THE IMPACT OF ETHNICITY AND ATRIAL FIBRILLATION ON EPIDEMIOLOGY AND OUTCOMES OF PERIPHERAL ARTERIAL DISEASE

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ABSTRACT

Peripheral arterial disease (PAD) is a pandemic with increasing prevalence worldwide. There is evidence that epidemiology and natural history of PAD differ among different ethnic groups. In addition, there is increasing interest on the coexistence of PAD and atrial fibrillation (AF), which significantly increases the risk of adverse events, mainly mortality and stroke. This thesis aims to investigate the association between ethnicity, AF and PAD and its effect on epidemiology and outcomes.

In Chapter 2 a systematic review and meta-analysis of literature was performed to investigate ethnic differences in prevalence of PAD in the general population and in patients with diabetes. Black ethnicity was associated with significantly higher rates of PAD compared to White ethnicity in general population studies. On the other hand, Asians had significantly lower rates of PAD compared to Whites in general population and in diabetic population studies.

In Chapter 3, a retrospective study of Hospital Episode Statistics (HES) database was performed in order to compare the outcomes of femoral-popliteal bypass operations and femoral angioplasty/stenting procedures among patients of White, Asian and Black ethnicity, for a 10-year period between 01/01/2006 and 31/12/2015. Patients of Black ethnicity were at higher risk of limb loss in 2 years after open or endovascular femoropopliteal interventions. Asians had similar rates of limb loss compared to Whites but had higher 2-year mortality in the endovascular group.

Chapter 4 investigated the impact of AF on a cohort of patients with PAD. A retrospective analysis of primary care data from The Health Improvement Network (THIN) database was performed and a comparison of outcomes was made between patients with PAD and AF (cases) and patients with PAD and no AF (controls). AF was found to be a predictor of mortality, cerebrovascular events and development of heart failure in patients with PAD, but AF was not associated with development of ischaemic heart disease or limb loss.

Chapter 5 was an ancillary analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, investigating the impact of PAD on a cohort of patients with AF. A post-hoc analysis of the clinical trial dataset demonstrated that PAD was associated with higher mortality in patients with AF. In the subgroup of non-anticoagulated patients PAD was a strong predictor of stroke.

DEDICATION

To my family, Evanthia and Margarita, with gratitude for their endless support.

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GLOSSARY OF TERMS

ABC	Atrial fibrillation Better Care
ABPI	Ankle- Brachial Pressure Index
AF	Atrial Fibrillation
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
CAD	Coronary Artery Disease
CHA_2DS_2-VASc	Congestive Heart failure, Hypertension Age> 75 years, DM, Stroke, Vascular disease
CI	Confidence Interval
CRP	C-Reactive Protein
DM	Diabetes Mellitus
eGFR	Estimated Glomerular Filtration Rate
GENOA	Genetic Epidemiology Network of Arteriopathy
HDL	High-Density Lipoprotein
HF	Heart Failure
HR	Hazard Ratio
IHD	Ischaemic Heart Disease
IL-6	Interleukin-6
LDL	Low-Density Lipoprotein
OR	Odds Ratio
PAD	Peripheral Arterial Disease
PAI-1	Plasminogen Activator Inhibitor-1
REACH	Reduction of Atherothrombosis for Continued Health
THIN	The Health Improvement Network
TIA	Transient Ischaemic Attack
UK	United Kingdom
USA	United States of America

VWf	von Willebrand factor

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CHAPTER 1: INTRODUCTION

1.1 Peripheral arterial disease

1.1.1 Introduction

Peripheral arterial disease (PAD) is a term that refers to the partial or complete occlusion of the arteries outside the brain and the heart, including carotid artery disease, upper extremity arterial disease, mesenteric artery disease, renal artery disease and lower extremity artery disease.[1] In this Thesis the term PAD will be used to refer to lower extremity arterial disease. PAD can be a manifestation of generalised atherosclerotic disease and accumulation of atherosclerotic risk factors. It is associated with high morbidity and mortality, functional decline, and disability.[2–4]

1.1.2 Epidemiology of peripheral arterial disease

It is estimated that the global prevalence of the disease has raised by 23.5% between 2000 and 2010 with an estimate of 202 million affected individuals worldwide.[5] Mortality and disability related to PAD have also significantly increased during the last two decades; in Western Europe and North America PAD causes 3.5 deaths per 100,000 population per year.[4] Only 1/4 to 1/3 of patients with PAD have symptoms, thus the majority of cases are undiagnosed.[6,7]

Initial studies on epidemiology of PAD focused on detecting symptomatic disease and mostly vascular claudication. Different questionnaires such as the World Health Organization Questionnaire[8] and the Edinburgh Claudication Questionnaire[9] have been

therefore developed. Using this method to measure the prevalence of symptomatic PAD in the UK, it was estimated to be 2.2% in men and 1% in women aged 45 to 65.[10]

The most commonly used screening tool for PAD is the Ankle-Brachial Pressure Index (ABPI), which is obtained by measuring resting systolic blood pressures in supine position at the brachial, posterior tibial and dorsalis pedis arteries, using a doppler device. The ABPI for one side is the ratio of the highest ankle pressure on the ipsilateral lower limb divided with the highest brachial pressure from the two upper limbs.[11] An ABPI<0.9 is considered an indicator of haemodynamically significant arterial stenosis and can diagnose PAD with 95% sensitivity and almost 100% specificity.[12] Several epidemiological studies have used this method to define the prevalence of PAD with the advantage of detecting both symptomatic and asymptomatic cases. The Edinburgh Artery Study in the UK, examining 1592 participants aged 55 to 74 years, has reported the prevalence of intermittent claudication defined by the WHO questionnaire as 4.5% and the prevalence of asymptomatic PAD defined by low ABPI<0.9 as 16.6%.[6]

1.1.3 Risk factors for peripheral arterial disease

Known risk factors for PAD are advanced age, male gender, smoking, diabetes mellitus, hypertension, dyslipidaemia, chronic renal failure, hypercoagulable states and hyperhomocysteinaemia.[12]

Age

Rates of PAD increase with age; while it is uncommon condition in those younger than 40 years, it affects 3% to 10% of older adults and more than 20% of those older than 70 years. [6,13,14]

Gender

Both symptomatic and asymptomatic PAD has been considered to be more common in men. However, there are studies with contradictory findings, reporting similar PAD rates in men with some of the most recent reports putting the previously assumed male predominance of PAD into question. [12] This has been attributed to the shift in risk factor profile and the age distribution of the population. The population is aging, there are more women in the elderly age groups and the prevalence of PAD in women is increasing disproportionally after menopause, possibly due to the loss of protective effects of oestrogens. In addition, although there has been a significant decline in smoking rates during the last 50 years, this decline has been steeper in the ratio of male smokers compared to female smokers. Lastly, the screening strategies for PAD have evolved during the last decades with widder adaptation of ABPI as a screening tool. There have been recent guidelines suggesting a higher ABPI value, higher than one as cut-off for diagnosis of PAD. This results in more asymptomatic PAD cases being detected and could possibly alter the gender distribution of PAD.[15,16]

Smoking

Active smokers have been reported to have from two up to six-fold risk of developing PAD, compared to non-smokers.[17,18] The occurrence of PAD and intermittent claudication is related to number of cigarettes smoked. Smoking has been related to post-operative failure of lower limb bypass, reduced benefit from antiplatelet treatment and higher risk of amputation. Smoking cessation improves survival and reduces the risk of having a surgical procedure or an amputation in patients with

PAD.[19] One year after discontinuing smoking the risk of developing intermittent claudication is similar to non-smokers.[20]

Diabetes

Diabetes mellitus (DM) affects more than 170 million people worldwide and this number is estimated to double by 2030.[21] Among patients with PAD, 20-30% are diabetic and among patients with diabetes, 20%- 30% have been found to have abnormal ABPI.[22] The incidence of PAD in diabetic patients, the clinical severity of the disease and adverse outcomes such as death and limb loss are related to the duration of diabetes and levels of glycosylated haemoglobin.[23]

Patients with diabetes and PAD tend to present more often with critical ischaemia and gangrene and with more diffuse atherosclerotic disease that can involve multiple arterial territories. It has been well established that diabetics have a pattern of peripheral arterial disease that mostly affects the infrapopliteal vessels contrary to non-diabetic patients.[23]

Hypertension

Various studies have demonstrated association between hypertension and PAD.[24,25] In the Rotterdam Study, using regression models, PAD was related to hypertension used as nominal variable (Odds Ratio (OR)= 1.32), as well as the measured systolic blood pressure used as continuous variable (OR= 1.30 for every 10mmHg increase in SBP).[26]

Dyslipidaemia

In the Framingham Study a raised total cholesterol >240 mg/dl was associated with higher risk of PAD, while HDL had a protective effect (OR= 0.9 per 5mg/dl increase in HDL).[17] It has been suggested that the ratio of total to HDL cholesterol is a stronger predictor of PAD. The effect of hypercholesterolaemia is exacerbated by smoking, while lipid lowering treatment reduces the occurrence of intermittent claudication and the progression of the disease.[12]

Renal Failure

Renal failure and PAD share common risk factors such as diabetes, age and hypertension. There is evidence that there is causal relation between those conditions. In different studies using multivariate models, chronic kidney disease (defined by EGFR< 60ml/min/1.73m$^{2)}$ as well as increased blood creatinine levels have been independent predictors for PAD.[13,27]

1.1.4 Clinical presentation of peripheral arterial disease

Most of the cases of PAD remain asymptomatic, despite the presence of haemodynamically significant arterial lesions and the significant reduction in ABPI. Intermittent claudication in its typical form is pain on the calf muscle and occasionally on the thigh or the buttock, occurring on exertion, which settles at rest within 10 minutes. However many patients experience atypical lower limb symptoms that do not fit with the classical presentation[28,29] The presence of intermittent claudication can be influenced by various factors including the mobility of the patient, perception of pain, adaptation of muscle metabolism to reduced blood supply, development of vascular collaterals, it is not therefore considered a prognostic indicator for development of

more severe disease. In fact, in many cases the initial presentation of PAD is its more advanced form that includes pain of legs at rest, trophic lesions, ulceration or gangrene which is described by the term “critical ischaemia”.[12] The Fontaine and the Rutherford are the most commonly used classification systems for PAD in regard to clinical severity (*Table 1*).[12]

Table 1 Fontaine and Rutherford classifications of peripheral arterial disease.

Fontaine		**Rutherford**		
Stage	**Clinical**	**Grade**	**Category**	**Clinical**
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate-severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischaemic rest pain	II	4	Ischaemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
		III	6	Major tissue loss

1.1.5 Management of peripheral arterial disease

Conservative management

All patients with PAD should be managed with proactive risk factor optimization, which includes smoking cessation, control of diabetes hyperlipidaemia and hypertension.[12] Standard medical therapy is the combination of one antiplatelet with statin, which

offers primary prevention of myocardial infraction, stroke and cardiovascular mortality.[30–33] Various studies have demonstrated the benefits of a supervised exercise program in patients with intermittent claudication, which can achieve improvement of walking distance, functional performance and quality of life comparable to invasive treatment.[34,35]

Surgical Revascularization

Aim of invasive treatment in claudicants is mainly to control symptoms and improve functionality and quality of life, rather than saving the leg, taking into account the relatively small risk of claudication progressing into critical ischaemia.[11]

On the other hand, patients presenting with critical ischaemia are at increased risk of limb loss and an intervention is required in most occasions. That depends on the general condition, comorbidities of the patients, anticipated risk and success rate of the intervention.

The revascularization options include endovascular techniques (balloon angioplasty, stent deployment and atherosclerotic plaque debulking), open surgical procedures (mainly endarterectomy and bypass) or combination of the two (hybrid procedures). Selection of appropriate method aims to secure adequate inflow and outflow for the treated arterial segment. It depends on anatomical location of the disease (aortoiliac, femoropopliteal, infrapopliteal), morphology, length, type of the lesion (stenosis or occlusion). The femoropopliteal segment is the most commonly affected location in patients with PAD, it is therefore the target for the majority of revascularization procedures.[11,12] The BASIL trial has suggested that an open surgical or endovascular

approach for critical ischaemia in patients with infrainguinal disease have similar results in regard to amputation free survival and overall survival.[36,37]

Amputation

An amputation above the level of the ankle is considered major amputation. The indication is life threatening infection, non-salvageable leg due to extensive tissue loss, arterial disease not amenable to any revascularization, uncontrolled ischaemic rest pain.[12]

1.1.6 Outcomes of peripheral arterial disease

PAD is an independent predictor of coronary artery disease (CAD), cerebrovascular disease, cardiovascular mortality and overall morality, even after adjustment for traditional risk factors.[38] In a meta-analysis of cohort studies, the hazard ratios (HR) for overall mortality, cardiovascular mortality and major coronary events in 10 years at presence of a low ABPI<0.9 are 2.34 (95%CI 1.97- 2.78), 2.92 (95%CI 2.31- 3.70) and 2.16 (95%CI 1.76- 2.66) respectively in men, and 2.35 (95%CI 1.76- 3.13), 2.97 (95%CI 2.02- 4.35) and 2.49 (95%CI 1.84- 3.36) respectively in women.[39] Additionally, low ABPI doubles the 5 year risk of stroke and fatal stroke[40] and is associated with increased carotid and coronary artery atherosclerosis defined by sonographic measurements and coronary calcium scoring respectively.[41,42] PAD has been associated with worse prognosis after a stroke and increased risk of recurrent cerebrovascular events.[43] Studies show association between PAD and several other conditions such as heart failure,[44] atrial fibrillation,[45,46] chronic kidney disease and aortic aneurysm.[45]

The pathophysiologic mechanisms that generate these associations have not been completely described. PAD may be a manifestation of generalised atherosclerotic disease and accumulation of shared risk factors or it may itself causally precipitate those adverse outcomes.[38]

For patients with asymptomatic PAD or intermittent claudication the 5-year mortality and amputation rates are 10-15% and 1.0-3.3% respectively in different studies. On the other hand, prognosis for patient with critical ischaemia is a lot worse with 1-year mortality and amputation rates of 25% and 30% respectively.[12]

1.2 Ethnic differences in peripheral arterial disease

1.2.1 Introduction

Current knowledge of epidemiology and natural history of PAD is based on research of mainly Caucasian populations. However, ethnic minorities account for 14% of the population of England and Wales with a trend to rise. South Asians and Blacks/ Afro-Caribbeans are the main minority groups in these countries, accounting for 7.5% and 3.3% of population respectively.[47]

Definition of ethnicity is complex and multidimensional. It is based on shared cultural traditions, ancestry, language, history, diet, religion, or physical appearance. Ethnicity should be therefore self- defined and every effort to categorise individuals or groups of people according to ancestry or external characteristics alone has several limitations.[48] However such simplistic definitions of ethnicity are commonly used in medical literature in the absence of more detailed data.

1.2.2 Ethnic differences in atherosclerotic risk factors

Several studies suggest that atherosclerotic risk factor profile varies between different ethnic populations. In the UK there are more smokers among Whites/ Europeans, followed by Afro-Caribbeans and South Asians.[49,50] The same applies in North American general population studies[25,51] and the difference is more pronounced in women.[49,52] However in a study investigating patients undergoing surgical revascularization, Black patients were more likely to be active smokers compared to Whites.[53]

South Asians living in Canada have higher prevalence of diabetes, higher values of total cholesterol, LDL cholesterol and triglycerides and lower HDL cholesterol compared to White- Europeans. South Asians also demonstrate worse glucose tolerance even among non-diabetic subjects.[51] Studies from UK reach similar conclusions, reporting an unfavourable lipid profile[49,52,54] and a three to five times higher prevalence of diabetes in South Asians compared to Whites.[49,52] The same applies to non-immigrant South Asian population based in India.[55] On the other hand mean blood pressure and rates of hypertension in South Asians are similar to those in Europeans.[56,57] Despite South Asians being often treated as one homogenous group, different sub-populations present with different characteristics. For example a study comparing Indian, Pakistani and Bangladeshi immigrants in UK, reports significantly more smokers and more unfavourable lipid profile among Bangladeshis.[52]

Black ethnicity is associated with high rates of hypertension and higher values of mean systolic and diastolic blood pressure, in general population studies from the USA[25,58] and the UK[56]. In addition, blacks tend to develop hypertension at younger age and have different response to antihypertensive treatment.[59] Prevalence of diabetes in Blacks appears to be considerably higher when compared to Europeans but lower compared to South Asians.[25,49,60] Blacks appear to have better lipid profile than the other two ethnic groups with lower total cholesterol and triglycerides and higher HDL cholesterol.[49]

The results of the international “Reduction of Atherothrombosis for Continued Health” (REACH) study on subjects at high risk or established atherosclerotic disease are in

accordance with general population studies: prevalence of diabetes in South Asians, Blacks and Whites was 57.9%, 55.0%, and 38.8% respectively while corresponding prevalence of hypertension in these groups was 83.7%, 93.0% and 79.1%. Blacks were more likely to have poorly controlled blood pressure, whereas they had the lowest rate of hyperlipidaemia (51.4%).[61]

1.2.3 Ethnic differences in biomarkers of atherosclerotic disease

Several biomarkers have been suggested to play a role in prevalence, severity and progression of PAD as well as functional decline, limb loss, adverse cardiovascular and cerebrovascular events and mortality.[62,63] Different studies have therefore attempted to assess the use of biomarkers as tools for screening for PAD, for risk stratification or even targeting medical treatment. Although this research has shed more light in the complex underlying pathophysiology of PAD, to date no biomarker or set of biomarkers specific for PAD have been identified.[64,65]

A few studies suggest that prevalence of atherosclerotic biomarkers varies between ethnic groups. A general population study has reported higher blood concentrations of lipoprotein (a), fibrinogen, homocysteine and plasminogen activator inhibitor-1 (PAI-1) in South Asians compared to whites.[51] Moreover, African Americans in two general population studies have higher concentrations of lipoprotein (a), fibrinogen, homocysteine, interleukin-6 (IL-6), C-reactive protein (CRP), D-dimers, factor VIII, plasmin- antiplasmin complex and von Willebrand factor (vWF). Even though most of those markers (with the exception of factor VIII) were significantly associated with PAD, they could not completely explain the higher rates of PAD in this ethnic group with multiple regression models.[24,66] A large study from the USA who investigated the

role of three factors of inflammation (CRP, fibrinogen and leukocyte count) has shown that all these factors could independently predict PAD and in addition, the relation between high CRP levels and prevalence of PAD was stronger in the Black ethnic group. Authors suggested that there may be a threshold effect of inflammation and that higher proportion of Blacks have been found to have threshold levels of inflamation.[67] A UK study comparing South Asians and Afro-Caribbeans, reports higher concentrations of P-selectin and lower concentrations of D-dimers in South Asians. The concentrations of CRP, vWF and IL-6 were not significantly different.[68]

1.2.4 Ethnic differences in epidemiology and distribution of atherosclerotic arterial disease

Prevalence of PAD varies between different ethnic groups. General population studies from the USA consistently demonstrate more than two times higher prevalence of PAD in Blacks compared to Whites. Black ethnicity is an independent predictor of PAD and retains significance even after adjustment for major atherosclerotic risk factors such as hypertension and diabetes.[25,69] The impact of South Asian ethnicity has been investigated mainly on cross-sectional studies on diabetic outpatients; South Asian diabetics have 50% lower prevalence of PAD compared to Europeans.[70] However, a general population screening study in UK did not find any significant difference between South Asian and Afro-Caribbean participants. The sample size of this study was relatively small with wide confidence intervals.[60]

There is evidence that distribution of PAD also varies, with South Asians and Blacks showing a predisposition to more distal patterns of the disease such as infrainguinal or

infragenicular rather than aorto-iliac, which is not completely explained by the higher rates of diabetes and other risk factors. Additionally, South Asians tend to suffer far more frequently from thromboangiitis obliterans compared to other ethnic groups.[71,72]

Distribution of atherosclerotic disease is different among ethnic groups. South Asians have higher rates of coronary artery disease with lower rates of cerebrovascular disease and PAD.[8,13] A sonographic study reports less extent of carotid atherosclerosis in South Asians which is combined with paradoxically higher rates of cardiovascular disease.[51] Similarly Chaturvedi et al, by defining coronary artery calcification score on multislice computer tomography, have shown that Indian men in the UK have less extent of PAD for a given extent of coronary artery disease, compared to white Europeans[73]. In a meta-analysis of cross-sectional studies reporting the prevalence of PAD among patients with coronary artery disease, South Asian patients were found to have 50% lower prevalence of PAD compared to White patients.[70]

Blacks present with higher rates of cerebrovascular disease and PAD[61,71] and they have been found to have a higher burden of carotid atherosclerosis compared to South Asians in sonographic studies.[74]

1.2.5 Ethnic differences in outcomes of atherosclerotic disease

In the REACH study, among selected patients with atherosclerotic disease, the risk of overall mortality, cardiovascular mortality and stroke after 2 years follow up was higher in Blacks followed by Whites and South Asians. This was despite the higher prevalence of ischaemic heart disease in South Asians and medical treatment being similar in all ethnic groups.

There is limited data that South Asians in UK are submitted to less revascularizations and have 50% lower risk of major amputation[75]. Similarly, South Asians diabetics have less amputations than Europeans.[76,77] However these studies do not take into account the lowest prevalence of PAD in South Asians and should be used with caution when assessing the outcomes of PAD in this ethnic group.

In order to further assess the existing evidence on ethic differences in outcomes of revascularization procedures, a review of literature was conducted. The Medline database was enquired for studies comparing White, Black and Asian ethnic groups. Nine studies were identified, 8 from North America and 1 from UK. All studies were retrospective; two studies compare peripheral endovascular procedures, 6 open bypass operations and one both. All studies include a comparison between Black and White ethnicity but only one study investigates Asian ethnicity. Black patients presented with higher risk of early graft failure after infrainguinal bypass procedure in 5 studies and with lower limb salvage rates after an infrainguinal bypass procedure (3 studies) or a peripheral endovascular procedure (2 studies). On the other hand, two studies did not demonstrate any difference in limb salvage rates. A summary of the studies and main findings is included in *Table 2*.

Studies from the USA suggest that Blacks present with more severe PAD, they are more likely to have critical ischaemia, gangrene or sepsis at presentation and require revascularization operations at younger age.[78–80] In addition, several studies conclude that Black patients treated with lower limb bypass operations for PAD have higher rates of 30-day graft failure,[53,81–83] 5-year graft failure,[82] 30-day limb loss,[84] 1-year limb

loss,[83] and 5 year limb loss.[82] However, one study from the UK, including 125 patients submitted to distal bypass procedures, does not identify any significant difference in 1-year patency or 1-year amputation free survival between Blacks and Whites.[85] In a study of 834 men who underwent open or endovascular revascularisation, black ethnicity was associated with longer hospitalisation post revascularisation and lower limb salvage rates despite similar patency rates. The authors attribute the discrepancy in more severe disease and higher number of infragenicular procedures in Blacks.[79] On the other hand, a retrospective study in California hospitals involving 25,635 endovascular procedures concludes that Blacks suffered more amputations in 30 days (OR= 1.99, 95%CI 1.56- 2.55) and in 1 year (OR= 1.85, 95%CI 1.54- 2.12) post procedure and more reinterventions in one year (OR= 1.17, 95%CI 1.06- 1.30) compared to whites; these relations remain significant even after adjustment for demographic characteristics, comorbidities, atherosclerotic risk factors and severity of PAD. This study did not take into account anatomical data and does not report rates of tibial vessel disease in each ethnic group.[80] More studies with more detailed anatomical information, comparing similar revascularization interventions are required in order to conclude whether comorbidities, disease stage and anatomical distribution of PAD justify the worse outcomes observed in Blacks.

Table 2. Studies comparing revascularization outcomes in different ethnic groups.

Author	Year	Study type	Data source	Years studied	Population	Intervention	Mortality	Limb outcomes
Singh[81]	2008	Retro-spective	National Surgical Quality Improvement Program database (USA)	1995-2003	W: 10602 B: 2578	All infrainguinal bypass		30-day graft failure: W= 4.5%, B= 6.7% OR= 1.40; 95% CI 1.30- 1.50, p<0.01
Robinson[82]	2009	Retro-spective	Single centre database	1985-2007	W: 1408 B: 181	Infrainguinal bypass with autologous vein	30-day W= 2.3%, B= 2.8% (p= 0.47) 5-year survival W= 61%, B=58%	30-day graft failure: W= 5%, B= 11% 5-year primary patency: W= 69%, B= 58% (p<0.01) 5-year limb salvage: W= 91%, B= 84% (p<0.01)
Nguyen[83]	2009	Retro-spective	PREVENT III multicentre trial dataset including patients with critical ischaemia. (North America)		B: 249 O: 1155	Infrainguinal bypass with autologous vein	30-day Overall 2.7% no significant difference 1-year Overall 16% no significant difference	30-day graft failure: Higher in Black men (OR=2.99; 95% CI 1.74- 6.07, P<0.01) 1-year primary patency: no difference 1-year amputation Overall 16%, Higher in Blacks (HR= 2.00; 95% CI 1.20- 3.33, P<0.01)*
Tiwari[85]	2011	Retro-spective	Single centre database (Kings College Hospital, London)	2004-2009	W: 86 B: 39	distal bypass for critical leg ischemia	30-day W= 2.3%, B= 2.6%	1-year primary patency W= 44.6%, B= 51.3%, p=0.46 No difference in primary-assisted, secondary patency and amputation-free survival

Chong[86]	2011	Retro-spective	Single centre medical records (California)	1994-2007	280 patients 374 procedures W: 60% B: 12% A: 5%	endovascular interventions on femoral and popliteal arteries		Primary failure (Mean FU 3.6 years) Overall: no difference, p=0.12 Stenting procedures: no difference, p=0.48 Angioplasty procedures: W= 60%, B= 39%, A= 29% p<0.01
Selvarajah[53]	2014	Retro-spective	National Surgical Quality Improvement Program database (USA)	2005-2011	W: 12536 B: 2940	All infrainguinal bypass	30-day W= 2.3%, B= 2.9% (p=0.12)	30-day graft failure: W= 15.4%, B= 16.6% OR= 1.26; 95% CI 1.05- 1.51, p= 0.01*
Loja[80]	2015	Retro-spective	Patient Discharge Data from California's Office of Statewide Health Planning and Development	2005-2009	W: 17433 B: 1163	All peripheral endovascular interventions	1-year W= 9.8%, B= 12.5%	30-day major amputation W= 1.7%, B= 6.2% OR= 1.99; 95% CI 1.56- 2.55; p < 0.01* 1-year major amputation W= 4.1%, B=13.8% OR= 1.85; 95% CI 1.54- 2.12, p < 0.01* 1-year reintervention W= 32.9%, B= 36.6% OR= 1.17; 95% CI 1.06- 1.30, p< 0.01*
Rivero[79]	2016	Retro-spective	Single centre database (New York)	2003-2012	W: 925 B: 137 (all male)	Any revascu-larization (open,	30-day open W=1.9%, B= 4.8% (p=0.42)	5-year limb salvage Open: No difference (p= 0.20)

						endovascular, hybrid)	30-day endovascular W= 1.4%, B=0% (p=0.28)	Endovascular: W= 84% B= 69% (p= 0.03) Hybrid: No difference (p= 0.25) No difference in primary patency rates
Yang[84]	2019	Retro-spective	National Surgical Quality Improvement Program database (USA)	2013	W: 1732 B: 288	All infrainguinal bypass	30-day W= 2%, B= 2% (p=0.9)	30-day limb loss: W= 3%, B= 8% OR= 2.8; 95% CI 1.76- 4.56, p < 0.01*

W= White, B= Black, A= Asian, O= Other, FU= Follow-Up, OR= Odds Ratio, CI= Confidence Interval *= multivariate adjustment

1.3 Atrial Fibrillation and peripheral arterial disease

1.3.1 Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia which is characterized by the absence of regular, uniform atrial contractions and irregularly irregular ventricular rhythm. Its burden for healthcare systems is rising and is associated with increased morbidity, mortality and disability and reduced quality of life.[87]

1.3.2 Epidemiology of atrial fibrillation

It was estimated that in 2010, AF affected 8.8 million people in the European Union,[88] and 6.1 million in USA.[87] Those numbers have doubled during the last decade[89] and are expected to more than double during the next decades.[90] Current prevalence in adult population is 2% with an incidence of 28 new cases per 1000 persons per year.[91] Prevalence increases with age and ranges from 0.12%- 0.16% in those younger than 49 years to 3.7%- 4.2% in those between 60-70 years, and 10%–17% in those older than 80. Men have a 20% higher risk of having AF. Epidemiology of AF appears to present ethnic variations with lower rates in Asians, Hispanics, and Blacks, with corresponding adjusted OR 0.68, 0.58 and 0.49 respectively using Whites as reference.[92] Significant proportion of patients with AF is asymptomatic, hence real prevalence of the condition is expected to be higher than the one estimated.[89]

1.3.3 Risk factors for atrial fibrillation

Several established cardiovascular risk factors such as DM, hypertension cigarette smoking and obesity have been associated with higher rates of AF.[93] Huxley et al in their general population study on 14.598 middle-aged individuals, have demonstrated

that 57% of new AF cases can be attributed to those risk factors with hypertension being the most important. That led the authors to the conclusion that most of AF cases could be prevented with appropriate risk factor modification.[94]

Other well-known risk factors for AF include cardiac pathologies, like heart failure, valvular heart disease and ischaemic heart disease. Several echocardiographic findings like atrial dilatation, hypertrophy of the ventricles diastolic and systolic dysfunction have also been associated with AF.[93]

More recently described risk factors for AF are metabolic syndrome, obstructive sleep apnoea[93] and several plasma circulating biomarkers such as natriuretic peptide[95] and C-reactive protein (CRP)[96].

1.3.4 Complications of atrial fibrillation

A study on administrative data in USA reported among patients with newly diagnosed AF, a mortality of 10.8% in 30 days, 24.7% in 1 year and 42% in 3 years.[91] A Swedish study reports 5 and 10-year mortality rates 40% and 60% respectively.[97] AF has been estimated to increase risk of death by 1.5 times in men and 1.9 in women.[98] It is estimated that AF is associated with a fivefold risk of stroke compared to normal individuals and that 23.5% of strokes in older patients (>80 years) are related to AF.[89,99] Risk of ischemic stroke in AF patients on anticoagulation, has decreased from 4.8% per year in 1992 to 2% in 2002. However, the rates of hemorrhagic stroke have not significantly changed (0.16%-0.29%)[100]. Patients with AF are also at three times higher risk of heart failure, double risk of dementia and cognitive disorders, significantly

increased risk of extracranial thromboembolic events, myocardial infraction, chronic kidney disease, overall poor health and hospitalisations.[87]

1.3.5 Atrial fibrillation and peripheral arterial disease

AF and PAD share several common risk factors such as hypertension, DM and coronary artery disease.[87] PAD predisposes to AF. In the REACH registry patients with PAD had prevalence of AF of 11.5% compared to 6.2% in those with high risk for atherosclerosis but without established disease.[101] In the Multi-Ethnic Study of Atherosclerosis, among patients without previous significant cardiovascular history, subjects with PAD expressed by a low ABPI (ABPI<1.0), were at higher risk of developing incidental AF after a median follow up of 8.5 years (HR= 2.3, 95%CI 1.8- 3.0) in unadjusted model.[46] In a study of 81,892 postmenopausal women without baseline AF, followed up for 10 years, previously diagnosed PAD was independently associated with incident AF (HR= 1.53, 95%CI 1.37- 1.72).[102] A UK study on administrative data confirms the same relation.[45]

Atherosclerotic vascular disease can predict adverse events such as stroke, thromboembolism and death in subjects with AF.[103] It has therefore been included as one of the components of the CHA_2DS_2-VASc score (Congestive Heart failure, Hypertension Age>75 years, DM, Stroke, Vascular disease) in order to stratify risk in AF patients.[104] In a Taiwanese cohort of AF patients with median follow up of 4.5 years, PAD was significantly associated with ischemic stroke (OR=1.81, 95%CI 1.19- 2.77).[105] In a Spanish cohort with 2.4 years follow up, low ABPI was associated with all-cause

mortality (HR= 2.76, 95%CI 1.08- 7.06) and major bleeding events (HR=2.47, 95%CI 1.01-6.04).[106]

Inversely AF can predict worse prognosis of patient with PAD. In the REACH registry, in a cohort of 3,655 patients with baseline PAD, coexisting AF was associated with higher risk of cardiovascular death, cardiovascular and cerebrovascular events and amputations.[107] Similarly in a single centre study in UK, among patients admitted with PAD, coexisting AF would predict higher in hospital mortality.[108]

1.4 Hypothesis to be tested.

This thesis is going to test the following hypothesis:

1. Prevalence of PAD is lower in Asians and higher in Blacks.
2. Patients of Black ethnicity in England have higher rates of limb loss and re-interventions after revascularization procedures, similarly to what is observed in studies from North America.
3. AF causes increased rates of death, stroke, IHD and limb loss in patients with PAD.
4. PAD causes increased rates of death or stroke in patients with AF.

1.5 Statistical analysis

The author has received training in medical statistics and use of SPSS software in University of Birmingham as a taught element of this Degree. All statistical analysis has been performed by the author and has been overseen by his supervisors with the exception of propensity score matching used in Chapter 4. This was performed by Dr Rasiah Thayakaran in Institute of Applied Health Research in the presence of the author.

Descriptive statistics throughout the Thesis and cox-regression analysis used in chapters 4 and 5 were processed with IBM SPSS Statistics, Version 23. Meta-analysis of studies in chapter 2 was performed using Comprehensive Meta-Analysis (CMA), Biostat, Inc.

CHAPTER 2: ETHNIC DIFFERENCES IN THE PREVALENCE OF PERIPHERAL ARTERIAL DISEASE. A COMPREHENSIVE REVIEW OF LITERATURE AND META-ANALYSIS.

2.1 Abstract

Background: Previous studies have demonstrated higher rates of PAD in blacks and lower in Asians compared to whites. The aim of this study is to undertake a comprehensive review of literature and identify ethnic differences in the epidemiology of PAD in general and in diabetic population.

Methods and Results: A systematic review and meta-analysis of literature was performed for studies reporting PAD prevalence in general or diabetic populations, as well as studies that compare PAD prevalence in different ethnic groups. Mean prevalence for each ethnic group was calculated and p values and odds ratios were used to demonstrate significant differences between ethnic groups. Mean prevalence of PAD in general population for Whites, Blacks and Asians was 3.5%, 6.7% and 3.7% respectively. Meta-analysis of comparative studies demonstrated significantly higher prevalence of PAD in Blacks (OR=1.97, 95% CI 1.92 to 2.02; p<0.001) and significantly lower prevalence amongst Asians (OR=0.66, 95% CI 0.63 to 0.70; p<0.001), when compared to white ethnicity as reference. In the diabetic population, the mean prevalence of PAD for Whites, Blacks, East Asians and South Asians is 17%, 25.3%, 13.5% and 7.6% respectively. In comparative studies of diabetic population, South

Asians had a significantly lower prevalence of PAD (OR=0.32, 95% CI 0.28 to 0.37; p<0.001) compared to whites but there was no significant difference between blacks and whites (OR=0.87, 95% CI 0.72 to 1.06; p=0.173). Overall females have higher rates of PAD, both in general (3.8% vs 3.2%; p<0.001) and in diabetic population (13.7% vs 10%; p<0.001).

Conclusion: Blacks appear more prone to PAD, in contrast to Asians who seem to have lower prevalence of PAD when compared to whites. Further research is needed in order to identify the factors that generate this difference.

2.2 Introduction

Current knowledge of epidemiology and natural history of PAD is based mainly on research of populations of white ethnicity.[71] This is despite clear evidence of some ethnic differences in cardiovascular disease and associated risk factors, such as, coronary artery disease, diabetes and hypertension.[56] Given more studies exploring ethnic differences in PAD, we performed a systematic review and meta-analysis to undertake a comprehensive review of the literature and identify ethnic differences in the epidemiology of PAD.

2.3 Methods

This review was registered to International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42016041390), and PRISMA guidance was followed throughout all steps[109]. A search of MEDLINE and EMBASE databases has been performed for papers on PAD prevalence and ethnic variations, published between 1/1/1980 and 1/6/2016, with an abstract in English. Search terms included the words "vascular disease", "peripheral arterial disease", "arterial disease", "PAD", "prevalence", "ethnic", "ethnicity", "race" in different combinations. In addition, a review of reference lists for relevant studies was undertaken.

Studies have been assessed according to previous guidance for quality assessment of epidemiological studies.[110] Participant selection process and study samples have been assessed for representability in relation to the population they originate from. Studies investigating inpatients or outpatients, selected populations with specific comorbidities or risk factors (smoking, hypertension, known cardiovascular or cerebrovascular

disease, renal disease) and populations at extremes of age (mean age >80) or with a sample of less than 100 subjects have not been included. Study methodology has been assessed in regard to the method used to define PAD. Only studies using an objective consistent method of defining PAD were included. Publications retrieving their data from the same cohort and sub-studies have been identified and excluded as duplicates. Initially studies reporting prevalence of PAD in general population have been retrieved and summarised in Table 3. In addition, studies that compare PAD prevalence between different ethnic groups in their cohorts were identified (Table 4) and used for meta-analysis. Odds ratios for black and Asian ethnicity using white ethnicity as reference were calculated.

The second analysis included publications reporting PAD prevalence in diabetic patients which are presented in Table 5. In addition, studies that compare PAD prevalence among diabetic patients of different ethnicity (Table 6) were meta-analysed and odds ratios have been calculated using white diabetic patients as reference.

Meta-analysis has several advantages over narrative reviews. It imposes a systematic review of literature with well specified criteria for study inclusion avoiding subjective judgement of the included studies. In addition, meta-analysis allows quantitative synthesis of data of different studies, it facilitates reaching a conclusion when studies report contradicting results and it provides more precise effect estimates. On the other hand, meta-analysis has several limitations. It is prone to publication bias since studies may be published selectively, favouring studies that demonstrate significant results. Moreover, included studies may have considerable variability in terms of design, data

collection, definitions of exposures and outcomes and confounding factors. Statistical heterogeneity between studies is a common problem with meta-analysis. [111,112]

Studies were categorised in relation to the main ethnic group of their population according to their country of origin, unless otherwise stated in the publication. Populations from European, African and South American countries were classified as Whites, Blacks and Hispanics respectively. All studies from United States that were included, provide specific data on their ethnic distribution. Populations originating from India, Pakistan and Bangladesh were categorised as South Asian, while those originating from China, Taiwan, Singapore, Korea, and Japan were categorised as East Asian, in accordance with the trend in medical literature.

Chi-square test was used to detect significant differences in PAD prevalence among different groups, expressed with p values lower than 0.05. Heterogenicity for each meta-analysis was assessed by calculating Q, I square and Tau square values. Descriptive statistics were calculated with IBM SPSS statistics version 23, odds ratios and forest plots were processed with Comprehensive Meta-Analysis (CMA), Biostat, Inc.

Table 3. Studies reporting prevalence of PAD in general population.

	Author	Year Published	Country	Sample origin	Sample size Male/ Female	Mean age (years)	Female %	PAD definition	Pad Prevalence % Male/ Female
1	Grøndal N[113]	2015	Denmark	Male population of Central Denmark Region 65-74 years	18749	70	0	ABPI <0.9 ABPI >1.4	10.9
2	Argyriou C[7]	2013	Greece	Population of region of Thessaly 50- 79 years	436	71	28.4	ABPI <0.9 or >1.4	13
3	Alzamora MT[114]	2013	Spain	Randomly selected people ascribed to 29 participating primary care centres >49 years	3307 M: 1444 F: 1863	64.2 ± 8.7	56.3	ABPI <0.9	5.8 M: 7.3 F: 4.7
4	Félix-Redondo FJ[115]	2012	Spain	Random sample from healthcare database 25- 79 years	2833 M: 1317 F: 1516	51.2	53.5	ABPI <0.9 or Known PAD	3.7 M: 5.0 F: 2.6
5	Makowsky M[116]	2011	Canada	General population of Edmonton, Alberta >50 years	361	65.1 ± 9.5	55	ABPI <0.9, OR Exercise ABPI<0.90, OR TBI< 0.70	4.4
6	Kröger K[117]	2006	Germany	General population of an urban area 45- 75 years	4735 M: 2357 F: 2378	_	50.2	ABPI <0.90	5.76 M: 6.4 F: 5.1
7	Signorelli S[118]	2010	Italy	People listed in participating GPs 30 – 80 years	3412 M: 1364 F: 2048	54.4 ± 12.6	60	ABPI <0.9	2.3 M: 3.8 F: 1.4
8	Ramos R[119]	2009	Spain	General population of city of Girona 35- 79 years	6172 M: 2903 F: 3269	M: 56.6 ± 12.3 F: 55.9 ± 12.3	53	ABPI <0.9 (> 1.39 excluded)	4.5 M: 5.2 F: 3.9

9	Blanes JI[120]	2009	Spain	General population of 12 regions 55- 84 years	846	67.2 ± 7.5	55.9	ABPI <0.9	8
10	Sigvant B[121]	2007	Sweden	Nationwide general population 60- 90 years	5080 M: 2301 F: 2779	71 (IQR 13)	55	ABPI < 0.9	18 M: 16.5 F: 19.2
11	Carbayo JA[122]	2007	Spain	General population of province of Albacete >40 years	784 M: 350 F: 434	60.0 ± 11.6	55.4	ABPI <0.9 (>1.4 excluded)	10.5 M: 11.4 F: 9.7
12	Eldrup N[123]	2006	Denmark	General population of Copenhagen >20 years	4159	58 ± 16	59	ABPI <0.9	2.84
13	Fowler B[124]	2002	Austalia	Men >65 years in the area of Perth	4470	_	0	ABPI < 0.9	16.6
14	Murabito JM[17]	2002	USA	General population >40 years	3313 M: 1554 F: 1759	59	53.1	ABPI <0.90 (>1.5 excluded)	3.6 M: 3.9 F: 3.3
15	Meijer WT[125]	2000	Netherlands	General population study >55 years	6450 M: 2589 F:3861	M 68.3± 8.4 F 70.3± 9.7	59.8	ABPI <0.9	19 M: 16.9 F: 20.5
16	Hooi JD[126]	1998	Netherlands	General population of province of Limburg 40- 78 years	3650	59	53	ABPI <0.95	12.5
17	Binaghi F[127]	1994	Italy	Population of a town >20 years	577 M:237 F: 340	_	_	Questionnaire/ US doppler	4.7 M: 8.4 F: 2
18	Fowkes FG[6]	1991	UK	Population of Edinburgh 55- 74 years	1592	_	_	ABPI<0.7 OR hyperaemic drop>35% OR ABPI <0.9 AND hyperaemic drop >20%	8

19	Guerchet M[128]	2012	Congo & Central Africa	General population study in 2 cities >65 years	976 M: 389 F: 587	73.6 ± 6.5	60.1	ABPI <0.90	24.2 M: 20.6 F: 26.6
20	Fowkes FG[129]	2006	South Africa	General population of a rural area >35 years	322 M: 70 F: 252	58.5± 13.7 53.5± 13.9	78.3	ABPI <0.9	16.2
21	Cho WP[130]	2015	Korea	Male members of a Senior Citizens Association >65 years	1609	72.14 ± 5.15	0	ABPI <0.9	4.9
22	Liang Y[131]	2014	China	General po pulation of a community >60 years	1499 M: 615 F: 884	68.5 ± 4.9	59	ABPI <0.9	5.7 M: 5.2 F: 6
23	Zhan Y[26]	2012	China	Population of Beijing >60 years Without history of stroke or CAD	2267 M: 872 F: 1395	67.9 ± 6.0	61.5	ABPI <0.90	5.7 M: 4.2 F: 6.5
24	Lee YH[132]	2011	Korea	General population of 5 different towns > 50 years	2517	65.9 ± 7.9	0	ABPI <0.9 (>1.5 excluded)	4.1
25	Ohnishi H[133]	2010	Japan	General population of two different communities 40- 93 years	2402 M: 900 F: 1502	64.9 ± 10.9	62.5	ABPI <0.9	1.7 M: 1.9 F: 1.7
26	Wang Y[134]	2009	China	General population of 6 cities	21152 M: 10862 F: 10290			ABPI <0.9	3.1 M: 2.5 F: 3.7
27	Sritara P[135]	2007	Thailand	Current and former employees of an organisation 52- 73 years	2305 M: 1724 F: 581	59.8 ± 4.9	25	ABPI <0.9 (>1.3 excluded)	5.2 M: 4.1 F: 8.6

28	Garofolo L[136]	2007	Brasil	population study of Japanese-Brazilians >30	1008 M 459 F 549	56.5± 12.7	54	ABPI <0.9	20.4 M: 19.1 F:20.7
29	He Y[137]	2006	China	General population of Beijing >60 years	2334 M: 943 F: 1391	68.5± 5.4	59.6	ABPI <0.9 (>1.5 excluded)	19.8 M: 14.8 F: 23.2
30	Kweon SS[138]	2005	Korea	General population study of 5 different regions 45-74 years	1942 M: 681 F: 1261	61.9± 6.7 61.1± 7.1	64.9	ABPI <0.90	2.0 M: 2.2 F: 1.8
31	Chuang SY[139]	2005	Taiwan	General population of one city >40 years	1329 M: 609 F: 720	55.0± 11.1	54.2	ABPI <0.9	2.2 M: 2.8 F: 1.7
32	Fujiwara T[140]	2004	Japan	General population of a rural area >40 years	1398 M: 544 F: 854	65.7± 9.8	61.1	ABPI <0.9	2.7 M: 3.1 F: 2.5
33	Hozawa A[141]	2004	Japan	General population of one city >70 years	946	75.2± 4.6	55	ABPI <0.9	5.7
34	Wang J.[142]	2003	China	Population of Beijing 60- 95 years	2126 M: 943 F: 1183	68.54 ± 5.43	50.7	ABPI <0.9	15.9 M:11.8 F:19.2
35	Takei H. [143]	1995	Japan	Population of a village 60- 79 years	348 M: 128 F: 220	69		Weak/ Absent pulses Low ABPI	0.6
36	Curb JD[144]	1996	USA	Population of Japanese American men in Hawaii 71- 93 years	3450		0	ABPI <0.9	13.6

37	Subramaniam T[145]	2011	Singapore	Different ethnic groups of Singapore population	Total: 4129 Chinese: 2436 Malays: 875 Indians: 818	49.9± 11.8	51.8	ABPI <0.9 (>1.4 excluded)	4.3 3.5, M: 3.0, F: 3.9 5.2, M: 4.1 F: 6.2 5.6, M: 4.8 F: 6.4
38	Premalatha G[146]	2000	India	General population of Chennai >20 years	631 M: 243 F: 388	46 ± 15	60	ABPI <0.9	3.2
39	Allison MA[147]	2015	USA	Hispanic/Latino population of the US >45 years	9648 M: 4380 F: 5268	56	55	ABPI <0.9	5.7
41	Makdisse M[148]	2008	Brazil	General population of 72 cities	1159	43.8 ± 14.7	53.3	ABPI <0.9 (>1.4 excluded)	10.5
42	Buitrón-Granados LV[149]	2004	Mexico	People subscribed to one primary care centre >40 years	400 M: 114 F: 286	_	71.5	ABPI <0.9	10 M: 14 F: 8.4
43	Fabsitz RR[150]	1999	USA	Population of American Indians from different areas 45- 74 years	4304 M: 1744 F: 2560	_	60	ABPI < 0.9	5.3 M: 4.8 F: 5.6

ABPI= ankle brachial pressure index, F= female, M= male, PAD= peripheral arterial disease, TBI= toe brachial index

Table 4 General population studies comparing the prevalence of PAD in different ethnic groups.

	Author	Date Published	Country	Sample origin	Sample size		Mean age (years)	Female %	PAD definition	Pad Prevalence per ethnic group %
1	Berger JS[151]	2013	USA	Nationwide screening program 40- 99 years	Whites Blacks Asians Hispanics Native Amer	2947561 111456 71198 87615 102163	64.1 ± 10.2	62.5	ABPI <0.9	M: 3.0 F: 3.6 M: 5.4 F: 6.8 M: 1.8 F: 2.4 M: 2.0 F: 2.4 M: 5.7 F: 6.4
2	Bennett PC[60]	2010	UK	South Asian and Blacks >45 years in Birmingham area	Blacks South Asians	216 358	63 ± 11 61 ± 11	53.2 42.3	ABPI <0.9 >1.39 excluded	10.2 13.2
3	Ostchega Y[14]	2007	USA	Nationwide population study >60 years	White Black Mexican Amer	2274 M: 1174 F: 1100 614 M: 310 F: 304 828 M: 417 F: 411	71	49.1	ABPI<0.9 >1.5 excluded	11.7 * M: 12.1 * F: 11.3 * 19.5 * M: 19.2 * F: 19.3 * 15.6 * M: 15.6 * F: 15.6 *
4	Criqui MH[25]	2005	USA	Random sample from current and retired employees of the University of California and families	White Black Hispanic Asian	1401 322 341 279	M: 60.1 F: 58.8	65.7	ABPI <0.90 or history of PAD	4.9 7.8 1.8 1.4
5	Ix JH[152]	2011	USA	General population of 4 communities >65 years	White Black	4589 830	72.7	57.5	ABPI <0.9 or Known PAD	12.9 22.1

6	Holland AT[153]	2011	USA	Population registered in a health care organization	White Asian Asian Indian	72701 21722 5154		56 57 46	ICD 9 codes	1.9 0.9 1.4
7	Allison M[24]	2006	USA	General population from 6 communities 45- 84 years	White Black Chinese Hispanic	2552 1853 796 1452	62.2	52.9	ABPI <0.9 >1.4 excluded	3.6 7.2 2 2.4

ABPI= ankle brachial pressure index, F= female, M= male, PAD= peripheral arterial disease, *= Age adjusted

Table 5 Studies reporting prevalence of PAD in diabetic patients.

	Author	Date Published	Country	Population studied	Sample Size	Mean Age	Female %	PAD definition	PAD %
1	Bundó M[154]	2010	Spain	T 2 diabetics attending a diabetic centre without known PAD	232 M: 97 F: 135	65 ± 11	58.2	ABPI<0.9	15.5 M: 16.5 F: 14.8
2	Faglia E[155]	2005	Italy	Newly diagnosed T 2 diabetics in 265 diabetology centres	2559 M: 1496 F: 1063	58.7 ± 10.5	41.5	ABPI <0.9	21.1
3	Janka HU[156]	1980	Germany	Diabetic patients attending one diabetic centre	623 M: 255 F: 368	_	59.1	30 mmHg reduction of SBP in one limb	15.9 M: 18 F: 14.4
4	Mwebaze RM[157]	2014	Uganda	Diabetic patients in outpatient clinic >30 years	146 M: 75 F: 71	53.9 ± 12.4	48.6	ABPI <0.9	39 M: 44 F: 33.8
5	Umuerri EM[158]	2013	Nigeria	T 2 diabetic patients in outpatient department	388	_	62.9	ABPI <0.9	35.6
6	Fan LC[159]	2013	Taiwan	T 2 diabetics with no PAD symptoms	552 M: 232 F: 320	69.5 (IQR 62-76)	58	ABPI <0.9 (> 1.3 excluded)	9.2 M: 9.9 F: 8.8
7	Wang L[160]	2011	China	Diabetic outpatient and inpatients in a hospital >60	2010 M: 854 F: 1156	69.8±6.6	57.5	ABPI <0.9 (>1.4 excluded)	24.1 M: 25.4 F: 23.4
8	Li X[161]	2012	China	T 2 diabetics attending in outpatient department	3924 M: 2111 F: 1813	56.1 ± 11.0	46.2	ABPI <0.9	5.2 M: 5.2 F: 5.5
9	Chou CK[162]	2008	Taiwan	T 2 Diabetics attending one diabetic clinic >60	580	70.2 ± 6.5	49	ABPI <0.90	13

10	Maeda Y[163]	2008	Japan	Diabetic outpatients in 23 hospitals	3906 M: 2317 F: 1589	60.8 ± 11.9	40.7	ABPI <0.9	7.6 M: 7.3 F: 8.1
11	Guan H[164]	2007	China	Type 2 diabetic in 15 hospitals >50	1397	63.7 ± 8.2	_	ABPI <0.9	19.5 M: 18.4 F: 20.5
12	Rhee SY[165]	2006	7 Asian countries	T 2 Diabetic patients with one additional risk factor (smoking, hypertension, dyslipidaemia) >50 years	6625 M: 2873 F: 3752	63.7 ± 8.2	56.6	ABPI <0.90 (>1.3 excluded)	17.7 M: 17 F: 18.3
13	Eshcol J[166]	2014	India	T 2 diabetic patients attending a diabetic centre >20 years	2493 M: 1544 F: 949	51 ± 10	38.1	ABPI <0.9 (> 1.3 excluded)	7.6 M: 5.1 F: 11.8
14	Doza B[167]	2012	India	T 2 Diabetics attending one diabetic centre	1121 M: 671 F: 450	M: 52.97 ± 10.04 F: 54.76 ± 8.81	40.1	ABPI <0.90	4.6 M: 4.5 F: 4.7
15	Agarwal AK[168]	2012	India	T 2 diabetics attending one diabetic clinic	146 M: 79 F: 67	59.4 ± 7.2	45.9	ABPI <0.9	14.3 M: 13.9 F: 14.9
16	Ali Z[169]	2012	Pakistan	T 2 diabetics attending a diabetic clinic	387 M: 128 F: 259	52.2 ± 9.7	66.9	ABPI <0.9	39.3 M: 24.2 F: 46.7
17	Akram J[170]	2011	Pakistan	T 2 diabetics patients in eight centres >40 years	830 M: 409 F: 421	54.2 ± 8.9	50.7	ABPI <0.9	31.6 M: 29.8 F: 33.3
18	Mohan V[171]	1995	India	NIDDM patients attending one diabetic centre	4941 M: 3167 F: 1774	_	35.9	ABPI <0.9	3.9 M: 3.2 F: 5
19	Andrade J.L.[172]	2004	Brazil	Diabetic patients in outpatient clinic, 22- 89 years	236 M: 123 F: 113	62.1	48	ABPI <0.9	18.2

ABPI= ankle brachial pressure index, F= female, M= male, PAD= peripheral arterial disease

Table 6. Studies comparing PAD prevalence among diabetic patient of different ethnicities

	Author	Date Published	Country	Sample origin	Sample size		Mean age (years)	Female %	PAD definition	Pad Prevalence per ethnic group %
1	Mehta RL[173]	2011	UK	Patients attending a specialist outpatient diabetes clinic	White South Asians	4222 1442	_	45.1 46.9	As per records	4.5 1.8
2	Abbott CA[174]	2010	UK	T 2 diabetic patients in primary care	White Indian Asian	180 180	59.1 ± 9.7 57.4 ± 9.9	46.7 47.2	ABPI <0.85	9.1 4.0
3	Abbott CA[175]	2005	UK	Diabetic patients in primary and secondary care	European Afro-Caribbean South Asians	13387 370 1862	62.3 ± 14.1 62.0 ± 9.7 54.9 ± 11.8	46.1 47.4 46.3	2 or fewer of the 4 pedal pulses present	21.9 20.3 7.1
4	Chowdhury TA[54]	2002	UK	Newly diagnosed diabetic patients 20- 40	European South Asians	127 165	35.3 ± 2.3 33.5 ± 2.4	43.3 41.8	Loss of one peripheral pulse or symptoms	3.9 5.4
5	Samanta A[176]	1991	UK	Diabetic patients attending one diabetic clinic	Caucasian Asian	451 456	51.9 ± 16 52.7 ± 12.3	41 37.9	Symptoms of PAD	9.3 M: 11.7 F: 5.9 3.7 M: 3.9 F: 3.5
6	UK Prospective Diabetes Study XII[177]	1994	UK	newly diagnosed Type 2 diabetic patients 25- 65 years	Caucasian Afro-Caribbean South Asian	4177 387 534	M 51.8 ± 8.8 F 52.9 ± 8.7 M 51.6 ± 7.4 F 50.2 ± 7.2 M 46.8 ± 8.6 F 47.6 ± 8.8	41.9 43.4 32.2	2 or fewer of the 4 pedal pulses present	13.1 M: 11 F: 16 11 M:8 F: 15 5.3 M: 4 F: 8

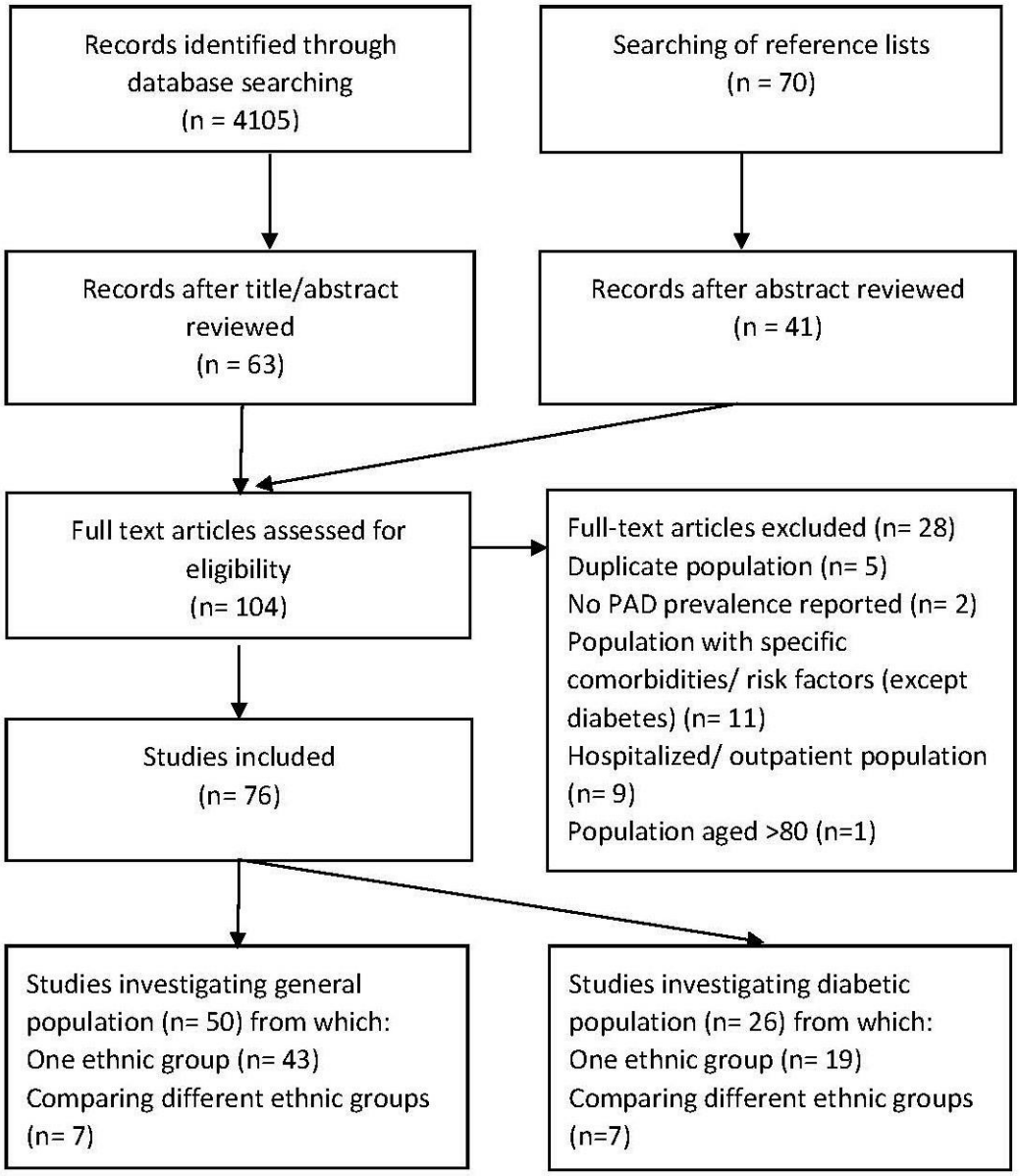
7	Alcolado JC[178]	1992	UK	Hypertensive Type 2 diabetic outpatients in a diabetic clinic	White Black Asian	67 79 42	_	45	ABPI <1	46.3 43 28.6

ABPI= ankle brachial index, F= female, M= male, PAD= peripheral arterial disease

2.4 Results

A total of 4105 citations have been reviewed. After screening of titles and/or abstracts 63 full text articles have been selected. Research of reference lists of those articles identified another 41 relevant studies. After review of full text articles 76 publications were found to meet the inclusion criteria (Figure 1).

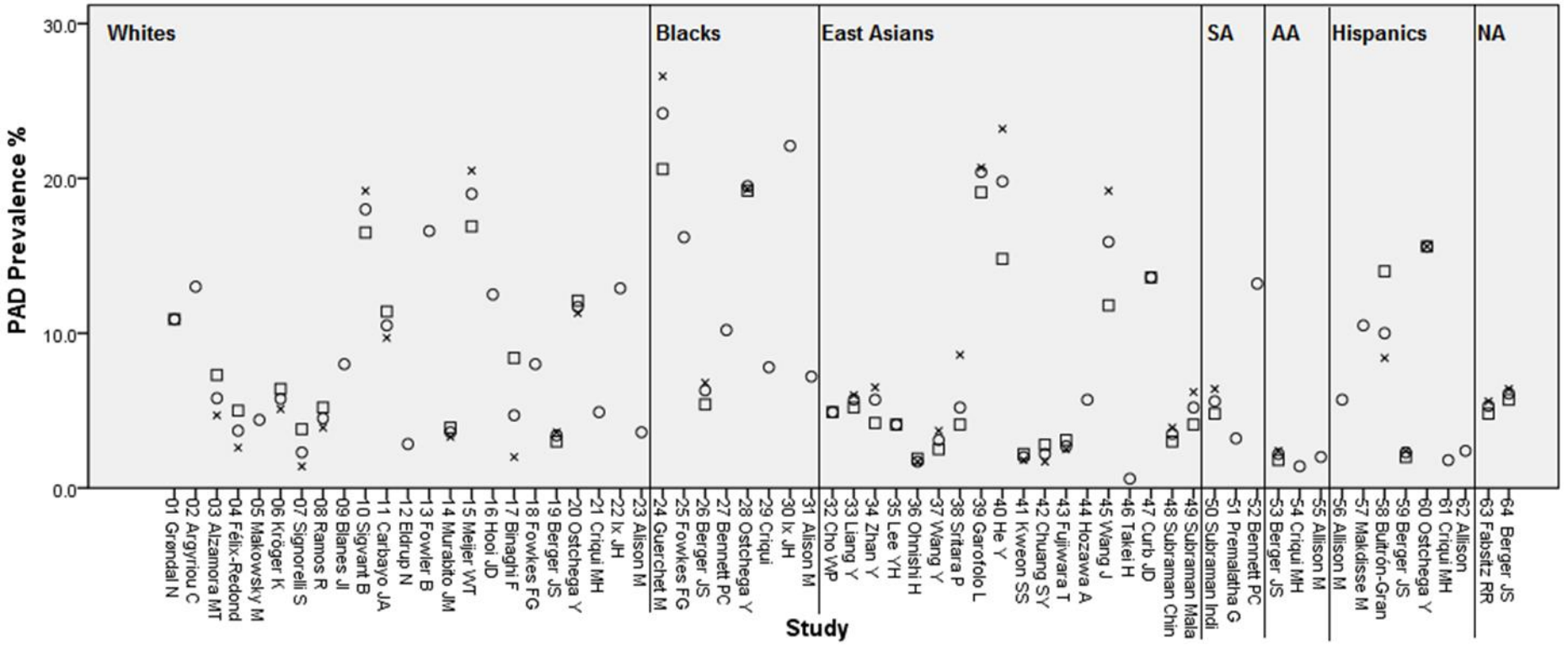
Figure 1. Search strategy and selection of included studies.



Forty-three studies reporting PAD prevalence in general population as well as 7 studies that compare PAD prevalence between 2 or more different ethnic groups were retrieved (n= 3,462,955) and summarised in Figure 2. The mean prevalence of PAD from all studies is 3.7% (95%CI 3.68- 3.72) with the highest prevalence (24.2%) reported in an African and the lowest (0.6%) in an East Asian population. The mean prevalence for Whites overall, for white men and for white women is 3.53 (95%CI 3.51- 3.56), 3.11% (95%CI 3.08- 3.14) and 3.66% (95%CI 3.63- 3.69) respectively, while corresponding values for Blacks are 6.68% (95%CI 6.54- 6.82), 5.64% (95%CI 5.42- 5.86), 7.02% (95%CI 6.8- 7.21) and for Asians 3.71% (95%CI 3.61- 3.82), 3.64 (95%CI 3.49- 3.8), 3.67% (95%CI 3.52- 3.81) respectively. Overall females demonstrate slightly higher rates of PAD (3.8% vs 3.2%; $p<0.01$), which remains statistically significant in the white and black ethnic groups ($p<0.01$) but it does not reach significance for the Asian group ($p=0.84$).

Five studies comparing Black to White ethnicity and four studies comparing Asian to White ethnicity, were included in the meta-analysis and results are presented in Figure 3 and Figure 4. Prevalence of PAD is significantly higher in Blacks (OR=1.97, 95% CI 1.92 to 2.02; $p<0.01$) and significantly lower in Asians (OR=0.66, 95% CI 0.63 to 0.70; $p<0.01$) when using whites as reference.

Figure 2. Reported PAD prevalence in general population in different studies.



o= overall, x= female, □= male, SA= South Asian, AA= Asian American, NA= Native American

Figure 3. Odds ratio for PAD, black vs white ethnicity (Q= 1.211, Tau^2= 0.00, I^2= 0.00).

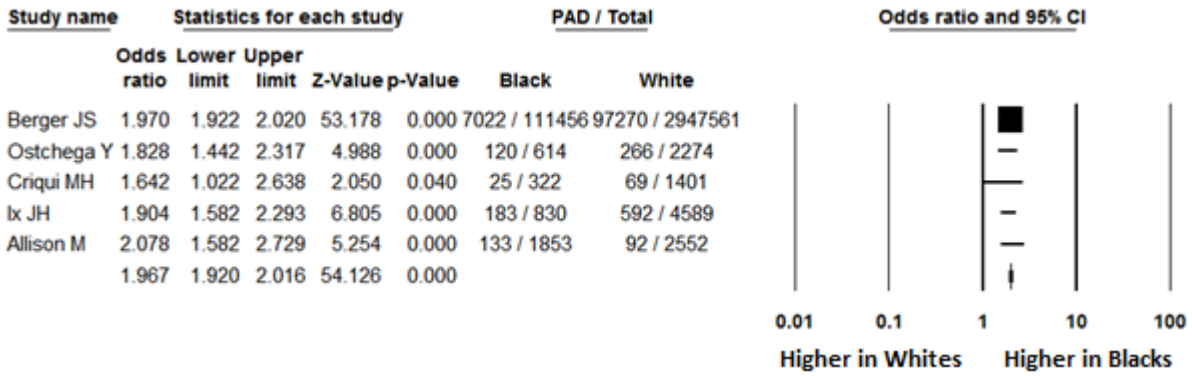
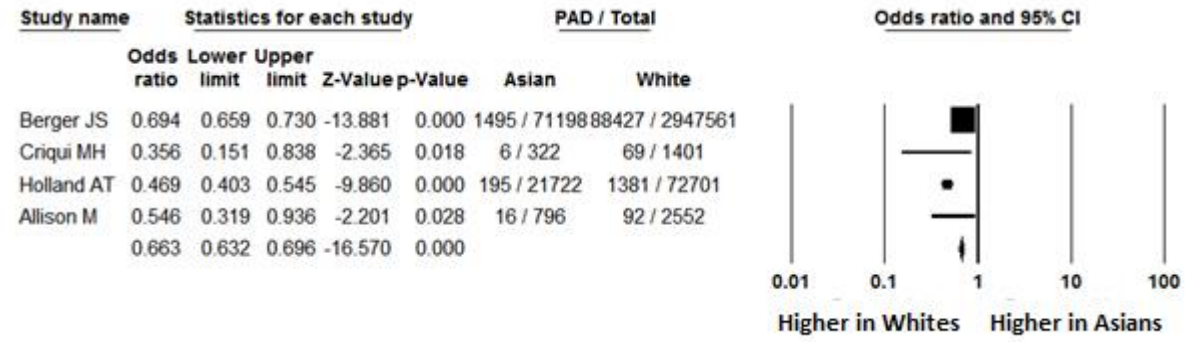


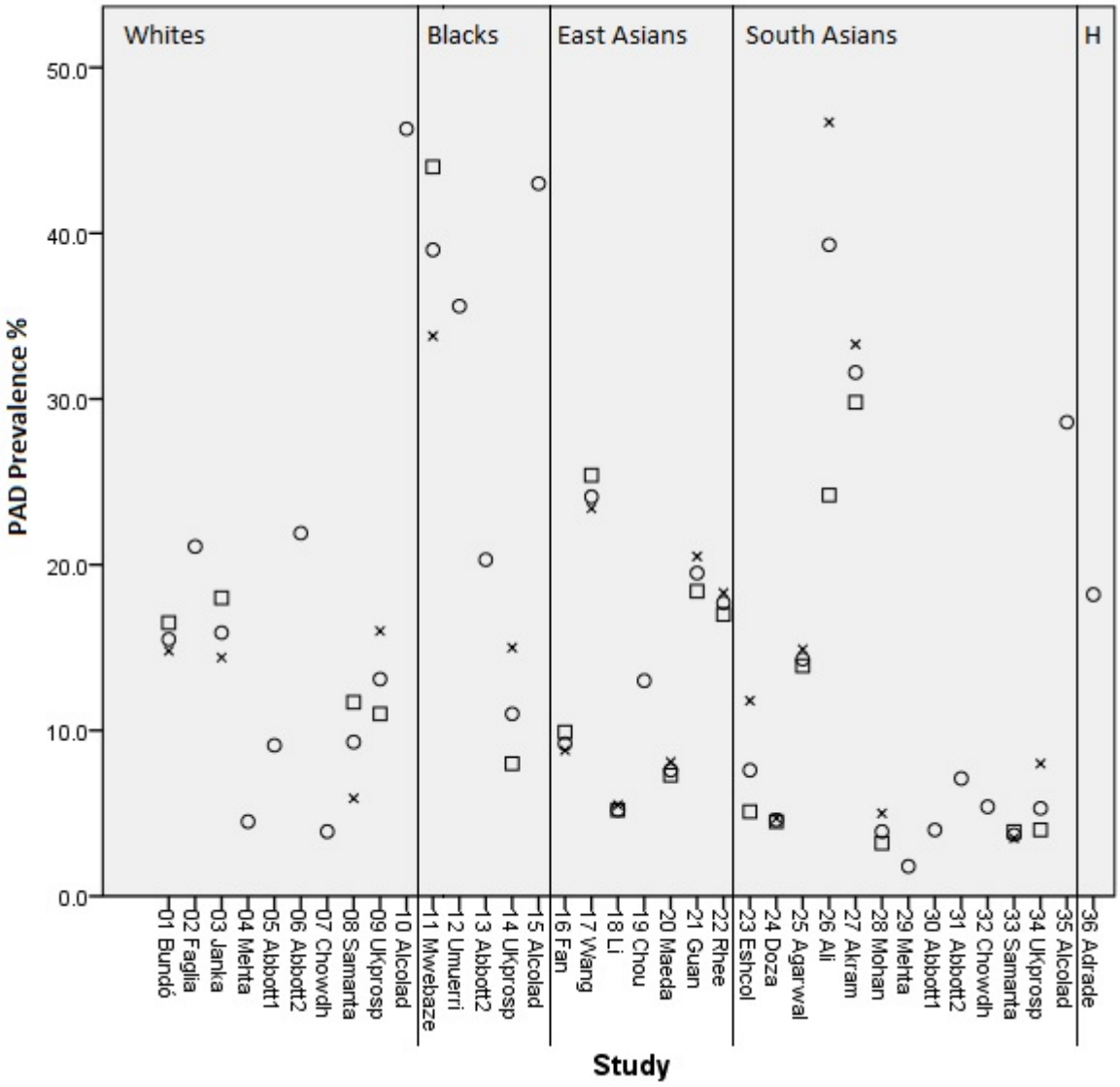
Figure 4. Odds ratio for PAD, Asian vs white ethnicity (Q = 25.784, Tau^2= 0.068, I^2= 88.365).



Nineteen studies with a total population of n=60695, reporting PAD prevalence in diabetics, are summarized in Figure 5. The mean prevalence was 13.93% (95% CI 13.66- 14.21) and the ranging is from 1.8% to 46.3%. For studies on Whites, Blacks, East Asians and South Asians the mean prevalence is 17.05% (95%CI 16.59- 17.51), 25.31% (95%CI 23.01- 27.61), 13.46% (95%CI 12.97- 13.95) and 7.62% (95%CI 7.18- 8.06) respectively. In studies including sex-specific data, the prevalence of PAD was significantly lower in diabetic males (9.97%, 95%CI 9.48%- 10.45%) compared to females (13.74%, 95%CI 13.15- 14.33), $p<0.01$.

Three studies, comparing black to white diabetics (Figure 6) and seven studies comparing South Asian to white diabetics (Figure 7) were included in the meta-analysis. There was no significant difference between blacks and whites (OR=0.87, 95% CI 0.72 to 1.06; p=0.17), while South Asians have significantly lower prevalence of PAD (OR=0.32, 95% CI 0.28 to 0.37; $p<0.01$).

Figure 5. Prevalence of PAD in diabetics in different studies.



o= overall, x= female, □= male, H= Hispanics

Figure 6. Odds ratio for PAD, black vs white diabetics (Q=0.230, Tau^2= 0.00, I^2= 0.00).

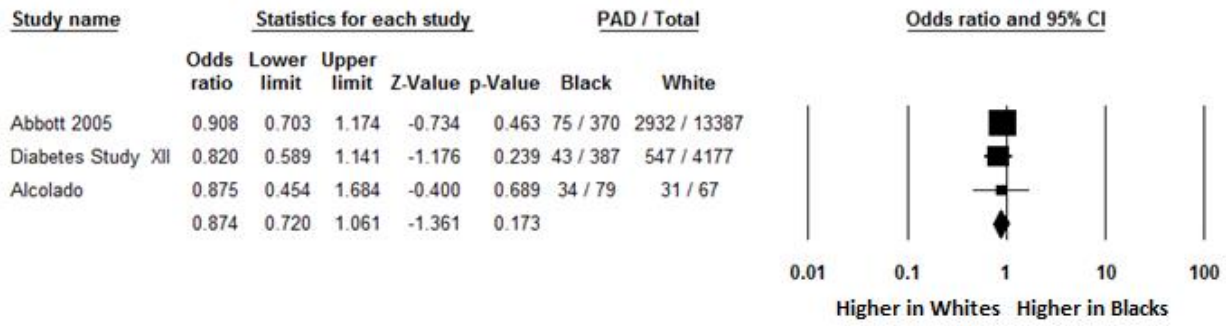
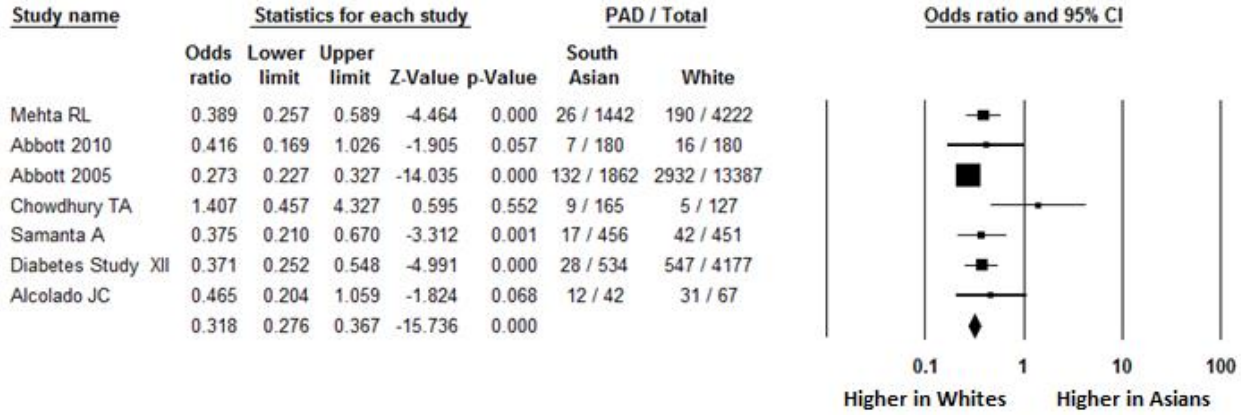


Figure 7. Odds ratio for PAD, South Asian vs White diabetics (Q=12.475, Tau^2= 0.059, I^2= 51.905).



2.5 Discussion

This study demonstrates that PAD is a global public health problem, however there is high variation in the reported prevalence of PAD in different populations, even in those belonging to the same ethnic group. Women are traditionally considered to be less affected by PAD[12], which is not consistent with the findings of this study. Our systematic analysis showed higher prevalence of PAD in women, which was significant for general population as well as diabetic population studies. This finding is in accordance with more recent observations that demonstrate a shift in the gender distribution of PAD as discussed in Chapter 1.1.3.[15,16]

In this review, Blacks appear more vulnerable to PAD in general population studies. The same applies in prevalence studies on diabetics, however, three comparative studies on diabetic population do not demonstrate a significant difference. Several studies have demonstrated that multivariate adjustment for traditional cardiovascular risk factors[25,69] such as smoking, hypertension, diabetes does not completely explain the higher risk for PAD in Blacks. Other studies tried to explain this observation by measuring several biomarkers known to be related to cardiovascular disease such as homocysteine, C-reactive protein, interleukin-6, fibrinogen, D-dimer, plasmin- antiplasmin, lipoprotein (a), tumour necrosis factor-alpha, von Willebrand factor, prothrombin fragment 1-2. Despite the higher prevalence of those biomarkers in Blacks, they could not completely explain their higher PAD rates.[24,66] Additionally, Blacks have been reported to present more often with critical limb ischaemia[53], to have worst outcomes after an arterial bypass[53] or an endovascular procedure[80] and to suffer from higher major lower limb amputation rates[75].

On the other hand, South Asians and East Asians demonstrate lower prevalence of PAD compared to Whites, in both general and diabetic population studies. Paradoxically, lower PAD

rates for South Asians are not consistent with their higher rates of cardiovascular disease and diabetes[70,179,180]. Indian men have been found to present with less extent of PAD for a given extent of coronary artery disease, compared to white Europeans[73]. South Asians in UK suffer 40% less major amputations compared to white Europeans[75].

This study has several limitations. It is appreciated that the broad categorization of study populations in ethnic groups does not take into account national or regional differences that may be present. From the comparative studies, those that compare PAD prevalence in general population come from the United States and they essentially refer to all Asian Americans as one ethnic group, while all studies comparing PAD prevalence in diabetics come from the United Kingdom and they investigate populations of South Asian origin

Although certain inclusion criteria where set to minimise selection bias, this cannot be excluded, as there is heterogeneity between studies regarding age of sample population, sex distribution, and cardiovascular risk factors. The sampling of included general population studies originates from various sources such as primary care or insurance company registries, areas of residence and specific working environments which could generate selection bias. The presence of reporting bias is very likely considering that some broad geographic areas such as Africa, South America and South Asia have very small representation in the retrieved studies, contrary to Europe, North America and East Asia. In addition, we have included studies published from 1980 to 2016. During this long time interval prevalence of PAD is expected to have changed. Detection bias is unlikely, due to observational cross-sectional nature of included studies and the objective clinical criteria used to identify PAD. Although definition of PAD is variable among studies; the large majority uses an ankle brachial pressure index lower than 0.9.

2.6 Conclusion

Ethnic differences in the prevalence of PAD are evident. Better understanding of environmental or genetic factors that generate those differences may result in more effective prevention, screening, and evidence-based management of the disease.

CHAPTER 3: COMPARISON OF OUTCOMES OF LOWER LIMB REVASCULARIZATION PROCEDURES AMONG ETHNIC GROUPS IN ENGLAND.

3.1 Ethnic differences in outcomes of lower limb revascularization procedures. A retrospective analysis of Hospital Episode Statistics.

3.1.1 Abstract

Background: Various studies, mainly from North America report worse outcomes in ethnic minority populations submitted to revascularization for peripheral arterial disease. Limited data in relation to ethnicity are available from Europe. The aim of this study is to investigate outcomes from lower limb revascularization procedures in ethnic minorities in England.

Methods: The "Hospital Episode Statistics" database has been searched using ICD-10 codes to identify all cases of femoral-popliteal bypass operations and femoral angioplasty or stenting procedures from English NHS Hospitals between 01/01/2006 and 31/12/2015. Subsequent mortality, second open or endovascular infrainguinal procedures and major amputations on the same limb within 2 years after the initial procedure have been recorded. Patients were broadly categorized according to ethnicity as Whites, Asians and Blacks. Chi-square test was used to demonstrate significant differences among ethnic groups and odds ratios were calculated using White ethnic group as reference.

To complement the HES analysis with patient level data, a retrospective review of Queen Elizabeth Hospital Birmingham records was conducted. Patients who had a lower limb bypass operation from 01/01/2013 to 30/03/2015. Baseline characteristics as well as data on mortality, subsequent procedures, bypass graft patency and limb loss were collected. A comparison of baseline characteristics and outcomes of patients of different ethnic groups was performed.

Results: In the examined 10-year period, 20825 femoral-popliteal bypass procedures and 70,887 femoral endovascular procedures were recorded. In patients who had bypass operations 30-day and 2-year mortality were 2.8% and 16.8% with no significant ethnic differences. Patients of Black ethnicity had higher risk of limb loss compared to Whites (23.2% vs 15.6%, OR =1.63, 95%CI 1.21-2.19, p<0.01). There was no significant difference in amputation rates between Asians and Whites (16.2% vs 15.6%, p=0.94).

In patients who had endovascular procedures 2-year mortality in Whites, Asians and Blacks was 18.3%, 22.1% and 19.5%, p<0.001, rates of second endovascular procedure were 12.1%, 13.1% and 13.5%, p=0.24, rates of subsequent open infrainguinal procedure were 5.6%, 4.5% and 8.0%, p<0.001 and rates of major amputation were 4.8%, 4.1% and 7.0%, p<0.001 respectively. Mortality was higher in Asians (Odds Ratio [OR] =1.26, 95% Confidence Interval [CI] 1.10- 1.45, p<0.01) compared to Whites. On the other hand, Blacks underwent more open arterial operations (OR=1.48, 95%CI 1.19- 1.83, P<0.01) and more amputations (OR=1.49, 95%CI 1.18- 1.87, p<0.01) during the 2- year examined period.

The study of Queen Elizabeth Hospital Birmingham records was underpowered because of under-representation of ethnic groups and could not generate any meaningful results.

Conclusion: Patients of Black ethnicity are at higher risk of limb loss after open or endovascular femoropopliteal interventions. In addition, 2-year mortality after femoral angioplasty/stenting is higher in Asians. Reasons of these ethnic differences in outcomes merit further study.

3.1.2 Introduction

Various studies have demonstrated worse outcomes after revascularization procedures in ethnic minority groups. Most of that evidence originates from North America, while very limited evidence is available for ethnic minority populations in Europe. Ethnic minority patients in the US, specifically of African-American and Hispanic origin, have worse outcomes after lower limb bypass and endovascular operations. Whether these differences can be attributed to different prevalence of cardiovascular risk factors, socioeconomic or genetic factors remains unclear. Ethnic minorities comprise 14% of population of England with the main ethnic groups being Asians (7.5%) and Black/ African/ Caribbean (3.3%)[181].

The US health care system differs from those in the UK and Europe and it is not well established if the observed ethnic differences in the US also exist in the UK. Data from the UK are limited with one single centre/ single surgeon series reporting no significant difference in distal bypass graft patency between Caucasians and Afro- Caribbeans.[85]

We therefore conducted a retrospective study of English hospital statistics to identify possible differences in outcomes of peripheral bypass and endovascular procedures in these groups. In order to achieve comparable results, we focused on procedures performed for disease of the femoropopliteal segments including femoral-popliteal bypass procedures and femoral artery angioplasty/ stenting. We hypothesised that differences in outcomes of revascularization procedures observed in the US would also apply in ethnic minority populations in England.

3.1.3 Methods

This is a retrospective study using UK Hospital Episode Statistics (HES). The HES is the administrative dataset for the English National Health Service (NHS), which contains information regarding every admission of any patient to English NHS hospitals. HES data are anonymised by the allocation of a unique identifier to each patient, so individuals can be tracked as their care moves from consultant to consultant on any particular admission, and between hospital admissions. The dataset therefore allows long term follow up of individual patients with respect to multiple hospital admissions. Advantages of such datasets have been documented in literature as they encompass large populations, they are easily available and amenable to computerised data extraction.[182] International Classification of Diseases (ICD-10) codes[183] were used to detect corresponding clinical diagnoses and different treatments. Ethnicity is self-defined by patients on admission, and as reported before, it is recorded in the HES database in 79.4% of hospital admissions. The HES database is linked with the Office of National Statistics (ONS) mortality data, so that deaths are recorded in the database even when they occur outside of hospital.[184]

Data extraction was performed by the Health Informatics Department of University Hospitals Birmingham. A data analyst has been allocated to the project and several meetings were held to discuss the feasibility, outline and progress of the study. Important problems have occurred: HES data sharing policy would not allow access to raw data and would not allow disclosure of outcomes occurring to less than 5 patients. In addition, due to limited staff availability, there were significant delays in data extraction. Given the time constrains and the limited resources, and since HES was

initially intended to be the primary data source for this Thesis a pragmatic decision was made to proceed with this study despite the lack of patient level data and the consequent limitations. Considering the paucity of data on outcomes of revascularization procedures in minority ethnic groups in England, this study could serve as an initial observation and could potentially bring into light an unnoticed problem and generate further research.

Previous studies comparing outcomes of revascularization procedures between different ethnic groups have investigated a mixture of open, endovascular or hybrid interventions with heterogeneity regarding the treated arterial segment (aortoiliac, infrainguinal or infrapopliteal) and report different ratios of open/ endovascular interventions in different ethnic groups. This has generated discrepancies in outcomes between different studies and some researchers suggest that worse outcomes of revascularization procedures in Blacks are explained by more distal distribution of PAD.[79,80]

Given the expected large sample size that would give adequate statistical power and with the intention to reduce the confounding effect of different disease distribution in different ethnic groups, decision was made to only compare similar interventions in the same arterial territory. Due to time and resource limitations this study only examined interventions in the femoropopliteal segment considering that this is the most commonly treated segment and that these interventions are very specifically defined with ICD-10 codes.

The author worked with the data analyst during data extraction to ensure that the study design is followed. A list of relevant ICD-10 codes for each medical diagnosis, intervention and outcome examined as well as premade tables specifying the data to be extracted have been created by the author and have been handed over to the data analyst to be populated. In order to compare the outcomes of similar interventions, data extraction and analysis was conducted separately for each of the two examined cohorts of patients (bypass surgery or endovascular treatment).

HES database has been searched to detect all femoropopliteal bypass operations, including procedures with either vein or prosthetic bypass graft, as well as all femoral artery angioplasty and/or stenting procedures performed in English NHS Hospitals during the 10-year period between 01/01/2006 and 31/12/2015. Based on recorded ethnicity, patients were categorized in one of the three main ethnic groups: White, Asian, Black/ African/ Caribbean.[181] Patients with recorded "Mixed Ethnicity" or missing ethnicity were excluded from the study. Demographic characteristics and previous diagnosis of hypertension, diabetes, heart failure, ischaemic heart disease, stroke and atrial fibrillation at the time of the index procedure were recorded using relevant ICD-10 codes.

Comparison of baseline characteristics and outcomes was made between patients of different ethnic groups using descriptive statistics. All patient's records were studied for a two-year period after the initial intervention and the outcomes examined were 30-day and 2-year mortality, re-interventions and major amputations. In order to better assess the durability of the initial intervention, decision was made to look for

subsequent procedures in the same arterial territory; only infrainguinal open and endovascular procedures were therefore recorded. Analysis was done with MedCalc Version 14.8.1. Chi-squared test was used and p value was calculated to demonstrate significant differences, defined as $p<0.05$. Odds ratios (OR) were calculated using White ethnic group as reference.

For the study on femoropopliteal bypass operations an attempt was made to match the side of the initial bypass operation with the side of subsequent events based on laterality codes; this was not possible for 23% of open, 26.5% of endovascular reinterventions and 33.4% of amputations due to lack of laterality codes. In addition, according to HES data sharing policy we could not report outcomes in small absolute numbers of patients, less than 5, which was the case for ethnic minority patients receiving a prosthetic graft. With these limitations an initial analysis was made including the whole cohort regardless of laterality codes and then further analysis was performed on the subgroup of patients with available laterality information receiving a vein graft.

For the study on femoral angioplasty/ stenting, only procedures with laterality codes, allowing matching the side of the initial procedure with the side of subsequent events, were included in the analysis of limb related outcomes. For estimation of mortality, the whole dataset was used, regardless of laterality codes.

Missing data is a common problem in research, however there no universal best strategy to deal with it. Prevention of data missingness at the stage of data collection is the best solution but this was beyond the author's control. The most widely used

method for dealing with missing data during analysis is simple omission of missing data. However, this strategy has limitations and under certain circumstances can introduce bias.[185] The two main prerequisites to use this strategy are adequate statistical power and the assumption that data are missing at random.[186] The large sample allowed the use of this method without affecting the power of the study. The missing data in this study were procedure laterality codes and ethnicity codes. Regarding the former, it is logical to assume that they are missing at random. For the latter we cannot exclude the possibility that they are not missing at random and this is a potential source of bias. However, the lack of raw data would not allow the use of alternative methods such as imputation.

3.1.4 Results

Femoropopliteal bypass

In the time period 2006 to 2015, a total number of 23.269 femoropopliteal bypass procedures were performed with 20825 (89.5%) having ethnicity data: 20.408 (98%) White, 167 (0.8%) Asian and 250 (1.2%) Black ethnicity. Asian patients were significantly younger, were more likely to be male and had higher prevalence of diabetes and ischaemic heart disease compared to other ethnic groups. Whites had higher prevalence of AF, while there was no significant difference in rates of heart failure and hypertension. Prosthetic graft was used in 27% of cases with no significant difference among ethnic groups (*Table 7*).

Table 7. Baseline characteristics in different ethnic groups undergoing femoropopliteal bypass.

	White	Asian	Black	p*	p**
N	20408	167	250		
Mean age (SD)	68.9 (11.1)	63.9 (13.7)	68.2 (12.5)	<0.01	0.32
Male %	70.4	85.0	64.4	<0.01	0.04
Diabetes %	29.7	63.5	48.4	<0.01	<0.01
Hypertension %	52.9	52.7	58.4	0.96	0.08
Ischaemic Heart Disease %	26.4	43.1	21.6	<0.01	0.09
Heart Failure %	4.8	6.0	6.0	0.47	0.38
Atrial Fibrillation %	11.6	6.0	8.8	0.02	0.17
Prosthetic graft%	27.0	28.7	25.2	0.62	0.52

*comparing White with Asian ethnicity, ** comparing White with Black ethnicity

Overall, 30-day and 2-year mortality in this population were 2.8% and 16.8% with no statistically significant difference between ethnic groups. When the whole cohort was analysed regardless of procedure laterality codes, Asians were submitted in more endovascular procedures in the follow up period compared to Whites (33.5% vs 25%, p= 0.01). On the other hand, Black patients were at higher risk of major amputation compared to Whites (23.2% vs 15.6%, OR=1.63, 95% CI 1.21-2.19, p<0.01) and Asians (16.2%). There was no significant difference in the rates of second open arterial procedures among ethnic groups (*Table 8*).

When only procedure with laterality codes were included, bypass procedures with vein conduit were matched with outcomes on the same limb. There was no significant difference in the rates of subsequent open or endovascular procedures among ethnic groups. However, Black patients were at higher risk of limb loss compared to Whites (14.3% vs 7.9%, OR=1.95 95% CI 1.27-2.99, p<0.01) and Asians (7.5%), (*Table 9*

Table 9).

Table 8. Outcomes of femoropopliteal bypass in different ethnic groups (2 year follow up). Data not specific for laterality.

	White	Asian	Black	p*	p**
N	20408	167	250		
30-day mortality %	2.8	4.2	2.0	0.28	0.45
2-year mortality %	16.8	20.4	18.0	0.22	0.61
2nd open procedure %	20.9	24.6	18.8	0.25	0.46
Endovascular procedure %	25.0	33.5	30.4	0.01	0.06
Major amputation %	15.6	16.2	23.2	0.94	<0.01

*comparing White with Asian ethnicity, ** comparing White with Black ethnicity

Table 9. Outcomes of femoropopliteal bypass using vein graft in different ethnic groups (2 year follow up). Matched laterality of initial procedure and related outcomes.

	White	Asian	Black	p*	p**
N	13825	106	175		
2nd open procedure %	9.1	5.7	11.4	0.22	0.30
Endovascular procedure %	12.3	15.1	16.0	0.38	0.14
Major amputation %	7.9	7.5	14.3	0.90	<0.01

*comparing White with Asian ethnicity, ** comparing White with Black ethnicity

Femoral angioplasty/ stenting

In the time period 2006 to 2015, a total number of 85,540 patients had their first endovascular procedure in the femoral artery, with 75,453 (88.2%) having ethnicity data as follows: 68,622 (96.8%) White, 1121 (1.6%) Asian and 1144 (1.6%) Black ethnicity. Asian patients were significantly younger, more likely to be male and had higher prevalence of diabetes and ischaemic heart disease compared to other ethnic groups. Black patients had higher prevalence of hypertension and heart failure while whites had higher prevalence of AF. Asians and blacks had equally higher rates of previous stroke compared to whites (*Table 10*).

Table 10. Baseline characteristics in different ethnic groups undergoing femoral angioplasty/ stenting.

	Whites	Asians	Blacks	p*	p **
N	73041	1188	1224		
Mean age (SD)	71.7 (11.4)	67.4 (11.5)	70.6 (12.4)	<0.01	<0.01
Male %	62.4	78.6	58.0	<0.01	<0.01
Diabetes %	32.7	68.9	59.9	<0.01	<0.01
Hypertension %	46.4	53.4	54.3	<0.01	<0.01
Ischaemic Heart Disease %	24.2	41.0	21.2	<0.01	0.02
Heart Failure %	5.3	6.9	8.0	0.01	<0.01
Stroke %	0.3	0.8	0.8	<0.01	<0.01
Atrial Fibrillation %	11.8	6.0	7.6	<0.01	<0.01

(*= comparing Whites with Asians, ** = comparing Whites with Blacks)

Overall, 30-days and 2-year mortality in this population were 2% and 18.4% with Asians having significantly higher 30day (OR=1.73, 95%CI 1.26- 2.37, p<0.01) and 2year (OR=1.26, 95%CI 1.10- 1.45, p<0.01) mortality compared to Whites. There was no significant difference in mortality between Blacks and Whites.

Limb related outcomes with known laterality were available in 70.887 patients. There was no significant difference among ethnic minority groups in the rates of second endovascular procedure in the two-year period. However Black patients were more likely to need open revascularization (OR=1.48, 95%CI 1.19- 1.83, p<0.01) and were at higher risk of major amputation (OR=1.49, 95%CI 1.18- 1.87, p<0.01) compared to Whites. There was no significant difference in limb outcomes between Asians and Whites (*Table 11*).

Table 11. Outcomes of infrainguinal endovascular procedures in different ethnic groups. Only procedures with laterality codes used for limb outcomes

	Whites	Asians	Blacks	p*	p**
Mortality					
N	73041	1188	1224		
30-day mortality %	2.0	3.5	2.0	<0.01	0.96
2-year mortality %	18.3	22.1	19.5	<0.01	0.30
Limb Outcomes					
N	68622	1121	1144		
open operation %	5.6	4.5	8.0	0.15	<0.01
2nd endovascular procedure %	12.1	13.1	13.5	0.34	0.18
major amputation %	4.8	4.1	7.0	0.31	<0.01

(*=comparing Whites with Asians, **=comparing Whites with Blacks)

3.1.5 Discussion

The principal finding of this study is the higher risk of limb loss for black patients who underwent infrainguinal endovascular interventions and femoropopliteal bypass operations in England. This observation has implications for risk assessment and mitigation, to reduce the risks of poor outcomes in these Black ethnicity patients. In addition, Black patients were more likely to be submitted in a subsequent open revascularization procedure after an initial femoral angioplasty.

Two previous studies investigating the outcome of endovascular procedures, reach similar conclusions. Loja et al report higher reintervention rates and higher amputation rates in Blacks, 1 month and 1 year after endovascular procedures for PAD.[80] Rivero et al also report worse limb salvage rates 5 years after endovascular procedures in Black patients compared to Whites (69% vs 84%) despite patency rates being similar for both ethnic groups (5-year primary patency 65% in Blacks and 60% in Whites, p=0.99).[79] However, another study on femoral and popliteal endovascular interventions by Chong et al reports similar patency rates among White, Black and Asian patients.[86]

In our study ethnic groups present with different characteristics and risk factor profiles. Asians are younger, more likely to be male and present with higher prevalence of diabetes, followed by Blacks and Whites. Blacks present with higher rates of hypertension compared to the other ethnic groups and Whites have higher rates of AF. These differences in medical background are present in previous studies on patients receiving peripheral angioplasties.[79,80,86] These findings are also in accordance with previous reports from general population studies[25,56,58,92] as well as studies on patients with atherosclerotic disease.[61] Several studies have performed regression analysis to eliminate the effect of these factors on outcomes and concluded that Black ethnicity remains and independent risk factor for limb loss and worse patency rates after open[53,84] or endovascular interventions.[80]

Patients of Asian ethnicity had similar outcomes to White patients in regard to limb salvage rates despite their different risk factor profile and higher prevalence of

diabetes. To the best of our knowledge there is no previous study comparing the outcomes of lower limb bypass between these ethnic groups.

The factors that generate worst outcomes in Black patients have not been thoroughly investigated. Risk factor profile varies among ethnic groups. Black ethnicity is associated with high rates of hypertension [25,5856]while prevalence of diabetes in Blacks appears to be considerably higher when compared to Whites but lower compared to Asians.[25,49,60]Those differences apply in our study population and also in previous cohorts of patients submitted to lower limb revascularization.[53,82,84,187] In addition, ethnic groups present with differences in epidemiology and distribution of atherosclerotic disease, with Black patients showing higher prevalence of PAD[188] and a predisposition to more distal patterns of the disease, which is not completely explained by the higher rates of diabetes and other risk factors.[71,72]

Whether those differences can explain the worse outcomes of revascularization procedures in Black patients is controversial. In a retrospective study of 834 male patients receiving lower limb revascularization, Rivero et al demonstrated that Black patients have higher rates of diabetes, dialysis dependence, hypertension, infrapopliteal disease, gangrene and foot sepsis. In multivariate analysis, the effect of race in limb loss was not significant with authors making the conclusion that worse limb salvage in Black patients is related to anatomic factors, advanced disease and other negative prognostic factors.[79]

On the other hand, studies have shown that despite different risk factor profile, Black ethnicity independently predicts worse outcomes after lower limb bypass. In a study

by Robinson et al, including 1646 patients, after controlling for demographic, medical, anatomic factors and disease severity, Black patients were at higher risk of graft failure (HR 1.33 95% CI 1.02-1.73, p=0.035) and limb loss (HR 1.45 95% CI 0.97-2.17, p=0.073). [82] Similarly, in a retrospective review of 16,276 cases, Sivarajah et al report higher rates of early graft failure in Black patients (adjusted OR 1.26, 95% CI 1.05-1.51, p=0.011) after controlling for above confounders.[53] In addition, when specifically investigating selected populations with certain comorbidities, those differences in outcomes remain: among patients on dialysis, Black ethnicity was related to higher rates of graft failure and limb loss after lower limb bypass[189] and among diabetic patients receiving revascularization, Black patients with diabetes had higher rates of limb loss regardless of type of revascularization.[190]

Racial disparities in outcomes of surgical treatment and healthcare overall are a known problem. A systematic review of previous studies originating mainly from the US, demonstrates that race can be related to socioeconomic status and insurance status of patients. This can result in inequalities in access to healthcare, delayed or suboptimal surgical treatment and poorer outcomes. In addition, Black patients in the US have been reported as less likely to receive surgical treatment in a high-volume centre, less willing to undergo surgery in small number of studies and more prone to late presentation with more advanced disease. [191] In their study Arya et al confirm that low socioeconomic status is related to more amputations in PAD, however even when socioeconomic status was the same, Black patient still suffered more amputations. This observation suggests that Black race has direct effect on negative outcomes, not totally mediated by socioeconomic factors.[192] In an attempt to eliminate healthcare

provider bias, it has been demonstrated that even after controlling for hospital performance, Black patients with PAD were at higher risk for amputation. That was also the case when specifically investigating patients treated in high-volume, teaching hospitals.[193]

Another important finding is the higher mortality in patients of Asian ethnicity in the endovascular group, despite their younger age. This may reflect the higher prevalence of IHD and diabetes in this group. In fact, patients of Asian descent present with different distribution of atherosclerotic disease and have been reported to have higher rates of coronary artery disease and lower rates and lower severity of PAD.[51,73,188] On the other hand, Black and White patients present with similar mortality rates, which is consistent in all studies comparing mortality rates after open[53,79,82,83,85] or endovascular[79,80] procedures. Thirty-day and 2-year mortality rates in this study are comparable to figures from previous publications.[194,195]

Comparing the ethnic distribution in our study population (98% Whites, 0.8% Asians and 1.2% Blacks) there is an obvious difference to the corresponding figures in general population of the UK as per 2011 Census (86% Whites, 7.5% Asians, 3.3% Blacks).[181] This is partially explained by the exclusion of a proportion of ethnic minority patients who were recorded as “mixed” or “unknown” ethnicity according to the study methodology. This could also be attributed to the lower prevalence of PAD in Asians and also the different distribution of PAD among ethnic groups; Blacks and Asians present more often with distal distribution of the disease in the infrapopliteal segment, and would therefore be less likely to be offered femoral-popliteal bypass or

femoral angioplasty. In addition, another study of UK Hospital Statistics has shown that Blacks are more likely to be submitted to primary amputation without prior revascularization.[75] Whether patient preference contributed to this observation cannot be answered with available data.

Strengths and Limitations

Main strength of this study is the large number of patients and procedures, as it attempted to include all femoral endovascular procedures and femoral-popliteal bypass operations that took place in England during the studied period. However, it has certain limitations. It is a retrospective of administrative data, based on a clinical coding system, which lacks the accuracy of clinical data. There have been no data on the clinical severity of the disease or the presence of critical ischaemia at the time of intervention and no information about the anatomic distribution PAD in other segments or the complexity of the treated lesion. In addition, despite the large total number of patients, ethnic minority groups are very underrepresented in this study with a significant proportion of cases (11.8%) having been excluded due to missing ethnicity data or “mixed ethnicity”. Significant number of cases lacked laterality data, which mainly affected the bypass study, however in the subgroup where laterality data was available, results were similar. In the endovascular study, the large number of cases could generate statistically significant differences that may lack clinical significance. Most importantly, despite the obvious differences in risk factor profiles, the nature of the data would not allow further adequate statistical analysis with either regression or propensity score analysis to eliminate the effect of those possible

confounders. Several attempts were made to overcome the limitations imposed by the lack of raw data. Different datasets such as ResearchOne and THIN have been assessed for usability but they contained insufficient procedure data. A retrospective search of University Hospital of Birmingham records was conducted but the study was underpowered.

3.1.6 Conclusion

Risk of limb loss is higher in Blacks when compared to Whites after an open or endovascular procedure in the femoral-popliteal segment. This study adds on the evidence that Black ethnicity is related with higher failure rates after lower limb revascularization. Proactive risk factor modification of these patients is highly recommended and reasons of these ethnic differences in outcomes of revascularization procedures merit further study.

3.2 Ethnic differences in outcomes of lower limb bypass procedures. A retrospective analysis of Queen Elizabeth Hospital Birmingham records.

3.2.1 Introduction

As shown in the study using HES data, patients of Black ethnicity are at higher risk of limb loss after a lower limb bypass operation. However, there have been significant limitations. This study aims to validate the results from HES using patient level data and to identify possible causes for this observation, taking into account important information such as clinical severity and anatomic distribution of PAD, bypass graft patency and prevalence of potential risk factors in every individual patient.

3.2.2 Methods

This is a study on patients who underwent lower limb bypass procedures under the care of the Vascular Unit of Queen Elizabeth Hospital Birmingham. The Unit treats elective or emergency vascular patients who present within the catchment area of "University Hospitals Birmingham NHS Foundation Trust" and "Sandwell and West Birmingham Hospitals NHS Trust". Patients requiring lower limb revascularization, have appropriate imaging and are offered relevant treatment either surgical or endovascular according to judgement of responsible consultant, fitness for surgery, patient's preference and multi-disciplinary discussion. All major arterial surgery is conducted in Queen Elizabeth Hospital Birmingham by consultant vascular surgeons or registrars under supervision. Patients are assessed with ultrasound scan to determine suitability of veins to be used as conduit for bypass. Ipsilateral long saphenous vein is conduit of choice and in case that it is not suitable, contralateral leg long saphenous

vein, arm vein or prosthetic graft is used according to clinical judgement. After discharge, patients with lower limb bypass are placed under surveillance as per local protocol, which involves doppler ultrasound of graft at 1 month, 3 months, 6 months and one year after the initial operation.

Patients who had a lower limb bypass operation for PAD, during the time period from 01/01/2013 to 30/03/2015 were detected from a prospectively populated database. A retrospective review of hospital records was then performed, which included operation notes, clinic consultations, discharge summaries and imaging studies. Procedures performed for other pathologies such as aneurysmal disease and trauma were excluded. Baseline characteristics as well as data on mortality, subsequent procedures, bypass graft patency and limb loss were collected with the study ending the 01/09/2017. All cases were censored from the date of the initial operation until the end of the study, the death of the patient or the occurrence of the examined outcomes. A bypass graft was considered as patent until the date of a documented clinical examination or imaging study that suggested graft occlusion.

Patient ethnicity is self-defined and recorded on admission, one patient with no ethnicity data available was excluded. A comparison of baseline characteristics of patients of different ethnic groups was performed.

The study has been approved by the local Clinical Audit Team (Ref: CARMS-13473). Analysis was performed with IBM SPSS Statistics, Version 23 and statistically significant relations were defined by p values lower than 0.05.

3.2.3 Results

In total 176 procedures took place on 155 patients. Ethnic groups were unevenly represented (139 Whites, 10 Blacks, 6 South Asians). A summary of baseline and procedural characteristics is demonstrated in Table 12. White patients were significantly older followed by Asians and Blacks. Among Blacks there was significantly higher prevalence of end stage renal failure. Asians had higher rates of diabetes and more distal bypass operations, while Blacks were more likely to present with clinically advanced PAD and tissue loss; however, none of those relations was statistically significant.

The median duration of follow-up, after the initial bypass procedure was 1095 days (IQR= 794). During this period 41 patients (26.5%) died, and from the treated limbs 28 (15.9%) had a major amputation, 39 (22.2%) a second open arterial operation and 49 (27.8%) an endovascular intervention. There was no statistical difference in any of these outcomes among ethnic groups.

Table 12 Clinical and procedural characteristics of patients receiving a lower limb bypass (grouped by ethnicity)

	White	Asian	Black	p
N	139	6	10	
Age Median (IQR)	70	53	65	0.03
Patient characteristics				
Male %	65.5	100	70	0.21
Diabetes %	31.7	66.7	40	0.19
Hypertension %	66.7	70	66.7	0.98
Atrial Fibrillation %	14	0	0	0.4
Smoking%	33.1	33.3	20	0.69

ESRF%	2.9	0	20	0.02
Clinical Stage of PAD				
Claudication%	24.7	33.3	8.3	0.70
Rest pain%	31.6	33.3	33.3	
Tissue loss%	43.7	33.3	58.3	
Procedure details				
Right Limb%	51.3	66.7	41.7	0.60
Prosthetic graft%	9.5	16.7	16.7	0.64
Distal Run-off vessel				
Above knee popliteal%	31.6	16.7	25	0.25
Below knee popliteal%	30.4	0	33.3	
Distal vessel%	38	83.3	41.7	
Outcomes				
Death%	26.6	16.7	30	0.83
Graft Occlusion%	37.3	33.3	41.7	0.94
Amputation%	15.2	0	33.3	0.14

ESRF: End Stage Renal Failure

3.2.4 Discussion

This study was underpowered due to small representation of ethnic minority groups and was not successful in providing robust results. By making a power calculation, with expected amputation rates after bypass procedures similar to those from HES study (16.6% for whites and 23.2% for blacks) a number of 197 Black patients would be required to demonstrate a significant difference (with calculated p value <0.05). Despite not statistically significant, Black patients in this study show a tendency for more graft failures and amputations. Patient characteristics in this study show a lot of similarity with HES data, in terms of age, with Asian patients being younger, male to

female ratio (higher in Asians), prevalence of diabetes in each ethnic group (higher in Asians), and prevalence of AF (higher in Whites). No safe conclusions can be made.

CHAPTER 4: THE IMPACT OF ATRIAL FIBRILLATION ON OUTCOMES OF PERIPHERAL ARTERIAL DISEASE. ANALYSIS OF ROUTINELY COLLECTED PRIMARY CARE DATA.

4.1 Abstract

Background: The combination of peripheral arterial disease (PAD) and atrial fibrillation (AF) is linked with high risk of mortality and stroke. This study aims to investigate the impact of AF on patients with diagnosed PAD.

Methods: This is a retrospective study using The Health Improvement Network (THIN) database, which contains prospectively collected data from participating primary care practices. Patients with a new diagnosis of PAD between 01/08/1995 and 01/05/2017 were identified in the database alongside relevant demographic information, clinical history and medications. Every patient in the dataset with PAD and baseline AF (case), was matched to a patient with PAD without AF (control) with similar characteristics using propensity score matching. Cox-regression analysis was performed and hazard ratios (HR) calculated for the outcomes of death, stroke, ischaemic heart disease (IHD), heart failure and major amputation.

Results: Prevalence of AF in this cohort was 10.2%. All patients with PAD and AF (n=5685) were matched 1:1 with 5685 PAD patients without AF but otherwise similar characteristics. After multivariate analysis, AF was independently associated with mortality (HR: 1.18, 95% CI 1.12- 1.26, p< 0.01), cerebrovascular events (HR: 1.35, 95%CI 1.17- 1.57, p< 0.01) and heart failure (HR: 1.87, 95%CI 1.62- 2.15, p< 0.01) but

not with IHD (HR: 0.97 95%CI 0.81- 1.78, p= 0.78) or limb loss (HR: 1.06, 95%CI 0.85-1.32, p= 0.59). In the subgroup analysis confined to non-anticoagulated patients, these associations remained significant.

Conclusion: In PAD patients, AF is a risk factor for mortality, stroke and heart failure. This emphasizes the need for proactive surveillance and holistic management of PAD patients who have AF.

4.2 Introduction

Peripheral arterial disease (PAD) is a major health problem associated with functional decline[3] and more than double risk of overall mortality, cardiovascular mortality, major coronary events and cerebrovascular events.[39,40] Proactive surveillance of PAD patients and recognition of potential risk factors for these adverse outcomes is of paramount importance. The prevalence of AF in PAD patients is high, ranging from 8% to 17.9% in different cohorts.[108,196] There is an increasing evidence that coexistence of these conditions further increases the risk of mortality and stroke.[197,198]

The management of AF has progressed towards integrated or holistic care, based on the ABC (Atrial fibrillation Better Care) pathway, incorporating a. Anticoagulation/ Avoidance of stroke, b. Better symptom management and c. Cardiovascular and Comorbidity optimization.[199,200] As part of the C criterion of the ABC pathway, attention to associated comorbidities is recommended. Given that PAD is common amongst AF patients[106,198,201] and since AF patients are commonly managed in the primary care setting, additional insights into the clinical epidemiology and risks of AF amongst PAD patients in primary care are needed, to plan surveillance and management pathways.

In this study, we aimed to investigate the significance of AF as a risk factor in a cohort of PAD patients.

4.3 Methods

This is a retrospective study of The Health Improvement Network (THIN) database. Data in the database are prospectively collected by participating primary care practices

after every encounter with the registered patient. It includes clinical diagnosis and symptoms, laboratory results, drug prescriptions and data on smoking habits which are recorded using the hierarchical "Read Code" System.[202] In addition, THIN data comprise demographic information, measurements of height and weight as well as information on social deprivation, which is expressed as quintiles of Townsend score[203]. It has been previously demonstrated that THIN data can be generalized to the whole UK population in regard to demographics, mortality rates and prevalence of major health conditions[204]. The study protocol was approved by the Scientific Review Committee (ref: 17THIN061).

The database has been researched to identify all patients with a new diagnosis of PAD during the time period from 01/08/1995 to 01/05/2017. To ensure data quality, only practices registered with the database for more than a year were included. Baseline demographics, significant previous diagnosis (including AF), medication, smoking history, Townsend score, body mass index (BMI) and kidney function expressed by glomerular filtration rate (GFR) have been recorded. A comparison of baseline characteristics was performed between the group of patients with PAD without AF and the groups of patients with PAD and AF, using descriptive statistics.

Causal inference is a challenge in all observational studies due to differences in baseline covariates and the possibility of bias. Propensity score matching and regression analysis are two statistical methods commonly used to reduce bias. Propensity score matching is increasingly used in medical research because it has several advantages over regression: it allows a study design similar to the design of randomized control trials, it focuses directly on the examined variable and it avoids

comparisons between non-comparable subjects.[205] In this study because of the large difference in baseline characteristic between the two examined groups, decision was made to use propensity score matching to allow comparison between subjects with similar characteristics. Regression analysis was then used to compare the outcomes between the two groups, in order to adjust for any residual differences in baseline covariates in the matched dataset.

Propensity score matching was conducted using R 4.1 and the MatchIt package (Stuart, King, Imai and Ho, 2011). Dataset was searched for outliers- none were identified. For continuous variables, missing values were removed and for categorial variables, missing values were considered as a missing category within that particular variable. Propensity score was estimated by running a logit model and matching method was based on nearest matching. Every patient in the dataset with PAD and baseline AF (case), was matched one to one to a patient with PAD without AF (control) with the nearest possible characteristics in regard to age, sex, ethnicity, smoking, BMI, Townsend index, renal function, medical treatment, history of diabetes, hypertension, stroke or transient ischaemic attack, heart failure, ischaemic heart disease and year of entry in the study.

All cases were censored from the date of PAD diagnosis (index date) until the exit date which corresponds to one of the following: the date of death, the date of transfer to a different practice, the date when their practice stopped providing data or the end of the data collection the 17/01/2018. Cox-regression analysis was performed and hazard ratios (HR) with their 95% confidence intervals (CIs) were calculated for the outcomes of death, stroke, ischaemic heart disease (IHD), heart failure and major amputation

(transtibial or higher). Only new diagnoses of stroke, IHD, HF and amputation that occurred during the follow up period were considered as incident outcomes; subjects with the investigated diagnoses at baseline were excluded from analysis. This method is commonly used in THIN database studies because it mitigates the risk of considering subsequent clinical codes related to the same clinical problem as a new adverse event. The variables included in the model were age, sex, ethnicity, smoking status, BMI, renal function, Townsend index, drug treatments (lipid lowering, antiplatelets and oral anticoagulants), background diagnosis of hypertension, diabetes and AF (Figure 8). Statistically significant relations have been defined by p values lower than 0.05. Statistical analysis was performed using IBM SPSS Statistics, Version 23.

As shown before, anticoagulation treatment can mitigate the increased risk of adverse outcomes imposed by coexisting AF and PAD[201]. A subgroup analysis was therefore performed, including only the patients who were not receiving any anticoagulation, in order to assess the relation of AF and PAD in this group.

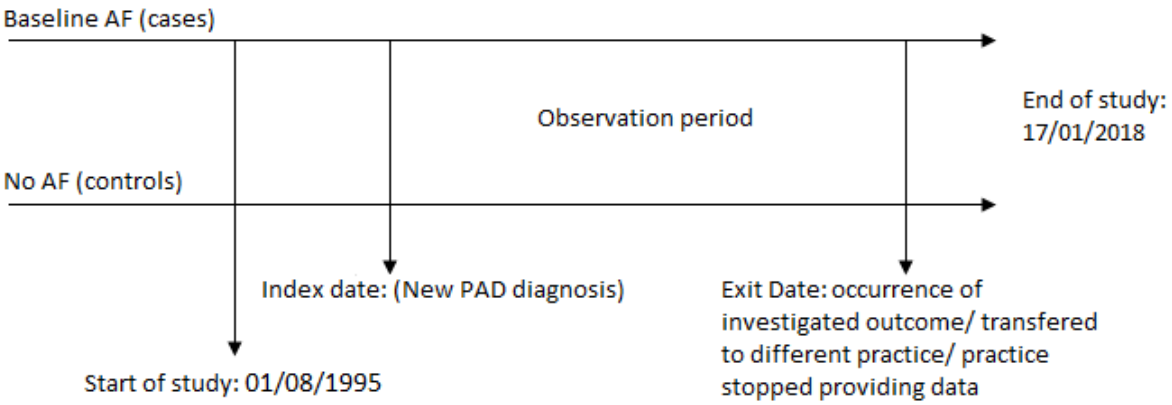


Figure 8 Visual representation of study timeline- comparison between exposed group (AF+ PAD) and control group (PAD without AF).

4.4 Results

During the studied period of 22 years, 55,540 patients with new diagnosis of PAD were detected in the database with 5,685 (10.2%) having coexisting AF. After propensity score matching two equal groups were created: PAD and AF (N= 5685, cases) and PAD with no AF (N= 5685, controls). Baseline characteristics in the initial dataset and after propensity score matching are summarized in Table 13 and

Table 14.

On multivariate cox-regression analysis AF was significantly associated with mortality (HR: 1.18, 95%CI 1.12- 1.26, p< 0.01), incident cerebrovascular events (HR: 1.35, 95%CI 1.17- 1.57, p< 0.01) and heart failure (HR: 1.87, 95%CI 1.62- 2.15, p< 0.01), with no significant relation with IHD (HR: 0.97 95%CI 0.81- 1.78, p= 0.78) and limb loss (HR: 1.06, 95%CI 0.85- 1.32, p= 0.59), (*Table 15*).

Subgroup analysis

In total 5431 patients with PAD that were not receiving oral anticoagulation were included in this analysis. The prevalence of AF in this subgroup was 43.1% (N=2339). On multivariate cox-regression analysis, AF was significantly associated with mortality (HR: 1.34, 95%CI 1.24- 1.45, p< 0.01), incident cerebrovascular events (HR: 1.55, 95%CI 1.27- 1.88, p< 0.01) and heart failure (HR: 2.03, 95%CI 1.63- 2.53, p< 0.01), while there was no significant relation with IHD (HR: 0.98, 95%CI 0.74- 1.29, p= 0.87) and limb loss (HR: 1.23, 95%CI 0.86- 1.75, p= 0.25).

Table 13 Baseline characteristics of patients with PAD and AF compared with PAD patients without AF in the initial dataset, before propensity score matching

	PAD with no AF	PAD and AF	P
N	49,855	5,685	
Age (IQR)	69.1 (11.7)	77.6 (9.3)	<0.01
Male %	60.7	59.9	0.240
BMI Category %	2.2	4.8	<0.01
Obese	21.2	23.3	<0.01
Overweight	33.3	32.7	<0.01
Normal	31.2	31.2	<0.01
Underweight	2.6	2.9	<0.01
Missing	11.8	9.9	<0.01
Smoking Status			

Smoker %	39.8	16.5	<0.01
Discontinued %	32.7	41.9	
Never smoker %	24.5	39.1	
Missing %	2.9	2.5	
Diabetes %	24.3	29.2	<0.01
Hypertension %	50.5	62.8	<0.01
IHD %	26.3	43.3	<0.01
Heart Failure %	5.6	28.4	<0.01
Stroke-TIA %	12.3	25.5	<0.01
Medication			
Lipid lowering %	55.6	61.9	<0.01
Anticoagulants %	5.7	58.9	<0.01
Antiplatelets %	63.4	77.8	<0.01

Table 14. Baseline characteristics of patients with PAD and AF compared with PAD patients without AF, after propensity score matching

	PAD with no AF	PAD with AF
N	5685	5685
Age Median (IQR)	78.0 (14.2)	78.3 (12.7)
Male (%)	3322 (58.4%)	3405 (59.9%)
BMI category		
Obese (%)	1297 (22.8%)	1326 (23.3%)
Overweight (%)	1972 (34.7%)	1860 (32.7%)
Underweight (%)	140 (2.5%)	163 (2.9%)
Normal (%)	1624 (28.6%)	1776 (31.2%)
Missing (%)	652 (11.5%)	560 (9.9%)
Smoking status		
Smoker (%)	1066 (18.8%)	940 (16.5%)
Discontinued (%)	2243 (39.5%)	2383 (41.9%)
Never smoker (%)	2193 (38.6%)	2220 (39.1%)
Missing (%)	183 (3.2%)	142 (2.5%)
Diabetes (%)	1588 (27.9%)	1659 (29.2%)
Hypertension (%)	3429 (60.3%)	3570 (62.8%)
eGFR< 30 (%)	281 (4.9%)	271 (4.8%)
IHD (%)	2403 (42.3%)	2462 (43.3%)
Heart Failure (%)	1532 (26.9%)	1614 (28.4%)
Stroke-TIA (%)	1330 (23.4%)	1451 (25.5%)
Medication		
Lipid-lowering (%)	3364 (59.2%)	3521 (61.9%)
Anticoagulant (%)	2593 (45.6%)	3346 (58.9%)
Antiplatelet (%)	4408 (77.5%)	4423 (77.8%)

eGFR= estimated Glomerular Filtration Rate, BMI= Body Mass Index, TIA= Transient Ischaemic Attack, IHD= ischaemic heart disease

Table 15. Comparison of outcomes between patients with PAD and AF (cases) Vs PAD patients without AF (controls).

Value	Death		Stroke or TIA		IHD		HF		Amputation	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Total number	5685	5685	4234	4355	3223	3282	4071	4153	5605	5588
Incidence N (%)	2617 (46.0%)	2417 (42.5%)	392 (9.3%)	345 (7.9%)	209 (6.5%)	234 (7.2%)	518 (12.7%)	313 (7.5%)	172 (3.1%)	163 (2.9%)
Person years FU	24,410	24,037	15,942	19,133	10,581	12,784	14,242	18,174	19,850	23,301
Unadjusted HR (95% CI) AF vs no AF	1.19 (1.13- 1.26)		1.30 (1.13- 1.50)		0.99 (0.82- 1.19)		1.93 (1.68- 2.22)		1.10 (0.89- 1.36)	
p value	<0.01		<0.01		0.91		<0.01		0.38	
Adjusted HR (95% CI) AF vs no AF	1.18 (1.12- 1.26)		1.35 (1.17- 1.57)		0.97(0.81- 1.78)		1.87 (1.62- 2.15)		1.06 (0.85- 1.32)	
p Value	<0.01		<0.01		0.78		<0.01		0.59	

FU= Follow Up, HR= Hazard Ratio, CI= Confidence Interval, TIA= Transient Ischaemic Attack, IHD= Ischaemic Heart Disease, HF= Heart Failure

4.5 Discussion

Principal finding of this study is that AF has a negative prognostic impact on patient with PAD and is related to higher mortality and higher risk of stroke and development of heart failure.

This is in accordance with previous reports, in a recent metanalysis of 6 prospective studies on patients with symptomatic PAD, the average prevalence of AF was 11.4% and this was significantly associated with mortality (OR: 2.52, 95%CI 1.91- 3.34) and major adverse cardiovascular events (OR: 2.54, 95%CI 1.78- 3.63).[206] When analysing the subgroup of patients not receiving oral anticoagulation these associations were strengthened.

There was no relation between baseline AF and rates of major amputation in this study. Previous evidence on the impact of AF on limb outcomes in PAD patients is limited. A study based on Taiwanese health insurance data has reported eight times higher risk of amputation in patients with newly diagnosed PAD and AF compared to PAD patients without AF; however, the population characteristics in this study are different with very low reported prevalence of AF (0.4%).[207] A single hospital study in England, has shown that PAD patients with AF are more prone to emergency PAD-related admissions and in hospital mortality.[108] A sub-study of EUCLID trial on PAD patients has identified AF as one of the main risk factors for the development of acute lower limb ischaemia (HR: 1.8, 95%CI 1.1- 3.2).[208] In the REACH registry, among patients with PAD, the presence of the AF at baseline doubles the risk of amputation

at 2 years, but was not predictive of revascularization or deterioration of vascular claudication.[107]

AF is a known predictor of mortality, stroke and heart failure in general population studies.[87,89,91,97,99] AF and PAD share several common risk factors such as hypertension, DM and coronary artery disease.[87] In our study we have shown that despite controlling for those risk factors the impact of AF on PAD patients remains significant. The exact mechanism that generates this association needs further investigation. AF is the main cause of cardioembolic stroke and is related with three times higher risk of extracranial systemic thromboembolism.[209,210] In addition, AF is associated with a prothrombotic, hypercoagulable state, endothelial disfunction and chronic inflammation as demonstrated with higher level of circulating biomarkers of coagulation cascade and inflammation.[210,211] AF is an indicator of systemic atherosclerosis and potentially increased burden of atherosclerotic disease, as has been demonstrated in two previous studies were AF patients presented with increased carotid intima-media thickness on ultrasound.[212,213]

Several studies demonstrate the merit of screening for AF in high risk patients[214,215] which has been reflected in recent ESC guidelines.[200] The findings of the study emphasize the need of comprehensive assessment of PAD patients for AF, given the high prevalence and associated risks. These patients need to be proactively treated according to the integrated ABC pathway and offered oral anticoagulation, heart rate control and optimization of risk factors and co-morbidities.[199,200]

Strengths and Limitations

This study's strength is its large sample of patients and long duration of follow up, but on the other hand there are several limitations. It is a retrospective study of administrative data which lack the accuracy of clinical data. Our data would not allow to make any distinction according to the burden/ clinical severity of PAD and clinical type of AF (permanent, paroxysmal persistent) and to investigate the impact of incident cases of AF.

In conclusion, this study emphasizes the high risk of adverse outcomes in patients with PAD and coexisting AF. Proactive surveillance and optimal medical management of these patients is mandated.

CHAPTER 5: PERIPHERAL ARTERIAL DISEASE IN A COHORT OF ATRIAL FIBRILLATION PATIENTS. THE ATRIAL FIBRILLATION FOLLOW-UP INVESTIGATION OF RHYTHM MANAGEMENT (AFFIRM) STUDY

5.1 Abstract

Background: Peripheral arterial disease has been linked with worse outcomes in patients with atrial fibrillation. The aim of this study is to assess the impact of peripheral arterial disease on mortality and stroke in a cohort of atrial fibrillation patients.

Methods: This was an ancillary analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial. A comparison of baseline characteristics was made between atrial fibrillation patients with and without diagnosed peripheral arterial disease. Multivariate cox regression analysis was performed to compare the risk of stroke, death and cardiovascular death among the two groups.

Results: The prevalence of peripheral arterial disease in the whole cohort of 4060 atrial fibrillation patients was 6.7%. Patients with peripheral arterial disease tended to be older, had higher prevalence of diabetes mellitus, hypertension and smoking, they were more likely to give a history of coronary artery disease, heart failure, cardiac surgery or cardiac intervention and stroke or TIA (all $p<0.05$). After multivariate adjustment, peripheral arterial disease was significantly associated with overall higher

mortality (HR: 1.34, 95%CI 1.06- 1.70, p= 0.016) in atrial fibrillation patients, but the rates of ischaemic stroke were similar in the two groups (3.9% vs 3.5%, p= 0.874).

Subgroup analysis confined to the non-anticoagulated atrial fibrillation patients showed that peripheral arterial disease was an independent predictor of ischaemic stroke (HR: 3.37, 95%CI 1.25- 9.09, p< 0.016).

Conclusion: Peripheral arterial disease predicts higher mortality in atrial fibrillation, and was an independent predictor of ischaemic stroke in non-anticoagulated atrial fibrillation patients. Proactive surveillance and optimization of medical management in this group of patients is warranted, given the high risks associated with peripheral arterial disease where atrial fibrillation is also present.

5.2 Introduction

Atrial fibrillation and peripheral arterial disease are two conditions associated with high risk of cardiovascular and cerebrovascular complications and mortality.[39,40,98,99,216] There is evidence that coexistence of both these clinical conditions can result to an additive risk of adverse events.[103] Indeed, atherosclerotic vascular disease has been linked with stroke, thromboembolism and death in subjects with atrial fibrillation and has been therefore included as one of the components of risk scores, such as the CHA_2DS_2-VASc score (Congestive Heart failure, Hypertension Age> 75 years, DM, Stroke, Vascular disease) in order to stratify risk in atrial fibrillation patients.[104]

The aim of this study is to assess the impact of peripheral arterial disease on mortality and stroke in a cohort of atrial fibrillation patients, as an ancillary analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial.

5.3 Methods

The design and the primary results of the AFFIRM study have been reported.[217,218] Briefly, the AFFIRM was a randomized, multicenter comparison of treatment strategies (rate control strategy or rhythm control strategy) in patients with atrial fibrillation who were at least 65 years of age or who had other risk factors for either stroke or death. Each participating site's Institutional Review Board approved the study protocol, and each patient signed informed consent.

Patients were categorized according to a positive or negative history of peripheral arterial disease, which was investigator defined. A history of significant cardiovascular diagnoses, associated risk factors and medication was recorded at the time of

randomization, with an interview administered questionnaire. After randomization patients were assigned to regular follow up and clinical events including death, cardiovascular death and ischaemic stroke were recorded.

Statistical analysis

Descriptive statistics were used to compare baseline characteristics and clinical events in the two groups. Chi-square test was used to identify significant differences in nominal variables. Continuous variables were assessed for normality and Mann–Whitney U test was performed to compare medians of non-normally distributed variables.

For each of the examined outcomes (death, cardiovascular death, stroke) univariate and multivariate cox regression analysis was performed to estimate hazard ratios at presence of peripheral arterial disease and other clinically relevant variables. Potential confounders that were inserted in multivariate regression were: age, gender, main cardiovascular risk factors (smoking, diabetes, hypertension), medical history (myocardial infraction, previous stroke or transient ischaemic attack, heart failure) and medical treatment (warfarin, aspirin, lipid lowering medication). A forward conditional process was used, in order to select variables to be included in the final model. Statistical analysis was performed with IBM SPSS Statistics, Version 23. Significant differences were defined by p values lower than 0.05.

The same analysis was performed for the subgroup of atrial fibrillation patients not receiving oral anticoagulation in order to assess the impact of peripheral arterial disease on outcomes (particularly ischaemic stroke).

5.4 Results

Study enrolled 4060 patients at 213 sites in North America. A diagnosis of peripheral arterial disease was reported in 282 (6.7%) patients. Patients with peripheral arterial disease tended to be older, had higher prevalence of diabetes, hypertension and smoking, they were more likely to give a history of coronary artery disease, heart failure, cardiac surgery or cardiac intervention and stroke or TIA (all $p<0.05$). There was no significant difference in the ratio of patients on oral anticoagulation in the two groups (85.1% vs 84.5%, $p=0.864$)

Mean follow up was 3.5 years (range, 2-6 years). Patients with and without peripheral arterial disease were evenly assigned in the two arms of the study. In total, 666 (16.4%) patients died, including 331 (8.2%) cardiovascular deaths and 157 (3.9%) ischaemic stroke events during follow up.

Baseline characteristics of the two groups and clinical outcomes are summarized in Table 16. During the follow up period peripheral arterial disease patients had higher mortality (29.4% vs 15.4%, $p<0.001$) and cardiovascular mortality (16% vs 7.6%, $p<0.001$), but there was no significant difference in the rates of ischaemic stroke (3.9% vs 3.5%, $p=0.77$).

Table 16. Baseline characteristics of atrial fibrillation patients with and without peripheral arterial disease.

	No PAD N= 3778 (93.3 %)	**PAD** N= 282 (6.7%)	**p**
Demographics			
Median Age (IQR)	71 (11)	72 (10)	0.002
Male %	60.4	65.2	0.108
Ethnic Minority %	11.3	12.1	0.700
History prior to randomization %			
Hypertension	70.1	80.9	<0.001
Diabetes	19.2	30.5	<0.001
Smoking	11.4	23.8	<0.001
Coronary artery disease	36.4	62.4	<0.001
Myocardial Infraction	16.1	34.4	<0.001
Angina	24.2	46.5	<0.001
Congestive Heart Failure	21.7	41.8	<0.001
CABG	11.2	30.1	<0.001
Cardiac Intervention	8.3	14.5	<0.001
Pacemaker	5.9	9.6	0.013
Stoke/ TIA	12.9	19.5	0.002
Pulmonary Disease	13.4	29.4	<0.001
Medication prior to randomisation %			
Aspirin	26.3	30.5	0.127
Warfarin	85.1	84.5	0.800
Aspirin and Warfarin	16.6	21.6	0.031
Angiotensin/ ACE inhibitor	38.2	48.6	0.001
Beta blocker	42.7	40.9	0.561
Diuretic	41.7	55.7	<0.001
Nitrate	17.4	36.5	<0.001
Lipid lowering agent	21.5	35.1	<0.001
Study arm and follow up			
Median follow up days (IQR)	1311(705)	1225 (740)	0.161
Rate control arm	50	49.3	0.853
Events after randomisation %			
Stroke	3.9	3.5	0.772
Death	15.4	29.4	<0.001
CV Death	7.6	16.0	<0.001
Stroke or death	18.1	31.2	<0.001

PAD= Peripheral Arterial Disease, IQR= interquartile range, CABG= coronary artery bypass graft, TIA= transient ischaemic attack, ACE= angiotensin converting enzyme, CV= cardiovascular

On univariate Cox regression analysis, peripheral arterial disease predicted all-cause mortality (hazard ratio (HR): 2.07, 95% confidence interval (CI) 1.65- 2.61, p< 0.001), cardiovascular mortality (HR: 2.27, 95% CI 1.66- 3.11, p<0.001) and the combined outcome of stroke or death (HR: 1.87, 95% CI 1.50- 2.33, p< 0.001) but there was no significant correlation between peripheral arterial disease and risk of ischaemic stroke. On multivariate analysis, peripheral arterial disease remained an independent predictor for overall mortality (HR: 1.34, 95%CI 1.06- 1.70, p= 0.016) and the combined outcome of stroke or death (HR: 1.28, 95%CI 1.02- 1.61, p= 0.037) but not for cardiovascular mortality (p=0.178) or stroke (p=0.674), (*Table 17*).

Table 17. Multivariate Cox regression: factors predicting adverse clinical events and corresponding hazard ratios.

	HR	**95% CI**	**P**
Death			
Age	1.06	1.05- 1.08	<0.01
Female gender	0.83	0.71- 0.98	0.03
History of PAD	1.34	1.06- 1.70	0.02
History of MI	1.49	1.25- 1.78	<0.01
History of Stroke or TIA	1.58	1.30- 1.92	<0.01
History of CHF	2.29	1.95- 2.69	<0.01
History of Diabetes	1.51	1.27- 1.79	<0.01
History of Smoking	1.60	1.29- 1.98	<0.01
Warfarin	0.68	0.56- 0.83	<0.01
Lipid-lowering agents	0.79	0.64- 0.96	0.02
Stroke or Death			
Age	1.06	1.05- 1.07	<0.01
History of PAD	1.28	1.02- 1.61	0.04
History of MI	1.55	1.32- 1.83	<0.01
History of Stroke or TIA	1.55	1.29- 1.86	<0.01
History of CHF	2.05	1.76- 2.39	<0.01
History of Diabetes	1.48	1.26- 1.74	<0.01
History of Smoking	1.55	1.27- 1.90	<0.01
Warfarin	0.72	0.61- 0.87	<0.01

Lipid-lowering agents	0.74	0.61- 0.89	<0.01
Cardiovascular Death			
Age	1.05	1.03- 1.07	<0.01
History of MI	1.90	1.51- 2.40	<0.01
History of Stroke or TIA	2.01	1.56- 2.60	<0.01
History of CHF	3.17	2.53- 3.97	<0.01
History of Diabetes	1.64	1.30- 2.08	<0.01
History of Smoking	1.44	1.06- 1.97	0.02
Stroke			
Age	1.03	1.01- 1.05	<0.01
Female gender	1.59	1.15- 2.19	<0.01
History of MI	1.93	1.33- 2.80	<0.01
History of Stroke or TIA	1.59	1.07- 2.37	0.023
History of Diabetes	1.50	1.04- 2.15	0.030
Lipid-lowering agents	0.56	0.35- 0.88	0.011

HR= hazard ratio, CI= confidence interval, PAD= peripheral arterial disease, MI= myocardial infraction, TIA= transient ischaemic attack, CHF= congestive heart failure

Sensitivity analyses

The subgroup not receiving oral anticoagulation consisted from 626 patients. Rates of death, cardiovascular death and stroke in this group were 21.4%, 9.3% and 4.6% respectively. On univariate analysis, peripheral arterial disease was associated with death (HR: 2.40, 95%CI 1.44- 4.00, p= 0.001), cardiovascular death (HR: 2.98, 95%CI 1.46- 6.06, p= 0.003), ischaemic stroke (HR: 3.42, 95%CI 1.30- 8.97, p= 0.012) and the combined outcome stroke or death (HR: 2.49, 95%CI 1.54- 4.04, p< 0.001). On multivariate cox regression model, peripheral arterial disease was an independent predictor of ischaemic stroke (HR: 3.37, 95%CI 1.25- 9.09, p< 0.016), (t*able 18*).

Table 18. Multivariate Cox regression in non-anticoagulated subgroup: factors predicting stroke and corresponding hazard ratios.

	HR	**95% CI**	**P**

Stroke			
History of PAD	3.37	1.25- 9.09	0.02
History of MI	3.00	1.36- 6.61	<0.01
Lipid-lowering agents	0.09	0.01- 0.70	0.02

HR= hazard ratio, CI= confidence interval, PAD= peripheral arterial disease, MI= myocardial infraction

5.5 Discussion

Principal finding of this study is the association of peripheral arterial disease with worse survival in atrial fibrillation patients. Secondly, peripheral arterial disease was an independent predictor of ischaemic stroke amongst non-anticoagulated patients with atrial fibrillation which is perhaps the more appropriate subgroup of interest, since we are asking the question if peripheral arterial disease is a stroke risk factor per se (hence, requiring anticoagulation), and the event rates presented are not influenced by anticoagulation.

In general population studies, peripheral arterial disease is considered an indicator of generalised atherosclerosis and is associated with increased risk of overall mortality, cardiovascular mortality, major coronary events and stroke.[39,40] This study adds to existing evidence, showing that peripheral arterial disease is a predictor of mortality in patients with atrial fibrillation and reaffirms findings from other cohorts. In a Danish prospective cohort study of 3325 patients with atrial fibrillation, the adjusted hazard ratios (HR) for stroke, death and combined endpoint of stroke or death at presence of peripheral arterial disease were 0.87 (95%CI 0.52- 1.46), 1.76 (95%CI 1.30- 2.37) and 1.37 (95%CI 1.03- 1.81) respectively.[197] Similarly in the prospective APARACIS Study, in a cohort of 2,027 patients with atrial fibrillation, abnormal ankle-brachial pressure index (ABPI) predicted vascular death (HR: 2.05, 95%CI 1.25- 3.34) and myocardial infraction (HR: 2.71, 95%CI 1.41- 5.99), with 65.2% of the patients being on oral anticoagulation. [198] On the other hand, a sub-study on 2975 patients from the EORP-AF cohort, with 59.9% of patients receiving oral anticoagulation, did not demonstrate

independent relation between peripheral arterial disease and mortality or CV mortality.[219] Second, peripheral arterial disease did not cause significant increase in stroke rate in this study, when the whole cohort was examined, with 85% of the patients being on warfarin. This is consistent with the findings from previous studies[197,198].

However, in non-anticoagulated patients, we found that peripheral arterial disease is a strong and independent predictor of stroke. This justifies its inclusion into stroke risk stratification scheme, such as the CHA_2DS_2VASc score, scoring 1 point for a V criterion[220 221]. Similarly, in a Taiwanese cohort of 7920 non-anticoagulated patients with atrial fibrillation, peripheral arterial disease was independently associated with ischaemic stroke (OR: 1.81, 95%CI).[105] Oral anticoagulation has been reported to reduce stroke by 64% and all-cause mortality by 26% in atrial fibrillation[222], which possibly explains the strengthened correlation between peripheral arterial disease and stroke in patients that do not receive oral anticoagulant therapy.

Limitations

This study has several limitations. It is a retrospective study on a trial dataset that was designed for different research questions. The definition of peripheral arterial disease is based on clinical history and previous diagnosis of the disease. It is known that in the majority of cases peripheral arterial disease is asymptomatic[6,223], we can therefore expect that this condition was possibly under-diagnosed. Additionally, those cases who were recorded, were most likely the symptomatic ones, which could reflect more advanced peripheral arterial disease and higher burden of atherosclerosis in these

patients. However, there are no available data on stage and severity of peripheral arterial disease. Cohort studies that used screening tests (ABPI measurements) to detect peripheral arterial disease, have reported prevalence of peripheral arterial disease in patients with atrial fibrillation from 21% to 27% [106,198] which is considerably higher than the rate of diagnosed peripheral arterial disease in this study (6.7%). Despite the difference in prevalence of peripheral arterial disease, the conclusions from these studies were similar, indicating worse survival in atrial fibrillation patients with peripheral arterial disease.

5.6 Conclusion

Peripheral arterial disease is associated with higher mortality in atrial fibrillation, and is an independent predictor of ischaemic stroke in non-anticoagulated atrial fibrillation patients. Proactive surveillance and optimization of medical management in this group of patients is warranted, given the high risks associated with peripheral arterial disease where atrial fibrillation is also present.

CHAPTER 6: DISCUSSION AND CONCLUSION

This Thesis attempted to improve understanding in two emerging concepts: the interaction between ethnicity and PAD as well as the interaction between AF and PAD. It has been demonstrated that ethnicity may influence the epidemiology and the outcomes of PAD. The review of literature performed in Chapter 2 demonstrates that prevalence of PAD is higher in populations of Black ethnicity and lower in Asian populations when compared with White populations with similar findings when investigating patients with diabetes. In Chapter 3, a descriptive study of Hospital Episode Statistics has shown that Black patients with PAD in England are at higher risk of limb loss after a bypass operation or endovascular intervention for femoropopliteal disease compared to Whites, while South Asian patients have similar risk to Whites. This Thesis has added on the existing evidence that coexisting AF and PAD significantly increase the risk of adverse outcomes. In Chapter 4, analysis of primary care data from the THIN database has shown that AF is a risk factor for mortality, cerebrovascular events and heart failure in patients with PAD. In Chapter 5, an ancillary analysis of the AFFIRM Trial dataset indicated that PAD is a risk factor for mortality in patients with AF and a strong risk factor for stroke in the subgroup of patients that were not on anticoagulation.

As discussed in the relevant chapters these differences cannot be totally attributed to the different prevalence of known cardiovascular risk factors. We can therefore hypothesize that there are several confounding factors and mechanisms that could

explain these results. Those could be classified as genetic, pathophysiological, behavioural/ environmental.

Genetic Factors

There is increasing evidence that complex genetics are contributing to the epidemiology and pathophysiology of PAD and AF. It has been demonstrated that heritability is an important factor for the development of PAD. In the Swedish Twin Registry, the odds ratio of having PAD in individuals whose twin had PAD compared with individuals whose twin did not have PAD was 17.7 (95%CI 11.7- 26.6) for monozygotic twins and 5.7 (95%CI 4.1- 7.9) for dizygotic twins.[224] In a study of asymptomatic siblings of patients with premature PAD (aged<49 years), ultrasound has detected occult lower extremity atherosclerosis in half of the subjects.[225] The GENOA study and the Framingham Offspring cohort study also found modest heritability in ABPI variations.[226,227]

There are indications that genetic factors may contribute to ethnic differences in PAD. In the Bogalusa Heart Study, post-mortem examination of adolescent and young adults found more extensive aortic surface involvement with fatty streaks in Blacks compared with Whites (37% vs 16%, p=0.0003). This was independent of gender, age at death, and cardiovascular risk factors such as serum lipids and lipoproteins, blood pressure and obesity.[228] Data from the National Health and Nutrition Examination Survey show that Blacks have lower mean ABPI compared to Whites even when examining younger (aged<50 years) and healthy individuals without cardiovascular risk factors.[229] Genetics may also influence one ethnic group's susceptibility to certain cardiovascular

risk factors or alter response to medical treatments.[230,231] For example, national guidelines in the UK recommend different antihypertensive treatments for Black patients. [232]

To date, no definitive genetic markers have been identified for PAD. This may be because of the heterogeneity of clinical presentation of PAD, the modest effect of examined genes and the interaction between genetic and other risk factors like smoking and diabetes.[233]

It has been documented that complex genetic mechanisms are linked with AF with more than 160 genes having been associated with AF during the last decades. The exact role of genetics in epidemiology, pathophysiology and association of AF with other diseases such as atherosclerotic disease is the field of ongoing research.[234,235]

Better understanding of genetics of AF and PAD could improve our understanding of their pathophysiology, their natural history and their interaction and could clarify the role of ethnicity. This would help identify individuals at high risk and offer targeted interventions or even individualized treatment, reducing morbidity and mortality.[236]

Pathophysiological Factors

There is emerging evidence that AF and PAD share several common pathophysiological mechanisms. The critical role of endothelial dysfunction, inflammation, platelet activation, oxidative stress and hypercoagulability in pathogenesis of atherosclerosis is well established. Endothelial dysfunction occurs early in the development of atherosclerosis as a response to noxious stimuli such as turbulent flow, shear stress, unfavourable lipid profile or smoking. This results in reduced nitric oxide (NO)

bioavailability and disruption of the normal vasodilatory, anti-inflammatory and anti-thrombotic properties of the endothelium. Endothelial injury increases its permeability, precipitates adhesion of leucocytes and initiates inflammatory response with release of cytokines, growth factors and free radicals. Migration and proliferation of smooth muscle cells causes remodelling of the vessel wall and development of atherosclerotic plaque. Platelet activation occurs as a response to endothelial damage, reactive oxygen species and pro-inflammatory mediators. Activated platelets express adhesion molecules, release mediators that enhance the inflammatory process and the expansion of the plaque and contribute to a procoagulant phenotype by promoting the coagulation cascade. Macrophages and T lymphocytes accumulate it the lesion, with further release of inflammatory mediators, further cellular damage, amplification of the inflammatory response and progression of atherosclerosis. [236–239] Inflammation is a key factor in the evolution from atherosclerosis to atherothrombosis.[240] Increased CRP levels have been associated with increased risk of coronary heart disease, ischaemic stroke and vascular mortality.[241]

There is emerging evidence about the importance of the same mechanisms in AF. Endothelial/ endocardial cell damage with oedema and fibrinous transformation are a common finding. There is reduced NO synthesis, increased platelet activation and hypercoagulability.[210] Increased levels of circulating inflammatory cytokines and inflammatory cells as well as infiltration of myocardium by macrophages are indicative of an inflammatory state.[210,242,243] There is close relationship between inflammation, endothelial dysfunction, platelet activation, thrombogenesis and prognosis of AF.[242,244–246] Inflammatory markers, mainly CRP and IL-6 are associated with increased

risk of stroke and thromboembolism in AF, however this association seems to be mostly driven by the comorbidities related with inflammation.[240,245]

It is therefore evident that there is a considerable overlap between the pathophysiology of PAD and AF and this could partially explain the observed disproportionally higher risk of adverse cardiovascular events when these two conditions coexist. The endothelial disfunction, inflammation, oxidative stress, hypercoagulability, and platelet activation caused by each of these conditions could potentially interfere with the pathophysiology and natural history of the other. [247] It has been hypothesized that atherosclerotic disease could generate a systemic inflammatory response, with circulating cytokines and inflammatory cells travelling downstream to the myocardial cell and initiating the pathophysiological process that leads to AF. A different hypothesis is that both conditions may share a common origin, initiating with a low grade inflammation in the vessel which escalates and leads to the development of either atherosclerosis or AF.[248]

However, our knowledge of these complex pathophysiological mechanisms is only just emerging with many important questions yet to be answered. The exact role of inflammation in the course of PAD and AF is not yet fully understood. It has not yet been established if inflammation is the cause or the consequence of these conditions and if inflammation is the manifestation of underlying comorbidities. The prognostic value of biomarkers and the role of anti- inflammatory interventions in AF and PAD are still controversial. Further research on these mechanisms could potentially lead to the

development of new strategies for prevention and treatment of these conditions.[236,245,248]

Ethnic differences in epidemiology and outcomes of PAD could also be attributed to variations of the same pathophysiological pathways, although the available evidence to support this hypothesis is currently scarce. It has been shown that different ethnic groups have different circulating levels of biomarkers of inflammation, endothelial damage and thrombosis. In two studies where multivariate regression was used, these biomarkers could only partially justify the higher prevalence of PAD in African Americans compared to Whites.[24,66] Whether the observed difference in biomarker levels has any impact on the clinical course of PAD and the failure rates of revascularization procedures in different ethnic groups is currently unknown.

Behavioural and Environmental factors

Several environmental factors that are not commonly accounted for such as diet, psychological factors, physical inactivity and sleep quality could possibly influence the natural history of PAD and AF. All these factors are related to socioeconomic status and ethnicity. It has been shown that low socioeconomic position predisposes to inflammation, which is only partially explained by the higher prevalence of traditional risk factors such as smoking, alcohol use and obesity. Stress can result in systemic inflammation mediated either by the hypothalamus- pituitary- adrenal axis or by autonomic nervous system.[249] Studies in the US have demonstrated that female gender, Black race, low income and low level of education are all significantly related to increased CRP and systemic inflammation.[250] Similarly in the UK healthy Indian

Asians have been found to have higher CRP concentrations compared to Whites.[251] There is evidence that this process starts quite early in the life of affected individuals, African American and Hispanic children whose parents were born abroad, are at significantly higher risk of systemic inflammation even after adjustment for relevant demographic characteristics and health conditions. A proposed explanation for this finding is the exposure to different environmental factors, discrimination, physical and psychological stress.[252] The interaction between low socioeconomic position, race and poor health is complicated and multifactorial, African Americans of high education and high income are still not gaining the same health related advantages compared to Whites of similar socioeconomic position. This has been attributed to institutional, and structural discrimination and higher levels of effort required for upward social movement, resulting in depression and anxiety.[253–255]

Poor sleep quality and quantity predisposes to cardiovascular and metabolic diseases.[256] There is increasing evidence that minority ethnic groups in the US suffer from higher rates of sleep disorders and sleep apnea compared to Whites. These disorders are related to inflammation and activation of the sympathetic nervous system and have been hypothesized to contribute to the higher prevalence of cardiovascular disease and cardiovascular risk factors such as diabetes and hypertension in African Americans.[257,258]

The importance of a healthy diet for prevention of cardiovascular disease is well established.[259] Dietary differences among ethnic groups are dependent on many factors such as awareness, income and socioeconomic status, culture and religion.[260]

Data about the impact of dietary differences in health disparities and about the efficacy of interventions aiming to improve dietary habits in ethnic minority groups are currently missing and this area would merit further research.[261,262]

Several studies have suggested that inequalities related to access to healthcare could be accounted for the worse cardiovascular outcomes in ethnic minorities. Data from the US suggest that African Americans are less likely to be aware of their cardiovascular risk factors such as diabetes and hypertension and less likely to achieve adequate control.[257] The UK seems to be performing better is some of these areas with recent data indicating that the standard of care for diabetic patients from minority ethnic groups is equivalent to that of the general population, with healthcare practitioners demonstrating high level of awareness about the increased cardiovascular risks in these groups.[43] It has been therefore assumed that access to an equal national healthcare system such as the NHS could alleviate some of the ethnic differences in healthcare outcomes, although the evidence is lacking.[264] On the other hand, other reports highlight important barriers to access to healthcare for ethnic minorities in the UK. Those barriers seem to affect several areas, with big deficiencies identified in relation to access to mental health services as well as provision of interpreting services, discriminatory treatment and data monitoring.[265] It is estimated that language barriers compromise access to healthcare for almost 300,000 members of ethnic minorities in the UK.[266] It is widely accepted that the problem of healthcare disparities is multifactorial and has got its origins far beyond the healthcare system, in the social structure and the cultural environment where ethnic minorities live. These can influence the effectiveness of screening strategies, the adherence to evidence

based treatment, the uptake of preventive measures and the reaction to potential side effects from therapies. [25,257] As a result, any attempt to address this complex issue limited within the confines of the healthcare system is bound to fail. Tackling health inequalities would require investing in strategies with a holistic approach to the problem, involving practitioners and researchers from multiple disciplines such as clinical medicine, sociology, public health and basic science.

LIST OF PUBLICATIONS ARISING FROM THIS THESIS

Vitalis A, Shantsila A, Kay M, Vohra RK, Lip GYH. Outcome of Femoral Angioplasty/Stenting Procedures in Different Ethnic Groups in England: A Retrospective Analysis of Hospital Episode Statistics and Review of Literature. J Endovasc Ther. 2022 Jan 13:15266028211070967. doi:10.1177/15266028211070967.

Vitalis A, Nirantharakumar K, Thayakaran R, Vohra RK, Kay M, Shantsila A, Lip GYH. The Impact of Atrial Fibrillation on Outcomes of Peripheral Arterial Disease: Analysis of Routinely Collected Primary Care Data. Am J Med. 2022 Apr;135(4):488-492. doi:10.1016/j.amjmed.2021.10.021.

Vitalis A, Shantsila A, Lip GYH. Reply to Kawada: Peripheral Arterial Disease, Stroke, and Mortality in Patients with Atrial Fibrillation. Am J Med. 2022 Feb;135(2):e59-e60. doi:10.1016/j.amjmed.2021.09.019.

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LIST OF PRESENTATIO NS ARISING FROM THIS THESIS

Vascular Society Annual Meeting, 2020
The impact of atrial fibrillation on patients with peripheral arterial disease. A retrospective study of a large healthcare database in United Kingdom. A. Vitalis, K. Nirantharakumar, R. Thayakaran, A. Shantsila, M. Kay, R.K. Vohra, G.Y.H. Lip

European Society of Cardiology (ESC) Congress, 2020
Atrial fibrillation in a cohort of patients with peripheral arterial disease. A retrospective study of a large healthcare database in United Kingdom. A. Vitalis, A. Shantsila, R. Thayakaran, K. Nirantharakumar, G.Y. Lip

European Society of Cardiology (ESC) Congress, Barcelona 2017
Peripheral arterial disease in a cohort of atrial fibrillation patients. The Atrial Fibrillation Follow Up Investigation Of Rhythm Management (AFFIRM) study. A. Vitalis, GYH. Lip, M. Proietti, B. Olshansky, A. Shantsila

Vascular Society Annual Meeting, Manchester 2017
Comparison of outcomes of femoropopliteal bypass procedures among ethnic groups in England. A retrospective analysis of Hospital Episode Statistics. A. Vitalis, M. Kay, A. Shantsila, G.Y.H. Lip, R.K. Vohra.

Comparison of outcomes of femoral angioplasty/stenting procedures among ethnic groups in England. A retrospective analysis of Hospital Episode Statistics. A. Vitalis, M. Kay, A. Shantsila, G.Y.H. Lip, R.K. Vohra.

Cardiovascular sciences away day, Birmingham 2016
Ethnic differences in the prevalence of peripheral arterial disease, a review of literature. A. Vitalis

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