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Correlations between Peripheral Artery Disease and Cardiovascular Disease Outcomes

by

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Dedication

This thesis is dedicated to three individuals who have shaped my life in immeasurable ways. First, to my husband, Tom, with much love and thanks for his unfailing encouragement and support. Second, I owe a debt of gratitude to my parents, Dan and Enid, who have been with me every step of the way as incomparable role models and a source of inspiration. Your love and support nurtured my scientific curiosity and has driven me to great achievements. Thank you.

Abstract

Lower-extremity peripheral artery disease (PAD) is a manifestation of atherosclerotic disease in the lower limbs. PAD is a risk factor for poor outcomes including myocardial infarction, stroke, and mortality. Despite the potential benefits of early PAD detection, in the majority of PAD cases patients are asymptomatic, and as a result, PAD is underdiagnosed and undertreated. Furthermore, additional evidence is needed to clarify if PAD prevalence varies between ethnic groups. In short, the true burden of PAD is unknown.

The main objective was to explore the prognostic relationship between PAD and outcomes in patients undergoing coronary angiography. Prospective collection of an ankle-brachial index (ABI), a non-invasive test with a high sensitivity and specificity for detecting PAD, was undertaken in 1100 patients. As ABI is often dichotomized for use in PAD detection and risk stratification, we examined continuous ABI as a risk marker and predictor of outcomes. We also undertook a systematic review of PAD prevalence studies and a cross-sectional analysis of cohort data to investigate the ethnic burden of PAD.

Patients undergoing coronary angiography who have PAD (ABI $\leq$ 0.90) had 4.3 times more complex coronary artery disease (CAD) (adjusted OR 4.3, 95% CI 1.2, 14.9; p=0.022), 3.5 times more myocardium at risk (adjusted OR 3.5, 95% CI 1.7, 7.1; p=0.001), and less complete coronary revascularization (adjusted OR 3.0, 95% CI 1.1, 8.8; p=0.039) than patients with a normal ABI. At the other end of the ABI spectrum, there was no positive association between

ABI > 1.40 and systolic inter-arm blood pressure difference (IAD) ≥ 10mmHg; rather there was a trend for a negative association (adjusted OR 0.3, 95% CI 0.1, 1.3; p=0.117).

Differences in PAD prevalence were found in our systematic review where South Asians had significantly less PAD than White Europeans. Interestingly, no differences in PAD prevalence were found across six ethnic groups of patients undergoing hemodialysis.

Our results support ABI use in screening and risk prediction in patients undergoing coronary angiography. More evidence is needed to determine the mechanisms for ethnic differences in PAD prevalence and further discussion of ABI is necessary to develop population appropriate guidelines.

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List of Symbols, Nomenclature, or Abbreviations

ABI	Ankle-brachial index
AHA	American Heart Association
APPROACH	Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CKD	Chronic kidney disease
CKDCS	Canadian Kidney Dialysis Cohort Study
CVD	Cerebrovascular disease
DM	Diabetes mellitus
ESRD	End stage renal disease
GFR	Glomerular filtration rate
HDL	High-density lipoprotein
HR	Hazard ratio
ICD	International classification of disease
IAD	Inter-arm blood pressure difference
LDL	Low-density lipoprotein
MI	Myocardial infarction
NHANES	National Health and Nutrition Examination Survey
NSTEMI	Non-ST segment elevation myocardial infarction
OR	Odds ratio
PAD	Peripheral artery disease
PCI	Percutaneous intervention

List of Symbols, Nomenclature, or Abbreviations continued

RR	Relative risk
SA	South Asian
SD	Standard deviation
STEMI	ST segment elevation myocardial infarction
SYNTAX	SYNergy between PCI with TAXUS™ and Cardiac Surgery
WE	White European

CHAPTER 1: LITERATURE REVIEW

1.1 Epidemiology of Peripheral Artery Disease

Lower-extremity peripheral artery disease (PAD) is characterized by inadequate blood flow in the lower limbs due to atherosclerosis, leading to progressive stenosis and ultimately occlusion of blood flow. More common in the elderly and certain ethnic groups, PAD shares a number of risk factors with coronary artery disease (CAD) and cerebrovascular disease (CVD).

1.1.1 *Pathophysiology of Atherosclerosis*

The blood vessel wall is composed of three layers: the intima, the media, and the adventitia. The intima is a single layer of endothelial cells exposed to the lumen which acts as a barrier and releases anti-thrombotics to prevent blood clotting. The media layer is composed of smooth muscle cells and an extracellular matrix (ECM) of fibrillar collagen and elastin. This middle layer is regulated by secretion of vasodilators or vasoconstrictors from the endothelial cells that cause the cells to relax or contract. The third layer, the adventitia, is composed of connective tissue that gives the vessel support.

Atherosclerotic development begins as a result of endothelial dysfunction. Endothelial cells are affected by physical forces such as hypertension, disrupted laminar flow, and by chemical forces such as high concentrations of blood glucose, imbalanced lipid levels, and toxic materials introduced to the blood stream from smoking. Any or all of these factors can cause the endothelial cells to release reactive oxygen species which affect cellular functions, including

changes in the concentrations of anti-thrombotics, vasodilators, and the release of inflammatory cytokines.

Damaged endothelial cells become permeable to lipoproteins, allowing them to penetrate into the intima layer. Lipoproteins carry water-insoluble lipids in the blood and by emulsification allow lipids to move through the water inside and outside of the cell. Within the intima layer, low-density lipoproteins (LDL) molecules bind to the cell wall where the increase in reactive oxygen species causes oxidation of LDL. This oxidation (and/or glycation in the presence of high glucose concentrations) attracts monocytes which differentiate into macrophages. The macrophages then ingest the modified LDL molecules forming cholesterol and lipid filled foam cells. These foam cells form the fatty streak which is the first visible stage of atherosclerosis development.[1,2]

Stimulated by the development of the foam cells, smooth muscle cells move into the intima layer from the media layer and proliferate. At the same time, leukocytes are activated by cytokines and growth factors released from the foam cells. Together, the leukocytes and foam cells unite under a fibrous cap of ECM tissue forming an atheroma on the vessel wall. The lesion development advances as thrombogenic factors are released from within the cap causing platelets in the blood to adhere to the plaque. The lesion will continue to grow resulting in stenosis and ultimately occlusion of the blood vessel.

Atherosclerotic plaque can be found throughout the circulatory system and is often discussed in relation to the cerebrovascular and coronary circulations, and to a lesser extent, the peripheral vascular system.

1.1.2 *Diagnosis*

One of the challenges in early detection of PAD is that in up to 85% of cases, patients are asymptomatic.[3] When symptoms do present, they fall into two categories: functional or chronic ischemia.[4] As atherosclerotic buildup occurs in the lower limbs, blood flow increases in velocity and turbulence causing a decrease in perfusion pressure distal to the stenosis.[2] An imbalance between the demand and supply of oxygen in the tissues results in ischemia. In functional ischemia, the oxygen supply when the leg muscles are at rest is sufficient; however, during exercise when oxygen demand increases, an inadequate amount of oxygen is perfused to the tissues. This is manifested as claudication: pain in the legs while walking that is relieved with rest. Classic claudication symptoms include pain or discomfort in the calf muscles; atypical claudication can include pain in the upper thighs and buttocks. In chronic ischemia, demand for oxygen exceeds supply even at rest, resulting in constant and debilitating claudication symptoms.

Clinical assessment of PAD usually begins with a medical history and review of symptoms. Claudication symptoms can be identified using a validated questionnaire, such as the Edinburgh Claudication Questionnaire, that evaluates walking impairment and ischemic pain during exercise and at rest.[5] Physical assessment of femoral bruits and pedal pulses can identify stenosis and loss of distal blood flow. Observations of hair loss and cyanotic discoloration of the foot can indicate insufficient blood perfusion, while in more advanced cases ulcerations of the lower limbs caused by vascular insufficiency can indicate the presence of PAD, along with necrosis and gangrene.[2]

The gold-standard diagnosis method for PAD is the ankle-brachial index (ABI).[6] ABI is a relatively simple and non-invasive test that compares the systolic blood pressures in the brachial arteries to systolic pressures in the posterior tibial and dorsalis pedis arteries. The resulting index measurement indicates the presence or absence, as well as the severity, of PAD. An ABI ≤ 0.90 is considered diagnostic for PAD, with disease severity increasing as the ABI decreases.[7] ABI 0.90 to 0.99 is considered borderline PAD, with values 1.00 to 1.40 considered normal.[7] Values greater than 1.40, referred to vascular calcification artifact, are due to stiff and sometimes incompressible arteries, a condition found frequently in diabetic patients, where the medial layer of the artery becomes calcified.[8]

1.1.3 *Risk Factors*

Risk factors for PAD development are considered either traditional or novel. Traditional risk factors are the same as the risk factors identified for CAD and CVD, although the strength of association with each type of vascular disease differs. Novel risk factors consist mainly of biomarkers and are the subject of the most recent literature. More than 95% of patients diagnosed with PAD will have one or more risk factors.[9]

Traditional risk factors

Age

As with most chronic diseases, the prevalence of PAD increases with age. The association of age and PAD was established early on with a number of landmark studies. Developing a PAD risk profile using 38 years of follow-up data from the Framingham Heart Study, Murabito et al., found that the rates of intermittent claudication were highest in the 65 to 74 year age group.[10]

The mean age of patients with intermittent claudication was higher than patients without symptoms, and with every ten year increase in age the odds of developing PAD increased 1.5 times (95% CI 1.3, 1.6).[11] These results have been supported in several subsequent studies including a recent National Health and Nutrition Examination Survey (NHANES) study that showed the prevalence of PAD in patients ≥ 70 years of age was 14.5% compared to 4.7% in patients aged 60 to 69, and only 2.5% in patients aged 50 to 59.[9]

Smoking

There is consistent evidence establishing smoking as the most important modifiable risk factor in the development of PAD.[1,12] Up to 50% of the incidence of PAD may be attributable to smoking and PAD is more likely to be found in both current and former smokers compared to non-smokers.[13,14] A meta-analysis of 55 studies found an adjusted OR 3.08 (95% CI 2.56, 3.69) for the presence of PAD in current smokers compared to non-smokers.[12] While the risk of developing PAD is lower in former smokers compared to current, it is still elevated compared to non-smokers.[12] Not only does smoking increase the risk of PAD development, it is also associated with higher rates of poor outcomes including amputation, less successful CABG procedures, and decreased survival.[1] Notably, there is a stronger association between PAD and smoking than between CAD and smoking, the reasons for which are currently unknown.[1,12,14]

Diabetes

Diabetes mellitus is another modifiable risk factor with a strong association with PAD.[1] Presence of diabetes results in a 1.5 to 4 fold increase in PAD risk.[1] This strong risk association is related to the duration of disease and to how well the disease is controlled. In a 12 year study of 48,707

health professionals, the adjusted relative risk (RR) of incident PAD in diabetics was 2.61 (95% CI 1.98, 3.45), increasing with the duration of diabetes (1 to 5 years RR 1.39, 95% CI 0.82, 2.36); 6 to 10 years RR 3.63 (95% CI 2.23, 5.88); 11 to 25 years RR 2.55 (95% CI 1.50, 4.32); >25 years RR 4.52 (95% CI 2.39, 8.58)].[15] In addition, a meta-analysis of 13 observational studies found a 28% increase in the relative risk of incident PAD for each percent increase in glycosylated hemoglobin (HbA1c) (RR 1.28, 95% CI 1.18,1.39).[16] The risk factors and incidence of PAD are similar between type 1 and type 2 diabetes, however male gender, smoking, and obesity are most strongly linked with type 2.[17]

Hypertension

The prevalence of hypertension in patients with PAD ranges from 50% to 92%.[1] After adjusting for age and gender, hypertensive patients are 1.75 times more likely to develop PAD compared to normotensive individuals.[9] A systematic review of global studies that used ABI to diagnose PAD showed that, in high income countries, hypertension posed a relative risk of 1.55 (95% CI 1.42, 1.71) for PAD development.[18] The severity of hypertension also appears to be linked to the progression of PAD. Stage 2 hypertension (systolic pressure ≥ 160 mmHg or a diastolic pressure ≥ 100 mmHg) is more likely to be found in patients with intermittent claudication than patients with stage 1 hypertension (systolic pressure 140 to 159 mmHg or a diastolic pressure 90 to 99 mmHg).[11] Although hypertension is associated with both PAD and CAD, the PARTNERS study showed that PAD patients were undertreated for both hypertension and lipid disorders compared to patients with CAD.[3]

Dyslipidemia

In a recent NHANES survey, PAD patients had more blood lipid disorders compared to those without PAD (60.6% vs. 44.9%) (adjusted OR 1.68, 95% CI 1.09, 2.57).[9] The strongest lipid predictor of PAD is the ratio of total cholesterol to high-density lipoproteins (HDL) (RR 3.9, 95% CI 1.7, 8.6), while the most frequent lipid disorder found in non-coronary vascular disease is hypertriglyceridemia in combination with low concentrations of HDL.[19] This lipid state is most commonly found in diabetics and may explain at least in part why diabetic patients exhibit a higher PAD prevalence.[19]

Novel risk factors

There is a paucity of prospective studies examining the causal relationship between novel risk factors and the development of PAD. However, there is a wide range of potential novel risk factors for vascular disease currently under investigation. Some of the most important novel risk factors for PAD include increased concentrations of inflammatory markers such as c-reactive protein (CRP) and fibrinogen; lipid parameters such lipoprotein(a) and Apo lipoproteins A and B; and nutritional markers such as homocysteine.[19,20]

CRP levels typically increase during an inflammatory state. While non-specific to prognosis, CRP has been recognized by the Centers for Disease Control (CDC) and the American Heart Association (AHA) as an independent risk marker for cardiovascular disease.[21] In looking at novel risk factors and incident PAD, Ridker et al., found that CRP was the strongest novel independent predictor of PAD (RR 2.8, 95% CI 1.3, 5.9).[19] Elevated CRP levels also added to

the predictive power of traditional lipid measures.[19] In addition, CRP has an inverse correlation with ABI.[21]

In the same study, fibrinogen and Apo lipoprotein B were the only other biomarkers with a significant association with PAD development. [19] Concentrations of Apo lipoprotein A were actually lower in patients who developed PAD compared to those who did not. [19] Lipoprotein(a) is a distinct novel risk factor as its concentrations are mainly determined by genetics rather than vascular or environmental risk factors.[20,23,24] Investigations of lipoprotein(a) are common in ethnic studies of CAD and PAD. Elevated homocysteine is associated with male sex and smoking, however the mechanisms by which homocysteine contributes toward increased risk of PAD and low ABI are unknown.[20]

1.1.4 *Prevalence*

The prevalence of PAD has increased worldwide by almost 25% over the last decade to an estimated 202 million cases in 2010, with an unadjusted global prevalence of 8.3%.[18] Prevalence rates differ with the population studied and prevalence rates that increase with age are ubiquitous across PAD studies. For example, worldwide, the prevalence of PAD in men aged 45 to 49 years from high-income countries is 5.3% compared to 18.8% in men aged 85 to 89 years. [18] Reports of sex differences in PAD prevalence, however, have been contradictory. The 2005 AHA PAD guidelines recognized male sex as a PAD risk factor, however several subsequent studies have shown PAD prevalence is similar between genders and possibly higher in women compared to men.[25,26]

In North American studies, PAD prevalence ranges between 3.7% and 29% with the vast majority of studies in the general population reporting PAD prevalence just above 4%.[3,9,27-30] Studies in patients with suspected or established coronary disease report higher PAD rates between 10% and 15%.[31-34]

Lastly, there are significant prevalence variations between ethnic groups where the highest prevalence is generally found in Blacks and the lowest in Asians and Hispanics. (See section 1.2 Ethnic Considerations in Vascular Disease).

1.1.5 *Outcomes*

The general prognosis for PAD includes an increased risk of amputation, myocardial infarction (MI), stroke, and death. Even in the general population, the risk of all-cause mortality is significantly greater in PAD patients. In a systematic review of eleven studies, the adjusted relative risk for mortality was 1.60 (95% CI 1.32, 1.95) for ABI $\leq$ 0.90.[35] The increased risk of ischemic events correlates with the excess CAD and CVD accompanying PAD.[6]

In patients with established CAD, PAD is an important prognostic indicator. A pooled analysis of eight randomized controlled trials of patients undergoing coronary percutaneous intervention (PCI) showed patients with PAD had a higher incidence of MI up to six months post-PCI (9.1% vs. 7.7%, p=0.048).[36] Patients presenting for PCI with PAD also had less procedural success (95% vs 97%, (p<0.001), and higher rates of in-hospital complications including stroke (0.6 vs. 0.3, p=0.034), transient ischemic attack (TIA) (0.4 vs. 0.1, p=0.01), recurrent ischemia (5.6% vs. 2.8%, p<0.001), target vessel revascularization (2.4% vs. 1.1%, p=0.01), and gastrointestinal

bleeding (1.9 vs. 0.9, p<0.001).[37,38] The presence of PAD also decreased Kaplan-Meier estimates of survival-free of death/MI/CABG/target vessel revascularization over two years (hazard ratio (HR) 1.36, 95% CI 1.22, 1.51).[37] In CABG patients, PAD (ABI < 0.85) was found to be an independent predictor of stroke and TIA (HR 3.00, 95% CI: 1.50, 5.98) and coronary events (HR 2.35, 95% CI 1.00, 5.52).[39]

In addition to increased vascular events, PAD also increases the risk of mortality. In the landmark Bypass Angioplasty Revascularization Investigation (BARI) trial researchers examined the prognostic value of non-coronary atherosclerosis in patients with known CAD.[40] Five year cumulative survival was 75.8% for patients with non-coronary atherosclerosis compared to 90.2% in those without (p<0.001).[40] The risk for mortality was 1.7 times greater for those with non-coronary atherosclerosis, and 1.5 times greater for those with lower-extremity PAD than those with isolated coronary disease.[40] These results are supported by several studies that show PAD is a significant predictor of all-cause mortality, including a two to six fold increase in cardiovascular mortality.[6,31,33,36,38,41]

1.2 Ethnic Considerations in Vascular Disease

To date, PAD research has been focused predominately on white populations, however, there is increasing recognition that difference ethnic groups have different propensities to develop symptomatic and asymptomatic PAD.[20,42-44]

Ethnic differences in disease prevalence are known to exist for CAD.[45-48] In comparison to Europeans and Chinese descendants living in Canada, persons of South Asian descent have a

higher mean carotid intimal-media thickness.[45] The prevalence of CAD in this population is also higher at 11% compared to 5% in Europeans, and 2% in Chinese. [45] South Asians have more traditional CAD risk factors, such as elevated blood glucose and lipid abnormalities, compared to the other ethnic groups, as well as a higher incidence of novel risk factors. [45] Despite accounting for the differences in both traditional and novel risk factors, South Asians still have a higher odds of developing CAD compared to Europeans (OR 4.51, 95% CI 1.46, 13.89). [45]

Similar to the situation seen in CAD, differences in PAD prevalence also appear to exist between ethnic groups. Meta-analysis of several ethnic groups in the United States showed that African Americans > 40 years of age had the highest PAD prevalence rates (11.6%), followed by American Indians (6.1%), non-Hispanic Whites (5.5%), Asian Americans (2.6%), and Hispanics (2.1%).[29] In the United Kingdom (UK), PAD prevalence was shown to be 13.2% in South Asians compared to 10.2% in Blacks.[49]

Confounding ethnic differences in PAD prevalence are the ethnic variations in risk factors. While African Americans have a higher prevalence of PAD compared to Non-Hispanic Whites, they also have higher rates of diabetes and hypertension.[43] However, after adjustment for both traditional and novel risk factors, the odds of developing PAD are still nearly 50% greater for African Americans (OR 1.47, 95% CI 1.07, 2.02).[43]Adjustment for traditional and novel risk factors has been shown to decrease the strength of association between African American ethnicity and PAD by 57%, however the ethnic discrepancy between African Americans and Non-Hispanic Whites persists.[44] Similar results were seen in the Hispanic population who have a higher prevalence of dyslipidemia but a much smaller risk of PAD compared to Non-Hispanic

Whites (OR 0.45, 95% CI 0.29, 0.70). Hispanics also have a lower risk of PAD compared to the Chinese despite a higher prevalence of diabetes (OR 0.44, 95% CI 0.24, 0.78).[43] The different levels of risk illustrated by the same risk factors have raised questions about possible genetic susceptibility for PAD development.[44]

1.2.1 South Asian Paradox

In acknowledging the ethnic diversity in CAD and PAD prevalence, it is important to recognize ethnic differences in the relationships between risk factors and disease. South Asians, i.e., persons of Indian, Pakistani, Sri Lankan, and Bangladeshi descent, have a disproportionately high CAD prevalence compared to other ethnic groups.[45,47,50] Complications from CAD can present up to a decade earlier in South Asian populations. In an international case-control study, South Asians presented with their first MI at the median age of 52 years, compared to Europeans at 62 years, and the world-wide median age of 58 years.[51] Mortality rates from ischemic heart disease (IHD) are 1.5 times greater in South Asians than the general UK population, increasing up to 4.0 times greater in South Africa and North America.[52,53] In Canada, IHD mortality rates remain the highest among South Asians with a proportional IHD mortality of 42% in South Asian men compared to 29% in White European men.[54] Increased cardiovascular morbidity and mortality in South Asians may be due to their high diabetes prevalence. Rates of type 2 diabetes are three to five fold higher in South Asians compared to Europeans, and as a result, South Asians have a two to three fold higher risk of diabetes mortality than White Europeans.[47,54]

Given the strong association between diabetes, PAD, and CAD, South Asians would be expected to exhibit a comparably higher incidence of PAD. However, studies have suggested that the

incidence of PAD is lower in South Asians compared to White Europeans.[55-57] This paradox underscores the importance of ethnic-specific epidemiology of atherosclerotic diseases, particularly PAD, and the need to develop ethnic appropriate diagnostic guidelines.

1.3 Outstanding Questions

Ethnic differences in the prevalence of PAD is a growing area of research. Determination of the magnitude of these differences and reasons for the disparity may further understanding of the role of novel risk factors or genetic determinants in vascular disease. Population-based research studies are required to determine how the presence of PAD results in negative outcomes. Evidence from these studies could expose what proportion of the outcome is due to PAD compared to its associated risk factors. Finally, there is a lack of clarity in PAD definitions. Agreement between clinicians and researchers on these terms would help support further investigations about the use of ABI in diverse populations. For optimal use of ABI as a clinical tool we need to investigate if screening for PAD in certain populations would improve individual risk assessment, particularly in regards to clinical outcomes.

1.4 Thesis Objectives

The objectives of this thesis are threefold. First, to explore the prognostic relationship between PAD and outcomes in a population of patients undergoing coronary angiography; second, to examine the utility of continuous ABI rather than dichotomous cutoffs as a risk marker and predictor of outcomes; and third, to investigate the burden of PAD in different ethnic populations.

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CHAPTER 2: PARADOXICALLY LOWER PREVALENCE OF PERIPHERAL ARTERY DISEASE IN SOUTH ASIANS: A SYSTEMATIC REVIEW AND META-ANALYSIS*

2.1 Abstract

Background: While people of South Asian (SA) descent have higher rates of cardiovascular disease compared to people of White European (WE) descent, a paradoxically lower prevalence of lower-extremity peripheral artery disease (PAD) has been suggested in SA. Our intent was to systematically review the literature on PAD prevalence in people of SA descent and to conduct a meta-analysis to identify differences in PAD prevalence between SA and WE.

Methods: Standard Cochrane systematic review methodology was used for conducting a literature review of published research. Population prevalence studies of PAD in SA with a WE comparison group were included. Full text studies were selected and reviewed by two authors with independent data extraction. Prevalence differences between SA and WE were analyzed using odds ratios.

Results: 129 studies were initially identified and ultimately 15 studies involving 240,003 subjects were included. Only one study reported direct comparative general PAD prevalence between SA and WE (OR 0.26, 95% CI 0.17, 0.38; $p<0.001$, n=77,855). Fourteen studies with comparative prevalence data between SA and WE in high risk populations confirm significantly lower odds of PAD in SA with coronary artery disease (CAD) (OR 0.47, 95% CI 0.39, 0.56; $p<0.001$, n=139,313) and diabetes (OR 0.44, 95% CI 0.30, 0.63; $p<0.001$, n=22,835).

Conclusions: Reported PAD prevalence is significantly lower in SA than WE for both the CAD and diabetes populations. Explanations for these findings, if true, are unclear. These results

underscore the need for further study to clarify mechanisms of ethnic divergence in PAD prevalence.

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2.2 Introduction

Lower-extremity peripheral artery disease (PAD) is a recognized risk factor for amputation, myocardial infarction (MI), and stroke.[1,2] In fact, PAD is more than a risk factor; it is a direct indicator of the extent of atherosclerotic disease. PAD itself shares a number of common contributing risk factors with coronary artery disease (CAD) and cerebrovascular disease (CVD), including hypertension, dyslipidemia, smoking, and diabetes.[1,2] Therefore, the presence of PAD can indicate widespread atherosclerotic disease in other vascular beds.[3-5] Despite the benefits of detecting PAD early, the majority of PAD cases are asymptomatic and, as such, PAD is under diagnosed.[4,6]

South Asians, people of Indian, Pakistani, Sri Lankan and Bangladeshi descent, experience higher rates of cardiovascular disease and cardiovascular mortality when compared to persons of White European descent.[7-11] Even South Asian immigrants to Western countries who have adopted the cultural, behavioral and dietary patterns of their new country continue to have higher CAD risk than the local population.[10,12] This risk is partially driven by the fact that South Asians also have one of the highest prevalence of diabetes, a well-known cardiovascular risk factor.[8,13,14] From other PAD studies focusing on ethnicity, particularly in African Americans, high rates of CAD and diabetes have translated into high PAD prevalence as expected by the physiological linkages between atherosclerotic disease and diabetes even after adjustment for both traditional and novel cardiovascular risk factors.[15,16] Despite high incidence of diabetes and cardiovascular disease in South Asians, some studies have suggested lower PAD prevalence in this ethnic group. [9,14,17,18] This may lead to decreased vigilance of a condition already under-diagnosed and may also impact diagnosis and treatment of cardiovascular risk factors.

Given the increasing ethnic diversity in Western countries, it is important to recognize the differences in the epidemiology of PAD between ethnic groups and respond with appropriate treatments and guidelines. Our objective is to compare the population prevalence of PAD in persons of South Asian descent to persons of White European descent through a systematic review and meta-analysis of the literature.

2.3 Methods

Search Strategy

Standard Cochrane systematic review methodology as outlined by the Cochrane Collaboration[19] was used to conduct a librarian-assisted literature review of published papers on PAD prevalence. The following databases were searched: MEDLINE (1950-Apr 2013), EMBASE (1980-Apr 2013), BIOSIS Previews (1926-Apr 2013), PubMed (1966-Apr 2013), Web of Science (1900-Apr 2013), and Scopus (1982-Apr 2013). A manual search and a review of reference lists from primary studies was also undertaken. Search terms were determined by review of previous related literature and included, but were not limited to, "peripheral vascular disease," "peripheral arterial disease," "atherosclerosis," "peripheral occlusive artery disease," "claudication," "peripheral ischemia," "PAD," "PVD," "diabetes mellitus," " diabetes complications," "diabetic foot," "Asian continental ancestry group," "Asian," "Indian," "Indo-Asian," "South Asian," "ethnic difference," "ethnicity," "race difference" "ankle brachial," "doppler," "foot pulse" and "prevalence." To ensure a comprehensive search, term truncation, subject heading explosion and validated search filters were used when appropriate. A complete search strategy is available from the authors.

Selection Criteria

We included population prevalence studies of PAD in South Asians with a White European comparison group. South Asians were defined as persons of Indian, Pakistani, Bangladeshi, Sri Lankan, Ceylonese, Nepalese, Bhutanese or Maldivian descent. The comparison group of White Europeans refers to light-skinned persons who are of European ancestry. As the term Caucasian is often misused when referring to White Europeans, articles using this term were included in the review. Eligible studies included patients with other co-morbidities such as CAD or diabetes mellitus where PAD prevalence was a secondary measure. Each publication was assessed for study quality, however, risk of bias did not disqualify the study for inclusion. We did not place any limitations on the PAD diagnosis methods or year of publication and there were no restrictions on the language of publication.

Study Selection Process

Initial screening of abstracts and/or titles was undertaken by the primary author. Studies identified for full review were then examined by two authors to assess eligibility according to the inclusion criteria specified. Outcomes of interest were extracted independently by two reviewers and compared for discrepancies. During the appraisal for inclusion and subsequent data extraction, any issues or differences of opinion were resolved by discussion until a consensus was reached. In one case we contacted the author for further clarification on their study.

Data Extraction and Analysis

Extracted variables included ethnicity, sample size, age, gender, body mass index (BMI), smoking, co-morbid conditions, method of PAD diagnosis, and reported PAD prevalence. The denominator for PAD prevalence was assumed to be the study sample size unless otherwise

stated. Any studies that did not indicate PAD diagnosis method were assumed to not have used ABI.

All studies identified for inclusion underwent data analysis. PAD prevalence was divided *a priori* into three groups: the general population with no co-morbidities and two chronic disease populations: CAD and diabetes. Data were combined and reported as weighted averages with standard deviation or 95% confidence intervals using SPSS software (SPSS Inc., Version 17: Chicago, Illinois) and STATA (StataCorp LP. Version 12.1: College Station, Texas). Random-effects meta-analysis illustrated by forest plots within Review Manager (RevMan. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) was used to calculate odds ratios and heterogeneity. Measures of heterogeneity between the studies were reported as I^2. Studies were further divided by method of PAD diagnosis: the gold standard ankle-brachial index (ABI) versus other diagnosis methods.

2.4 Results

Literature Search

A total of 21,615 citations were reviewed; 15 studies, with a total of 240,003 patients, were included for the complete statistical analysis (Figure 2-1). The studies were published between 1991 and 2013 with 13 published after 2000.

Of the included studies one study was conducted in the general population (n=77,855), seven (n=162,148) focused on CAD patients and seven (n=22,835) focused on diabetes patients (Table 2-1). Of the CAD studies, three were from the United Kingdom (UK) (n=10,028), and four were from Canada (n=129,285). All of the diabetes studies originated in the UK (n=22,835).

Quality of Studies

Many of the studies included in the analysis were limited by unclear PAD diagnosis methods**.** Only three of the 15 studies (1 CAD, 2 DM, n=636) used the gold standard ABI to diagnose PAD cases. An additional six (41%, n=17,898) studies made PAD diagnoses using clinical symptoms, six (41%, n=221,469) used information from databases with or without International Classification of Disease Codes (Table 2-1). For the studies that used ABI, the cutoff value for a positive diagnosis of PAD ranged from 0.85 to 1.00.

There is a possibility of selection bias, as 80% (12 studies, n=146,539) of included studies drew samples from research centres, hospitals and diabetes clinics where patients generally have more advanced disease profiles with multiple co-morbidities when compared to the population at large. In reporting their sampling methods, 80% (12 studies, n=238,438) used either all available patients, consecutive or random sampling.

Population Characteristics

There was evidence of heterogeneity across the comparison studies that underwent meta-analysis (CAD I^2 = 25%, DM I^2 = 66%) with demographic variation between the population groups of patients with CAD and diabetes (Figures 2-2, 2-3). The CAD population was significantly older and had a higher percentage of males than the diabetes population in both ethnic groups, while BMI and smoking rates were lower in the CAD population than the diabetes population (all $p<0.001$).

Within each disease subgroup of CAD and diabetes, when compared to White Europeans the South Asian populations were significantly younger (CAD: 60.4 ± 1.2 years vs. 64.6 ± 0.4 years, p<0.001; diabetes: 54.8 ± 5.5 years vs. 61.4 ± 5.3 years, p<0.001); had more males (CAD: 76.9% vs. 72.8%; diabetes: 55.7% vs. 54.3%), had a lower BMI (CAD: 25.7 ± 0.5 vs. 28.0 ± 0.3, p<0.001; diabetes 28.6 ± 1.7 vs. 30.5 ± 2.8, p<0.001) and lower smoking rates (CAD: 20.4% vs. 20.7%, p=0.004; diabetes 21.4% vs. 52.4%, p<0.001) (Table 2-2).

PAD Prevalence

i) PAD prevalence in the general population

There was one comparative study between South Asians and White Europeans in a general population. They reported a significantly different PAD prevalence of 1.4% in the South Asian population and 1.9% in the White European population (OR 0.26, 95% CI 0.17, 0.38; p<0.001).[20]

ii) PAD prevalence in studies of people with CAD

In the pooled analysis of the CAD comparison studies, PAD prevalence in the South Asian ethnic group was significantly lower than the White European group (OR 0.47, 95% CI 0.39, 0.56; p<0.001) with low heterogeneity (I^2=25%) (Figure 2-2, Table 2-3). Only one CAD study reported use of ABI and the reported PAD prevalence for both South Asians and White Europeans was significantly higher than the non-ABI studies (p<0.001) (Table 2-4). The difference in PAD prevalence between the two ethnic groups in the ABI study was only marginally statistically significant (OR 0.53, 95% CI 0.26, 1.06; p=0.07) (Figure 2-2).

iii) PAD prevalence in studies of people with diabetes

For the comparison studies between South Asians and White European diabetes patients, South Asians had significantly lower PAD prevalence rates than White Europeans (OR 0.44, 95% CI 0.30, 0.63; p<0.001) with moderate heterogeneity (I^2=66%) (Figure 2-3, Table 2-3). Two of the five comparison studies used ABI for PAD diagnosis (OR 0.44, 95% CI 0.24, 0.81; p=0.009; I^2=0%) (Figure 2-4) and the difference in PAD prevalence between the non-ABI and ABI studies was significant (p=0.001 and p=0.044 for South Asians and White Europeans respectively) (Table 2-4).

iv) Ethnic differences in PAD prevalence and ABI

In each disease subgroup, there was a significant difference in PAD prevalence between the ABI and non-ABI studies (Table 2-4). However, the comparison studies that used ABI showed smaller differences in PAD prevalence between ethnic groups and had an OR closer to one when compared to studies using clinical diagnosis (Figure 2-3,2-4).

2.5 Discussion

There is well-documented evidence that South Asians have a markedly higher prevalence of diabetes and CAD compared to other ethnic groups.[7,8,13,14,31] Based on known atherosclerotic risks, we would expect a higher PAD prevalence in South Asians as compared to White Europeans, yet our systematic review data suggests a paradoxically lower prevalence of PAD in South Asians. These findings support current research that certain ethnic groups are more prone to location specific manifestations of atherosclerosis.[32] The mechanism of the paradox (if true) is unknown and requires further investigation. This meta-analysis also confirms findings in previous individual studies that the prevalence of PAD is higher in studies using ABI. The

underlying interpretation is that many patients are asymptomatic and, therefore, the true burden of PAD is unknown unless ABI is measured.

Previous studies comparing ethnic differences in PAD prevalence have found ethnic disparities. A study of a multiethnic sample from the National Health and Nutrition Examination Survey (NHANES) reported an ABI-determined PAD prevalence of 7.8% among African Americans compared to 5.1% in Mexican Americans and 3.4% in Whites despite conventional risk factor control being similar between the different ethnic groups.[33] African Americans have consistently reported higher PAD prevalence compared to Hispanics and Whites in multi-ethnic US studies.[34] Not surprisingly, African Americans also have higher reported prevalence of cardiovascular disease, stroke, and hypertension compared to all other ethnic groups in the United States.[35]

South Asian studies suggest that the ethnic differences found in PAD prevalence are related to the heterogeneity of risk factors found in South Asians where traditional risk factors alone do not explain the higher cardiovascular burden in this ethnic group.[3] While smoking is a strong risk factor for PAD, smoking rates are generally less in South Asians (particularly in females) than White Europeans, however adjustment for smoking rates or pack years does not explain the ethnic discrepancy in PAD prevalence.[3,18] Measuring carotid intima media thickness among South Asians and White Europeans, the SHARE investigators discovered that despite a higher rate of cardiovascular events, South Asians have significantly less carotid atherosclerotic thickness ($p=0.00098$).[7] They suggested that the high prevalence of glucose and lipid abnormalities in this ethnic group could cause decreased plaque stability, leading to more cardiovascular events. South Asians do indeed have a number of metabolic abnormalities, including high serum levels of apolipoprotein B, triglycerides, lipoprotein(a), [7,36,37] as well as

low levels of high density lipoproteins and apolipoprotein A.[37] This unique lipid profile combined with higher levels of thrombotic factors of homocysteine, fibrinogen and the plasminogen activator inhibitor (PAI-1)[37] along with insulin resistance[38] may indicate that vascular disease risk in this ethnic group has less to do with the amount or location of the atherosclerotic plaque and more with its thrombotic tendency. In addition, c-reactive protein (CRP), an inflammatory mediator, has been shown to be independently associated with cardiovascular disease even after adjustment of known confounders.[39] CRP levels differ significantly between ethnic groups, with South Asians having higher levels than persons of White European descent (adjusted mean CRP 2.59mg/L (±0.12) South Asians; 2.06mg/L (±0.12) Europeans).[39] From these findings, it is possible that despite having less atherosclerosis as evidenced by lower PAD prevalence and less intima media thickness, South Asians still have higher rates of cardiovascular events and cardiovascular mortality due to inflammation and thrombosis of unstable plaque.

Limitations

A systematic review is retrospective by nature and is restricted to a secondary analysis of aggregate data. There was low heterogeneity between the CAD studies and moderate heterogeneity between the diabetes studies which most likely originates from the different methods of PAD diagnosis and demographic variation. In addition, prevalence calculations were not adjusted for risk factors in all the original studies. Those studies where prevalence was adjusted or matched for age and/or sex are noted in Table 2-1. While heterogeneity between studies is a clear limitation, our conclusions are based on the best available evidence.

In addition, the majority of papers included in this review originate in the UK and Canada. As a result, the study populations may be influenced by differing cultural perceptions and social factors that may contribute to a bias in reporting of symptoms such as claudication.[9] These factors are difficult to account for in a combined analysis. It is also important to note that we cannot separate data from recent immigrant and local populations, however as stated previously, research indicates that immigrants who adopt their new country's lifestyle maintain the same atherosclerotic risk as persons in their homeland.[10,12]

Finally, these conclusions are drawn from studies sampled from clinical populations that may not reflect true population prevalence. The PAD prevalence may be higher than reported even in ABI studies as arteriosclerosis and arterial calcification, which are more common in diabetic patients, lead to non-compressible arteries which can result in an underestimated PAD prevalence.[9,17] We did exclude studies that involved amputation which could underestimate the PAD prevalence, however there are many contributing factors to amputation outside of atherosclerotic disease.

Implications

South Asians with CAD or diabetes appear to have less PAD than White Europeans; however this information should not decrease the importance of PAD screening in South Asians with multiple risk factors. In a number of populations, there is definitive evidence that PAD worsens prognosis and that diabetes is a strong risk factor for the development of PAD.[2] Early detection of PAD is an opportunity for prevention and/or improved prognosis of cardiovascular outcomes that should not be overlooked.

2.6 Conclusion

Based upon the best available evidence from 15 studies in 240,003 patients, South Asians have a paradoxically lower prevalence of PAD both overall and in higher risk populations of those with CAD or diabetes. Further investigation is required to determine the underlying pathophysiologic mechanism leading to differences in manifestations atherosclerotic disease between ethnic groups; specifically if these differences are driven by novel risk factors or genetic susceptibility.

Table 2-1. Studies included in the systematic review

Source	Study population (ethnicity)	Country of study	N	PAD diagnosis	PAD prevalence (%)
General population					
Holland et al., 2011[20]	Asian Indian Non-Hispanic White	US	5154 72701	Database / ICD codes	1.4* 1.9*
Coronary artery disease					
Dhanjal et al., 2001[10]	Malaysian Indo-Asian UK Indo-Asian UK Caucasian	Malaysia UK	42 28 20	Clinical symptoms, previous diagnosis	2.4 3.6 30.0
Gupta et al., 2002[21]	South Asian Non South Asian	Canada	553 553	Clinical symptoms, previous intervention	7.0^ 15.6^
Chaturvedi et al., 2006[18]	Indian Asian European	UK	84 83	ABI <0.99	20.2 32.5
Khan et al., 2010[22]	South Asian White	Canada	2190 38479	Database / ICD codes	1.8 2.5
Quan et al., 2010[23]	South Asian Non-Asian, non-Chinese Canadian	Canada	3061 77314	Database / ICD codes	5.2 9.3
Albarak et al., 2012[24]	South Asian Non-Asian, non-Chinese Canadian	Canada	487 6648	Database / ICD codes	0.8 1.3
Jones et al., 2012[25]	South Asian Caucasian	UK	1805 7966	Database / ICD codes	1.3 2.8
Diabetes mellitus					
Samanta et al., 1991[9]	Indian Asian Caucasian	UK	456 451	Clinical symptoms / previous intervention	3.7 9.3
Alcolado et al., 1992[26]	Asian White	UK	42 67	ABI <1.00	28.6 46.3
Chowdhury and Lasker, 2002[11]	South Asian European	UK	165 127	Clinical symptoms	5.45 3.9
Abbott et al., 2005[27]	South Asian European	UK	1862 13387	Clinical symptoms	7.1* 21.9*
Abbott et al., 2010[28]	South Asian European	UK	180 180	ABI <0.85	4.0^ 9.1^
Mehta et al., 2011[29]	South Asian White European South Asian White European	UK	163 1169 1279 3053	Database / ICD codes	1.8 2.7 1.8 5.3
Ali et al., 2013[30]	South Asian White	UK	149 105	Clinical symptoms / vascular angiogram	12.1 15.2

Clinical symptoms include: one or more missing pedal or peripheral pulses, history of claudication, rest pain, gangrene. Previous intervention includes: peripheral arterial angioplasty, surgery or amputation. Not all database studies reported using ICD codes. *Age and/or sex adjusted, ^age and/or sex matched

Table 2-2. Population characteristics for South Asian and White European PAD comparison studies

Characteristic	CAD			DM		
	SA	WE	p-value	SA	WE	p-value
Age (yrs.)	60.4 (1.2)	64.6 (0.4)	<0.001	54.8 (5.5)	61.4 (5.3)	<0.001
Male (%)	76.9	72.8	<0.001	55.7	54.3	<0.001
BMI	25.7 (0.5)	28.0 (0.3)	<0.001	28.6 (1.7)	30.5 (2.8)	<0.001
Smoker (%)	20.4	20.7	0.004	21.4	52.4	<0.001

SA: South Asian; WE: White European; CAD: Coronary artery disease; DM: Diabetes mellitus; Smoker: current or former. Values are mean (SD).

Table 2-3. PAD prevalence in comparative studies between South Asians and White Europeans

Study Type	Overall PAD Prevalence % (95%CI)		
	SA	WE	p-value
Coronary artery disease population	3.4 (3.0,3.8) (n=8,250)	7.0 (6.9,7.2) (n=131,063)	<0.001
Diabetes mellitus population	5.2 (4.5, 5.8) (n=4,296)	17.5 (16.9,18.0) (n=18,539)	<0.001

SA: South Asian; WE: White European.

Table 2-4. PAD prevalence in comparative studies between South Asians and White Europeans using different PAD diagnosis methods

Study Type	PAD Prevalence SA % (95%CI)			PAD Prevalence WE % (95%CI)		
	Non-ABI	ABI	p-value	Non-ABI	ABI	p-value
Coronary artery disease population	3.3 (2.9,3.7) (n=8,166)	20.2 (12.3,30.4) (n=84)	<0.001	7.0 (6.9,7.1) (n=130,980)	32.5 (22.7,43.7) (n=83)	<0.001
Diabetes mellitus population	5.0 (4.3,5.7) (n=4,074)	8.7 (4.9,12.4) (n=222)	0.001	17.4 (16.9,18.0) (n=18,292)	19.2 (14.5,23.9) (n=247)	0.044

SA: South Asian; WE: White European; ABI: ankle-brachial index.

Figure 2-1. Identification of included studies

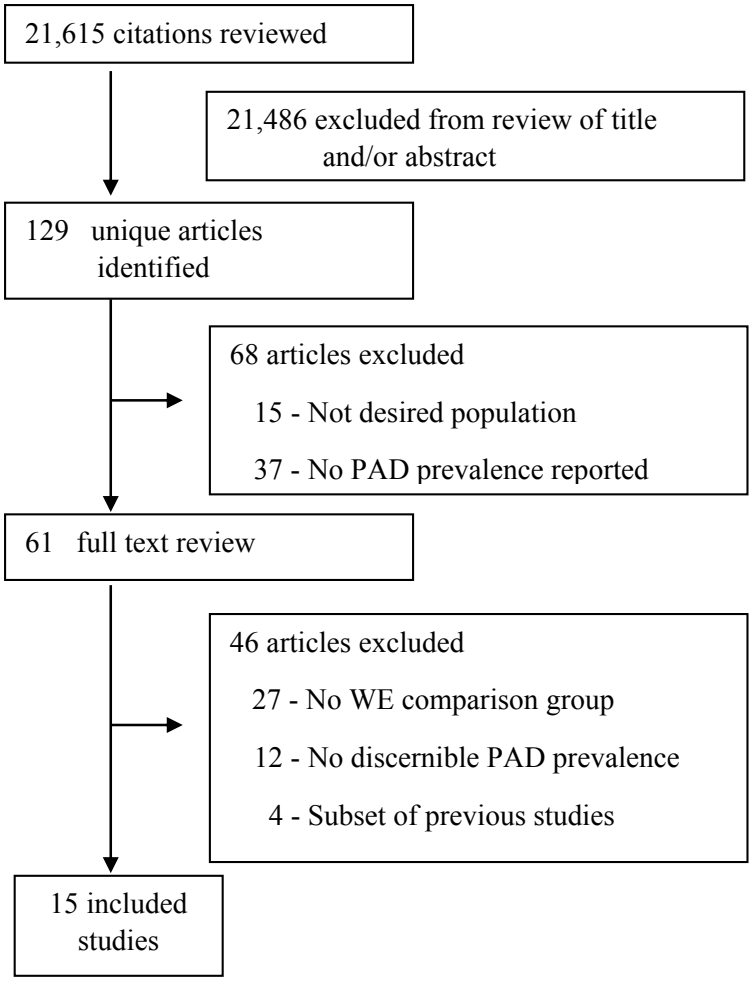


Figure 2-2. Forest plot of CAD comparison studies

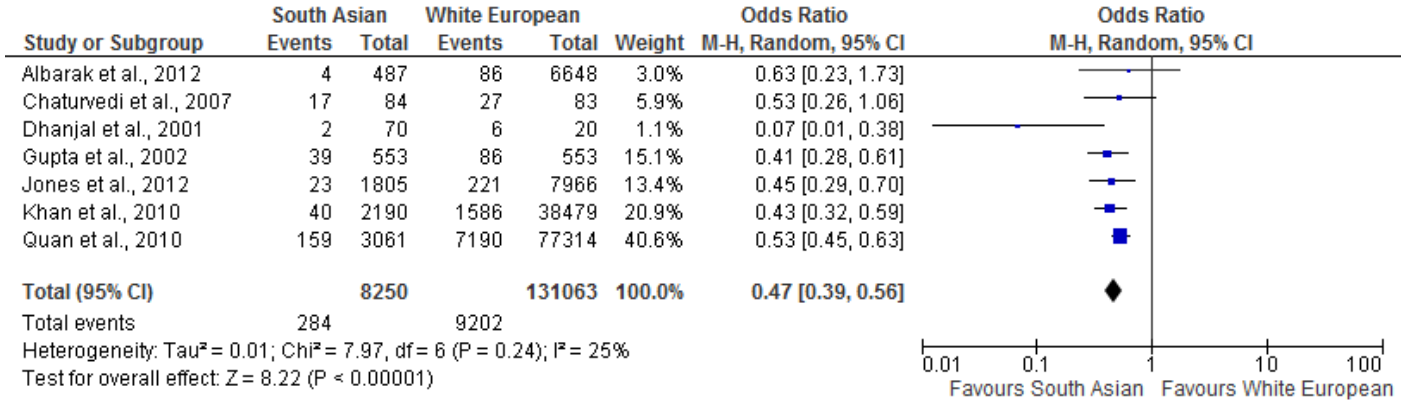


Figure 2-3. Forest plot of diabetes comparison studies

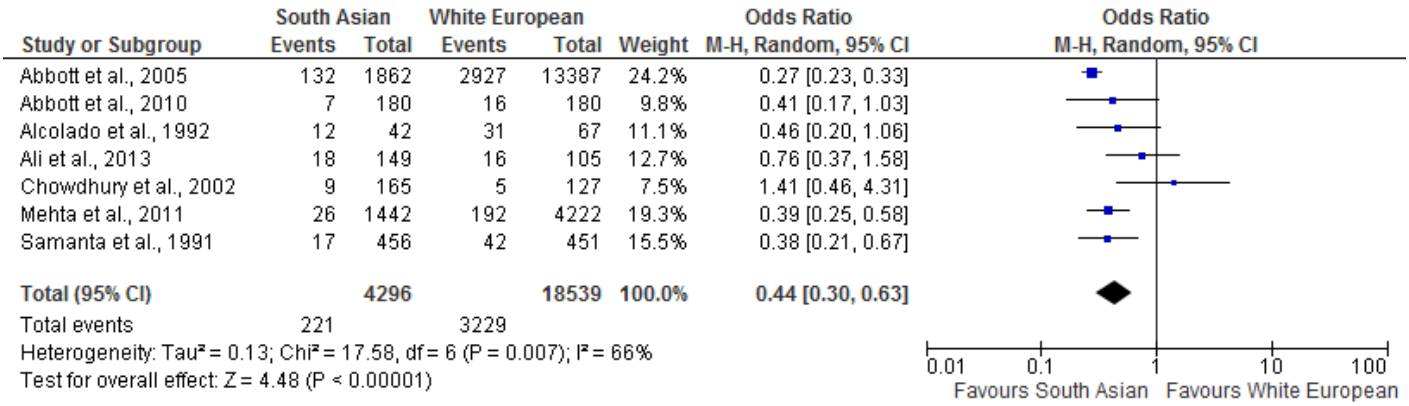
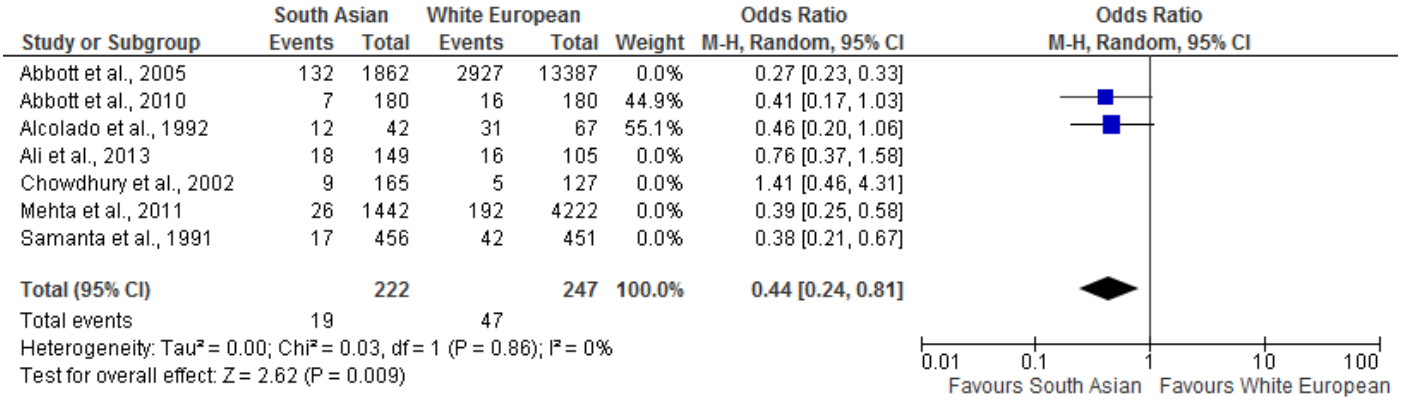


Figure 2-4. Forest plot of diabetes comparison studies using ABI



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CHAPTER 3: ETHNIC DIFFERENCES IN PREVALENCE OF PERIPHERAL ARTERY DISEASE IN PATIENTS UNDERGOING HEMODIALYSIS

3.1 Abstract

Introduction: Hemodialysis patients experience poor outcomes associated with the presence of atherosclerosis, particularly lower-extremity peripheral artery disease (PAD). Prevalence of PAD is known to vary between ethnic groups, however no information on ethnic-specific PAD prevalence in a hemodialysis cohort is available.

Methods: Data from the Canadian Kidney Dialysis Cohort Study (CKDCS) was used in a secondary analysis of 1293 adults starting hemodialysis in three major Canadian centres. PAD diagnosis was determined through structured interview and supplemented by clinical record.

Results: Overall PAD prevalence was 19.1% with no significant difference between ethnic groups. Ethnic differences observed in diabetes prevalence in the full hemodialysis group were not present in the subset of PAD patients.

Conclusions: There were no apparent ethnic differences in PAD prevalence between ethnic groups in patients undergoing hemodialysis. Ethnicity does not appear to be a major factor in the prevalence of atherosclerotic disease in this population.

3.1 Introduction

Patients with chronic kidney disease (CKD) requiring hemodialysis have high rates of lower-extremity atherosclerosis, where prevalence of peripheral artery disease (PAD) ranges from 16.6% to 38.5%, compared to 4.4% to 29% in the general population.[1-4] In patients receiving hemodialysis, PAD is associated with increased hospitalization (hazard ratio (HR) 1.19, $p<0.0001$) and increased rates of myocardial infarction (MI) and stroke.[5,6] Concomitant PAD is also an independent predictor of mortality in hemodialysis patients (HR 1.67, $p=0.004$).[7]

Similarly, PAD is also an independent predictor of these poor outcomes in patients with coronary artery disease (CAD), and within this population there is significant ethnic variation in PAD prevalence.[8-10] Black populations have high rates of diabetes and CAD and a high prevalence of PAD compared to all other ethnic groups.[11-13] While South Asians also have a high prevalence of PAD risk factors including diabetes and CAD, they appear to have a paradoxically lower prevalence of PAD compared to White Europeans.[14]

Prognosis of CKD also varies among ethnic groups.[15] Chinese and South Asians at equal glomerular filtration rates (GFR) and proteinuria levels have a lower risk of mortality than Whites.[15] When comparing Black and White ethnic groups, although the Black population develops end stage renal disease (ESRD) much earlier, once the disease progresses to where the patient requires dialysis, mortality in the White population becomes significantly higher.[10]

While ethnic differences have been observed in both CKD and PAD prevalence, few studies have focused on the ethnic PAD prevalence within the hemodialysis cohort.[10] Our study examines the differences in PAD prevalence in patients undergoing hemodialysis.

3.2 Methods

Study design

We conducted a secondary analysis of data from the Canadian Kidney Dialysis Cohort Study (CKDCS).[16] The CKDCS is a large, prospective observational study of all consenting adults commencing hemodialysis treatment in multiple ethnically diverse major centres across Canada.[16] CKDCS was conducted according to the principles of the Declaration of Helsinki and approved by the ethics boards of each participating centre.[16]

Study participants

Our study sample included 1293 adult (≥18 years of age) hemodialysis patients from Edmonton, Calgary and Vancouver. All available patients from the database were included provided they had completed the baseline cohort study questionnaire between March 23, 2005 and December 20, 2011.

Data collection

Baseline demographic data and clinical history from CKDCS was collected by structured interview and supplemented by clinical record. The baseline data collection was conducted within eight weeks of the patient starting hemodialysis.

Data analysis

For this secondary analysis, the patient was considered to have PAD if they answered yes to having any one of the following: previous claudication symptoms, current claudication symptoms, gangrene, previous vascular intervention or previous amputation due to vascular disease. Data are presented as number of cases with characteristic of interest and as a percent of the total available responses for that ethnic group. Prevalence differences were compared using Chi-squared tests and one-way ANOVA with Tukey's HSD (SPSS Inc., Version 17: Chicago, Illinois).

3.4 Results

Characteristics of the patients included in the study, stratified by ethnic group, are shown in Table 3-1. The mean age of the population sample was 60.3 years (SD 15.6). Aboriginals were significantly younger compared to Whites ($p<0.001$). Prevalence of hypertension ranged from 84.6% in Middle Eastern patients to 94.8% in South Asians. Documented CAD was less common, with an average prevalence of 24.7% ranging from 7.7% in Middle Easterners to 25.8% in Aboriginals. Diabetes was present in 51.4% of the cohort, with Aboriginals having a significantly higher prevalence compared to Whites (68.8% vs. 48.3%, $p<0.001$). Compared to Aboriginals, Blacks, and Whites, South Asians had borderline significantly fewer cases of long-duration diabetes (> 10 years, $p=0.046$). Large diversity in smoking habits was found across the ethnic groups with Whites and Aboriginals having significantly lower rates of non-smokers compared to the other ethnic groups.

In the 247 patients identified with PAD there were no significant ethnic differences in the comorbidities between ethnic groups with the exception of patients who had never smoked, warfarin use, and patients diagnosed with diabetes within the last year (Table 3-2). Asians and South Asians had significantly less smokers compared to Whites, while Whites had significantly less warfarin use compared to Blacks and South Asians, albeit with very few cases. The mean age was 60.8 years (SD 13.7) and the majority of patients were male (59.5%). Hypertension was highly prevalent with an average of 90.7%, ranging from 89.2% in Whites to 100% in five of the seven ethnic groups. The overall prevalence of diabetes was also high at 66.8%, ranging from 65.5% in Whites to 100% in Pacific Islanders.

Overall PAD prevalence was 19.1% (n=247), ranging from 7.7% to 20.3% across the various ethnic groups. PAD prevalence was highest in Whites (20.3%) followed by Aboriginals (19.4%). The lowest prevalence was in persons from the Middle East (7.7%) followed by Pacific Islanders (9.8%). There were no statistically significant differences in PAD prevalence between ethnic groups.

3.5 Discussion

PAD has been associated with higher morbidity and mortality in both CKD and CAD patients.[5,10] Ethnic variations in prevalence of PAD have been found in the CAD population, yet little data is available to examine these patterns in patients with CKD receiving hemodialysis.[10] In our study, we did not find any statistically significant differences in PAD prevalence by ethnicity, suggesting ethnicity may not play a major role in PAD prevalence in this population.

Overall we found a PAD prevalence of 19.1% in the hemodialysis cohort. These results agree with previous studies which found a 19% prevalence in European patients with chronic renal failure stages IV/V[17] (no dialysis) and a study of ESRD hemodialysis patients across ten European countries where the PAD prevalence ranged from 17.5% to 37.8%.[5] These rates are slightly higher than the 15% reported by the United States Renal Data System (USRDS) of patients undergoing incident dialysis where PAD was defined using only clinical symptoms.[2] Although we found PAD prevalence in Asians was one of the lowest at 10.9%, the difference was not statistically significant. However, other studies in Japan have reported a PAD prevalence of 22.1% in hemodialysis patients using the gold standard ankle-brachial index (ABI) diagnosis,[7] which reflects a limitation in our case definition (as up to 50% of patients with PAD are asymptomatic).[4]

One unexpected finding was a similar PAD prevalence between Whites and South Asians. Previous research has indicated that South Asians have significantly less PAD compared to White Europeans.[14] We hypothesized this ethnic disparity would be similar in hemodialysis patients. One possible explanation for the similar rates is that CKD has a similar pathogenesis as PAD since both are "peripheral" organs, so once CKD has led to the need for hemodialysis, PAD has already taken hold. Further research into changes of PAD prevalence through different stages of CKD for the different ethnic groups may shed some light on this finding.

This study was limited in that the gold standard for diagnosis of PAD, ABI, was not available. Sole reliance on clinical symptoms likely results in an up to 85% underestimation of PAD

prevalence.[4] The number of cases in each ethnic group with PAD was relatively small, therefore we may have been statistically underpowered to detect a difference.

3.6 Conclusion

We did not observe ethnic differences in PAD prevalence in this hemodialysis cohort. Ethnicity is not likely a key factor in the prevalence of PAD in hemodialysis patients. The high prevalence of PAD supports further research in the utility of PAD screening in early stages of CKD to implement treatments for PAD earlier.

Table 3-1. Patient characteristics

	All patients	Aboriginal	Asian	Black	South Asian	Middle Eastern	Pacific Islander	White / Caucasian	p value
N	1293	93	55	35	58	13	41	998	
Mean age (years)	60.3 (15.6)	53.1 (14.0)	57.9 (16.4)	56.7 (17.5)	59.4 (16.7)	55.2 (14.5)	56.8 (14.8)	61.5 (15.4)	<0.001
Male	796 (61.6)	44 (47.3)	33 (60.0)	25 (71.4)	37 (63.8)	8 (61.5)	26 (63.4)	623 (62.4)	0.216
Hypertension	1124 (87.2)	79 (86.8)	50 (92.6)	30 (85.7)	55 (94.8)	11 (84.6)	36 (87.8)	863 (86.6)	0.548
CAD	318 (24.7)	24 (26.1)	10 (18.2)	3 (8.6)	17 (29.3)	1 (7.7)	7 (17.5)	256 (25.7)	0.102
Diabetes	664 (51.4)	64 (68.8)	32 (58.2)	19 (54.3)	34 (58.6)	9 (69.2)	24 (58.5)	482 (48.3)	0.003
Heart failure	233 (18.4)	20 (23.0)	6 (10.9)	10 (29.4)	11 (20.4)	1 (7.7)	3 (7.5)	182 (18.6)	0.112
Stroke	115 (8.9)	5 (5.4)	3 (5.5)	4 (11.4)	6 (10.3)	2 (15.4)	3 (7.5)	91 (9.1)	0.754
Warfarin use	15 (1.2)	1 (1.1)	0	1 (2.9)	1 (1.7)	0	0	12 (1.2)	0.886
Statin use	106 (8.2)	8 (8.6)	4 (7.3)	3 (8.6)	5 (8.6)	0	4 (9.8)	82 (8.2)	0.966
Duration of diabetes									
<1 year	20 (3.7)	1 (1.9)	2 (7.7)	0	1 (3.7)	0	1 (6.3)	15 (3.7)	0.842
1-5 years	48 (8.8)	2 (3.8)	3 (11.5)	2 (15.4)	5 (18.5)	1 (14.3)	2 (12.5)	33 (8.2)	0.373
5-10 years	65 (12.0)	7 (13.2)	1 (3.8)	0	7 (25.9)	2 (28.6)	3 (18.8)	45 (11.2)	0.082
>10 years	410 (75.5)	43 (81.1)	20 (76.9)	11 (84.6)	14 (51.9)	4 (57.1)	10 (62.5)	308 (76.8)	0.046
Smoking status									
Never	531 (41.5)	27 (30.0)	44 (83.0)	17 (50.0)	42 (75.0)	9 (69.2)	27 (67.5)	365 (36.8)	<0.001
Current	212 (16.5)	26 (28.9)	2 (3.8)	6 (17.6)	2 (3.6)	2 (15.4)	0	174 (17.5)	<0.001
Former	539 (41.9)	37 (41.1)	7 (13.2)	11 (32.4)	12 (21.4)	4 (30.8)	13 (32.5)	453 (45.7)	<0.001
PAD	247 (19.1)	18 (19.4)	6 (10.9)	6 (17.1)	9 (15.5)	1 (7.7)	4 (9.8)	203 (20.3)	0.288
Previous PV intervention	71 (5.8)	7 (7.9)	0	1 (2.9)	3 (5.5)	0	1 (2.7)	59 (6.2)	0.386
History of claudication	122 (9.9)	7 (8.0)	4 (7.8)	2 (6.1)	4 (7.5)	0	1 (2.5)	104 (10.9)	0.185
Current claudication symptoms	73 (52.1)	4 (50.0)	3 (27.3)	1 (50.0)	2 (66.7)	1 (50.0)	1 (16.7)	61 (57.5)	0.293
Gangrene	42 (3.3)	6 (6.5)	0	2 (5.7)	2 (3.5)	0	2 (4.9)	30 (3.0)	0.369
Amputation*	55 (4.3)	5 (5.4)	1 (1.8)	3 (8.6)	3 (5.3)	0	2 (4.9)	41 (4.1)	0.746

Values are n (%) or mean (SD).
Coronary artery disease (CAD), peripheral vascular (PV), peripheral artery disease (PAD)
*Due to vascular disease

Table 3-2. Characteristics of patients with PAD

	All patients	Aboriginal	Asian	Black	South Asian	Middle Eastern	Pacific Islander	White/ Caucasian	p value
N	247	18	6	6	9	1	4	203	
Mean age (years)	60.8 (13.7)	54.1 (9.9)	54.9 (13.9)	57.3 (20.9)	63.2 (14.2)	69.4	63.7 (9.2)	63.1 (13.6)	0.119
Male	147 (59.5)	10 (55.6)	4 (66.7)	4 (66.7)	5 (55.6)	1 (100)	4 (100)	119 (58.6)	0.690
Hypertension	224 (90.7)	17 (94.4)	6 (100)	6 (100)	9 (100)	1 (100)	4 (100)	181 (89.2)	0.740
CAD	90 (36.4)	5 (27.8)	1 (16.7)	2 (33.3)	1 (11.1)	0	3 (75.0)	80 (39.4)	0.076
Diabetes	165 (66.8)	12 (66.7)	5 (83.3)	5 (83.3)	6 (66.7)	0	4 (100.0)	133 (65.5)	0.466
Heart failure	64 (26.6)	4 (25.0)	0	2 (33.3)	2 (25.0)	1 (100)	1 (25.0)	54 (27.0)	0.527
Stroke	26 (10.5)	1 (5.6)	0	0	0	0	0	25 (12.3)	0.647
Warfarin use	3 (1.2)	0	0	1 (16.7)	1 (11.1)	0	0	1 (0.5)	0.002
Statin use	24 (9.7)	0	0	1 (16.7)	3 (33.3)	0	0	20 (9.9)	0.164
Duration of diabetes									
<1 year	2 (1.4)	0	1 (20.0)	0	0	0	0	1 (0.8)	0.021
1 to 5 years	9 (6.2)	0	0	0	0	0	0	9 (7.6)	0.836
5 to 10 years	17 (11.7)	1 (8.3)	0	0	2 (50.0)	0	1 (50.0)	13 (10.9)	0.082
>10 years	117 (80.7)	11 (91.7)	5 (83.3)	3 (100)	2 (50.0)	0	1 (50.0)	96 (80.7)	0.383
Smoking status									
Never	76 (31.1)	4 (22.2)	5 (100)	1 (16.7)	6 (66.7)	0	2 (50.0)	58 (28.9)	0.004
Current	50 (20.5)	5 (27.8)	0	2 (33.3)	0	0	0	43 (21.4)	0.402
Former	118 (47.8)	9 (50.0)	0	3 (50.0)	3 (33.3)	1 (100)	2 (50.0)	54 (27.0)	0.345

Values are n (%) or mean (SD)
Coronary artery disease (CAD), peripheral vascular (PV), peripheral artery disease (PAD)
*Due to vascular disease

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CHAPTER 4: PERIPHERAL ARTERY DISEASE AND LOW ANKLE-BRACHIAL INDEX PREDICT HIGHER CORONARY SYNTAX SCORES, MORE MYOCARDIUM AT RISK, AND INCOMPLETE CORONARY REVASCULARIZATION

4.1 Abstract

Introduction: Peripheral artery disease (PAD) is strongly associated with coronary artery disease (CAD) and poor outcomes after coronary revascularization. We hypothesized that patients with PAD characterized by a low ankle-brachial index (ABI) ≤ 0.90, have more complex CAD and more myocardium at risk than patients with normal ABI (1.00 to 1.40) and that their coronary revascularization is less complete.

Methods: 814 consecutive patients drawn from a prospective cohort of adults referred for coronary angiography underwent ABI measurement using standard Doppler ultrasound technique. Reviewers blinded to the patient's ABI calculated SYNTAX scores and Duke Jeopardy scores at baseline and Duke Jeopardy scores again at three months post angiography. Patients were followed for one year for the outcomes of myocardial infarction, stroke, target vessel revascularization, and death.

Results: Of 814 patients, 7.6% had PAD (ABI ≤ 0.90), 8.5% had borderline PAD (ABI 0.90 to 0.99), 76.8% were normal (ABI 1.00 to 1.40), and 7.1% had vascular calcification artifact (ABI > 1.40). Patients with PAD were more likely to have a high SYNTAX score (≥ 33) with an odds ratio of 4.3 (95% CI 1.2, 14.9; p=0.022) compared to those with normal ABI after adjustment for traditional cardiovascular risk factors. Similarly, there was a positive association between baseline high Duke Jeopardy score (≥ 8) and PAD (adjusted OR 3.5, 95% CI 1.7, 7.1; p=0.001). Post-revascularization high Duke Jeopardy scores (≥ 5) were also positively associated with

PAD (adjusted OR 3.0, 95% CI 1.1, 8.8; p=0.039). The overall adjusted hazard ratio for cardiovascular events or death in those patients with PAD was 2.0 (95% CI 1.0, 3.9; p=0.037).

Conclusions: PAD is associated with higher SYNTAX scores. Patients with PAD have more myocardium at risk and less complete coronary revascularization than patients with a normal ABI. Differences in CAD complexity and coronary revascularization in PAD patients may explain why PAD is associated with an excess of cardiovascular events in patients with CAD.

4.2 Introduction

Lower-extremity peripheral artery disease (PAD) is strongly associated with coronary artery disease (CAD) and poor outcomes after coronary revascularization.[1,2,3] PAD is an independent predictor of short and long term mortality following percutaneous coronary intervention (PCI), lower procedural success for stent placement, higher occurrence of myocardial infarction (MI), and higher rates of stroke and transient ischemic attack.[4-6] PAD has also shown a strong correlation with coronary lesion complexity.[7-10] The complexity of cardiovascular disease is commonly measured using the SYNergy between PCI with TAXUS™ and Cardiac Surgery (SYNTAX) score which encompasses the number of significant lesions as well as their complexity and location in the coronary tree.[11] Also influenced by the location and size of the lesion, the Duke Jeopardy score conveys the volume of myocardium distal to the lesion that is likely under perfused and at risk of necrosis.[12-14] Measurement of myocardium at risk is a useful tool for clinical decision making relating to reperfusion and determination of prognosis.

We hypothesized that patients with PAD, as determined by a low ankle-brachial index, have more complex CAD and more myocardium at risk than patients with normal ABI and have less complete coronary revascularization.

4.3 Methods

Participants

Adult patients 18 years of age and older referred for coronary angiogram for CAD were consecutively sampled from the catheterization recovery areas of two urban hospitals between March 2010 and September 2012. Subjects underwent an initial screening for eligibility based on their indication for coronary angiography on the procedure requisition form. Subjects being

assessed for heart transplant, valve disease, pulmonary hypertension or congenital heart disease were excluded, along with emergency cases. Potentially eligible subjects were then approached to participate and underwent a secondary screening for eligibility based on their responses and chart information. Subjects with a previous coronary artery bypass graft, as well as those who were unable to communicate in English or were unable to have an ABI measured due to sores or ulcers were excluded at the secondary screening. All participants who met the eligibility criteria provided written informed consent. The Health Research Ethics Board of the University of Alberta approved the research protocol.

Data collection

ABI was performed on each patient prior to coronary angiography. With the patient in a supine position, manual non-simultaneous systolic blood pressure was measured bilaterally at the brachial, posterior tibial, and dorsalis pedis arteries using a L150 Summit Doppler (Wallach Surgical, Trumbull, CT, USA) with 8MHz vascular probe. Demographic and co-morbidity data were collected from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) database, a prospective database that records all coronary catheterizations performed in Alberta.[15]

SYNTAX and Duke Jeopardy scores were calculated following the baseline angiography procedure prior to any revascularization. SYNTAX scores were calculated based on the functional and anatomical characteristics of the lesions using an online calculator (www.syntaxscore.com).[16] Duke Jeopardy scores were calculated a second time if coronary revascularization was attempted within three months of the initial angiography procedure. For

Duke Jeopardy scoring, the coronary circulation was divided into six arterial segments and each segment with a proximal lesion >70% was considered jeopardized to a maximum score of 12.[14] Research team members involved in calculation of the SYNTAX and Duke Jeopardy scores were blinded to the patient's ABI and PAD history.

Patients with angiographically confirmed CAD (≥ 50% stenosis or < 50% stenosis with history of acute coronary syndrome) underwent telephone follow up at 30 days, six months, and one year from study entry. Data was collected for outcomes of MI, stroke, target vessel revascularization, and death. For patients who did not complete the telephone follow-ups (23.1%), outcome data was collected from APPROACH which is linked to Alberta Vital Statistics, thus follow up was complete for mortality and target vessel revascularization outcomes, provided the patient remained in Alberta.

Statistical Analysis

ABI was calculated by dividing the highest pressure of the posterior tibial or dorsalis pedis arteries in each leg by the highest brachial pressure. The lowest ABI value was used except in cases where the lower value was normal and the higher value was greater than 1.40, then the higher value was used. While ABI is measured on a continuous scale, ABI ≤ 0.90 is considered diagnostic for PAD, ABI 0.90 to 0.99 is borderline PAD, ABI 1.00 to 1.40 is normal and ABI > 1.40 is considered vascular calcification artifact, a hardening of the arteries by calcification.[17]

Comparisons between ABI groups and the variables listed in Table 4-1 were analyzed using Fisher's exact test and one-way ANOVA with Tukey's post hoc test. The association between

SYNTAX scores and ABI groups was examined using stepwise logistic regression, while relationships between pre- and post-revascularization Duke Jeopardy scores with the ABI groups were examined using purposeful selection methods in logistic regression. Threshold level for a high SYNTAX score was based on previous literature,[18] while Duke Jeopardy score thresholds were calculated using the entire sample mean plus one standard deviation, rounded to the nearest integer. Outcome data was analyzed using Cox proportional hazards model with forward step-wise regression adjusted for age and sex.

4.4 Results

The baseline characteristics of the study population, stratified by ABI group, are shown in Table 4-1. Of the 814 patients enrolled in the study, 7.6% (n=62) had PAD, 8.5% (n=69) had borderline PAD, 76.8% (n=625) were in the normal range, and 7.1% (n=58) had vascular calcification artifact. Patients with PAD were significantly older than the normal group (69.9 vs. 61.0 years), had significantly fewer males (56.5% vs. 74.6%), and a higher prevalence of hypertension (89.5% vs. 74.5%). Diabetes prevalence was significantly higher in the group with vascular calcification artifact compared to all others, while there were no significant differences in the prevalence of hyperlipidemia across the strata of ABI. Patients with vascular calcification artifact had a significantly lower prevalence of current smokers compared to the other three groups, however there was no difference in smoking status between PAD patients and those with normal ABI.

Measures of CAD complexity and myocardium at risk, stratified by ABI group, are shown in Table 4-2. The overall mean SYNTAX score was 11.4 (SD 11.4) with the highest score in the

PAD group. A SYNTAX score of zero was found in 23.6% (n=192) of patients. Sixty percent of the cohort (n=492) had low SYNTAX scores (1 to 22), 9.8% (n=80) had intermediate SYNTAX scores (23 to 33), while 6.1% (n=50) had high SYNTAX scores (≥ 33). Prevalence of PAD increased as SYNTAX scores increased with 7.7% (n=35) prevalence in patients with low SYNTAX scores, 13.3% (n=11) prevalence in patients with intermediate SYNTAX scores, and 20.0% (n=10) in patients with high SYNTAX scores. Patients with PAD or vascular calcification artifact had significantly higher SYNTAX scores than patients with a normal ABI ($p<0.001$ and $p=0.032$). Duke Jeopardy scores were highest in patients with PAD both pre- and post-revascularization. The mean initial Duke Jeopardy score was 3.9 (3.8 SD) decreasing to 2.0 (2.5 SD) post revascularization. Prevalence of subjects with an initial Duke Jeopardy score ≥ 8 and concomitant PAD was significantly less than those with a post Duke Jeopardy score ≥ 5 and PAD (16.0% vs. 17.6%, $p=0.021$).

Presence of PAD was positively correlated with SYNTAX score ($r= 0.16$, $p<0.001$) and a high SYNTAX score ≥ 33 was significantly more likely to be found in patients with PAD after adjustment for age, sex, hypertension, diabetes, and current smokers (OR 4.3, 95% CI 1.2,14.9; $p=0.022$) compared to patients with a normal ABI (Table 4-3). PAD was also positively correlated with Duke Jeopardy scores pre- and post-revascularization ($r=0.18$, $p<0.001$ and $r=0.15$, $p=0.001$). Patients with PAD had 3.5 times more initial myocardium at risk (adjusted OR 3.5, 95% CI 1.7, 7.1; $p=0.001$) and 3.0 times more myocardium at risk post revascularization (adjusted OR 3.0, 95% CI 1.1, 8.8; $p=0.039$) compared to patients with a normal ABI (Tables 4-4, 4-5).

The age and sex adjusted hazard ratio for cardiovascular events or death in those patients with PAD was 2.0 (95% CI 1.0, 3.9; p=0.037) which became non-significant after adjusting for post Duke Jeopardy scores (HR 1.7, 95% CI 0.8, 3.9; p=0.187). Eighty six patients (10.6%) did not qualify for follow up due to having < 50% stenosis and no history of ACS. These patients were less likely to be male (60.5% vs. 74.3%, p=0.010), smoked less (20.0% vs. 33.8%, p=0.030), and had more heart failure (21.4% vs. 7.8%, p=0.002) compared to patients who underwent follow-up.

4.5 Discussion

PAD is a measure of atherosclerotic burden, and is associated with poorer outcomes. We found that patients with PAD referred for coronary angiography did indeed have greater CAD complexity (as measured by SYNTAX score) and more myocardium at risk (as measured by Duke Jeopardy score). We also confirmed previous findings that patients with PAD had worse outcomes, and our results are consistent with less complete coronary revascularization being a contributing cause.[1,2,3]

Previous research studies have examined the relationship between CAD complexity and different measures of non-coronary atherosclerosis including carotid and brachial-ankle pulse wave velocity (cPWV, baPWV), carotid intima media thickness, and ABI.[7-9,19,20] The findings all support a strong correlation between PAD and CAD complexity. Pulse wave velocity, a measure of arterial stiffness, has been shown to be independently associated with the number of coronary vessels with greater than 50% narrowing.[9] Using the SYNTAX scoring system for CAD complexity, high baPWV was significantly associated with SYNTAX scores >18 (OR 4.13, 95%

CI 1.12, 5.27).[20] Negative correlation between ABI and SYNTAX (r = -0.172, p=0.001) has also been established,[8] along with significantly higher SYNTAX scores when ABI ≤ 0.90. In a cohort of patients with a first time diagnosis of non-ST segment elevation myocardial infarction (NSTEMI), Korkmaz et al., reported SYNTAX scores were significantly higher for patients with ABI ≤ 0.90 and ABI 0.90 to 0.99 compared to ABI 1.00 to 1.29 ($p<0.0001$).[7] Again, SYNTAX scores were significantly higher when ABI ≤ 0.90 compared to ABI > 0.90 (14 vs. 10; $p<0.001$) in a population undergoing coronary angiography.[21] Our results confirm these prior observations.

There are fewer published data relating ABI and differences in myocardium at risk following coronary revascularization. Our findings indicate that patients with PAD have more myocardium at risk and that there is a significant difference in the completeness of their revascularization compared to those without PAD. These results are similar to a study by Igarashi et al., who found ABI was negatively correlated with the percentage of ischemic myocardium (r = -0.26, $p<0.001$).[22] Patients with subclavian artery stenosis also had a higher percentage of ischemic myocardium (9.0 ± 8.5% vs. 5.6 ± 6.6%, $p < 0.05$) determined by single-photon emission computed tomography (SPECT) compared to patients without stenosis.[22] Our findings support that in addition to being associated with higher SYNTAX scores, PAD is associated with more myocardium at risk both before and after coronary revascularization.

Our study has some limitations. The study design was observational and therefore residual confounding may remain. In addition, the prevalence of PAD in our population and the number of cardiovascular events at one year were lower than expected, limiting the ability of our analysis to adjust for possible confounders; we chose to adjust for traditional CAD risk factors that

showed significant differences across the ABI groups using purposeful selection methods in logistic regression in order to accommodate our relatively small sample size.

4.6 Conclusion

Complexity of CAD is greater for patients with PAD, and the amount of myocardium at risk is greater for patients with PAD both before and after coronary revascularization. Patients with PAD have worse cardiovascular outcomes, and incomplete coronary revascularization may be a contributing factor.

Table 4-1. Patient Characteristics

	PAD ABI ≤ 0.90	Borderline PAD ABI 0.90 to 0.99	Normal ABI 1.00 to 1.40	Vascular calcification artifact ABI > 1.40	p value
Total N	62	69	625	58	
Male (%)	35 (56.5)	42 (60.9)	466 (74.6)	50 (86.2)	<0.001
Mean age (years)	69.9 (11.8)	65.3 (11.7)	61.0 (11.3)	65.5 (10.9)	<0.001
Co-morbidities					
Hypertension	51 (89.5)	58 (86.6)	408 (74.5)	47 (83.9)	0.006
Hyperlipidemia	49 (86.0)	57 (87.7)	472 (85.4)	47 (83.9)	0.948
Diabetes	20 (47.6)	23 (39.7)	149 (32.3)	26 (52.0)	0.012
Heart failure	9 (21.4)	4 (7.8)	29 (6.8)	9 (23.1)	0.001
Cerebrovascular disease	4 (10.5)	4 (8.0)	11 (2.7)	3 (7.9)	0.012
Chronic Obstructive Pulmonary Disease	8 (20.0)	8 (15.7)	50 (11.9)	1 (2.6)	0.083
Renal insufficiency	8 (20.5)	7 (13.7)	30 (7.7)	10 (25.0)	0.001
Family history of CAD	16 (35.6)	21 (39.6)	227 (48.4)	19 (45.2)	0.276
Smoking status					
Never	6 (12.0)	16 (25.4)	118 (23.8)	10 (22.7)	0.267
Current	23 (46.0)	24 (38.1)	158 (31.9)	7 (15.9)	0.012
Former	21 (42.0)	23 (36.5)	219 (44.2)	27 (61.4)	0.079
Indication for catheterization					
STEMI	3 (4.9)	5 (7.4)	69 (11.1)	2 (3.4)	0.132
NSTEMI	26 (42.6)	21 (30.9)	185 (29.8)	23 (39.7)	0.105
Unstable angina	7 (11.5)	10 (14.7)	104 (16.7)	6 (10.3)	0.514
Stable angina	18 (29.5)	25 (36.8)	202 (32.5)	18 (31.0)	0.837

Values are n (%) or mean (SD).

Table 4-2. Measures of CAD complexity and myocardium at risk

	PAD ABI ≤ 0.90	Borderline PAD ABI 0.90 to 0.99	Normal ABI 1.00 to 1.40	Vascular calcification artifact ABI > 1.40	p value
Mean SYNTAX score	17.6 (12.4)	12.4 (11.7)	10.3 (10.7)	14.5 (14.5)	<0.001
Mean Initial Duke Jeopardy Score	6.3 (4.1)	4.4 (4.1)	3.5 (3.5)	4.6 (4.3)	<0.001
Mean Post Revascularization Duke Jeopardy Score	3.3 (3.3)	2.1 (2.4)	1.8 (2.3)	2.7 (2.6)	0.001

Values are mean (SD).

Table 4-3. Relationship between high SYNTAX score (≥ 33) and ABI

	PAD ABI ≤ 0.90	Borderline PAD ABI 0.90 to 0.99	Normal ABI 1.00 to 1.40	Vascular calcification artifact ABI > 1.40
Odds Ratio	4.3	3.6	1.0	1.5
95% CI	1.2, 14.9	1.1, 14.9		0.4, 6.0
p value	0.022	0.031		0.566

Adjusted for age (quartiles), sex, hypertension, diabetes, current smoking.

Table 4-4. Relationship between high initial Duke Jeopardy Score (≥ 8) and ABI

	PAD ABI ≤ 0.90	Borderline PAD ABI 0.90 to 0.99	Normal ABI 1.00 to 1.40	Vascular calcification artifact ABI > 1.40
Odds Ratio	3.5	1.7	1.0	1.8
95% CI	1.7, 7.1	0.9, 3.2		0.9, 3.5
p value	0.001	0.132		0.087

Final model predictors include ABI groups, diabetes and current smokers.

Table 4-5. Relationship between high post Duke Jeopardy Score (≥ 5) and ABI

	PAD ABI ≤ 0.90	Borderline PAD ABI 0.90 to 0.99	Normal ABI 1.00 to 1.40	Vascular calcification artifact ABI > 1.40
Odds Ratio	3.0	1.0	1.0	2.9
95% CI	1.1, 8.8	0.3, 3.6		0.9, 9.0
p value	0.039	0.983		0.063

Final model predictors include ABI groups, diabetes and sex

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CHAPTER 5: INTER-ARM BLOOD PRESSURE DIFFERENCE IS NOT ASSOCIATED WITH HIGH ANKLE-BRACHIAL INDEX

5.1 Abstract

Introduction: Systolic inter-arm blood pressure difference (IAD) ≥ 10mmHg is associated with peripheral artery disease (PAD), identified as ankle-brachial index (ABI) ≤ 0.90, and confers risk for subsequent negative outcomes. We sought to determine if IAD is also associated with ABI > 1.40, or vascular calcification artifact.

Methods: 985 consecutive adults undergoing elective coronary angiography underwent ABI measurement using standard Doppler ultrasound technique. Bilateral brachial blood pressure measures from the ABI calculation were used to measure IAD. Patients were followed for one year for cardiovascular related outcomes, including myocardial infarction, target vessel revascularization, stroke, and death.

Results: Overall, 12.6% of patients had IAD ≥ 10mmHg, and 6.9% had vascular calcification artifact. PAD (ABI ≤ 0.90) was more likely to be found with IAD ≥ 10mmHg (adjusted OR 3.5, 95% CI 1.4, 8.9; p=0.008), than patients with a normal ABI. There was no positive association between IAD ≥ 10mmHg and vascular calcification artifact; there was instead a trend for a negative association (p=0.117). Concomitant IAD ≥ 10mmHg and vascular calcification artifact was a relatively rare event, and the effect of IAD ≥ 10mmHg on prognosis for those with vascular calcification artifact could not be accurately measured.

Conclusions: IAD ≥ 10mmHg is relatively rare in subjects with vascular calcification artifact. Screening for IAD ≥ 10mmHg in subjects with vascular calcification artifact in order to improve risk stratification is unlikely to have utility.

5.2 Introduction

Inter-arm blood pressure difference (IAD) is thought to confer additional risk for cardiovascular events such as myocardial infarction (MI), stroke, and death.[1-4] While an IAD of less than 10mmHg is considered normal, meta-analyses of observational studies have found a prevalence of 19.6% for a systolic difference of 10mmHg or greater, and a prevalence of 4.2% for a systolic difference greater than 20mmHg.[5] IAD is associated with peripheral artery disease (PAD), identified by ankle-brachial index (ABI) ≤ 0.90.[5,6] PAD alone increases the risk of MI, stroke, and target vessel revascularization as well as cardiovascular and all-cause mortality,[7-10] and combined PAD and systolic IAD $\geq$ 10mmHg appear to confer a doubling of mortality risk (RR 2.4: 95% CI 1.53, 3.87).[2] While IAD may have prognostic utility,[2] routine screening for IAD has yet to be adopted in national hypertension guidelines.[11,12]

The ABI measure can be limited by vascular calcification artifact, which can cause falsely elevate ABI. High ABI values greater than 1.40 are thought to be due to arterial stiffening related to medial calcinosis, a situation that is frequently encountered in patients with diabetes or chronic kidney disease.[13] As with low ABI values (≤ 0.90), high ABI values are also associated with poor outcomes, including increased risk for cardiovascular events and mortality.[14,15] However, whether IAD is associated with vascular calcification artifact, and whether combined vascular calcification artifact and IAD $\geq$ 10mmHg confer more risk for adverse cardiovascular events and mortality is not known.

Our objective was to determine whether IAD ≥ 10mmHg is associated with vascular calcification artifact, and whether IAD ≥ 10mmHg influences prognosis in subjects with vascular calcification artifact.

5.3 Methods

Study Design and Participants

The Health Research Ethics Board of the University of Alberta approved the research protocol of this prospective observational cohort study. Outpatients and inpatients 18 years and older referred for an angiogram due to suspected coronary artery disease (CAD) were consecutively sampled from catheterization labs in two urban hospitals between March 2010 and October 2013. Subjects were excluded if they were being assessed for a heart transplant, valve disease, congenital heart disease or pulmonary hypertension. Patients who did not undergo catheterization within three months of study entry, had only one brachial blood pressure measurement, as well as those who were unable to communicate in English or were unable to have an ankle-brachial index measure due to sores or ulcers were also excluded. We did not include those patients undergoing emergency catheterization. Eighty-four percent of the confirmed eligible patients agreed to participate in the study. Among those who declined, the main reasons cited were fatigue, anxiety regarding their imminent catheterization procedure, and not being easily reached by telephone for the outcome follow-ups.

Data Collection

Prospective patients were pre-screened by study staff in the catheterization lab recovery area based on their indication for coronary catheterization on the procedure requisition. Patients were

approached while waiting for their procedure and screened a second time for eligibility based on patient response and chart information. Written consent was collected from all eligible patients.

With the patient lying in a supine position manual non-simultaneous measurement of systolic blood pressure was performed on the brachial, posterior tibial, and dorsalis pedis arteries bilaterally using an 8mHz Doppler ultrasound (Summit Doppler, Wallach Surgical, Trumbull, CT, USA). Inter-arm differences greater than 10mmHg were confirmed by repeat measurement. Demographic, anthropometric, and co-morbidity data were collected from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease database (APPROACH).[16] APPROACH is a prospective database that records all coronary catheterizations performed in Alberta.

Seventy-nine percent of patients qualified for follow up with angiographically confirmed CAD ($\geq$ 50% stenosis or < 50% stenosis with history of acute coronary syndrome (ACS)) and underwent telephone follow up at 30 days, six months, and one year from study entry. Data was collected for outcomes of MI, target vessel revascularization, stroke, and death. For the 181 (23.3%) patients who could not be contacted, outcome data was collected from APPROACH which is linked to Alberta Vital Statistics, thus follow up was complete for mortality and target vessel revascularization outcomes, provided the patient remained in Alberta.

Data Analysis

ABI was determined by dividing the highest pressure of the posterior tibial and dorsalis pedis arteries in each leg by the highest brachial pressure. The highest value from either the left or

right side was used as the ABI value. Comparisons of patient characteristics illustrated in Table 5-1 were determined using Fisher's exact test or an independent t-test. Logistic regression was used to calculate odds ratios for IAD across the strata of ABI. Cox regression was used to evaluate the hazard of IAD ≥ 10mmHg and ABI > 1.40 on a composite outcome of MI, target vessel revascularization, stroke or death at one year. All statistical analyses were completed using SPSS (SPSS Inc., Version 17.0: Chicago, Illinois).

5.4 Results

The baseline characteristics of the included subjects, stratified by presence or absence of IAD ≥ 10mmHg, are shown in Table 5-1. Patients were of similar age (62.8 vs. 63.2 years) with similar proportions of males (75.0% vs. 73.4%). There were no significant differences between groups for the standard cardiovascular risk factors of hypertension, hyperlipidemia, diabetes or smoking.

The overall prevalence of IAD ≥ 10 mmHg was 12.6%, and the overall prevalence of vascular calcification artifact was 6.9%. Patients with IAD ≥ 10mmHg had a significantly lower mean ABI (1.11 vs. 1.21; $p < 0.001$) and more PAD (11.3% vs. 3.9%, $p=0.001$) than patients with IAD < 10mmHg.

Subjects with both vascular calcification artifact and IAD ≥ 10 mmHg were uncommon; there were only three such subjects in the cohort, resulting in a significantly lower prevalence of vascular calcification artifact at 2.4% for the IAD ≥ 10 mmHg group, compared to 7.5% for the IAD < 10 mmHg group ($p = 0.036$).

An IAD ≥ 10mmHg was significantly more likely to be found in patients with PAD than patients with a normal ABI (1.00 to 1.40) after adjusting for traditional cardiovascular risk factors (adjusted OR 3.5, 95% CI 1.4, 8.9; p=0.008, Table 5-2). In patients with vascular calcification artifact, there was a non-significant trend where IAD ≥ 10mmHg was less likely to be found compared to patients with a normal ABI (adjusted OR 0.3, 95% CI 0.1,1.3; p=0.117). There were too few subjects with IAD ≥ 10mmHg and vascular calcification artifact to reliably estimate the hazard ratio, with one of the three subjects (33.3%) reporting a negative outcome (age and sex adjusted OR 2.3, 95% CI 0.3, 18.4; p=0.417).

5.5 Discussion

IAD ≥ 10mmHg is known to be associated with PAD and confer excess risk for adverse outcomes, but the relationship between vascular calcification artifact and IAD ≥ 10mmHg has not previously been reported. Concordant with prior literature, we found a positive association between PAD and IAD ≥ 10mmHg. However, we did not observe a similar positive association between vascular calcification artifact and IAD ≥ 10mmHg. Instead, we found relatively few subjects with both vascular calcification artifact and IAD ≥ 10mmHg, and a trend for an inverse association between vascular calcification artifact and IAD ≥ 10mmHg (p = 0.117). Though previous studies have confirmed that the presence of IAD ≥ 10mmHg confers excess risk for adverse cardiovascular events in those subjects with concomitant PAD, we found too few subjects with both vascular calcification artifact and IAD ≥ 10mmHg to reliably estimate whether the presence of IAD ≥ 10mmHg alters prognosis for those with vascular calcification artifact. These findings suggest that the underlying pathophysiology of the vascular calcification artifact may be different than that which causes IAD. Moreover, our data suggest that there is

likely little utility in screening subjects with vascular calcification artifact for IAD ≥ 10mmHg in order to predict risk for adverse outcomes, since having both abnormalities is comparatively rare.

Our data are similar to prior reports with respect to prevalence of the combination of both vascular calcification artifact and IAD ≥ 10mmHg. Though reported prevalence of vascular calcification artifact in the literature ranges from 1.7% to 37.2%,[13,14] our finding of 6.9% is similar to a study of hospitalized internal medicine patients which reported a prevalence of 8%.[15] For IAD, a pooled analysis of four studies of diverse populations and measurement methods found a prevalence of IAD ≥ 10mmHg ranging from 2.7% to 31.2% with a mean of 19.6%, compared to our IAD ≥ 10mmHg prevalence of 12.6%.[5]

There is little utility in screening for IAD ≥ 10mmHg in patients with vascular calcification artifact. The occurrence of patients with both abnormalities is rare and the ABI may be falsely elevated due to calcification of the medial layer rather than the presence of atherosclerosis. Future prognostic studies would be useful to confirm the trend towards a negative association between IAD ≥ 10mmHg and vascular calcification artifact.

Limitations

Our study is observational, and residual confounding may remain. We recruited our study cohort from subjects undergoing coronary angiography, and it is possible that the prevalence estimates obtained from our cohort may be different from estimates obtained from different populations. The data in this study were collected using a single manual blood pressure taken bilaterally on the arteries of the arms and legs. Simultaneous multiple electronic ABI measurement might

reduce measurement error, however a study by Real de Asúa et al., reported that multiple sequential measurements did not significantly affect the calculation of ABI and subsequent diagnosis of PAD.[17] A systematic review and meta-analysis by Clark et al., comparing the relative risk of pre-existing CAD and IAD based on simultaneous vs. non-simultaneous measurement did not find a significant difference between the methods.[2] The individuals involved in the data collection received specific ABI training and any measurement bias introduced by human error is likely not significant. With our relatively small sample sizes in the PAD and vascular calcification artifact groups for patients with IAD ≥ 10mmHg, we are likely underpowered to detect a significant hazard ratio.

5.6 Conclusion

While we confirmed a positive association between the IAD ≥ 10mmHg and PAD, we did not find a similar positive association between IAD ≥ 10mmHg and vascular calcification artifact. Concomitant IAD ≥ 10mmHg and vascular calcification artifact is rare, and the effect of IAD ≥ 10mmHg on prognosis of those with vascular calcification artifact could not be accurately measured. Screening for IAD ≥ 10mmHg in subjects with vascular calcification artifact to improve risk stratification is unlikely to be useful.

Table 5-1. Patient Characteristics

	IAD < 10mmHg	IAD ≥ 10mmHg	p value
Number of patients	861	124	
Male (%)	642 (75.0)	91 (73.4)	0.740
Mean age (years)	62.8 (0.4)	63.2 (1.1)	0.763
Hypertension	590 (78.7)	95 (79.2)	1.000
Hyperlipidemia	675 (88.4)	100 (88.5)	1.000
Diabetes mellitus	239 (38.1)	38 (38.4)	1.000
Renal failure	4 (0.8)	0	1.000
Current/former smoker	526 (77.0)	81 (81.0)	0.442
Mean ABI	1.21 (0.01)	1.11 (0.02)	<0.001
Mean systolic blood pressure (mmHg)	123.0 (0.7)	123.3 (1.8)	0.872
Mean inter-arm difference (mmHg)	3.8 (0.1)	13.3 (0.5)	<0.001
PAD (ABI ≤ 0.90)	34 (3.9)	14 (11.3)	0.001
Borderline PAD (ABI 0.90 to 0.99)	33 (3.8)	6 (4.8)	0.620
Vascular calcification artifact (ABI > 1.40)	65 (7.5)	3 (2.4)	0.036

Values are n (%) or mean (SD).

Table 5-2. Adjusted Odds Ratios of IAD ≥ 10 mmHg and ABI

ABI	OR	95% CI	p-value
PAD (≤ 0.90)	3.5	1.4, 8.9	0.008
Borderline PAD (0.90 to 0.99)	1.5	0.5, 4.6	0.494
Normal (1.00 to 1.40)	Reference		
Vascular calcification artifact (> 1.40)	0.3	0.1, 1.3	0.117

Adjusted for age, sex, hypertension, hyperlipidemia, smoking and diabetes

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CHAPTER 6: ANKLE-BRACHIAL INDEX AND PREDICTION OF CORONARY ARTERY DISEASE COMPLEXITY

6.1 Abstract

Introduction: Our aim was to determine if ankle-brachial index (ABI) could non-invasively identify the presence of coronary artery disease (CAD) and inform clinical decision making regarding more invasive measures of CAD.

Methods: 814 consecutive adults referred for coronary angiography underwent ABI measurement using standard Doppler ultrasound technique. SYNTAX scores were calculated to determine CAD complexity.

Results: ABI ≤ 0.90 had a positive predictive value of 91.9% to identify SYNTAX scores greater than zero. ABI ≤ 0.90 had a sensitivity of 9.2% and a specificity of 97.4% to detect a SYNTAX score greater than zero with a likelihood ratio of 3.5.

Conclusions: The presence of an ABI ≤ 0.90 is a useful non-invasive screening tool for identifying CAD and informing decisions regarding use of coronary catheterization.

6.2 Introduction

Peripheral artery disease can be defined as a range of non-coronary arterial syndromes that are caused by the altered structure and function of the arteries that supply the brain, visceral organs, and extremities. Lower-extremity peripheral artery disease (PAD) involves atherosclerotic disease progression in the vessels of the pelvis and legs, and is an independent predictor of cardiovascular events.[1] Patients with PAD have higher incidence of myocardial infarction, stroke, and transient ischemic attacks, and have a 1.6 times greater risk of all-cause mortality.[2-4]

Ankle-brachial index (ABI) is a ratio of systolic pressures in the lower and upper extremities, and is the gold standard for diagnosis of PAD.[5] It is relatively simple, non-invasive, inexpensive, and an ABI ≤ 0.90 has a sensitivity of 79-95% and specificity of 95-98% for angiograph-diagnosed PAD. Both PAD and ABI are also strongly correlated with multiple measures of coronary artery disease (CAD) including the SYNergy between PCI with TAXUS™ and Cardiac Surgery (SYNTAX) score.[6-12]

In the present study, ABI was assessed in a cohort of coronary angiography patients and the results compared to SYNTAX scores. SYNTAX scores are based on the location and complexity of coronary lesions and are currently used to objectively quantify the degree of coronary atherosclerosis revealed by angiography.[13,14] SYNTAX scores guide decision making regarding revascularization with percutaneous intervention (PCI) or coronary artery bypass graft (CABG) approaches.[14] Our aim was to determine if the diagnostic ability of ABI to predict SYNTAX scores could non-invasively identify the presence of CAD and inform clinical decision making

where a patient may be more likely to undergo coronary catheterization if there is evidence of a prognosis-altering lesion.

6.3 Methods

Participants

Outpatients and inpatients 18 years of age and older referred for coronary angiogram for suspected CAD were consecutively sampled from the catheterization recovery areas of two urban hospitals between March 2010 and September 2012. Emergency cases and patients being assessed for heart transplant, valve disease, pulmonary hypertension or congenital heart disease were excluded. We also excluded patients with a previous coronary artery bypass graft, as well as those who were unable to communicate in English or were unable to have an ABI measured due to sores or ulcers. Patients who did not undergo catheterization within three months of study entry were not included in the data analysis.

Recruitment

Patients underwent an initial screening for eligibility based on their indication for coronary angiography on the procedure requisition form. Potentially eligible patients were then approached to participate and underwent a secondary screening for eligibility based on their responses and chart information. Eighty-four percent of the confirmed eligible patients agreed to participate. All participants who met the eligibility criteria provided written informed consent. The Health Research Ethics Board at the University of Alberta approved this research protocol.

Data Collection and Test methods

An ABI was assessed for each patient prior to coronary angiography. With the patient in a supine position, manual non-simultaneous systolic blood pressure was measured bilaterally at the brachial, posterior tibial, and dorsalis pedis arteries using a L150 Summit Doppler (Wallach Surgical, Trumbull, CT, USA) with an 8MHz vascular probe. While ABI is measured on a continuous scale it is often categorized: ≤ 0.90 is a diagnosis of PAD, 0.90 to 0.99 is borderline PAD, 1.00 to 1.40 is normal, and ABI > 1.40 is recognized as vascular calcification artifact, a hardening of the arteries due to calcification.[15] As ABI was measured prior to the angiography procedure, the SYNTAX score and extent of CAD was not yet determined.

SYNTAX scores reflect the number and complexity of lesions as well as their location in the coronary tree.[12] Designed as a classification system that accounts for the anatomy and functional impact of coronary lesions,[13] interventional cardiologists categorize a SYNTAX score ≤ 22 as low, a score 23-32 as intermediate, and a score ≥ 33 as high to inform decisions regarding the best method of revascularization.[13,14] A SYNTAX score of zero indicates there is no measureable CAD.[16] In this study, SYNTAX scores were calculated with an online calculator (www.syntaxscore.com) using the coronary angiography results. Research team members who calculated SYNTAX scores were blinded to the patient's ABI and PAD history.

Supplementary co-morbidity data were collected from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) database. APPROACH is a prospective database that records all coronary catheterization and surgeries performed in Alberta.[17]

Statistical Analysis

ABI was determined by dividing the highest pressure of the posterior tibial and dorsalis pedis arteries in each leg by the highest brachial pressure. The lowest ABI measured was used as the ABI value, except when the lower value was normal and the higher value was greater than 1.40. In these cases the higher value was used. Statistical analyses were calculated using SPSS (SPSS Inc., Version 17: Chicago, Illinois).

6.4 Results

Baseline characteristics of the study cohort, stratified by the presence of CAD measurable by SYNTAX score, are shown in Table 6-1. Patients with confirmed CAD (as defined by a SYNTAX score greater than zero) were significantly older (63.2 vs. 59.7 years), more likely to be male (78.3% vs. 55.2%) had more hyperlipidemia (88.2% vs. 76.2%) and less heart failure (7.0% vs. 16.4%) compared to patients without any measurable CAD. Myocardial infarction (either ST segment elevation myocardial infarction (STEMI) or non-ST segment elevation myocardial infarction (NSTEMI)) was presented more often in patients with SYNTAX scores greater than zero ($p<0.01$). Prevalence of PAD was higher in the CAD group, with a lower mean ABI (1.13 vs. 1.16) than the group without measurable CAD.

Diagnostic statistics for ABI ≤ 0.90 to detect CAD complexity as determined by SYNTAX scores are shown in Table 6-2. ABI ≤ 0.90 has a 91.9% positive predictive value (PPV) for SYNTAX scores greater than zero and a likelihood ratio of 3.5. PPV decreased as the SYNTAX scores increased, while the likelihood ratio of ABI ≤ 0.90 to detect SYNTAX score increased as

the complexity of CAD increased. ABI values of 0.9 to 0.99 did not have high PPV or likelihood ratios.

6.5 Discussion

In our population of patients referred for cardiac catheterization, we found that 91.9% with an ABI ≤ 0.90 had CAD as defined by a SYNTAX score greater than zero. With a low sensitivity and a high specificity, an ABI ≤ 0.90 had a likelihood ratio of 3.5 for identifying measurable CAD. The likelihood ratio decreased to 3.0 for patients with high SYNTAX scores and to 2.2 for patients with intermediate SYNTAX scores. Our results show that ABI ≤ 0.90 can non-invasively identify patients with CAD and potentially inform decision making regarding use of coronary catheterization, however it is less useful in predicting a prognosis-altering lesion.

Our finding of low sensitivity for ABI to predict CAD complexity was also seen in a previous study which examined the diagnostic relationship between ABI and CAD complexity using target vessel location and lesion type as a measure for the degree of CAD.[7] In non-diabetic patients, ABI ≤ 0.90 had a sensitivity of 23.9% and a specificity of 92.8% for detecting CAD.[7] With concomitant diabetes, sensitivity and specificity increased to 31.4% and 94.9%, respectively.[7] Low sensitivity has also been reported in the prediction of cardiovascular outcomes by ABI. In a systematic review of nine studies using ABI cutoffs between 0.80 and 0.90 to predict incident cardiac events, ABI had a sensitivity of 16.5% and a specificity of 92.7%.[18]

While our study suggests a low ABI can indicate the presence of coronary disease and inform clinical decision making regarding use of coronary catheterization, a study by Ezhumalai et al.,

proposed that ABI < 0.90 could be used as a surrogate marker for CAD with a sensitivity of 91.5% and a specificity of 100% to detect CAD severity (measured by the number of major coronary arteries showing >50% stenosis with angiography) compared to carotid intima media thickness.[19] Unlike the SYNTAX score, looking only at the stenosis does not account for characteristics of the lesion and functional impact on coronary blood flow, factors that affect the technical ability to successfully revascularize the patient.[13,14] Based on our findings, ABI ≤ 0.90 is a non-invasive method to identify significant CAD, but is not an accurate surrogate marker for CAD complexity.

The prevalence of concomitant ABI ≤ 0.90 with intermediate and high SYNTAX scores was small (n=12 and 10 respectively). This may account for the low sensitivity we calculated. The small number of PAD patients overall (n=62, 7.6%) illustrates the strength of the predictive value of ABI in this cohort.

6.6 Conclusion

As a simple, non-invasive measure, ABI ≤ 0.90 could provide clinicians with information about the complexity of a patient's coronary disease and inform decisions on undertaking more invasive measures of CAD.

Table 6-1. Patient Characteristics

	All	No CAD SS = 0	CAD SS > 0	p value
Total N	814	192	622	
Male (%)	593 (72.9)	106 (55.2)	487 (78.3)	<0.001
Mean age (years)	62.4 (11.6)	59.7 (11.9)	63.2 (11.4)	<0.001
Co-morbidities				
Hypertension	564 (77.5)	116 (71.6)	448 (79.2)	0.054
Hyperlipidemia	625 (85.5)	125 (76.2)	500 (88.2)	0.001
Diabetes	218 (35.7)	44 (33.3)	174 (36.3)	0.540
Heart failure	51 (9.2)	21 (16.4)	30 (7.0)	0.003
Cerebrovascular disease	22 (4.1)	5 (4.2)	17 (4.1)	1.00
Chronic Obstructive Pulmonary Disease	67 (12.2)	12 (9.8)	55 (12.9)	0.434
Renal insufficiency	55 (10.5)	10 (8.5)	45 (11.1)	0.497
Family history of CAD	283 (46.5)	63 (46.3)	220 (46.5)	1.00
Current/former smoker	502 (77.0)	111 (76.0)	391 (77.3)	0.739
Indication for catheterization				
STEMI	79 (9.8)	6 (3.1)	73 (11.8)	<0.001
NSTEMI	255 (31.6)	41 (21.5)	214 (34.7)	0.001
Unstable angina	127 (15.7)	41 (21.5)	86 (13.9)	0.017
Stable angina	263 (32.5)	58 (30.4)	205 (33.2)	0.481
Ankle-brachial index (ABI)				
Mean ABI	1.14 (0.2)	1.16 (0.2)	1.13 (0.3)	0.034
≤ 0.90	62 (7.6)	5 (2.6)	51 (9.2)	0.002
0.90 to 0.99	69 (8.5)	11 (5.7)	58 (9.3)	0.138
1.00 to 1.40	625 (76.8)	162 (84.4)	463 (74.4)	0.004
>1.40	58 (7.1)	14 (7.3)	44 (7.1)	0.874

Values are n (%) or mean (SD). SYNTAX score (SS).

Table 6-2. Diagnostic statistics for SYNTAX score and ABI ≤ 0.90

	Zero SYNTAX (SS=0)	All SYNTAX (SS>0)	Low SYNTAX (SS=1-22)	Intermediate SYNTAX (SS=23-32)	High SYNTAX (SS≥33)
PPV	15.9%	84.1%	66.7%	8.7%	8.7%
NPV	75.7%	24.3%	40.1%	90.0%	94.1%
Sensitivity	5.7%	9.3%	9.3%	7.5%	12.0%
Specificity	90.7%	94.3%	92.9%	91.4%	91.8%
LR	0.6	1.6	1.3	0.9	1.5

Positive predictive value (PPV), negative predictive value (NPV), likelihood ratio (LR), SYNTAX score (SS).

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CHAPTER 7: CONTINUOUS ANKLE-BRACHIAL INDEX AS AN INDEPENDENT PREDICTOR OF OUTCOMES IN CORONARY ARTERY DISEASE: AN INTERIM ANALYSIS

7.1 Abstract

Introduction: Ankle-brachial index (ABI) has a high sensitivity and specificity for detecting lower-extremity peripheral artery disease (PAD), which is recognized as a risk marker for poor patient outcomes. Although atherosclerotic disease is continuous in nature, a dichotomous ABI cutoff is commonly used for risk stratification. Our aim was to examine the relationship between continuous ABI and poor outcomes and evaluate its usefulness for risk assessment in coronary artery disease (CAD) patients.

Methods: 947 consecutive adults referred for coronary angiography underwent ABI measurement using standard Doppler ultrasound technique. Patients with angiographically confirmed stenosis ≥ 50% or < 50% and a history of acute coronary syndrome were followed for one year. We analyzed the relationship between ABI as a continuous measure and a composite outcome of major cardiovascular events (myocardial infarction, target vessel revascularization, stroke or death) at one year.

Results: Continuous ABI ≤ 1.40 is significantly correlated with poor cardiovascular outcomes ($r = -0.12$, $p=0.001$). In patients with CAD, for every 0.1 unit decrease in ABI, the odds of a having a poor outcome increases by 20% (OR=1.20).

Conclusions: Continuous ABI provides prognostic information useful for individual risk assessment in patients with CAD.

7.2 Introduction

Lower-extremity peripheral artery disease (PAD) is a manifestation of atherosclerosis in the lower limb vessels. PAD is associated with poor outcomes including increased risk of myocardial infarction (MI), stroke, and mortality.[1,2] Previous studies indicate that more than 50% of PAD cases are asymptomatic, therefore reliance on symptoms underestimates the prevalence and overall contribution of PAD to outcomes.[3] Ankle-brachial index (ABI) is a simple and non-invasive measure of PAD involving a comparison of the systolic blood pressures between the lower limbs and the arms. ABI has a high sensitivity and specificity for detecting PAD, and is recognized as the gold standard for PAD diagnosis.[1,3-5]

Although atherosclerotic disease represents a continuum, clinicians and researchers dichotomize the ABI when evaluating prognosis. ABI ≤ 0.90 is the widely accepted cutoff for PAD diagnosis, however, there are issues with using a single threshold for all gender and ethnic groups. ABI has been reported as being higher in women compared to men,[6] which could explain the growing evidence of a higher PAD prevalence in women.[7,8] Similar discrepancies between values of ABI and subsequent PAD prevalence have also been noted between Non-Hispanic Whites and Blacks.[6,9]

As the research supporting use of ABI in risk stratification continues to advance, a better understanding of the relationship between ABI and outcomes could help improve individual risk assessment along with prognosis and treatment. We sought to determine the quantitative contribution of the continuous value of ABI as an independent predictor of poor cardiovascular outcomes (MI, target vessel revascularization, stroke, or death) following cardiac catheterization.

7.3 Methods

Participants

Hospitalized and ambulatory patients 18 years of age and older referred for coronary angiography for suspected coronary artery disease (CAD) were consecutively sampled from the recovery areas of two urban hospitals between March 2010 and November 2012. Subjects being assessed for heart transplant, valve disease, pulmonary hypertension or congenital heart disease were excluded, as were emergency cases. Subjects who were unable to communicate in English or were unable to have an ABI measured due to sores or ulcers were also excluded. Subjects underwent an initial screening for eligibility based on their indication for coronary angiography on the procedure requisition form. Potentially eligible subjects were then approached by study staff to participate and underwent a secondary eligibility screening based on their responses and chart information. All participants who met the eligibility criteria provided written informed consent. The Health Research Ethics Board of the University of Alberta approved the research protocol.

Data collection

ABI was performed on each patient prior to coronary angiography. With the patient in a supine position, manual non-simultaneous systolic blood pressure was measured bilaterally at the brachial, posterior tibial, and dorsalis pedis arteries using a L150 Summit Doppler (Wallach Surgical, Trumbull, CT, USA) with an 8MHz vascular probe. Claudication symptoms were determined using the Edinburgh Claudication Questionnaire.[10] Demographic and co-morbidity data were collected from the Alberta Provincial Project for Outcome Assessment in Coronary

Heart Disease (APPROACH) database, a prospective database that records all coronary catheterizations performed in Alberta.[11]

Patients with angiographically confirmed CAD (with ≥ 50% stenosis or < 50% stenosis with history of acute coronary syndrome) received telephone follow up at 30 days, six months, and one year from study entry. Data was collected for outcomes of MI, target vessel revascularization, stroke, and death. All patients were followed until an event of interest, at which point they were censored. For patients who did not complete the telephone follow-ups (22.1%), outcome data was collected from APPROACH which is linked to Alberta Vital Statistics, thus follow up was complete for mortality and target vessel revascularization outcomes, provided the patient remained in Alberta.

Statistical Analysis

ABI values were calculated by dividing the highest pressure of the posterior tibial or dorsalis pedis arteries in each leg by the highest brachial pressure. The lowest ABI measurement was used except in cases where the lower value was normal and the higher value was greater than 1.40, then the higher value was used. While ABI is measured on a continuous scale, for some calculations we used the 2011 American College of Cardiology Foundation (ACCF)/ American Heart Association (AHA) recommendations of ABI ≤ 0.90 as a diagnosis of PAD, ABI 0.90 to 0.99 as borderline PAD, ABI 1.00 to 1.40 as normal and ABI > 1.40 as vascular calcification artifact, a hardening of the arteries by calcification.[12]

For continuous ABI we excluded patients with ABI > 1.40 as they likely have a different underlying physiology than atherosclerosis found in ABI ≤ 1.40.[13] Patients with ABI > 1.40 have an increased mortality hazard compared to an ABI between 1.11 and 1.40, which has the lowest level of risk, confirming a J-curved association between ABI and poor outcomes.[14]

Comparisons between ABI groups and the variables listed in Table 1 were analyzed using Fisher's exact test and one-way ANOVA with Tukey's post hoc test. Forward stepwise logistic regression adjusted for traditional CAD risk factors was used to examine the association between continuous ABI and cardiovascular outcomes. Hazard ratios were determined using Cox proportional hazards model for a composite outcome of MI, target vessel revascularization, stroke or death within one year. All data was analyzed using SPSS (SPSS Inc., Version 17.0. Chicago, Illinois).

7.4 Results

The baseline characteristics of the study population, overall and stratified by ACCF/AHA recommended ABI cutoffs, are shown in Table 7-1. The 947 patients enrolled in the study were mainly male (73.8%), most self-identified as White European (88.6%), and ranged in age from 31 to 89 years with a mean age of 62.9 (SD 11.5) years. Patients with an ABI on either end of the spectrum were significantly older than patients with a normal ABI (1.00 to 1.40), while patients with low ABI (≤ 0.99) were less likely to be male. Overall prevalence of hypertension and diabetes was high at 77.7% and 37.2% respectively, with significant differences across the ABI spectrum. More than three quarters of the cohort identified themselves as current or former smokers.

Classic claudication symptoms were found in 10.5% of patients and 2.2% had atypical claudication. Patients with claudication symptoms had a significantly higher prevalence of hypertension (p=0.009), more diabetes (p=0.024), and a lower ABI (p<0.001) compared to patients without symptoms. Overall PAD prevalence was 9.2%, with 8.7% having borderline PAD, and 7.5% having vascular calcification artifact. The majority of patients (74.7%) with ABI ≤ 0.90 did not have a previous PAD diagnosis.

Coronary angiography revealed stenosis ≥ 50.0% in 78.8% of patients, with a mean APPROACH Lesion score of 31.4 (SD 29.6) out of 100 and a mean Duke Jeopardy score of 4.1 (SD 4.0) out of a possible 12, prior to any revascularization. Frequency and type of cardiovascular outcomes as a first event are shown in Table 7-2. Ninety patients (9.5%) did not qualify for follow-up due to coronary stenosis <50% and no history of acute coronary syndrome. These patients were significantly younger (60.1 vs. 63.2 years, p=0.014), were less likely to be male (58.9% vs. 75.4%, p=0.001), had more heart failure (24.1% vs. 7.9%, p=0.001), and had less dyslipidemia (76.7% vs. 87.8%, p=0.017) compared to the patients who qualified for follow-up.

The composite cardiovascular outcome at one year was significantly correlated with continuous ABI (r = -0.12, p=0.001). For each 0.1 unit decrease in continuous ABI, a patient had a 20% increase (OR=1.20) in the odds of a negative outcome. We did not find a significant hazard ratio for continuous ABI and the composite outcome at one year, although using the traditional PAD cutoff at ABI ≤ 0.90 the hazard was over two times greater (adjusted HR 2.2, 95% CI 1.2, 4.1; p=0.014).

7.5 Discussion

Our objective was to evaluate the role of continuous ABI and its relationship with poor outcomes in a cohort with CAD. Atherosclerotic disease is continuous in nature, and although ABI is a continuous measure, it is usually dichotomized for the screening and diagnosis of PAD and subsequent risk stratification. These cutoff values are inconsistent across published research and multiple guidelines for ABI use can be contradictory.[15] We confirmed a negative correlation between ABI and poor outcomes and determined that each 0.1 unit decrease in the ABI results in a 20% increase in the odds of a negative outcomes.

Use of arbitrary dichotomous ABI cutoff values across all population groups may distort estimates of individual risk for cardiovascular outcomes and overall burden of PAD. Low ABI values have been independently associated with both women and black ethnicity, two populations with higher PAD prevalence rates.[9,16,17] In a cross-sectional study of healthy patients free of PAD risk factors and a normal ABI between 1.00 and 1.30, the mean ABI in women was 0.02 lower than men.[6] This may explain recent reports of higher PAD prevalence in women, especially when atherosclerotic disease rates are generally higher in men.[6-8] While high PAD prevalence in Blacks compared to Whites has been well established,[16,18,19] significantly lower mean ABI has also been reported in low risk Blacks compared to Non-Hispanic Whites (1.11 vs 1.13; $p<0.001$).[9] Although the differences in ABI between genders and ethnic groups are small, they could be important in risk reclassification on an individual level and the overall measure of PAD burden.

While evidence for the role of continuous ABI for individual risk assessment continues to develop, guidelines for the interpretation of the ABI continue to change. In 2011, the ACCF/AHA recommended ABI ≤ 0.90, ABI 0.90 to 0.99, and ABI > 1.40 cutoff values be considered abnormal in their practice guidelines for management of PAD.[12] Previously, ABI ≤ 0.90 and ABI >1.30 were recommended cut points on the ABI spectrum.[1] These cutoffs were amended based on a meta-analysis of 16 cohort studies by the Ankle-Brachial Index Collaboration.[14] Using data from 24,955 men and 23,339 women without a history of CAD, the research team compared hazard ratios for mortality, cardiovascular mortality, and major adverse coronary events over ten ABI categories, one for each 0.1 increase in the ABI, starting with 0.6 and ending with 1.40.[14] ABI 1.11 to 1.40 was determined as a reference range, as patients with ABI 0.90 to 1.10 had increased risk of cardiovascular death.[14] It is striking that the ACCF/AHA did not provide an explanation as to why their recommended ABI cutoffs differ from the evidence they cited.

Limitations

In this interim analysis we chose to adjust for traditional CAD risk factors using stepwise forward regression models to accommodate our relatively small sample size. Patients who could not be contacted for follow up were not censored as the APPROACH database would provide us with information on coronary revascularization (and revascularization due to an MI) and death provided the patient remained in Alberta. Therefore, the strength of the association between continuous ABI and poor outcomes reported may be underestimated.

Clinical implications

Our data suggest that PAD should be viewed as a part of the continuous spectrum of atherosclerosis rather than as a dichotomous indicator of risk. This could provide clinicians greater accuracy in individualized risk assessment. Further evaluation of ABI and subsequent PAD prevalence in different populations is warranted.

7.6 Conclusion

Continuous ABI is a valuable independent prognostic indicator for negative outcomes in patients undergoing coronary angiography. Individualized risk assessment in patients with established CAD could be improved through use of continuous ABI, rather than dichotomous cutoffs.

Table 7-1. Patient Characteristics

	All	PAD ABI ≤0.90	Borderline PAD ABI 0.90 to 0.99	Normal ABI 1.00 to 1.40	Vascular calcification artifact ABI >1.40	p value
Total N	947	87	82	707	71	
Male (%)	698 (73.8)	52 (59.8)	49 (59.8)	534 (75.6)	63 (88.7)	<0.001
Mean age (years)	62.9 (11.5)	70.1 (10.7)	65.4 (11.6)	61.4 (11.2)	66.6 (10.5)	<0.001
White European ethnicity	839 (88.6)	83 (95.4)	74 (90.2)	616 (87.1)	66 (93.0)	0.068
Co-morbidities						
Hypertension	662 (77.7)	72 (87.8)	69 (87.3)	464 (74.4)	57 (85.1)	0.007
Dyslipidemia	741 (86.9)	70 (88.6)	69 (88.5)	543 (86.5)	59 (86.8)	0.990
Diabetes	268 (37.2)	33 (53.2)	28 (40.6)	176 (33.3)	31 (50.8)	0.002
Heart failure	62 (9.4)	12 (19.7)	5 (8.2)	35 (7.1)	10 (20.0)	0.001
Cerebrovascular Disease	30 (4.7)	6 (10.5)	4 (6.6)	16 (3.4)	4 (8.2)	0.099
Chronic Obstructive Pulmonary Disease	76 (11.6)	11 (19.0)	9 (14.5)	55 (11.4)	1 (2.0)	0.110
Renal insufficiency	71 (11.6)	14 (24.6)	11 (18.3)	34 (7.7)	12 (24.0)	<0.001
Family history of CAD	326 (46.5)	27 (41.5)	24 (37.5)	255 (48.9)	20 (40.0)	0.252
Current/former smoker	580 (76.4)	61 (84.7)	55 (75.3)	424 (75.7)	40 (74.1)	0.358
Claudication	120 (12.8)	33 (38.8)	16 (19.5)	65 (9.3)	6 (8.5)	<0.001
Indication for catheterization						
STEMI	87 (9.2)	5 (5.7)	6 (7.3)	74 (10.5)	2 (2.8)	0.097
NSTEMI	292 (30.8)	35 (40.2)	26 (31.7)	204 (28.9)	27 (38.0)	0.082
Unstable angina	151 (15.9)	8 (9.2)	12 (14.6)	121 (17.1)	10 (14.1)	0.273
Stable angina	308 (32.5)	27 (31.0)	28 (34.1)	232 (32.8)	21 (29.6)	0.927
CAD severity						
Stenosis ≥ 50%	745 (78.8)	84 (96.6)	67 (82.7)	538 (76.3)	55 (77.5)	<0.001
APPROACH Lesion Score	31.4 (29.6)	44.1 (31.2)	36.7 (30.7)	28.9 (28.4)	33.7 (33.5)	<0.001
Duke Jeopardy Score	4.1 (4.0)	6.1 (4.1)	4.8 (4.3)	3.7 (3.8)	4.9 (4.3)	<0.001

Values are n (%) or mean (SD).

Table 7-2. Event rates for cardiovascular outcomes

	30 days (n=947)	6 months (n=912)	1 year (n=879)
Myocardial infarction	19 (2.0)	12 (1.3)	9 (1.0)
Target vessel revascularization	5 (0.5)	4 (0.4)	4 (0.5)
Stroke	6 (0.6)	0	2 (0.2)
Mortality	5 (0.5)	17 (1.9)	10 (1.1)
Composite outcome (all of above)	35 (3.8)	33 (3.6)	25 (2.8)

Values are first event, n (%).

7.7 References

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CHAPTER 8: DISCUSSION AND SUMMARY

8.1 Discussion

The aims of this dissertation were to determine if there are ethnic differences in PAD prevalence, and to examine the relationship between PAD and poor outcomes in patients with cardiovascular disease. We also investigated the utility of ABI ≤ 0.90 to predict CAD complexity and the role of continuous ABI rather than dichotomous cutoffs as a risk marker and predictor of outcomes. In the first instance we used a systematic review of PAD prevalence studies and a cross-sectional analysis of cohort data to investigate the burden of PAD in different ethnic populations. The relationship between PAD and poor cardiovascular outcomes was investigated in a population of patients undergoing coronary angiography, which also informed the studies exploring other uses of the ABI.

The impetus for this dissertation is the evident paradox currently existing in the literature wherein persons of South Asian descent have a lower prevalence of PAD compared with White Europeans, despite having higher rates of cardiovascular disease and diabetes. Using a systematic review and meta-analysis, the first study synthesized previous research of PAD prevalence in South Asians compared to White Europeans to confirm the presence of an ethnic discrepancy, and to determine the magnitude of these differences. Our results indicate there is a lower prevalence of PAD in South Asians compared with White Europeans, both in the general population and in patients with diabetes and CAD. In all instances differences were significant at $p<0.001$. In light of this outcome, we also tried to determine if ethnic variations were present in patients with chronic kidney disease (CKD) receiving hemodialysis. CKD is associated with atherosclerotic disease and PAD is associated with higher morbidity and mortality in CKD

patients. Using data from the Canadian Kidney Dialysis Cohort Study (CKDCS), we found the overall prevalence of PAD was 19.1% in the hemodialysis cohort, but there was no difference in PAD prevalence between ethnic groups.

To date, the majority of studies on PAD have been focused on White Europeans; however, differences in PAD prevalence between ethnic populations are beginning to emerge. Our systematic review, the highest level of evidence available in the evaluation of prevalence studies, confirms ethnic disparity in PAD prevalence across multiple clinical populations. In contrast to Blacks, who exhibit more risk factors for PAD and a concomitantly higher prevalence of the disease compared with White Europeans, South Asians have a lower incidence of PAD despite possessing more risk factors.[1] This paradox supports the need for further research into the underlying physiological and genetic mechanisms involved in the etiology of atherosclerosis in diverse populations. Even in low risk patients, ethnic differences in ABI values persist. Singh et al., compared ABI values in middle-aged subjects (40 to 50 years) without hypertension, dyslipidemia, diabetes, CKD or CAD, who were not current smokers.[2] Despite a paucity of risk factors, non-Hispanic Blacks had a lower ABI than non-Hispanic Whites ($p<0.001$).[2] One explanation for the ethnic differences is that residual confounding from risk factors cannot be completely accounted for in trying to identify the true burden of PAD. Without adjusting for these apparent ethnic differences, however, using one single ABI cutoff value for different ethnic groups can lead to errors in risk stratification.[2,3] Whether risk re-classification would have a significant clinical impact is unknown.

To address the other objectives of this dissertation, we designed and carried out a prospective study using ABI measurements obtained from 1100 patients undergoing coronary angiography. ABIs were combined with demographic and comorbidity data from the APPROACH database to yield a comprehensive dataset. In exploring the relationship between PAD and poor outcomes, we speculated that the reason for these poorer outcomes could be due to more myocardium at risk and to incomplete coronary revascularization. Indeed, patients with PAD undergoing coronary angiography had greater CAD complexity (p=0.022) and more myocardium at risk, both pre- and post-revascularization (p=0.001, p=0.039), compared with patients without PAD. While we determined low ABI was associated with more severe coronary atherosclerosis, we did not observe a similar positive association at the other end of the ABI spectrum. Using IAD ≥ 10mmHg as a marker of subclavian artery stenosis, concurrent vascular calcification artifact (ABI > 1.40) and IAD ≥ 10mmHg was a rare event with 2.4% prevalence and a trend for an inverse association (adjusted OR 0.3, 95% CI 0.1, 0.3, p=0.117).

Even in patients with confirmed CAD, PAD is often underdiagnosed. Diagnosis of previously unknown PAD has been reported in over 45% of primary care patients, and in 15% of patients under the care of a cardiovascular specialist.[4,5] Results from our study show that 78.8% of patients in whom we measured an ABI of less than 0.90 did not have a previous PAD diagnosis. With PAD patients having more residual myocardium at risk following coronary revascularization, ABI screening and aggressive modification of risk factors would appear to be even more important. ABI screening would improve individual risk prediction, particularly for patients with low ABI values. While risk stratification can predict poor outcomes in patients with

vascular calcification artifact, there is little utility in additional screening of IAD ≥ 10mmHg in these patients.[6]

Finally, our results show that 91.9% of patients with PAD had significant CAD, as evidenced by a SYNTAX score greater than zero. With a likelihood ratio of 3.5 for predicting CAD, ABI ≤ 0.90 is a useful, non-invasive screening tool for identifying CAD, improving individual risk assessment, and informing decisions on the use of coronary catheterization. Stepping away from the arbitrary ABI cutoffs and using continuous ABI, the odds of having a negative outcome increase by 20 percent for every 0.1 unit decrease in the ABI in patients with CAD. This illustrates that continuous ABI can provide prognostic information for individual risk assessment.

8.2 Limitations

Prospective data collection of from our clinical cohort was carried out using only a single manual blood pressure measurement on each artery. While this may be a source of measurement error, others have reported that the use of multiple, single blood pressure measures does not significantly affect the final ABI value or PAD diagnosis when compared with sequential measurement.[7] Research team members were trained in ABI technique by a single vascular specialist and therefore inter-operator bias was minimized. Our study cohort was recruited from patients referred for coronary angiography and prevalence estimates from this cohort may differ from those in other populations. The overall PAD prevalence of 9.5% in this cohort was lower compared to 10% to 15% reported in the literature for patients with CAD.[5,8-10] Combined with a relatively low event rate for cardiovascular outcomes, some calculations could be underpowered to detect significant differences. Use of secondary data in the ethnicity studies meant using a

PAD diagnosis based on clinical symptoms rather than ABI. PAD prevalence reported in these studies is likely underestimated.

8.3 Summary

The recognition that PAD is a risk factor for poor CAD outcomes is similar to the situation seen in patients with diabetes in the past, i.e., it is acknowledged, but often unmeasured and poorly understood. The observation that diabetes was associated with a higher risk for cardiovascular disease led to more research that culminated in more intensive risk factor management resulting in lower blood pressure and cholesterol targets for these patients. We now recognize that patients with PAD have more complex CAD and more residual myocardium at risk following coronary revascularization. ABI screening could encourage individualized risk assessment and possibly lessen the severity and number of poor outcomes. ABI is a valuable clinical tool for detecting PAD and providing prognostic information at minimal risk to the patient and use of ABI needs to be encouraged. Furthermore, identifying the role of ethnicity in PAD development and prevalence could lead to treatments to mitigate the poor outcomes associated with this disease.

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