg-pain during consultations with clinicians (Hirsch et al., 2005). Typical lower limb ischaemia symptoms have an indolent onset that patients often attribute to the deconditioning of aging and may not bring this history as the chief complaint to their primary care clinician (Hirsch et al., 2005). Furthermore, descriptions of claudication may be atypical and classic claudication symptoms may be masked by symptoms from concomitant diseases. Vascular claudication must also be distinguished from other illnesses that cause exertional leg pain such as severe venous obstructive disease, chronic compartment syndrome, lumbar disease and spinal stenosis, osteoarthritis, and inflammatory muscle diseases. Clinicians must therefore possess a sound knowledge of the distinguishing features of these various causes of leg pain.

Several validated questionnaires exist to assist in the diagnosis of IC. The WHO/Rose Questionnaire on intermittent claudication was developed in 1962 for use in epidemiological surveys; however, issues relating to poor sensitivity led to the further development of IC tools such as the Edinburgh claudication questionnaire (ECQ) (Leng, 1992) and the King’s College Questionnaire (Morgan et al., 2001).

**The Edinburgh Claudication Questionnaire**

The ECQ is an established validated tool for the diagnosis of IC, consisting of six questions (Appendix 1). It not only determines the presence or absence of IC but also grades positive cases in terms of its severity and whether it is a typical presentation or not. If the pain is only precipitated by walking up
hill or in a hurry, then it is termed “grade 1”. If, however, it also occurs when walking at an ordinary pace on a level, then it is termed “grade 2”. Typical claudication is recorded when pain occurs in the calf, regardless of whether pain also occurs in other sites, whereas, atypical claudication refers to pain in the thigh or buttock in the absence of any calf pain.

The ECQ was tested on 300 subjects aged over 55 years attending their general practitioner, and found to be 91.3% (95% CI 88.1–94.5%) sensitive and 99.3% (95% CI 98.9–100%) specific in comparison to the diagnosis of intermittent claudication made by a physician (Leng and Fowkes, 1992). The repeatability of the questionnaire after 6 months was excellent (kappa = 0.76, \( p < 0.001 \)). However, an obvious limitation of the utilisation of a symptom based questionnaire to diagnose PAD is that it of course, will fail to identify all asymptomatic cases, which account for approximately two thirds of the total PAD prevalence in a community setting (Tendera et al., 2011). It is therefore not surprising that the reported sensitivity of the ECQ to detect PAD as diagnosed via CTA is only 56% (Haigh et al., 2013). The ECQ is considered in further detail in chapter 16.

### 2.1.2.3 Doppler wave-form analysis

A Doppler unit works by emitting a beam of ultrasound into blood vessels via a small probe. Moving blood cells in the path of the beam cause a frequency shift in the ultrasound which is reflected back to the probe (AbuRahma et al., 2010). There are various methods of displaying the Doppler reflected ultrasonic beam; it can be projected audibly via a loud speaker or converted into a visual analogue waveform. The detection of auditory Doppler signals from a hand-held Doppler unit is a constituent of the gold standard procedure for ABI measurement (Section 2.2). Trained clinicians can also audibly distinguish between multiphasic, pulsatile signals which are indicative of normal blood flow, and non-pulsatile, low pitched, monophasic signals associated with reduced blood flow.

Many hand-held Doppler units now also visually display the Doppler waveform for further analysis. A normal multiphasic Doppler arterial waveform is shown in figure 2.1. Waveforms indicating disease are described as biphasic or monophasic due to an absence of parts B and/or C. In addition, part A of diseased waveforms often characteristically has poor upslope and downslope and rounded peaks.

![Figure 2.1: Normal arterial Doppler waveform (multiphasic).](image)

Key: (A) systolic component; (B) early diastolic component; (C) late diastolic component.

Image source: Aburahma et al., 2010
Doppler waveform (DW) analysis is limited by the fact that waveforms may be affected by temperature and the presence of congestive heart failure (AbuRahma and Jarrett, 2010). Furthermore, it is operator dependent in that it requires the Doppler probe to be carefully positioned at a specified angle and pressure over the artery in order to obtain a good quality signal.

2.1.2.4 Pulse volume wave-form analysis

Pulse volume waveform (PVW) analysis utilises volume plethysmography to evaluate blood flow in the lower extremity (Weinburg, 2010). Volume changes in the foot and ankle, which correspond with stages of the cardiac cycle, are detected via pressure sensors (pneumoplethysmography) or photo detectors (photoplethysmography). A pressure transducer converts these small pressure changes into a small electrical signal which is amplified and displayed as a waveform plotted against time. The contour and amplitude of recorded PVWs can be analysed both qualitatively and quantitatively to gain information regarding the arterial status of the limb (this is discussed in detail in Chapter 14).

A normal pulse volume waveform recording is shown in figure 2.2. A brisk upstroke and sharp peak occur during systole, followed by a gradual downslope which occurs in diastole. A reflective wave, or dicrotic notch, represents reflected blood flow.

![Figure 2.2: Normal pulse volume waveforms](image)

Key: 1 = brisk systolic upstroke, 2 = sharp systolic peak, 3 = gradual downslope, 4 = dicrotic notch

Image source: Huntleigh Diagnostics – reproduced with permission.

Until recently, this diagnostic technique has been confined to the realms of the vascular laboratory but recent technological advances have made diagnostic modality more amenable for use in primary care and non-specialist environments; there is however, a lack of research with regard to the feasibility of this.

As with DW analysis, there are also physiological limitations related to PVW analysis; pulse volume waveforms are dependent on peripheral blood flow and this may be influenced by factors other than vessel patency (Weinburg, 2010). In the upper limb for example, where sympathetic nerve input has a great deal of influence on blood flow, PVWs may not always indicate the true nature of blood flow.
capabilities of the limb. Severe congestive heart failure may also slow blood flow and mimic inflow disease.

A study by Ro et al. (2013) evaluated the sensitivity and specificity of subjective PVW analysis and Doppler waveform (DW) analysis compared to the gold standard of computed tomography angiography (CTA) diagnosed PAD. Test results from a total of 97 patients (194 legs) revealed that the sensitivity and specificity of PVW analysis compared to the CTA were 82% and 77% respectively; the sensitivity and specificity of DW analysis were 91% and 65% respectively.

2.1.2.5 Duplex ultrasonography

Duplex ultrasonography represents a further extension of the utility of pulsed ultrasound Dopplers via their combination with B-mode scanners (AbuRahma et al., 2010). This allows not only detailed visualisation and imaging of the vessel being studied but also detects blood flow velocity at multiple points within its lumen. Currently, colour Duplex ultrasonography represents the most common modality used in modern vascular laboratories. With reported sensitivity for diagnosis of PAD compared to CTA of 96% and specificity of >95% (Collins et al., 2007) it is clearly the superior non-invasive modality which can diagnose PAD with a high degree of accuracy. However, it is limited by the fact that it requires highly trained ultrasonographers and is therefore not amenable for use in non-specialist environments such as primary care.

2.1.2.6 Toe brachial index

The TBI is frequently cited as an alternative to the ABI which is of particular use for patients with co-existing diabetes, chronic kidney disease, or advanced age which are conditions associated with medial arterial calcification (MAC), which can lead to falsely elevated ankle pressures due to vessel stiffness (section 2.2.3). The toe vessels have been reported to be less susceptible to MAC, hence the usefulness of the TBI (Leskine et al., 2002). The TBI measures the large toe’s systolic pressure via photoplethysmography against the brachial systolic pressure which is measured with the Doppler. (Andras and Ferket, 2014). Historically, reliable measurement of the TBI has been hindered by expensive and cumbersome techniques for its measurement, resulting in its confinement for use in vascular laboratories only. However, recently developed methods have been introduced which allow access to bedside assessment of the TBI. Hoyer et al. (2013) conducted a robust literature review regarding the TBI for the diagnosis of PAD. They concluded that in contrast to the well defined evidence based limits of the ABI, the diagnostic
criteria of an abnormal TBI remain ambiguous and evidence is insufficient to recommend a specific cut-off as diagnostic of PAD. They also note that current studies in normal populations and studies investigating the correlation of the TBI and angiography are sparse and highlight the need for further large scale trials.

2.1.2.7 Non-invasive diagnosis of PAD within the diabetic population.

The vascular assessment of the diabetic limb is known to pose additional challenges for clinicians. There is continued debate regarding the influence of peripheral neuropathy and arterial calcification on the reliability of vascular screening in diabetes. Arterial wall calcification causes increased rigidity, making palpation of foot pulses more difficult and artificially elevating the ABI. Williams et al. (2005) highlighted the difficulty of screening for PAD in the diabetic population. They evaluated the efficacy of palpation for foot pulses, the ABI, the toe-brachial index (TBI) and Doppler waveform analysis in screening for PAD in diabetics via comparison with the gold standard non-invasive assessment, duplex arterial ultrasound. One hundred and thirty eight limbs in sixty eight individuals with no critical ischaemia were examined. Limbs were grouped on the presence or absence of diabetes, clinically detectable peripheral neuropathy, and PAD identified by the arterial Duplex scan. The absence of one or more foot pulses had reduced sensitivity and poor specificity in both the diabetic and neuropathic groups (Diabetic non-neuropathic group: sensitivity 87%, specificity 53%; Diabetic neuropathic group: sensitivity 81%, specificity 56%). Similarly, there was a reduction of the sensitivity of the ABI and TBI in the neuropathic group (ABI: from 71 to 38%, TBI: from 81 to 61%). These conclusions were echoed in subsequent studies by Clairotte et al. (2009) and Potier et al. (2011). A more recent study by Aubert et al. (2013) examined the influence of vascular calcification on efficiency of screening tests for peripheral arterial disease in 200 subjects with diabetes at high risk of cardiovascular disease. They found that pulse palpation for missing or weak pulses had a higher sensitivity for detecting PAD (as diagnosed by Duplex ultrasound scan) than the ABI (90% vs. 42.3% respectively, p <0.001). They also reported that the high rate of false negative results for the ABI was associated with below knee vascular calcification. They authors concluded that examination consisting of both pulse palpation and the ABI was the best strategy to screen for PAD in diabetics which offered a sensitivity of 92% but a specificity of only 32%.

In summary: there are several non-invasive methods of assessing the arterial status of the lower limbs, each with their own merits and limitations. In clinical practice, these methods are frequently used in combination, according to the preferences and abilities of individual clinicians, and
depending on the availability of the necessary equipment. The ABI, as a primary focus of the research reported within this thesis, will now be considered in further detail.

2.2 The Ankle Brachial Index

2.2.1 ABI: Background information

The use of the Ankle Brachial Index (ABI) dates back to the 1950s, when Windsor was the first to compare peripheral systolic pressure with central systolic pressure for the purpose of identifying PAD (Windsor, 1950). Yao et al. (1968) further developed this concept when they reported that the severity of PAD correlated with a drop in ABI; this ability to quantify PAD subsequently resulted in the ABI being widely adopted into clinical practice. More than four decades on, the ABI not only remains the cornerstone of non-invasive assessment of the patient with PAD, but, as discussed in this thesis, it also has an evolving role in screening individuals for asymptomatic PAD in order to identify those who are at high cardiovascular risk.

The ABI is a measure of the blood pressure in the arteries supplying the legs relative to central, aortic pressure (approximated by measuring the blood pressure in the arms). There are several different methods of determining these blood pressures which include the use of:

- a continuous wave Doppler ultrasound device in combination with a manual sphygmomanometer (current gold standard for ABI measurement);
- automated oscillometric ABI devices;
- automated photoplethysmographic ABI devices; and
- automated pneumoplethysmographic ABI devices.

The current gold standard for ABI measurement entails the use of a hand-held continuous wave Doppler ultrasound device to allow a clinician to audibly detect returning blood flow following the deflation of a blood pressure cuff. The pressure at which the blood flow returns represents the systolic blood pressure of that artery. This measurement is undertaken on each arm in turn, and then on up to three vessels in the feet (dorsalis pedis, posterior tibial and peroneal arteries), before manually determining the ABI of each leg according to the following calculation:

\[
ABI = \frac{\text{Higher ankle systolic blood pressure}}{\text{Higher brachial systolic pressure}}
\]

In a vascular system without atherosclerosis, the blood pressure in the large arteries is more or less equal and hence the ABI would be approximately 1.0. A haemodynamically significant stenosis in a
large artery somewhere between the aorta and the ankle will reduce blood flow distal to the stenosis with a resultant drop in the systolic blood pressure and an ABI of <1.0.

The American College of Cardiology/American Heart Association (Rooke et al., 2011) classifies the ABI as follows (Table 2.1).

<table>
<thead>
<tr>
<th>ABI</th>
<th>Classification of Peripheral Arterial Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.9</td>
<td>Diagnostic of Peripheral Arterial Disease</td>
</tr>
<tr>
<td>0.9-0.99</td>
<td>Borderline Peripheral Arterial Disease</td>
</tr>
<tr>
<td>1.0-1.29</td>
<td>Normal</td>
</tr>
<tr>
<td>≥1.3</td>
<td>Abnormally high (may indicate medial arterial calcification)</td>
</tr>
</tbody>
</table>

Table 2.1: Classification of the Ankle Brachial Index according to the ACC/AHA (Rooke et al., 2011)

### 2.2.2 Sensitivity and specificity of the ABI

An ABI of ≤0.9 is considered diagnostic of PAD, and this is based on this cut-off point being shown, in several clinical trials, to be up to 95% sensitive in detecting angiogram positive disease and approximately 99% specific in identifying healthy subjects (Fowkes, 1988). In actual fact, more recent studies have reported much lower sensitivities of the ABI for detecting PAD, in the region of 79% according to Lijmer (1996) and 68% according to Schröder (2006). Such inconsistencies could be related to limitations of the ABI (Section 2.2.5) rather than the arbitrary cut-off point used as diagnostic of PAD. Inconsistent results could also be attributed to a lack of clear definition as to what constituted PAD according to angiography in terms of anatomical location and stenosis diameter (Ro et al., 2013). Xu et al. (2013) conducted a robust meta-analysis to investigate the diagnostic value of the ABI (when measured via Doppler ultrasound) in PAD. Studies (n=4, participants: n=569) were included if they had assessed the sensitivity and specificity of ABI≤0.9 to detect a stenosis ≥50% as identified by angiography. The pooled sensitivity and specificity of ABI≤0.9 for PAD diagnosis were 75% and 96% respectively.

### 2.2.3 Limitations of the ABI

Despite being widely regarded as a simple, non-invasive and reproducible test (Fowkes et al., 1988; Ray et al., 1994), the ABI has recognised limitations. The most prominent of these relates to the artefactual elevation of arterial occlusion pressures in the lower limb, which can result in an inaccurate and non-diagnostic ABI. This can be attributed to factors such as peripheral oedema, lipodermatosclerosis associated with venous insufficiency, and circular arteriosclerotic lesions (Kröger et al., 2006). However, the most common aetiology relates to the accumulation of calcium
and phosphate in the medial layer of the arterial wall which subsequently makes it difficult to compress the vessel; this is known as Mönckeberg’s medial sclerosis or medial artery calcification (MAC) (Rocha-Singh et al., 2014). MAC is associated with advancing age and hypertension (Hirsch et al., 2005), and also diabetes mellitus (Formosa et al., 2013) and chronic kidney disease (Nitta, 2011; Mizobuchi et al., 2009). Experienced practitioners are usually alerted to the possibility of a falsely elevated or inaccurate ABI when the audible signal from the Doppler is abnormal or when the clinical presentation of the assessed limb does not correspond with the ABI result (discussed further in Section 14.0). However, whether non-specialist, primary care practitioners would have the skills and knowledge to make such a judgment is unclear.

Al-Qaissi et al. (2009) point out that a further significant issue associated with the use of the ABI arises from the lack of standardisation of its methodology. Modification of the ABI calculation for the purpose of CV risk assessment is discussed in Section 2.5.3. However, several variations of the calculation of the value are also common place within epidemiological PAD studies. The higher of the two pressures in the dorsalis pedis (DP) or the posterior tibial (PT) arteries is conventionally taken as the ABI numerator whilst the higher of the two brachial pressures is the denominator. However, there is research to suggest that averaging the DP and PT pressures correlates more closely with limb pressures (McDermott et al., 2000) and some practitioners may therefore prefer this method. Similarly, equipment choice may differ with some individuals choosing to use a hand-held Doppler ultrasound to measure the brachial pressure whilst others may utilise the Korotkoff method which tends to yield lower values (Jeelani et al., 2000). As well as producing differing results in individual patients, these different methodologies are open to different forms of bias and will therefore be associated with different levels of reproducibility depending on the clinical circumstances (Carauna et al., 2005). As discussed in Section 2.2, the American Heart Association has attempted to address this issue by setting out an evidence-based recommended procedure for ABI measurement (Aboyans et al., 2012).

Additional issues associated with the ABI relate to the practicality of the test as well as the skills and knowledge required to undertake this procedure (these are discussed in more detail in Section 11.0).

### 2.2.4 Alternative methods of ABI measurement

It is clear that any strategies to simplify ABI measurement and make it less time consuming would result in greater acceptability and utilisation of the procedure in the primary care environment. In recent years, the use of automated devices to assess the ABI have been developed with reported advantages such as reduced measurement time (as the patient does not need to be rested beforehand), greater ease of use and reduced operator variability. Most commonly, these devices
involve the use of oscillometric technology to measure the systolic blood pressures, but more recently, photoplethysmographic and pneumoplethysmographic methods have also been utilised for this purpose. Technical information regarding the functioning of these devices and further consideration of their associated evidence base is further considered in Part 4 of this thesis. A brief summation of current evidence regarding the validity of automated ABI devices is provided below.

Oscillometric ABI devices
Several studies have assessed the validity of automated oscillometric ABI devices but results have been inconsistent. Some studies suggest that values obtained using automated oscillometric equipment closely resemble those obtained using the sphygmomanometer and Doppler probe (Beckman et al., 2006: correlation coefficient = 0.78, p<0.01; Harrison et al., 2011: correlation coefficient = 0.92, p<0.01). Others, however, dispute this; a blinded study by Ramanathan et al. (2003) found no correlation (correlation coefficient = 0.4, p>0.05) between values obtained from all four limbs using these two sets of equipment in a sample of 50 healthy volunteers. Jonsson et al. (2001) concluded that oscillometric measurement of the ABI is unreliable in individuals with PAD as it overestimated ankle systolic pressure by a mean of 29mmHg in 47 patients with pre-identified leg ischaemia. Further studies are considered in detail in Section 12.1 and Table 12.7.

Photoplethysmographic ABI devices
A review of the literature revealed only one study which investigated the validity of two separate automated ABI devices which utilise photoplethysmography to measure the ABI (Beutner et al., 2012). The study was limited by a small sample size with a small proportion of diseased participants. Results, however, showed good correlation with results obtained via the traditional Doppler method.

Pneumoplethysmographic ABI devices
To date, only one study has evaluated the validity of an automated device which utilises pneumoplethysmography (Dopplex Ability, Huntleigh Healthcare) to measure the systolic pressures in all four limbs simultaneously before automatically calculating the ABI. Lewis (2011) found that results from this device correlated well (r=0.89, p<0.05) with Doppler results, with the added benefit of a marked reduction (7.1 minutes versus 16.5 minutes plus resting time) in the time needed to perform the test (as simultaneous cuff inflation negates the need for the patient to be rested). Notably, this study is unpublished but is available via the device manufacturer’s website. Additional
research is therefore needed to further investigate and validate devices utilising pneumoplethysmography as their measurement principle.

To summarise, it appears that automated ABI devices could potentially provide a solution for several of the problems associated with the ABI. However, additional research within this field is required, particularly in relation to plethysmographic devices.

2.3 PAD prevalence

Current epidemiological definition of PAD is based on the ankle brachial index (ABI) which as described in section 2.2, is globally recognised and considered to be a valid and reproducible method of diagnosing both clinical and subclinical PAD. A literature review revealed in excess of 120 studies which have examined the prevalence of PAD in varying populations worldwide. Prevalence rates of course, depend not only on the groups being studied, but also on the ABI methodology and cut-off point used as diagnostic of PAD. This is demonstrated in Table 1, Appendix 2, which presents a sample of such studies. In 2012, the American Heart Association (AHA) released a scientific statement setting out an evidence based, recommended procedure for ABI measurement and interpretation (Aboyans et al., 2012); they proposed that this methodology should be used in all future epidemiological studies to ensure consistency and aid in the assessment and comparison of PAD prevalence data.

2.3.1 Global PAD prevalence

PAD prevalence in general populations, based on ABI≤0.9, is in the range of 3-10%, increasing to 15%-20% in those older than 70 (Sigvant et al., 2007). Hence PAD is a prevalent disease which is strongly age related. Fowkes et al. (2013) estimated that in 2010, 202 million people were living with PAD globally, and this figure is set to rise in coming years. Hirsch and Duval (2013) recently referred to PAD as a global pandemic, and a key component of the global burden of non-communicable diseases.

2.3.2 UK PAD prevalence

Although PAD prevalence data from large international registries such as REACH (Reduction of Atherothrombosis for Continued Health; Ohman et al, 2006) and the AGATHA (A Global Atherothrombosis Assessment) study (Fowkes et al., 2006) included small UK components (0.9% of total population in REACH and 5.2% AGATHA), data specific to the UK were not published. The
review of the literature revealed that prevalence data specific to the UK are sparse, with all published studies having been undertaken in Scotland (Table 2.2). Prevalence rates are again in the region of 8-11% but differing study populations and differing methods of PAD diagnosis and ABI measurement make comparisons difficult. Furthermore, prevalence rates are subject to change as a result of factors such as increasing longevity and improved survival from coronary artery disease (CAD) and stroke, which may allow the disease to become more manifest. Health improvement strategies, such as public-place smoking bans which have proven effective in lowering death rates from cardiovascular disease may, on the other hand, cause a reduction in PAD prevalence.

<table>
<thead>
<tr>
<th>Author, date &amp; location</th>
<th>Study population</th>
<th>N</th>
<th>Criteria for PAD diagnosis</th>
<th>Method of ABI measurement and calculation</th>
<th>Prevalence of PAD</th>
<th>Study strengths/weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edinburgh Artery Study; Fowkes et al., 1991. Edinburgh, Scotland.</td>
<td>Age 55-74, recruited from 10 general practices</td>
<td>1592</td>
<td>ABI&lt;0.7 or hyperaemic drop of &gt;35% or ABI&lt;0.9 and hyperaemic drop of &gt;20%.</td>
<td>Limited data available regarding ABI measurement and calculation. Brachial pressure measured in right arm only.</td>
<td>8% asymptomatic. Additional 4.6% symptomatic as indicated by response to WHO questionnaire (Rose, 1962)</td>
<td>59 % response rate. Transport or an examination at home offered for those having difficulty attending the clinic in an effort to avoid recruitment bias.</td>
</tr>
<tr>
<td>Campbell et al., 2007. North East Scotland.</td>
<td>Age&gt;60 with hypertension but no cardiovascular disease or diabetes, recruited from one general practice.</td>
<td>363 (pilot study)</td>
<td>ABIs0.9</td>
<td>Used standard method of ABI calculation as recommended by ACC/AHA guidelines (Aboyans et al., 2012) and TASC II (Norgren et al., 2007) guideline.</td>
<td>8% (7% previously undiagnosed)</td>
<td>63% response rate. Recruitment limited to one general practice.</td>
</tr>
<tr>
<td>Price et al., 2008. Central Scotland.</td>
<td>Age&gt;50, free of clinical cardiovascular disease at baseline.</td>
<td>28,980</td>
<td>ABIs0.9</td>
<td>Used the lowest systolic pressure at the ankle to calculate the ABI. Prevalence will therefore be elevated in comparison to studies which use the standard method of calculation.</td>
<td>10.9%</td>
<td>22% response rate – possible recruitment bias with less healthy being less likely to participate – hence, prevalence may be underestimated.</td>
</tr>
</tbody>
</table>

Table 2.2: Summary of UK PAD epidemiological studies

2.4 PAD and its associated cardiovascular risk

The Framingham study was the first major epidemiological study to demonstrate that a reduced ABI, symptomatic or not, resulted in an increased mortality (Criqui et al., 1992). Since these early observations, a number of major studies have reported similar outcomes in different populations,
underlining the fact that reduced ABI is a marker of advanced atherosclerotic disease and carries an increased risk of death, myocardial infarct, and other atherosclerotic complications. Moreover, existing evidence demonstrates that PAD conveys independent increased risk in addition to that expected by concomitant traditional cardiovascular risk factors and disease (Aboyans et al., 2011). Heald et al. (2006) conducted a systematic review of 11, high quality, population-based cohort studies and concluded that a low ABI is associated with subsequent all-cause mortality, cardiovascular mortality, coronary heart disease and stroke with a high degree of consistency. Although inter-study differences (such as differing ABI cut off points and varying ABI measurement techniques) resulted in a somewhat heterogeneous group of studies, the overall findings associating ABI with cardiovascular risk were remarkably constant. The strength of the relationship between low ABI and coronary artery disease had been noted to vary, with odds ratios ranging from 1.4 to 3.0 depending on the underlying risk of the population studied (Aboyans et al., 2012). With regard to cerebrovascular disease, odds ratios range from 1.3 to 4.2.

2.5 The case for PAD screening

2.5.1 Evidence of benefit associated with PAD screening

Based on the evidence provided by the cohort studies (Section 2.4), which demonstrated a clear association between low ABI and cardiovascular risk, several international guidelines (CCS, 2005; SIGN, 2006; TASC 2007; ACC/AHA, 2011; ESC, 2011; NICE 2012a) now recommend the same strategy of cardiovascular risk modification for persons with PAD as for those with coronary artery disease (Table 2.3). Randomised trials have shown that aggressive risk factor modification (angiotensin-converting enzyme inhibitors, antiplatelet, and statin therapy) is effective in preventing CVD in PAD patients (Yusuf et al., 2000; Baigent et al., 2005). However, notably, the patients included in these trials had established, symptomatic PAD. Many experts believe that the benefits of treating symptomatic persons with PAD can and should be extrapolated to asymptomatic persons because CV events are similar in these groups (Lin et al., 2013). Evidence in support of this comes from the German Epidemiological Trial on Ankle Brachial Index (getABI) (Diehm et al., 2004), which was a large (n=6880), well conducted prospective study of unselected persons aged over 65. The study included a comparison of coronary artery disease (CAD) and CV risk in persons with symptomatic PAD (n=593) versus those with asymptomatic PAD (defined by ABI<0.9)(n=836). They found that low ABI was associated with an increased risk for CV events, but there was no statistically significant difference.
<table>
<thead>
<tr>
<th>Guideline and Year of Publication</th>
<th>For or against screening</th>
<th>Subjects to be Screened</th>
<th>Screening Methods</th>
<th>Recommendations/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States Preventive Services Task Force (USPSTF) Screening for peripheral arterial disease and cardiovascular disease risk assessment with the Ankle-Brachial Index in Adults: USPSTF recommendation statement (Moyer et al., 2013)</td>
<td>Insufficient evidence to make a recommendation</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
| National Institute for Health and Care Excellence (NICE) Lower limb peripheral arterial disease guideline (NICE, 2012a). | For | • Subjects with symptoms of PAD  
• Diabetics  
• Subjects with non-healing wounds/unexplained leg pain  
• Subjects who are being considered for interventions to the leg or foot  
• Subjects who need compression hosiery | • Patient history  
• Clinical examination of lower limbs including palpation of femoral, popliteal and foot pulses  
• ABI measurement | “Offer all people with PAD information, support, and treatment with respect to secondary prevention of cardiovascular disease, in line with published NICE guidance on smoking cessation, diet, weight management and exercise, lipid modification and statin therapy, the prevention, diagnosis and management of high blood pressure, the prevention, diagnosis and management of diabetes, and antiplatelet therapy”. |
| European Society of Cardiology (ESC) Guidelines on the diagnosis and treatment of peripheral arterial diseases (Tendera et al., 2011). | Not considered | Not considered | Not considered | Not considered |
| American College of Cardiologists and the American Heart Association (ACC/AHA) Guidelines for the management of patients with peripheral arterial disease (Rooke et al., 2011). | For | • Aged ≥65  
• Age≥50 with a history of smoking or diabetes  
• Subjects with exertional leg symptoms | Resting ABI | • Smoking cessation strategies  
• Antiplatelet therapy for both symptomatic and asymptomatic PAD patients  
• Antihypertensive therapy for patients with lower extremity PAD to achieve a goal of ≤140/90 (non-diabetics) or ≤130/80 (diabetics and those with chronic renal disease)  
• Diabetics with PAD should have a HbA1c < 7%  
• Statins are indicated for patients with PAD to achieve a target LDL cholesterol of <100mg/dl. |

Table 2.3: Summary of PAD guidelines
<table>
<thead>
<tr>
<th>Guideline and Year of Publication</th>
<th>For or against screening</th>
<th>Recommendations/Rationale</th>
<th>Subsequent Treatment for Subjects with PAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trans-Atlantic Inter-Society Consensus for the management of peripheral arterial disease (TASC II) (Norgren et al., 2007).</td>
<td>For</td>
<td>Subjects with exertional leg symptoms</td>
<td>Smoking Cessation strategies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subjects age 50-69 with cardiovascular risk factors</td>
<td>Weight reduction strategies for those overweight (BMI 25-30) or obese (BMI&gt;30).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All patients over 70</td>
<td>Lipid control LDL cholesterol &lt;2.59mmol/l. If PAD coexists with vascular disease in other beds then LDL cholesterol should be &lt;1.81mmol/l</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subjects with a 10-year risk of a cardiovascular event between 10 and 20%.</td>
<td>BP should be controlled to &lt;140/90 or &lt;130/80 if they also have diabetes or renal insufficiency.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patients with diabetes and PAD should have aggressive blood glucose control HbA1c &lt;7% or as close to 6% as possible</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antiplatelets for symptomatic PAD patients and patients with other forms of CVD. Consider antiplatelets in asymptomatic PAD patients that do not have other forms of CVD.</td>
</tr>
<tr>
<td>Scottish Intercollegiate Guidelines Network (SIGN) Diagnosis and management of peripheral arterial disease (SIGN, 2006)</td>
<td>Not considered</td>
<td>Not considered</td>
<td>Not considered</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Smoking cessation advice/ therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lipid lowering with a statin if total cholesterol &gt;3.5mmol/l</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Optimal glycaemic control for diabetics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weight reduction advice/treatment for obese individuals</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-hypertensives</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antiplatelets</td>
</tr>
<tr>
<td>Canadian Cardiovascular society: Consensus conference: peripheral arterial disease (Abramson et al., 2005)</td>
<td>For</td>
<td>Men Age&gt;40</td>
<td>Aggressive lifestyle change (smoking cessation, regular exercise)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women Age&gt;50 or postmenopausal</td>
<td>Lipid lowering agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subjects with recognized cardiovascular risk factors</td>
<td>Antiplatelets (aspirin/clopidogrel)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Glucose control agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-hypertensives (ACE inhibitors first choice)</td>
</tr>
</tbody>
</table>

Table 2.3 continued: Summary of PAD guidelines
2.5.1 Evidence of benefit of associated with PAD screening continued:

Currently, there is limited research which has directly examined the impact of early cardiovascular risk modification for asymptomatic, screen-detected PAD patients; this is the primary issue of contention associated with PAD screening and the reason why there has been no national instigation of a formalised screening programme as there has been for abdominal aortic aneurysm (AAA) screening, for example. Current evidence appears to be confined to four studies: the Aspirin for Asymptomatic Atherosclerosis (AAA) trial (Fowkes et al., 2010) used the ABI to screen 28,980 community dwelling adults aged 50-75 years with no history of CVD. A total of 3350 participants diagnosed with PAD on the basis of ABI were randomly assigned to receive 100mg aspirin or placebo. At 8.2 years of follow-up, no differences in the primary outcome of fatal or non-fatal CV events were seen between the aspirin and control groups (13.7 vs. 13.3 events per 1000 person-years).

The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) study (Belch et al., 2008) also found that 100mg aspirin vs. placebo had no benefit in preventing fatal and non-fatal cardiovascular events among asymptomatic PAD patients (HR=0.98, CI: 0.76-1.26). Notably, these results are consistent with trial evidence concerning patients with clinically established PAD which also demonstrated no statistically significant benefit of aspirin on total CV events (Berger et al., 2009). However, the Heart Outcomes Prevention Evaluation (HOPE) trial (Ostergren et al., 2004) evaluated the impact of ramipril (an ACE inhibitor), on the prevention of fatal and non-fatal myocardial infarction or stroke among patients with PAD, including those with sub-clinical PAD. Subjects with subclinical PAD that were randomised to receive ramipril had a lower number of CV events in comparison to the placebo group (RR: 0.72, CI: 0.56-0.92).

Pande et al. (2011) analysed data from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2004 with mortality follow-up through to 2006. Of 7458 participants, age ≥40 years without known atherosclerotic disease, 5.9 ± 0.3% (mean ± SD) had PAD (ABI ≤ 0.9). After exclusion of individuals with known cardiovascular disease, subjects with PAD had higher mortality rates (16.1 ± 2.1%) than subjects without PAD or cardiovascular disease (4.1 ± 0.3%), with an adjusted hazard ratio of 1.9 (95% confidence interval, 1.3 to 2.8; P=0.001). Among PAD subjects without cardiovascular disease, use of multiple preventive therapies was associated with 65% lower all-cause mortality (hazard ratio, 0.35; 95% confidence interval, 0.20 to 0.86; P=0.02).

Hence, it appears that current research has produced mixed results as to the value of early CV intervention for asymptomatic PAD patients. This, however, is a very much an active field of research. The Viborg Vascular screening trial is a large population based screening trial which is
underway in Denmark; this study is randomly assigning 50,000 men aged 65-74 years to screening for PAD and abdominal aortic aneurysm versus no screening (Grøndal et al., 2010). According to Lin et al. (2013), primary outcome data, including all-cause and CVD mortality, should be available in late 2018. It is likely that as new data from on-going research emerge, this will add to the body evidence regarding the value of screening for PAD.

2.5.2 Under-treatment of PAD
The potential for patients to benefit from being diagnosed with sub-clinical PAD depends on whether their CV risk is subsequently managed appropriately and in accordance with current guidelines. Research (discussed below) has demonstrated that even when a diagnosis of PAD has been made, PAD patients are under-treated. PAD guidelines dating back to 2003 have been recommending the same strategy of cardiovascular risk modification for persons with PAD as for those with coronary artery disease (Hirsch et al., 2006). Despite this, under-treatment of PAD was demonstrated on a global level in the REACH (Reduction of Atherothrombosis for Continued Health ) registry where, compared with the total population, patients with PAD were significantly less likely to receive antihypertensive (92.4% vs. 95.8%; p<0.001) and lipid lowering (70.0% vs 75.2%; p<0.001) therapies (Bhatt et al., 2006). The less aggressive treatment of PAD patients in comparison to patients with CAD and CBVD was reflected in the significantly smaller proportion of patients with PAD who had not smoked within 12 months and had achieved target blood pressure, cholesterol and glucose levels. These results were echoed in small UK studies by Coulston et al (2008) and D'Souza et al (2008) which looked specifically at the management of cardiovascular risk factors in patients with PAD in primary care settings.

2.5.3 Ankle Brachial Index and Cardiovascular Risk Assessment
Cardiovascular risk assessment tools
In examining the case for PAD screening, it is also necessary to consider how the ABI could potentially contribute to cardiovascular risk assessment. Currently, CV risk is assessed and quantified using scoring systems such as the Framingham Risk Score (FRS) (Wilson et al., 1998) or the more recently developed SCORE (Conroy et al., 2003) and QRISK2 (Collins and Altman, 2012) algorithms. However, data from several studies have demonstrated that abnormal ABI is highly prevalent among individuals not considered at high risk of cardiovascular events as defined by such scoring systems (Dhangana et al., 2011). According to Grondal & Lindholt (2009), nearly 25% of cardiovascular deaths
occur in individuals believed to possess low cardiovascular risk by traditional risk stratification models.

A meta-analysis of 16 population cohort studies by the Ankle Brachial Index Collaboration (Fowkes et al., 2008) concluded that measurement of the ABI may improve the accuracy of cardiovascular risk prediction beyond the FRS. This has resulted in calls for the ABI, as a non-invasive and inexpensive test, to be added as an additional risk parameter to cardiovascular risk tools. However, a recent study by Murphy et al. (2012) examined the predictive ability of ABI compared with FRS by conducting a post-hoc analysis of data from the Atherosclerosis Risk in Communities Study (ARIC). They concluded that the independent effect of ABI when adjusted for FRS was small in magnitude and did not support FRS modification to include ABI. Newer CV risk scoring systems such as SCORE and QRISK2 are considered improvements on the FRS as a result of their incorporation of additional risk factors such as family history and social deprivation. However, notably, no studies have assessed the contribution of the ABI to these superior CV scoring tools.

Cardiovascular risk across the ABI spectrum
In recent years, several studies have demonstrated that increased cardiovascular risk is not only associated with the lower end (≤0.9) of the ABI spectrum, but also with the higher end (≥1.3) (Resnick et al., 2004; O’Hare et al., 2006; Criqui et al., 2010). Although other studies have however reported inconsistent results (Sutton-Tyrrell et al., 2008; Wattanakit et al., 2007), this may represent an extension of the utility of the ABI beyond PAD diagnosis. This is discussed in detail in Chapter 9, Section 9.0.

Modification of the ABI calculation
Since multiple blood pressures may be obtained in the lower extremities (i.e., using the posterior tibial and dorsalis pedis arteries), there are several possible methods of calculating the ABI. For example, the ABI could be calculated using the highest, lowest, or mean ankle pressure in a given leg. Current guidelines recommend using the higher ankle pressure for ABI calculation (see Table 6.1); however, according to Jahn et al. (2014) this can fail to identify a relevant number of patients with isolated occlusions of single crural arteries. Although such crural artery occlusions are not necessarily relevant for symptomatic PAD, they may have an impact on cardiovascular mortality (Kröger et al., 2006). In the get-ABI study, the sensitivity for detection of a history of cardiac events was highest (46.1%) using the lowest ankle pressure, but specificity was highest using the highest ankle pressure (83.6%) (Lange et al., 2007). Similarly, in the prospective Tampere study, Finland (n =
817 patients), using the lowest ankle systolic pressure yielded the highest prevalence of PAD (47.7%), had the best sensitivity and identified the highest number of patients with coronary artery disease and cerebrovascular disease. This, however, was at the cost of reduced specificity (Oksala et al., 2010). Aboyans et al. (2012) caution against using this approach, as although it may increase the sensitivity for identification of high risk patients, the overall level of risk for those with ABI≤0.9 would be lower because of reduced specificity and the inclusion of numerous cases with early disease.

2.6 Cost Implications of PAD

To date, there have been no direct studies, relating to the cost effectiveness of PAD screening with an ABI. However, Sigvand and colleagues (2011) utilised a Markov model (Briggs et al., 2003) to simulate asymptomatic PAD health and economic outcomes over a lifetime and assess the cost-effectiveness of drug treatments to reduce cardiovascular events. Five treatment strategies were considered: low dose aspirin, angiotensin converting enzyme (ACE) inhibitors, non-aspirin antiplatelet therapy, statins for lipid lowering, and no active treatment. Rates of cardiovascular events without treatment were derived from epidemiological cohort studies carried out in the 1980s and early 1990s. Older studies were utilised to ensure the inclusion of subjects rarely using preventive drugs who could thus be considered relevant for estimating event rates in the untreated groups. Reductions in risk of cardiovascular events were the key inputs for the model and were derived from four clinical trials (one for each drug). The benefit of each drug was considered in terms of the number of life years gained, the number of cardiovascular events, such as angina or stroke, and quality-adjusted life-years (QALYs). The study concluded that PAD drug treatments are cost effective and this particularly applies to angiotensin converting enzyme inhibitors. However, it was also noted that although aspirin is recommended by current PAD guidelines and is relatively cheap in comparison to other medications, its effectiveness is limited. Sigvand and colleagues’ study was reviewed by the Centre for Reviews and Dissemination which is part of the National Institute for Health Research (NIHR); the methods and sources utilised in this study were considered valid and robust, hence corroborating the study’s overall validity.

Evidence regarding the financial cost implications of symptomatic PAD is provided by Smolderen et al. (2012) who examined the two year vascular hospitalisation rates and associated costs in patients enrolled in the REACH registry in France (n=4693) and Germany (n=5594). Patients were divided into four groups: those with multiple risk factors for cardiovascular disease, those with coronary artery disease, those with cerebrovascular disease, and those with peripheral arterial disease. They found that the costs were highest for the PAD group (€3182.1 for France, €2724.4 for Germany) and lowest
for the MRF group (€749.1 for France, €2724.4 for Germany). Peripheral revascularisations and amputations were the greatest contributors to costs for all risk groups. Hence identifying PAD at an early stage and preventing its progression is likely to be cost effective.

### 2.7 Current perspectives of PAD screening

Despite the current lack of evidence demonstrating direct benefits of PAD screening, it is advocated by the majority of international PAD guidelines (Table 2.3). Currently, only the United States Preventive Task Force (USPTF) guidance does not recommend it; this is based on, what it considers to be insufficient evidence to make such a recommendation (Moyer et al., 2013). Some countries now offer remuneration for ABI measurement in Primary Care (e.g. the Netherlands, Australia). Although this is not the case in the UK, General Practices are now awarded Quality and Outcomes Framework (QOF) points for having a register of patients with PAD and for meeting PAD related targets (Table 2.4). QOF is a fundamental part of the General Medical Services (GMS) contract in the UK and is a system to remunerate general practices for providing good quality care to their patients.

| • Being able to produce a register of people with peripheral arterial disease. |
| • The percentage of patients with peripheral arterial disease with a record in the preceding 15 months that aspirin or an alternative anti-platelet is being taken (unless a contraindication or side-effects are recorded) (threshold 40-90%). |
| • The percentage of patients with peripheral arterial disease in whom the last blood pressure reading (measured in the preceding 15 months) is 150/90 or less (threshold 40-90%). |
| • The percentage of patients with peripheral arterial disease in whom the last total cholesterol (measured in the preceding 15 months) is 5.0mmol/l or less (threshold 40-90%). |

Table 2.4: PAD indicators according to the UK Quality and Outcomes Framework (NICE, 2012b)

There is, however, no incentive to screen patients without symptoms of the disease in the UK. Notably, the UK National Screening Committee handbook for vascular risk assessment, risk reduction and risk management (Davies et al., 2012) refers to the ABI within a list of emerging novel risk factors, but reports that there is insufficient evidence to justify its inclusion in risk assessment scores at present. However, the UK Department of Health has recently published the “Cardiovascular disease outcomes strategy” (DH, 2013a) which sets out 10 key actions intended to improve patient outcomes and save money. The concept of early identification of cardiovascular risk factors and disease emerges as a pivotal theme throughout the document, with particular reference to PAD.
2.8 Targeting of PAD screening strategies

A multitude of observational studies have investigated the prevalence of PAD in varying cross-sections of national and international populations in an effort to determine how potential PAD screening strategies should be targeted (Appendix 2). Although there appears to be no absolute consensus, Ferket et al. (2012) observed that suggested target groups generally comprise middle-aged subjects with one or more cardiovascular risk factors, or the elderly. Notably, the National Institute for Health and Care Excellence (NICE) only recommends routine PAD screening for individuals who are diabetic or who have symptoms suggestive of PAD (NICE, 2012a); this therefore would miss all cases of asymptomatic PAD in a non-diabetic population.

Cimminiello et al. (2011) reasoned that there would be little value in screening for PAD in individuals who are already known to have CAD, CVD or diabetes as these patients are likely to already be the subject of secondary preventive strategies. The Reduction of Atherothrombosis for Continued Health (REACH) registry (Bhatt et al. 2006) demonstrated that individuals that have PAD in addition to CAD or CBVD are at an overall higher risk of mortality than those with CAD or CVD alone; it would therefore be reasonable to suppose that such individuals should be subject to more stringent preventive interventions. There is, however, a lack of research or guidance with regard to this issue and as such, there would be little to gain from diagnosis of asymptomatic PAD for these individuals.

2.9 Primary Care PAD Screening

Currently the criteria for instigating a formalised screening programme, as set out by the World Health Organisation, cannot be fulfilled with regard to PAD. Hence screening for PAD depends on local health policy and is often left to the judgement of individual health professionals. Current research suggests that screening for PAD is rarely performed (Rooke et al., 2011). Historically, this has been attributed to poor awareness of the disease, lack of utilisation of screening tools and a lack of familiarity with guidelines. Whether this may have been subject to change in recent years, as a result of publication of PAD guidelines from several national and international organisations for example, is unknown.

Existing literature appears to concur that PAD screening should come under the remit of primary care, and that the ABI should be used as the diagnostic screening tool. However, the issue of whether the necessary skills for ABI measurement and PAD screening exist within this setting remains unclear. The Scottish Intercollegiate Guidelines Network (SIGN) states that “there is a pool of expertise for measuring the ABI of patients in the community” (SIGN, 2006, pg. 13) but this statement is not substantiated. Relevant research in this field is sparse and of poor quality. Nicolaï et al. (2009) compared 99 ABI measurements undertaken in 45 primary care practices with those
performed in the vascular laboratory; they concluded that the ABI is often not correctly determined in primary care practice and attributed this to inaccurate methods of blood pressure measurement and calculation of the index. However, this study was methodologically flawed, not least because there were several weeks between the primary care measurements and the vascular lab measurements meaning that any anomalies could have been due to normal biological variation of the ABI. Other studies however, concluded that measurements by GPs and nurses are highly reproducible (Holland-Letz et al., 2007) whilst others have suggested that ABI reproducibility is dependent on the experience and training of the observer (Ray et al., 1994; Kaiser et al., 1999; Matzke et al., 2003).

The practicality of ABI measurement constitutes a further contentious issue associated with PAD screening. Some authors argue that ABI measurement is simple and quick, and could be easily undertaken in general practice (Heald et al., 2006). Others however, report it to be time consuming, taking between 51 and 90 minutes according to French (2005). Notably, most guidelines recommend a rest period where the patient must lie supine for between 5-15 minutes prior to the actual measurement procedure. This purpose of this is to allow equalisation of hydrostatic pressure differences in the lower limbs; it does however, of course significantly increases the total test time. A study of 886 American primary care physicians identified that time constraints, lack of reimbursements and staff availability were major barriers to ABI use (Mohler et al., 2004). Most GPs reported measuring an ABI within 15 minutes; however, over half regarded this as prohibitively too long. Furthermore, Bendermacher et al. (2012) considered the workload required to screen all patients over the age of 50 in general practices in the Netherlands, concluding that it was not achievable, and suggested a clinical prediction model to determine who should undergo ABI measurement.

2.10 Chapter summary

A diagrammatic representation of the content of this literature review is included in Figure 2.3. It should be noted that where appropriate, more extensive consideration of existing research and background information has been included at the beginning of the relevant chapters of this thesis.
Figure 2.3: Diagrammatic representation of literature review content
(red text denotes issues and topics of research subsequently explored in this thesis)
There is no doubt that PAD is an important health problem. It is prevalent and associated with adverse CV outcomes. It also has significant financial implications; from a health policy perspective, PAD will continue to exert tremendous pressure on public health care resources over the next quarter of a century. There has been national and international recognition of these far-reaching, detrimental repercussions as evidenced by the publication of PAD guidelines by several professional bodies and organisations. In the UK, this has also been reflected in current health policy which has highlighted the importance of early PAD detection and sought to optimise PAD treatment via the inclusion of PAD indicators to the QoF system.

However, this literature review has identified several areas of ambiguity associated with the concept of screening for PAD. These areas can be sub-divided into three categories under the simple headings of “why?”, “who?” and “how?”.

### 2.10.1 Why is there is need for PAD screening?

- The primary purpose of PAD screening is to identify asymptomatic cases of the disease. This allows subsequent instigation of secondary preventive strategies which aim to reduce the CV risk known to be associated with PAD, and prevent progression of the disease.

- There is a paucity of evidence, in the form of randomised control trials, demonstrating the benefit of early cardiovascular risk modification for asymptomatic, screen-detected PAD patients. However, this is an area of considerable active research, and results from large longitudinal studies which were designed to address this issue are due to be published in coming years.

- Existing evidence had demonstrated that patients had little to gain from a PAD diagnosis as management of CV risk factors in patients with PAD is poor. This, however, may have been subject to change as a result of (i) an expanding research base which has highlighted adverse consequences associated with the disease; (ii) the publication of PAD guidelines recommending stringent CV risk modification for persons with PAD; and (iii) changes to local health policy.

- There has been no consideration of the patient perspective of PAD screening, in terms of whether they perceive it to be a worthwhile venture.

### 2.10.2 Who should be screened for PAD?

- There is no absolute consensus as to who should PAD screening should target.
There is a paucity of current epidemiological PAD data specific to the UK.

The potential for screening subjects to benefit from being diagnosed with sub-clinical/asymptomatic PAD should be a key consideration in the determination of who screening should target. The main objective of screening should therefore be the identification of those who have not previously been pin-pointed as being at high cardiovascular risk; as such those with existing CV disease and diabetes should be excluded.

2.10.3 Who should undertake PAD screening?

Current literature suggests that PAD screening should be undertaken within the remit of primary care but there is limited evidence with regard to the feasibility of this. Further research is needed to determine if sufficient skills and knowledge already exist within this environment or if there would be educational prerequisites prior to the instigation of any formalised screening strategy. Similarly, the practicality of PAD screening within primary care also requires investigation.

2.10.4 How should PAD screening be undertaken?

There are several methods available for the non-invasive diagnosis of PAD although the ABI is widely considered to be the most appropriate screening tool. As such, the ABI has been extensively investigated and its limitations have been widely documented. Literature regarding the application of the ABI within primary care for the purpose of PAD screening is however limited. Furthermore, recent technological advances in relation to ABI measurement also require evaluation.

2.11 Project design

The over-arching aim of the research reported within this thesis is to contribute to the current PAD evidence base in order to address the ambiguities outlined above. This was achieved via four studies which were undertaken concurrently to provide a unique insight into how different aspects of PAD screening are inter-related. The studies included:
1. The PIPETTE Study – a prospective observational study involving a trial of a proposed PAD screening strategy.

2. The IVAM study – an investigation of inter-observer variability of ABI measurement between an expert in ABI measurement (a Consultant vascular surgeon) and (i) the PhD researcher and (ii) an automated ABI device.

3. The DUAL study – a comparative study of the Doppler method of ABI measurement versus a newly developed automated ABI device. This study was embedded within the PIPETTE and IVAM studies.

4. GP survey – a survey regarding ABI measurement which was distributed to all general practices within Wales.

The individual study objectives and methodologies are described in Part 2 of this thesis. Results are subsequently presented not in relation to the study from which they originated, but instead in terms of how they contributed to addressing the three issues of why, who and how (with regard to PAD screening). Figure 2.4 illustrates how each of the studies contributed to the three issues.

![Diagram illustrating the contribution of individual studies to each of the three project objectives]

Figure 2.4: Contribution of individual studies to each of the three project objectives
Part 2 : Study Methodologies
Chapter 3: The PIPETTE study
(Peripheral Arterial Disease in Primary Care: targeted screening and subsequent management).

3.0 Background
The design and trial of a PAD screening strategy formed the basis of the PIPETTE study. From the outset, a key objective was to identify PAD in patients who could potentially benefit from the diagnosis. Based on this, it was decided that screening should target individuals with at least two pre-identified cardiovascular risk factors but no known cardiovascular disease or diabetes mellitus. The rationale for choosing this study population comes from the possibility that if PAD is identified in these patients, then they may subsequently benefit from implementation of secondary preventative strategies (whereas patients already known to be at high cardiovascular risk are already likely to be receiving preventative management). A recent, large, pan-European study (PANDORA; Belgium, France, Greece, Italy, The Netherlands, Switzerland) was of similar design (Cimminiello et al., 2010).

3.1 Aims and objectives
The fundamental and overarching aim of the PIPETTE study was to determine if a primary care screening programme for PAD is feasible and of value in a targeted population of South Wales. This overall aim was divided into six key objectives as outlined below (Figure 3.1):

1. To determine if the study population (as defined by the inclusion and exclusion criteria) was an appropriate target group for a PAD screening programme.
2. To determine the 'number needed to screen' to detect one person with PAD in the study population.
3. To determine the practicality of the proposed PAD screening programme, in terms of the time needed to screen one person.
4. To determine the acceptability of the proposed PAD screening programme to patients/service users.
5. To determine if the primary care management of PAD is effective in:
   (i) improving patients' lifestyle; and
   (ii) lowering patients' cardiovascular risk score.
6. To determine the implications of identifying PAD in the context of current cardiovascular risk assessment in primary care (specifically in relation to QRISK®2 which is a cardiovascular risk algorithm which is currently recommended by the Welsh Government; further information regarding QRISK®2 is provided in Section 3.6.1.
Figure 3.1: Aims and objectives of PIPETTE study
A further, subsidiary objective was to compare a newly developed automated ABI device which utilises pneumoplethysmography to measure and calculate the ABI (dopplex® Ability, Huntleigh Healthcare, Cardiff, UK), with the equipment traditionally used (handheld continuous wave Doppler ultrasound with a sphygmomanometer) for the purpose of measuring and calculating the ABI. This forms part of a separate study (the DUAL study) which is embedded within the PIPETTE and IVAM studies (Chapter 5).

### 3.2 Study setting

The study was hosted by Professor Jonathan Richards at Morlais medical practice in Merthyr Tydfil [Cwm Taf University Health Board (CTUHB), South Wales]. This is an area with high levels of deprivation and morbidity. The Welsh Index of Multiple Deprivation (Welsh Government, 2011) ranks small areas in Wales in terms of deprivation. In Merthyr, 32% of areas fall in the 10% most deprived areas in Wales and overall the majority of its areas are more deprived than the Wales average. There are high levels of unemployment; in 2008, only 67% of working age adults were in employment (compared to 71% in the whole of Wales) (Welsh Government, 2010). Data from the Welsh Health Survey (2003–07) demonstrated that Merthyr consistently has higher levels of adverse health behaviours and higher levels of morbidity in comparison to Wales as a whole (Welsh Government, 2010).

CTUHB has the highest level of cardiovascular disease mortality below age 75 compared to any other health board in Wales (Figure 3.2). Furthermore, CTUHB also has the highest levels of emergency admissions for both CHD and stroke (Figures 3.3 and 3.4) (Public Health Wales Observatory, 2013); hence underlining a particular need for health promotion strategies to prevent CVD in the first place, improved strategies for identifying CVD at a latent stage, and optimisation of secondary prevention strategies for those already known to have CVD. Based on the above statistics, it was hypothesised that results from this study would exhibit some of the highest levels of PAD in Wales.
Figure 3.2: CVD mortality under 75, 2009-2011, European age-standardised rate per 100,000 persons, Wales health boards. (Public Health Wales Observatory, 2013)

Figure 3.3: CHD emergency admissions, 2009/10-2011/12, European age-standardised rate per 100,000, persons, all ages, Wales health boards (Public Health Wales Observatory, 2013)

Figure 3.4: Stroke emergency admissions, 2009/10-2011/12, European age-standardised rate per 100,000, persons, all ages, Wales health boards (Public Health Wales Observatory, 2013)
3.3 **Study design considerations**
Difficulty recruiting to health research in primary care is well documented (Bower et al., 2009) and this can be partly attributed to logistical issues such as domestic/work issues, illness and transport. Furthermore, attendance to screening has been shown to decline with age (Grøndal and Lindholt, 2009) whilst conversely, the incidence of PAD increases with age. This study aimed to address these issues by offering study participants an option of being seen in their own homes or at Morlais medical practice. Sixty three per cent of participants chose to be seen at home whilst the remaining 37% were seen at Morlais practice.

3.4 **Study personnel**
Study personnel consisted of three members:
Dr Mark Williams (MW) of the University of South Wales was the study lead, (and PhD Director of Studies for Jane Davies). MW was responsible for facilitation and coordination of the study; this included activities such as management of the study timeline, facilitation of stakeholder meetings and ensuring adherence to governance issues.
Professor Jonathan Richards (JR), general practitioner at Morlais Medical Practice, was the study principal investigator. JR was the clinical lead for the study and was also responsible for identifying individuals eligible to participate and for contacting them on behalf of the study team.
Jane Davies (JD), as the PhD researcher, was responsible for project conception and subsequent study design. JD also took the role of study chief investigator (CI) and research nurse, and attended to all study administration and clinical procedures.

3.5 **Ethical approval**
The PIPETTE study was granted ethical approval by the South East Wales Research Ethics Committee in March 2012 (REC reference no: 12/WA/0075) and completed Cwm Taf University Health Board governance checks in May 2012. The study was sponsored by the University of South Wales.

3.6 **Protocol**
The study consisted of a non-interventional, longitudinal design which utilised quantitative methods to assess outcomes. It consisted of two phases;

- Phase 1 involved identification of individuals eligible to participate and subsequent screening of the study population for PAD.
• Phase 2 involved reviewing those with PAD at two 6 monthly intervals to
  
  (i) Identify any interventions instigated by the GP as a result of the diagnosis, along with assessment of the effectiveness of such interventions in achieving reductions in the participant’s CV risk score as defined by QRISK2.
  
  (ii) Identify the occurrence of any CV events.

Phases 1 and 2 are further discussed in Sections 3.6.1 and 3.6.2 respectively.

Figure 3.5 outlines the study design and procedures.
Figure 3.5: PIPETTE study flowchart

PHASE 1

JRF (Study PI) identified list of individuals eligible for participation via GP database

100 eligible individuals sent invitation to participate. (Subsequent number of invites dependent on response rate of previous cohort)

Participant information sheet sent to those who registered their interest in participating. Telephone contact by PhD researcher (ID) to confirm study details and arrange appointment for visit 1.

When 75% of positive responses had been enrolled, invites for next cohort were dispatched

(n=368) Visit 1 (ID): consent, complete case report form, physical assessment, GPPAQ, dietary questionnaire, ABI measurement, patient perspective questionnaire, EQD.

(n=12) ABI≤0.9 (PAD confirmed). Continue study.

(n=356) ABI>0.9 (No PAD) Exit study. Data used to inform population statistics

PHASE 2

Visit 2 (ID): Perform venepuncture for blood tests: fasting lipids, fasting glucose, urea & electrolytes, CRP and uric acid. Complete CV risk assessment (GRRSK2)

Inform participant’s GP of findings

Visit 3 (ID): 6 month follow-up. Repeat physical assessment & questionnaires as per visit 1. Review participant’s medical notes for CV events, secondary care referrals, new medications and interventions

Visit 4 (ID): 12 month follow-up. As visit 3

Compilation and analysis of data
3.6.1 Phase 1

3.6.1.1 Identification of Study Population

Identification of the study population was undertaken by study principal investigator (JR) via a search strategy of the electronic patient database at Morlais medical practice. This was achieved by including or excluding specified Read-codes for certain conditions as dictated by the inclusion and exclusion criteria which are detailed in Table 3.1 and 3.2 respectively. Figure 3.6 outlines the electronic search strategy.

- Men aged ≥45 or Women aged ≥55 (age-related CVD risk factor)
- At least one additional CVD risk factor from the following:
  - Cigarette smoking or regular exposure to passive smoke (i.e. living with a smoker).
  - Hypertension (systolic BP≥140mmHg or diastolic BP≥90mmHg or taking antihypertensives).
  - Low High Density Lipoproteins (HDL’s) <1.0mmols/l, high Low Density Lipoproteins (LDL’s)>3.3mmols/l, high Triglycerides >1.7mmols/l or taking lipid lowering medication.
  - Family history of premature coronary heart disease (first degree male relative aged <55years, first degree female relative <65years).
  - Elevated waist circumference (≥102cm non Asian men, ≥90cm Asian men, ≥88cm non Asian women, ≥80cm Asian women).
- BMI >25.
- Willingness to participate in the study.
- Capable of giving informed consent.

<table>
<thead>
<tr>
<th>Table 3.1: PIPETTE study inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Diabetes mellitus (type 1 or 2).</td>
</tr>
<tr>
<td>- Known coronary heart disease, including history of myocardial infarction, angina (stable or unstable), coronary artery procedures (coronary artery bypass graft or percutaneous coronary intervention), or evidence of clinically significant myocardial ischaemia.</td>
</tr>
<tr>
<td>- Known cerebrovascular disease (e.g. history of transient ischaemic attack or stroke).</td>
</tr>
<tr>
<td>- Known non-coronary forms of atherosclerotic disease (e.g. abdominal aortic aneurysm).</td>
</tr>
<tr>
<td>- Serious or unstable medical or psychological conditions that, in the opinion of the investigator or patient’s GP, would compromise the patient’s safety or successful participation in the study.</td>
</tr>
<tr>
<td>- Current or recent (preceding 4 months) participation in clinical research trial (this does not apply to participation in non-interventional research).</td>
</tr>
<tr>
<td>- Patient who is unwilling or unable to provide informed consent.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3.2: PIPETTE study exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Known coronary heart disease, including history of myocardial infarction, angina (stable or unstable), coronary artery procedures (coronary artery bypass graft or percutaneous coronary intervention), or evidence of clinically significant myocardial ischaemia.</td>
</tr>
<tr>
<td>- Known cerebrovascular disease (e.g. history of transient ischaemic attack or stroke).</td>
</tr>
<tr>
<td>- Known non-coronary forms of atherosclerotic disease (e.g. abdominal aortic aneurysm).</td>
</tr>
<tr>
<td>- Serious or unstable medical or psychological conditions that, in the opinion of the investigator or patient’s GP, would compromise the patient’s safety or successful participation in the study.</td>
</tr>
<tr>
<td>- Current or recent (preceding 4 months) participation in clinical research trial (this does not apply to participation in non-interventional research).</td>
</tr>
<tr>
<td>- Patient who is unwilling or unable to provide informed consent.</td>
</tr>
</tbody>
</table>
The electronic search strategy produced a list of patients, which was presented in order of patient numbers (used by the practice for patient identification). It was then necessary for JR to personally review each of the patient medical records on this list. This was for the purpose of verification (in case read-codes had been incorrectly recorded) and to check for criteria for which an electronic search was not possible. For example, at the time of the search there was not a read code for prior participation in a research trial. JR also reviewed consultation notes and utilised his personal knowledge of his patient case load to determine the existence of medical or psychological conditions that might compromise the patient’s safety or successful participation in the study. This was a time intensive process and hence it was decided to divide recruitment into nine cohorts to make it more manageable. All exclusions were recorded by JR and retained for future analysis in order to identify possible selection bias (Table 3.3)
<table>
<thead>
<tr>
<th>Exclusions due to time delay from list compilation to recruitment:</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Died since electronic list compilation</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>• Diagnosis of CVD or diabetes since electronic list compilation</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>• Total (1):</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>9</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Exclusions</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Unable to consent due to dementia/learning difficulties</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>• Co-morbidities (e.g. cancer) made participation inappropriate</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>• Mental health problems made participation inappropriate</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>• Considered too frail</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>• History of aggression</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>• Total (2):</td>
<td>12</td>
<td>13</td>
<td>12</td>
<td>12</td>
<td>13</td>
<td>14</td>
<td>9</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

| Total number of exclusions [Total(1) + Total (2)]             | 13| 14| 15| 20| 19| 18| 14| 15| 15 |
| Original sample size                                          | 100| 134| 168| 208| 153| 136| 125| 138| 53 |
| Corrected sample size                                         | 99 | 133| 165| 200| 147| 132| 121| 129| 45 |
| Exclusions as % of corrected sample size                     | 12%| 10%| 7%| 6%| 9%| 11%| 7%| 5%| 16%|
| Final sample size                                             | 87 | 120| 153| 188| 134| 118| 111| 123| 38 |

Table 3.3: Reasons for PIPETTE study exclusions

3.6.1.2 Recruitment

Recruitment began on 19\textsuperscript{th} May 2012 and was completed on 1\textsuperscript{st} May 2014. The recruitment process was divided into nine cohorts for the purpose of making the process more manageable and to prevent lengthy time periods between invitation to participate and study enrolment. The size of each cohort and the time period between successive cohorts was determined by the PhD researcher, and was dependant on factors such as:

(i) the positive response to invitation rate;
(ii) how the previous cohort had progressed;
(iii) JR’s capacity to review the next cohort list; and
(iv) the existence of additional study/research demands.

Following the review and exclusion process, all patients remaining on the cohort list were sent an invitation to participate by JR, on behalf of the study team. Participation was on an “opt-in” basis and those who were interested were asked to either return a reply slip (in a pre-paid and addressed
envelope), or to email or telephone the study chief investigator (JD). Interested patients were then sent the study information sheet and subsequently contacted by JD to confirm that they understood and were satisfied with the details of the study. If the patient was in agreement, an appointment for visit 1 was then made.

3.6.1.3 Sample size

The original target sample size was 720 participants. This was determined pragmatically and was based on the number of participants which could be enrolled by one study investigator (JD) in the given time frame of 36 months. Monthly recruitment targets were set by the study team with review of recruitment rates at quarterly meetings. Figure 3.7 illustrates the recruitment rates over the study period.

After recruiting the first two cohorts, it became apparent that JR’s work commitments were resulting in a required timescale of up to three months to review the patient list for each subsequent cohort. This meant that there were periods when recruitment became stagnant (visible as plateaus in blue and red lines in Figure 3.7). It was not possible for any other member of the study team to assist with this process because ethical approval stipulated that other team members were not allowed to access patient identifying information prior to gaining their consent. Hence, the study team was unable to devise a suitable solution to address this issue and the target sample size was revised to 510.

From the outset, it was acknowledged that the PIPETTE study was limited as a result of it being part a PhD project due to the usual time and financial constraints and thus it could not achieve the epidemiological impact of a large trial like the PANDORA study \( n = +9000 \) (Cimminiello et al., 2011). However, the main purpose this study was to evaluate the feasibility of assessing PAD in the primary care setting, and the sample size of 510 was deemed sufficient to provide data from which to draw clinically relevant conclusions in this population.

A total of 1101 invitations to participate were sent out. From these, there were 441 positive replies, of which, 369 went on to enrol in the study. This equates to a mean response rate of 40% and a mean recruitment rate of 34% (Figure 3.8). One participant withdrew consent following visit 1, hence resulting in a final sample size of 368.
Figure 3.7: PIPETTE recruitment
(purple = invites sent out; green = recruitment target; blue = positive responses; red = recruited).

Figure 3.8: PIPETTE response and recruitment rates per cohort
Blue: response rate, red: recruitment rate
3.6.1.4 Visit 1

All visit 1 procedures were undertaken by JD. At this visit, details of the study were reiterated and eligibility criteria checked. The participant had an opportunity to ask questions prior to completing an informed consent form. A participant Case Report Form, Visit 1 (Appendix 2) was utilised to collect participant data including personal history, demographic data and medical history (including medications).

Physical Assessment

A physical assessment was undertaken which included:

- Body mass index (BMI) calculation - height was measured in metres (without shoes) using a Seca Leicester Portable stadiometer. Weight was measured in kilograms (without outer clothes and shoes) using a Seca 877 floor scales for mobile use (Class III). Body mass index was calculated as follows: BMI=weight in Kilograms ÷ (height in metres)^2. If participants were unable to stand, the last available measurement from the general practice database was used; if there was no information available or if it was clearly inaccurate, an estimation was made.

- Measurement of waist and hip circumference (in cm) was undertaken according to the World Health Organisation’s data gathering protocol (WHO, 2008). Waist circumference was measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest, using a stretch-resistant tape that provided a constant 100g tension. Hip circumference was measured around the widest portion of the buttocks, with the tape parallel to the floor. Participants were considered to have an elevated waist circumference if their measurement was ≥88cm for women or ≥102cm for men.

- Radial pulse measurement was undertaken by palpating the radial pulse and counting the number of pulses for a one minute period. The regularity of the pulse was also noted.

- Brachial arterial blood pressure measurement was undertaken using a Welch Allyn aneroid sphygmomanometer and stethoscope in accordance with the British Hypertension Society guidelines (2012) for blood pressure measurement (Appendix 4).

- Measurement of arterial O₂ saturation was undertaken utilising a Pulmolink pulse oximeter.
Examination of legs and feet for clinical signs of PAD including the presence of: reduced or absent pulses in the legs/feet, non-healing wounds to the legs/feet, thickened nails, smooth shiny skin, hair loss to legs/feet, pallor or cyanosis to legs/feet, pallor on elevation of legs, legs/feet appearing flushed in a dependent position, and reduced temperature in one or both legs/feet.

Ankle Brachial Index measurement

The Ankle Brachial Index (ABI) was calculated for both legs using two different methods (see DUAL study for a detailed description of the methodologies, Chapter 6):

Method 1: utilising an automated ABI device.
Method 2: utilising a hand-held Doppler with an aneroid sphygmanometer (gold standard for ABI measurement).

Method 1 was always undertaken first for convenience as, according to manufacturer instructions, the automated device does not require individuals to be rested in the supine position prior to measurements.

Following measurement 1, participants were rested for five minutes prior to commencement of the second measurement with the Doppler ultrasound.

The time taken to undertake each measurement (including positioning of the participant, measurement of systolic pressures and calculation of the ABI) was measured and recorded by the PhD researcher utilising a Casio HS-80TW-1EF handheld stopwatch.

Questionnaires

The participant was then asked to complete five short questionnaires (with the assistance of JD):

1. **The General Practice Physical Activity Questionnaire** (GP-PAQ) (Appendix 5) – this was commissioned by the Department of Health and developed by the London School of Hygiene and Tropical Medicine as a validated short measure of physical activity. It provides a 4-level Physical Activity Index (PAI) categorising patients as active, moderately active, moderately inactive, and inactive. These levels are correlated to cardiovascular risk (DH, 2013).

2. **A dietary questionnaire** (Appendix 6). This consists of a modified version of “Starting the Conversation” which is an eight item validated food instrument questionnaire designed for use in primary care and health promotion settings (Cronin et al., 2013). The tool was derived from a 54 item instrument which was specifically designed for cardiovascular disease reduction (Jilcott et al., 2007). It was developed in the USA and utilises American food
terminology; this was therefore modified to incorporate British food terms. With this questionnaire, the lower the attained score, the healthier the diet (from a cardiovascular disease perspective).

3. **A quality of life survey** (SF-12v2) A generic, multipurpose short-form survey with 12 questions which, when combined, scored and weighted, results in two scales of mental and physical functioning and overall health-related quality of life (Appendix 7).

4. **Questionnaire regarding the participant’s experience of having their ABI measured** using each of the two methods outlined above (Appendix 8).

5. **Edinburgh Claudication questionnaire** (Appendix 1) This is a validated questionnaire which is used as a tool for diagnosis of intermittent claudication, which is the most common symptom of PAD (Leng and Fowkes, 1992). Further details of this questionnaire are provided in section 16.1.

An important prerequisite for the choice of the above questionnaires was that each of them should take no longer than five minutes for completion. This was to try and avoid participant fatigue. Visit 1 took approximately 90 minutes to complete for each participant.

**3.6.1.5 Cardiovascular Risk Assessment**

Data attained from the aforementioned measurements and physical examinations were input into the QRISK®2 cardiovascular risk algorithm (University of Nottingham, 2012) to calculate a 10 year cardiovascular risk score for each participant (Appendix 9). Participants that were found not to have PAD did not have a blood sample taken for a lipid screen and hence the lipid related information required for the QRISK®2 algorithm was taken from the most recent result within their medical record (if there were no results available, it was possible to calculate the score with the box left blank). The relative risk, which is defined as the individual’s actual risk score divided by the score of a typical person with the same age, sex, and ethnicity, was also calculated by the QRISK®2 algorithm and recorded for the purpose of the study.

**3.6.1.6 The Welsh Index of Multiple Deprivation**

The Welsh Index of Multiple Deprivation (WIMD) is the official measure of deprivation in Wales (Welsh Government, 2011). The Welsh government divided Wales into 1896 lower layer super output areas (LSOAs) with each area containing approximately 1500 people. The WIMD is produced as a set of ranks which depends on eight different types of deprivation (Table 3.4); a rank of 1 assigned to the most deprived LSOA.
Table 3.4: Types of deprivation according to the Welsh Index of Multiple Deprivation

- Income
- Housing
- Employment
- Access to services
- Education
- Health
- Community safety
- Physical environment

A list of WIMDs and corresponding postcodes is available via the Welsh Government and this was used to determine the WIMD for the area in which each participant resided.

3.6.1.7 PAD diagnosis within the PIPETTE study

Method 2 for ABI measurement represents the current gold standard for non-invasive diagnosis of PAD and hence results from this test were utilised as definitive for PAD in this study (as opposed to results from the automated ABI device). If either of the ABI results (one for each leg) obtained using method 2 was ≤ 0.9 then the patient was considered to have PAD and continued in the study to have visits 2, 3 and 4. The participant was reassured regarding their PAD diagnosis and any questions were answered. An appointment was made for visit 2 at this time.

Participants with an ABI of >0.9 exited the study at this stage.

If there was any doubt regarding a PAD or non-PAD diagnosis (if, for example, the participant appeared to be exhibiting symptoms of PAD but their ABI was within normal limits), then the participant in question was referred to their GP for further investigation and exited the study at this point. This occurred for only one participant (see Section 15.2.2).

Diagnosis of PAD in this study depended upon ABI measurements undertaken by a single investigator (JD). Validation of ABI measurements undertaken by JD is considered in Chapter 4 as part of the IVAM study.

3.6.2 Phase 2

3.6.2.1 Visit 2

The primary purpose of visit 2 was to obtain a fasting venous blood sample from participants found to have PAD. This visit was undertaken at the convenience of the participant and as soon as possible after visit 1. The participant was asked to refrain from eating and drinking (with the exception of
water) from 9pm the night before the visit; the visit was then made at approximately 9am the next day to ensure a fasting period of at least 12 hours. Venepuncture was performed by JD; CTUHB policies which were applicable to this procedure were adhered to at all times.

The following blood tests were performed:

1. Urea and Electrolytes – the prevalence of moderate or severe chronic kidney disease (CKD) is high in patients with PAD (Duncan et al., 2010) and hence this test was undertaken to identify previously undiagnosed renovascular disease. Furthermore, vascular calcification (VC), particularly medial (Monckeberg’s medial sclerosis) arterial calcification, is common in patients with CKD and this is associated with increased cardiovascular morbidity and mortality (Rocha-Singh et al., 2014). VC may result in artefactually raised ankle systolic pressures which obviously hinders the process of screening for PAD utilising the ABI. In addition, the pathology laboratory also utilised the serum creatinine level to calculate the estimated glomerular filtration rate (eGFR) for participants with PAD. This was then used to categorise any apparent renal disease according to the National Institute for Health and Care Excellence, Chronic Kidney Disease guidance (NICE, 2014).

2. Fasting glucose – one in three people with diabetes have PAD (Diabetes UK, 2013) so this test was undertaken to determine if any patients identified as having PAD also had undiagnosed diabetes. In addition, VC, as discussed in point 1 above, is also common in diabetes.

3. Fasting lipid screen – this was undertaken to obtain an accurate picture of the participants’ lipid profile in order to identify factors contributing to atherosclerosis. Participant Total cholesterol : High Density Lipoprotein ratios were subsequently utilised within the QRISK2 algorithm to obtain accurate risk scores.

4. C-Reactive Protein (CRP) – an elevated level of CRP is an established risk marker for ischaemic cardiovascular disease (Pearson et al., 2003). CRP is an inflammatory marker and as discussed in section 1.1, inflammation is an important part of the process of atherosclerosis

5. Uric acid – in recent years, evidence has accumulated in prospective observational studies that demonstrates a link between hyperuricaemia and cardiovascular mortality (Krishnan and Sokolove, 2011).

Blood samples were analysed at the pathology department of Prince Charles hospital, Merthyr Tydfil.
Blood test results were used in conjunction with the information collected in visit 1 to calculate an accurate and up to date cardiovascular risk score for the participant using the QRISK\textsuperscript{2} algorithm. At this point in the study, all results to date were given to the participant’s GP for them to use their clinical judgement to initiate any treatments/referrals as they deemed necessary.

3.6.2.2 Visits 3 and 4
Visit 3 took place 6 months post enrolment in the study and visit 4 took place 12 months post enrolment. Both visits entailed the same procedures (detailed below).

Participant general practice records were reviewed by the PhD researcher prior to the actual participant consultation and the purpose of this was to determine if, since enrolment in the study, the following had occurred:

- cardiovascular events;
- secondary care referrals;
- instigation of new medications or interventions.

The visit 3/4 CRF is included in Appendix 10. The physical assessment and questionnaires described in visit 1 were repeated at these visits.

3.7 PIPETTE population demographics
A total of 369 participants were recruited for the PIPETTE study. One participant withdrew consent after recruitment hence leaving a sample size of 368 for data analysis.

Demographics of the PIPETTE study population, according to gender, are presented in Table 3.5.
<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>All</th>
<th>Statistical Test Applied</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62 ± 9</td>
<td>65 ± 7</td>
<td>64 ± 8</td>
<td>Mann–Whitney U test</td>
<td>Mean Rank Male: 169</td>
<td>Age was statistically significantly higher for females than for males.</td>
</tr>
<tr>
<td></td>
<td>45 - 84</td>
<td>55 - 86</td>
<td>45-86</td>
<td></td>
<td>Mean Rank Female: 203.16</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>U = 19899.500</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Z = -3.070</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>( p = 0.002 )</td>
<td></td>
</tr>
<tr>
<td>Age group %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 - 54</td>
<td>20% (40)</td>
<td>0% (0)</td>
<td>11% (40)</td>
<td>Chi-square (( \chi^2 ))</td>
<td>( \chi^2(2) = 13.096 )</td>
<td>There is a statistically significant association between smoking status and gender. Inspection of standardised residuals reveals: There were less female ex-smokers than expected (SR: -2.0, ( p &lt; 0.05 )).</td>
</tr>
<tr>
<td>55 - 64</td>
<td>40% (81)</td>
<td>49% (81)</td>
<td>44% (162)</td>
<td></td>
<td>( p = 0.001 )</td>
<td></td>
</tr>
<tr>
<td>65 - 74</td>
<td>29% (59)</td>
<td>40% (67)</td>
<td>34% (126)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75 - 84</td>
<td>11% (21)</td>
<td>10% (16)</td>
<td>10% (37)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 85</td>
<td>0% (0)</td>
<td>2% (3)</td>
<td>1% (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking Status:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>12% (24)</td>
<td>11% (18)</td>
<td>11% (43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>43% (87)</td>
<td>26% (44)</td>
<td>36% (131)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non smoker</td>
<td>45% (90)</td>
<td>63% (103)</td>
<td>53% (194)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol (Units/week)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD Range</td>
<td>14 ± 18</td>
<td>4 ± 8</td>
<td>9 ± 15</td>
<td>Mann–Whitney U test</td>
<td>Mean Rank Male: 208.7</td>
<td>Number of alcohol units consumed per week was statistically significantly higher for males than females.</td>
</tr>
<tr>
<td></td>
<td>0-100</td>
<td>0-50</td>
<td>0-100</td>
<td></td>
<td>Female: 132.88</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>U = 8,461.500</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Z = -7.479</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>( p = 0.001 )</td>
<td></td>
</tr>
<tr>
<td>Family History of</td>
<td></td>
<td></td>
<td></td>
<td>Chi-square (( \chi^2 ))</td>
<td>( \chi^2(1) = 4.045 )</td>
<td>There is no statistically significant association between family history of premature CHD and gender.</td>
</tr>
<tr>
<td>Premature CHD:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>( p = 0.058 )</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22% (44)</td>
<td>31% (52)</td>
<td>26% (96)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>78% (157)</td>
<td>69% (115)</td>
<td>74% (272)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>137 ± 14</td>
<td>139 ± 15</td>
<td>140 ± 16</td>
<td>Mann–Whitney U test</td>
<td>Mean Rank Male: 179.1</td>
<td>Systolic arterial blood pressure was not statistically significantly different according to gender.</td>
</tr>
<tr>
<td></td>
<td>104–180</td>
<td>98–179</td>
<td>98–198</td>
<td></td>
<td>Female: 191</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>U = 17.869</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Z = 1.072</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>( p = 0.284 )</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.5: PIPETTE study population demographics
Red text denotes statistically significant results
<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Male</th>
<th>All</th>
<th>Statistical Test Applied</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=201</td>
<td>n=167</td>
<td>n=368</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Yes</strong></td>
<td>22% (44)</td>
<td>31% (52)</td>
<td>26% (96)</td>
<td>Mann-Whitney U test</td>
<td>Mean Rank Male: 179.1</td>
<td>Systolic arterial blood pressure was not statistically significantly different according to gender.</td>
</tr>
<tr>
<td><strong>No</strong></td>
<td>78% (157)</td>
<td>69% (115)</td>
<td>74% (272)</td>
<td></td>
<td>Male: 191, U=17,869, Z=1.072, P=0.284</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>137 ± 14</td>
<td>139 ± 15</td>
<td>140 ± 16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>104 – 180</td>
<td>98 – 179</td>
<td>98-198</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>82 ± 10</td>
<td>79 ± 9</td>
<td>81 ± 10</td>
<td>Mann-Whitney U test</td>
<td>Mean Rank Male: 203.44</td>
<td>Diastolic arterial blood pressure was statistically significantly higher in males than females.</td>
</tr>
<tr>
<td></td>
<td>40 – 104</td>
<td>60 – 107</td>
<td>40-113</td>
<td></td>
<td>Female:161.7, 12,967.500,  U=12,976.500, Z=3.773, P&lt;0.001</td>
<td></td>
</tr>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension*:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Yes</strong></td>
<td>73% (145)</td>
<td>79% (131)</td>
<td>76% (278)</td>
<td>Chi-square (χ²)</td>
<td>χ²(1) = 1.797, P=0.180</td>
<td>There is no statistically significant association between the presence of hypertension (any) and gender.</td>
</tr>
<tr>
<td><strong>No</strong></td>
<td>27% (54)</td>
<td>21% (35)</td>
<td>24% (90)</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Systolic&gt;140mmHg</td>
<td>32% (64)</td>
<td>42% (69)</td>
<td>36% (133)</td>
<td>Chi-square (χ²)</td>
<td>χ²(7) = 10.858, P=0.140</td>
<td>There is no statistically significant association between the presence of any of the individual categories of hypertension and gender.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic&gt;90mmHg</td>
<td>5% (10)</td>
<td>1% (1)</td>
<td>3% (11)</td>
<td>Fishers Exact Test (F)</td>
<td>F=10.363, P=0.157</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both (†systolic &amp; ‡diastolic)</td>
<td>20% (40)</td>
<td>15% (25)</td>
<td>18% (65)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taking antihypertensives:</td>
<td>40% (80)</td>
<td>43% (72)</td>
<td>41% (152)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taking antihypertensives but blood pressure not at target:</td>
<td>21.5% (43)</td>
<td>25% (42)</td>
<td>22% (81)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive but not on antihypertensives:</td>
<td>36% (71)</td>
<td>32% (53)</td>
<td>35% (124)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse Pressure</td>
<td>55 ± 13</td>
<td>59 ± 13</td>
<td>59 ± 14</td>
<td>Mann-Whitney U test</td>
<td>Mean Rank Male: 167.32</td>
<td>Median pulse pressure was statistically significantly lower in males than females.</td>
</tr>
<tr>
<td></td>
<td>30 – 96</td>
<td>32 – 94</td>
<td>30-106</td>
<td></td>
<td>Female: 205.18</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.5: PIPETTE study population demographics

Red text denotes statistically significant results. *as defined in inclusion criteria (Table 3.1)
<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>All</th>
<th>Statistical Test Applied</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=201</td>
<td>n=167</td>
<td>n=368</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate</td>
<td>73 ± 12</td>
<td>76 ± 11</td>
<td>74 ± 12</td>
<td>Mann-Whitney U test</td>
<td>Median Rank Male: 167.81</td>
<td>Median heart rate was statistically significantly lower in males than females.</td>
</tr>
<tr>
<td></td>
<td>48 - 107</td>
<td>40 - 114</td>
<td>40 - 114</td>
<td></td>
<td>Female: 200.42</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>U=13461.500</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Z=-2.943</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P= 0.003</td>
<td></td>
</tr>
<tr>
<td>Irregular pulse on</td>
<td>6% (11)</td>
<td>1% (2)</td>
<td>4% (13)</td>
<td>Chi-square (χ²)</td>
<td>χ²(1) = 3.632,</td>
<td>There is no statistically significant association between the presence of an irregular pulse and gender.</td>
</tr>
<tr>
<td>examination:</td>
<td>94% (189)</td>
<td>99% (162)</td>
<td>96% (351)</td>
<td></td>
<td>p=0.057</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>74% (149)</td>
<td>65% (108)</td>
<td>77% (249)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>17% (34)</td>
<td>25% (41)</td>
<td>23% (74)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No data available</td>
<td>9% (18)</td>
<td>11% (18)</td>
<td>10% (36)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidaemia*:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>74% (149)</td>
<td>65% (108)</td>
<td>77% (249)</td>
<td></td>
<td></td>
<td>There is no statistically significant association between the presence of dyslipidaemia and gender.</td>
</tr>
<tr>
<td>No</td>
<td>17% (34)</td>
<td>25% (41)</td>
<td>23% (74)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No data available</td>
<td>9% (18)</td>
<td>11% (18)</td>
<td>10% (36)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides &gt; 150mg/dL</td>
<td>44% (80)</td>
<td>26% (28)</td>
<td>32% (119)</td>
<td>Chi-square (χ²)</td>
<td>χ²(1) = 2.580,</td>
<td>There is no statistically significant association between the presence of dyslipidaemia and gender.</td>
</tr>
<tr>
<td>or 1.7mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.142</td>
<td></td>
</tr>
<tr>
<td>High Density Lipoprotein</td>
<td>16% (29)</td>
<td>4% (6)</td>
<td>10% (35)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(HDL) &lt; 40mg/dL or ≥1.0mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Density Lipoprotein</td>
<td>38% (69)</td>
<td>48% (61)</td>
<td>38% (140)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(LDL) ≥ 130mg/dL or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3.3mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taking lipid lowering</td>
<td>30% (54)</td>
<td>19% (29)</td>
<td>23% (83)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>29.1 ± 4.8</td>
<td>29.3 ± 5.2</td>
<td>29 ± 5</td>
<td>Mann-Whitney U test</td>
<td>Mean Rank Male: 187.64</td>
<td>Body Mass Index was not statistically significantly different according to gender.</td>
</tr>
<tr>
<td></td>
<td>20.4 – 53.6</td>
<td>19.0 – 44.2</td>
<td>19.54</td>
<td></td>
<td>Female: 180.06</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.5: PIPETTE study population demographics
Red text denotes statistically significant results
Table 3.5: PIPETTE study population demographics

Red text denotes statistically significant results.

* As defined in inclusion criteria – Table 3.5

<table>
<thead>
<tr>
<th><strong>BMI Classification</strong></th>
<th><strong>Male</strong></th>
<th><strong>Female</strong></th>
<th><strong>All</strong></th>
<th><strong>Statistical Test Applied</strong></th>
<th><strong>Results</strong></th>
<th><strong>Conclusion</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (BMI 18.5–24.99)</td>
<td>18% (35)</td>
<td>20% (34)</td>
<td>19% (69)</td>
<td>Mann-Whitney U test</td>
<td>U=17,287.00, Z=0.682, P=0.495</td>
<td>Classification of BMI was not significantly different according to gender.</td>
</tr>
<tr>
<td>Over-weight (BMI 25–29.99)</td>
<td>48% (90)</td>
<td>36% (59)</td>
<td>42% (155)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese Class I (BMI 30–34.99)</td>
<td>24% (48)</td>
<td>25% (42)</td>
<td>25% (90)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese Class II (BMI 35–39.99)</td>
<td>8% (15)</td>
<td>13% (22)</td>
<td>10% (37)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese Class III (BMI 40+)</td>
<td>3% (6)</td>
<td>5% (9)</td>
<td>4% (15)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Elevated waist circumference:** | **Male** | **Female** | **All** | | **Statistical Test Applied** | **Results** | **Conclusion** |
|--------------------------------|----------|------------|---------|-----------------------------|-------------|----------------|
| Yes | 64% (128) | 66% (110) | 64% (229) | Chi-square ($\chi^2$) | $\chi^2(1) = 0.205$, $p=0.661$ | There is no statistically significant association between the presence of elevated waist circumference and gender. |
| No | 36% (72) | 34% (56) | 36% (128) | | | |

<table>
<thead>
<tr>
<th><strong>Waist circumference:</strong></th>
<th><strong>Male</strong></th>
<th><strong>Female</strong></th>
<th><strong>All</strong></th>
<th>Mann-Whitney U test</th>
<th>Mean Rank Male: 217.97 Female: 142.87</th>
<th>Waist circumference was statistically significantly higher in males than females.</th>
</tr>
</thead>
<tbody>
<tr>
<td>104 ± 12 75 - 143</td>
<td>64 ± 13 64 - 136</td>
<td>100 ± 14 64-143</td>
<td></td>
<td></td>
<td>U=9855, Z=6.752, P=0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Waist: Hip ratio</strong></th>
<th><strong>Male</strong></th>
<th><strong>Female</strong></th>
<th><strong>All</strong></th>
<th>Independent samples t test</th>
<th>Mean difference: 0.12 (95% CI, 0.11 to 0.13), t(365)= 16.442, p&lt;0.01, d=1.72</th>
<th>Males had a statistically significant higher waist to hip ratio than females.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.97 ± 0.07 0.78 – 1.18</td>
<td>0.85 ± 0.07 0.7– 1.15</td>
<td>0.92 ± 0.09 0.7-1.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Total Number of CV risk factors</strong></th>
<th><strong>Male</strong></th>
<th><strong>Female</strong></th>
<th><strong>All</strong></th>
<th>Mann-Whitney U test</th>
<th>Mean Rank Male: 189.40 Female: 178.60</th>
<th>Total number of CV risk factors was not statistically different according to gender.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 3 4 5 6</td>
<td>9% (17)</td>
<td>13% (21)</td>
<td>10% (38)</td>
<td></td>
<td>U=15,798, Z=1.004, P=0.315</td>
<td></td>
</tr>
<tr>
<td>23% (47)</td>
<td>27% (45)</td>
<td>25% (92)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35% (71)</td>
<td>26% (44)</td>
<td>31% (115)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25% (50)</td>
<td>29% (48)</td>
<td>27% (98)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8% (16)</td>
<td>5% (9)</td>
<td>7% (25)</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Chronic Kidney Disease</strong></th>
<th><strong>Male</strong></th>
<th><strong>Female</strong></th>
<th><strong>All</strong></th>
<th>Chi-square ($\chi^2$)</th>
<th>$\chi^2(1) = 0.000$, $p=0.996$</th>
<th>There is no statistically significant association between the presence of Chronic Kidney Disease and gender.</th>
</tr>
</thead>
</table>

Table 3.5: PIPETTE study population demographics
<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>All</th>
<th>Statistical Test Applied</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=201</td>
<td>n=167</td>
<td>n=368</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Yes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attrial Fibrillation</td>
<td></td>
<td></td>
<td></td>
<td>Chi-square ($\chi^2$)</td>
<td>$\chi^2(1) = 3.828, p=0.05$</td>
<td>There is no statistically significant association between the presence of atrial fibrillation and gender.</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td></td>
<td></td>
<td></td>
<td>Chi-square ($\chi^2$)</td>
<td>$\chi^2(1) = 0.018, p=0.892$</td>
<td>There is no statistically significant association between the presence of rheumatoid arthritis and gender.</td>
</tr>
<tr>
<td><strong>P</strong>IPPAQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td></td>
<td></td>
<td></td>
<td>Mann-Whitney U test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53% (108)</td>
<td></td>
<td></td>
<td></td>
<td>Mean Rank Male: 200.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4% (9)</td>
<td></td>
<td></td>
<td></td>
<td>Female: 165.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18% (37)</td>
<td></td>
<td></td>
<td></td>
<td>U=13,579.500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23% (47)</td>
<td></td>
<td></td>
<td></td>
<td>Z=-3.620</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderately Inactive</strong></td>
<td></td>
<td></td>
<td></td>
<td>$P&lt;0.001$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>61% (226)</td>
<td></td>
<td></td>
<td></td>
<td><strong>Women were statistically significantly less likely to be classed as active, according to the GPPAQ, than men.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6% (10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12% (20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11% (19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderately Active</strong></td>
<td></td>
<td></td>
<td></td>
<td>Mann-Whitney U test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>61% (226)</td>
<td></td>
<td></td>
<td></td>
<td>Mean Rank Male: 195.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5% (19)</td>
<td></td>
<td></td>
<td></td>
<td>Female: 170.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15% (57)</td>
<td></td>
<td></td>
<td></td>
<td>U=14,398</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18% (66)</td>
<td></td>
<td></td>
<td></td>
<td>Z=-2.286</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Active</strong></td>
<td></td>
<td></td>
<td></td>
<td>$P=0.022$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.6 ± 2.6</td>
<td></td>
<td></td>
<td></td>
<td><strong>Median healthy eating score was statistically significantly higher in males than females.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 - 14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.0 ± 3.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 -14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Physical Health Score</strong></td>
<td></td>
<td></td>
<td></td>
<td>Mann-Whitney U test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SF-12)</td>
<td>46.6 ± 13.1</td>
<td>41.5 ± 14.1</td>
<td>43.6 ± 13.6</td>
<td>Mean Rank Male: 190.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>5.8 – 61.9</td>
<td>12.4 – 64.4</td>
<td>14 – 27</td>
<td>Female: 153.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
<td>U=11,608.500</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mental Health Score</strong></td>
<td></td>
<td></td>
<td></td>
<td>Mann-Whitney U test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SF-12)</td>
<td>55.9 ± 7.3</td>
<td>52.5 ± 9.6</td>
<td>54.6 ± 8.6</td>
<td>Mean Rank Male: 187.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>24.9 – 72.5</td>
<td>26 – 70</td>
<td>25 – 74</td>
<td>Female: 156.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
<td>U=12,206</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>QRSIK2 Score</strong></td>
<td></td>
<td></td>
<td></td>
<td>Mann-Whitney U test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>18.4 ± 9.3</td>
<td>15.4 ± 8</td>
<td>17 ± 9</td>
<td>Mean Rank Male: 205.04</td>
<td></td>
<td><strong>QRSIK2 scores were statistically significantly higher for males than for females.</strong></td>
</tr>
</tbody>
</table>

*Table 3.5: PIPETTE study population demographics*

Red text denotes statistically significant results.
Table 3.5: PIPETTE study population demographics

Red text denotes statistically significant results

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>All</th>
<th>Statistical Test Applied</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>2.9 – 40.7</td>
<td>4 – 38.2</td>
<td>3 – 41</td>
<td>U=12,492</td>
<td>J=4158</td>
<td>Median relative risk scores according to QRISK2 were not significantly different according to gender.</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.3 ± 0.5</td>
<td>1.3 ± 0.5</td>
<td>1.3 ± 0.5</td>
<td>Mann-Whitney U test</td>
<td>Mean Rank Male: 177.06 Female: 192.32</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.7 – 4.5</td>
<td>0.6 – 3.4</td>
<td>0.6 – 5.6</td>
<td></td>
<td>U=18,089</td>
<td></td>
</tr>
<tr>
<td>WIMD (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Z=1.378</td>
<td></td>
</tr>
<tr>
<td>Group 1: 1:379inc</td>
<td>30</td>
<td>38</td>
<td>34</td>
<td>Mann-Whitney U test</td>
<td>U=14,977.500</td>
<td>WIMD was not statistically significantly different according to gender.</td>
</tr>
<tr>
<td>Group 2: 380-758inc</td>
<td>34</td>
<td>32</td>
<td>33</td>
<td></td>
<td>Z=1.427</td>
<td></td>
</tr>
<tr>
<td>Group 3: 759-1137inc</td>
<td>24</td>
<td>30</td>
<td>21</td>
<td></td>
<td>P=0.154</td>
<td></td>
</tr>
<tr>
<td>Group 4: 1138-1516inc</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 5: 1517-1896inc</td>
<td>9</td>
<td>8</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.7.1 Gender and ethnic origin

The study population was 100% of white British ethnic origin. Participants were, on average, 64 years old (±8) and the ratio of male: female participants was 55:45. The mean age of male participants was statistically significantly lower than the mean age of female participants (male: 63±9, female: 65±7, p<0.01) (Figure 3.9); this can be attributed to the age related inclusion criterion being lower for men (Table 3.2).

3.7.2 Welsh Index of Multiple Deprivation

The Welsh Indices of Multiple Deprivation (Section 3.6) for the study population ranged from 4 – 1579. The indices were divided into quintiles for analysis. For example, group 1 contained all participants with a WIMD within the range of 1-379 inclusive; this group equates to the most deprived 20% of areas in Wales. Whilst group 5, which contained all participants with a WIMD within the range of 1517 and 1896 inclusive, equates to the least deprived 20% of areas within Wales. The majority of the study population came from the most deprived areas in Wales with only 9% coming from the least deprived areas (Figure 3.10).
3.7.3 Population anthropometrics

The mean Body Mass Index (BMI) of participants was 29 (±5) and this did not differ significantly according to gender. Participants were categorized according to the World Health Organisation BMI classification (WHO, 2006)(Appendix 11); Only 19% had a BMI that is considered to be normal, with the remainder being overweight (42%) or obese (39%) (Figure 3.11).

Sixty four per cent of participants had a waist circumference that exceeded the World Health Organisation’s gender specific recommended limits (WHO, 2011). Mean waist circumference was 100cm (±14) and as would be expected, male participants had statistically significantly higher waist circumferences than female participants (104 ± 12cm vs 94 ± 13cm, p<0.001), and also a statistically significantly higher waist to hip ratio than women (0.97 ± 0.07 vs 0.85 ± 0.07, p<0.001). Interestingly, 50% of participants that did not have an elevated waist circumference according to the WHO limits, were still classed as overweight according to their BMIs (Figure 3.12).
Figure 3.11: PIPETTE study population according to WHO BMI classification

Figure 3.12: Association between BMI and elevated waist circumference
Blue = waist circumference elevated, Red = waist circumference not elevated
3.7.4 Haemodynamic measurements

The mean systolic blood pressure of the population was 140mmHg (±16) and the mean diastolic blood pressure was 81mmHg (±10). Although systolic blood pressure did not differ according to gender, males had statistically significantly higher diastolic blood pressures than females (male: 82 ± 10, female: 79 ± 9, p=0.001) (Table 3.5).

The mean pulse pressure (systolic blood pressure – diastolic blood pressure) of the study population was 59 (±14). The median pulse pressure of men was statistically significantly lower than the median pulse pressure of women (55 ± 13 v 59 ± 13 respectively, p=0.001). The mean pulse rate was 74 beats per minute (±12) and the median male heart rate was 73 beats per minute (±12) whilst the female median heart rate was 76 (±11); a p value of 0.003 shows that this is a statistically significant difference (Table 3.5).

3.7.5 Presence of cardiovascular risk factors

The mean number of cardiovascular risk factors in addition to age was 3 (±1) and this did not differ significantly according to gender (Figure 3.13) (Table 3.5). Twenty six per cent of the population had a family history of premature coronary heart disease (CHD), 76% had some form of hypertension, 77% had some form of dyslipidaemia and 64% had an elevated waist circumference (further details of what constituted hypertension, dyslipidaemia and elevated waist circumference are provided in Table 3.1). Three per cent of the participants had chronic kidney disease and 2% had rheumatoid arthritis. Whilst three per cent of the population were known to have atrial fibrillation, a further one percent were noted to have an irregular pulse on examination. The presence of any of these cardiovascular risk factors did not differ significantly according to gender (Table 3.5).

3.7.6 Hypertension

Forty one per cent of the population were taking anti-hypertensives and of those, 53% were not at target blood pressure (systolic target BP≤140mmHg, diastolic target BP≤90mmHg); these figures did not differ according to gender. A further 35% of participants were hypertensive but were not taking anti-hypertensive medication (Table 3.5).
3.7.7 **Dyslipidaemia**

Twenty three per cent of the population were taking lipid lowering medications, with men being significantly more likely to have been taking them compared to women (30% vs. 19%, p=0.036). UK guidance at the time the study was undertaken recommended the prescription of lipid lowering medications only for persons with an overall 10 year CV risk of >20%. As men within the PIPETTE study were more likely to have higher CV risk scores according to the QRISK®2 algorithm (see pg. 96), then it follows that they were more likely to exceed this threshold, hence explaining this finding. Men were also statistically significantly more likely to have raised triglyceride levels (44% vs 26%, p=0.001) and low levels of high density lipo-proteins (HDLs) (16% vs. 4%, p=<0.001).

3.7.8 **Cardiovascular Risk Assessment Scores**

The mean QRISK®2 score was 17 (±9) and was statistically significantly higher for males than females (18.4 ± 9.3 v 15.4 ± 8, p<0.001). Participant mean relative risk according to QRISK®2 was 1.3 (±0.5); this did not differ significantly according to gender.
3.7.9 **Lifestyle Factors**

Over half of the study population were non-smokers (53%), with a further 36% being ex-smokers and only 11% current smokers. There were statistically significantly less female ex-smokers and more female non-smokers than predicted by a Chi-square test ($p=0.001$). The mean number of reported alcohol units consumed per week was $9 \pm 15$ with 47% reportedly drinking alcohol only occasionally or not at all. The proportion of the population who reported drinking in excess of the current weekly limits of units of alcohol, as recommended by the UK Department of Health (2013c), was low at 14% (men: 18%, women 10%). Men consumed statistically significantly more alcohol units per week than women ($14 \pm 8$ vs. $4 \pm 8$ respectively, $p<0.001$) and were less likely to consume alcohol occasionally only, or be teetotal, compared to women (32% vs. 66% respectively, $p<0.001$).

Sixty one per cent of the population were classed as inactive according to the General Practice Physical Activity Score (GPPAQ) with a further 5% being classed as moderately inactive. Fifteen per cent were classed as moderately active and a further 18% classed as active (Figure 3.14). Although women were statistically significantly less likely to be classed as active, according to the GPPPAQ, than men (11% vs. 23% respectively, $p<0.001$), they had healthier diets as indicated by significantly lower median healthy eating scores (8 vs. 9 respectively, $p=0.02$).

**Figure 3.14: GPPAQ Activity levels according to gender**
### 3.7.10 Quality of life scores

The population mean physical health score according to the SF-12 was 43.6 ± 13.6 and the mean mental health score was 54.6 ± 8.6. Men had statistically significantly higher median scores than women for both physical and mental health (physical health score: male 51.7, female 43.2, p=0.001; mental health score: male 57.3, female 56.1, p=0.005) (Figure 3.15).

![Box and whisker plots for SF-12 scores according to gender](image)

**Figure 3.15:** Box and whisker plots for SF-12 scores according to gender

Horizontal bar represents median, box length represents interquartile range. Outliers identified by "○" and "△" plots.

### 3.7.11 Ankle Brachial Index

The mean ABI for males was significantly higher than the mean ABI of females for both right and left legs; this applied for both Doppler ultrasound measurements and automated device measurements (Table 3.5). Gender differences in ABI have been reported in many population studies (London et al., 1995; Smith et al., 2003; Aboyans et al., 2007). This can be partly attributed to gender related height differences, with men being on average taller and hence having higher ankle blood pressures as a result of progressive systolic blood pressure increase with greater distance from the heart (Aboyans et al., 2012). Among participants without traditional CVD risk factors in the San Luis Valley Diabetes study, female ABIs were 0.07 less than male ABIs. Adjustment for height reduces but does not eliminate observed differences (Hiatt et al., 1995). Similarly in the Multi-Ethnic Study of Atherosclerosis (MESA) study, after multivariate adjustments, ABI was 0.02 lower for women (Aboyans et al., 2007).

### 3.7.12 Discussion of PIPETTE Study Population

It was anticipated that the study population would exhibit higher rates of specific cardiovascular risk factors and more adverse health related lifestyles than the age-matched general population of
Wales. This is attributed firstly to the fact that this study purposively recruited individuals with such cardiovascular risk factors, and secondly, to the fact that Cwm Taf University health board and Merthyr Tydfil have been shown, in any case, to have higher rates of these risk factors than Wales as a whole (Table 3.6).

Figure 3.16 depicts the prevalence, by age group, of these cardiovascular risks factors and other key health related lifestyles for both the PIPETTE study and the Welsh Health Survey (WHS, 2011-12). It can be seen that the PIPETTE study population did indeed have a statistically significantly higher rate of being over-weight/obesity than the WHS data across the age groups (p=0.012) (Figure 3.16A). There was also a trend for higher rates of hypertension across the age-groups in the PIPETTE population versus the WHS data, although this was not statistically significant (p=0.174) (Figure 3.16B).

However, Table 3.6 and Figures 3.16C and 3.16D demonstrate that conversely, the PIPETTE study population had statistically significantly lower rates of smoking (p=0.024) and inactivity (p=0.026), than the WHS data. There was also a trend for lower rates of excess alcohol consumption in the PIPETTE population versus the WHS, although this was not statistically significant (p=0.103). This may possibly represent a recruitment bias as it appears that individuals who chose to participate in the PIPETTE study had, on average, healthier life styles, according to these variables, than an age-matched population of Wales. Recruitment bias is considered in further detail in Section 3.7.12.1.

<table>
<thead>
<tr>
<th>Cardiovascular Disease Risk Factor</th>
<th>*Current Smoker</th>
<th>*BMI≥25 (Overweight or obese)</th>
<th>*Hypertensive</th>
<th>Classed as physically Inactive</th>
<th>Consumption of Excess Alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIPETTE study</td>
<td>11%</td>
<td>81%</td>
<td>76%</td>
<td>67%</td>
<td>14%</td>
</tr>
<tr>
<td>Merthyr Tydfil</td>
<td>25%</td>
<td>65%+</td>
<td>24%</td>
<td>69%</td>
<td>40%</td>
</tr>
<tr>
<td>Cwm Taf University Health Board</td>
<td>26%+</td>
<td>65%+</td>
<td>24%+</td>
<td>73%</td>
<td>45%</td>
</tr>
<tr>
<td>Wales</td>
<td>23%</td>
<td>58%</td>
<td>20%</td>
<td>71%</td>
<td>43%</td>
</tr>
</tbody>
</table>

Table 3.6: Comparison of the prevalence of cardiovascular risk factors within the PIPETTE study with local health authority, local health board and national data.
* Included within PIPETTE study inclusion criteria.
+Result statistically significantly higher than result for Wales as a whole.
(Data from Welsh Health Survey 2011-2012, reference: Welsh Government, 2013)
Prevalence of cardiovascular risk factors/key health related lifestyles

Figure 3.16: Prevalence of cardiovascular risk factors/key health related lifestyles, according to age group, for the PIPETTE study and Welsh Health Survey (2011-12)
3.7.12.1 Recruitment bias

Age, gender, smoking status and Welsh Index of Multiple Deprivation were recorded for each patient invited to take part in the PIPETTE study; this allowed for assessment of possible recruitment bias related to these factors. Whilst there was no statistically significant association between age group and participation in the study ($\chi^2(3) = 6.547$, $p = 0.088$), gender and participation in the study ($\chi^2(3) = 7.471$, $p = 0.079$), and WIMD group and participation in the study ($\chi^2(4) = 7.571$, $p = 0.105$), it was found that smokers were statistically significantly less likely to participate in the study than non-smokers or ex-smokers (Figure 3.17) ($\chi^2(2) = 17.764$, $p < 0.001$).

![Figure 3.17: PIPETTE study participation rate according to smoking status](image)

However, even if all of the smokers who were invited to participate had been recruited, the maximum percentage of smokers in the study population could not have exceeded 20%. This could be partly attributed to smokers being more likely to have already established diagnosed cardiovascular disease hence resulting in their exclusion from this study.

3.7.13 Summary of PIPETTE study population

In summary: the PIPETTE study population consisted of 368 participants with a mean age of 64. There was no ethnic variation with all participants describing themselves as white Welsh or white British. A large proportion of the population (67%) came from areas with the highest levels of deprivation in Wales, whereas only 11% came from areas with the lowest levels of deprivation.
Study inclusion criteria specified that participants should have at least two cardiovascular risk factors, one of which was age-related. The mean number of additional cardiovascular risk factors was three and these were most likely to include the presence of hypertension (76%), dyslipidaemia (77%) and elevated body mass index/waist circumference (81%), rather than current smoking status (11%) or family history of premature coronary heart disease (26%).

Analysis of lifestyle related risk factors suggests a more health conscious population that were less likely to smoke (p=0.024), and less likely to be classed as inactive (p=0.026), than an age-matched general population of Wales. Evidence of a recruitment bias in terms of smoking status has been identified with smokers being less likely to have participated in the study than non-smokers or ex-smokers (p<0.001).

Men reported being more active than women (p<0.001) and had higher scores for mental and physical health according to SF12 (p=0.005 and p=0.001 respectively). They were, however, more likely to drink alcohol in excess of recommended limits (p=0.015), have raised triglyceride levels (p=0.001), diminished high density lipoprotein (HDL) levels (p<0.001) and to be taking lipid lowering medication than women (p=0.036). Men also reported less healthy diets than women as indicated by statistically significantly lower dietary scores (p=0.02).

### 3.8 Data analysis

All data analysis was performed using IBM SPSS software (version 21, New York, USA). The threshold of statistical significance was set at p<0.05. Details of statistical tests used are provided in Appendix 12.
3.9 PIPETTE study: key results and conclusions

Extensive consideration of the results and conclusions from the PIPETTE study is detailed in parts 3 and 5 of this thesis. A summary of key results and conclusions is presented below:

- The prevalence of PAD within the PIPETTE study population was 3.3%; the bias adjusted prevalence rate was 4.3% (Chapter 8).
- Factors found to be significantly associated with PAD included advancing age (p=0.049), current smoking (p<0.01), pulse pressure (p<0.01), rheumatoid arthritis (p<0.01), positive ECQ result (p<0.01) and the presence of clinical signs of PAD (p<0.01) (Chapter 8).
- Based on the attained prevalence rate, the number needed to screen (NNS) to detect one new case of PAD was 31 (Chapter 8).
- Refining the study population, based on factors found to be significantly associated with PAD, to those over the age of 50, with a history of smoking, and at least one clinical sign of PAD would dramatically reduce the NNS to 4, whilst still identifying 92% of PAD cases (Chapter 8).
- QRISK2 score predicted high cardiovascular risk in 92% of PAD subjects, hence suggesting that ABI would have little to contribute via its addition to the algorithm (Chapter 8).
- The high ABI group within the PIPETTE study presented with a mixed cardiovascular profile and it was unclear how this would translate into actual cardiovascular risk. As such, it was recommended that individuals with high ABI should undergo additional cardiovascular risk assessment and diagnostic tests (Chapter 9).
- Phase 2 of the PIPETTE study suggested an improvement in the pharmacological management of PAD, although lifestyle modification strategies were shown to be not only infrequently used but also of limited effectiveness in achieving behaviour change. Despite this, primary care management of PAD within the PIPETTE study was effective in lowering CV risk of PAD participants as evidenced by reductions in QRISK2 scores (Chapter 17).
- An apparent lack of awareness of PAD within the PIPETTE study population appears likely, as evidenced by the fact that one third of those identified as having PAD were symptomatic of the disease and yet had not presented to a clinician. As such, there appears to be a need for PAD educational/promotional strategies to be targeted at the general public (Chapter 17).
- Several limitations relating to the PIPETTE study were identified; these potentially reduce the strength and generalisation of the results listed above (discussed in individual corresponding chapters).
Chapter 4: The IVAM Study

Inter-observer Variability of ABI Measurement: Expert vs. PhD researcher vs. Automated ABI device

4.0 Aims and objectives

Objectives of this study were three-fold:

1. To validate the ABI measurements made by the PhD researcher for the purpose of the PIPETTE (Chapter 3) and DUAL (Chapter 5) studies; this was achieved via assessment of the agreement of ABI measurements undertaken by an expert (a consultant vascular surgeon) with measurements undertaken by the PhD researcher (Jane Davies).

2. To establish if ABI results from an automated ABI device correlate/agree with ABI measurements undertaken by an expert (consultant vascular surgeon).

3. To assess the time taken for the expert, PhD researcher and the automated ABI device to undertake ABI measurements.

4.1 Study setting

The study was undertaken at the outpatient clinic of a vascular surgeon at Prince Charles Hospital, Merthyr Tydfil (Cwm Taf University Health Board, NHS, South Wales).

4.2 Study personnel

Study personnel consisted of three members:

Dr Mark Williams (MW) of the University of South Wales was the study lead (and PhD Director of Studies for Jane Davies). MW was responsible for facilitation and coordination of the study; this included activities such as management of the study timeline and ensuring adherence to governance issues.

Mr Kevin Conway (KC) was the study principal investigator. KC was the clinical lead for the study and was also responsible for identifying individuals eligible to participate and contacting them on behalf of the study team. KC also undertook ABI measurements, using a hand held Doppler device, on each of the study participants. He is considered a local expert in this field because his role as a consultant vascular surgeon requires frequent (approximately 10 times per week on average) and accurate use of the ABI to assess the arterial status of the lower limbs of patients with varying degrees of PAD. His ABI results are often verified via repeat ABI measurement by technicians in the vascular laboratory, who are also considered experts in the procedure. Hence, KC’s ABI measurements were considered the ‘reference standard’ for the purpose of this study.
Jane Davies (JD), as the PhD researcher, took the role of the study chief investigator and was responsible for project conception, subsequent study design and all study administration. JD applied and operated the automated ABI device for every subject and also undertook ABI measurements, using a hand held pocket Doppler device, on each of the study participants.

4.3 Ethical Approval
The IVAM study was granted ethical approval by the South East Wales Research Ethics Committee on 26/09/12 (REC Reference Number: 12/WA/0243; this study was originally known as the IVORY study). Due to the study principal investigator (KC) taking an extended period of leave from his post, governance checks by Cwm Taf University Health Board were not completed until 26/02/13. Recruitment began in March 2013 and was completed in December 2013. The study was sponsored by the University of South Wales.

4.4 Methodology
The design for this study (Figure 4.1) was purposely simplistic to allow for its unobtrusive incorporation into the everyday running of an outpatient clinic. Each participant had their ABIs measured once by each of three ‘observers’:

- An expert (KC) (utilising an aneroid sphygmomanometer in combination with a Doppler ultrasound device)
- A PhD researcher (JD) (utilising an aneroid sphygmomanometer in combination with a Doppler ultrasound device)
- An automated ABI device, hereafter referred to as AD (applied and operated by JD).
4.4.1 Study Population

The study population was derived from patients who had been newly referred to Mr Kevin Conway either for assessment of possible, new-onset PAD, or for re-assessment of existing PAD. Referral letters were screened by KC to determine if patients met the study inclusion and exclusion criteria (detailed in Tables 4.1 and 4.2 respectively). Potential participants were sent an invitation to
participate and a study information sheet with their outpatient clinic appointment. When the patient subsequently attended for their appointment, KC asked if they would like to participate; if they agreed, the study ABI measurements were undertaken on that same day.

- Suspected or confirmed symptomatic peripheral arterial disease.
- Willingness to participate in study.
- Capable of giving informed consent.

Table 4.1: IVAM study inclusion criteria

- Severe peripheral arterial disease (e.g. previous amputation, gangrene or pain at rest)
- Inability to lie supine for the duration of ABI measurement (e.g. due to heart failure or musculoskeletal condition).
- Unable to have blood pressure measured in both upper and both lower limbs (e.g. due to previous mastectomy, the presence of lymphoedema or A-V fistula).
- Known Atrial Fibrillation (this may cause the ABI result to vary.)
- Serious or unstable medical or psychological conditions that, in the opinion of the investigator, would compromise the patient’s safety or successful participation in the study.
- Current or recent (preceding 4 months) participation in clinical research trial (this does not apply to participation in non-interventional research).
- Unwilling or unable to provide informed consent.

Table 4.2: IVAM study exclusion criteria

4.4.2 Sample size
The sample size for this study was 12 participants which equated to 24 measurements (one for each leg); this was based on the minimum number of measurements required to undertake a meaningful Bland Altman analysis of results (Section 7.0.1), which according to van Langen et al. (2009) is 20 measurements. An additional two participants were recruited to allow for possible observer measurement failure.

4.4.3 Study Procedures
Patients who agreed to participate in the study were subsequently seen by JD, who reiterated details of the study and checked eligibility criteria. Participants had the opportunity to ask questions prior to completing an informed consent form.
Basic demographic details (age and gender) were collected and recorded on the participants’ CRFs.

**ABI measurement**

As in the PIPETTE study, the first measurement of each participant’s ABIs was undertaken by JD utilising the AD as, according to the manufacturer’s guidelines, this does not require individuals to be rested prior to measurements. The procedure for this measurement is detailed in the DUAL study: Section 5.4.1.

Participants remained supine between measurements, and rested for a period of five minutes between each set of readings. Either JD or KC then undertook a measurement of the ABIs using the Doppler device ultrasound device and aneroid sphygmomanometer (order randomised via a toss of a coin). The procedure for the Doppler ABI measurement is detailed in the DUAL study: Section 5.4.2.

Following a further rest period of five minutes, the remaining observer undertook the final set of ABI measurements with the Doppler ultrasound.

The same equipment (detailed in the DUAL study, Section 5.3) was utilised by both observers for the Doppler ABI measurements for each participant.

### 4.5 IVAM study population demographics

The study population had a mean age of 65 years (SD: 12; range: 36-87) and 58% were male (Table 4.3). There was no significant difference in age according to gender (p=0.639). According to ABI measurements from KC (considered to be the reference standard for this study), the ratio of diseased participants (ABI≤0.9) to non-diseased participants (ABI>0.9) was 58:42. Diseased and non-diseased participants did not differ significantly in terms of age and gender (Table 4.3). The minimum ABI measured was 0.4 and the maximum was 1.35 (mean: 0.89, SD: ±0.29).

<table>
<thead>
<tr>
<th></th>
<th>Diseased (ABI≤0.9)</th>
<th>Non-Diseased (ABI&gt;0.9)</th>
<th>Statistical Test and Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years):</strong></td>
<td>64 ± 13</td>
<td>69 ± 12</td>
<td>Mann-Whitney U test: U=68, z=0.247, p=0.834</td>
</tr>
<tr>
<td><strong>Gender:</strong> Male:Female</td>
<td>63:37</td>
<td>50:50</td>
<td>Chi-Square test: X²(1)=0.343, p=0.558</td>
</tr>
</tbody>
</table>

*Table 4.3: IVAM Study Population Demographics according to PAD status*
4.6 IVAM study: key results and conclusions

Extensive consideration of the results and conclusions from the IVAM study is detailed in part 3 of this thesis. A summary of key results and conclusions is presented below:

- The PhD researcher was found to slightly under-estimate ABIs in comparison to the expert as illustrated by a positive bias (Chapter 7)
- The 95% limits of agreement between the two observers were ±0.15 (Chapter 7)
- The inter-observer variability between the two observers was 8% overall, 11% for diseased subjects and 6% for non-diseased subjects (Chapter 7).
- Results consistently demonstrated a high level of agreement between ABI measurements undertaken by the expert and those undertaken by the PhD researcher, which was comparable to reported agreement levels between other ‘experts’. It was concluded that the PhD researcher measured the ABI with the hand-held Doppler with the same level of accuracy and precision as someone who is considered to be an expert in the procedure. This then served to validate all other ABI measurements undertaken by the PhD researcher for the purpose of the PIPETTE and DUAL studies.
- The utility of the IVAM study to serve as a pilot for a larger and more comprehensive study aimed at investigating the accuracy of ABI measurement within primary care, was noted (Chapter 7).
Chapter 5: The DUAL study

Doppler Ultrasound versus Dopplex Ability for the measurement of the Ankle Brachial Index

5.0 Aims and objectives

Objectives of the DUAL study were four-fold:

1. To determine the agreement between the Doppler ultrasound ABI measurements with ABI measurements made with an automated ABI device.
2. To determine the participant perspective of the two different methods of ABI measurement.
3. To determine the time taken to perform the two different methods of ABI measurement.
4. To determine the value of analysis of pulse volume waveforms (PVW) as an adjunct to ABI measurement in the diagnosis of PAD.

5.1 Study details

Information regarding study setting, study personnel, study population, and ethical approval are detailed in the corresponding sections of the PIPETTE and IVAM studies (Chapters 3 and 4).

5.2 Sample size

The study sample was derived from the PIPETTE and IVAM studies (Figure 5.1). Reasons for non-measurements of ABIs within the PIPETTE and IVAM studies are detailed in Table 5.1.
Figure 5.1: Composition of DUAL study sample

<table>
<thead>
<tr>
<th>PIPETTE Study</th>
<th>IVAM Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurements by: PhD researcher</td>
<td>Measurements by: Vascular Consultant</td>
</tr>
<tr>
<td>Visit 1 (all participants)</td>
<td></td>
</tr>
<tr>
<td>368 participants x 2 legs = 736 measurements</td>
<td>12 participants x 2 legs</td>
</tr>
<tr>
<td>Visit 3 (PAD participants)</td>
<td>Subtotal = 24 measurements</td>
</tr>
<tr>
<td>12 participants x 2 legs = 24 measurements</td>
<td></td>
</tr>
<tr>
<td>Visit 4 (PAD participants)</td>
<td></td>
</tr>
<tr>
<td>12 participants x 2 legs = 24 measurements</td>
<td></td>
</tr>
<tr>
<td>Subtotal = 736 + 24 + 24 = 784 ABI measurements</td>
<td>Subtotal = 24 measurements</td>
</tr>
</tbody>
</table>

Non-measurements = 101 (Ability: 56, Doppler: 30, Both: 17) |
Non-measurements = 1 (Ability: 1, Doppler: 0, Both: 0) |
Non-measurements = 1 (Ability: 1, Doppler: 0, Both: 0) |

Remaining Total: 784 – (56+30+17) = 681 |
Remaining Total: 24 – 1 = 23 |
Remaining Total: 24 – 1 = 23 |

Total: 727 ABI measurements for comparison

| Table 5.1: Reasons for non-measurements of ABIs |

<table>
<thead>
<tr>
<th>PIPETTE study</th>
<th>IVAM study</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhD Investigator (Doppler) (n=784)</td>
<td>PhD Investigator (Doppler) (n=24)</td>
</tr>
<tr>
<td>Automated ABI device (n=784)</td>
<td>Consultant (Doppler) (n=24)</td>
</tr>
<tr>
<td>Automated ABI device (n=24)</td>
<td></td>
</tr>
<tr>
<td><strong>Total Non-measurements:</strong></td>
<td><strong>Failed Measurements:</strong></td>
</tr>
<tr>
<td>47</td>
<td>0</td>
</tr>
<tr>
<td>73</td>
<td>0</td>
</tr>
</tbody>
</table>
5.3 Study Equipment

The automated device (AD) used within the PIPETTE and IVAM studies was a dopplex® Ability (DA100PB) (Huntleigh Healthcare, Cardiff, UK). This device utilises pneumoplethysmography to automatically measure and calculate the ABI. It also provides a recording of pulse volume waveforms (PVW) for each leg which can be qualitatively interpreted to aid in the diagnosis of PAD. The same dopplex® Ability unit was used throughout the PIPETTE and IVAM studies. However, as a result of ongoing product development by Huntleigh Healthcare, there were several updates of the Ability software during the study period.

The same set of equipment was utilised by both JD and KC for the Doppler ABI measurements for each PIPETTE and IVAM participant; namely, an aneroid sphygmomanometer (Welch Allyn Inc, NY, USA) in combination with a hand-held Doppler device (Doppler MD2, 8MHz probe, Huntleigh Healthcare, Cardiff, UK).

All study measurements were timed using a Casio HS-80TW-1EF handheld stopwatch. Equipment used in study measurements was new at the project outset and was calibrated and maintained in accordance with the manufacturer’s guidelines, to ensure accuracy of results.

5.4 Study Procedures

In both the PIPETTE and IVAM studies the AD measurement was always undertaken first for convenience purposes as this method does not require a rest period prior to the procedure.

5.4.1 Procedure for ABI measurement using the automated ABI device

The procedure for ABI measurement using the AD is detailed in Figure 5.2. In the event of a failed measurement, the procedure was repeated if this was acceptable to the participant and if time schedule of the PhD investigator permitted.

The dopplex® Ability unit was connected to a laptop which recorded all data for future analysis. Plots of occlusion and detection pressures versus time, which map the deflation of the cuffs and detection of the arterial pulse, can be viewed for each limb; from these it is possible to see how the systolic pressures were determined (Section 11.1).
• The participant was asked to lie supine, with their head and heels supported, on an examination couch. They were advised to remain still and refrain from talking during the measurements.

• In order to time the procedure, a stop-watch was started as the PhD researcher (JD) started to apply blood pressure cuffs.

• The dual chamber cuffs were applied to each of the participant’s limbs according to the manufacturer’s guidelines (Section 11.1).

• The unit start button was pressed and the measurement of the limb systolic pressures commenced. The device then automatically measured and calculated the participant’s ABIs.

• An audible alarm from the automated device signified the end of the test, the stopwatch was then stopped and the test time recorded by the investigator on the CRF.

• The ABI of both legs was displayed on the screen of the automated device. In the IVAM study this was obscured from the view of the investigator (JD) in order to achieve blinding (as this may have influenced the result when she subsequently measured the ABI using the hand-held Doppler). The result was printed out and placed in a sealed envelope within the CRF by an outpatient clinic nurse. It was not possible to achieve this blinding in the PIPETTE study as JD worked as a lone investigator.

Figure 5.2: Procedure for ABI measurement using the automated ABI device

• The participant was rested in the supine position, head and heels supported, on an examination couch if the measurements were undertaken in Morlais Medical practice or an outpatient clinic. If the measurements were undertaken in the participant’s own home, they were asked to lie either on a bed or the floor if this was acceptable to them. The rest period was 10 minutes.

• The participant was advised to remain still and refrain from talking during the measurement.

• In order to time the procedure, a stop-watch was started as the investigator started to apply the blood pressure cuff to the first limb.

• The size of the participant’s limb was assessed and an appropriately sized cuff fitted to the sphygmomanometer (the width of the cuff contoured at least 40% of the limb circumference).

• The cuff was first applied to the participant’s right upper arm and inflated to suprasystolic pressure. While the pressure was slowly released, the blood flow over the brachial artery was assessed using a Huntleigh hand held pocket Doppler device (Doppler MD2, 8 MHz) and a standard ultrasound gel as an ultrasound couplant. The first pulse sound audible through the Doppler device as the cuff is deflated was recorded as the systolic blood pressure for the artery being assessed.

• This process was repeated for the other limb arteries in the following specified order: right dorsalis pedis artery, right posterior tibial artery, left dorsalis pedis artery, left posterior tibial artery and finally left brachial artery.

• Systolic pressures were recorded on the appropriate CRF/results sheet and the participant’s ABIs were calculated for each leg by dividing the higher ankle pressure by the higher brachial pressure. ABI’s were recorded to two decimal places.

• On completion of the ABI calculation, the stopwatch was ceased and the time recorded on the CRF/results sheet by the investigator.

• In the IVAM study, the investigator placed the results sheet in a sealed envelope within the CRF to achieve blinding of the next investigator to undertake a Doppler measurement.

• The investigator was asked to record any comments regarding the procedure on the results sheet or CRF (e.g. if they found it difficult to detect a signal for a particular artery).

Figure 5.3: Procedure for ABI measurement using the hand-held continuous wave Doppler ultrasound (Aboyans et al., 2012)
5.4.2 **Procedure for ABI measurement using the hand-held, continuous wave Doppler ultrasound.**

Both JD and KC followed a set procedure for ABI measurement using the Doppler ultrasound as set out in the American Heart Association’s scientific statement for ABI measurement (Aboyans et al., 2012) (Figure 5.3).

5.4.3 **DUAL study population demographics**

The total study population consisted of 380 participants with a mean age of 64 years (range: 36-87); 57% of the population were male (n=215).

5.5 **The DUAL study: key results and conclusions**

Extensive consideration of the results and conclusions from the DUAL study is detailed in part 4 of this thesis. A summary of key results and conclusions is presented below:

- The automated device showed good agreement with Doppler as evidenced by Cohen’s k=0.61 (95% CI, 0.54 to 0.6, p<0.01) (Chapter 12).
- Automated device sensitivity to detect PAD according to Doppler ABI was 76%, specificity was 95%, negative predictive value was 97%, positive predictive value was 54% and accuracy was 94% (Chapter 12).
- The failed measurement rate of the automated device was 5.3%. The primary identifiable reason for measurement failure related to high ankle systolic pressures not being displayed by the automated device (Chapter 12).
- Analysis of the detection and occlusion plots provided by the automated device suggested possible Doppler measurement error in 34% of measurements where there was a difference of >0.15 between the two measurement techniques. It was subsequently concluded that Doppler ABI may not be the most appropriate reference standard for use in such comparative studies (Chapter 12).
- Both measurement techniques were largely acceptable to those undergoing the tests. Overall, participants preferred the Doppler ABI measurements over the automated device ABI measurements and this appeared to be associated with the perceived comfort and operator control of the procedure (Chapter 13).

Continued on p. 87
• The total time taken to undertake ABI measurement was significantly less for the automated device than the Doppler (7:55 vs. 17:45 mins:secs respectively, p<0.01) and was attributed to Doppler ABI measurements requiring a 10 minute rest period prior to the test procedure (Chapter 13).

• A further advantage of the automated device was noted to be its inclusion of a secondary method of PAD assessment in the form of pulse volume waveform analysis. Four additional cases of likely PAD were identified amongst participants who were found to have normal or high ABIs using this modality; hence highlighting one of the major recognised limitations of the ABI as a diagnostic marker (Chapter 15). Pulse volume waveform analysis was subsequently highlighted as an important area for future research.

• Overall, it was concluded that the automated device appears to represent an improvement on currently available oscillometric automated ABI devices, as evidenced by considerably lower measurement failure rates. Advantages of the device included its inclusion of a secondary method of PAD assessment (PVW analysis) and significantly reduced total test times which increase the feasibility of routine PAD assessment and ABI measurement in the primary care environment. However, it was also concluded that the device currently lacks sufficient positive predictive value to be used as a standalone PAD screening device. Areas for improvement of the device were identified (Chapter 12).
Chapter 6: General Practice Survey

Survey of the current utility of the ankle-brachial index (ABI) within general practices within Wales

6.1 Aims and Objectives

This survey aimed to determine the current utility of ABI measurement in general practices across Wales, including:

1. the occupations of those who perform ABI measurement;
2. frequency of ABI measurement;
3. reasons for ABI measurement;
4. methodology utilised for ABI measurement;
5. prior training for ABI measurement; and
6. subsequent management of patients found to have PAD.

6.2 Method

A self-reporting questionnaire (Appendix 13) was distributed via seven health boards, to all general practices within Wales (n=478); branch practices were not included as staff may work at both main and branch practices which may have resulted in duplication of results. Questionnaires were sent to practice managers and an accompanying letter requested that the survey be passed on to an appropriate person for completion.

6.3 Study Personnel

Study personnel consisted of three members:

Jane Davies (JD), as the PhD researcher, was responsible for project conception and the subsequent questionnaire design and pilot process. JD (with the assistance of JK) was also responsible for obtaining permission from each of the seven Welsh health boards to distribute the questionnaire. JD distributed all questionnaires, coded responses where necessary, and collated results.

Dr Mark Williams (MW) of the University of South Wales was the study lead (and PhD Director of Studies for Jane Davies). MW was responsible for overseeing the design of the questionnaire as well as facilitation and coordination of the study; this included activities such as timeline management and ensuring adherence to governance issues.
Professor Joyce Kenkre (JK) of the University of South Wales (and PhD Supervisor for JD) also oversaw the study and assisted in obtaining permission from Health Boards to distribute the questionnaire.

6.4 Questionnaire design

Guidelines for the measurement and calculation of the ABI are available from multiple sources (Table 6.1). Whilst some are more explicit than others, they all broadly advocate the same methodology. The questionnaire was designed to assess six fundamental points of the guidelines advocated ABI method (detailed in Table 6.2, along with their associated rationales). It is acknowledged that measurement of the ABI includes more complex components such as the choice of Doppler probe frequency and angulation of Doppler probes to achieve good signals; however, the aim of the survey was to determine if the fundamental underpinnings of correct ABI measurement exist.

As general practice survey response rates are often low (Bonevski et al., 2011), several strategies were employed in an attempt to address this issue: the questionnaire was designed to be minimally time consuming with predominantly close-ended, tick-box questions, with a pre-paid return envelope included. Returned questionnaires were entered into a prize draw (a £50 gift voucher for each health board).

JD pre-piloted the questionnaire by asking previous colleagues (a vascular consultant, district nurse and podiatrist) with varying experience of ABI measurement, to complete it and provide feedback regarding its content, layout, language etc. The questionnaire was also piloted at a local general practice by interviewing a practice nurse and general practitioner a few days after they had completed the questionnaire. The purpose of this was two-fold; firstly to determine the face validity of the questionnaire by assessing if their verbal responses corresponded with their written responses. Secondly, to determine the acceptability of the questionnaire in terms of how they perceived it and how long it took to complete it etc. Furthermore, the questionnaire was sent out to one health board at a time and responses were reviewed to identify any problems or issues prior to sending out to the next health board. None of these processes identified any issues which required modification of the questionnaire.
<table>
<thead>
<tr>
<th>Rest Period</th>
<th>Equipment for measurement of brachial systolic pressure</th>
<th>Number of brachial pulses to be assessed</th>
<th>Equipment for measurement of ankle systolic pressure</th>
<th>Ankle pulses which should be assessed</th>
<th>Method of Calculation of the ABI</th>
</tr>
</thead>
<tbody>
<tr>
<td>American College of Cardiology/American Heart Association (ACC/AHA) (Rooke et al., 2011)</td>
<td>Rest supine for 10 minutes</td>
<td>Handheld Doppler ultrasound device &amp; sphygmomanometer</td>
<td>2</td>
<td>Handheld Doppler ultrasound device &amp; sphygmomanometer</td>
<td>Dorsalis Pedis artery and Posterior Tibial artery</td>
</tr>
<tr>
<td>Scottish Intercollegiate Guidelines Network (SIGN) 2006</td>
<td>Not mentioned</td>
<td>Handheld Doppler ultrasound device &amp; sphygmomanometer</td>
<td>2</td>
<td>Handheld Doppler ultrasound device &amp; sphygmomanometer</td>
<td>Dorsalis Pedis artery/ Anterior Tibial artery &amp; Posterior Tibial artery. If these cannot be located, assess the Peroneal Artery</td>
</tr>
<tr>
<td>Trans-Atlantic Intersociety Consensus (TASC) (Norgren et al., 2007)</td>
<td>Not mentioned</td>
<td>Doppler Instrument &amp; sphygmomanometer</td>
<td>2</td>
<td>Doppler Instrument &amp; sphygmomanometer</td>
<td>Dorsalis Pedis artery &amp; Posterior Tibial artery.</td>
</tr>
<tr>
<td>Society for Vascular Technology of Great Britain and Ireland (SVT) 2010</td>
<td>Rest supine for 5-10 minutes prior to procedure</td>
<td>Handheld continuous wave Doppler ultrasound device &amp; sphygmomanometer</td>
<td>2</td>
<td>Handheld continuous wave Doppler ultrasound device &amp; sphygmomanometer</td>
<td>Dorsalis Pedis artery &amp; Posterior Tibial artery.</td>
</tr>
<tr>
<td>European Society of Cardiology (ESC) (Tendera et al., 2011)</td>
<td>Not mentioned</td>
<td>Handheld Doppler ultrasound device &amp; sphygmomanometer</td>
<td>2</td>
<td>Handheld Doppler ultrasound device &amp; sphygmomanometer</td>
<td>Posterior Tibial artery &amp; Anterior Tibial artery.</td>
</tr>
<tr>
<td>National Institute for Health and Care Excellence (NICE) 2012a</td>
<td>Rest supine when possible. Rest period should be “long enough for blood pressure to return to normal”</td>
<td>Handheld Doppler ultrasound device &amp; sphygmomanometer</td>
<td>2</td>
<td>Handheld Doppler ultrasound device &amp; sphygmomanometer</td>
<td>Three arteries, one of which must be the Peroneal artery as this &quot;may be the only one present in some people, particularly those with diabetes&quot;.</td>
</tr>
<tr>
<td>American Heart Association (AHA) – scientific statement (Aboyans et al., 2012)</td>
<td>Rest 5-10 minutes in supine position</td>
<td>Handheld Doppler ultrasound device &amp; sphygmomanometer</td>
<td>2</td>
<td>Handheld Doppler ultrasound device &amp; sphygmomanometer</td>
<td>Dorsalis Pedis artery &amp; Posterior Tibial artery.</td>
</tr>
</tbody>
</table>

Table 6.1: Summary of guidelines for the measurement of the Ankle Brachial Index
<table>
<thead>
<tr>
<th>Aspect of ABI measurement assessed</th>
<th>Recommended by</th>
<th>Rationale</th>
</tr>
</thead>
</table>
| 1. Patient rested in supine position for at least 10 minutes prior to ABI measurement? | SVT (2010)  
NICE (2012)  
AHA (2012) | • ABI averages 0.35 higher in the seated position as opposed to supine (Aboyans et al., 2012)  
• There is no evidence to recommend a minimum period but it should be long enough for blood pressure to return to normal (NICE, 2012). The effect of the duration of the rest period on the reliability of the ABI measurement is unknown, with most studies using 5-10 minutes (NICE, 2012). |
| 2. Equipment needed to measure the brachial systolic blood pressure correctly identified as being a Doppler Ultrasound and sphygmomanometer | All guidelines  
ACC/AHA (2005)  
SIGN (2006)  
TASC (2007)  
SVT (2010)  
ESC (2011)  
NICE (2012)  
AHA (2012) | • Using the Korotkoff method to measure the brachial pressure has been shown to yield lower values compared to Doppler (Ieliani et al., 2000).  
• Similarly, automated oscillometric blood pressure devices have been shown to underestimate brachial pressure (Heinemann et al., 2008; Landgraf et al., 2010).  
• As the brachial pressure forms the denominator of the ABI, underestimation will result in falsely elevated ABIs. |
| 3. Brachial systolic pressure measured in both arms | All guidelines  
ACC/AHA (2005)  
SIGN (2006)  
TASC (2007)  
SVT (2010)  
ESC (2011)  
NICE (2012)  
AHA (2012) | • A pressure difference between left and right brachial arteries of at least 20mmHg is present in 3.5% of normal healthy population (Smith et al., 2009).  
• A recent meta-analysis found that a difference of 15mmHg or more is actually associated with 2.3 times increased risk of PAD (Clark et al., 2012).  
• It is therefore paramount that both brachial pressures are measured to prevent missed diagnoses and/or in correct classification of PAD. |
| 4. Equipment needed to measure the ankle systolic blood pressure correctly identified as being a Doppler Ultrasound and sphygmomanometer | All guidelines  
ACC/AHA (2005)  
SIGN (2006)  
TASC (2007)  
SVT (2010)  
ESC (2011)  
NICE (2012)  
AHA (2012) | • Oscillometric devices have been found to overestimate ankle systolic pressure (Korme et al., 2009) resulting in falsely elevated ABIs and reduced sensitivity for detecting PAD (Nelson et al., 2012; Sinsky et al., 2013; Takahashi et al., 2013).  
• Most oscillometric devices are unable to detect low pressures (<50mmHg) and hence recording failures are frequent in cases of moderate to severe PAD (Aboyans et al., 2012). |
| 5. More than one pulse assessed at each ankle/foot | All guidelines  
ACC/AHA (2005)  
SIGN (2006)  
TASC (2007)  
SVT (2010)  
ESC (2011)  
NICE (2012)  
AHA (2012) | • Guidelines differ with regard to which of the three ankle arteries should be assessed, although they all agree that it should be more than one.  
• NICE guidance specifies that the arteries assessed should always include the peroneal artery as this may be the only one present in some people, particularly those who are diabetics (NICE, 2012). |
| 6. ABI calculated by dividing the higher of the ankle systolic blood pressures by the higher of the brachial systolic blood pressures | All guidelines  
ACC/AHA (2005)  
SIGN (2006)  
TASC (2007)  
SVT (2010)  
ESC (2011)  
NICE (2012)  
AHA (2012) | • Although several authors have argued that utilising the lower ankle systolic pressure as the numerator in the ABI would result in greater sensitivity for the identification of early PAD (Espinola-Klein et al., 2008; Allison et al., 2010), others have argued that the higher pressure should be used to prevent over diagnosis in healthy subjects (Aboyans et al., 2012).  
• Others contend that standardisation of the calculation is the important issue, because this would optimize accuracy and consistency of results universally while ensuring PAD diagnoses are based on the same parameters (Bhatt et al., 2006; Al-Qasri et al., 2009). |

Table 6.2: Aspects of ABI measurement assessed by general practice survey.
6.5 Ethical Approval

This study did not require NHS research ethical committee approval (according to the UK Health Research Authority guidance, (Medical Research Council, 2013). However, approval to distribute the questionnaire was obtained from the research and development department of each of the seven health boards. Completion of the survey constituted consent.

6.6 Data Analysis

The majority of questions within the survey required tick box answers which were pre-coded; these categorical data were subsequently entered into a statistical software package (IBM SPSS statistics, version 21, New York, USA) for analysis. Questions 3, 10, 11b and 14 were open-ended and required post-hoc analysis to identify response themes; these were subsequently also coded into categories for data analysis.

As all data were categorical, Pearson’s chi square ($\chi^2$) tests were used to evaluate how likely it was that any observed difference between the variables arose by chance. In each case the null hypothesis was that there was no association between the variables. Two sided P<0.05 was regarded as significant. Standard residuals were inspected to provide further information as to where and to what extent associations were detected. Due to the small sample sizes of some groups of data, the expected count of several cells was less than five; this is insufficient to perform a Pearson’s chi square test (Ludbrook, 2008), hence in these cases Fisher’s Exact test was used as recommended by Agresti (1992).

6.7 General Practice Survey: key results and conclusions

Extensive consideration of the results and conclusions from the general practice survey is detailed in part 3 of this thesis. A summary of key results and conclusions is presented below:

- The survey response rate was low at 20%; this constitutes a major limitation of the survey which limits the generalisation and strength of results.
- Survey responses indicated that ABI measurement is primarily performed by nurses (93%) within general practice setting.
- The primary reason for ABI measurement relates to wound management (90%).
- ABI measurement is used infrequently (73% < 4 times per month) and often incorrectly (42% out of compliance with current ABI guidance).

Continued on p. 93
• Only 52% of general practitioners and 16% of nurses reported that patients with an ABI ≤ 0.9 require aggressive cardiovascular disease risk factor modification (as recommended by current national and international guidelines).

• It was concluded that ABI measurement is an under-utilised and often incorrectly performed procedure in the surveyed general practices. Prior to its potential adoption as a formalised screening tool for cardiovascular disease, there is a need for a robust training programme with standardised methodology in order to optimise accuracy and consistency of results. The significance of a diagnosis of PAD, in terms of associated increased cardiovascular risk and the necessary risk factor modification, needs to be highlighted.
Part 3 : WHO?

Who should potential PAD screening strategies target?

Who should undertake any potential PAD screening strategies?
Part 3: Prelude

The literature review identified that there is no absolute consensus as to who PAD screening should target. Furthermore, there is limited current epidemiological PAD data specific to the UK on which to base this decision. The first aim of part 3 of this thesis is therefore to add to the current PAD evidence base with regard to these issues; this is considered in Chapters 7-9.

Chapter 7 details results from the IVAM study which demonstrate how the PhD researcher compared to an expert in the procedure of ABI measurement; this then serves to validate ABI results undertaken within the PIPETTE study (subsequently discussed in Chapters 8 & 9).

Chapters 8 & 9 detail epidemiological data and results originating from Phase 1 of the PIPETTE study in order to consider how a potential PAD screening strategy should be targeted.

As discussed in section 2.4.3, cardiovascular risk has been shown to be associated with both low and high ABI, hence it is useful to consider the PIPETTE study population across the ABI spectrum. On this basis, for the purpose of the subsequent results analysis, PIPETTE participants were categorised into one of four PAD status groups according to their Doppler ABI results:

(i) PAD – participants were placed in this group if the ABI of one or both of their legs was ≤0.9; this is based on previous studies having demonstrated that an ABI≤0.9 is up to 95% sensitive and 99% specific for angiographically diagnosed PAD (Fowkes, 1988).

(ii) Borderline PAD – participants were placed in this group if the ABIs of both of their legs fell within the range of >0.9 to <1.0. This group is termed “borderline PAD” as individuals without lower extremity atherosclerosis should have an ABI>1.0 (Fung, 1984).

(iii) Normal ABI – participants were placed in this group if the ABIs of both legs fell within the range ≥1.0 to <1.3; current literature widely quotes this range as being normal.

(iv) High ABI – participants were placed in this group if the ABI of one or both of their legs was ≥1.3. Although the optimal upper limit of normal ABI is unknown (McDermott et al., 2005), this is the high-end cut-off point recommended by the American College of Cardiology/American Heart Association (Rooke et al., 2011).

Chapter 8 details low ABI results (the PAD and borderline PAD groups) and chapter 9 details high ABI results.

A secondary aim of part 3 of this thesis is to consider who, from the UK healthcare system, should be responsible for PAD screening. The literature review suggests that a specialist secondary care screening programme, such as the recently instigated AAA (abdominal aortic aneurysm) screening (UK National screening committee, 2013), is not required. Rather, it is the apparent simplicity of the PAD screening process, which appears to be amenable for use by
generic health professionals, which underpins the argument in support of screening for this disease. Numerous authors have alluded to PAD screening being undertaken in an office setting, perhaps as part of a generalised CV risk assessment. Few studies however, have examined the feasibility of this; hence the final chapter (10) of part 3 of this thesis details the results of a general practice survey which explored the current utility of the ABI in general practices across Wales and considers if the requisite skills and knowledge for PAD screening exist within the primary care setting.
Chapter 7: Validation of ABI measurements undertaken within this research project; results from the IVAM study

7.0 Assessment of agreement of ABI results between the expert and the PhD researcher

Agreement of ABI results between the expert and the PhD researcher was assessed via three statistical methodologies: Bland-Altman plot, calculation of inter-observer variability, and calculation of Cohen’s kappa.

7.0.1 Bland-Altman Plot

The Bland-Altman plot (Bland and Altman, 1986) is considered by many to be the recognised statistical methodology for studies evaluating either new measuring tools or measurement personnel, against a reference technique or measurer (Zaki et al., 2013). For each subject, the difference between the ABIs, as measured by the two observers, is plotted against the mean of the two ABIs. Bland Altman plots therefore graphically represent data, and also provide a number of objective measures (the bias, standard deviation and 95% limits of agreement) of how well the observers agreed with each other. The ABI results of the expert and PhD researcher are presented as a Bland-Altman plot in Figure 7.1 and equality plot in Figure 7.2. The PhD researcher slightly underestimated ABIs in comparison to the expert as illustrated by a positive bias of 0.02. The 95% limits of agreement between the two observers were ±0.15.
Figure 7.1: Agreement between expert and PhD researcher.
- mean difference or bias
- 95% confidence limit (±1.96*SD)

Figure 7.2: Equality plot of expert and PhD researcher
- Regression line, ---- 95% CI, ------ line of equality
7.0.2 Inter-observer variability

Inter-observer variability (IOV) is the most commonly reported method of assessing agreement between observers measuring ABIs. The IOV between the expert and PhD researcher was 8%; variability was higher for diseased participants (11%) than non-diseased participants (6%).

7.0.3 Cohen's Kappa

Each limb assessed within the study was classified as either having PAD (ABI ≤ 0.9) or not having PAD (ABI > 0.9). According to Cohen's κ there was very good classification agreement between the expert and PhD researcher, κ = 0.84 (95% CI, 0.8 to 0.87), *p* < 0.01.

7.1 Discussion

Table 7.1 summarises studies which have investigated variability of ABI measurements (undertaken with a hand-held Doppler device) and reported results in terms of inter-observer variability (IOVs).

<table>
<thead>
<tr>
<th>Authors, Date of Publication</th>
<th>Subjects</th>
<th>Observers</th>
<th>Inter-observer variability</th>
<th>Study Strengths/limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fowkes et al., 1988</td>
<td>Individuals with symptomatic PAD (n=24 limbs)</td>
<td>Vascular laboratory technicians versus vascular laboratory technicians (n=4)</td>
<td>16%</td>
<td>Included only diseased subjects</td>
</tr>
<tr>
<td>Kaiser et al., 1999</td>
<td>Individuals with ABI &lt;0.95 or intermittent claudication (n=6 participants)</td>
<td>GPs versus Vascular laboratory assistants</td>
<td>Most experienced: 10% Least experienced: 13.8%</td>
<td>Small subject sample size. Included only diseased subjects.</td>
</tr>
<tr>
<td>Holland-Letz et al., 2007</td>
<td>Individuals aged &gt;65 (n=144 limbs)</td>
<td>Family Physician or nurse (n=2) versus Vascular experts (n=2)</td>
<td>9%</td>
<td>Large sample size. Largely non-diseased sample group (only 2 individuals had an ABI &lt;0.9)</td>
</tr>
<tr>
<td>Van Langen et al., 2009</td>
<td>Individuals with intermittent claudication (n=40 participants)</td>
<td>Vascular technicians versus vascular technicians (n=2)</td>
<td>10%</td>
<td>Only included diseased subjects.</td>
</tr>
</tbody>
</table>

Table 7.1: Summary of studies of ABI inter-observer variability
Several factors such as differing sample sizes, differing subject and observer groups, and variation in statistical approaches require consideration when comparing attained results from the IVAM study with existing published studies.

It can be seen that the IOVs of ABI measurement are in the range of 9-16% in both hospital and community settings. According to Nicolai et al. (2009), an IOV of ≤10 -15% is regarded as acceptable for clinical tests. The overall inter-observer variability between the PhD researcher and the expert within the IVAM study is marginally lower than any of the previously reported results (8%); however, no other studies had a similar sample group in terms of almost equal representation of diseased and non-diseased participants. Holland-Letz et al. (2007) reported the lowest level of variation between observers but their participants were largely healthy in terms of their ABI. This is important because variability has been reported to be higher, at least slightly, in diseased participants than normal participants (Fowkes, 1988); this was indeed also found to be the case in this study. Presumably, this can be attributed to difficulties in detecting arterial blood flow in those with PAD. The IOV of highly experienced observers or ‘experts’ when measuring the ABIs of diseased participants was found to be 10% by both Kaiser et al. (1999) and van Langen et al. (2009). In the IVAM study, the IOV between the PhD researcher and the expert when examining diseased participants narrowly exceeded this value at 11%; however, this demonstrates a similar level of agreement as to that attained between ‘experts’.

Endres et al. (2006) assessed the reliability of ABI measurement between 6 angiologists and 6 family physicians in 108 subjects aged 65-70, 8% of which had PAD. They presented their results as Bland Altman plots and reported 95% limits of agreement as ±0.23. In the IVAM study the limits of agreement between the PhD researcher and Consultant were narrower at ±0.15 hence indicating a higher level of agreement.

7.2 Study Limitations
The IVAM study has obvious limitations in terms of its small sample size and limited number of observers; such shortcomings can be attributed to time and resource restrictions which are frequently associated with PhD projects. No attempt was made to validate the ABI measurements of the Consultant by, for example, comparing his ABI results to arterial Duplex scans and angiography. A further limitation relates to the fact that there is likely to be a degree of error that is inherent in the ABI measurement procedure regardless of who performs it. It is not possible to determine either
the extent of this error or a categorically ‘correct’ ABI; this of course, should be borne in mind when considering results.

7.3 Conclusions
The statistical methodologies used to assess results from the IVAM study have consistently demonstrated a high level of correlation/agreement between ABI measurements undertaken by the expert and those undertaken by the PhD researcher. This level of agreement has been shown to be comparable with previously reported agreement levels between other ‘experts’ in the procedure. Hence it can be concluded that the PhD researcher measures the ABI using a handheld Doppler ultrasound with the same level of accuracy and precision as someone who is considered to be an expert in the procedure. This then serves to validate the ABI measurements undertaken by the PhD researcher for the purpose of the PIPETTE and DUAL studies which are discussed in Chapters 8 and 12 respectively.

7.4 Future research
A further important outcome of the IVAM study is that it has also served as a pilot for a future study aimed at investigating the accuracy of ABI measurement within primary care. If routine primary care screening for PAD, for the purpose of cardiovascular risk assessment, was to become a reality, this could result in patients being prescribed various secondary preventive medications, such as aspirin or statins, on the basis of ABI results. It would therefore be paramount that ABI measurement was being undertaken consistently, and to a high degree of accuracy within this setting. To date, relatively few studies have examined these issues and those which have been completed were mostly undertaken in the Netherlands or Germany; factors such as variation in training mean that these results may not be applicable to the UK and other countries. Furthermore, results have been inconsistent with some studies claiming that measurements by GPs and primary care nurses are highly reproducible, whilst others have suggested that ABI reproducibility depends on the experience and training of the observer.
Future research should therefore focus on accuracy of ABI measurement in the primary care setting; it should involve investigation of inter-observer variability of Doppler ABI measurements between vascular experts in secondary care and members of a primary care team. It is envisaged such research should entail a direct comparison of at least six primary care professionals (two GPs, two practice nurses, two district nurses) with six secondary care professionals (vascular Consultant, vascular registrar, two vascular laboratory technicians and two vascular clinical nurse specialists).
This study design would serve not only to inform how primary care staff compare to the secondary care experts but will also provide information regarding intra-group comparisons (e.g. how vascular consultants compare to vascular technicians).

As the dopplex® Ability has been shown to be a potential accurate alternative to traditional ABI measurement with a Doppler (Chapter 12), it should also be included in future comparative ABI studies. Cuff application and operation of the Ability should be undertaken by different observers in order to assess if this affects variability rates.

The IVAM study has served to highlight several methodological issues which require consideration in future research. For example, it has demonstrated that variability is greater in diseased participants hence underlining the need for future samples to contain both diseased (known PAD) and normal participants; this would also ensure a sample which is representative of patients encountered in primary care. The IVAM study has also demonstrated that factors such as time pressures and staff availability meant that incorporating even a very simplistic study into the everyday running of an outpatient clinic was problematic. This inevitably means that a larger, more complex study would need to be undertaken in research setting which may then make it more difficult to recruit participants and ensure the participation of health professionals as observers.
WHO SHOULD A POTENTIAL SCREENING STRATEGY FOR PAD TARGET?

Chapter 8: PIPETTE Phase 1, Low ABI Results

8.0 The PAD group

8.0.1 PIPETTE: PAD prevalence

The prevalence of PAD, as defined by an ABI≤0.9, within the PIPETTE study was 3.3%. Figure 8.1 illustrates the prevalence of PAD per age group according to gender. Although prevalence did not differ significantly according to gender (male prevalence = 3.5%, female prevalence = 3%; p=0.115), it can be seen that prevalence rates generally increased with age, particularly for females (Figure 8.1). It should be noted that there is no prevalence rate for men aged 85+ as the study did not enrol anyone within this group. Similarly, the study recruited women over the age of 55, so there is no female data for the 45-54 age category. Notably, male prevalence rates are higher than female rates for lower age groups, but the opposite is true for higher age groups (Table 8.4, p. 113)

![Figure 8.1: Gender-specific prevalence of PAD by age group. Blue = male, Red = female](image)

Blue = male, Red = female
8.0.2 Adjustment for recruitment bias

The PIPETTE study has been shown to have been subject to a recruitment bias (Section 3.7.2). Hence, the prevalence rate was adjusted to account for this; the calculations are shown below:

Firstly, the confidence intervals of the observed number of PAD cases according to smoking status group were calculated (Table 8.1).

<table>
<thead>
<tr>
<th></th>
<th>Lower CI of observed figures</th>
<th>Observed figures</th>
<th>Upper CI of observed figures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ex-smokers</td>
<td>1.31</td>
<td>6</td>
<td>10.68</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>0</td>
<td>0</td>
<td>2.73</td>
</tr>
<tr>
<td>Smokers</td>
<td>1.55</td>
<td>6</td>
<td>10.44</td>
</tr>
<tr>
<td>Total</td>
<td>2.86</td>
<td>12</td>
<td>23.8</td>
</tr>
</tbody>
</table>

Table 8.1: Confidence Intervals of observed numbers of PAD cases

The representation factors of each of the smoking status groups were calculated: smokers were under-represented (6 cases), representation factor=1.75. Ex-smokers were over-represented (6 cases), representation factor=0.84. Non-smokers were slightly over-represented (0 cases), representation factor=0.94.

Confidence intervals were therefore multiplied by the representation factors (Table 8.2)

<table>
<thead>
<tr>
<th></th>
<th>Lower CI of adjusted figures</th>
<th>Adjusted figures</th>
<th>Upper CI of adjusted figures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ex</td>
<td>1.10</td>
<td>5.05</td>
<td>9.00</td>
</tr>
<tr>
<td>Non</td>
<td>0</td>
<td>0</td>
<td>2.58</td>
</tr>
<tr>
<td>Smokers</td>
<td>2.72</td>
<td>10.50</td>
<td>18.28</td>
</tr>
<tr>
<td>Total</td>
<td>3.83</td>
<td>15.56</td>
<td>29.86</td>
</tr>
</tbody>
</table>

Table 8.2: Confidence intervals of adjusted numbers of PAD cases.

According to these calculations, the adjusted number of PAD prevalence cases would be 16. This equates to a higher prevalence rate of 4.3% (95% CI: 1% to 8.1%).
8.0.3 Factors associated with PAD

Age and PAD status
The median age of study participants showed a gradual decline as the ABI increased across the PAD status groups (Figure 8.2)(Spearman’s rho: \( r_s = -0.153 \), \( p < 0.001 \)).

![Figure 8.2: Age according to PAD status](image)

Consideration of the PIPETTE population in terms of age groups (Figure 8.3) showed that the PAD group had more participants in both the 75-84 age group and the 85+ age group than predicted (Chi-square (\( \chi^2 \)) test: \( p < 0.05 \) and \( p < 0.001 \) respectively). Similarly the Borderline PAD group also had more participants in the 75-84 age group than expected (\( p < 0.05 \)).

Smoking Status and PAD Status
All PAD cases within the PIPETTE study were either current smokers or ex-smokers. The PAD group had statistically significantly less non-smokers (\( \chi^2: p < 0.05 \)) and more smokers (\( p < 0.01 \)) than predicted (Figure 8.4).
Figure 8.3: PIPETTE study participants by age group and PAD status
Red – age 45-54, Green – age 55-64, Yellow – age 65-74, Blue – age 75-84, Pink – age 85+

Figure 8.4: PIPETTE study participants by smoking status and PAD status
Blue – smokers, Red – ex-smokers, Green – non-smokers
Pulse pressure and PAD status

Pulse pressure is defined as the difference between systolic arterial blood pressure and diastolic arterial blood pressure. Figure 8.5 shows a reduction in median pulse pressure as the ABI increased across the continuum of PAD status groups (Spearman’s rho: $r_s = -0.403$, $p = 0.002$) and between groups (Kruskal-Wallis test: $p = 0.005$).

![Figure 8.5: Pulse pressure according to PAD status](image)

 Pulse pressure was significantly higher in the PAD group than in the Normal ABI group ($p=0.045$) and the High ABI group ($p=0.02$) (Dunn’s (1964) procedure with a Bonferroni correction for multiple comparisons).

Total number of cardiovascular risk factors and PAD status

The number of CV risk factors was different between PAD status groups (Kruskal-Wallis test: $p = 0.018$); all participants within the PAD group had at least four CV risk factors (Figure 8.6).
The number of CV risk factors was significantly higher for the PAD group than the Borderline PAD group (p = 0.01), the Normal ABI group (p = 0.002) and the High ABI group (p = 0.005) (Dunn’s (1964) procedure with a Bonferroni correction for multiple comparisons).

Rheumatoid Arthritis and PAD status

There were statistically significantly more participants with rheumatoid arthritis (RA) in the PAD status group than predicted (Chi-square ($\chi^2$) test: p < 0.01) (Figure 8.7).
Edinburgh Claudication Questionnaire (ECQ)

A positive ECQ result was significantly associated with the PAD group (Chi-square ($\chi^2$) test: $p < 0.01$) (Figure 8.8).

![Edinburgh Claudication Questionnaire results according to PAD status group](image)

**Figure 8.8: Edinburgh Claudication Questionnaire results according to PAD status group**
Red – positive ECQ result, Blue – negative ECQ result

Clinical Signs of PAD

The PAD group exhibited, on average, two clinical signs of PAD; all other PAD status groups did not, on average, exhibit any clinical signs of PAD (Kruskal-Wallis test: $p < 0.001$) (Table 8.4).

8.0.4 Logistic Regression

In view of the aforementioned results, a logistic regression was performed to further ascertain the effects of age, current smoking status, pulse pressure, positive ECQ result, clinical signs of PAD and the presence of RA on the likelihood that participants have PAD. The logistic regression model was statistically significant, $\chi^2(4) = 28.165$, $p<0.005$. The model explained 30% (Nagelkerke $R^2$) of the variance in PAD and correctly classified 97% of cases. Sensitivity, however, was low at 25%, although specificity was high at 99%. Of the six predictor variables, three were statistically significant: current smoking status, the presence of RA, and positive ECQ result (as shown in Table 8.3). In the PIPETTE study, smokers were almost 10 times more likely to exhibit PAD than non-smokers. Similarly, the
presence of RA was associated with 15 times increased risk of PAD, and a positive ECQ result was associated with a 14 times increased risk.

<table>
<thead>
<tr>
<th>Step 1a</th>
<th></th>
<th>B</th>
<th>S.E</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95% C.I. for EXP (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Smoking status</td>
<td>2.272</td>
<td>0.818</td>
<td>7.711</td>
<td>1</td>
<td>0.005</td>
<td>0.696</td>
<td>1.951</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.083</td>
<td>0.051</td>
<td>2.604</td>
<td>1</td>
<td>0.107</td>
<td>1.086</td>
<td>0.982</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid Arthritis</td>
<td>2.740</td>
<td>1.183</td>
<td>5.368</td>
<td>1</td>
<td>0.021</td>
<td>15.484</td>
<td>1.525</td>
</tr>
<tr>
<td></td>
<td>ECQ</td>
<td>2.665</td>
<td>1.007</td>
<td>7.003</td>
<td>1</td>
<td>0.008</td>
<td>14.371</td>
<td>1.996</td>
</tr>
<tr>
<td></td>
<td>Pulse Pressure</td>
<td>0.016</td>
<td>0.025</td>
<td>0.423</td>
<td>1</td>
<td>0.516</td>
<td>1.017</td>
<td>0.968</td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>-11.308</td>
<td>3.416</td>
<td>10.957</td>
<td>1</td>
<td>0.001</td>
<td>000</td>
<td></td>
</tr>
</tbody>
</table>

a. Variables entered on step 1: Smoking status, Age, RA, ECQ, Pulse Pressure

Table 8.3: Binary logistic regression results for the presence of PAD

8.0.5 QRISK®2

QRISK®2 score was statistically significantly different between the PAD status groups (p=0.001) (Figure 8.9).

![QRISK®2 score according to PAD status group](image)

The score of the PAD group was statistically significantly higher than in the Normal ABI group (Kruskal-Wallis test: p = 0.001) and also the High ABI group (Kruskal Wallis; p = 0.031).
Relative Risk according to QRISK®2 and PAD status

The QRISK®2 algorithm calculates an individual’s relative risk of having a cardiovascular event compared to an individual of the same age, sex and ethnicity. QRISK®2 relative risk was statistically significantly higher in the PAD group than in the Normal ABI group (Kruskal-Wallis: p = 0.014) (Figure 8.10).

Figure 8.10: QRISK®2 relative risk according to PAD status

Of the twelve participants with ABI≤0.9, eleven (92%) had a QRISK2 score of greater than 20, which at the time of the study was the recommended threshold for commencement of CV risk preventive strategies such as statins (NICE, 2012a) (Figure 8.11).

Figure 8.11: QRISK®2 scores of PAD participants.
8.0.6  **PAD prevalence according to Low ABI calculation**

As discussed in section 2.4.3, the standard recommended procedure for the calculation of the ABI is to divide the higher of the ankle systolic pressures by the higher of the brachial systolic pressures. A number of authors however, have called for the ABI to be calculated using the lower ankle systolic pressure for the purpose of CV risk assessment; this is then termed the Low ABI result.

Using the Low ABI results within the PIPETTE study, results in a PAD (ABI ≤0.9) prevalence of 10.8%. The majority of factors which were shown to be significantly associated with PAD using the standard ABI calculation (section 8.2) are also significantly associated with PAD using the low ABI calculation, namely: current smoking status, p<0.001; pulse pressure, p=0.42; rheumatoid arthritis, p=0.006, relative risk according to QRISK, p=0.044; positive ECQ result, p<0.001). The following factors were no longer significantly associated with PAD according to Low ABI: age, p=0.544; total number of CV risk factors, p=0.11; QRISK2 score, p=0.46). No additional factors were found to be associated with PAD according to the low ABI calculation.

8.1  **The Borderline PAD group**

8.1.1  **PIPETTE: Borderline PAD prevalence**

The prevalence of borderline PAD (ABI 0.91 – 0.99) was 5.3%. The female prevalence was 8% and the male prevalence was 3.5% (p=0.068).

8.1.2  **Factors associated with borderline PAD**

Statistical analysis revealed that only two factors were significantly associated with borderline PAD (Table 8.4). Firstly, the borderline PAD group had more participants in the age 75-84 group than predicted by a Chi square test (p<0.05). Secondly, the borderline PAD group had significantly less CV risk factors than the PAD group (p=0.01) (Figure 8.6).
Table 8.4: Analysis of PIPETTE data according to PAD status groups

Red text denotes statistically significant results

<table>
<thead>
<tr>
<th>Age</th>
<th>PAD (ABI&lt;0.9)</th>
<th>Borderline PAD (ABI=0.9, &lt;1.0)</th>
<th>Normal ABI (ABI=1.0, ≤1.3)</th>
<th>High ABI (ABI&gt;1.3)</th>
<th>All</th>
<th>Statistical Test Applied</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=12</td>
<td>n=20</td>
<td>n=306</td>
<td>n=30</td>
<td>n=368</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>70.3 ± 9.2</td>
<td>66.7 ± 8</td>
<td>63.4 ± 8.2</td>
<td>63.8 ± 8.4</td>
<td>63.8 ± 8.3</td>
<td>Kruskal-Wallis test</td>
<td>χ²(3) = 7.6, p=0.055</td>
<td>There is no statistically significant association between age and PAD status.</td>
</tr>
<tr>
<td></td>
<td>56-86</td>
<td>56-82</td>
<td>45-85</td>
<td>45-81</td>
<td>45-86</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group %</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
| 45 - 54 | 0% (0)        | 0% (0)                         | 12% (37)                    | 10% (3)           | 11% (40) | Chi-square (χ²)          | χ²(12) = 21.086, p=0.049 | There is a statistically significant association between age group and PAD status. Inspection of standardised residuals reveals:
|     | 33% (4)       | 45% (9)                        | 44% (135)                   | 47% (14)          | 44% (162) |                          |         |             |
| 65 - 74 | 33% (4)       | 30% (6)                        | 35% (106)                   | 33% (10)          | 34% (126) |                          |         |             |
| 75 - 84 | 25% (3)       | 25% (5)                        | 9% (26)                     | 10% (3)           | 10% (37)  |                          |         |             |
| ≥ 85  | 8% (1)        | 0% (0)                         | 1% (2)                      | 0% (0)            | 1% (3)    |                          |         |             |
| Gender (M:F) | 58:42         | 35:65                          | 54:46                       | 73:27             | 55:45    | Chi-square (χ²)          | χ²(3) = 7.471, p=0.058 | There is no statistically significant association between gender and PAD status |
| Ethnicity: | White/British | 100%                           | 100%                        | 100%              | 100%     | Not required              |         |             |
| Smoking Status: | Current smoker | 50% (6)                       | 15% (3)                     | 10% (32)          | 11% (43)  | Chi-square (χ²)          | χ²(6) = 27.13, p<0.001 | There is a statistically significant association between smoking status and PAD status. Inspection of standardised residuals reveals:
|     | Ex-smoker     | 50% (6)                        | 20% (4)                     | 36% (110)         | 36% (131) |                          |         |             |
|     | Non-smoker    | 0% (0)                         | 65% (13)                    | 54% (164)         | 53% (194) | Fisher's Exact Test (F)  | F=24.302, p=0.001. |                          |         |             |

1. There were less non-smokers than expected in the PAD group (SR: -2.5, p<0.05)
2. There were more smokers than expected in the PAD group (SR: 4.0, p<0.01)
<table>
<thead>
<tr>
<th></th>
<th>PAD (ABI&lt;0.9)</th>
<th>Borderline PAD (ABI=0.9, &lt;1.0)</th>
<th>Normal ABI (ABI=1.0, 1.3)</th>
<th>High ABI (ABI&gt;1.3)</th>
<th>All (n=368)</th>
<th>Statistical Test Applied</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol (Units/Week)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Kruskal-Wallis test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD Range</td>
<td>10 ± 11</td>
<td>4 ± 8</td>
<td>9 ± 15</td>
<td>9 ± 15</td>
<td>9 ± 15</td>
<td>$\chi^2(3) = 7.323$, p=0.062</td>
<td></td>
<td>There is no statistically significant association between weekly alcohol consumption pressure and PAD status.</td>
</tr>
<tr>
<td>Alcohol consumption in excess of recommended limits (according to Wales Centre for Health, 2009)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chi-square test (\chi^2)</td>
<td>$\chi^2(3) = 2.217$, p=0.56</td>
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<tr>
<td>Yes</td>
<td>27% (3)</td>
<td>10% (2)</td>
<td>16% (45)</td>
<td>21% (6)</td>
<td>16% (56)</td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>73% (8)</td>
<td>90% (18)</td>
<td>84% (244)</td>
<td>79% (22)</td>
<td>84% (292)</td>
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<tr>
<td>Family History of Premature CHD:</td>
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<td></td>
<td></td>
<td></td>
<td>Chi-square test (\chi^2)</td>
<td>$\chi^2(3) = 1.393$, p=0.714, F=1.327, p=0.737</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17% (2)</td>
<td>25% (5)</td>
<td>26% (79)</td>
<td>33% (10)</td>
<td>26% (96)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>83% (0)</td>
<td>75% (15)</td>
<td>74% (227)</td>
<td>67% (20)</td>
<td>74% (272)</td>
<td></td>
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</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>144 ± 10</td>
<td>147 ± 14</td>
<td>139 ± 16</td>
<td>130 ± 15</td>
<td>140 ± 16</td>
<td>Kruskal-Wallis test</td>
<td>$\chi^2(3) = 7.082$, p=0.048</td>
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<tr>
<td>Diastolic blood pressure</td>
<td>76 ± 13</td>
<td>81 ± 12</td>
<td>81 ± 9</td>
<td>80 ± 10</td>
<td>81 ± 10</td>
<td>Kruskal-Wallis test</td>
<td>$\chi^2(3) = 2.645$, p=0.450</td>
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<tr>
<td>Hypertension: (defined as : raised systolic and/or raised diastolic BP and/or on medication for hypertension)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Chi-square test (\chi^2)</td>
<td>$\chi^2(3) = 5.839$, p=0.112, F=6.039, p=0.101</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>83% (10)</td>
<td>95% (19)</td>
<td>75% (229)</td>
<td>67% (20)</td>
<td>76% (278)</td>
<td></td>
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</tr>
<tr>
<td>PAD Status Groups</td>
<td>Statistical Test Applied</td>
<td>Results</td>
<td>Conclusions</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>n=368</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Systolic&gt;140mmHg</td>
<td>Chi-square ((\chi^2))</td>
<td>(\chi^2(21) = 27.458, p=0.156)</td>
<td>There is no statistically significant association between the presence of any of the individual categories of hypertension and PAD status.</td>
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<tr>
<td>Diastolic&gt;90mmHg</td>
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<tr>
<td>Both ((\uparrow) systolic &amp; (\uparrow) diastolic)</td>
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<tr>
<td>Taking antihypertensives:</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Taking antihypertensives but blood pressure not at target:</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hypertensive but not on antihypertensives:</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pulse Pressure</td>
<td>Kruskal-Wallis test</td>
<td>(\chi^2(3) = 13.023, p=0.005)</td>
<td>Pair-wise comparisons demonstrated that pulse pressure was statistically significantly higher in the PAD group than in: (i) the Normal ABI group (p=0.045) (ii) the High ABI group (p=0.020)</td>
<td></td>
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</tr>
<tr>
<td>Heart Rate</td>
<td>Kruskal-Wallis test</td>
<td>(\chi^2(3) = 1.479, p=0.687)</td>
<td>There is no statistically significant association between heart rate and PAD status.</td>
<td></td>
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</tr>
<tr>
<td>Irregular pulse on examination:</td>
<td>Chi-square ((\chi^2))</td>
<td>(\chi^2(3) = 1.948, p=0.563)</td>
<td>There is no statistically significant association between the presence of an irregular pulse and PAD status.</td>
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</tr>
</tbody>
</table>

Table 8.4: Analysis of PIPETTE data according to PAD status groups
<table>
<thead>
<tr>
<th>Dyslipidaemia:</th>
<th>PAD (ABI&lt;0.9)</th>
<th>Borderline PAD (ABI&lt;0.9, &gt;1.0)</th>
<th>Normal ABI (ABI≥1.0, ≤1.3)</th>
<th>High ABI (ABI&gt;1.3)</th>
<th>All</th>
<th>Statistical Test Applied</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>92% (11)</td>
<td>43% (13)</td>
<td>68% (207)</td>
<td>87% (26)</td>
<td>77% (249)</td>
<td>Chi-square (χ²)</td>
<td>χ²(39) = 36.125, p=0.602</td>
<td>There is no statistically significant association between the presence of dyslipidaemia and PAD status.</td>
</tr>
<tr>
<td>No</td>
<td>8% (1)</td>
<td>25% (5)</td>
<td>22% (67)</td>
<td>7% (2)</td>
<td>23% (74)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No data available</td>
<td>0% (0)</td>
<td>10% (2)</td>
<td>10% (32)</td>
<td>7% (2)</td>
<td>10% (36)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides &gt; 150mg/dL or 1.7mmol/L</td>
<td>25% (3)</td>
<td>15% (3)</td>
<td>33% (101)</td>
<td>40% (12)</td>
<td>32% (119)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Density Lipoprotein (HDL) &lt; 40mg/dL or 1.0mmol/L</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>10% (32)</td>
<td>1% (3)</td>
<td>10% (35)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Density Lipoprotein (LDL) ≥ 130mg/dL or ≥3.3mmol/L</td>
<td>25% (3)</td>
<td>40% (8)</td>
<td>38% (116)</td>
<td>43% (13)</td>
<td>38% (140)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taking lipid lowering medication</td>
<td>58% (7)</td>
<td>25% (5)</td>
<td>19% (58)</td>
<td>43% (13)</td>
<td>23% (83)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>27 ± 4</td>
<td>30 ± 6</td>
<td>29 ± 5</td>
<td>30 ± 5</td>
<td>29 ± 5</td>
<td>Kruskal-Wallis test</td>
<td>χ²(3) = 3.846, p=0.279</td>
<td>There is no statistically significant association between Body Mass Index and PAD status.</td>
</tr>
<tr>
<td>BMI Classification</td>
<td>Normal (BMI 18.5-24.99)</td>
<td>33% (4)</td>
<td>25% (5)</td>
<td>19% (58)</td>
<td>7% (2)</td>
<td>Kruskal-Wallis test</td>
<td>χ²(12) = 10.540, p=0.569</td>
<td>There is no statistically significant association between BMI classification and PAD status.</td>
</tr>
<tr>
<td>Over-weight (BMI 25-29.99)</td>
<td>42% (5)</td>
<td>30% (6)</td>
<td>42% (127)</td>
<td>59% (17)</td>
<td>19% (69)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese Class I (BMI 30-34.99)</td>
<td>17% (2)</td>
<td>25% (5)</td>
<td>26% (78)</td>
<td>17% (5)</td>
<td>42% (155)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese Class II (BMI 35-39.99)</td>
<td>8% (1)</td>
<td>10% (2)</td>
<td>10% (31)</td>
<td>10% (3)</td>
<td>25% (90)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Obese Class III (BMI 40+)</td>
<td>0% (0)</td>
<td>10% (2)</td>
<td>4% (11)</td>
<td>7% (2)</td>
<td>10% (37)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (metres)</td>
<td>1.66</td>
<td>1.63</td>
<td>1.67</td>
<td>1.69</td>
<td>1.67</td>
<td>Kruskal-Wallis test</td>
<td>χ²(3) = 3.897, p=0.273</td>
<td>There is no statistically significant association between height and PAD status.</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75</td>
<td>80</td>
<td>83</td>
<td>87</td>
<td>82</td>
<td></td>
<td>χ²(3) = 5.037, p=0.169</td>
<td>There is no statistically significant association between weight and PAD status.</td>
</tr>
</tbody>
</table>

Table 8.4: Analysis of PIPETTE data according to PAD status groups
<table>
<thead>
<tr>
<th>PAD Status Groups</th>
<th>PAD (ABI&lt;0.9) n=12</th>
<th>Borderline PAD (ABI=0.9, &lt;1.0) n=20</th>
<th>Normal ABI (ABI=1.0, &lt;1.3) n=306</th>
<th>High ABI (ABI&gt;=1.3) n=30</th>
<th>All n=368</th>
<th>Statistical Test Applied</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated waist circumference:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chi-square ($\chi^2$)</td>
<td>$\chi^2(3) = 0.056$, $p=0.993$</td>
<td>There is no statistically significant association between the presence of an elevated waist circumference and PAD status.</td>
</tr>
<tr>
<td>No</td>
<td>67 (8)</td>
<td>35 (7)</td>
<td>65 (197)</td>
<td>33 (10)</td>
<td>64% (229)</td>
<td>36% (128)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference:</td>
<td>98 ± 11 (83-114)</td>
<td>98 ± 16 (67-131)</td>
<td>100 ± 14 (64-143)</td>
<td>104 ± 13 (85-134)</td>
<td>100 ± 14 (64-143)</td>
<td>Kruskal-Wallis test</td>
<td>$\chi^2(3) = 3.778$, $p=0.286$</td>
<td>There is no statistically significant association between waist circumference and PAD status.</td>
</tr>
<tr>
<td>Waist: Hip ratio</td>
<td>0.95 ± 0.08 (0.71-1.08)</td>
<td>0.89 ± 0.09 (0.7-1.18)</td>
<td>0.92 ± 0.09 (0.79-1.1)</td>
<td>0.95 ± 0.08 (0.79-1.1)</td>
<td>0.92 ± 0.09 (0.7-1.18)</td>
<td>One-way ANNOVA</td>
<td>$F(3,363) = 2.283$, $p=0.079$</td>
<td>Waist to hip ratio was not statistically significantly different between PAD status groups.</td>
</tr>
<tr>
<td>Total Number of CV risk factors Mean ± SD Range</td>
<td>4 ± 1 (3-5)</td>
<td>3 ± 1 (1-5)</td>
<td>3 ± 1 (1-5)</td>
<td>3 ± 1 (1-5)</td>
<td>3 ± 1 (1-5)</td>
<td>Kruskal-Wallis test</td>
<td>$\chi^2(3) = 10.101$, $p=0.018$</td>
<td>Pair-wise comparisons demonstrated that the total number of CV risk factors was statistically significantly higher in the PAD group than in: (i) the Borderline PAD group ($p=0.01$), (ii) the Normal ABI group ($p=0.002$) (iii) the High ABI group ($p=0.005$)</td>
</tr>
<tr>
<td>Total Number of CV risk factors*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0% (0)</td>
<td>10% (2)</td>
<td>10% (32)</td>
<td>13% (4)</td>
<td>10% (38)</td>
<td></td>
<td></td>
<td>There is a statistically significant association between category of total number of risk factors and PAD status. Inspection of standardised residuals reveals: 1. The PAD group had more participants with 5 CV risk factors than expected (SR: 2.7, $p=0.01$)</td>
</tr>
<tr>
<td>3</td>
<td>0% (0)</td>
<td>20% (4)</td>
<td>26% (81)</td>
<td>23% (7)</td>
<td>25% (92)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>25% (3)</td>
<td>40% (8)</td>
<td>32% (98)</td>
<td>20% (6)</td>
<td>31% (115)</td>
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</tr>
<tr>
<td>5</td>
<td>67% (8)</td>
<td>15% (3)</td>
<td>25% (78)</td>
<td>30% (9)</td>
<td>27% (98)</td>
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<tr>
<td>6</td>
<td>8% (1)</td>
<td>15% (3)</td>
<td>6% (17)</td>
<td>13% (4)</td>
<td>7% (25)</td>
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<tr>
<td>GPPAQ</td>
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</tr>
<tr>
<td>Inactive</td>
<td>67% (8)</td>
<td>55% (11)</td>
<td>62% (190)</td>
<td>57% (17)</td>
<td>61% (226)</td>
<td>Kruskal-Wallis test</td>
<td>$\chi^2(3) = 0.921$, $p=0.820$</td>
<td>There is no statistically significant association between levels of reported activity according to the GPPAQ and PAD status.</td>
</tr>
<tr>
<td>Moderately Inactive</td>
<td>8% (1)</td>
<td>10% (2)</td>
<td>5% (15)</td>
<td>3% (1)</td>
<td>5% (19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately Active</td>
<td>8% (1)</td>
<td>10% (2)</td>
<td>16% (48)</td>
<td>20% (6)</td>
<td>15% (57)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Table 8.4: Analysis of PIPETTE data according to PAD status groups
<table>
<thead>
<tr>
<th>PAD Status Groups</th>
<th>PAD (ABI &lt; 0.9) n=12</th>
<th>Borderline PAD (ABI 0.9, ≤ 1.0) n=20</th>
<th>Normal ABI (ABI 1.0, ≤ 1.3) n=306</th>
<th>High ABI (ABI &gt; 1.3) n=30</th>
<th>All n=368</th>
<th>Statistical Test Applied</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>17% (2)</td>
<td>25% (5)</td>
<td>17% (53)</td>
<td>20% (6)</td>
<td>18% (66)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy Eating Score</td>
<td>9 ± 2</td>
<td>8 ± 3</td>
<td>9 ± 3</td>
<td>8 ± 3</td>
<td>8 ± 3</td>
<td>Kruskal-Wallis test</td>
<td>$\chi^2(3) = 1.911$, p=0.161</td>
<td>There is no statistically significant association between healthy eating score and PAD status.</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>Yes</td>
<td>0% (0)</td>
<td>5% (1)</td>
<td>3% (10)</td>
<td>0% (0)</td>
<td>Chi-square ($\chi^2$)</td>
<td>$\chi^2(3) = 1.655$, p=0.728</td>
<td>There is no statistically significant association between the presence of Chronic Kidney Disease and PAD status.</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>100% (0)</td>
<td>95% (19)</td>
<td>97% (296)</td>
<td>100% (30)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>Yes</td>
<td>8% (1)</td>
<td>5% (1)</td>
<td>3% (1)</td>
<td>3% (10)</td>
<td>Chi-square ($\chi^2$)</td>
<td>$\chi^2(3) = 2.083$, p=0.590</td>
<td>There is no statistically significant association between the presence of atrial fibrillation and PAD status.</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>92% (11)</td>
<td>95% (19)</td>
<td>98% (299)</td>
<td>97% (29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Yes</td>
<td>17% (2)</td>
<td>5% (1)</td>
<td>1% (4)</td>
<td>0% (0)</td>
<td>Chi-square ($\chi^2$)</td>
<td>$\chi^2(3) = 16.210$, p=0.012</td>
<td>There is a statistically significant association between the presence of rheumatoid arthritis and PAD status.</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>83% (10)</td>
<td>95% (19)</td>
<td>99% (302)</td>
<td>100% (30)</td>
<td>Fisher’s Exact Test (F)</td>
<td>$F=9.517$, p=0.02</td>
<td>Inspection of standardised residuals reveals: 1. There were more participants with rheumatoid arthritis than expected in the PAD group (SR: 3.7, p&lt;0.01).</td>
</tr>
<tr>
<td>Physical Health Score (SF-12)</td>
<td>Mean ± SD</td>
<td>41.3 ± 9.4</td>
<td>38.1 ± 14.4</td>
<td>44.1 ± 9.4</td>
<td>44.0 ± 14.2</td>
<td>43.6 ± 13.6</td>
<td>Kruskal-Wallis test</td>
<td>$\chi^2(3) = 5.152$, p=0.161</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>27 - 56</td>
<td>15 - 56</td>
<td>27 - 56</td>
<td>14 - 59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental Health Score (SF-12)</td>
<td>Mean ± SD</td>
<td>59.6 ± 6.1</td>
<td>55.6 ± 7.7</td>
<td>54.3 ± 8.7</td>
<td>55.3 ± 9.2</td>
<td>54.6 ± 8.6</td>
<td>Kruskal-Wallis test</td>
<td>$\chi^2(3) = 6.426$, p=0.093</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>50 - 69</td>
<td>40 - 70</td>
<td>25 - 74</td>
<td>30 - 70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRISK2 Score</td>
<td>Mean ± SD</td>
<td>54 ± 6</td>
<td>20 ± 10</td>
<td>17 ± 9</td>
<td>19 ± 10</td>
<td>Kruskal Wallis Test</td>
<td>$\chi^2(3) = 16.434$, p=0.001</td>
<td>Pair-wise comparisons demonstrated that QRISK2 score was statistically significantly higher in the PAD group than in: (i) the Normal ABI group (p=0.001) (ii) the High ABI group (p=0.031)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>11 - 32</td>
<td>7 - 41</td>
<td>3 - 41</td>
<td>6 - 41</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 8.4: Analysis of PIPETTE data according to PAD status groups

Red text denotes statistically significant results

<table>
<thead>
<tr>
<th></th>
<th>PAD (ABI≤0.9)</th>
<th>Borderline PAD (ABI&gt;0.9, &lt;1.0)</th>
<th>Normal ABI (ABI=1.0, ≤1.3)</th>
<th>High ABI (ABI&gt;1.3)</th>
<th>All</th>
<th>Statistical Test Applied</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Kruskal Wallis Test</td>
<td>(\chi^2(3) = 7.929, p=0.048)</td>
<td>Pair-wise comparisons demonstrated that Relative risk was statistically significantly higher in the PAD group than in the Normal ABI group ((p=0.014))</td>
</tr>
<tr>
<td>QRISK2 Mean ± SD</td>
<td>1.5 ± 0.5</td>
<td>1.4 ± 0.4</td>
<td>1.2 ± 0.5</td>
<td>1.3 ± 0.5</td>
<td>1.3 ± 0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WIMD (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Kruskal Wallis Test</td>
<td>(\chi^2(3) = 3.745, p=0.290)</td>
<td>There is no statistically significant association between category of WIMD and PAD status.</td>
</tr>
<tr>
<td>Group 1: 1-379inc.</td>
<td>50% (6)</td>
<td>32% (5)</td>
<td>34% (103)</td>
<td>31% (9)</td>
<td>34% (123)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2: 380-758inc.</td>
<td>33% (4)</td>
<td>30% (6)</td>
<td>33% (100)</td>
<td>38% (11)</td>
<td>33% (121)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3: 759-1137inc.</td>
<td>17% (2)</td>
<td>25% (5)</td>
<td>22% (66)</td>
<td>17% (5)</td>
<td>21% (78)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 4: 1138-1516inc.</td>
<td>0% (0)</td>
<td>5% (1)</td>
<td>2% (7)</td>
<td>7% (2)</td>
<td>3% (10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 5: 1517-1896inc.</td>
<td>0% (0)</td>
<td>15% (3)</td>
<td>9% (26)</td>
<td>7% (2)</td>
<td>9% (31)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
8.2 Discussion

8.2.1 PAD prevalence

The overall PIPETTE PAD prevalence rate was 3.3% and the bias adjusted rate was 4.3%. The table in Appendix 2 details a sample of 32 PAD prevalence studies which have been undertaken in countries across the world. Study number 11 (Fowkes et al., 2006), 18 (Kownator et al., 2009), 22 (Aboyans et al., 2011) & 25 (Cimminiello et al., 2011) screened similar populations as the PIPETTE study in that individuals with pre-identified CVD were excluded. Of these, only the studies by Aboyans et al. (MESA study, 2011) and Cimminiello et al. (PANDORA study, 2011) calculated the ABI using the standard calculation as recommended by the AHA (Aboyans et. al., 2012), that is, they used the higher of the ankle systolic blood pressures as the numerator in the ABI equation.

The MESA study screened 1932 individuals aged 45-84 and free from known clinical CVD at a research clinic in the USA; the prevalence of ABI<0.9 was 3.4%. The PANDORA study, which was a pan-European study of 9816 individuals with no known CVD or diabetes, reported a much higher prevalence rate of 17.8%. The PANDORA study differed from the MESA study in that its inclusion criteria specified that participants must have at least two CV risk factors, hence this may have accounted for some of the discrepancy in prevalence rates. The PIPETTE prevalence rate is much closer to the MESA prevalence rate than the PANDORA rate, despite it having an almost identical inclusion and exclusion criteria to the latter study.

The studies by Fowkes et al. (AGATHA study, 2006) and Kownator et al. (IPSILON study, 2009) both utilised the lower ankle systolic blood pressure to calculate the ABI. The AGATHA study was an international multicentre trial which screened 8891 participants aged >55 years with ≥2 CV risk factors. The prevalence of ABI≤0.9 was high at 31%; this was probably influenced by the fact that the study was undertaken in secondary care settings as well as primary care, where cardiologists, medical specialists and even vascular surgeons recruited participants. It is likely that these participants recruited within secondary care exhibited higher levels of morbidity hence possibly explaining the higher prevalence. The IPSILON study recruited 1340 participants with ≥2 CV risk factors and found that the prevalence rate of ABI<0.9 was 10.9% which is almost identical to the 10.8% PIPETTE Low ABI prevalence rate. In addition, the Scottish study by Price et al. (2008) which measured the Low ABIs of 28,890 participants of all patients listed on a community health index but excluded those with previous history of stroke and MI, reported an ABI≤0.9 of 10.9% which again is very close to the PIPETTE low ABI prevalence rate.

In summary, despite predicting that the PIPETTE study population would exhibit some of the highest levels of PAD in Wales, the attained prevalence rate (actual rate=3.3% and bias-adjusted rate=4.3%)
was at the lower end of the prevalence range of previous studies with similar populations. It is possible that differing health care systems in the countries where these studies originated meant that differing levels of CV disease had been pre-diagnosed and hence excluded from the study populations; this could account for a degree of the large disparities in results. Similarly, differing study methodologies and recruitment techniques could have also affected prevalence rates.

8.2.2 Factors associated with PAD

Gender
The PIPETTE study demonstrated that the prevalence of PAD did not differ according to gender (male: 3.5%, female: 3.0%, p=0.11). A literature review reveals that the influence of gender on the prevalence of PAD is controversial; although former studies detailed a lower frequency of PAD in women, current data suggest that PAD frequency in women may be equal to and perhaps greater than in men (Teodorescu et al., 2013). The American College of Cardiology/American Heart Association (ACC/AHA) 2005 practice guidelines for the management of patients with PAD maintain that male gender is a PAD risk factor; however, the data on which this statement was based dates back to 1985 (Hirsch et al., 2005). Results from more recent studies do not concur with this, and have reported the prevalence of PAD in women to be similar or higher than that of men (Diehm et al., 2004; Carbayo et al., 2007; Sigvant et al., 2007; Maeda et al., 2008; Moussa et al., 2009).

The PIPETTE study demonstrated that women exhibited lower rates of PAD than men until age 75, after which, the reverse is true. This fits with what is generally accepted about the prevalence of atherosclerotic diseases, where women present a lower rate of cardiovascular disease than men until their seventh decade, when the protective effect of female sex hormones no longer exists (Mosca et al., 1997). It is interesting to note that although not statistically significant, more women account for the borderline PAD group than men (65% vs. 35%). This could be attributed to the fact that women have intrinsically lower ABIs than men (as discussed in section 3.7.11, pg. 65) and perhaps supports the call of Hirsch and colleagues for gender-based PAD diagnostic thresholds (Hirsch et al., 2012).

Age
Existing data have consistently shown that PAD is strongly age related (Fowkes et al., 2013). Data from the PIPETTE study concurs with this as results have shown that the PAD group has a significantly higher mean age than the other PAD status groups (70 years vs. 67 years for borderline PAD group, 63 years for normal ABI group and 65 years for high ABI group; p=0.049).
Smoking status
Evidence of an association between active smoking and PAD is substantial; in keeping with current literature, the PIPETTE study also demonstrated that being a current smoker was significantly associated with PAD (p<0.01). Research suggests that smoking increases the atherosclerosis process by reducing the effect of nitric oxide vasodilation (Muir, 2009). A recent meta-analysis by Lu et al. (2014) included 68 studies which investigated smoking and PAD; the pooled odds ratio associated with being a current smoker was 2.71 (95% CI: 2.28 to 3.21), although notably there was a high level of study heterogeneity (I² 94.9%, p<0.001). The pooled odds ratio for ex-smokers was 1.67 (95% CI 1.54 to 1.81), although again there was moderate heterogeneity. Several studies have noted that in contrast to its relationship with coronary heart disease and stroke, previous smoking history appears to have a long legacy of increased risk of PAD (Fowler et al., 2002; He et al., 2006). Although all of the PAD cases within the PIPETTE study were either current smokers or ex-smokers, there was no significant association between past smoking history and PAD status (p=0.09).

Pulse pressure
The PIPETTE study demonstrated a moderate negative inverse association between pulse pressure and ABI; several existing studies have also reported this (Aboyans et al., 2011; Powell et al., 2011; Ramos et al., 2009). Aboyans et al. (2007) found that pulse pressure was negatively correlated with ABI in a sample of 1775 healthy Americans (MESA study). Powell et al. (2011) examined the relationship between reported hypertension and incident confirmed symptomatic PAD in 39,260 female health professionals. Their data demonstrated a strong prognostic role of uncontrolled blood pressure; in particular, uncontrolled systolic blood pressure in the clinical development of PAD in women. These findings provide evidence of the proatherogenic effect of hypertension in the development of PAD.

Rheumatoid arthritis
Rheumatoid arthritis (RA) is an autoimmune disease that results in a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks synovial joints. A review of the literature reveals only one study which has demonstrated a direct association between PAD and RA. Stamatelopoulos et al., (2010) examined the intima-media thickness (IMT) and atheromatous plaque presence and vulnerability in 80 RA patients without overt CV disease or diabetes and 80 age, gender and CVD risk factor controls. The presence of RA was found be an independent predictor of increased IMT (p=0.004) after adjustment for traditional CV risk factors.
Evidence regarding RA and generalised cardiovascular risk however is substantial. The QRISK2 study demonstrated that patients with RA have increased cardiovascular risk, where the adjusted hazard ratio for women was 1.5 (1.39 to 1.61) and 1.38 (1.25 to 1.52) for men (Hippsley-Cox et al, 2008); according to Crowson et al. (2013) this is similar to the risk imparted by diabetes mellitus. The increased risk applies to those with coronary artery disease (Solomon et al., 2006; Maradit-Kremers et al., 2005) and cerebrovascular disease (Wolfe et al., 2003).

It is thought that the increased cardiovascular risk can be attributed primarily to the chronic inflammation that is inherent to rheumatoid arthritis. The lipid profile in RA is characterised by suppression of total and low-density lipoproteins (LDLs) during periods of high grade inflammation, with a proportionately greater suppression of high-density lipoprotein (HDLs) levels, resulting in an unfavourable ratio of total to HDL cholesterol (Crowson et al., 2013). Furthermore, the inflammation of rheumatoid arthritis also appears to alter lipoprotein structure and function (Toms et al., 2010) by decreasing the usual anti-atherogenic effects of HDL (Watanabe et al., 2012).

A second contributing factor to the increased cardiovascular risk associated with RA concerns the medications used in its treatment. Corticosteroids have been widely used to control the pain and inflammation associated with RA flares; however, studies have shown that their use is associated with carotid plaque, arterial stiffness, decreased insulin sensitivity, elevated lipid levels and hypertension (Dessein et al., 2004; Hafstrom et al., 2007). In contrast, specific disease modifying drugs, such as methotrexate and tumour necrosis factor (TNF) inhibitors, have been associated with lower cardiovascular risk (Barnabe and Hanley, 2009; Micha et al., 2011). It therefore appears that the exact relationship between inflammation, pharmacological treatment and cardiovascular risk in RA is far from clear, and authors (Crowson et al., 2013) have called for further research in this field.

However, evidence regarding the link between RA and increased CV risk is sufficiently robust that CV risk assessment algorithms, such as QRISK2, now include a term for RA which is used in the calculation of cardiovascular risk.

8.2.3 Implications for future PAD screening

Based on the attained prevalence rate, the number needed to screen (NNS) to detect one new case of PAD was 31. Table 8.4 outlines the NNS and sensitivity for detecting PAD cases if the study population had been refined according to the factors found to be significantly associated with PAD.
### Table 8.5: Effects of refining the study population on screening outcomes

<table>
<thead>
<tr>
<th>Refining Factor</th>
<th>Adjusted sample Size</th>
<th>Number needed to screen</th>
<th>% of PAD cases which would have been detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Smoking Status: Current or ex-smokers included</td>
<td>173</td>
<td>15</td>
<td>100%</td>
</tr>
<tr>
<td>2. Age: ≥50 years</td>
<td>162</td>
<td>14</td>
<td>100%</td>
</tr>
<tr>
<td>3. (i) ≥ 1 clinical sign of PAD or (ii) Rheumatoid arthritis</td>
<td>47</td>
<td>4</td>
<td>92%</td>
</tr>
</tbody>
</table>

If the study population had been refined to participants over the age of 50, with a history of smoking (current or ex-smokers), the number needed to screen would have been reduced by more than a half to 14, and importantly no cases of PAD would have been missed. This concurs with the target screening population recommended by the ACC/AHA PAD guidelines (2011) (see Table 2.4: Summary of PAD guidelines). If the population was further refined to only include individuals with at least one clinical sign of PAD or rheumatoid arthritis, the NNS is dramatically reduced to 4, and this still would have identified 92% of PAD cases. Notably, adhering to the UK NICE PAD guidelines (Table 2.4) would have meant that only participants with symptoms of PAD or unexplained leg pain would have been screened; in the PIPETTE population, this would have resulted in a NNS of 8 with 83% of PAD cases being identified.

### 8.2.4 QRISK2 CV risk algorithm and PAD

Results demonstrated that both QRISK2 score and relative risk according to the QRISK algorithm were associated with PAD ($p = 0.031$ and $p = 0.014$ respectively). As discussed in Section 2.3, an ABI of ≤ 0.9 has been shown to be indicative of high CV risk. The QRISK2 CV risk score also predicted high CV risk in 92% of the PAD subjects, hence indicating that the ABI would have had little to contribute via its addition to the algorithm. Within general practice, a major advantage of using QRISK to assess CV risk is that it is incorporated into the electronic health record system (EMIS) of general practices. It automatically processes new information (such as a newly measured blood pressure) to produce a continuously updated prediction algorithm. Hence, a health professional can determine a patient’s QRISK2 score via the touch of a computer key, making it far more amenable than the ABI for use in primary care. However, according to the UK National Screening Committee (2012) a major drawback of QRISK concerns missing or out-of-date data which may reduce its accuracy and undermine confidence in its predictive capacity.
8.3 PIPETTE Study strengths and limitations

Although the findings presented within this chapter are largely in line with the current PAD evidence base, it is acknowledged that a major limitation of this study concerns the small sample size of the PAD status group (n=12). Logistic regression identified factors significantly associated with PAD but associated confidence intervals were broad and it is probable that the sample size contributed to this. Furthermore, the study population was derived from only one general practice and it cannot be determined if, or how, this may have affected results. For example, the low PAD prevalence rate attained within the PIPETTE study could have been attributed to the practice being particularly efficient at detecting and diagnosing cardiovascular disease prior to the instigation of the study. This would have resulted in a greater proportion of patients with cardiovascular pathologies being excluded from participation in the study at the outset.

In addition, there was no ethnic diversity within the PIPETTE study population (100% were of white British origin) meaning that it was not representative of the UK population, in which only 80.5% are of white British origin (Office of National Statistics, 2012). Again, this could have affected results as rates of cardiovascular disease are known to be higher in people of South Asian and African-Caribbean origin (Tillin et al., 2014).

One aspect of the PIPETTE study design could be considered both a strength and a limitation; allowing participants to participate in the study in their home environment could have increased the recruitment of those with mobility problems, transport issues or caring duties for family members, for example. This optimisation of participant recruitment could have resulted in improved epidemiological data in terms of more accurate PAD prevalence rates. Alternatively, incorporating home visits into the study design could have meant that the resultant study population was not representative of those individuals that would come forward for health service PAD screening which would likely be undertaken in a health care setting, hence meaning that results may not be transferable or applicable to an actual screening programme.

Confidence in diagnoses of PAD within the PIPETTE study can be derived from the fact that ABI measurements were undertaken by a single investigator, meaning that there were no issues relating to inter-observer variability. Furthermore, ABI measurements and PAD diagnosis were validated by means of the separate IVAM study (chapter 7).

Results from this study add to the evidence base regarding PAD prevalence in both the UK and globally; it is the first UK study of PAD prevalence that has been undertaken for seven years and the only UK study which has investigated PAD prevalence outside of Scotland. However, in view of the limitations discussed above, conclusions should be considered with caution; larger scale studies which incorporate a study population derived from multiple general practices are required to corroborate results.
8.4 Conclusions

This chapter aimed to determine who a potential PAD screening strategy should target via examination of data associated with low ABIs. Findings concur with the recommendations made by the ACC/AHA (2011): PAD screening should target individuals over the age of 50 with a smoking history. It is suggested that further refining the target population to those exhibiting at least one clinical sign of PAD and/or rheumatoid arthritis would further improve the efficiency of screening whilst still identifying a large majority of existing PAD cases.

As the QRISK2 algorithm also identified high CV risk in 92% of the PAD participants, it is concluded that the ABI could contribute little to CV risk assessment within this context.
Chapter 9: PIPETTE Phase 1, High ABI results

Although the CV consequences of low ABI were discussed in detail in Chapter 2 (Section 2.3), little consideration has been given to implications of a high ABI. Hence, a review of the relevant current literature is subsequently included:

9.0 High ABI Background Information

9.0.1 Definition

Although the American College of Cardiology/American Heart Association (ACC/AHA, 2005) classify a high ABI as ≥1.3, a literature review reveals several variations of this. Some authors recommend a high ABI is suspected if an ABI exceeds 1.15, whilst others have used cut off values of 1.3, 1.4 and 1.5 (Suominen et al., 2008). In some cases, it is not possible to occlude the arteries with a cuff even at pressures ≥300mmHg and in these cases the ABI is recorded as incompressible.

9.0.2 Aetiology

Elevated ankle pressures and ABIs may be attributed to factors such as peripheral oedema, lipodermatosclerosis associated with venous insufficiency, and circular ateriosclerotic lesions (Kroger et al., 2006). However, the most common aetiology relates to the accumulation of calcium and phosphate in the medial layer of the arterial wall; this is known as Monckeberg’s medial sclerosis or medial artery calcification (MAC) (Rocha-Singh et al., 2014) (Figure 9.1).

Figure 9.1: Arterial transection showing medial arterial calcification
(Image source: Mercer University, School of Medicine, 2014: reproduced with permission)
MAC is not generally associated with arterial luminal obstruction, however, a decrease in the elasticity and compliance of the vessel wall may ultimately lead to atherosclerosis, reduced perfusion and eventually, coronary artery disease and PAD. Age and hypertension have been shown to be the most important risk factors for calcification (Hirsch et al., 2005); from age 20-90 years, its incidence may increase by 30% (Hayden et al., 2005). Furthermore, the association between vascular calcification and diabetes mellitus (Edmonds, 1982; Formosa et al., 2013) and chronic kidney disease (Nitta, 2011; Mizobuchi et al., 2009) is well established. Several pathways have been proposed to explain arterial stiffening in diabetic patients. For example, insulin triggers smooth muscle proliferation (Stout, 1991) and hyperglycaemia is responsible for non-enzymatic glycosylation of several proteins, including collagen and elastin (Aboyans et al., 2007).

However, recently, Lilly and colleagues (2014) have suggested an alternative explanation for elevated ABIs in the general population. Whilst they acknowledge that MAC is the most likely contributing factor for elevated ABI in clinical populations with a high prevalence of vascular disease, they suggest that increased pulse pressure amplitude may be the primary cause of elevated ABIs in the general population. Their argument is based on the fact that pulse pressure amplifies as the energy wave generated by the heart travels to the periphery with summation of forward and reflected waves. Accordingly, high ankle pressures may simply reflect exaggerated amplification of the pulse pressure in some individuals, which increases ankle pressure relative to brachial pressure due to the comparably long travelling paths. Lilly et al. studied 6814 participants enrolled in the MESA study, who were free of cardiovascular disease at baseline. They assessed differences in total arterial compliance (ratio of stroke volume to pulse pressure) and aortic and carotid distensibility (measured with magnetic resonance imaging and duplex ultrasound) across ABI subclasses (≤0.9, 0.91-1.29, ≥1.3). They found that those with high ABI demonstrated greater aortic/radial pulse pressure amplification than those with a normal ABI. They also found that aortic and carotid distensibility as well as total arterial compliance was not reduced in subjects with an ABI≥1.3. Whilst the theory of Lilly and colleagues is plausible, this hypothesis requires further investigation in future research.

9.0.3 Elevated ABI and Cardiovascular Risk

Several studies have demonstrated that a high ABI is correlated with subclinical cardiovascular disease and is associated with higher rates of total and cardiovascular mortality in both general (Resnick et al., 2004; O’Hare et al., 2006; Criqui et al., 2010) and coronary populations (Aboyans et al., 2005) (Table 9.1). Furthermore, Suominen et al. (2008) found that a large proportion of individuals with high ABIs do actually have PAD. They conducted a retrospective clinical study
whereby 1762 patients referred to a vascular laboratory with suspicion of PAD, had their ABIs and toe pressures measured via photoplethysmography. ABI≥1.3 was considered falsely elevated and toe brachial index (TBI) <0.6 was considered diagnostic of PAD. Prevalence of elevated ABI was 8.4% and of those, 62% had PAD according to toe pressures and digital subtraction angiography. If the cut off point defining high ABI was changed to ≥1.4 and ≥1.5, the prevalence of PAD increased to 78% and 84% respectively. However, as the study participants were suspected to have PAD in the first place, results do not necessarily apply to the general population.

Only one study disputes the association between elevated ABIs and CV risk; Wattanakit and colleagues (2007) examined data from the Atherosclerosis Risk in Communities (ARIC) study (n=14,777) and found that individuals with ABIs >1.3 actually had a slightly lower age, gender and race adjusted CVD event rate per 1000 person years than individuals with a normal ABI (0.9-1.3) (High ABI group = 7.6 CVD events per 1000 person years, Normal ABI group = 8.1 CVD events per 1000 person years). Two points require consideration with regard to this study; firstly, the ARIC study utilised automated oscillometric equipment to measure ABIs and only assessed the ABI of one randomly chosen leg per participant. The use of oscillometric equipment to measure ABIs can be unreliable (discussed in detail in Section 12.1); this non-standard method of ABI determination could have resulted in participants being incorrectly classified into ABI groups. Secondly, the ARIC population was younger (maximum age: 64) than the populations of the studies which have demonstrated that high ABI is associated with increased mortality. According to Lilly et al (2014), it could be that these younger participants have higher ABIs as a result of increased pulse pressure amplitude rather than medial arterial calcification; and this then would constitute a benign form of elevated ABI.

9.0.4 Reporting of high ABI results

The Transatlantic Inter-Society Consensus for the management of peripheral arterial disease (TASC, 2000) recommended that future epidemiological studies should consider all forms of PAD, including elevated ABIs or MAC, more than a decade ago. However, despite this, and the fact that the majority of evidence points to a clear link between elevated ABIs and CV mortality, data regarding the prevalence of high ABIs are sparse in comparison to low ABI prevalence data (Table 9.1).
<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Year</th>
<th>Sample Size</th>
<th>Population</th>
<th>ABI methodology</th>
<th>High ABI definition</th>
<th>Prevalence</th>
<th>Length</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newman et al. (CHS)</td>
<td>USA</td>
<td>1999</td>
<td>5888</td>
<td>Age &gt; 65 Medicare eligible persons</td>
<td>Measured right brachial only and only posterior tibial ankle pressures.</td>
<td>ABI &gt; 1.3</td>
<td>13.5%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Resnick et al.</td>
<td>USA</td>
<td>2004</td>
<td>4393</td>
<td>Age 45-74 American Indians</td>
<td>Standard</td>
<td>ABI &gt; 1.3</td>
<td>15%</td>
<td>Mean: 8.3 years</td>
<td>Adjusted risk estimates: All cause mortality: 1.77 CVD mortality: 2.00</td>
</tr>
<tr>
<td>Kroger et al.</td>
<td>Germany</td>
<td>2006</td>
<td>4814</td>
<td>Age 45-75</td>
<td>Standard</td>
<td>ABI &gt; 1.3</td>
<td>10.1%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Wattanakit et al. (ARIC)</td>
<td>USA</td>
<td>2007</td>
<td>14,777</td>
<td>Age 45-64</td>
<td>Automated oscillometric equipment. Only assessed ABI of 1 leg.</td>
<td>ABI &gt; 1.3</td>
<td>5.5%</td>
<td>Mean 12.2 years</td>
<td>Age, sex and race adjusted CVD event rates per 1000 person years: 7.6 in the High ABI group versus 8.1 in the normal ABI group (ABI 0.9 – 1.3)</td>
</tr>
<tr>
<td>Suomirnen et al.</td>
<td>Finland</td>
<td>2008</td>
<td>1762</td>
<td>Patients referred to vascular laboratory with suspected PAD</td>
<td>Automated plethysmographic ABI equipment</td>
<td>ABI &gt; 1.3</td>
<td>8.4%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Allison et al. (PARTNERS program)</td>
<td>USA</td>
<td>2008</td>
<td>7155</td>
<td>Age &gt; 50</td>
<td>Standard</td>
<td>ABI &gt; 1.3</td>
<td>6.3%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lilly et al. (MESA)</td>
<td>USA</td>
<td>2014</td>
<td>6814</td>
<td>Aged 45-84 free from clinically apparent CVD</td>
<td>Standard</td>
<td>ABI &gt; 1.3</td>
<td>9.6%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Criqui et al.</td>
<td>USA</td>
<td>2010</td>
<td>6647</td>
<td>Aged 45-84 free from clinically apparent CVD</td>
<td>Standard</td>
<td>ABI &gt; 1.4</td>
<td>1.7%</td>
<td>Mean: 5.3 years</td>
<td>Hazard Ratio: 1.85</td>
</tr>
<tr>
<td>O’Hare et al.</td>
<td>USA</td>
<td>2006</td>
<td>5748</td>
<td>Age &gt; 50</td>
<td>Standard</td>
<td>ABI &gt; 1.4</td>
<td>Mean: 11.1 years</td>
<td>All cause mortality: 1.57 (95% CI: 1.07 to 2.31)</td>
<td></td>
</tr>
<tr>
<td>Meijer et al. (The Rotterdam Study)</td>
<td>Netherlands</td>
<td>1998</td>
<td>7715</td>
<td>Age &gt; 55</td>
<td>Only pressure at posterior tibial was measured. Unsure if both brachial measurements were undertaken</td>
<td>ABI &gt; 1.5</td>
<td>0.6% (response rate: 78%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Selvin et al. (National Heart and Nutrition Examination Survey)</td>
<td>USA</td>
<td>2004</td>
<td>2381</td>
<td>Age &gt; 40</td>
<td>Only right arm systolic pressure measured. Only posterior tibial pulse assessed at ankle.</td>
<td>ABI &gt; 1.5</td>
<td>0.2%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Aboyans et al.</td>
<td>USA</td>
<td>2005</td>
<td>1022</td>
<td>Patients undergoing coronary artery bypass grafts</td>
<td>Standard</td>
<td>ABI &gt; 1.5</td>
<td>12%</td>
<td>Mean: 4.4 years</td>
<td>Odds Ratio: 1.9 (independently predictive of overall and CV death)</td>
</tr>
<tr>
<td>Kroger et al.</td>
<td>Germany</td>
<td>2006</td>
<td>4814</td>
<td>Age 45-75</td>
<td>Standard</td>
<td>ABI &gt; 1.5</td>
<td>1.1%</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 9.1: Summary of studies reporting high ABI results
9.0.5 Prevalence of high ABI

Prevalence rates obviously vary depending on the cut off point used to define a high ABI. Using a liberal definition of ABI ≥ 1.3 as high, prevalence rates in the general population range from 5-15%, whereas using ABI≥1.5 to define high results in considerably reduced rates of 0.2-1.1%. In populations already known to have significant levels of CVD, as in the study by Aboyans and colleagues (2005), the prevalence of elevated ABI (≥1.5) is much higher at 12% (Table 9.1).

9.1 The High ABI PAD group

9.1.1 PIPETTE: High ABI Prevalence

Within the PIPETTE study population, the prevalence of ABI ≥1.3 was 8.2% (n=30); if the definition of elevated ABI was increased to ≥1.4 or ≥1.5, the prevalence decreases to 1.9% and 1.4% respectively.

The characteristics of the high ABI group (ABI≥1.3) are presented in Table 4.3; statistically significant factors and trends are discussed below.

9.1.2 Factors associated with high ABI

Gender

Statistical analysis of results revealed that there were significantly more males in the high ABI group (ABI≥1.3) than a non-high ABI group (ABI<1.3), 73% v 53% respectively, p=0.032 (Figure 9.2).

![Figure 9.2: Gender according to high and non-high ABI groups](image)

Blue = male, Red = female
Body Mass Index

The high ABI group also had a significantly greater proportion of participants with elevated BMI (25+), than each of the other PAD status groups (93% versus 67% of the PAD group, p<0.01; 75% of the borderline PAD group, p<0.01; and 81% of the normal ABI group, p=0.034) (Figure 9.3).

![Figure 9.3: Proportion of participants with elevated BMI (>25) according to PAD status groups](image)

Blood Pressure

Associations between blood pressure and PAD status groups are illustrated in Figure 9.4. Mean systolic blood pressure was significantly lower in the high ABI group compared to the other PAD status groups, 130mmHg v 144mmHg for the PAD group (p=0.04), 147mmHg for the borderline PAD group (p=0.031), and 139mmHg for the normal ABI group (p=0.049). The high ABI group also had lower mean pulse pressure than the other PAD status groups: 57mmHg v 68mmHg for the PAD group (p=0.02), 65mmHg for the borderline PAD group (p=0.039), and 58mmHg for the normal ABI group (p=0.241). Mean diastolic blood pressure and was marginally lower in the high ABI group compared to the borderline and normal ABI groups, although this was not statistically significant (p=0.45).
Figure 9.4: Mean blood pressure according to PAD status group
Blue diamonds: systolic blood pressure, red squares: diastolic blood pressure, green triangles: pulse pressure

Other non-significant trends in the data were also noted: the high ABI group had the lowest proportion of current smokers compared to the other PAD status groups (Figure 9.5, p=0.064).

Figure 9.5: Proportion of current smokers according to PAD status groups
The high ABI group also had the greatest proportion of participants with a family history of premature CHD although once again, this was not statistically significant (33% versus 17% in the PAD group, 25% in the borderline group, and 26% in the normal ABI group; p=0.714).

9.1.3 QRISK®2 cardiovascular risk and the high ABI group
The high ABI group presented with a mixed CV risk profile according to QRISK®2: 17% had a QRISK2 score of <10; 43% had a score of 10-20; and 40% had a score of >20%. Forty three per cent had a relative risk of ≤1.0, hence demonstrating that their score was less than or equal to the risk of an average individual of the same age, sex and ethnicity.

9.1.4 Analysis of pulse volume waveform (PVW) recordings of the high ABI group
Of the high ABI group, 10% (n=3) had abnormal pulse volume waveform (PVW) recordings that were suggestive of PAD, as evaluated by the PhD researcher and an independent expert (discussed in detail in Chapter 15). An example of the automated device printout of one such participant is shown in Figure 9.6.

![Figure 9.6: Example of a dopplex® Ability printout showing an elevated ABI with an abnormal pulse volume waveform; A: rounded systolic peaks, B: absence of defined dicrotic notch.](image)

9.1.5 Clinical signs of PAD within the high ABI group
Only 13% of the high ABI group displayed any clinical signs of PAD and no one within the group had a positive result to the Edinburgh claudication questionnaire.
9.2 Discussion

Results regarding the high ABI group are broadly in line with previously published data. Attained prevalence rates are similar to rates from studies with similar populations (Table 9.1). This study has demonstrated that individuals with elevated ABIs are more likely to be male and more likely to have elevated BMIs; this also concurs with the existing evidence base (Allison et al., 2008; Aboyans et al., 2011; Lilly et al., 2014). Studies have shown that ABI values may be intrinsically higher in men than in women, even after taking into account a series of anthropometric, biological and socio-economic variables. Hence it could be that a lower “normal” ABI in women could partially explain why female gender is positively associated with low ABI (<1.00) and male gender with high ABI (>1.3) (Aboyans et al., 2007).

As discussed in Section 9.0, medial arterial calcification (MAC) is the most widely quoted likely cause of elevated ABI. As advancing age and the presence of hypertension have been shown to be the most important risk factors for arterial calcification (Hirsch et al., 2005), it could be expected that elevated ABIs groups would consist of older individuals with higher rates of hypertension than a normal ABI group. However, studies by Wattanakit et al. (2007) and Lilly et al. (2014) found that age was not associated with high ABI and there was actually a significantly lower prevalence of hypertension in high ABI groups. These findings have been replicated in the PIPETTE study: the high ABI group had the lowest mean systolic, and pulse pressure compared to the other PAD status groups. Several studies, although not the PIPETTE study, have also found an inverse relationship between dyslipidaemia and high ABI (O’Hare et al., 2006; Aboyans et al., 2008; Lilly et al., 2014).

Hence, it appears that high ABI groups actually have mixed cardiovascular risk profiles; male gender and high BMIs confer increased cardiovascular risk, whilst lower systolic blood pressure, pulse pressure and lower rates of dyslipidaemia equate to decreased cardiovascular risk. This is perhaps reflected in the fact that mean QRISK2 scores and mean relative risk of the high ABI group in the PIPETTE study were marginally higher than those with ABIs in the normal range, but significantly lower than the borderline PAD and PAD groups (see Table 4.3).

However, this mixed cardiovascular risk profile, does not necessarily fit with the fact that the majority of evidence has demonstrated that individuals with high ABIs have higher rates of total and cardiovascular mortality (as discussed in Section 9.0.3). There are two possible explanations for this. Firstly, the high ABIs could be attributed to increased pulse pressure amplitude as described by Lilly et al., (2014) (Section 9.0.2), in which case the elevated ABI could be benign and would not necessarily represent increased cardiovascular risk. Lilly and colleagues hold that pulse pressure amplifies as the energy wave generated by the heart travels to the periphery with summation of forward and reflected waves. Accordingly, they believe that high ankle pressures may simply reflect
exaggerated amplification of the pulse pressure in some individuals, which increases ankle pressure relative to brachial pressure due to the comparably long travelling paths. If this theory is correct, then it would be reasonable to expect that taller individuals would be more likely to have higher ABIs as a result of the longer travelling paths that Lilly et al. refer to. However, analysis of PIPETTE data did not show any association between height and PAD status (Table 4.3, mean height of high ABI group: 1.69m versus PAD group: 1.66m, borderline PAD group: 1.63m, normal ABI group: 1.67m, p=0.273); it is possible that the study was insufficiently powered to detect this.

A second possible explanation for the disparity between the perceived cardiovascular risk profile and actual cardiovascular mortality rates of those with high ABIs is provided by Rocha-Singh et al. (2013). They believe that it could be that individuals with hypertension and dyslipidaemia are likely to also have atherosclerotic (occlusive) disease and the effect of this would be to lower the ABI and shift some patients with mild MAC into the normal ABI range.

Analysis of the PVW recordings of the high ABI group suggested that 10% of these were likely to have had PAD. Stein et al. (2006) examined the ABIs and PVW recordings of 396 subjects who had been referred to a vascular laboratory with suspicion of PAD. Of the 14% of subjects that were found to have elevated ABIs or incompressible arteries, 24% were found to have abnormal PVW recordings. This difference in rates of abnormal PVW recordings within those with elevated ABIs is likely to be due to the differing study populations, with those being referred to the vascular laboratory of course being more likely to have PAD.

9.3 Conclusions

The high ABI group within the PIPETTE study presents with a mixed cardiovascular risk profile and it is unclear how this would translate into actual cardiovascular risk. In comparison to the substantial evidence base that demonstrates that low ABI is associated with high cardiovascular risk, relatively few studies have shown that the same is true of high ABIs. Large scale studies that screen the general population for high ABI, with longitudinal follow-up of at least 10 years, are required in order to determine cardiovascular and all cause event and mortality rates. Until such research has been completed, the very fact that there is uncertainty in relation to this issue is sufficient to warrant additional CV risk assessment and diagnostic tests, such as Duplex ultrasound, for individuals found to have high ABIs. It is possible that analysis of pulse volume waveform recordings, as provided by the automated device used within the PIPETTE study, could also provide the secondary diagnostic technology needed to clarify the disease state of such individuals (this is discussed in detail in Chapter 12).
WHO SHOULD UNDERTAKE A PAD SCREENING STRATEGY?

Chapter 10 : General Practice Survey Results

To recap: it is unclear if the necessary skills for ABI measurement and PAD screening exist within the primary care setting. Hence, a self-reporting questionnaire was distributed to all 478 General Practices in Wales, in order to gain information regarding the current utility of the most common PAD screening tool, the ABI, within this setting.

10.0 Results

10.0.1 Response Rate

The overall response rate to the GP survey was 20% (95:478) and ranged from 16-41% across individual health boards: Cwm Taf University Health Board 16% (8:50), Aneurin Bevan University Health Board 22% (20:91), Cardiff & Vale University Health Board 19% (13:68), Abertawe Bro Morgannwg University Health Board 18% (14:77), Betsi Cadwaladr University Health Board 16% (19:119), Powys Teaching Health Board 41% (7:17), Hywel Dda University Health Board 25% (14:56). Thirty per cent (27:95) of returned surveys were completed by GPs, 6% (6:95) by nurse practitioners, 34% (32:95) by practice nurses and 5% (5:95) by district nurses. The remaining 25% were completed in collaboration between GPs and nursing staff.

10.0.2 Occupations of those performing ABI measurement

The majority (50.5%) of ABI measurements are undertaken by practice nurses within the responding general practices (Figure 10.1). Twenty seven per cent (26:95) of responding general practices were not undertaking ABI measurement, with patients needing this procedure often being referred to secondary care. Other practices relied on their district nursing colleagues (who, in Wales, are not generally based within general practices) to undertake the task.
10.0.3 Frequency of ABI Measurement

The majority of practices reported performing ABI measurements relatively infrequently at less than four times a month (73%) (Figure 10.2).
10.0.4 Reasons for ABI Measurement

Respondents were asked to indicate if there were any other reasons, besides the presence of signs and symptoms of lower limb arterial insufficiency, which would cause them to undertake or request ABI measurement. Whilst the management of lower limb oedema and leg ulceration/wounds accounted for 90% of responses to this question, it was interesting to note that 6% reported utilising the ABI in a cardiovascular screening capacity (Figure 10.3).

![Figure 10.3: Reasons for ABI measurement within general practices](image)

General practitioners (GPs) were the least likely occupational group to undertake ABI measurement. They were also the least likely to: (i) consider themselves, or be considered by colleagues, to be competent at ABI measurement, (ii) have received formal training for ABI measurement, and (iii) be compliant with current guidelines for ABI measurement \( (p<0.05) \) (Tables 10.1 & 10.2). Conversely, practice nurses were most likely to perform ABI measurement with 64% having received training for the procedure and 71% of practice nurse survey responders being compliant with ABI measurement guidelines. In general, nurses were much more likely to have received training for ABI measurement and more likely to be adhering to current ABI guidelines.
<table>
<thead>
<tr>
<th>General Practitioners</th>
<th>Practice Nurses</th>
<th>Nurse Practitioners</th>
<th>District Nurses</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Who typically perform ABI measurement within General Practices?</td>
<td>5.2 (5/95)</td>
<td>50.5 (48/95)</td>
<td>7.4 (7/95)</td>
<td>9.5 (9/95)</td>
</tr>
<tr>
<td>% who consider themselves or are considered by colleagues to be competent at ABI measurements</td>
<td>11</td>
<td>48</td>
<td>56</td>
<td>60</td>
</tr>
<tr>
<td>Training</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of General Practices with staff trained for ABI measurement</td>
<td>3</td>
<td>30</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>% of respondents who currently undertake ABI measurement and have received ABI training</td>
<td>20</td>
<td>64</td>
<td>43</td>
<td>100</td>
</tr>
<tr>
<td>ABI Methodology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% who correctly identified ABI method and equipment according to current guidelines:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All respondents</td>
<td>38</td>
<td>71</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>Respondents currently undertaking ABI measurement</td>
<td>0</td>
<td>68</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>1. % who would rest patients prior to ABI measurement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All respondents</td>
<td>65</td>
<td>93</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Respondents currently undertaking ABI measurement</td>
<td>0</td>
<td>89</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2. % who identified correct equipment used for Brachial SBP measurement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All respondents</td>
<td>80</td>
<td>93</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>Respondents currently undertaking ABI measurement</td>
<td>80</td>
<td>96</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>3. % who said they would measure the brachial SBP in both arms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All respondents</td>
<td>86</td>
<td>93</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Respondents currently undertaking ABI measurement</td>
<td>20</td>
<td>93</td>
<td>100</td>
<td>100</td>
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<tr>
<td>4. % who identified correct equipment used for Ankle SBP measurement</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>All respondents</td>
<td>88</td>
<td>96</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Respondents currently undertaking ABI measurement</td>
<td>80</td>
<td>96</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>5. % who said they would assess more than one foot/ankle arteries</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All respondents</td>
<td>83</td>
<td>93</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Respondents currently undertaking ABI measurement</td>
<td>60</td>
<td>93</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>6. % who said they would calculate ABI by dividing the highest ankle SBP by the higher brachial SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All respondents</td>
<td>46</td>
<td>75</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Respondents currently undertaking ABI measurements</td>
<td>20</td>
<td>79</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>% who experience difficulty locating ankle/foot pulses</td>
<td>54</td>
<td>59</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>% who experience difficulty maintaining position of Doppler probe whilst simultaneously pumping up BP cuff</td>
<td>39</td>
<td>33</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 10.1 Summary of general practice survey results
<table>
<thead>
<tr>
<th>Variable 1</th>
<th>Variable 2</th>
<th>Pearson’s Chi Square ($\chi^2$)</th>
<th>Fisher’s Exact Test</th>
<th>Significant Standardised Residuals and Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respondent Occupation</td>
<td>Correct/Incorrect methodology and equipment identified for ABI measurement</td>
<td>22.719</td>
<td>3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Respondent Occupation</td>
<td>Reports resting patients prior to ABI measurement?</td>
<td>20.612</td>
<td>6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Respondent Occupation</td>
<td>Reports use of automated equipment to measure brachial blood pressure?</td>
<td>1.876</td>
<td>3</td>
<td>0.518</td>
</tr>
<tr>
<td>Respondent Occupation</td>
<td>Reports assessment of only 1 pulse at the ankle?</td>
<td>17.867</td>
<td>6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Respondent Occupation</td>
<td>Difficulty finding pulses?</td>
<td>4.366</td>
<td>6</td>
<td>0.517</td>
</tr>
<tr>
<td>Respondent Occupation</td>
<td>Difficulty maintaining position of probe whilst inflating blood pressure cuff?</td>
<td>0.701</td>
<td>3</td>
<td>0.873</td>
</tr>
<tr>
<td>Respondent Occupation</td>
<td>Difficulty calculating ABI?</td>
<td>4.176</td>
<td>3</td>
<td>0.385</td>
</tr>
<tr>
<td>Respondent Occupation</td>
<td>Specified medical management of patients with PAD</td>
<td>30.210</td>
<td>6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ABI Training Status (received specialist training for ABI measurement or not?)</td>
<td>Correct/Incorrect methodology and equipment identified for ABI measurement</td>
<td>15.213</td>
<td>3</td>
<td>&lt;0.01</td>
</tr>
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<td>ABI Training Status (received specialist training for ABI measurement or not?)</td>
<td>Difficulty finding pulses?</td>
<td>3.707</td>
<td>4</td>
<td>0.260</td>
</tr>
<tr>
<td>ABI Training Status (received specialist training for ABI measurement or not?)</td>
<td>Difficulty maintaining position of probe whilst inflating blood pressure cuff?</td>
<td>2.070</td>
<td>4</td>
<td>0.355</td>
</tr>
<tr>
<td>ABI Training Status (received specialist training for ABI measurement or not?)</td>
<td>Difficulty calculating ABI?</td>
<td>0.061</td>
<td>2</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Table 10.2: Statistical analysis of general practice survey results
<table>
<thead>
<tr>
<th>Variable 1</th>
<th>Variable 2</th>
<th>Pearson’s Chi Square (χ²)</th>
<th>Fisher’s Exact Test</th>
<th>Significant Standardised Residuals and Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI Training Status (received specialist training for ABI measurement or not?)</td>
<td>Difficulty maintaining position of probe whilst inflating blood pressure cuff?</td>
<td>2.070</td>
<td>4</td>
<td>0.355</td>
</tr>
<tr>
<td>ABI Training Status (received specialist training for ABI measurement or not?)</td>
<td>Difficulty calculating ABI?</td>
<td>0.061</td>
<td>2</td>
<td>0.97</td>
</tr>
<tr>
<td>ABI Training Status (received specialist training for ABI measurement or not?)</td>
<td>Frequency of ABI measurement</td>
<td>18.13</td>
<td>10</td>
<td>0.053</td>
</tr>
<tr>
<td>Origin of specialist ABI training</td>
<td>Correct/Incorrect methodology and equipment identified for ABI measurement</td>
<td>16.68</td>
<td>11</td>
<td>0.118</td>
</tr>
<tr>
<td>Frequency of ABI measurement</td>
<td>Correct/Incorrect methodology and equipment identified for ABI measurement</td>
<td>17.66</td>
<td>5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Frequency of ABI measurement</td>
<td>Difficulty finding pulses?</td>
<td>3.71</td>
<td>4</td>
<td>0.447</td>
</tr>
<tr>
<td>Frequency of ABI measurement</td>
<td>Difficulty maintaining position of probe whilst inflating blood pressure cuff?</td>
<td>2.07</td>
<td>2</td>
<td>0.355</td>
</tr>
<tr>
<td>Frequency of ABI measurement</td>
<td>Difficulty calculating ABI?</td>
<td>0.06</td>
<td>2</td>
<td>0.97</td>
</tr>
<tr>
<td>Respondent Health Board</td>
<td>Correct/Incorrect methodology and equipment identified for ABI measurement</td>
<td>6.31</td>
<td>6</td>
<td>0.389</td>
</tr>
</tbody>
</table>

Table 10.2: Statistical analysis of general practice survey results
Points of ABI methodology assessed

<table>
<thead>
<tr>
<th>Points of ABI methodology assessed</th>
<th>Correct Responses</th>
<th>Incorrect Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient rested for at least 10 minutes prior to ABI measurement?</td>
<td>Yes (n=52)</td>
<td>No (n=11) Reason: Lack of time (n=8) Not considered necessary (n=3)</td>
</tr>
<tr>
<td>2. Equipment used for measurement of brachial systolic blood pressure?</td>
<td>Sphygmomanometer &amp; Doppler Ultrasound (n=46)</td>
<td>Automated blood pressure monitor (n=2) Stethoscope (Korotkoff method) (n=4)</td>
</tr>
<tr>
<td>3. Both brachial systolic blood pressures measured?</td>
<td>Yes (n=44)</td>
<td>No (n=2)</td>
</tr>
<tr>
<td>4. Equipment used for measurement of ankle systolic pressure?</td>
<td>Sphygmomanometer &amp; Doppler Ultrasound (n=44)</td>
<td>None (n=0)</td>
</tr>
<tr>
<td>5. Number of pulses assess on each foot/ankle?</td>
<td>More than one (n=42)</td>
<td>One (n=2)</td>
</tr>
<tr>
<td>6. Calculates the ABI by dividing the higher of the ankle systolic pressures by the higher of the brachial systolic pressures?</td>
<td>Yes (n=37)</td>
<td>No (n=5) Variations: Divides the lower ankle pressure by the lower brachial pressure (n=3) Divides the average ankle pressure by the average brachial pressure (n=2)</td>
</tr>
</tbody>
</table>

RESULTS
- 38.9% (37/95) of responding general practices are utilising correct method of ABI measurement and/or calculation according to current guidelines.
- 28.4% (27/95) of responding general practices are utilising incorrect method of ABI measurement and/or calculation according to current guidelines.
- 27.4% (26/95) of responding general practices do not undertake ABI measurements.

(Incomplete data for remaining 5.3%)

Figure 10.4: Diagrammatic representation of general practice survey responses
10.0.5 Methodology utilised for ABI measurement
There was considerable variation in the method utilised for ABI measurement and calculation. Only 58% of general practices undertaking ABI measurements were found to be compliant with current guidelines for the procedure. Figure 10.4 illustrates the proportion of survey responses which successfully progressed through each of the methodology assessment points as described in Table 6.2. Eighteen per cent of practices reported not resting their patients in the supine position prior to ABI measurement. Lack of time was the primary reason for not doing this (75%), whilst the remaining 25% of respondents thought it was unnecessary. Five per cent of respondents reported utilising the Korotkoff method to measure the brachial systolic pressure with a further 2% reportedly using automated blood pressures devices. Furthermore, 13% of respondents said that they would measure the brachial systolic pressure in one arm only. Thirty three per cent of respondents reported not calculating ABIs according to current guidance. In 17% of cases, this was because only one brachial pressure and/or only one ankle pressure had been measured. A further 12% reported using the lower of the ankle and/or brachial pressures, whilst the remaining 4% used the average of the ankle and/or brachial pressures when calculating the index.

10.0.6 Reported difficulties associated with ABI measurement
A large proportion of respondents reported difficulty in (i) locating pulses in the foot/ankle (59%), and (ii) maintaining the position of the Doppler probe whilst inflating the blood pressure cuff (33%). The survey provided opportunity to expand on these issues and 9% of respondents (all of which were nurses) independently stated that they addressed these problems by utilising another health professional to assist with the procedure.

10.0.7 Prior training for ABI measurement
Seventy six per cent (28:37) of respondents who were in compliance with current guidelines for ABI measurement reported having received formal training for the procedure. Accordingly, 73% (38:52) of respondents who were not in compliance with current guidelines had not received any formal training (p<0.05).
Training originated from a variety of sources with Tissue Viability Nurses/Wound Care Practitioners accounting for the largest proportion (41%). Eighty two per cent of respondents who received training from these clinical nurse specialists reporting measuring ABI’s in accordance with current guidance. Training via specialist clinics or as part of a formalised course also appears effective in achieving compliance with guidelines (Figure 10.5). Five per cent of respondents expressed their
frustration at a lack of refresher or update ABI education/courses to enable them to maintain their competency in the procedure.

Figure 10.5: Correct ABI measurement according to origin of training
Blue: correct, Red: incorrect

10.0.8 Subsequent management of patients found to have PAD.
Respondents were asked to indicate any medical management which they would instigate or expect to be instigated for patients who were found to have PAD. Twenty nine per cent referred to “aggressive” cardiovascular risk factor modification such as commencing antiplatelets, control of hypertension and hyperlipidaemia in combination with lifestyle advice; this is in line with current guidance issued by the European Society of Cardiology (Tendera et al., 2011) and National Institute for Health and Care Excellence (NICE, 2012a). A further 8% mentioned a lesser degree of cardiovascular risk modification involving only lifestyle factors such as encouraging smoking cessation and exercise. GPs were more likely to have mentioned cardiovascular disease risk factor modification than nurses (56% versus 16%, p<0.05).

10.1 Discussion
Results indicate that ABI measurement is very much a nursing task which is, at present, mainly performed for the purpose of wound management rather than for cardiovascular risk assessment. It is only utilised at approximately three quarters of respondents from general practices in Wales and those that do utilise it, do so on an infrequent basis. According to a literature review conducted by
Sihlangu & Bliss (2012), this raises issues of competency as studies have demonstrated greater variability in ABIs when measured by less experienced practitioners (Kaiser et al., 1999; Mätzke et al., 2003). In addition, this survey found that a large proportion of respondents experienced difficulties with the skilled or technical aspects of the procedure such as locating ankle pulses and maintaining the position of the Doppler probe; it is possible that these difficulties were also related to inexperience. A survey by Mohler et al. (2004) found that primary care staff reported increased use of the ABI following their participation in a PAD/ABI training programme. However, the survey was completed 1-3 months following programme completion so it is not known if this increase would have been sustained over a longer time period. This survey found that practices where no-one had received specialist training for ABI measurement were less likely to be performing the procedure (p<0.05).

10.1.1 Factors associated with deviations from the guideline advocated method of ABI measurement

This survey has found that deviations from the guideline advocated method of ABI measurement are commonplace and two inter-related factors have emerged as important with regard to this. The first concerns the time it takes to perform the measurement, as the majority of deviations can be attributed to attempts to reduce this. Not resting patients prior to measurement, using automated blood pressure monitors, measuring the brachial pressure in one arm only and assessing only one ankle pulse all equate to a reduction in the time it takes to perform the test. Mohler et al. (2004) and Bendermacher (2012) found that lack of time was a barrier to the use of the ABI in primary care. This issue is further compounded by the fact that the procedure sometimes requires two health care personnel. Results indicate that GPs are more likely to resort to these time-saving strategies (p<0.05) and this is not surprising considering that their allocated time for a complete patient consultation is often only 10 minutes.

The second factor concerns training, with those who had undergone specialised training for the procedure being much more likely to be adhering to the guidelines advocated method (p<0.01). Hence, it appears that training successfully educates practitioners regarding the importance of not “cutting corners” at the expense of the accuracy of results. Mohler et al. (2004) found that a targeted educational initiative can have significant impact on the use of the ABI in clinical practice which could offer dramatic benefits to improve PAD diagnosis.
10.1.2 Rationale for a standardised ABI methodology

The wider implications of clinicians not adhering to the guidelines and advocated methodology require consideration. Aboyans and colleagues (2012) recently highlighted that a lack of standardised ABI methodology is likely to have significant clinical, public health and economic repercussions. From a clinical perspective, a lack of ABI standardisation could lead to inappropriate clinical decisions as a result of PAD diagnoses being based on different measurement techniques and parameters. Furthermore, in Chapter 2 it was noted that varying ABI methodologies and diagnostic thresholds were also likely to have had profound effects from a research perspective; this was evidenced as significant variation in PAD prevalence estimates and data provided in the research studies detailed in Table 2.1; this subsequently made comparison of these data very difficult.

Techniques for the measurement of other vascular markers such as carotid intima-media thickness (Stein et al., 2008) or coronary artery calcium score (Greenland et al., 2007) have been standardised; Aboyans et al. (2012) argue that the same should be true for ABI measurement. They subsequently released a scientific statement setting out an evidence-based, recommended procedure for ABI measurement and interpretation; this concurs with the methodology assessed by this survey. The clinical rationale for the choice of this specified methodology arises from the fact that it has been utilised in the majority of studies demonstrating the association between low ABI and CV risk; it is not known whether the strength of these associations would differ with alternative measurement methods and thresholds of ABI.

10.1.5 Management of PAD patients

The under treatment of PAD patients has been well documented; the global Reach Registry demonstrated that patients with PAD were significantly less likely to be at target blood pressure, cholesterol and glucose levels in comparison to patients with coronary artery disease or cerebrovascular disease (Bhatt et al., 2006). The recent publication of PAD guidelines by various organisations (ESC: Tendera et al., 2011; NICE, 2012a) and the addition of PAD indicators to the 2012/13 Quality and Outcomes Framework (NICE, 2012b) in the UK may have served to increase awareness and improve the treatment of PAD. In addition, general practice computer software systems in the UK, such as EMIS (Egton Medical Information Systems), now generate pop-up reminders to consider an antiplatelet, and check blood pressure and serum lipids when coding a new diagnosis of peripheral arterial disease. It is difficult to establish if data from this survey represent improved medical management of PAD patients. It is clear however, that the large majority of nurses who responded to the survey consider the ABI only in terms of its repercussions for leg ulcer/wound management and are unaware of its association with increased cardiovascular risk.
10.3 Study Strengths and Limitations

The response rate to this survey was low but not atypical, as published medical practitioners response rates are often lower than 30% (Britt et al., 2007; Grava-Gubins and Scott, 2008). Mohler et al. (2004) utilised a survey to assess the utility and barriers to the use of the ABI in primary care practice. Primary care staff (physician and non-physicians) that had one month previously undergone a PAD and ABI preceptorship programme were either given or mailed the survey. It could be assumed that this participation in an educational programme would have served to raise awareness of the relevance of the survey and yet the response rate was still only 24%. Nevertheless, the possibility of response bias needs to be borne in mind when considering results of this survey. It is possible that those who do not utilise the ABI may have been less likely to complete the survey and hence its use may be over-estimated. Furthermore, the small number of nurse practitioner and district nurse respondents means that results relating to these occupational groups may not be representative of the professions as a whole. These limitations acknowledged, this survey is, to the authors’ knowledge, the only assessment of the utility of the ABI in the UK. Representation from both nurses and physicians from general practices in all areas of Wales has been achieved.

This study targeted primary care practitioners that were based within general practices as it is here that screening strategies are likely to be undertaken. It is acknowledged that ABI skills and knowledge exist in other sectors of primary care such as district nursing teams and podiatry for example. In addition, the usual validity concerns regarding self-reported behaviour in surveys apply and issues such the accuracy and reproducibility of ABI measurements have not been addressed. Hence these two points provide a focus for future research.

10.4 Conclusions

ABI measurement is an under-utilised and often incorrectly performed procedure in the surveyed general practices; lack of time and inadequate training have been identified as factors associated with this finding. Previous research undertaken in the USA (Mätzke et al., 2003) and the Netherlands (Nicolaï et al., 2009) made remarkably similar conclusions hence demonstrating that these identified issues are historically problematic and not confined to Wales and the UK.

Prior to the potential adoption of the ABI as a formalised screening tool for cardiovascular disease, there is a need for a robust training programme with standardised methodology in order to optimise accuracy and consistency of results. ABI Training programmes should include the methodological requirements for accurate and reproducible ABI measurement, as well as the theoretical basis and limitations of the test. The subsequent implications of a reduced ABI with regard to cardiovascular risk also need to be highlighted.

[This chapter has been published as an academic paper in the BMC Family Practice Journal (Appendix 15)].
Part 3: Summary of Conclusions

Who should potential PAD screening strategies target?

Who should undertake any potential PAD screening strategies?

- PAD screening should target individuals aged 50+ with a history of smoking (either current or ex-smokers).

- Further narrowing of the target population to patients with either at least one clinical sign of PAD or rheumatoid arthritis would greatly improve screening efficiency whilst maintaining a high sensitivity (92%) for PAD detection.

- The prevalence of high ABI within the study population was twice the prevalence of PAD. As it is unclear whether this represents increased CV risk, further CV risk assessment and/or PAD assessment with a superior diagnostic modality for individuals with high ABI may be warranted.

- Practitioners within general practices in Wales currently lack sufficient skills and knowledge of both ABI measurement and PAD, to undertake any formalised PAD screening strategy using the ABI as the diagnostic screening tool.

- Lack of time has been identified as a major barrier to the use of the ABI in general practice.

- As the QRISK®2 CV risk algorithm identified high CV risk in 92% of the PAD group, this then appears to offer a more viable alternative to the ABI for detecting high CV risk in the primary care setting.
Part 4 : HOW?

How should PAD screening be undertaken?
**Part 4: Prelude**

A review of the literature reveals six possible methods for the non-invasive identification of PAD (Figure P4.1 below). The aim of part 4 of this thesis is to explore and compare four of these methods via assessment of their accuracy, advantages, limitations and suitability for use within a non-specialist environment for the purpose of PAD screening.

![Diagram of Non-invasive identification of PAD methods](image)

**Part 4 prelude, figure 1: Methods of non-invasive PAD identification**

Chapter 11 presents background information with regard to the underlying technology of the diagnostic equipment discussed within part 4.

Chapters 12 and 13 detail the results of the DUAL study which involved a comparison of an automated pneumoplethysmographic ABI device with the traditional Doppler ultrasound method for ABI measurement; it considers the agreement, patient perspective and time taken to perform each of the measurement techniques.

Chapter 14 presents background information on pulse volume wave form analysis which is an alternative non-invasive method of diagnosing PAD.
Chapter 15 details the analysis of pulse volume waveforms from the PIPETTE study with consideration of their utility for PAD diagnosis.

Chapter 16 considers how the Edinburgh claudication questionnaire and clinical examination contributed to PAD diagnosis within the PIPETTE study.
Chapter 11: Technological background information

The ankle brachial index is considered the cornerstone of non-invasive diagnosis of PAD and the gold standard methodology for its measurement entails the use of a hand-held Doppler ultrasound device in combination with a manual sphygmomanometer. There are however, well documented issues associated with Doppler ABI measurements, the most significant of which relate to the skills and time needed to perform test. This ultimately results in infrequent and incorrect use of the ABI particularly in non-specialist environments such as primary care (Chapter 10). This, combined with the fact that there is increasing interest in the ABI as a marker of cardiovascular risk, has undoubtedly been the catalyst in the quest to develop an automated ABI device. The past decade has seen the introduction of several automated ABI devices to the commercial market. Such devices utilise varying modalities including oscillometry, photoplethysmography and less commonly, pneumoplethysmography, to measure and calculate the ABI. Background information regarding the underlying technology of such devices is discussed below.

11.0 Continuous wave Doppler ultrasound: background information.

Hocken (1967) was the first to note that using a stethoscope to identify Korotkoff sounds was not a satisfactory method of determining ankle blood pressure. Two years later, Yao et al. (1968) reported using ultrasound and the Doppler effect as a new method of recording arterial flow; this method remains the current gold standard for determining the systolic blood pressures in both the arms and legs for ABI calculation.

Continuous wave Doppler ultrasound (CWDU) involves the transmission of an ultrasound wave via a probe and an acoustic coupling gel into the body. The ultrasonic beam is reflected back to a receiver in the probe by all the structures in its path, including moving red blood cells. The movement of red blood cells causes a frequency shift (Doppler shift) in the reflected sound wave which is proportional to blood flow velocity. The reflected frequency is higher or lower than the transmitted frequency depending on the direction of flow relative to the Doppler beam. The signal is electrically mixed with the transmitting frequency and processed to produce a frequency in the audible range. Listening for the return of this audible sound following the deflation of a blood pressure cuff is used to determine the arterial systolic blood pressure of a limb, which can then be used to calculate the ABI. In addition to this, trained technicians can distinguish normal signals from those received proximal to, within, or distal to a stenosis or occlusion (AbuRahma and Jarrett, 2010). Figure 11.1 shows measurement of the systolic pressure at the ankle using a hand-held CWDU with a sphygmomanometer.
It should be noted that the use of the CWDU to determine blood pressures represents its utility in its simplest form. Extensions of its functions include, for example, the use of segmental Doppler pressures to localise disease, and colour spectral waveform analysis whereby the Doppler signal has been converted to visible analogue waveforms. Such uses are not a focus of the current research and hence are not considered further within this thesis.

![Measurement of ankle systolic pressure](image)

**Figure 11.1**: Measurement of ankle systolic pressure (at the posterior tibial artery) using a hand-held continuous wave Doppler ultrasound with sphygmomanometer. (Image source: Huntleigh Diagnostics: reproduced with permission)

### 11.1 Automated pneumo-plethysmographic ABI device: background information.

The automated device (AD) utilised within the studies reported in this thesis was a Dopplex Ability (Huntleigh Healthcare, UK); this is a recently developed system which utilises pneumo-plethysmography to measure systolic pressures in all four limbs simultaneously before automatically calculating the ABI. It consists of four dual-chamber cuffs which are applied to each of the patient’s limbs. Figure 11.2 shows a diagrammatic version of the AD and Figure 11.3 shows the AD in use. The cuffs are colour coded to ensure that they are applied to specific limbs. Each cuff consists of an upper occlusion chamber and a lower sensor chamber. For the arms: the occlusion chamber is applied to the upper-arm in the same way that a standard blood pressure cuff would be applied. The attached sensor chamber is then applied to the forearm (Figure 11.4). As with standard blood pressure measurement, it is important that the correct size cuff is used; the AD has a set of standard cuffs and large cuffs with clearly defined range markers. The connecting strip between chambers (marked with a white line) must be positioned over the brachial artery.
Figure 11.2: Diagrammatic representation of the automated device
(Image source: Huntleigh Diagnostics: reproduced with permission)

Figure 11.3: Measurement of the ABI using the automated device
(Image source: Huntleigh Diagnostics: reproduced with permission)
For the legs: the occlusion chamber is applied to the lower leg just above the malleolus, and the sensor chamber is applied around the foot at the metatarsal level (Figure 11.5).
The test is fully automated so when the patient is correctly positioned and the cuffs applied as described, the operator then presses the start button to commence a series of measurements. The test series starts by inflating the ankle cuffs to 45mmHg. This pressure is sufficient to occlude venous blood flow whilst maintaining arterial blood flow. It also provides adequate contact between the cuff bladder and the limb segment, without reducing the transmural pressure in the underlying arteries which could distort the recorded pulse contour. At this point, the AD records five seconds of pulse volume waveforms (PVWs) for each leg. Next, the arm cuffs inflate until the sensor-chamber detects that the arterial pulse has been occluded. The occlusion chamber then inflates a further 30mmHg (or to a maximum of 230mmHg) before slowly deflating at a rate of 4mmHg sec\(^{-1}\). During deflation the volume change in the distal (sensor) chamber is measured. The point at which this volume increases is the systolic pressure in the occlusion chamber. This is recorded as the systolic blood pressure of that limb. Next, the leg occlusion cuffs inflate to 180mmHg (Phase 1 inflation) and deflate to 50mmHg, and again the pressure at which the volume increases in the sensor chamber is recorded as the systolic pressure of that limb. If the AD detects that the leg arterial pulse(s) were not occluded at the maximum occlusion pressure of 180mmHg, a second cycle of leg cuff inflation occurs (phase 2 inflation), this time the occlusion cuffs inflate to a maximum occlusion pressure of 230mmHg and deflate to 140mmHg. The AD then collates the systolic pressures collected and automatically calculates the ABIs. The results are displayed on the screen of the AD and can also be printed out. An example of a Dopplex Ability printout is shown in Figure 11.6; it can be seen that the systolic pressures of each limb are shown, as well as the ABI and pulse volume waveform recording for each leg.

![Figure 11.6: An example of an automated device results print-out.](image.png)

It is also possible to connect the AD to a laptop so that results can be electronically recorded and retained for further analysis. Plots of occlusion and detection pressures versus time, which map the deflation of the cuffs and detection of the volume changes in the sensor chambers, can be viewed...
for each limb; from these it is possible to see how the systolic pressures were determined. The plots corresponding to the results shown in Figure 11.6 are shown in Figure 11.7. There is an individual plot for each limb.

The left arm plot has been enlarged in Figure 11.8 in order to assist in the explanation of how the systolic pressures are derived. It can be seen that the red line represents the decreasing pressure in the occlusion chamber [1], whilst the blue line represents the pressure in the sensor chamber [2]. Note that the scale for the occlusion chamber pressure (shown in red, on the left of the plot) is different to the scale for the sensor or detect chamber pressure (shown in blue, on the right of the plot). As the pressure in the occlusion chamber decreases, the pressure in the sensor chamber also gradually decreases until the point at which the arterial blood supply returns; this manifests itself as an upturn in the pressure (or volume) and a return of visible arterial pulsations [3]. When this happens, the corresponding pressure in the occlusion chamber [4] is taken to be the arterial systolic pressure of that limb; this is represented by the orange lines in Figure 11.7 and Figure 11.8.
Figure 11.7: Automated device plots depicting measurement of arterial systolic blood pressures per limb.
Figure 11.8: Diagrammatic representation of how the automated device measures limb arterial systolic pressures

1. Decreasing pressure in the occlusion chamber
2. Decreasing pressure in the sensor chamber
3. Point at which the pressure in the sensor chamber starts to increase and the arterial pulsations become visible.
4. Corresponding point (of arterial blood supply return) in the occlusion chamber. The pressure at this point (130 mmHg) is taken as the arterial systolic blood pressure of the limb.
11.1.1 Conditions for measurement of the ABI with the automated device

Patients must be supine for measurement of the ABI with the AD. However, the manufacturers state that as all four limb pressures are measured simultaneously, there is no need for a rest period prior to the measurement (as is required for ABI measurement with a Doppler ultrasound).

It is imperative that patients remain still and refrain from talking during the AD ABI measurement; failure to do so can produce a ‘noisy’ signal within the sensor chambers which, in turn, can lead to failed measurements or inaccurate results. Example of graphs showing artefact as a result of patient movement are shown in Figure 11.9. It can be seen that whilst the left arm, left leg and right leg all show artefact, the right arm does not.

11.2 Automated Oscillometric Devices

Oscillometric ABI devices function by detecting the pulsation of the artery, which is caused by contraction of the heart, as the pressure oscillation in the cuff. When the cuff around the limb is fully inflated, blood flow stops but pulsation of the artery continues and causes oscillation of the pressure in the cuff. As the pressure in the cuff is decreased slowly, the magnitude of the pressure oscillation in the cuff gradually increases and eventually reaches a peak. Further decreases of the cuff pressure cause the oscillation to decrease. The relationship between the change of pulse pressure and actual pressure is stored in memory and used to determine blood pressure. The cuff pressure when the oscillation increases rapidly is taken as systolic pressure, and that when the oscillation decreases rapidly is taken as the diastolic pressure.
Figure 11.9: Automated device plots showing artefact as a result of patient movement.
Chapter 12: The DUAL study results: ABI agreement between the Doppler and automated ABI device

12.0 Results

12.0.1 Automated device failed measurements

The automated device (AD) measurement failure rate was 5.3% (41/775). A measurement failure was deemed to have occurred if the automated device failed to provide an ABI result. Of the 41 failed measurements, the AD indicated that 16 were due to systolic pressures of one or more of the limbs being out-of-range. According to the manufacturer’s guidelines, out-of-range is defined as <80mmHg or >230mmHg for arm systolic pressures, and >205mmHg for leg systolic pressures. For a further 18 measurements, the AD indicated that the software algorithms were unable to calculate the systolic pressures of one or more of the limbs. For the remaining seven measurements, the AD failed to provide any result or error message.

Statistical analysis of the study population was undertaken to determine if there were any factors which were associated with failure of the AD to produce an ABI result (Table 12.1). A greater proportion of the individuals (to which the measurements pertained) within the failed measurements group had hypertension than in the successful measurements group (92% versus 75%, p=0.015).

As discussed in Section 11.1, the software which accompanies the AD allows viewing of the plots of occlusion and detection pressures versus time, which map the deflation of the cuffs and detection of the arterial pulse. From these, it is possible to see how systolic pressures were determined and also gain information regarding possible causes of measurement failure.

Inspection of the occlusion and detection plots of the failed AD measurements revealed four possible reasons for measurement failure (Table 12.2).
<table>
<thead>
<tr>
<th>Variable</th>
<th>Automated ABI device:</th>
<th>Statistical Test &amp; Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ABI result successfully obtained</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>N=734</em></td>
<td></td>
</tr>
<tr>
<td>Gender (male:female)</td>
<td>56:54</td>
<td>49:51</td>
</tr>
<tr>
<td>Age: mean (SD) Range</td>
<td>64(8)</td>
<td>64(8)</td>
</tr>
<tr>
<td></td>
<td>45-86</td>
<td>48-81</td>
</tr>
<tr>
<td>Height: mean (SD) Range</td>
<td>1.67(0.1)</td>
<td>1.6(0.7)</td>
</tr>
<tr>
<td></td>
<td>1.45-1.91</td>
<td>1.5-1.85</td>
</tr>
<tr>
<td>BMI: mean (SD) Range</td>
<td>29.1(5)</td>
<td>29.4(6)</td>
</tr>
<tr>
<td></td>
<td>19-54</td>
<td>20-46</td>
</tr>
<tr>
<td>QRisk2 Relative Risk: Mean (SD)</td>
<td>1.4(0.6)</td>
<td>1.43(0.3)</td>
</tr>
<tr>
<td></td>
<td>0.6-5.6</td>
<td>0.7-2.7</td>
</tr>
<tr>
<td>PAD Status Group* (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>98</td>
<td>2</td>
</tr>
<tr>
<td>Borderline PAD</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>Normal ABI</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>High ABI</td>
<td>91</td>
<td>9</td>
</tr>
<tr>
<td>% with Dyslipidaemia</td>
<td>79</td>
<td>87</td>
</tr>
<tr>
<td>% with hypertension</td>
<td>75</td>
<td>92</td>
</tr>
<tr>
<td>Total number of CV risk factors (%)</td>
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<td>0</td>
</tr>
<tr>
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<td>100</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>93</td>
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</tr>
<tr>
<td>4</td>
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<tr>
<td>5</td>
<td>92</td>
<td>8</td>
</tr>
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<td>6</td>
<td>88</td>
<td>12</td>
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<tr>
<td>Software Version (%)</td>
<td></td>
<td></td>
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<tr>
<td>224</td>
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</tr>
<tr>
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<td>237</td>
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<tr>
<td>242</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 12.1: Statistical analysis of factors associated with failed measurements according to the automated device
1. Artefact in the detection plots, which may, for example, have been caused by subject movement during the measurement procedure, can prevent the AD from being able to detect a returning arterial pulse following its occlusion. This resulted in measurement failures in seven cases. An example of measurement failure due to artefact is shown in Figure 12.1.

2. There were six cases where the first inflation of the leg cuffs was insufficient to occlude the arterial pulse. When this happens, the AD leg cuffs should automatically go to a second inflation to a higher end pressure (230mmHg); however, this failed to happen in these cases and measurement failures ensued. An example showing a measurement failure due to this type of error is shown in Figure 12.2.

3. The AD is programmed so that if a leg systolic pressure is detected that is above 205mmHg, it will not display the result nor utilise it to calculate an ABI. Hence it would appear that measurement failure had occurred in such cases (n=12). Not displaying ankle systolic pressures that are >205mmHg is based on the presumption that such pressures could be artefactually elevated; this is intended to alert the operator of this possible inaccuracy.

4. For the remaining 15 cases, a reason for measurement failure could not be determined for the reasons outlined in Table 12.2.

<table>
<thead>
<tr>
<th>Reason for measurement failure</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Artefact evident in arterial detection signal(s)</td>
<td>17% (7)</td>
</tr>
<tr>
<td>2. Failure of Dopplex Ability to go to second inflation of leg cuff(s)</td>
<td>15% (6)</td>
</tr>
<tr>
<td>3. High ankle systolic pressures not displayed by Dopplex Ability</td>
<td>30% (12)</td>
</tr>
<tr>
<td>4. Unknown</td>
<td>38% (16)</td>
</tr>
<tr>
<td>- Plots not available for inspection (recording failure)</td>
<td>15% (6)</td>
</tr>
<tr>
<td>- Complete device failure (no results available)</td>
<td>15% (6)</td>
</tr>
<tr>
<td>- Unable to determine reason for measurement failure</td>
<td>8% (3)</td>
</tr>
</tbody>
</table>

Table 12.2: Reasons for automated device measurement failures as determined via inspection of occlusion and detection plots.
Figure 12.1: Measurement failure due to artefact in detection plot of left leg, phase 2.
Figure 12.2: Measurement failure due to failure of the right leg cuff to go to phase 2 inflation (phase 1 right leg does not occlude arterial pulse).
12.0.2 Assessment of agreement between Doppler ultrasound method and automated device

Agreement between the Doppler ultrasound method and automated ABI device was assessed using five statistical strategies:

1. Visual assessment of the data via Bland-Altman plot with calculation of 95% limits of agreement.
2. Calculation of the data correlation coefficient.
3. Calculation of the variability between the two measurement techniques.
4. Calculation of the automated device’s sensitivity for detecting PAD and specificity for ruling it out, using the Doppler ABI results as the reference standard.
5. Agreement of classification using Cohen’s kappa statistic.

Whilst some of these tests equate to different ways of assessing the same end-point, all five have been undertaken as they are the most commonly used statistical assessment strategies utilised by similar existing studies, and this therefore aids in comparison of results.

Bland Altman Plot

The Bland Altman plot and equality plot of the results from the Doppler ultrasound and the AD are shown in Figures 12.3 and 12.4 respectively. The mean difference, or bias, between the two measurements was 0.02 ± 0.11, which means that on average, the automated device returned slightly lower ABIs than the Doppler ultrasound. The absolute mean difference between the measurements was 0.08 ± 0.08. 95% limits of agreement between the two measurement techniques were ± 0.22.
Figure 12.3: Agreement between Doppler ultrasound method and automated ABI device

- mean difference or bias
- 95% confidence limit (±1.96*SD)

Figure 12.4: Equality plot of Doppler ultrasound ABI and automated device ABI

- Regression line
- 95% CI
- line of equality
Correlation Coefficient
A Spearman's rank-order correlation was run to assess the relationship between the Doppler ultrasound ABI results and the automated device ABI results. Preliminary analysis showed the relationship to be monotonic, as assessed by visual inspection of the equality plot (Figure 12.4). There was a moderate positive correlation between the two measurement techniques, \( r_s(727) = 0.6, \ p < 0.005 \).

Inter-observer variability
The inter-observer variability (IOV) of the full DUAL dataset is 10.2%. Variability was higher for diseased participants than for non-diseased participants (Table 12.3).

<table>
<thead>
<tr>
<th></th>
<th>PAD group</th>
<th>Borderline PAD group</th>
<th>Normal ABI group</th>
<th>High ABI group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variability</td>
<td>10.6%</td>
<td>10.0%</td>
<td>9.7%</td>
<td>11.7%</td>
</tr>
</tbody>
</table>

Table 12.3: Variability of Doppler ultrasound ABI results and automated device ABI results according to PAD status.

Sensitivity and specificity for PAD diagnosis.
A final simplistic method of data analysis involves assessment of the accuracy of the automated ABI device in comparison to a gold standard, which in this case is the Doppler ultrasound (Table 12.4).

<table>
<thead>
<tr>
<th></th>
<th>Automated ABI device</th>
<th>Non-PAD</th>
<th>PAD</th>
<th>Negative Predictive Value</th>
<th>Positive Predictive Value</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-PAD</td>
<td>TN: 637</td>
<td>FN: 12</td>
<td></td>
<td>=TN/(TN+FN)=98%</td>
<td>=TP/(TP+FP)=47%</td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>FP: 41</td>
<td>TP: 37</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

specificity= TN/(TN+FP)=94%  Sensitivity= TP/(TP+FN)=76%  Accuracy= TN+TP/(TN+FN+FP+TP)= 93%

Table 12.4: Accuracy calculations of automated ABI device compared to gold standard Doppler ultrasound. (TN=true negative, FN=false negative, FP=false positive, TP=true positive).

Cohen’s Kappa
According to Cohen’s \( \kappa \) there was moderate classification agreement between the two measurement devices, \( \kappa = 0.54 \) (95% CI, 0.51 to 0.58), \( p < 0.01 \).
12.0.3 Assessment of ABI validity utilising the automated device plots of occlusion and detection pressures

In the same way that AD occlusion and detection plots were utilised to analyse reasons for measurement failures (section 12.0.1), such plots were also analysed to assess ABI validity. According to Fisher et al. (1996), a difference in ABI of >0.15 is considered to be clinically significant, hence all cases (n=100) where the discrepancy between the Doppler and AD ABI results were >0.15, were assessed. For 28 cases there were no available plots for analysis due to laptop recording failure.

Analysis of the plots of the remaining 72 cases revealed that reasons for measurement discrepancies of >0.15 fell broadly into five categories (Table 12.5).

<table>
<thead>
<tr>
<th>Reason for discrepancy (ABI difference&gt;0.15) between Doppler ABI and automated device ABI</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure of Dopplex Ability to go to second inflation of leg cuff(s)</td>
<td>18% (13)</td>
</tr>
<tr>
<td>Artefact evident in arterial detection signal(s)</td>
<td>24% (17)</td>
</tr>
<tr>
<td>Ability over-estimating brachial pressures</td>
<td>15% (10)</td>
</tr>
<tr>
<td>Ability Unknown error</td>
<td>11% (8)</td>
</tr>
<tr>
<td>Possible Doppler Error</td>
<td>32% (24)</td>
</tr>
</tbody>
</table>

Table 12.5: Reasons for discrepancies of >0.15 between automated device ABI results and Doppler ultrasound.

Failure of the automated device to go to second inflation of leg cuff(s)

An example of failure of the AD to go to phase 2 inflation of the leg cuffs has been provided in the failed measurement discussion (Figure 12.2); the difference in these cases was that instead of failing to provide a result, an inaccurate result was given.

Artefact in the detection signal

Similarly, an example of artefact in the detection signal has been provided in Figure 12.1, and again instead of measurement failure, this resulted in inaccurate ABIs.

Over-estimation of brachial systolic pressures by the automated device

There were 10 cases where the discrepancy appeared to be due to the AD overestimating brachial systolic pressures (Figure 12.5). This error was found to be due to an algorithm issue and was subsequently corrected in software versions 230+ (and hence only affected measurements for PIPETTE participants numbered 1-110 and did not affect any of the IVAM measurements).

*Discussed further in section 12.0.4.
Figure 12.5: Example of automated device detection and occlusion plots demonstrating measurement error of the brachial systolic pressure.
Indeterminate reason for automated device error
There were a further eight cases where the AD appeared to have made an error in determining the systolic pressures, but no specific reason for this could be identified.

Possible Doppler ultrasound error
There were 24 cases where the occlusion and detection plots appeared of high quality and the reported systolic pressures and ABIs all appeared accurate. In such cases, it is therefore reasonable to conclude that the discrepancy in ABI results could have been attributed to Doppler ultrasound measurement error.

12.0.4 Reassessment of agreement between Doppler ultrasound and automated ABI device following rectification of recognised software error
This PhD project was undertaken in collaboration with a commercial partner, Huntleigh Healthcare. As a result, data assessment was an ongoing process throughout the PIPETTE and IVAM studies. This meant that if problems were detected with the AD in the course of the studies, the manufacturer was made aware of this and was able to work together with the PhD researcher to rectify such issues.

One such issue concerned the AD’s overestimation of brachial systolic pressures in ten isolated cases as discussed in section 12.0.3. As the cause of this error was identified as a software algorithm error (versions 224 & 226) and was subsequently corrected, the agreement between the Doppler and the AD has been reassessed (using the same statistical strategies as above) with these cases 10 removed (Figures 12.6 and 12.7).
Bland Altman Plot (corrected DUAL dataset)

Figure 12.6: Agreement between Doppler ultrasound and automated ABI device (corrected DUAL dataset)

- mean difference or bias
- 95% confidence limit (±1.96*SD)
The mean difference, or bias, of the corrected DUAL dataset was unchanged from the original dataset at 0.02 ± 0.1, as was the absolute mean difference between the measurements (0.08 ± 0.08). 95% limits of agreement between the two measurement techniques were marginally lower at ± 0.21.

Figure 12.7: Equality plot of Doppler ultrasound ABI and automated device ABI (corrected DUAL dataset)

- Regression line, ---- 95% CI, ....... line of equality
Correlation Co-efficient of corrected DUAL dataset

Spearman's rank-order correlation was repeated using the corrected DUAL dataset and the previously noted positive correlation between the two measurement techniques (Section 11.1.3.2) strengthened from 0.6 to 0.74, \( r_s(717) = 0.74, p < 0.0005 \).

Sensitivity and Specificity for PAD diagnosis (from modified dataset)

<table>
<thead>
<tr>
<th>Gold Standard: Doppler</th>
<th>Automated ABI device</th>
<th>Non-PAD</th>
<th>PAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-PAD</td>
<td>TN: 637</td>
<td>FN: 12</td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>FP: 31</td>
<td>TP: 37</td>
<td></td>
</tr>
</tbody>
</table>

| Negative Predictive Value | \( = \frac{TN}{TN+FN} \) = 97% |
| Positive Predictive Value | \( = \frac{TP}{TP+FP} \) = 54% |

Specificity \( = \frac{TN}{TN+FP} \) = 95%
Sensitivity \( = \frac{TP}{TP+FN} \) = 76%
Accuracy \( = \frac{TN+TP}{TN+FN+FP+TP} \) = 94%

Table 12.6: Accuracy calculations of automated ABI device compared to gold standard Doppler ultrasound for modified dataset

Cohen’s Kappa for corrected dataset

Cohen’s \( \kappa \) improved from moderate classification agreement for the original DUAL dataset to good classification agreement between the two measurement devices for the corrected DUAL dataset, \( \kappa = 0.61 \) (95% CI, 0.54 to 0.65), \( p < 0.01 \).

12.0.5 Receiver operating characteristic curve of the automated device

Analysis of a receiver characteristic operator (ROC) curve revealed that the optimal automated device ABI cut-off point for diagnosis of PAD, as indicated by Doppler ABI ≤0.9, is 1.04 which provides a sensitivity of 98% and specificity of 75% (Figure 12.8).
12.0.6 Factors associated with the agreement between the Doppler ultrasound and automated device

Data were also analysed to determine if there were any factors associated with the difference (bias) between the ABI measurement techniques:

Gender

Females had a three times greater positive bias than males (0.03 vs. 0.01). Distributions of the differences between the Doppler ABIs and the AD ABIs according to gender were similar, as assessed by visual inspection. The difference between the two methods of measurement was statistically higher for females than males ($U = 65,642$, $z = 2.82$, $p = .005$) (Figure 12.9). However, the 95% limits of agreement were similar: male ± 0.22; and female ± 0.21.
Age-group

For the youngest age-group the bias was negative (Figure 12.10). There was a gradual increase in bias with increasing age group until age group 75-84 where it thereafter decreased (Kruskal-Wallis test, $\chi^2(4) = 16.616$, $p = .002$). A Bonferroni correction for multiple comparisons revealed statistically significant differences in the biases between age group 45-54 (mean rank=152.1) and age group 55-64 age group (mean rank=196.83) ($p=0.005$). Similarly, the differences in the biases between age group 45-54 (mean rank =119.14) and age group 65-74 (mean rank=171.14) were also statistically significant ($p=0.001$). Differences between the remaining groups were not significant.
A Spearman's rank-order correlation revealed a moderate positive correlation between age and the difference between the Doppler and automated device ABI results, $r_s(727) = 0.29$, $p = 0.007$.

**PAD status group**

For the PAD group the bias was negative (Figure 12.11). There was a gradual increase in bias across the PAD status groups as ABIs increased (Kruskal-Wallis test, $\chi^2(3) = 16,118$, $p = .001$). A Bonferroni correction for multiple comparisons revealed statistically significant differences in the biases between the PAD group (mean rank=251.1) and Normal ABI group (mean rank=313.86) ($p=0.04$). Similarly, the differences in the biases between the PAD group (mean rank=48.24) and the high ABI group 65-74 (mean rank=71.63) were also statistically significant ($p=0.001$), as were the differences between the borderline ABI group (mean rank=36.18) and the high ABI group (mean rank=49.29) ($p=0.045$).

A Spearman's rank-order correlation revealed a moderate positive correlation between mean ABI and the difference between the Doppler and automated device ABI results, $r_s(727) = 0.362$, $p < 0.001$.

**Hypertension Status Group**

Participants with hypertension had a five times greater positive bias than participants who were not hypertensive (0.032 vs. 0.006). Distributions of the differences between the Doppler ABIs and automated device ABIs according to hypertensive status were similar, as assessed by visual inspection. The difference between the two methods of measurement was statistically higher for
the hypertensive group (\( U = 39,742.5, z = -2.363, p = .018 \)) (Figure 12.12). The 95% limits of agreement were greater for the hypertensive group than the normotensive group (±0.23 vs. ±0.21).

There was no significant difference in the difference between the Doppler ABI results and the automated device ABI results according to total number of CV risk factors (Kruskal-Wallis H test: \( \chi^2(3) = 3.452, p = .0631 \)), version of Dopplex Ability software (\( \chi^2(6) = 0.510, p = 0.147 \)) and the dyslipidaemia status of participants (Mann-Whitney U test: U=37,000, z=1.656, p=0.098). Similarly, there was no significant association between the difference in measurements and BMI (Spearman’s \( r_s(727) = 0.062, p =.101 \)), or height (Spearman’s \( r_s(727) = 0.004, p =.924 \)).

**12.1 Discussion**

A review of the literature reveals only one study which has investigated the agreement between ABI measurement using an automated pneumoplethysmography device and a Doppler ultrasound device. The study, by Lewis et al. (2011) in fact used exactly the same automated equipment as the DUAL study (the Dopplex Ability, Huntleigh Healthcare, Cardiff). However, it is an unpublished paper which is available via the Huntleigh Healthcare website (see reference list). The subsequent discussion involves comparing DUAL data with results not only from the paper by Lewis and colleagues (2011) but also with data from papers which have examined oscillometric automated ABI devices and photoplethysmographic ABI devices.

Notably, there are in excess of 60 papers which have compared automated ABI measurement to Doppler ABI measurement. However, the majority of these studies involved automated devices that were designed for measuring brachial systolic pressure only and, as such, they were not designated...
ABI measurement systems. The subsequent discussion focuses primarily on automated devices specifically designed for ABI measurement.

Failed measurements
Within the DUAL study the failed measurement rate of the automated device was 5.3% (n=41). There were no Doppler ultrasound failed measurements. The study by Lewis et al. (2011), which entailed a randomised cross-over study of 295 limbs comparing rested and unrested Dopplex Ability measurements with Doppler ultrasound ABI measurements, did not report any failed measurements.

Measurement failure does, however, appear to be a significant issue associated with oscillometric ABI measurement. Several studies have reported that measurements could not be obtained when the ankle systolic blood pressure was <70mmHg (Benchimol et al., 2004; Macdonald et al., 2008; Kawamura et al., 2008). Another study reported that an oscillometric device failed to measure the ankle systolic pressures of any of three patients all of whom had ABIs <0.9 as determined by the Doppler (Kollias et al., 2011). Diehm et al. (2009) used an oscillometric ABI device to measure the ABI of 50 patients who were known to have chronic symptomatic PAD; they reported that the device failed to provide results for almost a quarter of these subjects (24%). Some authors (Verberk et al., 2012) suggest that in the case of erroneous or “0” oscillometric readings, the presence of PAD is highly probable and the patient should be referred for further investigation. However, not knowing for certain if arterial disease is present and not being able to quantify any existing disease, is far from satisfactory.

The capacity of the Dopplex Ability software to display measurement occlusion and detection curves (as discussed in Section 11.1) provided a unique opportunity to gain insight into failed and erroneous measurements.

Failed measurements and hypertension
Analysis of occlusion and detection curves indicated that 30% (n=12) of the automated device failed measurements could be attributed to the fact that it is programmed not to display ankle pressures in excess of 205mmHg. As individuals with hypertension are more likely to have ankle systolic pressures >205mmHg, this therefore explains the finding that the presence of hypertension was significantly associated with automated device failed measurements (p=0.015) (Table 12.1). It is therefore suggested that the automated device could be improved by displaying all derived systolic pressures; this would then allow the individual practitioner/device operator to determine if the
measurements are artefactually elevated. If this had been the case, measurement failures within the DUAL study would have been reduced to 3.7% of the total measurements.

Failed measurements and artefact in the detection signal
Twenty-four per cent of automated device measurement failures were attributed to artefact in the device detection signal. As discussed in Section 11.1, the automated device measures arterial systolic pressures via detection of pressure changes within an air-filled cuff bladder. This measurement principle is obviously susceptible to interference from factors such as patient movement, which can result in artefact in the detection signal. Such artefact can then give rise to measurement error or failure if the software algorithms are unable to calculate the systolic pressures. This is highlighted in the Dopplex Ability manufacturer’s instructions where it is stated that patients should be asked to refrain from talking and moving during the measurement process (Huntleigh, 2010). Similarly, they advise that if the patient coughs, sneezes or makes any other involuntary movement during the measurement procedure, then it may be necessary to repeat the test. It is also stated that the device is not suitable for use for individuals who may experience tremors, perhaps as the result of a neurological condition such as Parkinson’s disease, for example. Artefactual interference has been found to be an issue also associated with photoplethysmographic ABI measurements (Korhonen and Yli-Hankala, 2009), although there is no reference to it with regard to oscillometric ABI measurement within available literature.

Other reasons for measurement failure
Failure of the automated device to detect that leg cuffs had not inflated sufficiently to occlude the arterial pulse and to subsequently instigate a second phase of inflation accounted for 15% (n=6) of measurement failures. This is likely to be attributed to a software algorithm error which requires attention by the device manufacturers.

Agreement between automated ABI device and Doppler ultrasound
Results suggest that the automated device has moderate to good sensitivity (76%) for detecting cases of PAD in participants deemed to have the disease by the Doppler ABI results. However, it should be noted that thirty-five per cent of the diseased limbs within the DUAL study had an ABI of between 0.85 to 0.9. Therefore in these cases, the automated device needed only to return an ABI which was between 0.01 and 0.05 units higher than the Doppler results for the measurement to be
classed as a false negative. This is a limitation of using an arbitrary cut-off point to signify the presence or absence of a disease. This, of course also applies when considering specificity values.

It is therefore perhaps more useful to consider the Receiver Operating (ROC) curve (Figure 12.8) to gain more insight into the accuracy of the automated device. The area under the curve was 0.96 (95% CI: 0.94 – 0.98, p<0.001) indicating that the automated device had a high degree of accuracy in comparison to the Doppler results as gold standard. The optimal cut-off point for detecting PAD (as defined by Doppler ABI≤0.9) was 1.04 which gives a sensitivity of 98% and specificity of 75%.

Comparison of results with existing literature

Studies which have assessed the agreement between dedicated ABI automated devices and the Doppler ultrasound as the reference standard are summarised in Table 12.7 (p. 178). One study involved an automated pneumoplethysmographic ABI device, eleven involved automated oscillometric ABI devices, and two involved photoplethysmographic ABI devices. Studies frequently had multiple limitations such as relatively small sample sizes and samples consisting of either primarily healthy (non-PAD) participants or conversely, primarily diseased participants. This makes it difficult to assess how the device would perform in a general population. Similarly, authors of several studies reported a conflict of interest, usually as a result of involvement with the manufacturers of the devices being evaluated. Such studies appear to report higher levels of agreement with the reference standard than studies where there was no conflict of interest. This could be attributed to those with links to the device manufacturers having more experience and knowledge of the device hence resulting in more accurate results.

The DUAL study and the study by Lewis et al (2011) which both evaluated the same pneumoplethysmographic device (Dopplex Ability), by comparing it to the Doppler method, reported exactly the same 95% limits of agreement (±0.22). This was despite the DUAL study having an over-representation of healthy (non-PAD) participants, whilst the study by Lewis et al. conversely had an over-representation of diseased (PAD) participants. Considering the results of these two studies collectively does, however, appear to suggest consistency of performance across the spectrum of the ABI. Lewis et al. (2011) reported a higher correlation coefficient than the DUAL study (0.89 vs 0.74 respectively).

Comparison of the DUAL study agreement rates with existing oscillometric studies (Table 12.7) is hindered by the fact that there is considerable variation in how results were presented within studies. Whilst Bland-Altman plots are frequently used, some studies present data in terms of ABI
units whilst others use mmHg. Also, corresponding numerical data relating to the plots are not always stated and the reader is left to visually guess at what the limits of agreement may be. The majority of studies included present their results numerically often only in terms of correlation coefficients (normally Pearson’s r). Whether this is an appropriate means of statistical assessment is questionable as Pearson’s r has been noted to be limited in that it is sensitive only to a linear relationship between two variables (Dowdy and Wearden, 1983). The r values pertaining to the oscillometric devices range from 0.21 to 0.95. Notably, studies reporting higher r values often had samples with few or no PAD participants. Several studies emphasise a systematic tendency of oscillometric devices to over-estimate the ankle pressure in patients with low ankle pressures (Korno et al., 2009) which may explain why lesser correlations are detected when study populations have greater proportions of participants with PAD.

It is also useful to consider the work of Verberk et al. (2012) who conducted a systematic review and meta-analysis of 25 studies with 4186 subjects, assessing the usefulness of automated oscillometric devices for ABI and PAD estimation compared with the conventional Doppler ultrasound method. The 25 studies involved the use of 20 different oscillometric devices; notably only five of these devices were designed specifically for ABI measurements whilst the remainder were devices originally intended for determination of brachial systolic pressures only. Inter-study differences relating to considerable variation in the Doppler ultrasound methodology (including pulses assessed, number of readings taken and calculation of the index) resulted in a considerably heterogeneous group of studies. Results showed that oscillometric devices gave slightly higher ABI values than the Doppler; the average ABI difference (oscillometric-doppler) was 0.02 ± 0.18. The absolute difference was 0.048 ± 0.09. The mean difference was less for devices specifically designed for ABI measurement (-0.011 ± 0.02) than for oscillometric devices intended for brachial blood pressure measurement (0.036 ± 0.015). Cumulatively, the sensitivity for PAD diagnosis was 69% and specificity 96%. The authors of this systematic review/meta-analysis concluded that as oscillometric devices become less accurate in patients with lower ankle blood pressures, further investigation of this matter is required in the form of more clinical studies. They recommend that oscillometric devices can facilitate the detection of undiagnosed PAD, and that to improve the accuracy of PAD diagnosis, using an oscillometric ABI threshold of 1.0 for diagnosing PAD appears reasonable.

Beutner et al. (2012) compared two automated ABI devices which utilised photoplethysmography with the traditional Doppler method (Table 12.7). Both of these devices used the same measurement principle (plethysmography) as the automated device used in the DUAL study. They differed however in the method used for detection of the plethysmographic signal (see section
Results from this study are very similar to results from the DUAL study: sensitivity (Vicorder, Vascular Explorer, Dopplex Ability) = 70%, 65%, 76% respectively, specificity = 96%, 99%, 95% respectively. ROC analysis also revealed similar areas under the curve: 0.91, 0.94, 0.96 respectively. Beutner et al. report only one failed measurement for each of the devices assessed within their study. This study was limited by a small sample size with a small proportion of diseased participants.

Factors affecting the agreement between the two measures

DUAL study results have demonstrated that the difference between the ABI results of the two measurement techniques increased with age (r=0.362, p=0.002) and increasing ABI (p=0.001). Similarly, the difference is greater for participants with hypertension (p=0.018). Few studies have examined or reported on this issue of factors which affect the agreement between automated ABI devices and the Doppler method. A study by Takhashi et al. (2013) examined whether there were any factors (gender, age, smoking, alcohol, CVD, diabetes, hyperlipidaemia, and BMI) associated with differences between oscillometric and Doppler ABI measurements in 113 subjects aged 61-88; they concluded that there were none. However, Wohlfahrt et al. (2011) measured the ABIs of 839 subjects aged >25 years using the traditional Doppler method and an automated oscillometric device. They also noted that the difference between the ABIs returned via each of the measurement techniques increased significantly with increasing mean ABI (r=0.29, p<0.001).

The Doppler ABI: an imperfect reference standard

As discussed in section 12.0.3, inspection of the automated device occlusion and detection plots revealed that Doppler error may have been the causative factor relating to 34% of measurements where the difference between the two measurement techniques was >0.15. This is despite the fact that the PhD researcher has considerable experience in Doppler ABI measurement and furthermore, her ABI measurements were shown to be comparable to an expert (vascular surgeon) in the IVAM study (Chapter 7). As the Doppler ultrasound measurement process involves sequential measurement of limb systolic pressures, it is possible that temporal reduction in systemic blood pressure over time, could have contributed to this finding. This could have been further affected by factors such as white coat attenuation effect (Freitas et al., 2014). It is also important to take into consideration the fact that the automated device does not assess a specific artery, whereas the Doppler ultrasound method does. Instead, the systolic pressures attained for each limb represents the combined pressure of the sum of the blood flow through the area being assessed by the
automated device. Hence, this may also account for a degree of discrepancy between the two measurement techniques.

This then raises the question of whether Doppler ultrasound ABI measurements, which are liable to observer bias and error which are frequently associated with subjective measurements, should be utilised as the reference standard in such comparative studies. It may be more accurate and of greater diagnostic value to compare automated ABI devices with superior diagnostic modalities such as Duplex ultrasonography or computed tomography angiography (CTA). However, the financial cost of such studies and the invasive nature of CTA would of course also require consideration.

A literature search revealed only one study, by Ichihashi et al. (2014), which used CTA as the reference standard in a comparative study which investigated the accuracy of an automated oscillometric device. The retrospective study included 108 subjects (216 limbs) who had been referred to a vascular department with suspicion of PAD and as such, had undergone CTA as their normal course of investigation/treatment. ABI measurements with the oscillometric device were undertaken within one month pre or post CTA. Reported failed measurement rate of the device was only 4%; this appears low in comparison to failure rates reported in other similar studies (discussed in Section 12.1), especially in view of the fact that 78% of the study population were found to have PAD according to CTA. The area under the curve of the ROC analysis was 0.92 indicating that the automated device had a high level of accuracy. The optimal cut-off point to detect PAD was 0.99 which provided a sensitivity of 90% and specificity of 80%. A major limitation of this study concerns the lack of data in relation to how the oscillometric device functions. The authors refer to the device being able to assess individual arterial ankle pressures but they provide no explanation of how this is achieved. The authors of the paper declare no conflict of interest but it is noted, however, that one of the authors is employed by Omron, the manufacturers of the device being assessed.

12.2 Limitations of the DUAL study

Although the DUAL study consisted of a large sample, only a small proportion (3%) of participants were found to have PAD. Hence, whilst there has been adequate investigation of how the device performs when measuring the ABIs of healthy participants, further research is needed to assess its performance in diseased participants. A further limitation of the study relates to the fact that the PhD researcher, who performed the majority of the Doppler measurements within the DUAL study, was not blinded to the results of the automated device; this may have influenced her subjective Doppler ABI measurements. Furthermore, the PhD researcher applied the cuffs, and operated the automated device for all measurements. As she has extensive experience of this and has worked
with the device manufacturers, it could be that she was able to obtain more accurate results. Hence, future research should address this issue (discussed in Section 12.4).

### 12.3 Conclusions

The following conclusions can be made with regard to the automated ABI device (Dopplex Ability) used within the DUAL study:

- The failed measurement rate appears to be less than the published oscillometric failure rates but greater than photoplethysmographic failure rates. However, a lack of relevant, high quality studies and inadequate reporting of data prevent a definitive conclusion with regard to this issue.
- Its agreement with the Doppler method is good but further studies are needed to further investigate/corroborate these findings. Such studies should address the limitations of the DUAL study outlined in Section 12.4. Furthermore, the shortcomings of using Doppler ABI as the reference standard in comparative studies have been highlighted.
- Potential improvement of the device could be achieved via its modification to ensure that all attained systolic pressures are displayed.
- The device is susceptible to measurement error or failure caused by artefact in the detection signal which is associated with subject movement.
- Factors which adversely affect the agreement between the device and the Doppler ABI measurements have been identified as increasing age, increasing ABI and the presence of hypertension. Whether these factors affect the accuracy of the Doppler measurements, the automated device measurements, or both, cannot be determined. This therefore, provides a focus for future research.

Comparison of the three modalities used to achieve automated ABI measurement (pneumoplethysmography, oscillometry and photoplethysmography) has been hindered as a result of study heterogeneity, insufficient high quality studies, and differing methods of reporting results. Oscillometry has been investigated more extensively than the other two modalities; however, results regarding its accuracy and values are inconsistent. Hence, no conclusions can be made with regard to which modality is superior for automated ABI measurement. Recommendations for future
research which could address some of these identified issues are discussed in section 12.4. It is therefore not surprising that current PAD guidelines concur in that they do not recommend the use of automated ABI devices.

12.4 Recommendations for future research

Recommendations include design considerations for future studies evaluating the validity of automated ABI devices. In particular, study populations for research should consist of both diseased and healthy participants, which are likely to be representative of the entire spectrum of the ABI. For example, participants with varying degrees of PAD, ranging from critical limb ischaemia to asymptomatic PAD, should be included. Similarly, individuals who are likely to have elevated ankle pressures, such as diabetics and those with chronic renal failure, should also be included, in order to provide data as to how devices perform at the high end of the ABI spectrum. Sample sizes should consist of 100 participants as a minimum. Operators of the automated device should be representative of those who would be likely to utilise it in the clinical environment, such as practice nurses for example. Furthermore, studies undertaken should be independent of any influence or input from device manufacturers.

It is also recommended that a superior diagnostic modality, such as Duplex ultrasound, should be considered for use as the reference standard in future studies, in preference to the Doppler ultrasound. However, if the Doppler ultrasound is utilised as the reference standard, then observers should be blinded to results of the automated device. Furthermore, the specific Doppler methodology utilised should adhere to the AHA recommended procedure (Aboyans et al., 2012) for such measurements. This would ensure consistency across studies, allowing easier comparisons of results. Results of studies should be clearly reported and should include explicit information regarding any measurement failures.
<table>
<thead>
<tr>
<th>Study Details</th>
<th>Quality Assessment</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Authors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Sample Size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Study Type</td>
<td><strong>Strengths</strong>: Large sample size</td>
<td><strong>Sensitivity</strong></td>
</tr>
<tr>
<td>4. Device Used</td>
<td><strong>Limitations</strong>: No blinding of investigator undertaking Doppler measurements to automated device ABI results. Only 3% of study population had PAD.</td>
<td><strong>Specificity</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Declared conflict of interest</strong>: Study part of a PhD which was part sponsored by Huntleigh Healthcare</td>
<td><strong>Positive Predictive Value</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Negative Predictive Value</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Accuracy</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>Cohen’s Kappa</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>95% limits of agreement</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Correlation Co-efficient</strong></td>
</tr>
<tr>
<td>1. <strong>DUAL</strong> study, 2014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. <strong>N=727 limbs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. <strong>Cross-sectional study, aged 36-87, with CV risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. <strong>Dopplex Ability (Huntleigh Healthcare)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. <strong>Lewis et al., 2010</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. <strong>N=295 limbs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. <strong>Randomised cross over study, participants had been referred for investigation of possible claudication or absent pedal pulses.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. <strong>Dopplex Ability (Huntleigh Healthcare)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. <strong>Cortez Cooper et al. 2003</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. <strong>n=53 subjects with or without hypertension but other forms of known CV disease excluded</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. <strong>Cross-sectional study</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. <strong>Colin VP-2000, Colin Medical Instruments, San Antonio, Texas.</strong></td>
<td></td>
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</tr>
</tbody>
</table>

**Table 12.7: Agreement of automated ABI devices with the Doppler ultrasound as the reference standard.**

NR: not reported
<table>
<thead>
<tr>
<th>Study Details</th>
<th>Quality Assessment</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Osciollometry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Pan et al., 2007</td>
<td><strong>Strengths:</strong> Large sample size.</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>2. n=946 subjects, mean age 43</td>
<td><strong>Declared conflict of interest:</strong></td>
<td>NR</td>
</tr>
<tr>
<td>3. Cross-sectional study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Colin VP-1000</td>
<td>Limitations: Sample contained only diseased participants.</td>
<td></td>
</tr>
<tr>
<td>1. Diehm et al., 2009</td>
<td><strong>Declared conflict of interest:</strong> author received consulting fees from manufacturers of device.</td>
<td>NR</td>
</tr>
<tr>
<td>2. n=100 limbs with chronic symptomatic PAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Cross-sectional study</td>
<td>Note: Rate of failed measurements: 24% (Failed measurements were not included in limits of agreement and correlation co-efficient calculations.</td>
<td></td>
</tr>
<tr>
<td>4. BOSO ABI system, Jungingen, Germany</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Richart et al., 2009</td>
<td><strong>Limitations:</strong> No diseased subjects were included in statistical analysis of results. Exclusions of results from analysis with no explanation. Non-standard methodology utilised for Doppler measurements.</td>
<td>NR</td>
</tr>
<tr>
<td>2. n=105 subjects age 20-80</td>
<td><strong>Declared conflict of interest:</strong> none.</td>
<td></td>
</tr>
<tr>
<td>3. Cross-sectional study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. VP-2000, Omron Healthcare, Kyoto, Japan.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Kollias et al., 2011</td>
<td><strong>Strengths:</strong> Robust methodology.</td>
<td>NR</td>
</tr>
<tr>
<td>2. n=93 subjects attending diabetic or hypertension outpatient clinic.</td>
<td><strong>Limitations:</strong> Small sample size with small number of subjects with PAD.</td>
<td></td>
</tr>
<tr>
<td>3. Cross-sectional study</td>
<td><strong>Declared conflict of interest:</strong> Author affiliated with manufacturers of device. Study part sponsored by Microlife.</td>
<td></td>
</tr>
<tr>
<td>4. Microlife Watch BP office device, Widnau, Switzerland.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Wohlhafth et al., 2011</td>
<td><strong>Strengths:</strong> Large sample size.</td>
<td>77%</td>
</tr>
<tr>
<td>2. n=839 limbs, age&gt;25years</td>
<td><strong>Limitations:</strong> Non-standard methodology used for Doppler measurements. Non-measurements for 90 subjects – it cannot be determined if these were due to measurement failures</td>
<td></td>
</tr>
<tr>
<td>3. Cross-sectional study</td>
<td><strong>Declared conflict of interest:</strong> none</td>
<td></td>
</tr>
<tr>
<td>4. BOSO ABI device</td>
<td></td>
<td></td>
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</tbody>
</table>

Table 12.7: Agreement of automated ABI devices with the Doppler ultrasound as the reference standard. NR: not reported
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</thead>
<tbody>
<tr>
<td>1. Authors</td>
<td>Study Strengths &amp; Limitations</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>2. Sample Size</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>3. Study Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Device Used</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Harrison et al., 2011</td>
<td>Limitations: Sample did not contain participants with ankle systolic pressure of &lt;110mmHg, therefore unlikely to contain any PAD subjects.</td>
<td>NR</td>
</tr>
<tr>
<td>2. 80 limbs from participants without known CV disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Cross-sectional study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Vasera VS-1500AT, Fukuda, USA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Rosenbaum et al., 2012</td>
<td>Limitations: Non-standard method utilised for Doppler method: utilised a standard automated oscillometric brachial device with a hand-held Doppler device.</td>
<td>NR</td>
</tr>
<tr>
<td>2. 157 subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Cross-sectional study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. SCVL, &quot;screening cardiovascular lab&quot;, GenNov, Paris, France</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Sinski et al., 2013</td>
<td>Limitations: Small sample size. Sample likely to be diseased so not representative of general population</td>
<td>46%</td>
</tr>
<tr>
<td>2. n=80 subjects with confirmed coronary artery disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Cross-sectional study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. WatchBP Office ABI device, Widnau, Switzerland.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Takahashi et al., 2013</td>
<td>Strengths: Robust methodology. Limitations: Few subjects had PAD</td>
<td>50%</td>
</tr>
<tr>
<td>2. 113 subjects, aged 61-88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Cross-sectional Study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. VP-2000, Omron Healthcare, Kyoto, Japan.</td>
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<td></td>
</tr>
</tbody>
</table>

Table 12.7: Agreement of automated ABI devices with the Doppler ultrasound as the reference standard. NR: not reported
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<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Authors</td>
<td>Study Strengths &amp; Limitations</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>2. Sample Size</td>
<td>Limitations: Small sample size</td>
<td>65%</td>
</tr>
<tr>
<td>3. Study Type</td>
<td>Declared conflict of interest: None</td>
<td></td>
</tr>
<tr>
<td>4. Device Used</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Beutner et al., 2012</td>
<td>Limitations: Small sample size</td>
<td>70%</td>
</tr>
<tr>
<td>2. 134 limbs (112 known healthy, 22 known PAD)</td>
<td>Declared conflict of interest: None</td>
<td></td>
</tr>
<tr>
<td>3. Cross-sectional study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Vascular Explorer, Enverdis, Germany</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Beutner et al., 2012</td>
<td>Limitations: Small sample size</td>
<td></td>
</tr>
<tr>
<td>2. 134 limbs (112 known healthy, 22 known PAD)</td>
<td>Declared conflict of interest: None</td>
<td></td>
</tr>
<tr>
<td>3. Cross-sectional study</td>
<td></td>
<td></td>
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<tr>
<td>4. Vicorder, Skidmore Medical, UK</td>
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</table>

Table 12.7: Agreement of automated ABI devices with the Doppler ultrasound as the reference standard.  
NR: not reported
Chapter 13: The DUAL study results: time taken to perform measurements and patient perspective of measurement techniques.

13.0 Time taken to perform ABI measurements

Data regarding the time taken to perform ABI measurements are presented in Table 13.1. Doppler ultrasound times include the obligatory 10 minute rest period (total test time = rest time + procedure time). Automated device times include the time taken for application of the cuffs as well as the measurement procedure.

<table>
<thead>
<tr>
<th></th>
<th>Mean Time (Minutes : Seconds)</th>
<th>Standard Deviation (Minutes : Seconds)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doppler ultrasound</td>
<td>17:45</td>
<td>1:05</td>
<td>15:48 – 21:38</td>
</tr>
<tr>
<td>Automated device</td>
<td>7:55</td>
<td>1:29</td>
<td>5:20 – 13:02</td>
</tr>
</tbody>
</table>

Table 13.1: Mean time for ABI measurement

The mean difference between the time taken to perform the tests using the two different methods was 9:54 ± 1:5 (minutes : seconds). The median time duration was statistically significant higher (median difference 10:02) when ABI was measured with the Doppler (median: 17:29) compared to the median time when ABI was measured using the automated device (median: 7:29), (Wilcoxon signed-rank test, z = -22.508, p < 0.01).

However, if the 10 minute rest period is not included in the Doppler time, and the time therefore represents the actual procedure time only, then the median test time was not significantly different (Doppler median test time = 7:29; Automated device median test time = 7:29; z = -0.277, p=0.782).

13.0.1 Factors associated with time taken to perform Doppler ultrasound ABI measurements

Data were analysed to assess for factors associated with the time taken to perform Doppler ultrasound measurements.
PAD status groups

The time taken to perform the Doppler measurements was, on average, greater for diseased participants (ABI≤0.9) and those with ABI≥1.3, than for borderline PAD participants and normal ABI participants (Kruskal-Wallis test, $\chi^2(3) = 8.218, p = 0.042$) (Figure 13.1). A Bonferroni correction for multiple comparisons revealed statistically significant differences in the time taken to perform the Doppler measurement in the PAD group (mean rank=251.1) compared to the normal ABI group (mean rank=313.86) ($p=0.023$).

Total number of cardiovascular risk factors

The mean time taken to perform the Doppler measurements increased with increasing number of CV risk factors (Figure 13.2). For participants with one CV risk factor, the mean time was 17:18, two CV risk factors: 17:24, three CV risk factors: 17:32, four CV risk factors: 17:35, and five CV risk factors: 17:43 (Kruskal-Wallis test, $\chi^2(4) = 18.334, p = 0.001$). A Bonferroni correction for multiple comparisons revealed statistically significant differences in the time taken to perform the Doppler measurement in: (i) those with three CV risk factors compared to those with one CV risk factor ($p=0.002$), (ii) those with four CV risk factors compared to those with one CV risk factors ($p=0.004$), and (iii) those with five CV risk factors compared to those with one CV risk factor ($p=0.01$).

Total number of clinical signs of PAD

The differences in the time taken to perform the Doppler measurements differed significantly according to the total number of clinical signs of PAD ($\chi^2(5) = 13.013, p = 0.023$) (Figure 13.3). A Bonferroni correction for multiple comparisons revealed that the time taken for the Doppler measurements differed significantly when comparing those with 0 clinical signs with those with 2 clinical signs ($p=0.045$) and those with five clinical signs ($p=0.011$).
Figure 13.1: Time taken to perform Doppler ABI measurements according to PAD status.

Figure 13.2: Time taken to perform Doppler ABI measurements according to total number of CV risk factors.

Figure 13.3: Time taken to perform Doppler ABI measurements according to the total number of clinical signs of PAD.
13.0.3 Factors associated with time taken to perform automated device ABI measurements

Statistical analysis revealed that there were no factors that were significantly associated with the time taken to perform ABI measurements with the automated device.

13.1 Participant Perspective of ABI measurement

Participant perspective of ABI measurement was assessed in terms of: (i) perceived comfort of the procedure, (ii) acceptability of the time taken to perform the procedure, and (iii) acceptability of the overall measurement procedure.

Comfort of measurement procedure

The proportion of participants who rated the Doppler ABI measurements as comfortable or very comfortable was greater than the proportion who rated the automated device measurements as comfortable or very comfortable (97% versus 86%). Three per cent of participants found the automated device measurement painful and a further 1% reported it to be very painful. None of the participants reported the Doppler measurement to be painful or very painful. The differences in comfort ratings of the two measurements techniques were statistically significantly different (Wilcoxon signed-rank test, $z = -5.324$, $p < 0.01$) (Figure 13.4).

![Figure 13.4: Participants’ perceived comfort of ABI measurement](image)

Blue: Doppler ultrasound method, red: automated device method
Time taken to perform ABI measurements

On balance, participants perceived the automated device measurement to be faster than the Doppler measurement (Figure 13.5). Just one per cent of participants felt that the automated device measurements were slightly lengthy, compared with three per cent of participants rating the Doppler measurements as slightly lengthy. The differences in the ratings of the time taken to perform the measurement procedures, between the Doppler and automated device, were not statistically different ($p=0.134$).

![Figure 13.5: Participants’ view of ABI measurement time](image)

Blue: Doppler ultrasound method, red: automated device method.

Overall rating of measurement procedures

Participants were asked to rate their overall experience of the two measurement procedures (Figure 13.6). No-one rated either of the measurement techniques as unacceptable. Ratings for the two procedures were not statistically significant (Wilcoxon signed-rank test, $p=0.72$)
A scoring system was applied to results regarding the participant’s evaluation of the ABI measurements. A score of 1 was applied to the most negative response and a score of 5 was applied to the most positive for each of the aspects assessed (comfort, time, and overall rating). This meant from a maximum possible score of 15, a score of 1 indicated complete dissatisfaction with the measurement and a score of 15 indicated complete satisfaction.

There was a statistically significant higher median score (1 point on the scoring system) when ABI was measured with the Doppler (median: 13) compared to the median score when ABI was measured using the automated device (median: 12) (Wilcoxon signed-rank test, $z = -10.067$, $p < 0.01$). A Mann-Whitney U test was run to determine if there were differences in Doppler evaluation score between males and females; median score was statistically significantly higher for males than females, $U = 12,986$, $z = -2.401$, $p = 0.016$. Similarly, a Mann-Whitney U test also revealed that males again had higher score for the automated device evaluation than women ($U = 10,985$, $z = -4.775$, $p < 0.01$).
13.2 Discussion

13.2.1 Time taken to perform ABI measurements

Results demonstrate that the time taken to perform ABI measurement with the Doppler and the automated device did not differ significantly (Doppler mean time = 7:45; automated device mean time = 7:55, p = 0.782). However, if the obligatory 10 minute rest period was added to the Doppler procedure time, then results were statistically different (Doppler mean time = 17:45; automated device mean time = 7:55, p<0.01). Existing published data regarding the time taken to perform Doppler ABI measurement are sparse and lack of detail with regard to whether the rest period was included in the reported test time is commonplace. Pearson et al. (2003) assessed the time it took to perform an ABI measurement with a Doppler and found that the average could be as little as 5 minutes (range 3-11 minutes). Bendermacher et al. (2007) conducted a study which included 955 general practices in Denmark, and found that the time needed for an ABI measurement varied between 12 and 20 minutes. French (2005) however, surveyed 50 community and practice nurses in the UK and found that the reported test time could be as long as 90 minutes (range: 50–90 minutes). Time taken to perform automated oscillometric ABI measurements is usually reported to be less than the time for the Doppler method: 3.9 minutes vs. 11.4 minutes according to Diehm et al (2009), and 5.8 minutes vs. 9.3 minutes according to Kollias et al. (2011).

13.2.2 Factors associated with test time

The literature did not reveal any studies which have considered or reported on whether any particular factors affect the time taken to perform ABI measurements. The time taken for the PhD researcher to perform the Doppler measurements differed according to the participants’ PAD status, with the procedure taking longer for those subsequently found to have PAD or high ABI. This may be indicative of a more complex measurement process for such participants; the researcher may have slowed the measurement process perhaps in order to aid detection of the Doppler signal in PAD patients. Alternatively, it may have been necessary to repeat measurements for such participants. Doppler measurements were also slower for participants with more CV risk factors and more clinical signs of PAD. This could again be attributed to more intricate measurement procedures for such participants. Alternatively, it could be that as the PhD researcher was aware of the participants’ adverse CV risk profile and the clinical signs of PAD, then she perceived that she would be more likely to find PAD and subsequently slowed the measurements procedure. Obviously, this subjective observer bias does not apply to automated devices and hence the automated device demonstrated
consistency in the time it took to perform the measurements regardless of the participants’ characteristics.

13.2.3 Participant perspective of ABI measurement

Results indicated that, overall, participants preferred the Doppler ABI measurement over the automated device ABI measurement (p<0.01). This appeared to be due to issues relating to comfort rather than to the duration of the procedures. Participants were more likely to rate the automated device measurement as uncomfortable or painful than the Doppler measurement (14% vs. 3% respectively, p<0.01). Women were more likely to rate both the Doppler and the automated device measurements lower than men (p < 0.01).

Blood pressure measurement is considered a routine and benign procedure which patients frequently undergo during their contacts with healthcare providers. Available literature contains much reference to white coat hypertension, which is defined as elevated BP in the clinical environment and normal BP outside of the clinical environment (Pickering, 2005). However, this appears to be attributed to anxieties relating to the contact with health care professionals rather than the measurement procedure itself. Throughout the course of the PIPETTE and IVAM studies, the PhD researcher encountered several participants with marked anxiety relating to blood pressure measurement. This was related to fears that the blood pressure cuff would become too tight and “cut-off their blood supply” or “make their arm explode” (direct quotes from participants which were recorded in their CRFs). All of these participants (n=5) were women and all were being treated for hypertension. Their anxieties regarding the blood pressure measurement were of course likely to have perpetuated the issue as a result of anxiety causing elevation of blood pressure which in turn requires higher cuff pressures to occlude the arterial pulse. Each of these participants expressed a preference for manual blood pressure measurement rather than automated as they preferred the health professional to be in control of the measurement.

With regard to blood pressure measurement of the leg, again there is limited consideration of this in available literature. A study by Lazareth et al. (2009), assessed perceived comfort of ABI measurement using the traditional Doppler method in 100 consecutive in-patients with leg ulcers of varying aetiologies, using a visual analogue scale. For two participants, the measurement was too painful to allow its completion; however the majority of participants (76%) rated the procedure as not painful.
13.2.4 Study limitations
Doppler ABI measurements included within the DUAL study were undertaken by the PhD researcher or expert (vascular surgeon), both of whom are highly experienced in this procedure. This may have influenced the time taken for them to complete measurements and hence results cannot be generalised to other health professionals undertaking this task. Also, the automated device measurement was always undertaken first and this may have influenced participants' ratings of the two techniques.

13.3 Conclusions
The time taken to perform Doppler ABI measurement, in the hands of experienced practitioners, did not differ significantly from the time taken to perform automated ABI measurement. However, consideration of the total test time, by adding the obligatory ten minute rest period to the Doppler measurement times, did result in a statistically significant difference in time durations between the two techniques. This, of course, makes ABI measurement using an automated ABI device far more amenable than the Doppler, for use in primary care settings where time pressures are often considerable. Furthermore, reductions in the time needed to undertake the test and the fact that the AD could be operated by non-qualified staff could also make PAD screening more viable from a financial viewpoint.
Patient perspective of both generalised blood pressure measurement and ABI measurement has been given little attention in current literature. Results indicate that overall, both the Doppler measurement procedure and the automated device measurement procedure were largely acceptable to those undergoing the tests. Overall, participants preferred the Doppler ABI measurements over the automated ABI device measurements and this finding appeared to be associated with the perceived comfort of the procedures. Perceived lack of operator control over the automated device measurements could also be associated with this finding. This could be addressed by remaining in close proximity to patients undergoing the test and reassuring them that the measurement could be aborted at any time should it become too painful. However, further research into this issue is required (Section 13.4).

13.4 Future Research
Future research should investigate the time taken for practitioners with varying levels of experience, from both primary and secondary care, to perform ABI measurements using both the Doppler and automated ABI devices. The order in which the measurements are undertaken should be
randomised. A more in-depth qualitative assessment of patient perspective of the measurement procedures may be warranted in order to further investigate the issues related to comfort and perceived control of measurements as identified in this study. Future studies could also investigate operator preference of manual versus automated ABI measurement.
Chapter 14: Pulse Volume Waveform Analysis

14.0 Background Information

Pulse volume waveform (PVW) analysis is a non-invasive test that utilises volume plethysmography to evaluate blood flow in the lower extremity (Weinburg, 2010). Volume changes can be detected via pressure sensors (pneumoplethysmography) or photo detectors (photoplethysmography). With pneumoplethysmography, a PVW recording is derived by placing a cuff around the limb and inflating it to about 45mmHg; this compresses the veins but not the arteries. As arterial blood moves underneath the cuff through arteries, arterial branches and small vessels, momentary volumetric changes in the limb are converted into pulsatile pressure changes within the air-filled cuff bladder on the ankle. A pressure transducer converts these small pressure changes into a small electrical signal which is amplified and displayed as a waveform plotted against time (Huntleigh, 2014) (Figure 14.1).

With photoplethysmography, changes in blood volume, blood vessel wall movement, and the orientation of red blood cells affect the amount of light received by a photo detector (Allen, 2007). Pulse volume waveforms exhibit the same characteristics regardless of the method used to detect the volume changes (Figure 14.2).

14.0.1 Interpretation of Waveforms

Figure 14.2 illustrates the components of a normal PVW. There are two aspects of the waveform which require consideration for its interpretation:
1. The contour of a PVW tracing - this is closely associated with the intra-arterial pressure contour (Raines & Almeida, 2010). If, at rest, a reflected wave is absent, this implies the peripheral resistance distal to the point at which the tracing was taken has been reduced. Reduction in peripheral resistance is most often caused by proximal arterial obstruction.

2. The amplitude of the PVW - the greater the PVW amplitude, the greater the local pulsatile component of total flow. PVW amplitude is a function of local pulse pressure and pulse pressure is reduced with arterial occlusion proximal to the point at which the tracing is taken. Therefore, the more reduced the PVW amplitude, the greater the proximal obstruction and the poorer the local perfusion.

The PVW changes with the level of PAD proximal to the point where the tracing was taken. These include:

- Decrease in the rise of the upslope
- Rounding and delay in the pulse crest
- Decreased rate of fall of the downslope
- Absence of the reflected diastolic wave

The interpretation of PVR waveforms is usually undertaken by manually comparing them to the four level grading system set out by Rumwell and McPharlin (1998)(Figure 14.3).
Figure 14.3: PVW grading system (Reference: Rumwell and McPharlin, 1998).

**Grade A: Normal**

![Diagram of normal dicrotic notch]

- Sharp systolic peak with prominent dicrotic notch.

**Grade B: Mildly Abnormal**

![Diagram of minimal-mild PAD]

- Sharp peak, absent dicrotic notch; downslope is bowed away from baseline.

**Grade C: Moderately Abnormal**

![Diagram of mild-moderate PAD]

- Flattened systolic peak, upslope and downslope time decreased and nearly equal, absent dicrotic notch.

**Grade D: Severely Abnormal**

![Diagram of severe-critical PAD]

- Low amplitude or absent pulse wave with equal upslope and downslope time.
Pulse volume waveforms (PVWs) represent the sum of all blood flow through the examined area. Hence, a patient that has a significant obstruction to blood flow in one or more of their arteries but good collateral flow may have a normal waveform. PVWs cannot therefore, provide accurate diagnostic information as to where and to what extent a specific artery is diseased. However, they can provide useful functional information regarding the sum of blood flow to the legs; this may be helpful in determining whether a wound can potentially heal, for example. According to Weinberg (2010) PVWs are currently used in two instances:

1. As a preliminary test to evaluate if a patient’s symptoms may be related to poor arterial blood supply.
2. As a surveillance test to non-invasively monitor a patient after a vascular procedure or to follow a patient’s disease process when no immediate intervention is needed.

14.1 Current and future use of PVW recordings

Use of the PVW recording is recommended by both the European Society of Cardiology (Tendera et al., 2011) and the American College of Cardiology/American Heart Association (Anderson et al., 2013) as a second level assessment tool for patients with suspected PAD. It is recognised that PVW analysis can be utilised to establish an initial lower extremity PAD diagnosis, assess localisation and severity, and follow the status of lower extremity revascularisation procedures. More recently, authors are increasingly recognising that waveform analysis is of particular value in patients who may have artefactually raised ABIs (Lewis and Owens, 2010). For example, elderly, diabetic and renal patients (and also other groups with rarer systemic diseases, like systemic sclerosis or rheumatic diseases) may have calcification of the peripheral arteries causing them to be incompressible (as discussed in Section 2.9.3). In these cases, artefactually raised occlusion pressures secondary to the calcification, result in inaccurate and non-diagnostic ABIs.

14.1.1 Pulse volume waveform analysis versus Doppler waveform analysis

An alternative form of arterial waveform analysis which is commonly used for PAD assessment is Doppler waveform (DW) analysis. A key consideration when comparing these techniques concerns their amenability for use in a primary care setting where they could be used to screen for PAD. DW analysis requires skill on behalf of the operator whereby a Doppler probe has to be carefully positioned over an artery, at a specific angle and pressure. Oates et al. (2013) point out that the
cost, portability of equipment, and time taken to perform the DW make this modality more suited to a referral centre, where it would be more pertinent to perform a full duplex ultrasound which would provide both anatomical and haemodynamic information.

Until recently, PVW analysis was confined to the vascular laboratory where the equipment for performing segmental PVWs and pressures was cumbersome (Figure 14.4). The development of portable equipment with PVW recording capabilities, such as Huntleigh’s Dopplex Ability (Figure 14.5), has made this diagnostic technique much more amenable for use in a primary care setting. In contrast to DW, the procedure for obtaining pulse volume waveforms is simplistic and merely involves the application of a cuff to the foot, prior to automatic inflation and PVW recording. Operators of course require training for the subjective process of PVW interpretation. At present, there is limited research regarding the sensitivity and specificity, ease of use, and the cost and training required to achieve reliable results utilising this technique.

### 14.1.2 Limitations of PVW analysis

There are also physiological limitations related to PVW analysis; pulse volume waveforms are dependent on peripheral blood flow and this may be influenced by factors other than vessel patency (Weinburg, 2010). In the upper limb for example, where sympathetic nerve input has a great deal of influence on blood flow, PVWs may not always indicate the true nature of blood flow capabilities of the limb. Severe congestive heart failure may also slow blood flow and mimic inflow disease.
Figure 14.4: Pulse Volume Recorder used in vascular laboratories

Figure 14.5: Dopplex Ability (which incorporates pulse volume waveform recorder)
Image source: Huntleigh Diagnostics, reproduced with permission.
Chapter 15: Analysis of PIPETTE Pulse Volume Waveforms

15.0 Background

The shortcomings of the use of the ankle brachial index (ABI) to identify PAD have been discussed in Section 2.9.3. The most significant of these relates to the fact that medial artery calcification can sometimes result in falsely elevated or non-diagnostic ABIs. If the ABI is being used in isolation as a diagnostic test, this can ultimately lead to cases of PAD being missed. The merits and limitations of pulse volume waveform (PVW) analysis have also been discussed in Chapter 14; whether this diagnostic modality could be used in the primary care environment to identify PAD, either in combination with the ABI or as a stand-alone test, is unclear.

15.1 Chapter Aims

The fundamental objective of this chapter is to consider the utility of PVW analysis as a PAD diagnostic technique, including its suitability for use within the primary care environment. Aims were to determine:

- The agreement between two reviewers regarding the interpretation of PVWs
- The agreement between the two diagnostic modalities (ABI measured with Doppler ultrasound versus PVW analysis) for the diagnosis of PAD.

15.2 Method

The PVWs of all PIPETTE participants were analysed by both the PhD researcher and an independent expert (Dr Jane Lewis, Clinical Specialist Podiatrist and Therapies, Cardiff and Vale University Health Board). Dr Lewis is considered an expert as she has completed, and continues to undertake, considerable PVW research, which is reflected in several published papers related to this subject (Lewis and Owens, 2010; Lewis et al., 2011).

This study was single-blinded as Dr Lewis reviewed the PIPETTE PVWs without access to any corresponding clinical data, or knowledge of the PhD researcher’s gradings; nor was she aware of the purpose of the exercise. Each PVW was graded according to the 4-level grading system proposed by Rumwell and McPharlin (1998) (Figure 14.3).
15.2.1 PAD diagnosis

Prior to comparing the ABI with PVW analysis for identifying PAD, it is first necessary to define what exactly constitutes a PAD diagnosis according to these two modalities (Figure 15.1).

![Diagram of PAD diagnosis according to ABI and PVW analysis](image)

**Figure 15.1: Diagrammatic representation of PAD diagnosis according to ABI and PVW analysis**

### ABI PAD diagnosis

- If a participant’s ABIs for both legs were >0.9, then the participant did not have ABI defined PAD; this group is subsequently termed the “Non-PAD ABI group”. This group was also further sub-divided into “Non-PAD low ABI” and “Non-PAD normal ABI” groups; a detailed explanation of the rationale for these sub-groups is given in the prelude of Part 3 of this thesis.
- If a participant’s ABI was ≤0.9 for either leg, the participant was considered to have ABI defined PAD; this group is subsequently termed the “PAD ABI group”.

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PVW PAD diagnosis

- If the agreed PVW was graded B, C or D for either of the participant’s legs, then the participant was regarded as having “PVW defined PAD”.
- If the PVWs for both legs were graded A, then the participant did not have PVW defined PAD.
- If both reviewers agreed that one (or both) of a participant’s PVWs were graded A/B and the PVW of the other leg was not graded B, C or D, then the participant was regarded as having “possible PVW defined PAD”.

15.2.2 Validation of PVW analysis and ABI results

Four participants from the PIPETTE study were referred to a vascular surgeon (by their GPs) for further investigation as a result of PAD positive ABI and PVW results. Three of these participants had been diagnosed with PAD on the basis of their ABIs and PVWs. The remaining participant had normal ABIs but abnormal PVWs. All four of these participants subsequently underwent Duplex ultrasound scanning and angiography which confirmed the PAD diagnoses in all cases; in fact, all four participants subsequently underwent successfully angioplastic procedures. These four cases provide validation of a sample of the positive PAD cases within the study.

15.3 Exclusions

From a possible 736 PVWs (n=368 x 2 legs=736), 680 were suitable for grading; exclusions are detailed in Table 15.1. The 56 PVW exclusions related to 28 participants.

<table>
<thead>
<tr>
<th>Reason for Exclusion</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor quality PVW (showing considerable artefact)</td>
<td>28</td>
</tr>
<tr>
<td>Failed Dopplex Ability measurement</td>
<td>10</td>
</tr>
<tr>
<td>No Dopplex Ability print-out available</td>
<td>8</td>
</tr>
<tr>
<td>Unable to use Dopplex Ability: participant had previous mastectomy</td>
<td>6</td>
</tr>
<tr>
<td>Unable to use Dopplex Ability: 4 layer bandage in situ</td>
<td>2</td>
</tr>
<tr>
<td>Unable to use Dopplex Ability: ankle circumference too small</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 15.1: PIPETTE PVW analysis: reasons for exclusions
15.4 Results

15.4.1 Agreement of PVW interpretation between PVW reviewers

Cohen’s κ was run in order to assess the agreement of the PVW interpretation by the two reviewers; there was a very high degree of agreement, κ = .718 (95% CI, .679 to .757), p < 0.01. The two reviewers returned identical PVW gradings for 91% of results (n=619). For a further 8% (n=58) of PVWs, the reviewers returned what could be termed ‘near agreement’; this means that one of the reviewers gave an “across-gradings” response such as A/B which would be given when the waveform appeared to exhibit characteristics of both A and B gradings. If the other reviewer then gave a response which matched either of the across-grading categories (i.e. A or B), then this was classed as near agreement. The reviewers disagreed for the remaining 1% (n=7) of PVWs, although the disagreement was never greater than one grading. These disagreements related to 5 participants (for two participants, the reviewers disagreed for both legs). These participants were excluded from the subsequent analysis of the PVWs and ABIs, as the disagreement also meant that the reviewers could not agree regarding the participants’ overall PAD status according to the PVW.

![Diagram showing PAD status agreement to ABI results and PVW analysis](image-url)
15.4.2 PAD status agreement according to ABI results and PVW analysis

The agreement between the PVW analysis results with ABI results, according to the above PAD definitions, is represented in Figure 15.2.

True Positives: confirmed PAD diagnoses

Of the 12 cases that were diagnosed with PAD according to the Doppler ABI results, 11 were confirmed via PVW analysis.

False Negatives: disputed PAD diagnoses

There was only one case where the PVW grading disputed a positive PAD diagnosis according to the ABI. This participant had an ABI of 1.0 for her right leg and 0.88 for her left leg, hence suggesting mild PAD on the left. However, PVWs for both legs were graded A, which is normal, by both reviewers. The Dopplex Ability print-out for this participant is shown in Figure 15.3). A possible explanation for this disparity could be that the participant had developed a degree of collateral circulation hence resulting in a normal PVW for the left leg as well as the right (discussed in Section 14.0.1). This participant was classed as active according to the General Practice Physical Activity Questionnaire (GPPAQ) hence supporting this possible explanation as exercise promotes development of the collateral circulation (Gommans et al., 2014).

![Dopplex Ability printout showing PVW recording (left) which disputes PAD diagnosis (ABI≤0.9) according to Doppler ultrasound.](image)

True Negatives: confirmed negative PAD diagnoses

Of the 356 cases that did not have PAD according to Doppler ABI results, 323 had an evaluable PVW; subsequent analysis of these revealed normal waveforms for both legs in 284 of these, hence confirming the negative results.
False Positives: disputed negative PAD diagnoses

Negative ABI results were disputed in 39 cases. These 39 cases were further divided into (i) definite PAD cases according to PVWs and (ii) possible PAD cases according to PVW.

**Definite PAD cases according to PVW analysis**

There were four definite cases where the PVW grading disputed a negative PAD ABI diagnosis. In these cases both reviewers agreed that at least one of each participant’s PVWs was graded B, C or D, and this was despite the corresponding ABIs being within the normal range. An example of a Dopplex Ability print-out from one of these participants is shown in Figure 15.4.

![Dopplex Ability print-out showing normal ABIs according to Doppler ultrasound and Dopplex Ability but abnormal PVW recordings](image)

One of these cases within this group came from the normal ABI group, whilst the other three came from the high ABI group. All four of these cases were women. Statistical analysis revealed that this group did not differ significantly in terms of demographics and cardiovascular risk factors in comparison to the ABI defined PAD group; however, it is probable that the very small sample size of the definite PAD PVW group (n=4) was insufficient to detect such significant differences in any case.

When these four cases were added to the original PAD ABI group (n=12) to make a combined “definite PAD” group (n=16), the previously identified associations with PAD (Section 8.2.2), were strengthened as indicated by lower p values (with the exception of rheumatoid arthritis which remained significant but p value increased slightly) (Table 15.2). In addition, this combined definite PAD group was shown to have significantly more participants who were taking anti-hypertensives (p=0.023) and lipid lowering medications (p=0.01).
Possible PAD cases according to PVW analysis

For the 35 possible PAD according to PVW cases, reviewers agreed that the PVWs may have been abnormal despite normal corresponding ABIs; i.e. PVWs graded A/B whilst Doppler ABI>0.9. An example of one of the Dopplex Ability print-outs demonstrating this is shown in Figure 15.5. Six cases within this group came from the borderline PAD ABI group, 26 from the normal ABI group and three came from the high ABI group.

<table>
<thead>
<tr>
<th>Factors significantly associated with PAD</th>
<th>ABI defined PAD Group (n=12) v No PAD Group (n=352)</th>
<th>ABI &amp; PVW defined PAD Group (n=16) v Non PAD Group (n=348)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70 v 64 (p=0.029)</td>
<td>70 v 64 (p=0.02)</td>
</tr>
<tr>
<td>% age 75+</td>
<td>33 v 10(p=0.049)</td>
<td>25 v 11 (p=0.018)</td>
</tr>
<tr>
<td>% Current smoker</td>
<td>50 v 10(p&lt;0.001)</td>
<td>63 v 10 (p&lt;0.001)</td>
</tr>
<tr>
<td>Pulse Pressure</td>
<td>68 v 59 (p=0.005)</td>
<td>70 v 58 (p=0.002)</td>
</tr>
<tr>
<td>Total number of CV risk factors</td>
<td>4 v 3 (p=0.018)</td>
<td>4 v 3 (p&lt;0.001)</td>
</tr>
<tr>
<td>QRISK2 score</td>
<td>32.6 v 18.5 (p=0.001)</td>
<td>30.6 v 18.4 (p=0.001)</td>
</tr>
<tr>
<td>Relative risk according to QRISK2</td>
<td>1.6 v 1.3 (p=0.048)</td>
<td>1.8 v 1.3 (p=0.002)</td>
</tr>
<tr>
<td>Taking lipid lowering medications</td>
<td>58 v 24 (p=0.064)</td>
<td>50 v 23 (p=0.01)</td>
</tr>
<tr>
<td>% Taking anti-hypertensive medications</td>
<td>67 v 41 (p=0.072)</td>
<td>69 v 41 (p=0.023)</td>
</tr>
<tr>
<td>% with rheumatoid arthritis</td>
<td>16 v 1 (p=0.012)</td>
<td>13 v 1.4 (p=0.033)</td>
</tr>
</tbody>
</table>

Table 15.2: Factors significantly associated with PAD

It is useful to consider the characteristics of this group in comparison to the:
- definite PAD group [ABI defined PADS (n=12) plus PVW defined PADS (n=4)]
- remaining participants – the Non-PAD group (n=302) (Table 15.3).
<table>
<thead>
<tr>
<th>Demographics</th>
<th>Definite PAD group according to ABI &amp; PVW (n=16)</th>
<th>Compared to</th>
<th>Possible PAD group according to PVW (n=35)</th>
<th>Compared to</th>
<th>Non-PAD group according to ABI &amp; PVW (n=302)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>65</td>
<td>P=0.159</td>
<td>67</td>
<td>P=0.001</td>
<td>62</td>
</tr>
<tr>
<td>% age 75+</td>
<td>25</td>
<td>P=0.594</td>
<td>17</td>
<td>P=0.007</td>
<td>29</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>56</td>
<td>P=0.129</td>
<td>77</td>
<td>P&lt;0.001</td>
<td>41</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.64</td>
<td>P=0.310</td>
<td>1.6</td>
<td>P&lt;0.001</td>
<td>1.68</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>74</td>
<td>P=0.411</td>
<td>71</td>
<td>P&lt;0.001</td>
<td>84</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Social History</th>
<th>% Current smoker</th>
<th>P=0.001</th>
<th>9</th>
<th>P=0.384</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alcohol Units per week</td>
<td>P=0.254</td>
<td>5</td>
<td>P=0.012</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>% who consume alcohol in excess of recommended weekly limits</td>
<td>P=0.614</td>
<td>14</td>
<td>P=0.78</td>
<td>16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular Risk Factors</th>
<th>% with family history of premature CHD</th>
<th>P=0.298</th>
<th>40</th>
<th>P=0.059</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% with rheumatoid arthritis</td>
<td>P=0.174</td>
<td>3</td>
<td>P=0.449</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>% with chronic kidney disease</td>
<td>P=0.227</td>
<td>9</td>
<td>P=0.058</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Systolic Blood Pressure</td>
<td>P=0.203</td>
<td>139</td>
<td>P=0.947</td>
<td>139</td>
</tr>
<tr>
<td></td>
<td>Diastolic Blood Pressure</td>
<td>P=0.967</td>
<td>78</td>
<td>P=0.031</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>% Taking anti-hypertensive medications</td>
<td>P=0.179</td>
<td>49</td>
<td>P=0.292</td>
<td>39</td>
</tr>
</tbody>
</table>

| Pulse Pressure            | P=0.038 | 60 | P=0.503 | 58 |
| Heart Rate (Higher)       | P=0.295 | 71 | P=0.432 | 75 |
| % with irregular pulse    | P=0.204 | 3  | P=0.212 | 4  |
| % with dyslipidaemia      | P=0.391 | 85 | P=0.204 | 76 |
| Body Mass Index (BMI)     | P=0.855 | 28 | P=0.014 | 30 |
| % with elevated waist circumference | P=0.126 | 46 | P=0.015 | 67 |
| Waist Circumference (cm)  | P=0.155 | 91 | P=0.001 | 101|
| Waist to Hip ratio        | 0.94    | P=0.016 | 0.85 | P=0.001 | 0.92|
| Total number of CV risk factors * | 4 | P=0.053 | 3 | P=0.926 | 3 |

| CV Risk Assessment | QRISK2 Score | P=0.013 | 18.2 | P=0.149 | 17.3 |
|                   | Relative risk according to QRISK2 | 1.6 | P=0.015 | 1.3 | P=0.740 | 1.3 |

Table 15.3: Characteristics associated with definite PAD group, possible PAD group and non-PAD group
The possible PAD group was statistically different to the definite PAD group as it had a lower proportion of smokers (9% v 44%, p=0.001), a lower mean pulse pressure (60 v 67, p=0.038), lower mean waist to hip ratio (0.85 v 0.94, p=0.016), and lower QRISK2 score (18.2 v 21.3, p=0.013).

Compared to the non-PAD group, the possible PAD group was significantly older (mean age 67 v 62, p=0.001) and contained a significantly larger proportion of females (77% v 41%, p<0.001). There were also a number of significant differences which could have been related to/cause by the high proportion of females in the group; for example, the mean height was lower for the possible PAD group than the non-PAD group (1.6m v 1.68m, p<0.001). This also applied to other anthropometric measurements such as mean weight (71kg v 84kg, p<0.001), waist circumference (91cm v 101cm, p<0.001), and waist to hip ratio (0.85 v 0.92, p<0.001). In addition, the possible PAD group consumed, on average, less units of alcohol per week (5 v 10, p=0.012); this was also shown to be gender related in the analysis of the entire PIPETTE population (Table 3.5). Diastolic blood pressure was shown to be significantly lower in the possible PAD group (78 v 82, p=0.031); again it is well documented that diastolic pressure is lower in women (Kawada, 2014). The possible PAD group was less likely to be overweight than the non-PAD group as indicated by significantly lower BMIs (28 v 30, p=0.014) and a significantly lower proportion of people with elevated waist circumferences (46% v 67%, p=0.015).

15.4.3 PAD Sensitivity and specificity

Although angiography is the ultimate gold standard for assessment and identification of PAD, this diagnostic procedure is confined to the hospital environment and is not routinely used because of its invasiveness and associated complications (Oser, 1995). Doppler ultrasound, however, is the recognised gold-standard for measurement of the ABI and assessment of PAD outside of the vascular laboratory.

When assessing the efficacy of a new diagnostic modality such as PVW analysis, it is commonplace to statistically compare it to the recognised gold standard, which in this case is the Doppler ultrasound. Diagnostic accuracy is measured via calculation of the sensitivity, specificity, positive predictive value and negative predictive value of the new test. Table 15.4 outlines such calculations and results for the Doppler ABI versus PVW analysis.
### Gold Standard: Doppler ABI

<table>
<thead>
<tr>
<th>PVW analysis</th>
<th>Non-PAD</th>
<th>PAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-PAD</td>
<td>TN: 284</td>
<td>FN: 4</td>
</tr>
<tr>
<td>PAD</td>
<td>FP: 39</td>
<td>TP: 11</td>
</tr>
</tbody>
</table>

- **Negative Predictive Value** = \( \frac{TN}{TN+FN} = 99.6\% \)
- **Positive Predictive Value** = \( \frac{TP}{TP+FP} = 22\% \)
- **Specificity** = \( \frac{TN}{TN+FP} = 88\% \)
- **Sensitivity** = \( \frac{TP}{TP+FN} = 92\% \)
- **Accuracy** = \( \frac{TN+TP}{TN+FN+FP+TP} = 87\% \)

**Table 15.4:** Accuracy calculations of PVWs compared to gold standard Doppler ultrasound ABI.

As it is uncertain whether the 35 possible PAD cases according to PVWs are true PAD cases, then the analysis was repeated with only the definite PAD cases according to PVWs being included as PVW defined positive cases. The 35 possible PAD cases according to PVWs were included as negative PVW defined cases (Table 15.5). It can be seen that this greatly improves the positive predictive value of PVW analysis.

### Gold Standard: Doppler ABI

<table>
<thead>
<tr>
<th>PVW analysis</th>
<th>Non-PAD</th>
<th>PAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-PAD</td>
<td>TN: 319</td>
<td>FN: 1</td>
</tr>
<tr>
<td>PAD</td>
<td>FP: 4</td>
<td>TP: 11</td>
</tr>
</tbody>
</table>

- **Negative Predictive Value** = \( \frac{TN}{TN+FN} = 99.8\% \)
- **Positive Predictive Value** = \( \frac{TP}{TP+FP} = 73\% \)
- **Specificity** = \( \frac{TN}{TN+FP} = 98\% \)
- **Sensitivity** = \( \frac{TP}{TP+FN} = 92\% \)
- **Accuracy** = \( \frac{TN+TP}{TN+FN+FP+TP} = 99\% \)

**Table 15.5:** Accuracy calculations of PVWs compared to gold standard Doppler ultrasound, with possible PAD cases according to PVWs reclassified as negative for PAD.

Although ABI measurement using a hand-held Doppler ultrasound is regarded as the gold standard for PAD diagnosis in a non-specialist setting, its limitations are well documented (Section 2.9.3). In view of this, it was decided to repeat the above analysis, this time comparing the Doppler ultrasound with the PVWs as the designated gold standard (Table 15.6). It can be seen that although the specificity of the Doppler to rule out PAD is high at 98%, its sensitivity to detect it, is lower at only 73%.
Gold Standard: PVW analysis

<table>
<thead>
<tr>
<th>DopplerABI</th>
<th>Non-PAD</th>
<th>PAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>TN: 319</td>
<td>FN: 4</td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>FP: 1</td>
<td>TP: 11</td>
</tr>
<tr>
<td>specificity=TN/(TN+FP)=98%</td>
<td>Sensitivity=TP/(TP+FN)=73%</td>
<td>Accuracy=TN+TP/(TN+FN+FP+TP)=99%</td>
</tr>
</tbody>
</table>

Table 15.6: Accuracy calculations of Doppler ultrasound compared to gold standard PVW analysis, with possible PAD cases according to PVWs reclassified as negative for PAD.

15.5 Discussion

15.5.1 Agreement of PVW interpretation

The PhD researcher and PVW expert demonstrated a high degree of agreement for the interpretation of the PIPETTE PVWs. A literature search did not identify any papers which have investigated this subject and hence there are no data upon which comparisons of agreement rates can be made.

15.5.2 PAD diagnosis according to PVW analysis

Within the PIPETTE study the sensitivity and specificity of subjective analysis of PVW compared to ABI measurement with Doppler ultrasound as the gold standard, were 92% and 88% respectively. Research regarding PVW analysis for the identification of PAD is sparse. A literature review revealed only one study which also compared analysis of pulse volume waveforms with the Doppler ultrasound ABI as the gold standard; Allen et al. (2008) obtained bilateral PVWs from 111 individuals aged 42-91, using photoplethysmographic probes attached to the big toes. This study differed from PIPETTE not only in the methodology used to obtain the PVWs (PIPETTE: pneumoplethysmography; Allen et al.: photoplethysmography), but also in the method used to analyse PVWs. Whilst interpretation of the PVWs was achieved subjectively by two observers in the PIPETTE study, Allen and colleagues used computer software to objectively measure timings, amplitude and shape characteristics of PVWs. The software compared study measurements with previously defined normative pulse volume ranges which had been attained from a previous pilot study (Allen et al., 2005). Despite the methodological study differences, the sensitivity and specificity of PVW analysis attained within the study by Allen and colleagues were 93% and 89% respectively, which are almost identical to the results from the PIPETTE study.
A study by Ro et al. (2013) evaluated the sensitivity and specificity of the (i) ABI, (ii) subjective PVW analysis derived by photoplethysmography (PPG), and (iii) subjective Doppler waveform (DW) analysis compared to the gold standard of computed tomography angiography (CTA) diagnosed PAD. Test results from a total of 97 patients (194 legs) who had coincidently undergone CTA, ABI, PPG and DW were retrospectively reviewed. The PPG and Doppler waveforms were subjectively interpreted by a single physician. With PPG, diagnosis of PAD was based on loss of the dicrotic notch, decreased waveform amplitude and/or rounding of systolic peaks. For DWs, diagnosis of PAD was based on loss of triphasic pattern, decreased amplitude and/or loss of reverse flow component. The sensitivity and specificity of PPG PVW analysis compared to the CTA were 82% and 77% respectively; for DW analysis: sensitivity was 91% and specificity 65%, and for ABI: sensitivity was 70% and specificity 97%. The authors concluded that ABI should be combined with PPG PVW analysis or DW analysis in order to improve detection of PAD.

15.5.3 Assessment of the accuracy of PAD diagnosis via PVW analysis

With the exception of the four cases that were referred to a vascular surgeon and underwent angiology, the PIPETTE study was not able to formally validate any of the remaining PAD diagnoses. Similarly, the negative PAD cases were also not formally validated. At the conception of this PhD project, it was not anticipated that PVW analysis would constitute such a significant and clinically relevant proportion of this thesis. As such, a comprehensive validation process of PVWs was not planned and furthermore, the constraints which resulted from this study being undertaken as part of a time and funding-limited PhD prevented this from being added to the study design at a later date. The only alternative and available method of assessing if interpretation of the PVWs was likely to have been accurate involved comparing the characteristics of those who exhibited abnormal PVWs with factors that have previously been proven to be associated with PAD.

15.5.4 Factors associated with PVW defined PAD

The definite PAD cases according to PVWs have been shown to fit with the PAD risk factor profile previously identified via analysis of the ABI defined PAD cases. Namely, they consisted of older individuals with a smoking history, higher pulse pressures, greater numbers of CV risk factors and recognised high CV risk according to QRISK2 scores. Furthermore, this risk factor profile also concurs with the existing PAD evidence base (Section 8.2). Adding the four PVW defined PAD cases to the ABI defined PAD cases augments the statistical significance of the factors previously associated with PAD and also identified a further two statistically related factors; namely, the PAD cases were more likely.
to be taking anti-hypertensive and lipid lowering medications. Reports from the NHANES and PARTNERS studies have demonstrated that between 60-77% of individuals with PAD have elevated cholesterol (Novo, 2002; Sumner et al., 2012). The same studies have also consistently shown that hypertension is strongly associated with PAD; the NHANES and PARTNERS programmes report that hypertension was present in 74% and 92% of persons with PAD respectively. The fact that the PIPETTE participants who were found to have PAD are more likely to have been receiving treatment for these conditions is, of course, a positive finding.

Compared to the definite PAD group, the possible PAD group was shown to contain significantly less current smokers and had a lower mean pulse pressure. As these factors have been shown to be key contributing factors for PAD, not only within the PIPETTE study but also within the current literature, this then suggests that it is possible that this group may not, at least in part, contain true PAD cases. Furthermore, individuals in this group were actually healthier than the Non-PAD group in that they were less likely to be overweight. They also had comparable QRISK2 scores and relative risks as the Non-PAD group.

For all of these cases in the possible PAD group, the defining factor, which led to the A/B grading, was uncertainty regarding the presence of the dicrotic notch within the pulse volume waveforms. Two factors are important with regard to this. Firstly, the possible PAD group had a higher mean age than the Non-PAD group; Allen and Murray (2003) noted the dicrotic notch, which represents a reflective wave (Chapter 14), diminishes in older subjects. This can be attributed, in part, to age related increases in pulse wave velocity resulting in a faster reflected wave augmenting the forward wave. Hussain and Subhash (1998) examined the pulse volume waveform in 90 female and 90 male subjects and also found that dicrotism is less prevalent at older ages (p<0.001). Secondly, Hussain and Subhash also found that the dicrotic notch is reduced in females (p<0.001) and also diminishes with decreasing height (p<0.001). Gatzka et al. (2001) found that women have smaller and stiffer blood vessels which results in an earlier return of the reflective wave, resulting in it being absorbed into the forward systolic wave. As the possible PAD group did indeed consist of a significantly greater proportion of women (p<0.001), and had significantly reduced heights in comparison to the Non-PAD group (p<0.001), it is possible that the observed absence of the dicrotic notch in the majority of the corresponding PVWs could be attributed to normal physiological differences rather than the presence of PAD.

Hence to summarise, based on the above analysis of factors associated with PVW defined PAD, it appears that the definite PAD PVW cases are probably true PAD cases, but the possible PAD PVW cases are unlikely to have PAD.
15.5.5 Potential utility of PVW analysis in primary care

With the exception of the study by Ro and colleagues (2012) (Section 15.5.2), no other research has investigated the qualitative interpretation of PVWs. Similarly, there has been no consideration of whether PVW analysis could be used within a primary care environment to assist with PAD diagnosis. However, as the PVW is very similar to the continuous wave Doppler (CDW) waveform (Chapter 14) and the interpretation of both involves a similar subjective process, it is helpful to draw on research relating to classification of Doppler waveforms. A study by Scissons (2008) found that sonography professionals misclassified 27% of Doppler waveforms into triphasic, biphasic and monophasic groups. However, a more recent study (2013) by Young and colleagues compared the ability of student podiatrists and registered podiatrists to correctly classify 15 Doppler recordings from the posterior tibial artery. Students correctly classified 84% of recordings compared to 82% for the registered podiatrists. Hence whilst Scissons’ work demonstrates that professionals, who could be regarded as experts in the procedure of Doppler waveform analysis, incorrectly classify over a quarter of Doppler waveforms, Young et al. (2013) have shown that students who have received minimal training, are able to perform the task with a high degree of accuracy. It should be noted here, that the possible utility of PVW analysis in a primary care setting need only require distinction between normal and abnormal waveforms and not actual classification of the abnormal recordings. The overall objective of PVW analysis within a community setting would be to identify patients who require referral for further investigation, rather than to quantify the degree of PAD.

15.6 Limitations

Although the PhD researcher and Dr Jane Lewis displayed a high level of agreement for the interpretation of PVWs, this finding may not be generalisable to individuals who may be less experienced at this task. The lack of comprehensive validation of PVW PAD diagnoses has been highlighted in Section 15.2.2; it is therefore paramount that this is addressed in future research. Practitioners from the primary care environment should be compared to experts in the interpretation of PVWs and results should be verified via comparison with Duplex Ultrasound scan results, or if possible, CTA. It would also be of use to determine how PVWs correlate with other measures of atherosclerosis such as carotid intima media thickness. Longitudinal studies which assess the incidence of adverse cardiovascular event and mortality, based on their PWV interpretations, would be informative regarding the utility of PWV analysis as a marker of cardiovascular risk.
15.7 Conclusions

This chapter has demonstrated that 1.1% (n=4) of the PIPETTE study population were likely to have had some degree of PAD, as indicated by abnormal PVWs, despite having normal ABIs. This figure is likely to be higher in the general population due to the fact that diabetics were excluded from the PIPETTE study. Diabetes has been shown to be a significant contributing factor to medial artery calcification, which in turn causes elevated and non-diagnostic ABIs. Existing studies, although few in number, have confirmed the improved sensitivity of PVW analysis compared to the ABI for PAD diagnosis.

There is also a paucity of evidence relating to the subjective interpretation of PVWs and their possible utility in a primary care environment. The ambiguity surrounding the true PAD status of the 35 possible PVW PAD cases has highlighted that the relationship between the peripheral pulse volume waveform and subject age in health and arterial disease is complex. It is therefore concluded that age and gender matched normal ranges must be considered when evaluating PVWs. This, of course, makes the subjective process of PVW interpretation more complex and less amenable for use within non-specialist settings.

Further research regarding the diagnostic utility of PVW analysis is needed; recommendations as to the focus of such research have been discussed in Section 15.6. It is probable that the development of automated interpretation of PVWs, perhaps making use of the same artificial intelligence and pattern recognition software that is used, for example, in electrocardiographs (ECG) interpretation, would greatly improve the potential utility of PVWs in the primary care environment.

This chapter has been published as an academic paper in the European Wound Management Association (EWMA) journal (Appendix 16).
Chapter 16: Edinburgh claudication questionnaire and clinical examination for identification of PAD

Within primary care, evaluation of lower limb arterial status is frequently based on history taking and physical examination. PAD screening questionnaires such as the ROSE questionnaire (Rose, 1962) or Edinburgh claudication questionnaire (Leng, 1992) are commonly used tools which aid this process. However, whilst specific for PAD, these methods have been shown to have low sensitivity (Haigh et al., 2013). This chapter therefore considers the utility of these PAD diagnostic techniques within the PIPETTE study.

16.1 Edinburgh Claudication Questionnaire (ECQ)

16.1.1 ECQ background information

The ECQ is a validated tool, consisting of six questions, which is used to diagnose intermittent claudication (IC) (Leng, 1992). IC, the primary symptom of PAD; arises during activity when the blood and oxygen demand of the working skeletal muscle exceeds supply (Olson and Treat-Jacobsen, 2004). It manifests itself as cramping pains which occur most commonly in the calf muscles but also in the thighs and buttocks; the pain location depends on the location of the arterial blockage (Olin, 1993). Classic claudication is defined by the World Health Organisation as “calf pain that occurs during exercise and ceases within 10 minutes of rest” (Rose, 1962).

The ECQ not only determines the presence or absence of IC but also grades positive cases in terms of its severity and whether it is a typical presentation or not. If the pain is only precipitated by walking up hill or in a hurry, then it is termed “grade 1”. If, however, it also occurs when walking at an ordinary pace on a level, then it is termed “grade 2”. Typical claudication is recorded when pain occurs in the calf, regardless of whether pain also occurs in other sites, whereas, atypical claudication refers to pain in the thigh or buttock in the absence of any calf pain. Compared to physician diagnosis of IC, the ECQ was found to have 91% sensitivity and 99% specificity (Leng, 1992).

16.1.2 Results

Three per cent (n=11) of the PIPETTE population had a positive ECQ questionnaire.
Of the positive results, the majority were of typical presentation in that calf pain was the primary symptom rather than pain elsewhere. Most participants reported pain when walking on the flat at normal speed in addition to pain when walking up hill and at a faster pace; hence indicating more severe disease (Figure 16.1).

As would be expected, ABI defined PAD (≤ 0.9) was significantly associated with a positive ECQ result ($\chi^2(3) = 64.279$, $p < 0.01$). Participants with positive ECQ results had significantly lower BMIs than those with negative ECQ result (25.6 vs. 29.5 respectively, $p = 0.008$, Mann-Whitney U test). They were also less likely to be classed as active according to the general practice physical activity questionnaire (GPPAQ) than those with a negative result (27% v 34%, Fisher’s Exact test, $p = 0.048$).

There was also an association between total number of clinical signs of PAD and a positive ECQ result (Mann-Whitney U test, $p < 0.001$). Of the participants without any clinical signs of PAD, 100% had a negative ECQ. Of the participants with 5 clinical signs of PAD, 100% had a positive ECQ.

<table>
<thead>
<tr>
<th>Gold Standard: Doppler</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECQ</td>
</tr>
<tr>
<td>Non-PAD</td>
</tr>
<tr>
<td>PAD</td>
</tr>
<tr>
<td>specificity=</td>
</tr>
<tr>
<td>TN/(TN+FP)=98%</td>
</tr>
</tbody>
</table>

Table 16.1: Accuracy calculation of ECQ compared to Doppler ABI as the gold standard reference
Of the 12 ABI defined PAD participants, 5 were graded as positive for IC according to the ECQ. This equates to a sensitivity of 42% as compared to ABI defined PAD. The positive predictive value of the ECQ was 45% (Table 16.1). Of these positive results, one was grade 1-typical, and the remaining 4 were grade 2-typical (Figure 16.1).

Of the 356 ABI defined non-PAD participants, 6 were graded as positive for IC. This equates to a specificity of 98%. All of these participants that returned positive ECQ results had ABIs within the normal range (1.0-1.29). The negative predictive value of the ECQ was 97%. Of these false positive results, one was grade 1-typical, four were grade 2-typical and one was grade 2-atypical.

Within the ABI defined PAD group, men were more likely to have a positive ECQ grading than women (57% v 20%, χ²(3) = 6.456, p=0.049). Similarly, within the normal ABI group, men were again more likely to have a positive ECQ grading than women, albeit these were false positive results (3% v 0.7%, χ²(3) = 7.082, p=0.047) (Figure 16.2).

16.1.3 ECQ discussion

The attained sensitivity and specificity of the ECQ to detect PAD and rule out PAD within the PIPETTE study (42% and 98% respectively) are broadly in line with the results of previous studies. Bendermacher et al. (2006) assessed the sensitivity of the ECQ for detecting a PAD diagnosis according to ABI<0.9, in 4790 patients aged ≥55 years who visited their general practitioner with symptoms suggestive of IC or with one risk factor. They found the ECQ had a sensitivity of 56.2%, a
positive predictive value of 59.4% and negative predictive value of 96.4%. Haigh et al. (2013) reported the sensitivity of the ECQ to be 56% and the specificity >90%.

It is well established that many individuals with PAD do not present with classic symptoms (McDermott et al., 2001) and many are indeed asymptomatic (Hirsch et al., 2000). Hence, considering that the ECQ is a symptom based questionnaire, it is not surprising that its sensitivity is so low.

Results have demonstrated that women with PAD are far more likely to be asymptomatic than men with PAD (80% versus 43%, p=0.049); again this result replicates the findings of existing research. The Women’s Health and Aging study of 933 disabled women found that 35% had PAD as defined by an ABI of ≤0.9. Of these women with PAD, 63% had no exertional leg symptoms (McDermott et al., 2000). Similarly, in a population study of 5080 Swedish men and women, aged 60-90, Sigvant et al. (2007) found that asymptomatic PAD was more common in women than men (12.6% v 9.4%, p=0.03).

It is possible that some participants within the study may not have been active enough to precipitate symptoms of IC. This could have been due to the presence of mobility limiting co-morbidities such as chronic obstructive pulmonary disease, or alternatively to such individuals choosing to lead a more sedentary lifestyle. A study by McDermott et al. (2008) assessed functional performance, calf muscle characteristics, peripheral nerve function and quality of life in asymptomatic persons with PAD (n=215) compared with PAD participants with IC (n=72). They found that people who never experienced exertional leg symptoms had poorer functional performance, poorer quality of life and more adverse calf muscle characteristics compared with those with IC. Hence it was concluded that the asymptomatic PAD individuals were less physically fit and experienced more ill health than those with symptomatic PAD. The PIPETTE study, however, did not find any evidence to support these findings.
16.2 Clinical Examination

16.2.1 Clinical examination background information

According to Marston (2011), detailed examination of the legs can provide valuable information regarding the state of the peripheral circulation. Dillavou and Kahn (2003) recommend that physical examination should include palpation and documentation of femoral, popliteal and pedal pulses, and auscultation for femoral and carotid bruits. Legs should also be inspected for signs of chronic ischaemia, including pallor, cyanosis and non-healing wounds. Trophic ischaemia related changes such as hair loss, smooth shiny skin and thickened nails may also be present. The PIPETTE study assessed for these clinical signs as discussed in Section 3.6.1. (Figure 16.3).

16.2.2 Clinical Examination Results

![Figure 16.3: Frequency of clinical signs of PAD.](image)

Key:
- A Reduced/absent pedal pulses
- B Non-healing wounds
- C Thickened nails
- D Shiny skin
- E Hair loss
- F Pallor
- G Cyanosis
- H Pallor on elevation
- I Rubor in dependent position
- J Reduced temperature
Participants exhibiting ≥1 clinical sign of PAD were more likely to be older (mean age = 68 versus 62, \( p < 0.01^* \)) (Figure 16.4), inactive (82% vs. 63%, \( p = 0.002^* \)), current smokers (21% vs. 9%, \( p = 0.006^X \)), and have higher QRISK2 scores (mean score = 25 vs. 17, \( p < 0.01^*)\). They were also significantly more likely to have atrial fibrillation (10% vs. 1%, \( p < 0.01^* \)) and higher pulse pressures (mean pulse pressure = 64mmHg vs. 58mmHg, \( p < 0.01^* \)).

* Mann-Whitney U test

\( X \) Chi-square test

![Figure 16.4: Presence of clinical signs of PAD according to age group.](image1)

Blue: clinical signs of PAD evident, red: no clinical signs of PAD evident

There was an inverse association between the total number of clinical signs of PAD and ABI for both left and right legs (Figure 16.5).

![Figure 16.5: ABI according to number of clinical signs of PAD](image2)

* Blue: left leg (Spearman’s rho: \( r_s = -0.36, p < 0.001 \)), red: right leg (Spearman’s rho: \( r_s = -0.296, p < 0.001 \)).
The sensitivity of clinical examination to detect Doppler ABI defined PAD was 82% and specificity was also 82% (Table 16.2). Positive predictive value was low at only 13%.

<table>
<thead>
<tr>
<th>Gold Standard: Doppler ABI</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical Examination</strong></td>
</tr>
<tr>
<td>Non-PAD</td>
</tr>
<tr>
<td>PAD</td>
</tr>
</tbody>
</table>

specificity= \( \frac{TN}{(TN+FP)}=82\% \)
Sensitivity= \( \frac{TP}{(TP+FN)}=82\% \)
Accuracy= \( \frac{TN+TP}{(TN+FN+FP+TP)}=82\% \)

Table 16.2: Accuracy calculation of clinical examination compared to Doppler ABI as the gold standard reference

### 16.2.3 Clinical examination discussion

The literature review revealed little formalised evaluation of clinical examination for the diagnosis of PAD. Collins et al. (2006) screened 400 patients aged 50+ in primary care clinics for PAD which was diagnosed as ABI<0.9. They found that the sensitivity of pedal pulse palpation for the detection of PAD was 32% and specificity was 99%. It should be noted that the results analysis in Section 16.2.1 assessed the utility of ≥1 clinical sign of PAD rather than the individual predictive value of each of the included clinical signs. This was prevented by the small number of ABI defined PAD cases.

Not surprisingly, many of the factors found to be associated with ABI defined PAD were also found to be associated with clinical signs of PAD (age, smoking status, pulse pressure, QRISK2 score). Although analysis of the PIPETTE PAD status groups (Section 8.0) found no association between ABI ≤ 0.9 and the presence of atrial fibrillation (AF), an association between the presence of clinical signs of PAD and AF was established (p < 0.01). Existing studies have reported evidence of a strong relationship between this cardiac arrhythmia and PAD. For example, Violi et al. (2013) measured the ABIs of 2027 individuals who were enrolled in the Atrial Fibrillation Registry for the ARAPACIS (Ankle-brachial Index Prevalence Assessment: Collaborative Italian Study) study. They found that 21% of the study population who had non-valvular atrial fibrillation (NVAF) had an ABI ≤ 0.9 hence providing clear evidence of the link between systemic atherosclerosis and AF. It is possible that the PIPETTE study was insufficiently powered to demonstrate such an association.
16.4 Conclusions

It is concluded that both the ECQ and clinical examination, as stand-alone diagnostic techniques, lack sufficient sensitivity for accurate non-invasive diagnosis of PAD. The ECQ, as a symptom based questionnaire, of course has limited use when screening for asymptomatic disease. However, of the PAD cases detected within the PIPETTE study, one third were experiencing symptoms of PAD that necessitated subsequent endovascular procedures (Section 15.2.2). The ECQ correctly identified PAD in these cases. In keeping with current literature, this study has highlighted that women are more likely to present as asymptomatic PAD than men; this is a fact which health professionals should be aware of when assessing for PAD. Low positive predictive values for both of the diagnostic techniques considered within this chapter underline the need to confirm positive results with a superior diagnostic test.
Part 4: Summary of Conclusions

How should PAD screening be undertaken?

Table P4.1 (below) summarises how each of the non-invasive PAD diagnostic methods considered within this chapter compares to the Doppler ultrasound ABI as the gold standard reference technique.

<table>
<thead>
<tr>
<th>Test Modality</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Automated ABI device</td>
<td>76%</td>
<td>95%</td>
<td>54%</td>
<td>98%</td>
<td>94%</td>
</tr>
<tr>
<td>PVW analysis</td>
<td>92%</td>
<td>98%</td>
<td>73%</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>ECQ</td>
<td>42%</td>
<td>98%</td>
<td>45%</td>
<td>97%</td>
<td>96%</td>
</tr>
<tr>
<td>Examination for clinical signs of PAD</td>
<td>75%</td>
<td>82%</td>
<td>13%</td>
<td>99%</td>
<td>82%</td>
</tr>
</tbody>
</table>

Part 4 summary, table 1: Summary of diagnostic modalities compared to Doppler ABI as gold standard.

Clearly, the ECQ and examination for clinical signs of PAD lack adequate sensitivity and positive predictive value to be used as stand-alone diagnostic PAD techniques. However, as Vowden and Vowden (2004) point out, diagnosis of PAD in the primary care setting should not be based upon an isolated diagnostic test, but should incorporate a holistic patient assessment. It is likely that both the ECQ and clinical assessment of the patient will continue to form an important part of such assessments. In fact, part 3 of this thesis concluded that the presence of at least one clinical sign of PAD is one of the factors that could be used to determine who should go undergo additional screening procedures such as ABI measurement.

The pneumo-plethysmographic device used within the DUAL study had good agreement with the Doppler ultrasound in terms of attained ABIs. However, the short-comings of using the Doppler ultrasound as a reference standard have been highlighted (Section 2.9.3) and should be borne in mind when considering the implications of these results. The main limitation associated with the automated device concerned its susceptibility to measurement error caused by patient movement. Overall, participants rated the measurement procedure as less comfortable then the Doppler procedure, although despite this, no one rated the overall procedure as unacceptable for either device. Merits of the automated device include a reduced failed measurement rate in comparison to other automated ABI devices, and a marked reduction in the time needed to perform the test as a result of no required patient rest period.
Of the non-invasive diagnostic modalities, pulse volume waveform analysis provided the highest levels of sensitivity and specificity for PAD diagnosis compared to the Doppler as gold standard. This diagnostic method has also shown potential to diagnose cases of PAD that were not identified via ABI assessment and hence provides an important focus for future research. Issues relating to the subjective interpretation of PVWs and possible subsequent implications with regard to future utility for PAD diagnosis within the primary care environment have also been identified. As such, it is recommended that future research should also consider automated PVW interpretation.
Part 5 : WHY?

Why should PAD screening be undertaken?
Part 5: Prelude

The primary issue of contention associated with PAD screening concerns its worth in terms of whether screen detected PAD patients benefit from their diagnosis. Whilst a randomised control trial of PAD screening versus no screening was beyond the practical and financial limitations of this PhD project, the longitudinal aspect of the PIPETTE study (Phase 2) aimed to contribute to the evidence base relating to this issue. This was achieved by following up PIPETTE participants who were found to have PAD, at 6 and 12 months post-diagnosis (at visits 3 and 4 respectively), to determine (i) if primary care management of PAD concurred with current PAD guidelines and (ii) if their management had been successful in achieving positive lifestyles changes and reduction of overall CV risk. Hence, chapter 17 presents the results from Phase 2 of the PIPETTE study.
Chapter 17: PIPETTE phase 2 results

17.1 GP follow-up of participants identified as having PAD

Participants that were diagnosed with PAD in Phase 1 of the PIPETTE study were subsequently informed of the implications of the diagnosis by the PhD researcher. It was also strongly suggested that they should make an appointment with their GP to further discuss their diagnosis as well as possible management options. Of the 12 identified PAD cases, two declined to see their GP post diagnosis as they did not consider it necessary. They did however, consent to their GP being informed of their results by letter.

17.2 Results

17.2.1 CV events, diagnoses and secondary care referrals

None of the 12 PAD participants experienced any specific CV events, such as angina, MI, TIA or CVA, during the 12 month follow up period. However, two participants were referred to secondary care for cardiovascular purposes. One referral was to a vascular surgeon after an abdominal aortic aneurysm (AAA) was diagnosed via the national AAA screening programme. The other referral was to a cardiologist; aortic valve stenosis was subsequently diagnosed. In addition, one PAD participant was diagnosed with small cell lung cancer during the 12 month follow up period.

PAD referrals

One third of PAD participants (n=4), all of whom reported intermittent claudication, were subsequently referred, by their GP, to a vascular surgeon for further investigation of their PAD. PAD diagnoses were confirmed in all four cases via Duplex ultrasound scanning and all participants subsequently underwent successful angioplasty.

17.2.2 General Practice management of PAD participants

CVD management clinics

Three quarters of PAD participants (n=9) were added to their general practice registers for both PAD and CVD and subsequently were invited to attend yearly CVD management clinics.
17.2.3 Lifestyle modification strategies

Smoking management strategies
Of the six PAD participants that were current smokers at baseline, five saw their GP or practice nurse in the follow-up period. Of these, 80% were given smoking cessation advice, 20% were prescribed smoking cessation medications or aids (such as nicotine patches), and 60% were referred to a smoking cessation clinic/specialist service. The number of current smokers reduced by 17% (n=1) (McNemar’s test: \( p = 0.834 \)) and one participant reduced the number of cigarettes smoked from 20 per day to 15 per day. The remainder of participants did not alter their smoking habits.

Dietary Advice
None of the PAD participants were referred to a dietician although 33% were reportedly given dietary advice by their GP or practice nurse according to the general practice medical notes. Dietary scores however did not change significantly over the follow up period (Visit 1 median healthy eating score = 8.7, Visit 4 median healthy eating score = 9.2, Wilcoxon signed rank test: \( p = 0.396 \)).

Exercise Advice
According to the GPPAQ, there was no change in the activity levels of PAD participants over the course of phase 2 of the study (Wilcoxon signed rank test, \( p=0.785 \)), despite 40% reportedly having received exercise advice from their primary care physician.

Alcohol Advice
Similarly, there was no change in the reported number of alcohol units consumed per week (Visit 1 median = 8 units vs. Visit 4 median = 11, Wilcoxon signed rank test: \( p = 0.655 \)).

17.2.4 Pharmacological management of PAD

The proportion of PAD participants that were prescribed antiplatelets increased significantly from 16% at baseline (visit 1) to 42% at visit 3 (\( p=0.037 \)) and 75% at visit 4 (\( p=0.006 \)) (Table 17.1). Similarly, the proportion of participants prescribed lipid lowering medications increased significantly from visit 1 (50%) to visit 4 (83%) (\( p=0.048 \)); it is likely that this was the cause of a significant drop in the proportion of participants with elevated total cholesterol levels from 67% at visit 1 to 17% at visit 4 (\( p=0.048 \)).
The proportion of PAD participants prescribed anti-hypertensives did not change significantly throughout phase 2 of PIPETTE, nor did the proportion of patients with hypertension (Table 17.1).

<table>
<thead>
<tr>
<th>% Prescribed antiplatelets</th>
<th>Visit 1</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>P (McNemar’s Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16% (n=2)</td>
<td>42% (n=5)</td>
<td>75% (n=9)</td>
<td></td>
<td>V1 – V3 = 0.037*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>V1 – V4 = 0.006*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% Hypertensive Systolic BP≥140mmHg and/or Diastolic BP≥90mmHg</th>
<th>Visit 1</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>P (McNemar’s Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>75% (n=9)</td>
<td>67% (n=8)</td>
<td>67% (n=8)</td>
<td></td>
<td>V1 – V3 = 0.368</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>V1 – V4 = 0.368</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% Prescribed anti-hypertensives</th>
<th>Visit 1</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>P (McNemar’s Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>67% (n=8)</td>
<td>67% (n=8)</td>
<td>75% (n=9)</td>
<td></td>
<td>V1 – V3 = 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>V1 – V4 = 0.539</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% Hypertensive Systolic BP≥140mmHg and/or Diastolic BP≥90mmHg</th>
<th>Visit 1</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>P (McNemar’s Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>67% (n=9)</td>
<td>17% (n=2)</td>
<td>17% (2)</td>
<td></td>
<td>V1 – V3 = 0.048*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>V1 – V4 = 0.048*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% Prescribed lipid lowering medications</th>
<th>Visit 1</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>P (McNemar’s Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>67% (n=8)</td>
<td>67% (n=8)</td>
<td>75% (n=9)</td>
<td></td>
<td>V1 – V3 = 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>V1 – V4 = 0.539</td>
</tr>
</tbody>
</table>

Table 17.1: General practice pharmacological management of PIPETTE PAD participants
V1 = visit 1 at baseline, V3 = visit 3 conducted at 6 months post PAD diagnosis, V4 = visit 4 conducted at 12 months post PAD diagnosis

17.2.5 Effectiveness of general practice management strategies
Effectiveness of general practice management strategies was evaluated via the assessment of (i) changes to the population anthropometrics (Table 17.2) and haemodynamic measurements (Table 17.3), and (ii) changes to the CV risk of PAD participants according to their QRISK2 scores and relative risks (Figure 17.1).

<table>
<thead>
<tr>
<th>Median Weight (Kg)</th>
<th>Visit 1</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>P (Wilcoxon signed rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>71.3</td>
<td>73.1</td>
<td>73.1</td>
<td></td>
<td>V1 – V3 = 0.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>V1 – V4 = 0.72</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median Waist/Hip ratio</th>
<th>Visit 1</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>P (Wilcoxon signed rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.94</td>
<td>0.93</td>
<td>0.93</td>
<td></td>
<td>V1 – V3 = 0.79</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>V1 – V4 = 0.31</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median BMI</th>
<th>Visit 1</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>P (Wilcoxon signed rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.6</td>
<td>26.6</td>
<td>26.7</td>
<td></td>
<td>V1 – V3 = 0.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>V1 – V4 = 0.33</td>
</tr>
</tbody>
</table>

Table 17.2: PIPETTE PAD population anthropometrics at visits 1, 3, and 4

<table>
<thead>
<tr>
<th>Median Heart Rate (beats per minute)</th>
<th>Visit 1</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>P (Wilcoxon signed rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>78</td>
<td>74</td>
<td>73</td>
<td></td>
<td>V1 – V3 = 0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>V1 – V4 = 0.008</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median Systolic Blood pressure (mmHg)</th>
<th>Visit 1</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>P (Wilcoxon signed rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>143</td>
<td>150</td>
<td>145</td>
<td></td>
<td>V1 – V3 = 0.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>V1 – V4 = 0.44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median Diastolic Blood Pressure (mmHg)</th>
<th>Visit 1</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>P (Wilcoxon signed rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>78</td>
<td>76</td>
<td>72</td>
<td></td>
<td>V1 – V3 = 0.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>V1 – V4 = 0.72</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median Pulse pressure (mmHg)</th>
<th>Visit 1</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>P (Wilcoxon signed rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>67</td>
<td>67</td>
<td></td>
<td>V1 – V3 = 0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>V1 – V4 = 0.46</td>
</tr>
</tbody>
</table>

Table 17.3: PIPETTE PAD population haemodynamic measurements at visits 1, 3 and 4
The anthropometrics of the PIPETTE PAD population did not change significantly over the follow-up period (Table 17.2).

With the exception of heart rate, which decreased significantly during the follow-up period of the study, the haemodynamic measurements of the PIPETTE PAD population did not significantly alter from visit 1 to visits 3 or 4 (Table 17.3).

![Figure 17.1: Reduction in PAD participants’ mean QRISK2 scores and relative risk from visit 1 to visits 3 and 4](image)

Red circles = Mean QRISK2 score
Blue circles = Mean relative risk

The QRISK2 scores decreased for 75% of PAD participants (n=9) over the 12 month follow-up period post PAD diagnosis (Visit 1 median QRISK2 score = 27.4, Visit 4 median QRISK2 score = 24.8, Wilcoxon signed-rank test: p=0.048).

Similarly, the relative risk (RR) also decreased for 75% of participants over the 12 month follow up period (Visit 1 mean RR = 1.6 vs. Visit 4 mean RR = 1.3; Wilcoxon signed rank test: p = 0.049).
17.2.6 Progression of PAD

Figure 17.2: PAD participants – changes to right ABI over follow-up period

There was no significant change in ABI of the right leg over the follow up period (Visit 1 median ABI = 0.92, Visit 4 median ABI = 0.9, Wilcoxon Signed Rank test: p = 0.88).

Figure 17.3: PAD participants – changes to left ABI over follow-up period

However, the left ABI increased for 67% of the PAD participants (Figure 17.3); this equated to a significant increase in median left ABI from visit 1 (0.86) to visit 4 (0.94) (p = 0.028).
17.2.7 Symptomatic PAD

At baseline, 42% (n=5) of PAD participants were symptomatic of PAD as indicated by positive ECQ results. This had reduced to 17% (n=1) at visit 4 (McNemar’s test, \( p = 0.043 \)).

17.2.8 Quality of Life Scores

Neither physical health scores nor mental health scores according to SF-12 altered significantly during the 12 month follow-up period (Figure 17.4).

![Figure 17.4: Quality of life scores according to SF-12 throughout Phase 2 of PIPETTE study. Red circles = SF12 physical health score, blue circles = SF12 mental health score, * Wilcoxon signed rank test.](image)

17.3 Discussion

Within the relatively short follow-up period of one year, there were no CV events within the PIPETTE PAD population. Seventeen per cent (n=2) of PAD participants did however, have additional CV diagnoses which included aortic valve sclerosis and abdominal aortic aneurysm, during phase 2 of the study. This, in itself, can be taken as indication of the high CV risk that has been shown to be associated with PAD and ABI ≤ 0.9. In addition, the fact that one participant was also diagnosed with lung cancer during the follow-up period underlines the deleterious effects of smoking as a common causative factor for both diseases.
General practice management of PAD and its effectiveness

General practice management of PAD appeared to focus more on pharmacological management than lifestyle modification. At visit 4, 75% of PAD participants were being treated in accordance with current PAD guidance (outlined in Table 2.4) in that they had been prescribed antiplatelets, antihypertensives (if necessary) and cholesterol lowering medications (if necessary). It should be noted that two participants did not have any contact with their GP during the follow-up period and hence this figure could be under-represented.

Whilst the proportion of participants being prescribed antiplatelets increased significantly over the course of the study (Table 17.1), the proportion receiving antihypertensives did not change significantly and there was no change to median systolic and diastolic blood pressures (Table 17.2) with 67% of participants remaining hypertensive at visit 4 of the study. Conversely, the proportion of participants being prescribed lipid lowering medications increased significantly from 50% to 83% (p=0.048) which undoubtedly contributed to a significant decrease in the percentage of participants with a total cholesterol level > 4.0mmol/L from 67% at baseline to 17% at visit 4 (p=0.048).

Smoking cessation advice was the most frequently used lifestyle modification strategy which was reportedly provided to 80% of current smokers. It was however, of limited effectiveness as only one participant gave up smoking (p=0.834) with a further participant reportedly reducing the number of cigarettes smoked. Dietary advice and physical activity advice was provided to 33% and 40% of participants respectively but there was no significant change to dietary habits (p = 0.4) or physical activity levels (p = 0.79) as indicated by the dietary questionnaire or GPPAQ respectively, nor was there any change to participant anthropometrics (Table 17.2).

Median QRISK2 scores and relative risk according to the QRISK algorithm both decreased significantly during the course of the study (Figure 17.1) indicating successful reduction of CV risk. As discussed above, results have shown that the majority of the factors included in the QRISK algorithm (Appendix 9) did not change significantly in the follow up period (systolic blood pressure, BMI, smoking status, percentage taking anti-hypertensives). Additionally, no participants moved house; a change in post-code could have also affected QRISK2 scores. It therefore follows that this reduction in assessed CV risk must be attributed to the reduction of total cholesterol (Table 17.1) within the TC/HDL ratio.
How does this fit with existing research?

Historically PAD has been shown to be under treated on a global level; within the international REACH registry of almost 50,000 patients, PAD participants were significantly less likely to receive antihypertensive (92.4% vs. 95.8%; p<0.001) and lipid lowering (70.0% vs 75.2%; p<0.001) therapies than the total population (Bhatt et al., 2006). D’Souza et al. (2008) reviewed the risk factor treatment of 124 patients that were newly referred to the vascular units of two UK hospitals with suspected PAD; they found that only 64% of patients with PAD alone (no co-existing CAD) that had hyperlipidaemia had been prescribed statins, only 36% had been prescribed antiplatelet drugs and only 25% of smokers had received anti-smoking advice. It is possible however that the GPs of patients within this study had delayed treatment of CV risk factors for these patients until the vascular units had confirmed a diagnosis of PAD.

It could be expected that the publication of PAD guidelines in recent years, from various global organisations, as detailed in Table 2.3, would have served to raise the profile of PAD and its recommended treatment. However, whilst some research presents an improving scenario with regard to PAD risk factor modification (Jahn et al., 2011), other studies have demonstrated that the disparity between PAD treatment and CAD treatment stills exists (Stansby et al., 2011; Pereg et al., 2012). Jahn et al. (2011) undertook a prospective observational study of 5099 PAD patients in primary care in Germany. At an 18 month follow up, they found that 42% of patient had undergone exercise training, 91% smoking cessation strategies, 93% therapy for hypertension, 83% treatment for hypercholesterolaemia, and 87% antiplatelet therapy. They concluded that to a large extent, patients were managed in line with guidelines. Stansby et al. (2011) conducted a prospective study in which 473 patients with intermittent claudication, from 23 UK sites, were followed for a period of two years. At baseline, 26% of participants had hypertension (BP≥140/85mmHg); at two years, this figure had actually increased to 33% (p=0.01). However, the percentage of current smokers fell from 39% at baseline to 27% at two years (p<0.001).

A study by Pereg et al. (2012) compared LDL cholesterol control in 9138 patients six months after first coronary or peripheral vascular intervention. They found that patients who had undergone coronary intervention were treated more frequently with statins (89% v 61%, p<0.001) and more frequently achieved the LDL cholesterol goals (65% v 47%, p<0.001). However, patients who had undergone peripheral vascular intervention were also found to be less adherent to statin treatment than those who had undergone coronary intervention as assessed by the percentage of statin prescriptions that had been collected from pharmacies (34% versus 66% respectively, p<0.001). This then suggests a lack of patient awareness of the CV risk associated with PAD and the importance of CV risk reducing medications; this is further discussed in Section 17.3.3
Phase 2 of the PIPETTE study has shown that the pharmacological management of PAD patients is largely in line with current recommendations. It is likely that this is primarily due to the 2012 addition of PAD indicators to the UK Quality and Outcomes Framework (QOF). General Practices are now awarded QOF points for having a register of patients with PAD and for meeting PAD related targets (Table 17.4). QOF is a fundamental part of the General Medical Services (GMS) contract in the UK and is a system to remunerate general practices for providing good quality care to their patients.

- Being able to produce a register of people with peripheral arterial disease.
- The percentage of patients with peripheral arterial disease with a record in the preceding 15 months that aspirin or an alternative anti-platelet is being taken (unless a contraindication or side-effects are recorded) (threshold 40-90%).
- The percentage of patients with peripheral arterial disease in whom the last blood pressure reading (measured in the preceding 15 months) is 150/90 or less (threshold 40-90%).
- The percentage of patients with peripheral arterial disease in whom the last total cholesterol (measured in the preceding 15 months) is 5.0mmol/l or less (threshold 40-90%).

Table 17.4: PAD indicators according to the UK Quality and Outcomes Framework (NICE, 2012b)

Clinical information technology systems used within UK general practices, such as EMIS (Egton Medical Information Systems), are set up so that pop-up reminders relating to the QOF PAD indicators are automatically generated when a coding of PAD is added to a patient’s record. It should be noted that the QOF targets do not exactly match current PAD guideline recommendations (Table 2.3). For example, guidelines recommend a target blood pressure of ≤140/90 mmHg whereas QOF points are awarded for patients that have blood pressures of ≤150/90mmHg. This could, at least partly, explain why the percentage of PAD participants that were still classed as hypertensive (BP>139/89mmHg) at visit 4 was as high as 67%. If the higher QOF threshold had been used to define hypertension then this figure would have been reduced to 33% at visit 4.

17.3.3 Symptomatic PAD

A worrying finding of the PIPETTE study concerns the fact that one third of participants (n=4) who were diagnosed with PAD were experiencing severe symptoms of intermittent claudication and had PAD to an extent that required subsequent endovascular intervention. None of these participants
had previously reported their symptoms to a doctor as they regarded them as a “normal part of aging” or a sign of their lack of physical fitness. Existing studies have reported similar findings; according to Norgren et al. (2007) population studies have consistently shown that between 10% and 50% of patients with intermittent claudication have never consulted a doctor.

A literature review reveals three public health surveys which have assessed public awareness of PAD; two from the USA (Hirsch et al., 2007; Bush et al., 2008) and one from Canada (Lovell et al., 2009). Both Hirsch and colleagues (2007) and Lovell and colleagues (2008) demonstrated that approximately two thirds of people surveyed had never heard of PAD. In Hirsch's study, of those that were aware of it, half or fewer were unaware that smoking (44%) and diabetes (50%) could lead to PAD. Hence results from the PIPETTE study appear to suggest that this apparent profound lack of awareness of PAD has not improved in recent years. According to Hirsch et al. (2007) public awareness is a key step in any public CV health protective intervention. Without such awareness, the population at risk is not empowered to know how to obtain a timely diagnosis, early symptoms are not reported to clinicians, and informed treatment choices and adherence to risk reduction therapies cannot be easily achieved.

Significantly fewer participants were symptomatic of PAD at visit 4 than at baseline (17% vs. 42% respectively, \( p = 0.043 \)) and this can be directly attributed to 80% of symptomatic participants undergoing successful angioplasty. This was reflected in the observed significant increase of the left leg ABI from baseline to visit 4 (from 0.86 to 0.94, \( p = 0.028 \)). As participants were no longer symptomatic, it could have been expected that this might have translated into improved quality of life scores; however, neither physical nor mental health scores according to the SF-12 changed significantly over the course of the study (Figure 17.4). It is possible that symptoms of newly diagnosed co-morbidities, as discussed in Section 17.1, could have negated any angioplasty related improvements.

### 17.4 Study limitations

At the outset of this research project, it was anticipated that Phase 1 of the PIPETTE study would have identified considerably more PAD cases than the actual final PAD sample size of 12. Hence, the resultant small sample size that went on to Phase 2 of the PIPETTE study is a recognised study limitation and as such, results should be viewed with caution. A further limitation concerns the fact that lifestyle change (exercise, diet, smoking habits etc.) was largely assessed via reported behaviour changes only and not via objective measures. Also of note, was the fact that some participants required the assistance of the study investigator to complete the questionnaires which were utilised
to assess lifestyle. This meant that the investigator read out the questions and then ticked the answer boxes on behalf of the participant. It is possible that this may have introduced a source of bias as a result of participants possibly giving the answer which they perceived the investigator wanted to hear. A further methodological limitation arises from the fact that the dietary questionnaire was modified to incorporate British food terms; it is possible that this may have reduced the validity of the questionnaire and this should be borne in mind when considering results relating to the dietary habits of participants. Furthermore, it is possible that the presence of the PhD researcher within the general practice where the study was undertaken could have raised the profile of PAD amongst GPs and nurses who subsequently made treatment decisions for the PAD participants.

17.5 Conclusions
Pharmacological management of PAD within the PIPETTE study was largely in line with current PAD guidelines suggesting an improvement in this aspect of patient care in recent years. It is probable that the financial incentives associated with the UK QOF system have been instrumental in bringing about this change. Lifestyle modification strategies aimed at reducing CV risk however, were shown to be not only infrequently used, but also of limited effectiveness in achieving behaviour change. Despite this, primary care management of PAD within the PIPETTE study was effective in lowering the CV risk of the PAD participants as evidenced by reductions in QRISK2 scores. It appears that this can be largely attributed to reductions in cholesterol levels as a result of lipid lowering medications.

Results also suggest an apparent lack of public awareness of PAD and its associated CV risk, as indicated by the fact that a large proportion of PAD participants were actually symptomatic of the disease and yet had not presented to a clinician. The reluctance of a number of PAD participants to see their GP to discuss their diagnosis and management options post PAD diagnosis, despite being informed of its associated high CV risk by the PhD researcher, may also represent a lack of understanding of the disease. As such, there appears to be a need for PAD educational/health promotional strategies to be targeted at the general public.

17.6 Future Research
Future research should address the limitations outlined in Section 17.4. A larger scale study incorporating multiple general practices should focus specifically on further examination of the provision of lifestyle modification strategies, not only for PAD patients but also for patients with any
form of CV disease, as it was this aspect of treatment that was shown to be particularly inadequate within the PIPETTE study. Use of objective measures of lifestyle change, such as exhaled breath carbon monoxide levels, should be considered where feasible. Further assessment of pharmacological strategies to reduce CV risk should focus not only on whether specific medications have been prescribed but also whether patients are being treated to target levels, as this was shown to be an issue with regard to antihypertensives within the PIPETTE study. Finally, there is a need to further investigate the public’s apparent lack of awareness of PAD and its associated CV risk.

17.7 Participant perspectives of PAD screening

Although the PIPETTE study assessed participant perspective of the process of ABI measurement (section 13.1), it did not formally assess participant opinion of the overall concept of PAD screening. However, comments made to the study’s chief and principal investigators by participants were noted to be overwhelmingly positive and in favour of the instigation of PAD screening by the NHS. Several participants wrote letters of appreciation of the opportunity to participate in such a study; a selection of quotes from such letters is included in Appendix 14. Of course, these opinions are not necessarily representative of all who participated in the study, nor of those who declined to take part. This does, however, represent a further important and interesting aspect of PAD screening which could be formally assessed in future research.
Part 6: Conclusions & Future Research
Chapter 18

18.0 This project in context

This project has equated to a complex undertaking which needed to meet the objectives of several key stakeholders. First and foremost, it has been an educational project, aimed at generating new knowledge via the design and implementation of robust research, with the intention of meeting the requirements necessary for the award of PhD. Secondly, as a project with a commercial sponsor, it also needed to fit with the research agenda of its partner company (Huntleigh Healthcare). Thirdly, as a project funded by a Knowledge Economy Skills Scholarship (KESS), it also had to incorporate elements related to the integration of a high-level skills training programme, leading to a postgraduate skills development award.

18.1 Contribution to knowledge

The resultant project, which has consisted of a comprehensive, multi-faceted investigation into screening for PAD within the primary care setting, has been detailed within this thesis. It has generated new knowledge on two levels: firstly, the individual study components have produced original data and have contributed to the current PAD evidence base as outlined in Table 18.1. Secondly, the broad scope of the project, with four studies being undertaken concurrently, has provided a unique insight into how different aspects of PAD screening are inter-related (Figure 18.1). At the outset of this thesis, the areas of ambiguity associated with PAD screening were outlined in Figure 2.1; Figure 18.1 consists of an updated version of this diagram replete with the key findings from this project.
<table>
<thead>
<tr>
<th>Contribution to Knowledge</th>
<th>Possible Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiological Data</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Original – literature review reveals no data specific to Wales. Previous UK data are limited and may have been subject to change. | • Inform Welsh Government and may be used to inform local policy (L)  
• Allow the construction of a predictive model of PAD (G) and may contribute to the design of a potential PAD screening strategy (N) |
| **GP Survey**             |                  |
| Original (literature review did not reveal any published surveys/assessments of UK Primary Care ABI measurement) | • Inform the design of potential PAD/ABI training programmes (L, N, G) |
| **Practicality of ABI measurement (time needed to screen)** | Available evidence inconclusive. | • Inform design of potential PAD screening strategy (L, N, G) |
| **Acceptability of PAD screening to patients.** | Original (literature review did not reveal any published data regarding patient perception of PAD screening and ABI measurement). | • Inform design of potential PAD screening strategy (L, N, G) |
| **Primary Care management of CV risk factors in PAD patients** | Under-treatment of PAD has been documented in small UK studies previously. This may have been subject to change. Existing studies have examined risk factors in isolation – PIPETTE also examines the cumulative effect of risk factor modification in terms of CV risk scores. | • Inform regarding effectiveness of guidelines in improving PAD management (L, N)  
• Inform the design of potential PAD/ABI training programmes (L, N, G) |
| **ABI as potential additional parameter for CV risk stratification tools** | Original (has previously been studied in relation to FRS but not in relation to more recent CV risk assessment tools such as QRISK2). | • Add to body of research regarding this topic and may contribute to design of new CV risk stratification tools (L, N, G) |
| **Use of an automated ABI device which utilises pneumoplethysmography for ABI measurement within the context of a PAD screening study.** | Original - no published studies of automated ABI devices which work on the principle of pneumoplethysmography | • Generate evidence base regarding the use of pneumoplethysmography as possible alternative for identification and assessment of PAD (G) |
| **Use a pulse volume waveform analysis for identification of PAD** | Original – limited data available regarding analysis of PVWs for PAD diagnosis. PVWs not previously examined within the context of a PAD screening study | • Generate evidence base regarding PVWs as an adjunct for PAD diagnosis (G) |

**Key**  
L: Local  
N: National  
G: Global

Table 18.1: Project contribution to knowledge with possible outcomes
Figure 18.1: Diagrammatic representation of project conclusions
18.2 Key Conclusions

The key conclusions of this project and their collaborative implications for the future of PAD screening are considered below:

18.2.1 Targeting of PAD screening

The over-arching aim of this project was to further define and subsequently address some of the ambiguities associated with the concept of screening for PAD. A primary objective was to identify an appropriate target population for possible future PAD screening strategies. Results from the PIPETTE study have shown that screening individuals with at least two risk factors for cardiovascular disease but no known cardiovascular disease or diabetes results in a PAD prevalence of 4.3%. Refining this study population to those aged 50 and over, with a smoking history, and at least one clinical sign of PAD, would result in a high PAD yield, with one in four cases being positive for PAD, and a 92% detection rate. This therefore appears to represent an efficient screening strategy that would enable identification of individuals with previously undiagnosed high cardiovascular risk.

These results and conclusions must, of course, be considered in the context of the strengths and limitations of the PIPETTE study. Several methodological deficiencies relating to study design have been acknowledged (section 8.3). For example, the fact that the study was a single centre study consisting of a population with no ethnic diversity, reduces the generalisability of results. Strengths of the study, on the other hand, came from the fact that PAD diagnoses were validated by means of a separate small scale study (the IVAM study) and also from the incorporation of home visits into the study design to allow optimisation of participant recruitment. It is therefore contended that, despite its limitations, this study serves to add to the evidence base regarding the epidemiology of PAD both in the UK and globally. It is the first UK study of PAD prevalence that has been undertaken for seven years and the only UK study which has investigated PAD prevalence outside of Scotland.

18.2.2 The ABI as the PAD screening tool of choice

18.2.2.1 Doppler ABI measurement

The ABI, as measured with the Doppler ultrasound as the screening tool of choice, has been identified as a further issue associated with PAD screening. This project has shown that currently, within general practice, the ABI is infrequently and often incorrectly used. There appears to be considerable variation in the methodology used for its measurement, which could lead to inappropriate clinical decisions as a result of PAD diagnoses being based on different measurement
parameters. This, in turn, could have significant public health and economic repercussions. Furthermore, knowledge of PAD and its associated CV risk has been shown to be less than optimal, particularly for nurses.

The low, but not atypical, response rate (20%) to the general practice survey, upon which these results and conclusions are based, and the resultant possibility of response bias has been acknowledged as a limitation associated with this study. However, this study represents the only published assessment of the utility of the ABI undertaken within the UK; furthermore, representation from both nurses and physicians from general practices in all areas of Wales was achieved. Results were noted to be in keeping with previous research undertaken in the USA and the Netherlands hence suggesting that the identified issues are historically problematic and not confined to Wales and the UK.

It is therefore concluded that prior to the potential adoption of the Doppler ABI as a formalised screening tool for PAD and CVD, there is a need for a robust training programme with standardised methodology in order to optimise accuracy and consistency of results. Training programmes should include the methodological requirements for accurate and reproducible ABI measurement, as well as the theoretical basis and limitations of the test. The subsequent implications of a reduced ABI with regard to cardiovascular risk also need to be highlighted.

18.2.2.2 Automated ABI measurement

The use of automated ABI devices, which do not require operator skill, could provide an alternative solution to the identified skill deficit for ABI measurement within general practice. The large scale (n=727) DUAL study has shown that a device which utilises pneumoplethysmography to measure the ABI has a major advantage of significantly reduced test times compared to the Doppler, making it far more amenable for use within busy primary care settings. Whilst this device was shown to be superior to oscillometric ABI devices as a result of reduced failed measurement rates, it currently lacks sufficient positive predictive value (54%) for its use as a standalone PAD screening device. However, the limited proportion of PAD cases within the DUAL sample means that additional research, which specifically assesses the performance of the automated device in diseased subjects, is warranted.

18.2.3 PVW analysis for the diagnosis of PAD

A noted major advantage of the automated device used within the DUAL study relates to its incorporation of a secondary method of PAD assessment in the form of pulse volume waveforms.
Interpretation of PVWs for the diagnosis of PAD has, until recently, been confined to the realms of the vascular lab, and as yet its utility within the primary care environment has not been assessed. A major limitation of the ABI concerns its artefactual elevation in the presence of arterial calcification; a secondary method of PAD assessment is required in order to identify when this has occurred and it is possible that PVW analysis could fulfil this role. Within the PIPETTE study, this diagnostic modality identified an additional four probable cases of PAD, and this figure is likely to be greater within a general population where diabetics have not been excluded. However, it should be noted that this project did not incorporate any formalised procedure for validating the interpretation of PVWs, hence these results are tentative. This therefore represents an important area for future research which should aim to further explore the utility of PVW analysis within the primary care setting.

18.2.4 Benefits of PAD screening for patients

This project has also suggested that the issue of whether individuals stand to benefit from their PAD diagnosis is unclear. Whilst 75% of individuals diagnosed with PAD within the PIPETTE study were likely to have benefited from reduced CV risk as a result of being commenced on the best medical therapy for PAD, it could be argued that a large majority of these (92%) should have been commenced on these treatments as a result of their high QRISK2 scores in any case. Whilst treatment of PAD appears to have improved in recent years, probably as a direct result of QOF in the UK, there are still opportunities for further enhancement particularly in relation to lifestyle modification strategies.

An unexpected finding of this project was that such a large proportion (one third) of participants that were found to have PAD were symptomatic and even though the disease had been adversely affecting their lives for some time, they had not presented to a health care professional. This underlines the need for strategies to increase PAD awareness amongst the general public. Whilst such individuals spoke highly of PAD screening (Appendix 14) and the positive effects of angioplasty and being pain free, these improvements did not translate to improved quality of life scores. This finding could, however, have been affected by the high rate of comorbidities including rheumatoid arthritis and cancer, within the PAD group.

It should, however, be noted that these conclusions are based on results derived from phase 2 of the PIPETTE study, which was limited by its small (n=12) sample size. Furthermore, several possible sources of bias which could have affected results were identified; for example, the presence of the PhD researcher within the practice where the study was undertaken could have raised the profile of PAD amongst the clinicians that subsequently made treatment decisions for the PIPETTE PAD participants. As such, it is suggested that these results require verification in future research.
18.2.4 PAD screening: the broad perspective

Hence, in conclusion, it appears that the future of PAD screening is uncertain both in terms of its worth and how it should be undertaken. However, ongoing research and technological advances means that the evidence base within this field is continually evolving. In particular, an ongoing randomised control trial of PAD screening versus no screening is likely to provide more definitive information with regard to the benefit of PAD screening. It is clear that there is an urgent need to consider how best to raise public awareness of PAD in order to minimise unnecessary suffering from the symptoms of this disease.

18.3 Lessons learned

Many of the noted short-comings of this project can be attributed to the limitations of undertaking research with inherent time and budgetary restrictions. However, the value of research emanates not only from direct results attained, but also from the lessons learned in the process, and the resultant skills and knowledge that can be applied to future research. In retrospect, several aspects of this project, both major and minor, would be undertaken differently. For example, The PIPETTE study was successfully registered on the National Institute for Social Care and Health Research Clinical Research Centre (NISCHR) clinical research portfolio. This subsequently allows access to additional funding, made available via health board research and development departments, which could be used to expand the study into a multi-site investigation. In addition, throughout the course of the project, clinicians from several research active, general practices from varying parts of Wales and the UK expressed an interest in involvement in the PIPETTE research study. This suggests that it would have been feasible to set up the PIPETTE study as a multi-centre trial, to be run by individual principle investigators at each site, with the PhD researcher, as chief investigator overseeing the whole project. The resultant larger sample size that would be more representative of the UK population would have, of course, resulted in more robust study results and conclusions.

18.4 Future research

This project has served to highlight several areas for future research relating to PAD screening. These areas have been discussed in detail, with methodological considerations, in the final sections of corresponding chapters within this thesis. Main points are reiterated below:

Firstly, it has been identified that the ABI is reportedly under-used and often incorrectly performed
within general practices. There is therefore an urgent need to determine how this affects the accuracy of ABI measurement within the primary care setting as this has significant implications for both its current use and potential future use as a CV risk screening tool (Section 7.4). It is proposed that such studies should entail a direct comparison of at least six primary care professionals (two GPs, two practice nurses, two district nurses) with six secondary care professionals (vascular Consultant, vascular registrar, two vascular laboratory technicians and two vascular clinical nurse specialists). This study design would serve not only to inform how primary care staff compare to the secondary care experts but will also provide information regarding intra-group comparisons (e.g. how vascular consultants compare to vascular technicians).

The IVAM study has served to highlight several methodological issues which would also require consideration in such future research. For example, it has demonstrated that variability is greater in diseased participants hence underlining the need for future samples to contain both diseased (known PAD) and normal participants; this would also ensure a sample which is representative of patients encountered in primary care. The IVAM study has also demonstrated that factors such as time pressures and staff availability meant that incorporating even a very simplistic study into the everyday running of an outpatient clinic was problematic. This inevitably means that a larger, more complex study would need to be undertaken in research setting which may then make it more difficult to recruit participants and ensure the participation of health professionals as observers.

Although existing evidence suggests that automated ABI devices currently lack sufficient diagnostic accuracy to replace the Doppler ABI measurement, their ongoing improvement and development warrants their constant re-evaluation via high quality research studies (section 12.4). Such devices could potentially address many of the issues relating to practicality and the skills needed to undertake PAD screening; this therefore provides a further important focus of future research.

Such studies should be undertaken independently of the device manufacturers and operators of the equipment should be representative of those who would be likely to use it in the clinical environment. The study population of such studies should include both diseased and healthy participants which are likely to be representative of the entire spectrum of the ABI. It is also recommended that a superior diagnostic modality, such as Duplex ultrasound, should be considered for use as the reference standard in future studies, in preference to the Doppler ultrasound ABI. However, if the Doppler ABI is utilised as the reference standard, then observers should be blinded to results of the automated device. Furthermore, the specific Doppler methodology utilised should adhere to the AHA recommended procedure (Aboyans et al., 2012) for such measurements. This would ensure consistency across studies, allowing easier comparisons of results. Results of studies
should be clearly reported and should include explicit information regarding any measurement failures.

A review of current literature has demonstrated that the utility of PVW analysis for the identification of PAD has been given little consideration particularly in relation to its potential use in the primary care environment. This therefore represents a novel and exciting area for future research. Studies could assess if, following a short-training programme, primary care clinicians could utilise PVW analysis to identify patients who require further vascular assessment and management. Assessment of the correlation of PVW analysis with other markers of CV risk, such as carotid intima-media thickness, is also of particular interest. Limitations of PVW analysis also require further definition and studies should investigate the influence of factors such as temperature, height, gender and the presence of peripheral neuropathy on the PVW, for example.
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BIANCHI, J. 2005. LOI: an alternative to Doppler in leg ulcer patients... Lanarkshire Oximetry Index (LOI). *Wounds UK,* 1, 80.


COLLINS, T. C., SUAREZ-ALMAZOR, M. & PETERSON, N. J. 2006. An absent pulse is not sensitive for the early detection of peripheral arterial disease. Family Medicine, 38, 38-42.


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DUNN, O., J. 1964. Multiple comparisons using rank sums. Technometrics, 6, 241-252


combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA*, 300(2), 197-208.


LESKINEN, Y., SALENIUS, J. P., LEHTIMÄKI, T., HUHTALA, H. & SAHA, H. 2002. The prevalence of peripheral arterial disease and medial arterial calcification in patients with chronic renal failure:


Appendix 1: Edinburgh Claudication Questionnaire

Participant No:  
Date: ___/___/___

The Edinburgh Claudication Questionnaire

1. Do you get a pain or discomfort in your leg(s) when you walk?
   - Yes
   - No
   - I am unable to walk

*If you answered “yes” to question (1) – please answer the following questions.
Otherwise you need not continue.*

1. Does this pain ever begin when you are standing still or sitting?
   - Yes
   - No

2. Do you get it if you walk uphill or hurry?
   - Yes
   - No

5. Do you get it when you walk at an ordinary pace on the level?
   - Yes
   - No

6. What happens if you stand still?
   - Usually continues more than 10 minutes
   - Usually disappears in 10 minutes or less
7. Where do you get this pain or discomfort?

*Mark the places with an “X” on the diagram below:*
Results of Edinburgh Claudication Questionnaire

Definition of positive classification requires ALL of the following responses:-

- "Yes" to question 1.
- "No" to question 2.
- "Yes" to question 3.
- "Usually disappears in 10 minutes or less" to question 5.

A “No” response to question 4 indicates grade 1 Claudication

A “Yes” response to question 4 indicates grade 2 Claudication.

If these criteria are fulfilled, a definite claudicant is one who indicates pain in the calf, regardless of whether pain is also marked in other sites; a diagnosis of atypical claudication is made if pain is indicated in the thigh or buttock, in the absence of any calf pain. Subjects should not be considered to have claudication if pain is indicated in the hamstrings, feet, shins, joints or appears to radiate, in the absence of any pain the calf.

Reference: Leng et al. (1992)

<table>
<thead>
<tr>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative for Claudication</td>
</tr>
<tr>
<td>Positive for Claudication</td>
</tr>
<tr>
<td>Grade 1</td>
</tr>
<tr>
<td>Grade 2</td>
</tr>
<tr>
<td>Typical</td>
</tr>
<tr>
<td>Atypical</td>
</tr>
</tbody>
</table>
Appendix 2: Table of global PAD prevalence studies demonstrating variation in population groups studied, PAD detection methodology and attained prevalence rates

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Authors</th>
<th>Country</th>
<th>Year</th>
<th>Sample Size</th>
<th>Setting</th>
<th>Population</th>
<th>ABI methodology</th>
<th>PAD diagnosis</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fowkes et al. Edinburgh Artery Study</td>
<td>Scotland</td>
<td>1991</td>
<td>1592</td>
<td>Undertaken at clinic but also home visits for housebound</td>
<td>Age stratified sample age 55-74.</td>
<td>Limited data available regarding ABI measurement and calculation, brachial pressure measured in right arm only.</td>
<td>ABI&lt;0.7 or hyperemic drop of &gt;35% or ABI&lt;0.9 and hyperemic drop of &gt;20%.</td>
<td>Overall: 22.6% Symptomatic: 4.6% Asymptomatic: 8% (Response rate: 90%)</td>
</tr>
<tr>
<td>2</td>
<td>Hooi et al. (Limburg PAD study)</td>
<td>Netherlands</td>
<td>1997</td>
<td>3650</td>
<td>General practice</td>
<td>Stratified sample of registered population aged 40-78, from 18 general practices</td>
<td>Only 1 pulse assessed at ankle and divided by higher brachial pressure</td>
<td>ABI&lt;0.95</td>
<td>Overall: 12.5% Symptomatic: 3.8% Asymptomatic: 8.0% (Response rate: 78%)</td>
</tr>
<tr>
<td>3</td>
<td>Meijer et al. The Rotterdam Study</td>
<td>Netherlands</td>
<td>1999</td>
<td>7715</td>
<td>Research centre</td>
<td>Age65</td>
<td>Only pressure at posterior tibial was measured. Unclear if both brachial measurements were undertaken</td>
<td>ABI&lt;0.9</td>
<td>19.1% (Response rate: 78%)</td>
</tr>
<tr>
<td>4</td>
<td>Nawamani et al. Cardiovascular Health Study (CHS)</td>
<td>USA</td>
<td>1999</td>
<td>5888</td>
<td>Research Centre</td>
<td>Age65 medicare eligible persons</td>
<td>Measured right brachial only and only posterior tibial ankle pressures.</td>
<td>ABI&lt;0.9</td>
<td>13.5%</td>
</tr>
<tr>
<td>5</td>
<td>Hinch et al. PARNERS study</td>
<td>USA</td>
<td>2001</td>
<td>6979</td>
<td>Inclusion:</td>
<td>Age 50-69 with smoking history or diabetes or Age&gt;70</td>
<td>Standard*</td>
<td>ABI&lt;0.9</td>
<td>29%</td>
</tr>
<tr>
<td>6</td>
<td>Selvin &amp; Erlinger Results from NHANES survey 1999-2000</td>
<td>USA</td>
<td>2004</td>
<td>2174</td>
<td>Age&lt;40</td>
<td>Only right arm systolic pressure measured. Only posterior tibial pulse assessed at ankle. Systolic pressures were measured twice at each site for participants aged 40-59, but only once for participants aged 60-ABI+mean systolic pressure at ankle divided by mean systolic pressure at arm</td>
<td>ABI&lt;0.9</td>
<td>Overall: 4.3% Age&lt;70: 14.5%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Diehm et al. (getABI)</td>
<td>Germany</td>
<td>2004</td>
<td>6880</td>
<td>Primary Care</td>
<td>Age&lt;65</td>
<td>Used higher of ankle systolic and average of arm systolic unless there was a discrepancy of &gt;10mmHg, in which case the higher pressure was used</td>
<td>ABI&lt;0.9</td>
<td>19.8%</td>
</tr>
<tr>
<td>8</td>
<td>Fujiwara et al.</td>
<td>Japan</td>
<td>2004</td>
<td>1398</td>
<td>Age 40-92</td>
<td>Used automated PWV/ABI device</td>
<td>ABI&lt;0.9</td>
<td>Overall: 2.7% Male: 3.3% Female: 2.2%</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Hayez et al.</td>
<td>Switzerland</td>
<td>2005</td>
<td>1921</td>
<td>Primary Care</td>
<td>Consecutive patients were recruited</td>
<td>Standard*</td>
<td>ABI&lt;0.9</td>
<td>3.7% symptomatic &amp; additional 2.7% asymptomatic</td>
</tr>
<tr>
<td>10</td>
<td>Fowkes et al.</td>
<td>Africa</td>
<td>2006b</td>
<td>922</td>
<td>Stratified sample age&gt;35</td>
<td>Measured brachial systolic pressure in one arm only with</td>
<td>ABI&lt;0.9</td>
<td>Age 40-49: 3.9% Age 50-59: 11%</td>
<td></td>
</tr>
<tr>
<td>Study No.</td>
<td>Authors</td>
<td>Country</td>
<td>Year</td>
<td>Sample Size</td>
<td>Setting</td>
<td>Population</td>
<td>ABI methodology</td>
<td>PAD diagnosis</td>
<td>Prevalence</td>
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</tr>
<tr>
<td>11</td>
<td>Doubeni et al.</td>
<td>USA</td>
<td>2006</td>
<td>717</td>
<td>Primary Care</td>
<td>No known Cardiovascular disease</td>
<td>automated oscillometric device. Only assessed posterior tibial pulse at ankle.</td>
<td>ABI&lt;0.9</td>
<td>Age 60-69: 25.2% Age 70+: 39.7% Note: sample primarily women 80:20</td>
</tr>
<tr>
<td>12</td>
<td>Fowkes et al.  (AGATHA)</td>
<td>International multicentre (24 countries)</td>
<td>2006</td>
<td>8891</td>
<td>General practice &amp; secondary care (cardiologists, medical specialists, neurologists, vascular surgeons)</td>
<td>Consecutive recruitment by GP's and/or specialists depending on country preference. 2 groups: 1. Prior evidence of CVD 2. At risk of CVD (age 55 &amp; ≥2 risk factors)</td>
<td>Used average of brachial pressures unless there was a difference of &gt;10mmHg in which case the higher was used</td>
<td>ABI&lt;0.9</td>
<td>Group 1: 40.5% Group 2: 30.9%</td>
</tr>
<tr>
<td>13</td>
<td>Kroger et al. RECALL study</td>
<td>Germany</td>
<td>2006</td>
<td>4735</td>
<td>Research Centre</td>
<td>Age: 45-74</td>
<td>Standard*</td>
<td>ABI&lt;0.9</td>
<td>Men: 6.4% Women: 5.1%</td>
</tr>
<tr>
<td>14</td>
<td>Campbell et al.</td>
<td>Scotland</td>
<td>2007</td>
<td>364</td>
<td>General Practice</td>
<td>Age 60 &amp; Hypertensive</td>
<td>Standard*</td>
<td>ABI&lt;0.9</td>
<td>Overall: 8% (1% previously diagnosed)</td>
</tr>
<tr>
<td>15</td>
<td>Carbayo et al.</td>
<td>Spain</td>
<td>2007</td>
<td>784</td>
<td></td>
<td>Age 40</td>
<td>Standard*</td>
<td>ABI&lt;0.9</td>
<td>18% (asymptomatic PAD 7%)</td>
</tr>
<tr>
<td>16</td>
<td>Sigvart et al.</td>
<td>Sweden</td>
<td>2007</td>
<td>5080</td>
<td></td>
<td>Age standardised sample Age 60-90</td>
<td>Used lowest ankle pressure to calculate ABI and only measured right brachial systolic pressure</td>
<td>ABI&lt;0.9</td>
<td>10.9%</td>
</tr>
<tr>
<td>17</td>
<td>Price et al.</td>
<td>Scotland</td>
<td>2008</td>
<td>20980</td>
<td>Research clinics</td>
<td>Inclusion: • All patients listed on community health index</td>
<td>Divided lower ankle systolic pressure by higher of left and right brachial pressures</td>
<td>ABI&lt;0.9</td>
<td>10.9%</td>
</tr>
<tr>
<td>18</td>
<td>Maeda et al</td>
<td>Japan</td>
<td>2008</td>
<td>4249</td>
<td>Outpatients.</td>
<td>Diabetics (mean age 60.8)</td>
<td>Used automated PWV/ABI device</td>
<td>ABI&lt;0.9</td>
<td>7.6%</td>
</tr>
<tr>
<td>19</td>
<td>Kwonator et al.  (IPSILON study)</td>
<td>France</td>
<td>2009</td>
<td>1340</td>
<td>General practice</td>
<td>3 groups: 1. ≥2 sign suggestive of PAD 2. History of ≥1 atherothrombotic event 3. ≥2 cardiovascular risk factors (Groups mutually exclusive)</td>
<td>Divided lower ankle pressure by brachial pressure (not specified if bilateral brachial systolic pressures were undertaken)</td>
<td>ABI&lt;0.9</td>
<td>Overall: 27.8% Per Groups: 1. 38% 2. 25% 3. 10.4%</td>
</tr>
<tr>
<td>20</td>
<td>Ramos et al.</td>
<td>Spain</td>
<td>2009</td>
<td>6262</td>
<td>Primary Care</td>
<td>Random population sample Age 35-79</td>
<td>Used average of brachial systolic pressures unless there was a discrepancy of ≥10mmHg</td>
<td>ABI&lt;0.9</td>
<td>4.5% (only 0.62% had IC)</td>
</tr>
<tr>
<td>Study No.</td>
<td>Authors</td>
<td>Country</td>
<td>Year</td>
<td>Sample Size</td>
<td>Setting</td>
<td>Population</td>
<td>ABI methodology</td>
<td>PAD diagnosis</td>
<td>Prevalence</td>
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<tr>
<td>21</td>
<td>Alzamora et al.</td>
<td>Spain</td>
<td>2010</td>
<td>3786</td>
<td>Primary Care</td>
<td>Age &gt;49</td>
<td>Standard*</td>
<td>ABI&lt;0.9</td>
<td>7.6%</td>
</tr>
<tr>
<td>22</td>
<td>Signorelli et al.</td>
<td>Italy</td>
<td>2011</td>
<td>3412</td>
<td>Primary Care</td>
<td>All individuals registered with 10 general practitioners</td>
<td>Posterior or anterior tibial artery assessed at the ankle. Does not specify if both brachial systolic pressures were assessed. Three consecutive measurements were performed at each site. ABI= mean of the higher values at the ankle divided by the brachial pressure.</td>
<td>ABI&lt;0.9</td>
<td>2.3%</td>
</tr>
<tr>
<td>23</td>
<td>Aboyans et al.</td>
<td>USA</td>
<td>2011</td>
<td>1932</td>
<td>Research centre</td>
<td>Free from clinical CVD Age 45-84</td>
<td>Standard*</td>
<td>ABI&lt;0.9</td>
<td>3.4% (response rate: 37.49%)</td>
</tr>
<tr>
<td>24</td>
<td>Taylor-Piliae et al.</td>
<td>USA</td>
<td>2011</td>
<td>1017</td>
<td>All individuals registered with a &quot;major chronic disease&quot; or living &gt;50 miles from research clinic.</td>
<td>Standard*</td>
<td>ABI&lt;0.9</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Makowsky et al.</td>
<td>Canada</td>
<td>2011</td>
<td>361</td>
<td>Community Pharmacies &amp; Physician offices (note: 1 cardiology clinic)</td>
<td>Age &gt;50</td>
<td>Standard*</td>
<td>ABI&lt;0.9</td>
<td>4%</td>
</tr>
<tr>
<td>26</td>
<td>Cimmiintelli et al.</td>
<td>Pan-European</td>
<td>2011</td>
<td>9816</td>
<td>Primary &amp; Secondary care</td>
<td>Inclusion: Men age ≥45, women ≥55 plus at least one of the following CV risk factors: Smoking status, Hypertension (&gt;140/90) or taking anti-hypertensive meds, Dyslipidaemia (LDL≥2.3 mmol/L or HDL&lt;1.0 mmol/L), family history of premature coronary heart disease, elevated waist circumference (&gt;102 cm for male, &gt;88 cm for female).</td>
<td>Standard*</td>
<td>ABI&lt;0.9</td>
<td>Overall: 17.8% (previously undetected PAD) Italy: 22.9% Greece: 28% France: 12.2% Switzerland: 12.2% Netherlands: 8.1 Belgium: 7%</td>
</tr>
<tr>
<td>Study No.</td>
<td>Authors</td>
<td>Country</td>
<td>Year</td>
<td>Sample Size</td>
<td>Setting</td>
<td>Population</td>
<td>ABI methodology</td>
<td>PAD diagnosis</td>
<td>Prevalence</td>
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<tr>
<td>27</td>
<td>Wassel et al. The San Diego Population Study</td>
<td>USA</td>
<td>2011</td>
<td>2404</td>
<td>Undertaken at University</td>
<td>Current or former employees of University of California, San Diego &amp; their significant others. (note: ethnically diverse population, 58% Caucasian, 42% other racial or ethnic groups. Age range: 29-91</td>
<td>Average of two posterior tibial measurements was divided by the higher of the brachial systolic pressures</td>
<td>ABI&lt;0.9</td>
<td>3.6%</td>
</tr>
<tr>
<td>28</td>
<td>Bergiers et al. SELFRAIL study</td>
<td>Belgium</td>
<td>2011</td>
<td>239</td>
<td>Primary Care</td>
<td>Age&gt;80</td>
<td>Used automated oscillometric equipment</td>
<td>ABI&lt;0.9</td>
<td>40% (note: failed measurements in 27% of cases)</td>
</tr>
<tr>
<td>29</td>
<td>Bozkurt et al. CAREFUL study</td>
<td>Turkey</td>
<td>2011</td>
<td>530</td>
<td>Secondary Care: outpatient clinics</td>
<td>Inclusion: • history of atherothrombotic events • age 50-69 with ≥1 cardiovascular risk factor • age ≥70</td>
<td>Standard*</td>
<td>ABI&lt;0.9</td>
<td>20%</td>
</tr>
<tr>
<td>30</td>
<td>He et al.</td>
<td>China</td>
<td>2012</td>
<td>3128</td>
<td>Community based</td>
<td>• Inclusion: Age 45-75 and BP&lt;140/90 or on antihypertensive medications • Exclusion: Known cardiovascular disease, PAD, Chronic kidney disease, diabetes &amp; dyslipidaemia</td>
<td>Utilised automatic oscillometric device to measure systolic pressures at all limbs.</td>
<td>ABI&lt;0.9</td>
<td>9% (women: 10%, men: 7.4%)</td>
</tr>
<tr>
<td>31</td>
<td>Angriou et al.</td>
<td>Greece</td>
<td>2013</td>
<td>436</td>
<td>Primary Care (urban area of Greece)</td>
<td>Age 50-79 (mean age 71)</td>
<td>Standard*</td>
<td>ABI&lt;0.9</td>
<td>5.7%</td>
</tr>
<tr>
<td>32</td>
<td>Berger et al</td>
<td>USA</td>
<td>2013</td>
<td>3,319,993</td>
<td>Part of life line screening</td>
<td>A self-referred population who paid for their screening test</td>
<td>Only assessed PT at ankle (if this was undetectable, then dorsalis pedis was used)</td>
<td>ABI&lt;0.9</td>
<td>3.56%</td>
</tr>
</tbody>
</table>
Appendix 3: PIPETTE Case Report Form – visit 1

Pipette Case Report Form – Visit 1

<table>
<thead>
<tr>
<th>Participant Number:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date:</td>
</tr>
</tbody>
</table>

CRF – Visit 1, version 1, 18/02/2012
## Presence of Cardiovascular Risk Factors (tick those which apply)

<table>
<thead>
<tr>
<th></th>
<th>Pre-identified by GP</th>
<th>Identified at visit 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tobacco Usage/Exposure to tobacco</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Current Smoker</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>• Ex Smoker</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>• Passive Exposure to Smoke</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Systolic BP≥140mmHg or</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>• Diastolic BP≥90mmHg or</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>• Taking antihypertensive medication</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td><strong>Dyslipidaemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Triglycerides &gt;150mg/dL or 1.7mmol/L</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>• High Density Lipoprotein (HDL) &lt;40mg/dL or 1.0mmol/L, or</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>• Low Density Lipoprotein (LDL) ≥130mg/dL or ≥3.3mmol/L, or</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>• Taking lipid lowering medication</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td><strong>Elevated Waist Circumference</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Men (non Asian) ≥102cm</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>• Men (Asian) ≥90cm</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>• Women (non Asian) ≥88cm</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>• Women (Asian) ≥80cm</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td><strong>Elevated BMI (≥25)</strong></td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

CRF – Visit 1, version 1, 18/02/2012
Past Medical History

Age: ____________________________

Ethnicity: ____________________________

Chronic Kidney Disease? [ ]

Atrial Fibrillation? [ ]

Rheumatoid Arthritis? [ ]

Other? __________________________________________________________

Cigarettes per day: ____________________________

Alcohol Units per week: ____________________________

Current Medication

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Frequency</th>
<th>Prescribed (P) or Over the Counter (O)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CRF – Visit 1, version 1, 18/02/2012
### Physical Examination

<table>
<thead>
<tr>
<th>Measurement</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (m)</td>
<td></td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td></td>
</tr>
<tr>
<td>Hip Circumference (cm)</td>
<td></td>
</tr>
<tr>
<td>Heart Rate</td>
<td></td>
</tr>
<tr>
<td>O₂ Saturation</td>
<td></td>
</tr>
<tr>
<td>Sitting Blood Pressure (mmHg)</td>
<td></td>
</tr>
</tbody>
</table>

### Examination of Legs and Feet for Clinical Signs of PAD

<table>
<thead>
<tr>
<th>Sign</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced or absent pulses in legs or feet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non healing wounds to legs or feet (?arterial ulcers)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thickened nails</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smooth shiny skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair loss to legs and feet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pallor or cyanosis to legs/feet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pallor on elevation of legs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg/feet appear flushed in dependent position</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced temperature in 1 or both legs/feet</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**ABI Measurement**

Method 1 - Using hand-held continuous wave Doppler ultrasound with a sphygmomanometer.

<table>
<thead>
<tr>
<th></th>
<th>Systolic Pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Brachial</td>
<td></td>
</tr>
<tr>
<td>Left Brachial</td>
<td></td>
</tr>
<tr>
<td>Right Dorsalis Pedis</td>
<td></td>
</tr>
<tr>
<td>Right Posterior Tibial</td>
<td></td>
</tr>
<tr>
<td>Left Dorsalis Pedis</td>
<td></td>
</tr>
<tr>
<td>Left Posterior Tibial</td>
<td></td>
</tr>
</tbody>
</table>

ABI=Higher ankle pressure/higher brachial pressure

| Left ABI=              |                           |
| Right ABI=             |                           |

**Time procedure commenced:**

**Time procedure completed:**

**Time Taken (mins):**
Appendix 4: British Hypertension Society Guidelines for manual blood pressure measurement (BHS, 2012)

Blood Pressure Measurement

With Manual Blood Pressure Monitors

- The patient should be seated for at least 5 minutes, relaxed and not moving or speaking
- The arm must be supported at the level of the heart. Ensure no tight clothing constricts the arm
- Place the cuff on neatly with the centre of the bladder over the brachial artery. The bladder should encircle at least 80% of the arm (but not more than 100%)
- Estimate the systolic beforehand:
  a) Palpate the brachial artery
  b) Inflate cuff until pulsation disappears
  c) Deflate cuff
  d) Estimate systolic pressure
- Then inflate to 30mmHg above the estimated systolic level needed to occlude the pulse
- Place the stethoscope diaphragm over the brachial artery and deflate at a rate of 2-3mmHg/sec until you hear regular tapping sounds
- Measure systolic (first sound) and diastolic (disappearance) to nearest 2mmHg

<table>
<thead>
<tr>
<th>Cuff Sizes</th>
<th>Indication</th>
<th>Width (cm)*</th>
<th>Length (cm)**</th>
<th>BHS Guidelines Bladder width &amp; length (cm)**</th>
<th>Arm circ. (cm)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Adult/Child</td>
<td>10 - 12</td>
<td>18 - 24</td>
<td>12 x 18</td>
<td>&lt; 23</td>
<td></td>
</tr>
<tr>
<td>Standard Adult</td>
<td>12 - 13</td>
<td>23 - 35</td>
<td>12 x 26</td>
<td>&lt; 33</td>
<td></td>
</tr>
<tr>
<td>Large Adult</td>
<td>12 - 16</td>
<td>35 - 40</td>
<td>12 x 40</td>
<td>&lt; 50</td>
<td></td>
</tr>
<tr>
<td>Adult Thigh Cuff***</td>
<td>20</td>
<td>42</td>
<td>&lt; 52</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The range for columns 2 and 3 are derived from recommendations from the British Hypertension Society (BHS), European Hypertension Society (EHS) and the American Heart Association. Columns 4 and 5 are derived from only the BHS guidelines.
** Large bladders for arm circumference over 42cm may be required
*** Bladders of varying sizes are available so a range is provided for each indication (applies to columns 2 and 3)

Points to note:
The date of next servicing should be clearly marked on the sphygmomanometer (6 monthly). All maintenance necessitating handling of mercury should be conducted by the manufacturer or specialised service units.
Anaeroid manometers may deteriorate and so need regular checking.
Before measuring blood pressure in pregnancy or other special circumstances, ensure that the device used is clinically validated for that setting (www.bhsoc.org)
Appendix 5: General Practice Physical Activity Questionnaire (GPPAQ) (DH, 2013b).

**General Practice Physical Activity Questionnaire**

Date: 

Name: 

1. Please tell us the type and amount of physical activity involved in your work.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Please mark one box only</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>I am not in employment (e.g. retired, retired for health reasons, unemployed, full-time carer etc.)</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>I spend most of my time at work sitting (such as in an office)</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>I spend most of my time at work standing or walking. However, my work does not require much intense physical effort (e.g. shop assistant, hairdresser, security guard, childminder, etc.)</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>My work involves definite physical effort including handling of heavy objects and use of tools (e.g. plumber, electrician, carpenter, cleaner, hospital nurse, gardener, postal delivery workers etc.)</td>
<td></td>
</tr>
<tr>
<td>e</td>
<td>My work involves vigorous physical activity including handling of very heavy objects (e.g. scaffolder, construction worker, refuse collector, etc.)</td>
<td></td>
</tr>
</tbody>
</table>

2. During the last week, how many hours did you spend on each of the following activities? Please answer whether you are in employment or not.

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Some but less than 1 hour</th>
<th>1 hour but less than 3 hours</th>
<th>3 hours or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Physical exercise such as swimming, jogging, aerobics, football, tennis, gym workout etc.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>Cycling, including cycling to work and during leisure time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>Walking, including walking to work, shopping, for pleasure etc.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>Housework/Childcare</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e</td>
<td>Gardening/DoItYourself</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. How would you describe your usual walking pace? Please mark one box only.

- Slow pace (i.e. less than 3 mph)
- Steady average pace
- Fast pace (i.e. over 4 mph)
Appendix 6: Healthy Eating questionnaire

Participant No:  
Date: ___/___/___

**Healthy Eating Questionnaire**

Over the past few months:

<table>
<thead>
<tr>
<th>Question</th>
<th>Less than 1 time</th>
<th>1-3 times</th>
<th>4 or more times</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How many times a week did you eat fast food meals or snacks?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>2. How many servings of fruit did you eat each day?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>3. How many servings of vegetables did you eat?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>4. How many regular (not diet) fizzy drinks did you drink each day?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>5. How many times a week did you eat beans (like baked beans), chicken or fish?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>6. How many times a week did you eat oily fish like salmon, mackerel, or sardines?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>7. How many times a week did you eat red meat (e.g. beef, pork, lamb) and processed meat such as sausages and burgers?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>8. How many times a week did you eat snacks such as crisps or chocolate! (not low fat)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>9. How many times a week did you eat desserts, cakes, ice-cream (not the low fat kind)?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>10. How much margarine, butter or meat fat do you use for cooking or put on potatoes, bread etc?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

**Summary Score** (sum of all items)...........................................................................................................................................

*Adapted from “Starting the Conversation” (Pecston, 2011)*

CRF – Visit 1, version 1, 18/02/2012
**Appendix 7: SF-12 (Quality Metric, 2013)**

Participant No:
Date: ___/___/___

### SF-12v2™ Health Survey

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

<table>
<thead>
<tr>
<th>1. In general, would you say your health is:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
</tr>
<tr>
<td>☐</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes, limited a lot</td>
</tr>
</tbody>
</table>

| a. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf |
|__________________________________________|
| ☐ | ☐ | ☐ |

| b. Climbing several flights of stairs |
|____________________________________|
| ☐ | ☐ | ☐ |

<table>
<thead>
<tr>
<th>3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the time</td>
</tr>
</tbody>
</table>

| a. Accomplished less than you would like |
|______________________________|
| ☐ | ☐ | ☐ | ☐ | ☐ |

| b. Were limited in the kind of work or other activities |
|____________________________________|
| ☐ | ☐ | ☐ | ☐ | ☐ |

<table>
<thead>
<tr>
<th>4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the time</td>
</tr>
</tbody>
</table>

| a. Accomplished less than you would like |
|______________________________|
| ☐ | ☐ | ☐ | ☐ | ☐ |

| b. Did work or activities less carefully than usual |
|____________________________________|
| ☐ | ☐ | ☐ | ☐ | ☐ |

CRF – Visit 1, version 1, 18/02/2012
5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>c</td>
<td>c</td>
<td>c</td>
<td>c</td>
<td>c</td>
</tr>
</tbody>
</table>

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks...

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>c</td>
<td>c</td>
<td>c</td>
<td>c</td>
</tr>
</tbody>
</table>

a. Have you felt calm and peaceful?

b. Did you have a lot of energy?

c. Have you felt downhearted and depressed?

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>c</td>
<td>c</td>
<td>c</td>
<td>c</td>
<td>c</td>
</tr>
</tbody>
</table>

CRF – Visit 1, version 1, 18/02/2012
Appendix 8: Participant evaluation of ABI measurement questionnaire

Participant No:
Date: ___/___/___

Participant Evaluation of ABI Measurement

Method 1 – Using manual blood pressure cuff and Doppler (8-MHz Doppler-probe)

1. Please rate how comfortable you found the procedure:
   - Very Comfortable [ ] 3
   - Comfortable [ ] 1
   - Uncomfortable [ ] 3
   - Painful [ ] 2
   - Very Painful [ ] 1

2. How do you feel about the time it took to complete the procedure?
   - It took far too long [ ] 1
   - It was slightly lengthy [ ] 2
   - Indifferent [ ] 3
   - It didn’t take too long [ ] 4
   - It was very quick [ ] 5

3. Please rate the overall procedure:
   - It was very acceptable [ ] 5
   - It was acceptable [ ] 4
   - Indifferent [ ] 3
   - It was unacceptable [ ] 2
   - It was very unacceptable [ ] 1

4. Any comments?
   ........................................................................................................................................................................
   ........................................................................................................................................................................
   ........................................................................................................................................................................
   ........................................................................................................................................................................
   ........................................................................................................................................................................

CRF – Visit 1, version 1, 18/02/2012
Participant Evaluation of ABI Measurement

Method 2 – Using Dopplex Ability

1. Please rate how comfortable you found the procedure:-
   - Very Comfortable □ 5
   - Comfortable □ 4
   - Uncomfortable □ 3
   - Painful □ 2
   - Very Painful □ 1

2. How do you feel about the time it took to complete the procedure?
   - It took far too long □ 1
   - It was slightly lengthy □ 2
   - Indifferent □ 3
   - It didn’t take too long □ 4
   - It was very quick □ 3

3. Please rate the overall procedure:-
   - It was very acceptable □ 5
   - It was acceptable □ 4
   - Indifferent □ 3
   - It was unacceptable □ 2
   - It was very unacceptable □ 1

4. Any comments?

..............................................................................................................................................................................................
..............................................................................................................................................................................................
..............................................................................................................................................................................................
..............................................................................................................................................................................................
..............................................................................................................................................................................................
..............................................................................................................................................................................................

CRF – Visit 1, version 1, 18/02/2012
 Appendix 9: QRISK®2 cardiovascular risk algorithm (University of Nottingham, 2012).

### Participant No:
Date: ___/___/___

<table>
<thead>
<tr>
<th>QRISK2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age:</td>
</tr>
<tr>
<td>Sex:</td>
</tr>
</tbody>
</table>

Ethnicity:
- White (or not stated)
- Indian
- Pakistani
- Bangladeshi
- Other Asian
- Black Caribbean
- Black African
- Chinese
- Other Ethnic Group

Clinical Information

<table>
<thead>
<tr>
<th>Smoking Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smoker</td>
</tr>
<tr>
<td>Ex Smoker</td>
</tr>
<tr>
<td>Light Smoker (less than 10)</td>
</tr>
<tr>
<td>Moderate Smoker (10-19)</td>
</tr>
<tr>
<td>Heavy Smoker (More than 20)</td>
</tr>
</tbody>
</table>

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic?</td>
<td>Angina or Heart Attack in first degree relative &lt;60?</td>
</tr>
<tr>
<td>Chronic Kidney Disease?</td>
<td>Atrial Fibrillation?</td>
</tr>
<tr>
<td>Rheumatoid Arthritis?</td>
<td>On blood pressure treatment?</td>
</tr>
<tr>
<td>Cholesterol/HDL ratio?</td>
<td>Systolic Blood Pressure (mmHg)</td>
</tr>
</tbody>
</table>

Body Mass Index: Height (cm) Weight (Kg)

**QRISK2 SCORE (10 year risk)**

Pipette Case Report Form – Visit 3/4 (version 1), 01/02/2012
Appendix 10: PIPETTE Case Report From – visits 3 and 4

Participant No:
Date: ---/---/----

Case Report Form - Visit 3/4

Review of Medical Notes

1. Referred to secondary care for investigation/treatment of PAD? Yes ☐ No ☐ ☐
   If yes, date of referral: ___ / ___ / ___
   If yes, reason for referral: ..................................................................................................................
   ..........................................................................................................................................................
   ..........................................................................................................................................................
   ..........................................................................................................................................................

2. Referred to secondary care for investigation/treatment of CHD/CVD? Yes ☐ No ☐ ☐
   If yes, date of referral: ___ / ___ / ___
   If yes, reason for referral: ..................................................................................................................
   ..........................................................................................................................................................
   ..........................................................................................................................................................
   ..........................................................................................................................................................

3. Referred to secondary care for any other reason? Yes ☐ No ☐ ☐
   If yes, date of referral: ___ / ___ / ___
   If yes, details of referral: ..................................................................................................................
   ..........................................................................................................................................................
   ..........................................................................................................................................................
   ..........................................................................................................................................................

Pipette Case Report Form – Visit 3/4 (version 1), 18/02/2012
Visit 3 contd.

4. Cardiovascular Events/Diagnoses since visit 2

<table>
<thead>
<tr>
<th>Event/Diagnosis</th>
<th>Yes (please state date)</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms of PAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular Accident</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient Ischaemic Attack</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (please state)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. New medications commenced since Visit 2:

**Antiplatelets**

<table>
<thead>
<tr>
<th>Name</th>
<th>Date Commenced</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Lipid lowering**

<table>
<thead>
<tr>
<th>Name</th>
<th>Date Commenced</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Antihypertensives**

<table>
<thead>
<tr>
<th>Name</th>
<th>Date Commenced</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
New Medications contd.

Other

<table>
<thead>
<tr>
<th>Name</th>
<th>Date Commenced</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6. Documentation of non-pharmacological, cardiovascular risk management strategies since visit 2

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking Cessation Advice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking Cessation Medications (patches etc.) prescribed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking Cessation Referral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise Advice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>National Exercise Referral Scheme Referral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dietary Advice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dietary Referral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease management clinic Referral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (please state)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7. Bloods repeated since visit 2? Yes [ ] No [ ]

If yes, reason for repeating: .................................................................................................................................

........................................................................................................................................................................

Bloods Improved? ...................................................................................................................................................

........................................................................................................................................................................

........................................................................................................................................................................

........................................................................................................................................................................

Pipette Case Report Form – Visit 3/4 (version 1), 18/02/2012
Repeat of Physical Examination

Physical Examination

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Increase or decrease since visit 2?</th>
<th>Improvement?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (m)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip Circumference (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O₂ Saturation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting Blood Pressure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cigarettes per day:
(Decreased or increased since visit 2?)

Alcohol Units per week:
(Decreased or increased since visit 2?)

International Classification of adult underweight, overweight and obesity according to BMI

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
<th>Principal cut-off points</th>
<th>Additional cut-off points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.50</td>
<td>&lt;18.50</td>
<td>&lt;18.50</td>
</tr>
<tr>
<td>Severe thinness</td>
<td>&lt;16.00</td>
<td>&lt;16.00</td>
<td>&lt;16.00</td>
</tr>
<tr>
<td>Moderate thinness</td>
<td>16.00 - 16.99</td>
<td>16.00 - 16.99</td>
<td>16.00 - 16.99</td>
</tr>
<tr>
<td>Mild thinness</td>
<td>17.00 - 18.49</td>
<td>17.00 - 18.49</td>
<td>17.00 - 18.49</td>
</tr>
<tr>
<td>Overweight</td>
<td>≥25.00</td>
<td>≥25.00</td>
<td>≥25.00</td>
</tr>
<tr>
<td>Pre-obese</td>
<td>25.00 - 29.99</td>
<td>25.00 - 27.49</td>
<td>27.50 - 29.99</td>
</tr>
<tr>
<td>Obese</td>
<td>≥30.00</td>
<td>≥30.00</td>
<td>≥30.00</td>
</tr>
<tr>
<td>Obese class I</td>
<td>30.00 - 34.99</td>
<td>30.00 - 32.49</td>
<td>32.50 - 34.99</td>
</tr>
<tr>
<td>Obese class II</td>
<td>35.00 - 39.99</td>
<td>35.00 - 37.49</td>
<td>37.50 - 39.99</td>
</tr>
<tr>
<td>Obese class III</td>
<td>≥40.00</td>
<td>≥40.00</td>
<td>≥40.00</td>
</tr>
</tbody>
</table>

Appendix 12: Project Statistical Analysis

All data analysis was performed using IBM SPSS for windows statistical software (version 21).

**Categorical Data**
Categorical data were analysed using Pearson’s chi square ($\chi^2$) test to evaluate how likely it was that any observed difference between variables arose by chance. In each case the null hypothesis was that there was no association between the variables. Two sided $P<0.05$ was regarded as significant. Standard residuals were inspected to provide further information as to where and to what extent associations were detected. Due to the small sample sizes of some groups of data, the expected count of several cells was less than five; this is insufficient to perform a Pearson’s chi square test (Ludbrook, 2008), hence in these cases Fisher’s Exact test was used as recommended by Agresti (1992).

**Assessment of Continuous Data Distribution**
Continuous data distribution was assessed via the Shapiro-Wilk test if $n \leq 50$, or the Kolmogorov-Smirnov test if $n > 50$. If either of these tests returned a non significant $p$ value ($> 0.05$), the data were considered to be normally distributed.

**Parametric Tests: One-Way ANNOVA and (independent) T test**
For continuous data which were normally distributed, an Independent T test or One-Way Analysis of Variance (ANOVA) were used to determine whether there were any differences between the means of two or more independent groups. Prior to the utilisation of either of these tests, data were assessed to ensure that the following assumptions were met:

(i) There were no outliers (assessed via inspection of boxplots)
(ii) There was homogeneity of variances (assessed via Levene’s test).

If there were no outliers and homogeneity of variances was confirmed (as indicated by a $p>0.05$ in Levene’s test), a one-way ANNOVA test was conducted with a Tukey post-hoc test for multiple comparisons.

In the event that genuine outliers were present, both one-way ANNOVA and Kruskal Wallis H tests were performed and both results were reported.

If homogeneity of variances was violated (Levene’s test: $p \leq 0.05$), a Welch ANOVA was performed with a Games-Howell post-hoc test for multiple comparisons.
**Independent T test effect size**

Where significant results were attained using the T-test, effect size (Cohen’s $d$) was manually calculated according to the formula below, for the independent-samples t-test. To calculate this effect size the mean difference between the groups was divided by the pooled standard deviation, and then the square root was calculated, as shown below:

$$d = \frac{|M_1 - M_2|}{s_{pooled}}$$

where $||$ means the absolute value (negative value becomes a positive value) and,

$$s_{pooled} = \sqrt{\frac{s_1^2(n_1 - 1) + s_2^2(n_2 - 1)}{n_1 + n_2 - 2}}$$

$s$=standard deviation  
$n$=sample size  
$m$=mean

<table>
<thead>
<tr>
<th>Effect Size</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>small</td>
</tr>
<tr>
<td>0.5</td>
<td>medium</td>
</tr>
<tr>
<td>0.8</td>
<td>large</td>
</tr>
</tbody>
</table>

An effect size is an attempt to provide a measure of the practical significance of the result. The importance of the value of Cohen’s $d$ (as reported by Cohen (1998)).

**Non-parametric tests: Mann-Whitney U test and Kruskal-Wallis H test**

**Mann-Whitney U Test**

The Mann-Whitney U test (also called the Wilcoxon-Mann-Whitney test), which is a rank-based nonparametric test, was used to determine if there were differences between two groups on a continuous or ordinal dependent variable. As highlighted by Hart (2001), interpretation of results of the Mann-Whitney test depends on the distribution of data in the two groups being compared. If the two distributions had a different shape, the Mann-Whitney U test was used to determine
whether there were differences in the distributions of the two groups. However, if the two distributions were the same shape, the Mann-Whitney U test was used to determine whether there were differences in the medians of the two groups.

**Kruskal Wallis H Test**
The Kruskal-Wallis test is the non-parametric alternative to the one-way ANOVA and was used to determine whether there were any statistically significant differences between the distributions of three or more independent (unrelated) groups. For significant Kruskal Wallis test results, pairwise comparisons were subsequently performed using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons.
Appendix 13: General Practice Survey

Survey: Use of the Ankle Brachial Index in General Practice

1. Please tick the occupation of the person completing this survey:  
   - GP 
   - Nurse Practitioner 
   - Practice Nurse 
   - Other 
   - (please specify) ........................................

Reasons for Ankle Brachial Index (ABI) Measurement

2. If you suspect a patient to have Peripheral Arterial Disease, how would you confirm this? (Please tick all that apply)
   a. Clinical Examination  
   b. Edinburgh Claudication Questionnaire  
   c. ABI measurement  
   d. Other (please state)  

3. Besides signs and symptoms of arterial insufficiency, are there any other reasons which would cause you to perform or request ABI measurement? If yes, please state:
   - YES  
   - NO  
   (If 'YES' please state) .................................................................................................................

ABI Measurement

4. If you wanted to determine a patient’s ABI, would you carry out the measurement procedure yourself?
   - YES  
   - NO  

1
Survey: Use of the Ankle Brachial Index in General Practice

If you answered ‘NO’ to question 4, please indicate the occupation of the person who would carry out the measurement (please tick):

a. GP
b. Nurse Practitioner
c. Practice Nurse
d. District Nurse
e. Other

(please specify) ........................................

5. Please estimate how often, in an average month, ABI measurements are done in your practice?

f. 0 times
g. 1-3 times
h. 4-7 times
i. 8-10 times
j. >10 times
k. Don’t know

6. a. Please state the total number of GP’s at your practice:
   
b. How many of these are competent at ABI measurement:

7. a. Please state the total number of Nurse Practitioners at your practice:
   
b. How many of these are competent at ABI measurement:

8. a. Please state the total number of Practice Nurses at your practice:
   
b. How many of these are competent at ABI measurement:
9. a. Please state the total number of District Nurses at your practice:

b. How many of these are competent at ABI measurement:

10. Has anyone in your practice received specialist training for ABI measurement?

YES [ ] NO [ ]

If yes, please state who has received training and from whom: .................................................................................................................................
.................................................................................................................................
.................................................................................................................................

11. Please answer the following questions regarding the procedure of ABI measurement.

a. Do you rest your patient in a supine position for at least 10 minutes prior to undertaking the procedure? YES [ ] No [ ]

If you answered No to the above, please tick reason why:

Don't think it is necessary [ ] Lack of time [ ] Other (please state) [ ] Reason: .................................................................................................................................

b. Sometimes do you find the procedure of ABI Measurement difficult because of:

<table>
<thead>
<tr>
<th>Difficulty</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty finding pulses?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty holding the Doppler Probe in place whilst pumping up the blood pressure cuff?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty in the actual calculation of the ABI?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please state any other difficulties you have experienced with ABI measurement:
.................................................................................................................................
.................................................................................................................................
.................................................................................................................................
Survey: Use of the Ankle Brachial Index in General Practice

a. When measuring the brachial pressure, please indicate all of the pieces of equipment which you would use (please tick)
   i. Automatic blood pressure monitor
   ii. Manual blood pressure sphygmomanometer
   iii. Stethoscope
   iv. Doppler probe
   v. Other
   (Please state)........................................................................................................................................

b. When measuring the brachial pressure, do you:
   i. Measure the BP in 1 arm only
   ii. Measure the BP in both arms

c. When measuring the ankle pressures, what equipment would you use?
   i. Automatic blood pressure monitor
   ii. Manual blood pressure sphygmomanometer
   iii. Stethoscope
   iv. Doppler probe
   v. Other
   (Please state)........................................................................................................................................

d. When measuring the ankle pressures, what pulses would you assess? (Please tick all that apply)
   i. Dorsalis pedis
   ii. Posterior tibial
   iii. Anterior tibial

4
Survey: Use of the Ankle Brachial Index in General Practice

a. If you measured the brachial pressure in both arms, when calculating the result do you use the:
   i. Higher of the brachial pressures  
   ii. Lower of the brachial pressures  
   iii. Average of the brachial pressures  
   iv. N/A because only 1 measurement made  

b. If you measured more than 1 ankle pressure, when calculating the result do you use the:
   i. Higher of the ankle pressures  
   ii. Lower of the ankle pressures  
   iii. Average of the ankle pressures  
   iv. N/A because only 1 measurement made  

Referral to Secondary Care

2. Would you refer a patient for a vascular opinion without having done an ABI measurement?
   YES  
   NO  

3. Is there an ABI cut off point at below which you would always refer to secondary care for a vascular opinion? For example, would you refer all patients with an ABI of 0.9 or less for a vascular opinion?
   YES  
   NO  

   If yes, please state the cut off ABI value: ............... 
   Please expand on your answer if you wish: .......................................................................................................................... 

4. If a patient showed signs or symptoms of PAD or had an ABI of less than 0.9 and you chose not to refer for a vascular opinion, please briefly outline your management of the patient.
   .......................................................................................................................... 
   .......................................................................................................................... 
   ..........................................................................................................................
“Finding out that PAD was causing the pain in my legs and then having angioplasty has changed my life. I can now walk normally without pain and without the need to sit down frequently. I was delighted to be screened for PAD and feel strongly that a screening programme should be in place in the NHS.”

“Having a chance to be screened for PAD was great, not only because it put my mind at rest that I didn’t have it, but also because it gave me chance to think and talk about my cardiovascular health with a specialist nurse.”

“I would never have known how bad my leg was if I hadn’t had the PAD test. After having the balloon down, I am free of pain and can get on with my life. I think that screening in certain cases should be done.”

“My dad had PAD and ended up having his leg amputated so I was happy when I found out that I haven’t got it. It was good to talk to the nurse about what I can do to make sure I don’t get it in the future.”

“I was always having to stop and pretend to look in shop windows because of the terrible pain in my leg. Thanks to the research, that has all gone away and I can keep up with the wife. I’ve given up the cigs as well now.”
Current utility of the ankle-brachial index (ABI) in general practice: implications for its use in cardiovascular disease screening

Jane H Davies*, Joyce Kenkre and E Mark Williams

Abstract

Background: Peripheral arterial disease (PAD) is a marker of systemic atherosclerosis and associated with a three to six-fold increased risk of death from cardiovascular causes. Furthermore, it is typically asymptomatic and under-diagnosed; it has resulted in escalating calls for the instigation of Primary Care PAD screening via Ankle Brachial Index (ABI) measurement. However, there is limited evidence regarding the feasibility of this and if the requisite core skills and knowledge for such a task already exist within primary care. This study aimed to determine the current utility of ABI measurement in general practices across Wales, with consideration of the implications for its use as a cardiovascular risk screening tool.

Method: A self-reporting questionnaire was distributed to all 478 General Practices within Wales, sent via their responsible Health Boards.

Results: The survey response rate was 20%. ABI measurement is primarily performed by nurses (93%) for the purpose of wound management (90%). It is infrequently (73% < 4 times per month) and often incorrectly used (42% out of compliance with current ABI guidance). Only 52% of general practitioners and 16% of nurses reported that patients with an ABI of ≤ 0.9 require aggressive cardiovascular disease risk factor modification (as recommended by current national and international guidelines).

Conclusion: ABI measurement is an under-utilised and often incorrectly performed procedure in the surveyed general practices. Prior to its potential adoption as a formalised screening tool for cardiovascular disease, there is a need for a robust training programme with standardised methodology in order to optimise accuracy and consistency of results. The significance of a diagnosis of PAD, in terms of associated increased cardiovascular risk and the necessary risk factor modification, needs to be highlighted.

Keywords: Peripheral arterial disease, Doppler ultrasound, Atherosclerosis, Secondary prevention

Background

Peripheral arterial disease (PAD) is a marker of systemic atherosclerosis and has been associated with a three to six-fold increased risk of death from cardiovascular (CV) causes in multiple longitudinal studies [1]. Moreover, existing evidence demonstrates that PAD (both asymptomatic and symptomatic) conveys independent increased risk in addition to that expected by concomitant traditional CV risk factors and disease [2]. However, PAD is typically asymptomatic and under-diagnosed [3]. This has resulted in calls for the instigation of Primary Care PAD screening which would identify those at increased risk and potentially allow alteration of the disease trajectory via secondary risk factor modification [4]. Current guidelines recommend the same strategy of cardiovascular risk management for persons with PAD as for those with coronary artery disease (CAD) [3,5].

PAD can be diagnosed and also quantified by means of the ankle brachial index (ABI) which involves a comparison of the systolic pressure at the ankle with the systolic pressure at the arm; an ABI of ≤ 0.9 is considered diagnostic of the disease. The ABI is widely regarded as non-invasive, inexpensive, and easily used in a general
practice setting. However, there is limited evidence regarding the feasibility of PAD screening and if the requisite core skills and knowledge for such a task already exist within primary care. Bendermacher et al. considered the workload of screening all patients over the age of 50 in general practices in the Netherlands; they concluded that it was not achievable and suggested a clinical prediction model to determine who should undergo ABI measurement [6]. The Scottish Intercollegiate Guidelines Network (SIGN) state that there is a pool of expertise for measuring the ABI of patients in the community but they do not substantiate this and existing research regarding this issue has produced varying results [7].

This study aimed to determine the current utility of ABI measurement in general Practices across Wales, including: (i) the occupations of those who perform ABI measurement, (ii) frequency of ABI measurement, (iii) reasons for ABI measurement, (iv) methodology utilised for ABI measurement, (v) prior training for ABI measurement and, (vi) subsequent management of patients found to have PAD.

Method
A self-reporting questionnaire was distributed, via seven health boards, to all general practices within Wales (n = 478); branch practices were not included as staff may work at both main and branch practices which may have resulted in duplication of results. Questionnaires were sent to practice managers and an accompanying letter requested that the survey be passed on to an appropriate person for completion.

Guidelines for the measurement and calculation of the ABI are available from multiple sources [3-5, 7-10]. Whilst some are more explicit than others, they all broadly advocate the same methodology (Table 1). The questionnaire (Additional file 1) was designed by the authors to assess six fundamental points of the guidelines advocated ABI method (detailed in Table 2 along with their associated rationales). The questionnaire was piloted at a local general practice and approved by an independent expert (a Consultant Vascular Surgeon) prior to distribution. It is acknowledged that measurement of the ABI includes more complex components such as the choice of Doppler probe frequency and angulation of Doppler probes to achieve good signals; however, the aim of the survey was to determine if the fundamental underpinnings of correct ABI measurement exist.

As general practice survey response rates are often low [24], several strategies were employed in an attempt to address this issue: the questionnaire was designed to be minimally time consuming with predominantly close-ended, tick box questions, with a pre-paid return envelope included. Returned questionnaires were entered into a prize draw (a £50 gift voucher for each health board).

This study did not require ethical approval (according to the UK Health Research Authority guidance). However, approval to distribute the questionnaire was obtained from each of the individual health boards and completion of the survey constituted consent.

Results
The overall response rate was 20% (95/478) and ranged from 16-41% across individual health boards: Cwm Taf Health Board 16% (8/50), Aneurin Bevan Health Board 22% (20/91), Cardiff & Vale University Health Board 19% (13/68), Aberdare Bro Morgannwg Health Board 18% (14/77), Betsi Cadwaladr University Health Board 16% (19/119), Powys Teaching Health Board 41% (7/17), Hywel Dda Health Board 25% (14/56). Thirty per cent (27/93) of returned surveys were completed by GPs, 6% (6/93) by nurse practitioners, 34% (32/95) by practice nurses and 5% (5/95) by district nurses. The remaining 25% were completed as a collaboration between GPs and nursing staff.

Twenty seven per cent (26/95) of responding general practices were not undertaking ABI measurement, with patients needing this procedure often being referred to secondary care. Other practices relied on their district nursing colleagues (who, in Wales, are not generally based within general practices) to undertake the task.

The majority of practices reported performing ABI measurements relatively infrequently at less than four times a month (73%) (Figure 1). Respondents were asked to indicate if there were any other reasons, besides the presence of signs and symptoms of lower limb arterial insufficiency, which would cause them to undertake or request ABI measurement. Whilst the management of lower limb oedema and leg ulceration/wounds accounted for 90% of responses to this question, it was interesting to note that 6% reported utilising the ABI in a screening capacity (Figure 2).

General practitioners (GPs) were the least likely occupational group to undertake ABI measurement. They were also the least likely to: (i) consider themselves, or be considered by colleagues, to be competent at ABI measurement, (ii) have received formal training for ABI measurement, and (iii) be compliant with current guidelines for ABI measurement (Table 3). Conversely, practice nurses were the most likely to perform ABI measurement with 64% having received training for the procedure and 71% of practice nurse survey respondents being compliant with ABI measurement guidelines. In general, nurses were much more likely to have received training for ABI measurement and more likely to be adhering to current ABI guidelines.

There was considerable variation in the method utilised for ABI measurement and calculation. Only 58% of general practices undertaking ABI measurements were found to be compliant with current guidelines for the procedure.
<table>
<thead>
<tr>
<th>American College of Cardiology/American Heart Association (ACC/AHA) 2005</th>
<th>Rest supine for 10 minutes</th>
<th>Handheld Doppler ultrasound device &amp; sphygmomanometer</th>
<th>2</th>
<th>Handheld Doppler ultrasound device &amp; sphygmomanometer</th>
<th>Donals Pedis artery and Posterior Tibial artery</th>
<th>Higher ankle systolic pressure (for that leg) divided by higher brachial pressure of the two arms.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scottish Intercollegiate Guidelines Network (SIGN) 2006</td>
<td>Not mentioned</td>
<td>Handheld Doppler ultrasound device &amp; sphygmomanometer</td>
<td>2</td>
<td>Handheld Doppler ultrasound device &amp; sphygmomanometer</td>
<td>Donals Pedis artery/ Anterior Tibial artery and Posterior Tibial artery, if these cannot be located, assess the Popliteal Artery</td>
<td>Higher ankle systolic pressure (for that leg) divided by higher brachial pressure of the two arms.</td>
</tr>
<tr>
<td>Trans-Atlantic Intervenous Consensus (TASC) 2007</td>
<td>Not mentioned</td>
<td>Doppler Instrument &amp; sphygmomanometer</td>
<td>2</td>
<td>Doppler Instrument &amp; sphygmomanometer</td>
<td>Donals Pedis artery &amp; Posterior Tibial artery.</td>
<td>Divide both ankle pressures by higher brachial pressures.</td>
</tr>
<tr>
<td>Society for Vascular Technology of Great Britain and Ireland (SVT) 2010</td>
<td>Rest supine for 5-10 minutes prior to procedure</td>
<td>Handheld continuous wave Doppler ultrasound device &amp; sphygmomanometer</td>
<td>2</td>
<td>Handheld continuous wave Doppler ultrasound device &amp; sphygmomanometer</td>
<td>Donals Pedis artery &amp; Posterior Tibial artery.</td>
<td>Higher ankle systolic pressure (for that leg) divided by higher brachial pressure of the two arms.</td>
</tr>
<tr>
<td>European Society of Cardiology (ESC) 2011</td>
<td>Not mentioned</td>
<td>Handheld Doppler ultrasound device &amp; sphygmomanometer</td>
<td>2</td>
<td>Handheld Doppler ultrasound device &amp; sphygmomanometer</td>
<td>Posterior Tibial artery &amp; Anterior Tibial artery.</td>
<td>Higher ankle systolic pressure (for that leg) divided by higher brachial pressure of the two arms.</td>
</tr>
<tr>
<td>National Institute for Clinical Excellence (NICE) 2012</td>
<td>Rest supine when possible. Rest period should be &quot;long enough for blood pressure to return to normal.&quot;</td>
<td>Handheld Doppler ultrasound device &amp; sphygmomanometer</td>
<td>2</td>
<td>Handheld Doppler ultrasound device &amp; sphygmomanometer</td>
<td>These arteries, one of which must be the Peroneal artery as this &quot;may be the only one present in some people, particularly those with diabetes.&quot;</td>
<td>Higher ankle systolic pressure (for that leg) divided by higher brachial pressure of the two arms.</td>
</tr>
<tr>
<td>American Heart Association (AMA)-scientific statement 2012</td>
<td>Rest 5-10 minutes in supine position</td>
<td>Handheld Doppler ultrasound device &amp; sphygmomanometer</td>
<td>2</td>
<td>Handheld Doppler ultrasound device &amp; sphygmomanometer</td>
<td>Donals Pedis artery &amp; Posterior Tibial artery.</td>
<td>Higher ankle systolic pressure (for that leg) divided by higher brachial pressure of the two arms.</td>
</tr>
</tbody>
</table>
Table 2 Aspects of ABI measurement assessed by survey

<table>
<thead>
<tr>
<th>Aspect of ABI measurement assessed</th>
<th>Recommended by</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient rested in supine position for at least 10 minutes prior to ABI measurement?</td>
<td>SVT [9]</td>
<td>• ABI averages 0.05 higher in the seated position as opposed to supine [11].&lt;br&gt;• There is no evidence to recommend a minimum period but it should be long enough for blood pressure to return to normal [3]. The effect of the duration of the rest period on the reliability of the ABI measurement is unknown, with most studies using 5-10 minutes [5].</td>
</tr>
<tr>
<td>2. Equipment needed to measure the brachial systolic blood pressure correctly identified as being a Doppler Ultrasound and sphygmomanometer</td>
<td>All guidelines [3-5,7-10]</td>
<td>• Using the Korotkoff method to measure the brachial pressure has been shown to yield lower values compared to Doppler [11].&lt;br&gt;• Similarly, automated oscillometric blood pressure devices have been shown to underestimate brachial pressure [12,13].&lt;br&gt;• As the brachial pressure forms the denominator of the ABI, underestimation will result in falsely elevated ABIs.</td>
</tr>
<tr>
<td>3. Brachial systolic pressure measured in both arms</td>
<td>All guidelines [3-5,7-10]</td>
<td>• A pressure difference between left and right brachial arteries of at least 20 mmHg is present in 33% of normal healthy population [14].&lt;br&gt;• A recent meta-analysis found that a difference of 15 mmHg or more is actually associated with a three times increased risk of PAD [15].&lt;br&gt;• It is therefore paramount that both brachial pressures are measured to prevent missed diagnoses and in correct classification of PAD.</td>
</tr>
<tr>
<td>4. Equipment needed to measure the ankle systolic blood pressure correctly identified as being a Doppler Ultrasound and sphygmomanometer</td>
<td>All guidelines [3-5,7-10]</td>
<td>• Oscillometric devices have been found to overestimate ankle systolic pressure [16] resulting in falsely elevated ABIs and reduced sensitivity for detecting PAD [17-19].&lt;br&gt;• Most oscillometric devices are unable to detect low pressures (&lt;50 mmHg) and hence recording failures are frequent in cases of moderate to severe PAD [19].</td>
</tr>
<tr>
<td>5. More than one pulse assessed at each ankle/foot</td>
<td>All guidelines [3-5,7-10]</td>
<td>• Guidelines differ with regard to which of the three ankle arteries should be assessed, although they all agree that it should be more than one. &lt;br&gt;• NICE guidance specifies that the arteries assessed should always include the posterior tibial artery as this may be the only one present in some people, particularly those who are diabetics [5].</td>
</tr>
<tr>
<td>6. ABI calculated by dividing the higher of the ankle systolic blood pressures by the higher of the brachial systolic blood pressures</td>
<td>All guidelines [3-5,7-10]</td>
<td>• Although several authors have argued that utilising the lower ankle systolic pressure as the numerator in the ABI would result in greater sensitivity for the identification of early PAD [20,21], others have argued that the higher pressure should be used to prevent over-diagnosis in healthy subjects [10].&lt;br&gt;• Others argue that standardisation of the calculation is the important issue, because this would optimise accuracy and consistency of results universally hence ensuring PAD diagnoses are based on the same parameter [22,23].</td>
</tr>
</tbody>
</table>

Figure 3 illustrates the proportion of survey responses which successfully progressed through each of the methodology assessment points as described in Table 2. Eighteen per cent of practices reported not resting their patients in the supine position prior to ABI measurement. Lack of time was the primary reason for not doing this (75%), whilst the remaining 25% of respondents thought it was unnecessary. Five per cent of respondents reported utilising the Korotkoff method to measure the brachial systolic pressure with a further 2% reportedly using automated blood pressure devices. Furthermore, 13% of respondents said that they would measure the brachial systolic pressure in one arm only. Thirty three per cent of respondents reported not calculating ABIs according to current guidance. In 17% of cases, this was because only one brachial pressure and/or only one ankle pressure had been measured. A further 12% reported using the lower of the ankle and/or brachial pressures, whilst the remaining 4% used the average of the ankle and/or brachial pressures when calculating the index.

A large proportion of respondents reported difficulty in (i) locating pulses in the foot/ankle (59%), and (ii) maintaining the position of the Doppler probe whilst inflating the blood pressure cuff (33%). The survey provided opportunity to expand on these issues and 9% of respondents (all of which were nurses) independently stated that they addressed these problems by utilising another health professional to assist with the procedure.
Seventy six per cent (2837) of respondents who were in compliance with current guidelines for ABI measurement reported having received formal training for the procedure. Accordingly, 73% (5852) of respondents who were not in compliance with current guidelines had not received any formal training.

Training originated from a variety of sources with Tissue Viability Nurses/Wound Care Practitioners accounting for the largest proportion (41%). Eighty two per cent of respondents who received training from these clinical nurse specialists reporting measuring ABIs in accordance with current guidance. Training via specialist clinics or as part of a formalised course also appears effective in achieving compliance with guidelines (Figure 4). Five per cent of respondents expressed their frustration at a lack of refresher

or update ABI education/courses to enable them to maintain their competency in the procedure.

Respondents were asked to indicate any medical management which they would instigate or expect to be instigated for patients who were found to have PAD. Twenty nine per cent referred to “aggressive” cardiovascular risk factor modification such as commencing antplatelets, control of hypertension and hyperlipidaemia in combination with lifestyle advice; this is in line with current guidance issued by the European Society of Cardiology (ESC) and National Institute of Clinical Excellence (NICE) [3,5]. A further 8% mentioned a lesser degree of cardiovascular risk modification involving only lifestyle factors such as encouraging smoking cessation and exercise. GPs were more likely to have

Figure 1 Frequency of ABI measurement within general practices.

Figure 2 Reasons for ABI measurement.
### Table 3 Summary of survey results

<table>
<thead>
<tr>
<th>% Who typically performs ABP measurement within General Practice</th>
<th>General practitioners</th>
<th>Practice nurses</th>
<th>Nurse practitioners</th>
<th>District nurses</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Who consider themselves or are considered by colleagues to be competent at ABP measurements</td>
<td>11</td>
<td>48</td>
<td>56</td>
<td>60</td>
<td>32</td>
</tr>
<tr>
<td>Training</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of General Practitionans with staff trained for ABP measurement</td>
<td>3</td>
<td>30</td>
<td>4</td>
<td>5</td>
<td>42</td>
</tr>
<tr>
<td>% of respondents who currently undertake ABP measurement and have received ABP training</td>
<td>20</td>
<td>64</td>
<td>43</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>ABP Methodology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% who correctly identified ABP method and equipment according to current guidelines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- All respondents</td>
<td>38</td>
<td>71</td>
<td>80</td>
<td>100</td>
<td>61</td>
</tr>
<tr>
<td>- Respondents currently undertaking ABP measurement</td>
<td>0</td>
<td>68</td>
<td>80</td>
<td>100</td>
<td>66</td>
</tr>
<tr>
<td>Breakdown of individual assessment practices below</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. % who would test patients prior to ABP measurement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- All respondents</td>
<td>65</td>
<td>93</td>
<td>100</td>
<td>100</td>
<td>92</td>
</tr>
<tr>
<td>- Respondents currently undertaking ABP measurement</td>
<td>0</td>
<td>89</td>
<td>100</td>
<td>100</td>
<td>91</td>
</tr>
<tr>
<td>(reasons for not testing patients: lack of time 76% (4.11), not considered necessary 24% (4.71))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. % who identified correct equipment used for Brachial SBP measurement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- All respondents</td>
<td>89</td>
<td>93</td>
<td>80</td>
<td>100</td>
<td>87</td>
</tr>
<tr>
<td>- Respondents currently undertaking ABP measurement</td>
<td>80</td>
<td>96</td>
<td>100</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td>3. % who said they would measure the brachial SBP in both arms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- All respondents</td>
<td>86</td>
<td>93</td>
<td>100</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>- Respondents currently undertaking ABP measurement</td>
<td>29</td>
<td>93</td>
<td>100</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>4. % who identified correct equipment used for Ankle SBP measurement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- All respondents</td>
<td>88</td>
<td>96</td>
<td>100</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>- Respondents currently undertaking ABP measurement</td>
<td>89</td>
<td>96</td>
<td>100</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>5. % who said they would assess more than one foot/ankle arteries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- All respondents</td>
<td>83</td>
<td>93</td>
<td>100</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>- Respondents currently undertaking ABP measurement</td>
<td>69</td>
<td>93</td>
<td>100</td>
<td>100</td>
<td>91</td>
</tr>
</tbody>
</table>
Table 3 Summary of survey results (Continued)

<table>
<thead>
<tr>
<th>% who said they would calculate ABI by dividing the highest ankle SBF by the highest brachial SBF</th>
</tr>
</thead>
<tbody>
<tr>
<td>All respondents</td>
</tr>
<tr>
<td>Respondents currently undertaking ABI measurements</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% who experience difficulty locating ankle/foot pulses</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% who experience difficulty maintaining position of Doppler probe whilst simultaneously pumping up BP cuff</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
</tr>
</tbody>
</table>

mentioned cardiovascular disease risk factor modification than nurses (56% versus 16%).

Discussion

Results indicate that ABI measurement is very much a nursing task which is, at present, mainly performed for the purpose of wound management rather than for cardiovascular risk assessment. It is only utilised at approximately three quarters of respondents from general practices in Wales and those that do utilise it, do so on an infrequent basis. According to a literature review conducted by Siblangu & Bliss [25], this raises issues of competency as studies have demonstrated greater variability in ABI’s when measured by less experienced practitioners [26,27]. In addition, this survey found that a large proportion of respondents experienced difficulties with the technical aspects of the procedure such as locating ankle pulses and maintaining the position of the Doppler probe, and it is possible that these difficulties were also related to inexperience. A survey by Mohler et al. found that primary care staff reported increased use of the ABI following their participation in a PAD/ABI training programme [28]. However, the survey was completed 1-3 months following programme completion so it is not known if this increase would have been sustained over a longer time period. This survey found that reported use of the ABI was low regardless of whether training had been received or not.

Aboyans and colleagues recently highlighted that a lack of standardised ABI methodology is likely to have significant clinical, public health and economic repercussions [10]. They subsequently released a scientific statement setting out an evidence based, recommended procedure for ABI measurement and interpretation [10]; this concurs with the methodology assessed by this survey. The clinical rationale for standardisation arises from the fact that the majority of studies demonstrating the association between low ABI and CV risk, have used this recommended method and it is not known if this would differ with alternative methods.

This survey has found that deviations from the guideline advocated method of ABI measurement are commonplace and two inter-related factors have emerged as important with regard to this. The first concerns the time it takes to perform the measurement, as the majority of deviations could be attributed to attempts to reduce this. Not resting patients prior to measurement, using automated blood pressure monitors, measuring the brachial pressure in one arm only and assessing only one ankle pulse all equate to a reduction in the time it takes to perform the test. Mohler et al. [28] and Bendenmacher [6] found that lack of time was a barrier to the use of the ABI in primary care. This issue is further compounded by the fact that the procedure sometimes requires two health care personnel. Results indicate that GPs are more likely to resort to these time saving strategies and this is not surprising considering that their allocated time for a complete patient consultation is often only 10 minutes.

The second factor concerns training, with those who had undergone specialist training for the procedure being much more likely to be adhering to the guidelines advocated method. Hence, it appears that training successfully educates practitioners regarding the importance of not “cutting corners” at the expense of the accuracy of results. Mohler et al. found that a targeted educational initiative can have significant impact on the use of the ABI in clinical practice which could offer dramatic benefits to improve PAD diagnosis [28].

Management of PAD patients

The under treatment of PAD patients has been well documented; the global Reach Registry demonstrated that patients with PAD were significantly less likely to be at target blood pressure, cholesterol and glucose levels in comparison to patients with coronary artery disease or cerebrovascular disease [21]. The recent publication of PAD guidelines by various organisations [3,4] and the addition of PAD indicators to the 2012/13 Quality and Outcomes Framework [29] in the UK may have served to increase awareness and improve the treatment of PAD. In addition, general practice computer software
Figure 3 Diagrammatic representation of survey responses.

- 39% (37/95) of responding general practices are utilizing correct method of ABI measurement and/or calculation according to current guidelines.
- 20% (23/116) of responding general practices are utilizing incorrect method of ABI measurement and/or calculation according to current guidelines.
- 27% (24/90) of responding general practices do not undertake ABI measurements, (examples see page 9).
systems in the UK, such as EMIS (Egton Medical Information Systems), now generate pop-up reminders to consider aspirin, check BP and cholesterol when coding a new diagnosis of peripheral arterial disease. It is difficult to establish if data from this survey represent improved medical management of PAD patients. It is clear however, that the large majority of nurses who responded to the survey consider the ABI only in terms of its repercussions for leg ulcer/wound management and are unaware of its association with increased cardiovascular risk.

How this fits in

The global perspective of PAD screening is far from definitive; it is not universally advocated across international guidelines, and there is no consensus regarding who should be targeted. According to the United States Preventive Services Task Force [30] there is insufficient evidence to recommend PAD screening and this is based on a lack of randomised control trials of PAD screening versus no screening. Additionally, whilst some countries now offer remuneration for ABI measurement in Primary Care (e.g. the Netherlands, Australia), this is not the case in the UK or USA.

This survey has identified that a further potential issue of PAD screening relates to ABI measurement as the recommended screening tool. Its underutilisation and often incorrect use within general practice appears to be related to lack of time, but also suggests a current knowledge and skills deficit.

Study strengths and limitations

The response rate was low but not atypical, as published medical practitioners’ response rates are often lower than 30% [31,32]. Mohler et al. utilised a survey to assess the utility and barriers to the use of the ABI in primary care practice. Primary care staff (physician and non-physicians) that had one month previously undergone a PAD and ABI preceptorship programme were either given or mailed the survey. It could be assumed that this participation in an educational programme would have served to raise awareness of the relevance of the survey and yet the response rate was still only 24% [28]. Nevertheless, the possibility of response bias needs to be borne in mind when considering results of this survey. It is possible that those who do not utilise the ABI may have been less likely to complete the survey and hence its use may be over-estimated. Furthermore, the small number of nurse practitioner and district nurse respondents means that results relating to these occupational groups may be less representative of the professions as a whole. These limitations acknowledged, this survey is, to the authors’ knowledge, the only assessment of the utility of the ABI in the UK. Representation from
both nurses and physicians from general practices in all areas of Wales has been achieved.

This study targeted primary care practitioners that were based within general practices as it is here that screening strategies are likely to be undertaken. It is acknowledged that ABI skills and knowledge exist in other sectors of primary care such as district nursing teams and podiatry for example. In addition, the usual validity concerns regarding self-reported behaviour in surveys apply and issues such the accuracy and reproducibility of ABI measurements have not been addressed. Hence these two points provide a focus for future research.

Conclusions

ABI measurement is an under-utilised and often incorrectly performed procedure in the surveyed general practices: lack of time and inadequate training have been identified as factors associated with this finding. Previous research undertaken in the USA [28] and the Netherlands [33] made remarkably similar conclusions hence demonstrating that these identified issues are historically problematic and not confined to Wales and the UK.

Prior to the potential adoption of the ABI as a formalised screening tool for cardiovascular disease, there is a need for a robust training programme with standardised methodology in order to optimise accuracy and consistency of results. ABI Training programmes should include the methodological requirements for accurate and reproducible ABI measurement, as well as the theoretical basis and limitations of the test. The subsequent implications of a reduced ABI with regard to cardiovascular risk also need to be highlighted.

Additional file

Additional file 1: Survey: Use of the Ankle Brachial Index in General Practice.

Abbreviations

ABI: Ankle-brachial index; CAC: Coronary artery disease; CV: Cardiovascular; PAD: Peripheral arterial disease; GP: General practitioners; IMS: Eton Medical Information Systems Limited.

Competing interests

All authors declare that they have no competing interests.

Authors’ contributions

HJD and DWM designed the study. JR assisted in obtaining permission from Health Boards to distribute the questionnaire. HJD distributed questionnaires, coded responses, where necessary and collated results. HJD, JR and DWM interpreted results. HJD and DWM wrote the paper. All authors read and approved the final manuscript.

Authors’ information

This study was undertaken as part of HJD’s PhD which is being undertaken at the University of South Wales. DWM is HJD’s director of studies. JR is Professor of Primary Care at the University of South Wales and is also part of HJD’s supervisory team.

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References


The utility of pulse volume waveforms in the identification of lower limb arterial insufficiency

ABSTRACT
Background: The ankle brachial index is widely used for non-invasive assessment of lower limb arterial status, but has recognised limitations. The most significant limitation involves arterial calcification, which results in artefactually raised occlusion pressures and uninformative ankle brachial indices.

Hypothesis: Analysis of the pulse volume waveform is useful for identification of lower limb arterial insufficiency in the presence of arterial calcification.

Method: Individuals (n = 1101) registered at a Welsh general practice were invited to undergo cardiovascular risk assessment. The ankle brachial index was measured using an automated device utilising volume photoplethysmography and the traditional Doppler ultrasound method.

Results: Eight percent of participants (30/368) had an ankle brachial index >1.3, suggesting possible arterial calcification; consideration of the pulse volume waveform in these cases identified possible mild peripheral arterial disease in three cases (10%). Furthermore, in one case, the ankle brachial indices were within the normal range, but the pulse volume waveforms suggested a moderate degree of arterial insufficiency; this participant was subsequently diagnosed with bilateral superficial femoral artery stenoses and treated accordingly.

Conclusion: Pulse volume waveforms can be easily utilised as an adjunct to ankle brachial index measurement to identify patients who may benefit from further vascular assessment and intervention.

INTRODUCTION
The use of the ankle brachial index (ABI) dates back to the 1950s when Windsor was the first to compare peripheral systolic pressure with central systolic pressure for the purpose of identifying peripheral arterial disease (PAD). More than six decades later, the ABI remains the gold standard for non-invasive assessment of the arterial status of the lower limb. However, ABI has limitations, the most prominent of which relates to the artefactual elevation of arterial occlusion pressures in the lower limb, which can result in inaccurate and uninformative ABIs. This elevation can be attributed to factors such as peripheral oedema, lipodermatosclerosis, associated with venous insufficiency, and circumscribed atherosclerotic lesions. However, the most common aetiology relates to the accumulation of calcium and phosphate in the medial layer of the arterial wall, making compression of the vessel difficult. This phenomenon is known as Mönckeberg’s medial sclerosis or medial artery calcification (MAC). MAC is associated with advancing age and hypertension as well as diabetes mellitus and chronic kidney disease.

Experienced practitioners are usually alerted to the possibility of a falsely elevated or inaccurate ABI when the clinical presentation of the assessed limb does not correspond with the ABI result or when the audible signal emitted from a Doppler ultrasound device during the ABI measurement procedure does not correspond with the ABI result. A Doppler ultrasound signal indicating healthy or normal lower limb arterial flow has three distinct phases. On the other hand, a low pitched, monophasic sound indicates reduced blood flow and usually represents vessel disease. Some Doppler ultrasound devices also provide visualisation of the Doppler ultrasound waveform, which can also be analysed to determine if the waveform is triphasic, biphasic, or monophasic.
Pulse Volume Waveform (PVW) Recording
PVW recording constitutes a further non-invasive, diagnostic procedure that can be utilized to evaluate blood flow in the extremities. PVW corresponds to the phases of the cardiac cycle, with a brisk upstroke and sharp peak that occur during systole, followed by a gradual downslope that occurs in diastole (Figure 1). A reflective wave, or dicrotic notch, represents reflected blood flow.

According to Raines and Almeida, two aspects of the PVW require consideration for its qualitative interpretation: the contour and the amplitude of the waveforms. If, at rest, the reflected wave (dicrotic notch) is absent, this implies that the peripheral resistance distal to the point at which the recording is taken has been reduced. Reduction in peripheral resistance is most often caused by proximal arterial obstruction. Waveform amplitude is a function of local pulse pressure and is reduced with arterial occlusion proximal to the point at which the recording is taken. Therefore, the more reduced the amplitude, the greater the proximal obstruction and the poorer the local perfusion. Interpretation of PVWs can be undertaken by visually comparing them to a four-level grading system (Figure 2).

Until recently, PVW recording was confined to the vascular laboratory; however, the development of portable equipment with PVW recording capabilities has made this diagnostic technique much more amenable for use in other, non-specialist settings, such as primary care.

The aim of this study was to assess the utility of PVW recordings undertaken in a primary care setting by comparing simultaneously recorded ABI and PVW data taken during a cardiovascular screening study.

**METHODS**

As PAD is a marker of systemic atherosclerosis, the primary aim of the PIPETE (Peripheral Arterial Disease in Primary Care: Targeted screening and subsequent management) study was to assess cardiovascular risk by measuring the ABI. This prospective observational study was based in a South Wales (UK) General Practice. We invited 1101 individuals with at least two pre-identified cardiovascular risk factors without known cardiovascular disease or diabetes mellitus to participate. Ethical approval for this study was granted by the South East East Research Ethics Committee (REC No: 12/VA/0075), and all participants (n = 368) provided written consent.

First, while supine, participants underwent ABI measurement using an automated device utilizing volume plethysmography. The device utilizes dual chamber cuffs.
For each limb, an upper chamber occludes arterial blood flow, and the lower chamber utilizes pneumoplethysmography to detect returning pulsations as the pressure in the upper chamber is gradually reduced (Figure 3). This technology is used to measure and calculate ABIs for both legs simultaneously. The device also records a 5-second strip of PVWs for each foot (via the lower detection chamber) that are printed out along with ABI results for analysis. Following a 5-minute rest period, the ABI was measured again, this time utilizing the traditional manual method of Doppler ultrasound** and sphygmomanometry***. The Doppler ultrasound ABI measurement was performed in accordance with the evidence-based procedure recommended by Abeyans et al. All ABI measurements were performed by a qualified nurse with extensive experience in the procedures (JD).

JD subsequently graded the obtained PVW recordings according to Runwell and McPharlin’s grading system (Figure 2). The PVW recordings of all PIPETTE participants were also graded by JL (Clinical Specialist Podiatrist and Therapies, Cardiff and Vale NHS trust), an experienced researcher and practitioner in this field. The review was single-blinded as JL did not have access to participants’ clinical data or knowledge of JD’s gradings. The subsequent gradings were first reviewed to determine agreement between reviewers, and second to identify cases in which the ABI may have been artifically raised and potentially uninformative; namely cases with an ABI ≥1.3 and cases in which the ABI and PVW did not correspond.

RESULTS

The variability between the automatic* and manual** methods of deriving the ABI was 10.1% as defined by the standard deviation of the difference in the results divided by the mean.13 From 736 PVW recordings (n = 368 x 2 legs), 680 were suitable for grading. Fifty-eight recordings could not be graded because of poor quality PVW recordings (n = 28), failed measurements (n = 10), and problems associated with the automated device for various reasons (n = 18). For example, participants who had undergone a previous mastectomy could not undergo bilateral brachial blood pressure measurements. Both reviewers reported the same grading for 99% of the PVW recordings (n = 673). For the 1% (n = 7) of recordings for which the reviewers did not agree, the disagreement always involved one reviewer allocating grade A and the other grade B. Because this difference in grading also equated to disagreement regarding the PAD status of the participants, these cases were excluded from the subsequent results analysis.

An ABI of 1.3 is frequently used as a cut-off point to signify when results may be artefactually high; 8% (n = 30) of the ABIs in the PIPETTE study exceeded this value. Analysis of the corresponding PVW recordings suggested that 10% of these participants (n = 3) had abnormal waveforms, which were all graded B by both reviewers, suggesting the presence of mild PAD. Figure 4 shows an example of a participant with ABIs ≥1.3. However, inspection of the corresponding PVW revealed abnormal waveforms with the absence of the diastolic notch and rounded systolic peaks.

Both reviewers also identified a case in which although both the automatic and manual methods returned ABI results within the normal range (0.91-1.29), inspection of the PVW recordings revealed abnormal waveforms (Figure 5). Based on the abnormal PVWs, this participant was subsequently referred to a vascular surgeon for further investigation.

Figure 4: Example of a printout from an automatic ABI device showing an elevated ABI with an abnormal pulse volume waveform. A: rounded systolic peaks, B: absence of defined diastolic notch.

Figure 5: Example showing a normal ABI but abnormal PVW suggesting that this individual may have peripheral arterial disease and that calcification may have artefactually raised the ABI to within the normal range. The PVW shows flattened systolic peaks, and the upstroke and downstroke times are decreased and nearly equal.
Investigation and was found to have bilateral superficial femoral artery stenoses and subsequently underwent successful angioplasty.

**Discussion**

The 10.1% variability between the ABI measurements in this study matches the inter-observer variability observed between two experts (vascular laboratory technicians) who measured the ABI of 40 participants using Doppler ultrasound (inter-observer variability = 10.1%)\(^1\). According to Nicolai et al.,\(^2\) variability of ≤10-15% is regarded as acceptable for clinical tests.

An ABI ≥1.3 is considered to be artificially high, and MAC is likely to be a contributing factor. MAC is frequently associated with diabetes. Thus, although diabetics were excluded from the PIPETTE study, the percentage of patients with elevated ABIs was surprisingly high at 8%.

When an ABI exceeds the cut-off point of 1.3, this measurement cannot be relied upon to provide an accurate indication of the arterial status of the limb. Suominen et al.\(^3\) found that a large proportion of individuals with high ABIs actually had PAD. They conducted a retrospective clinical study in which 1762 patients, who were referred to a vascular laboratory with suspicion of PAD, had their ABI and toe pressures measured via photoplethysmography. An ABI ≥1.3 was considered abnormal, and a toe brachial index <0.6 was considered diagnostic of PAD. The prevalence of an elevated ABI was 8.4%, and of those, 62% had PAD according to toe pressures and digital subtraction angiography. In comparison, only 10% of PIPETTE participants with an ABI ≥1.3 were likely to have had PAD as indicated by their corresponding PWV recordings. This lower rate can likely be attributed to the differing study populations. Lilly et al.\(^4\) offer an explanation for this by proposing that some individuals have elevated ABIs due to an increased pulse pressure amplitude rather than MAC, which constitutes a benign form of elevated ABI.

Hence, when the ABI is elevated, practitioners must be able to utilise alternative strategies to determine if the arterial status of the limb is compromised. Experienced practitioners are likely able to make this judgement based on the nature of the audible Doppler signal and the clinical presentation of the patient. However, whether less experienced, non-specialist practitioners, such as novice community nurses, would have the knowledge, skills, and confidence to make such a judgement, is less clear. A study by Davies et al.\(^5\) highlighted that practitioners based in general practices in Wales experience issues with several practical and theoretical aspects of the ABI measurement procedure.

The PIPETTE study also highlighted that MAC can sometimes falsely elevate the ABIs of PAD patients to within the accepted normal range (0.9-1.29). Such patients must be identified promptly to ensure timely referral for further investigation and intervention. Subsequent optimisation of the arterial status of the limb will of course have beneficial effects for wound healing. An inexperienced nurse may have used the normal ABI results in the described case as an indication to apply compression and may have then failed to identify that the patient required further investigation. Inspection of the PWV provides a simple method of identifying such patients. Use of the PWV recording is recommended by both the European Society of Cardiology\(^6\) and the American College of Cardiology/American Heart Association\(^7\) as a second-level assessment tool for patients with suspected PAD. Thus, the PWV can be utilised to establish an initial diagnosis of lower extremity PAD.

**Advantages of PWV recordings**

An added advantage of PWV recordings that is particularly pertinent to wound care relates to the fact that these recordings represent the sum of all blood flow through the examined area. Hence, a patient with a significant obstruction to blood flow in one or more arteries, but good collateral blood flow may have a normal waveform. This could be useful in assessing whether a lower extremity wound has sufficient arterial blood supply to facilitate healing. Furthermore, the process of obtaining a PWV does not require operator skill and merely involves the application of a cuff to the foot or ankle; the device then automatically inflates, obtains, and displays the PWV. In contrast, the process of obtaining a Doppler waveform is operator dependent because a Doppler probe must be carefully positioned over an artery at a specific angle and pressure. Results can vary according to the Doppler angle used\(^8\).

**Limitations of PWV recordings**

PWV recording has recognised physiological limitations. First, the PWV depends on peripheral blood flow and thus, may be influenced by factors other than vessel patency such as sympathetic nerve input\(^9\). Second, severe congestive heart failure may also slow blood flow and mimic inflow disease\(^9\). Third, the PWV represents the total blood flow through the area being assessed, and therefore, cannot provide accurate diagnostic information regarding where and to what extent a specific artery is diseased. A further limitation of PWV recordings involves susceptibility to interference from factors such as patient movement, which can result in artefact in the detection signal and subsequent poor quality PWV recordings. This can sometimes be addressed with repeated measurements.
after repositioning the patient and reminding him or her of the importance of remaining still during the procedure.

Study Limitations

Although this study demonstrated that reviewers with considerable experience in interpreting PWV recordings agreed on the identification of apparently abnormal PWV recordings, this may not necessarily apply to practitioners less experienced at the task. Furthermore, the majority of obtained PWV gradings were not verified by comparison with a superior diagnostic modality such as Duplex ultrasound scanning.

CONCLUSIONS

This study highlighted the shortcomings of the ABI as a single diagnostic tool and demonstrated the need for a secondary mode of lower limb arterial assessment that is also easy for non-specialist practitioners to use. PWV recordings may be acceptable for fulfilling this role and may, thus, be particularly useful in the field of wound management.

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Implications for Clinical Practice

This study highlighted that:

- The prevalence of an elevated ABI (≥1.3) is relatively high even in a population in which diabetics were excluded.
- The ABIs of patients with PAD can sometimes be artifically raised to within normal limits.
- In such cases, simple analysis of PWV recordings is a useful adjunct for the identification of patients who require further vascular investigation.

Further Research

Further research should investigate the utility of PWV recordings by examining the associated sensitivity for detecting FAD or specificity for ruling out PAD. Further investigation is also required to determine the ease of use and the cost and training required to achieve reliable results.

References

Feasibility and Value of Screening for Peripheral Arterial Disease in a South Wales General Practice
(preliminary results from the PIPETTE Study)

Introduction
Aim
To determine if a primary care screening programme for Peripheral Arterial Disease (PAD) is feasible and of value in a targeted population of South Wales.

Peripheral arterial disease
Peripheral Arterial Disease (PAD) is a marker of systemic atherosclerosis with several studies demonstrating a graded inverse relationship of Ankle Brachial Index (ABI) to adverse cardiovascular events.

However, most individuals with PAD (ABI ≤0.8) are asymptomatic and the disease is therefore under-diagnosed.

This has resulted in calls for a Primary Care PAD screening strategy to identify those at increased risk and enable the instigation of secondary preventive measures.

Individuals with PAD (ABI ≤0.8) have a 3-8 fold increased rate of cardiovascular mortality compared to those without PAD (ESC, 2011)

Treatment of PAD: Current guidelines recommend the same strategy of cardiovascular risk modification for persons with PAD as for those with coronary artery disease (NICE, 2012; ESC, 2011). They include:

- Smoking cessation
- Diet: weight management and exercise
- Lipid modification and statin therapy
- The prevention of diabetes
- Management of diabetes
- The prevention of hypertension and the treatment of hypertension
- Antihypertensive therapy

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Methods
- Patients with at least two pre-identified cardiovascular risk factors but no known cardiovascular disease or diabetes from a South Wales General Practice were invited to participate.
- Participants underwent:
  - ABI measurement (Fig 2)
  - Physical examination
  - Cardiovascular Risk Assessment (utilising QRISK2 algorithm)

and completed:
- General Practice Physical Activity Questionnaire (GPAQ-DHO)
- Dietary Questionnaire
- SF12
- Edinburgh Claudication Questionnaire

Results
- Nr 230, Response Rate: 39%
- PAD Prevalence: 3.5% (n=1)
- Factors significantly associated with PAD include age, pulse pressure, total number of cardiovascular disease (CVD) risk factors, QRISK2 score and smoking status (Table 1).

Conclusions
- It is possible to screen for PAD in general practice but the low PAD yield suggests that the study population may not be an appropriate target group for a screening strategy.
- A large proportion of identified PAD participants could benefit from the instigation of secondary cardiovascular risk modification strategies as advised by current guidelines.

- PIPETTE recruitment continues (Target n=500) which will allow further analysis of the above results and statistical characterisation of a PAD specific group.