BURDEN ESTIMATES, POST-DIAGNOSIS CARE, AND OUTCOMES ASSOCIATED
WITH PERIPHERAL ARTERY DISEASE IN THE ATHEROSCLEROSIS RISK IN
COMMUNITIES STUDY

Corey Andrew Kalbaugh

A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in
partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department
of Epidemiology in the Gillings School of Global Public Health.

Chapel Hill
2016

Approved by:

Laura Loehr

Gerardo Heiss

Anna Kucharska-Newton

Jennifer L. Lund

Lisa Wruck

ABSTRACT

Corey Andrew Kalbaugh: Burden estimates, post-diagnosis care and outcomes associated with
peripheral artery disease in the Atherosclerosis Risk in Communities Study
(Under the direction of Laura Loehr and Gerardo Heiss)

Peripheral artery disease (PAD) is a progressive atherosclerotic disorder of the lower

extremities that causes adverse individual- and health care system-level consequences as

populations age. This doctoral dissertation research estimated the annual period prevalence and

incidence of PAD as well as the frequency of care and mortality following diagnosis in the

outpatient or inpatient setting.

The majority (>70%) of all PAD encounters occurred in the outpatient setting. The

weighted mean age-standardized prevalence and incidence of outpatient PAD was 11.8% (95%

CI: 11.5, 12.1) and 22.4 (95% CI: 20.8, 24.0) per 1000 person-years, respectively. Blacks had a

higher mean weighted mean age-standardized prevalence (15.6%; 95% CI: 14.6, 16.4) as

compared to whites (11.4%; 95% CI: 11.1, 11.7). Blacks also had a higher incidence rate of PAD

(31.3 per 1000 person-years; 95% CI: 27.3, 35.4) as compared to whites (25.4 per 1000 person-

years; 95% CI: 23.5, 27.3). PAD prevalence and incidence did not differ by gender alone.

One-thousand eighty six incident cases of PAD were identified from 2002-2010. PAD-

related post-diagnosis encounters were 2.15 (95% CI: 2.10, 2.21) and 1.02 (95% CI: 0.94, 1.10)

among those with an incident PAD diagnosis in the outpatient and inpatient setting, respectively.

Participants with PAD had an average of 6-8 primary care encounters per person-year over the

course of our study. PAD-related and all-cause hospitalization was 6.4% (95% CI: 4.8, 8.1) and

32.2% (95% CI: 29.0, 35.2) at one year among those with incident outpatient PAD.

Approximately 14% (95% CI: 9.3, 18.7) of participants diagnosed with inpatient PAD had a PAD-related rehospitalization at one year while 43.4% (95% CI: 36.3, 49.7) had an all-cause rehospitalization at one year. One year age-standardized case fatality was 7.1% (95% CI: 5.4, 8.7) and 16.0% (95% CI: 11.0, 21.1) among those diagnosed in the outpatient and inpatient setting, respectively.

Peripheral artery disease and utilization of outpatient health care services was common among men and women 65 years of age and older with enrollment in a Medicare fee-for-service program sampled of four US communities.

ACKNOWLEDGEMENTS

I have been honored to receive tremendous support over my years in this program. Support has come from committee members, professors, colleagues, friends and family. This dissertation would not be possible were it not for all of their combined efforts. I want to thank my committee members for the time they have each invested in me. I have worked with Gerardo Heiss, my committee chair, on this project since our grant writing course. His responsiveness and commitment to students is unparalleled. Laura Loehr, my dissertation advisor, has tremendous scientific acumen and I have always appreciated her realistic perspective and the time she has invested in me. Anna Kucharska Newton helped me to get this work funded and has poured countless hours into developing my ideas, writing, and understanding of epidemiology. Jenny Lund was always available for help and made my work much better, through long meetings and even phone calls when needed. Lisa Wruck contributed great expertise in the methodologic development of this project and others during my time at UNC. Many thanks to my two long-term officemates: Mehul Patel and Kapuaola Gellert. You are both patient and kind and were a great source of assistance, knowledge, and friendship. Other thanks to Sara Jones and Montika Bush, for programming support and friendship.

To just say "thanks" to friends and family is far too insignificant for all that you have sacrificed so that I might pursue this path. So just know that this would not be possible without all of you. To my Mom and Dad: I have always lived out of place of knowing that I was loved and supported and that is a credit to the type of people you both are. I know the value of hard work and of being a good person because of you. May this work honor the sacrifices that you

made so that I might get to this place. To Juli and Novella: You are my heart and I want to acknowledge that it is you who have sacrificed the most. There is nothing I could say that could appropriately thank you for standing beside me and supporting me. I am looking forward to what the rest of this life will look like with you. I love you.

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LIST OF ABBREVIATIONS

ABI	ankle-brachial index
AFU	Annual follow-up
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities Study
CA	Contrast angiography
CAD	Coronary artery disease
CHD	Coronary heart disease
CHS	Cardiovascular Health Study
CI	Confidence interval
CLI	Critical limb ischemia
CMS	Center for Medicare and Medicaid Services
CR	Comparability ratio
CPT-4	Current Procedural Terminology, 4th edition
CTA	Computed tomography angiography
DAG	Directed acyclic graph
DM	Diabetes mellitus
ECQ	Edinburgh Claudication Questionnaire
EAS	Edinburgh Artery Study
EMR	Electronic medical record
FFS	Fee-for-Service
FHS	Framingham Heart Study
FQHC	Federally Qualified Healthcare Center
HCPCS	Healthcare Common Procedure Coding System

HMO	Health maintenance organization
IC	Intermittent claudication
ICD-9-CM	International Classification of Diseases, Clinical Modification, version 9
IR	Incidence rate
LEA	Lower Extremity Arterial
MCA	Clinic algorithm
MedPAR	Medicare Provider Analysis and Review
MESA	Multi-Ethnic Study of Atherosclerosis
MI	Myocardial infarction
MRA	Magnetic resonance angiography
NAMCS	National Ambulatory Health Care Survey
NHANES	National Health and Nutrition Examination Survey
NPV	Negative predictive value
PABAK	Prevalence and bias adjusted Kappa
PAD	Peripheral artery disease
PARTNERS	PAD Awareness, Risk, and Treatment: New Resources for Survival program
PPV	Positive predictive value
PSV	Peak systolic velocity
PTA	Percutaneous Transluminal Angioplasty
REACH	Reduction of Atherothrombosis for Continued Health registry
RQ	Rose Questionnaire
SDCQ	San Diego Claudication Questionnaire
SDPS	San Diego Population Study

SEER	Surveillance, Epidemiology, and End Results
SES	Socioeconomic status
UCSD	University of California San Diego
WHI	Women's Health Initiative
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

Peripheral artery disease (PAD) is a prevalent atherosclerotic disorder characterized by plaque build-up in the lower extremities. Functional limitations resulting from PAD lead to poor quality of life, high health care utilization and costs of care, and an increase in mortality risk. A diagnosis of PAD suggests presence of atherosclerosis in other vascular beds, and PAD significantly increases the risk of coronary and cerebrovascular disease events. The direct and indirect contribution of this disease to the morbidity associated with other chronic disease conditions is important yet health professional and public awareness of PAD is low in comparison with awareness of other chronic cardiovascular diseases; up to 50% of those with PAD are unaware they have the disease and physicians often do not evaluate for the presence of PAD. Disease awareness is critical as the burden of PAD is expected to increase as our population ages.

Most estimates of the population burden of PAD evaluate hospitalized events, while excluding PAD diagnosed and treated in the outpatient setting [1]. Missing information on outpatient PAD is important because the evolution of endovascular technologies and wound care therapies, including angiogenesis, is changing the clinical location where PAD is managed [2, 3]. Disease manifestations which formerly required hospitalization can now be treated in an outpatient setting. Furthermore, initial diagnoses of PAD currently frequently occur in the outpatient setting. Since prior research has focused on PAD in the inpatient setting, the practice shift to the diagnosis and treatment of previously unmanaged PAD in the outpatient setting has resulted in a high, yet undocumented, burden of PAD [4-7]. The proposed work operates under

the hypothesis that the burden of PAD is underreported and that quantifying both inpatient and outpatient events is critical to a more accurate representation of PAD burden and to the assessment of post-diagnosis care.

Proposed analyses will provide an assessment of the frequency of care and outcomes associated with a PAD diagnosis. Administrative claims allow characterization of the care following a PAD diagnosis from the health care setting of the first diagnosis to the subsequent processes of PAD-related care at the outpatient and inpatient levels. Proposed research will address possible patient-level factors that affect a patient's transition from outpatient management to hospitalization, an area of research that is currently underreported in the literature.

The proposed research will take advantage of the Center for Medicare and Medicaid Services (CMS) Medicare claims available for residents of the Atherosclerosis Risk in Communities (ARIC) Study. By placing the assessment of PAD in four diverse geographic regions, for which there are available data on the prevalence and incidence of atherosclerotic conditions other than PAD, a unique opportunity exists for future research to evaluate the burden of PAD in relation to those conditions. Proposed assessment of potential disparities in the burden and post-diagnosis care of PAD across age, gender, and race subgroups, along with contextual information, will lead to an improved understanding of groups with high atherosclerotic burden. Information from the proposed research will provide a foundation for further work that examines co-occurrence of PAD and other cardiovascular diseases.

CHAPTER 2: STUDY OBJECTIVES AND SPECIFIC AIMS

The proposed study aims to estimate the prevalence and incidence of PAD and to estimate the frequency of care and outcomes following an incident PAD diagnosis among Medicare fee-for-service beneficiaries ages 65 years and older in the biracial ARIC study cohort [8].

Specific Aim 1: Estimate the annual period prevalence (2003-2012) and incidence (2005-2012) of PAD in the outpatient and inpatient setting among Black and White CMS Medicare fee-for-service beneficiaries in the ARIC study cohort (Manuscript 1; Chapter 5). Estimates will be stratified by age, gender and race to inform prevention efforts. Direct standardization methods will be used to estimate burden.

Specific Aim 2: Estimate the frequency of care and mortality following an initial diagnosis in the outpatient or inpatient or outpatient setting among Black and White CMS Medicare fee-for-service beneficiaries in the ARIC study cohort (Manuscript 2; Chapter 6). Direct standardization will be used to estimate age-standardized rates of encounters. Time-to-event analysis will be used to estimate the time to (re)hospitalization and case fatality. Race and gender differences in the rates of- and time-intervals between- outpatient and inpatient encounters will be examined.

This study will address an important gap in the PAD literature by providing methodologically replicable estimates of PAD burden and health care utilization using an administrative claims data source. The claims data will be linked with an ongoing cohort study and will provide a rich level of detail regarding covariates that is not possible in using claims

alone. Limitations that will affect the interpretation of findings include exclusion of participants with MA enrollment, misclassification of prevalent as incident events, and survivor bias associated with the cohort. Findings from the study will address issues of health care utilization and outcomes among elderly individuals with PAD that will improve the evidence base regarding the assessment of disease and disparities in care for PAD. This study will highlight the significance of PAD in an elderly population and could aid in identifying high burden groups, which could inform secondary prevention efforts.

CHAPTER 3: BACKGROUND AND SIGNIFICANCE

Peripheral artery disease is a prevalent atherosclerotic disorder characterized by plaque build-up in arteries distal to the abdominal aorta [9]. Current estimates suggest that more than 8 million individuals in the United States have PAD with increasing prevalence expected as the population ages [10]. Health professional and public awareness of PAD remains low in comparison with awareness of other cardiovascular diseases; up to 50% of those with PAD are unaware they have the disease and physicians often fail to evaluate for the presence of PAD [11]. PAD presents clinically as intermittent claudication (pain with exercise), or as critical limb ischemia (a PAD subtype that can be limb and life threatening) [12]. Functional limitations resulting from PAD lead to poor quality of life [13], high health care utilization [14], high costs of care [15], and an increase in mortality risk [16]. PAD is frequently associated with coexisting atherosclerosis in the coronary and cerebral arterial beds, and the direct and indirect contribution of this disease to the morbidity associated with other chronic disease conditions is significant [17]. PAD is largely managed in the outpatient setting with risk factor modification [18], exercise therapy [19], and pharmacologic therapy [20, 21]. Once the disease is severe enough to warrant invasive management, therapeutic choices include endovascular procedures [22], open surgical revascularization [23, 24], and limb amputation [25].

3.1 Anatomy and Pathophysiology of Peripheral Atherosclerosis

Processes involved in the development of peripheral atherosclerosis are similar to the pathogenesis of coronary, cerebral, and renal atherosclerosis [26]. Figure 1 provides an example of peripheral atherosclerosis in the posterior tibial artery. The current understanding of this process has been described by Libby (2000) as a three stage presentation: lesion initiation, lesion progression, and plaque complications [27]. Atherogenesis begins when blood leucocytes (white blood cells) attach to endothelial cells lining the intima layer of an artery [28].

Figure 2: Lower extremity atherosclerosis; adapted from NIH.gov

Adhesion molecules on vascular endothelial cells facilitate leukocyte adhesion. Chemokines direct leucocytes to enter into the arterial wall. A fibrous cap forms, signaling the end of the atherogenesis initiation process [29]. Atherogenesis progression takes place when proteins create a net positive balance of growth stimuli, such that smooth muscle cells proliferate and eventually migrate if platelets are activated [29]. The migration causes a thickening of the fibrous cap, which leads to thrombus formation. Clinically important atheroma complications are commonly the result of thrombus formation and disruption [27].

Figure 1: Lower extremity arterial system; adapted from qualityvascular.com

A plug containing platelets and fibrinogen molecules forms [30]. The plug can either remain attached to the arterial wall while it grows until it completely obstructs the vessel lumen or it can dislodge from

the vessel wall because of rapid arterial flow. If the plug dislodges, platelet rich emboli are released into the arterial tree. These obstructions deprive the tissues of crucial oxygenated blood necessary to meet the metabolic requirements of ambulation (claudication) or wound healing (critical limb ischemia) [30].

Changes in and disruption of the fibrous cap can cause blood flow-related conditions in the vessels of the lower extremities, including the descending abdominal aorta and the iliac, femoral, popliteal, and tibial arteries, as shown in Figure 2 [26]. Disease can be bilateral or unilateral, depending on anatomic location; disease tends to be bilateral in the iliac arteries and is more often unilateral in femoral/popliteal/tibial arteries [31].

3.2 Relationship of PAD to other Cardiovascular Diseases

The presence of PAD is indicative of increased atherosclerotic burden throughout the cardiovascular system [32, 33]. Aronow et al (1994) identified the coexistence of symptomatic peripheral, coronary, and cerebrovascular disease among 1886 patients 62 years of age and older in a long-term health care facility [34]. These investigators found that among those with symptomatic PAD, 58% also had coronary artery disease and 34% had cerebrovascular disease [34]. The Reduction of Atherothrombosis for Continued Health (REACH) registry, an international study of general physician practices comprising more than 65,000 individuals ages 45 and older, also measured coexisting vascular diseases. The REACH registry found that, of those with PAD, 65% had clinical evidence of either coronary or cerebrovascular disease [17].

Early detection of PAD and interventions aimed at preventing PAD progression can therefore be beneficial in delaying myocardial infarction, stroke, and other major circulatory system disorders [10, 25, 35]. Although potentially modifiable risk factors make PAD largely preventable, the disease is commonly under-diagnosed and remains an understudied public

health problem as compared to other cardiovascular conditions for which awareness is greater [11].

3.3 Clinical Manifestations of PAD

Natural history studies estimate that 20%-50% of individuals with detectable PAD are asymptomatic [12]. The most common PAD manifestation is intermittent claudication (IC), a condition producing leg cramping and pain during exercise that causes functional limitations and decreases quality of life [13]. Critical limb ischemia (CLI) is a more severe presentation of PAD, with symptoms that include ischemic rest pain and tissue loss due to non-healing wounds, ulcerations, and gangrene [36]. Figure 3 is a depiction of the most commonly seen clinical progression of PAD, from asymptomatic disease to gangrene presentation.
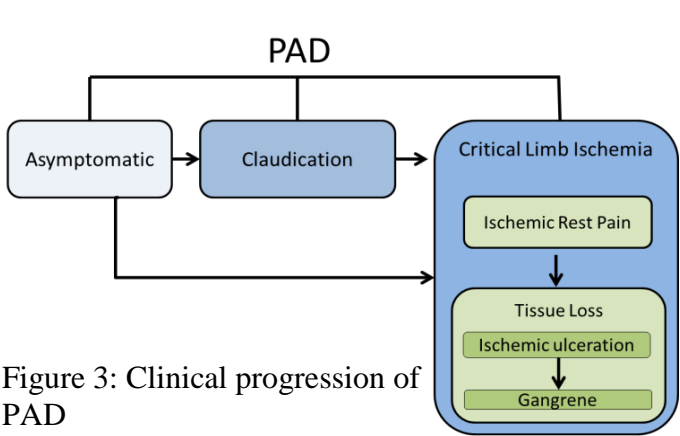
Figure 3: Clinical progression of PAD

Disease severity is frequently measured in a clinical setting using one of two classification schemes, as shown below in Table 1 [31, 37]. Briefly, the Rutherford classification system assigns grades and category scores for clinical presentations ranging from asymptomatic disease (Grade 0, Category 0) to major tissue loss (Grade III, Category 6) [31]. The Fontaine classification system classifies PAD according to stages, ranging from I (asymptomatic disease) to IV (ulceration or gangrene) [37].

Table 1. PAD classification schemes by severity

| Clinical Presentation | Rutherford Criteria | | Fontaine Criteria |
	Grade	Category	Stage
Asymptomatic	0	0	I
Mild claudication	I	1	IIa
Moderate claudication	I	2	IIb
Severe claudication	I	3	IIb
Ischemic rest pain	II	4	III
Ulceration	III	5	IV
Gangrene	III	6	IV

Adapted from Norgren et al (2007)

3.3.1 Claudication

Claudication (Rutherford I, Fontaine II), or pain with exercise, is the most common form of symptomatic PAD [38]. Claudication-induced pain can present as a cramping, aching, or general discomfort in the lower extremities [18]. Although this pain typically occurs in the calves, claudication can also occur in the thighs, buttocks, hips, and feet depending on the location of the underlying arterial blockage. Claudication in the upper two-thirds of the calf is indicative of superficial femoral artery (SFA) disease while disease in the lower third of the calf is indicative of popliteal disease [39]. In vascular-related claudication, the limb pain continues during exercise but subsides with rest, generally within five to ten minutes. Individuals affected by claudication may experience significant functional limitations and have a significantly lower quality of life compared to the general population [40]. A study of 201 claudicants who were administered the SF-36 quality of life questionnaire found statistically significant ($p<0.05$) health decrements compared to population norms at all measures of physical, emotional, mental, and general health [40].

Prevalence estimates of claudication in general populations vary significantly by country and increase with age [13]. For example, in the US-based, ARIC study, only one percent of participants 45-64 years of age had claudication, defined as a positive Rose questionnaire

(discussed in section 1.4) at baseline [41]. However, He et al (2006) used the Rose questionnaire and found a much higher prevalence of 11.3% in a population-based study of individuals 60 years of age and older in a small Chinese province [42]. Generally, population-based studies measuring claudication found increasingly higher prevalence the higher the mean age of participants. These studies will be reviewed in more detail in section 1.6 of this proposal.

Despite the progressive nature of atherosclerosis, approximately 75% of those with clinically diagnosed claudication will stabilize or improve over time [12]. The remaining 25% experience worsening claudication (10-20%) or progression to critical limb ischemia (5-10%). Of those with deteriorating symptoms, approximately 5% will require surgical intervention and 2% will require lower extremity amputation [12].

3.3.2 Critical Limb Ischemia

Critical limb ischemia (CLI) is the "end stage" of PAD resulting from a chronic lack of oxygen that is needed for limb vitality [43]. Clinically, CLI is defined by an international consensus as presence of any one of the following: 1) chronic ischemic rest pain or pain in the extremities while at rest, 2) ulceration of the lower extremity, or 3) gangrene due to occlusive PAD [44]. Although a small proportion of patients with diagnosed claudication will eventually deteriorate to CLI, CLI can manifest with no prior PAD history [45, 46].

Ischemic rest pain (Rutherford II, Fontaine III) is a chronic condition characterized by pain, numbness, or tingling at rest in the toes, metatarsal heads, or proximal foot. Once an individual has rest pain, the pain is characterized by three severity-based stages. Initially the pain starts and ends quickly and the person can remain supine for pain relief. The second stage requires the person to dangle their leg in order to relieve the pain. In the final stage, the person must remain seated for pain relief. Rest pain can be difficult to measure because of pain perception, as is the case in those with diabetic neuropathy [47].

The end stages of PAD involve tissue loss (Rutherford III, Fontaine IV) to an extremity and include ischemic ulceration or gangrene. Clinically these end-stage processes present as non-healing wounds on the toes, foot, shin, or heel. An ischemic lesion can result from minor trauma because of arterial insufficiency, although compromised arterial flow can preclude any size lesion from healing [47].

CLI is a rare outcome and is infrequently quantified in studies. A study among 5800 randomly selected participants in four regions of Sweden found a prevalence of CLI of 1.6% using a low ankle blood pressure measurement (<70 mm Hg) as the indicator of CLI presence [48]. A Norwegian study that quantified CLI by self-reported ulcers or rest pain, found an age-adjusted prevalence of 0.24% [49]. Ulcers were not categorized by cause and, thus, could be misclassified as CLI when the cause might be neuropathic or traumatic. One study estimated CLI incidence by examining a sample of CLI hospitalizations from 27 Northern Italy hospitals [50]. They found the annual incidence of CLI to be 260 per 1,000,000 person years. Incidence of CLI was 652 per 1,000,000 person-years among those 45 years of age and older [50]. Many studies have assumed a percentage of amputations are related specifically to CLI to quantify CLI incidence [25, 50, 51]. Information derived from this methodology is subject to substantial misclassification bias and true CLI incidence remains unknown.

Approximately one-half of individuals with CLI have arterial reconstruction and one-fourth is managed non-surgically. About 25% of individuals presenting with CLI will immediately undergo limb amputation surgery [25]. Non-healing ulcerations caused by lower extremity arterial disease are the leading cause of lower limb amputation in men and women in the US [52]. Only approximately one-fourth of CLI patients experience symptom resolution and amputation-free survival at one year following diagnosis [12].

3.4 Methods to Detect PAD

Prior to discussing the prevalence and incidence of PAD, I will introduce the various methods to identify and diagnose PAD in research and clinical settings.

3.4.1 Questionnaires

Leg pain can be multi-factorial and appropriate diagnoses are often difficult to determine with precision and reproducibility. Causes of leg pain can include IC, as well as sciatica or osteoarthritis. As a result of the challenges associated with appropriately diagnosing the cause of leg pain, a series of questionnaires have been created to better delineate PAD from other potential causes [53-55]. Commonly used questionnaires are discussed below.

3.4.1.1 WHO/Rose Intermittent Claudication Questionnaire

The Rose Questionnaire (1962) was created to target the diagnosis of IC in epidemiologic research and to facilitate international comparisons of prevalence estimates [53]. Initially, the Rose Questionnaire (RQ) was administered to thirty-seven individuals with IC and a control group of eighteen individuals with other types of diagnosed walking-induced leg pain (control group). Thirty-four (92%) of the 37 patients with IC met all six criteria outlined to delineate IC from other leg pain syndromes while none of the control group met the criteria [53].

The RQ was adopted by the World Health Organization (WHO/RQ, herein) in 1968 to determine PAD prevalence rates [56]. The WHO/RQ was modified in 1977 to enable self-administration [57]. Studies have found sensitivity values that range from 9%-92% and specificity values that range from 95%-100% [58].

Despite its ease of use and the various adaptations, there are limitations to using the WHO/RQ in population-based research. First, while false positives are exceedingly rare, false negatives are common which is consistent with the lower sensitivity reported above. Second, it is not possible to detect CLI using this instrument. Even with the surveys limitations, the

WHO/RQ is commonly used to screen for PAD and is the primary survey tool used to identify claudication in population-based research [42, 48, 59, 60].

3.4.1.2 Edinburgh Claudication Questionnaire

While the WHO/RQ is highly specific, the moderate sensitivity results shown across several population-based studies led scientists at the London School of Tropical Medicine and Hygiene to create a new questionnaire, the Edinburgh Claudication Questionnaire (ECQ) [54]. Leng et al (1992) found more than 50% of the false negatives generated by the WHO/RQ resulted from one question: *Does your pain disappear on walking?*[54] These investigators also found that the specificity was upheld by asking only three particular questions: 1) *Do you have pain when standing/sitting?* 2) *Do you have pain in the calf?* and 3) *Is your pain gone in 10 minutes of stopping?* [54]. The investigators pre-tested new questions and piloted their new survey in 300 subjects. The ECQ had a sensitivity of 91.4% and a specificity of 99.3%, and repeatability was excellent at six months (kappa=0.76) [54]. The ECQ is only moderately sensitive (~50%) in detecting PAD in high risk patients [61, 62]

3.4.1.3 San Diego Claudication Questionnaire

Neither the WHO/RQ nor the ECQ allow for leg-specific (right versus left) assessment of claudication symptoms. While calf pain is the most typical location of pain in those with claudication, the WHO/RQ and ECQ surveys also do not allow for assessment of non-calf claudication. With these limitations in mind, the San Diego Claudication Questionnaire (SDCQ) was created and tested among 508 patients [63]. The SDCQ contains questions about anatomic location of pain and the extremity (left, right, both) affected. In the study by Criqui et al (1996), the SDCQ identified 40% more claudication than the Rose in the same participants [55].

Each of these questionnaires has benefits and drawbacks, and each has been used extensively in population-based studies of PAD. A recent review article by Schorr and Treat-

Jacobson (2013) reported inconsistency across studies in how these questionnaires were utilized causing biased prevalence estimates [58]. Table 2 describes the questions contained within each of these three questionnaires and shows the differences between the questions used to assess claudication in each questionnaire. Estimate comparisons across studies are, therefore, difficult and fluctuate depending on the methodology and survey used.

Table 2. Claudication assessment questionnaire comparison

Question	Questionnaire		
	WHO/RQ*	ECQ[†]	SDCQ[‡]
Do you get a pain in either leg on walking?	Y	Y	Y
- or either buttock (Right or Left)			Y
Does this pain ever begin when you are standing still?	Y		Y
- or sitting		Y	Y
Do you get this pain in your calf (or calves?)	Y		
Where do you get this pain or discomfort?		Y	
In what part of the leg or buttock do you feel it?			Y
Do you get it when you walk uphill or hurry?	Y	Y	Y
Do you get it when you walk at an ordinary pace on the level?	Y		Y
Does the pain ever disappear while you are still walking?	Y		Y
What do you do if you get it when you are walking?	Y		Y
What happens to it if you stand still?	Y	Y	Y
How soon?			Y

∗ World Health Organization adaptation of the Rose Questionnaire; [†] Edinburgh Claudication Questionnaire; [‡] San Diego Claudication Questionnaire

3.4.2 Non-invasive Tests to Detect PAD

PAD is commonly diagnosed through non-invasive testing such as ankle-brachial index (ABI) measurement, which is discussed below. PAD prevalence is also frequently quantified via these same measurements. Most often, the prevalence of PAD in population-based studies is estimated by calculating ABI [11, 41, 42, 48, 59, 60, 64-80]. Infrequently, PAD is also measured using the reactive hyperemia test [81]. Each of these tests is described in more detail below.

3.4.2.1 Ankle-brachial Index Test

A physician or vascular laboratory technician can perform the ABI test, which requires a standard sphygmomanometer, a hand-held Doppler, and acoustic gel [36]. Systolic measurements are taken in the brachial artery in each of the upper arms and in both the posterior tibial and dorsalis pedis arteries of the legs. As PAD can be a unilateral disease the ABI is calculated for each limb separately. The value is determined as the ratio of the lowest systolic value obtained in the leg to the highest systolic value obtained in either arm. An ABI value <0.90 is indicative of PAD and is a cut-point used to detect asymptomatic PAD. The ABI test has a high sensitivity (>90%) and a high specificity (>90%) in detecting >50% occlusion in contrast angiography [26, 82]. However, inclusion criteria for studies, the number of times the measurement is repeated, and calculation methods, such as using the highest versus the lowest or median systolic values, vary widely resulting in low comparability across studies [83].

3.4.2.2 Reactive Hyperemia Test

The reactive hyperemia test is infrequently used to identify asymptomatic PAD [26]. According to the Edinburgh Artery Study protocol [81], the test is performed by occluding arterial flow above the knee for four minutes, following which ankle systolic pressure is then measured in both legs fifteen seconds after releasing the cuff. A drop in blood pressure of at least 35% is considered indicative of PAD. A hyperemic drop of 20-35% with an abnormal ABI is also indicative of PAD. The sensitivity and specificity of the reactive hyperemia test at predicting abnormal ABI is 64% and 94%, respectively [84].

3.4.3 Imaging Techniques Used to Identify PAD

Individuals with PAD that possibly warrant invasive intervention often first undergo imaging prior to revascularization. The gold standard is digital subtraction contrast angiography, although new technologies, such as duplex ultrasound, magnetic resonance angiography (MRA),

and computed tomography angiography (CTA) are less invasive ways to assess PAD [85]. Each of these techniques is described in the following section.

3.4.3.1 Contrast angiography to Identify PAD

Contrast angiography (CA) is the gold standard in identifying and characterizing PAD lesions [86]. In this procedure a small puncture in the common femoral or brachial artery allows access to the vasculature, such that sheaths and guidewires are inserted into the arterial tree and directed toward the site of expected anatomical lesions; these lesions are first identified through non-invasive testing. Radiopaque contrast is injected into the vessels in order to visualize stenotic or occluded arteries and determine appropriate invasive management. CA is an expensive procedure accompanied by significant risk, including a 0.16% mortality risk, and is associated with contrast-induced nephropathy and renal failure, pseudoaneurysm, hematoma, and other complications associated with vascular access[25, 86]. Figure 4a, below, is an image from a contrast angiography procedure.

3.4.3.2 Duplex Ultrasound to Identify PAD

Duplex ultrasound measures flow velocity using a Doppler instrument and provides real-time, B-mode imaging of the arterial system via duplex scanners [87]. Peak systolic velocity (PSV) is measured across the lower extremity arteries and changes in the velocity signal indicate severity of disease. A 50%-99% stenosis is detected by a doubling in the PSV when moving from a more proximal lesion (i.e. popliteal to tibial vessel) [36]. Arteries with no blood velocity are believed to be occluded [87]. Duplex ultrasound had a median sensitivity of 88% (range: 80%-98%) and a specificity of 96% (range: 89%-99%) in a systematic review of non-invasive methods of detecting PAD as compared to contrast angiography [85]. Findings suggest higher sensitivity in detecting disease among the iliac and femoral arteries as compared to the popliteal and tibial arteries [88, 89].

3.4.3.2 Magnetic Resonance Angiography to Identify PAD

Magnetic resonance angiography uses a super-conducting system and pulse sequencing to image blood flow and to measure the presence and size of atheroma [90, 91]. MRA eliminates exposure to ionizing radiation and recent advancements in non-iodine-based intravenous contrast agents allow a more accurate revascularization plan with MRA in comparison to duplex ultrasound [92]. In a systematic review where contrast angiography was the gold standard, MRA had a median sensitivity of 95% (range: 92%-99.5%) and a median specificity of 97% (range: 64%-99%) in identifying significant stenosis ($\geq$50%) [85]. MRA can overestimate degree of stenosis due to turbulence, it is not safe for patients with pacemakers or defibrillators, and imaging of metal stents and calcified arteries is challenged [86]. Figure 4b, below, is an MRA image of the lower extremity arterial system.

3.4.3.3 Computed Tomography Angiography to Identify PAD

Computed tomography angiography (CTA) is the most recently developed method used to identify PAD. It provides up to 128 simultaneous cross-sectional images of the arterial system [86], and uses a peripheral intravenous cannula to deliver iodinated contrast media [92]. A recent systematic review found that CTA is 91% sensitive (range: 89%-99%) and 91% specific (range: 83%-97%) in detecting significant ($\geq$ 50% stenosis or occlusion) disease [85]. CTA allows for more rapid and detailed image acquisition as compared to other imaging modalities [92]. Radiation dosage is significant, although it is less than what is received in contrast angiography procedures [86]. The risk of nephropathy and acute tabular necrosis is also significant because CTA requires a contrast agent [86, 92]. Figure 4c, below, is a CTA image of the lower extremity arterial system.
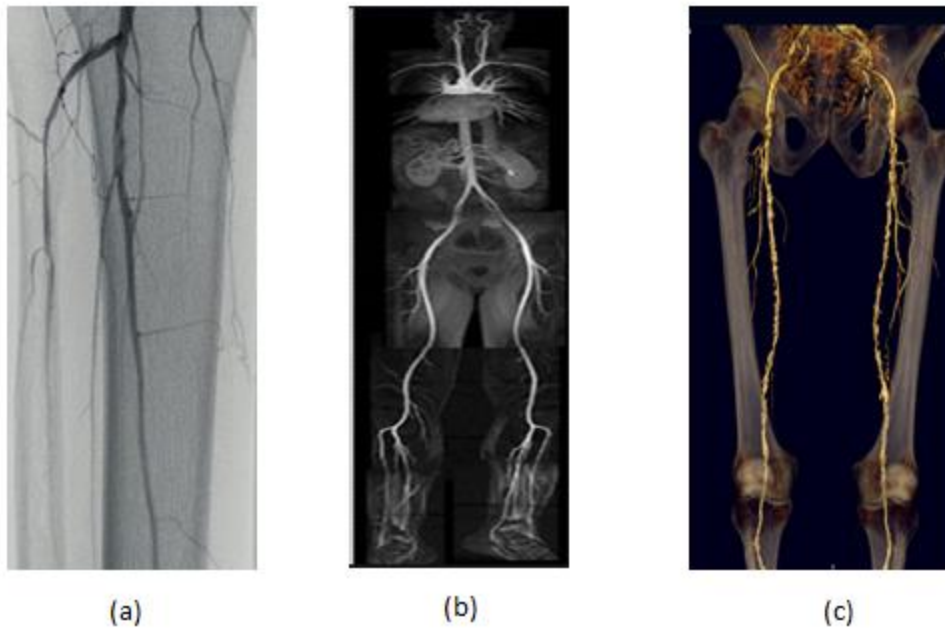
a) Contrast angiography of popliteal and tibial vessels; b) Magnetic resonance angiography of lower extremity arterial system; c) Computed tomography angiography of lower extremity arterial system; Figure 4a provided by Greenville Hospital System, Greenville, SC; Figure 4b, c adapted from hearthealthywomen.org

Figure 4: Evolution of imaging techniques

3.5 Clinical Management of PAD

Peripheral artery disease is managed both non-invasively and invasively, and each of these management strategies is described in the section below.

3.5.1 Non-invasive Management of PAD

Risk factor modification, exercise therapy, and pharmacologic intervention are often the first steps in management of PAD. The main targets of risk factor modification in individuals with PAD are tobacco cessation and diabetes control [18]. Tobacco cessation has been shown to decrease the risk of PAD progression and reduces cardiovascular events among claudicants [20]. Guidelines suggest that maintaining a glycated hemoglobin A_{1c} close to 6% or less is optimal in individuals with diabetes [25].

Risk factor modification is combined with exercise therapy and pharmacologic management in many claudicants. Supervised exercise programs, including 30 minutes of total walking time per day, at least three times per week, increase walking distances (compared to usual care or placebo) in individuals with claudication [19]. Regarding pharmacologic management, only one PAD-specific drug, Cilostazol, has repeatedly shown positive impacts on walking ability in randomized clinical trials [20, 21]. Often, these non-invasive options do not result in symptom resolution for the patient and the next steps include consideration of modalities for invasively treating PAD.

3.5.2 Invasive Management of PAD

There are three primary modalities for invasively treating PAD. These include endovascular management, open surgical bypass or endarterectomy, and lower limb amputation.

3.5.2.1 Endovascular Management

Endovascular management of PAD includes Percutaneous Transluminal Angioplasty (PTA) with or without a stent, first described in 1964 with the pioneering work of Dotter and Judkins [22]. Stents were not commonly used in the management of PAD until the 1980s [93].

Percutaneous treatments are minimally invasive and are associated with lower morbidity and mortality than open surgery or limb amputation. The major weakness of endovascular management is the frequent failure of these procedures to maintain arterial patency (i.e. to keep a blockage open) [26]. Endovascular management is most common among individuals with claudication and those with short-segment disease in the aorto-iliac region [4]. As an example, in a study of 1000 consecutive interventions for claudication, 643 were performed using endovascular technology and 701 were for aorto-iliac disease [7]. A study by Taylor et al (2007), however, suggests that there are some patients with critical limb ischemia for whom minimally invasive management is an appropriate strategy [94].

3.5.2.2 Open surgical Management

Two primary open revascularization options exist for clinically diagnosed PAD. Surgical endarterectomy, a procedure first described by Dos Santos (1947), involves removing thrombus from an arterial segment [23], and is commonly used for isolated common femoral artery disease [95]. An alternative to endarterectomy is the surgical bypass (bypass) procedure which first occurred in humans in 1906 [24]. Open surgical procedures cause higher morbidity and mortality than PTA, but have longer patency and require fewer repeat operations. Open management is most common among individuals with critical limb ischemia and those with long-segment arterial disease [26]. A recent study reported, however, that open management can be appropriate in certain individuals with claudication [7].

3.5.2.3 Limb Amputation Management

The final invasive treatment option for the severe and treatment resistant PAD is lower extremity limb amputation, which was first performed for PAD-related gangrene around 400 BC [96]. Lower limb amputation is indicated for life-threatening wound infection, uncontrollable rest pain, unreconstructable arterial disease, non-ambulatory patients, and others in whom treatment has failed [25]. Amputation is defined as primary, implying no prior intervention has been attempted, or secondary, in which a prior attempt at arterial reconstruction has failed, and is categorized, based on location of the amputation, as below-, through-, or above- the knee.

Limb amputation procedures are associated with high morbidity and mortality rates, particularly among diabetics [97]. In several studies, approximately 50% of individuals with lower extremity amputation (LEA) were deceased at two years [98, 99]. However, research indicates that LEA could be the best treatment for severe PAD if the result is early prosthetic fitting and a return to functional living [2].

3.5.3 Trends Associated with PAD Management

Recent evidence indicates increases in rates of endovascular management of PAD while the rates of limb amputation and bypass procedures are either stable or decreasing [100, 101]. O'Brien-Irr et al (2012) found that endovascular management increased while limb amputation procedures decreased between 2003 and 2008 [1]. Goodney et al (2009) found similar increases in endovascular procedures with a decrease in the use of bypass procedures by 42%, and declines in amputation over a ten-year period [102]. Evidence specific to trends among the Medicare population have not been examined and are a gap in the literature.

3.6 Epidemiology of PAD

Peripheral artery disease is inconsistently defined across studies, and source populations differ significantly to include a variety of population-based and clinical-based settings. The following section is meant to serve as an extensive literature review of the seminal PAD prevalence and incidence studies reported to date, while acknowledging cross-study comparisons are difficult because of methodological and source population differences. Appendix 2 contains tables that highlight the important features of these seminal studies and each table highlights a methodology used to define PAD. In reviewing this literature, important gaps in this literature will be identified that the proposed research will address. Prevalence studies will be discussed prior to studies that quantified PAD incidence. A section detailing the seminal CVD cohort studies that measured PAD will be discussed within the section on incidence, as will risk factors identified from these studies. The final topic of PAD epidemiology will be the use of administrative claims sources to quantify burden.

3.6.1 Prevalence of PAD

3.6.1.1 PAD Prevalence Based on ABI Measurement

The most common method of quantifying PAD prevalence in research studies is through measurement of the ABI, a procedure described above in section 1.4 of this research proposal. Prevalence of PAD originating from population-based studies from the U.S. ranged from 3.0% among the middle aged (45-64 years of age) participants in the ARIC cohort to 13.4% among older participants ($\geq$ 65 years of age) in the Cardiovascular Health Study (CHS) [41, 72]. Selvin et al (2004) observed a similar prevalence of PAD in the National Health and Nutrition Examination Survey (NHANES) (14.5%, 95% CI: 10.8%-18.2%) [64].

In studies identified through this review, prevalence estimates were uniformly higher among hospital-based or clinic-based cohorts compared to population-based studies. For example, the German Epidemiological Trial on Ankle Brachial Index (getABI study) measured ABI on 6,880 patients ($\geq$ 65 years) identified from 344 general practitioners across Germany. Using ABI <0.90 as the cut point, the age-adjusted prevalence of PAD was 19.8% [73]. A Houston-based study of primary care clinics and the DeBakey Veterans Administration hospital found an overall prevalence of 16.7% among 403 participants over the age of 50. Results were stratified by race and gender with particularly high prevalence estimates seen among black women (20.3%) and white men (20.1%) as compared to other white, black and Hispanic participants [78]. Further studies that used ABI measurement as the sole identifier of PAD are shown in Appendix Table 1 and Appendix Table 2.

Studies using only ABI are likely to underestimate PAD prevalence. While the ABI test may help identify asymptomatic PAD, studies that did not use a second measure, such as a questionnaire, are likely to underreport symptomatic disease.

3.6.1.2 PAD Prevalence Based on Questionnaires with or without ABI

Prevalence is commonly measured using only questionnaires although some studies use both a questionnaire and the ABI measurement to detect PAD. Estimates that use both methods are important because they can capture both asymptomatic and symptomatic disease. Not unexpectedly, prevalence estimates based on this combined methodology are uniformly higher than estimates based on ABI alone. As an example, the lowest prevalence identified in a search of the literature was from a population-based study of randomly selected individuals from four regions in Sweden. This study had an "any PAD" category, defined by ABI <0.90 or a positive Rose/WHO Questionnaire [48]. Prevalence of this definition of PAD was 17.9% (95%CI, 16%-20%); 11.1% had asymptomatic PAD identified by ABI and 6.8% had symptomatic disease. The highest prevalence of PAD identified through combined ABI and questionnaire method was 19.1% (95% CI: 18.1%-20%) in the Rotterdam Study, a population-based study in the Netherlands. This study also used ABI <0.90 to detect asymptomatic disease and the Rose/WHO Questionnaire to define symptomatic PAD [59]. Studies using this combined methodology had low response rates for enrollment. Many studies reported poor response rates for completion of the questionnaire. These studies also used different questionnaires to assess for claudication making cross study comparisons difficult [59, 80]. Results from other studies using this methodology are shown in Appendix Table 3.

As previously discussed, the WHO/RQ, one of the primary instruments used in studies of PAD prevalence, has a low sensitivity and likely underestimates disease burden, leading to misclassification bias. Studies that used the SDQC as an alternative to the WHO/RQ or the EQC should better represent PAD burden because the SDQC allows identification of non-calf IC. A study by Wang et al (2005), for example, identified an additional 1.7% of individuals who had either thigh or buttock claudication by using the SDQC [103].

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3.6.1.3 PAD Prevalence Based on Self-report and ABI or Questionnaires

Several studies of PAD prevalence used a combination of self-report with or without one other assessment modality to quantify PAD burden. The lowest estimate came from a population-based study in the industrialized urban regions of Western Germany that used ABI <0.90 or self-reported physician diagnosis to conclude an overall PAD prevalence of 6.8% [67]. The highest prevalence was found in the PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) program [11]. The PARTNERS program included 350 primary care practices in 27 sites (25 cities) across the US and enrolled individuals that were either 1) 50-69 years of age with a history of diabetes or smoking or 2) 70 years of age and older. Using ABI <0.90, or documented PAD in a medical record, PAD prevalence was 29% [11]. Studies quantifying PAD prevalence by a combination of self-report with one additional modality show inconsistent methodologies, causing a wide range of estimates. Estimate comparisons across studies, therefore, are difficult. Further information on studies using these criteria can be found in Appendix Table 4 and Appendix Table 5.

3.6.1.4 Summary of PAD Prevalence Studies

PAD prevalence estimates vary widely and are dependent on the methodology used to assess PAD. As would be expected, studies that used ABI in combination with a second detection method reported higher prevalence estimates than those that used a single assessment method. Studies conducted in populations with a higher mean age or in high risk populations, such as the CHS study of people 65 years of age and older, had the highest prevalence estimates. Studies such as the study in Western Germany, described above, which included healthy workers, showed much lower prevalence estimates. Existing estimates of PAD prevalence rarely reported on outpatient events or on CLI and, as such, the literature on these topics is sparse.

3.6.2 Incidence of PAD

Estimates of PAD incidence are exceedingly rare in population-based studies as PAD is an infrequently examined endpoint. Many of the studies that do measure PAD have different population bases and detection methods to assess PAD, making cross-study comparisons difficult. The following section details cohort studies that measured and have reported findings for incident PAD. Incidence of PAD obtained from longitudinal studies ranged from 1 per 1000 person years to 23.8 per 1000 person year. Estimates for PAD incidence are comparable to estimates for stroke and myocardial infarction incidence. Incidence of PAD is, however, lower than incidence of atrial fibrillation and heart failure [104]. Further information from a review of the literature presenting PAD incidence estimates is shown in Appendix Table 6.

3.6.2.1 Cohort Studies Measuring Incident PAD

Several major cardiovascular cohort studies that measured incident PAD are described below. These studies are highlighted because they are the seminal studies in the literature with well-defined methodologies and reported results. They are also primarily US-based, providing a reference point for the proposed research. With the exception of a study by Murabito et al (2005), which found that the incidence of claudication is declining over time, all literature reviewed indicates that PAD incidence is expected to increase as the population ages [105].

3.6.2.1.1 The Framingham Heart Study

The Framingham Heart Study (FHS) is a community-based cohort study from the community of Framingham, Massachusetts, an industrial and trading center of approximately 30,000 individuals [106]. A sample of 5,209 participants (29 to 62 years of age at baseline), chosen based on a local census list and stratified by family size and precinct of residence, was enrolled in the study. The investigators measured the presence of IC using criteria of cramping discomfort with exercise that was relieved with rest derived from a physician-administered

questionnaire. All IC cases were reviewed and adjudicated by a panel of investigators [107].

Over the first fourteen years of follow-up 125 cases of IC were identified with an average annual

incidence of IC of 26 per 10,000 person-years among males and 12 per 10,000 person-years

among women. A follow-up study assessed temporal trends of IC incidence over a fifty-year

period [105]. Incident cases increased through the 1970s with a peak rate of 34.5 per 10,000

from 1970-1979. The number of cases declined in the 1980s and 1990s and decreased to 22.5

per 10,000 from 1990-1999 [105].

While the FHS provided valuable insights into PAD etiology and trends associated with

PAD burden over more than sixty years of follow-up, the Framingham Study has several

limitations. The FHS excludes all minority groups and is poorly generalizable to the broader US

population. Claudication was defined only by medical history documentation, which might

result in misclassification bias.

3.6.2.1.2 Edinburgh Artery Study

The Edinburgh Artery Study (EAS) examined the natural history of PAD among 1,592

residents of Edinburgh, Scotland, 55 to 74 years of age [108]. EAS investigators used ABI

measurements with hyperemic drop calculation and administration of the WHO/RQ to estimate

asymptomatic and symptomatic PAD, respectively [108]. Follow-up for the EAS (Leng, 1996)

identified 116 incident IC cases (15.5 per 1000 person-years) over five years of follow-up. Men

had a higher incidence proportion of IC than women (8.7% vs. 6.6%). Over five years of follow-

up, 8.2% of those with IC had a myocardial infarction (MI), 9.6% developed new angina, and

6.8% had a major cerebrovascular event. Approximately 20% of those with IC were deceased at

five years of follow-up and 13.7% had experienced a cardiovascular-related death. Four percent

of those with baseline IC had required a limb amputation at five years [81].

The EAS was one of the first studies that monitored peripheral atherosclerosis endpoints, and is a rare study that reports incidence rates. The study includes information on individuals across social class and educational attainment and uses several measures to delineate PAD prevalence. Their inclusion of participants from poorer areas led to a lower response rate than they had expected.

3.6.2.1.3 Atherosclerosis Risk in Communities (ARIC) Study

The ARIC study is a bi-ethnic longitudinal study of the natural history of atherosclerotic diseases among 15,792 residents of four US communities: Forsyth County, North Carolina, Washington County, Maryland, Jackson, Mississippi, and suburban Minneapolis, Minnesota [8]. ARIC study participants were 45-64 years of age at baseline.

Zheng et al (2005) conducted a cross-sectional analysis using ABI <0.90 to identify PAD and found an age-adjusted PAD prevalence of 3.0% among ARIC study participants [70]. Age adjusted prevalence among gender and race subgroups was as follows: African American men, 3.1%; African American women, 4.4%; white men, 2.3%; white women, 3.2% [70]. Selvin et al (2006) used the Rose Questionnaire, ABI <0.90, or a PAD-related hospitalization to quantify incident PAD among those with diabetes in the ARIC cohort [109]. Crude incident rates reported for IC, low ABI, and PAD-hospitalization were 2.1, 18.9, and 2.9 per 1000 person-years, respectively, during 9.8 mean years of follow-up. Wattanakit (2005) conducted a similar study among diabetic participants in ARIC and found a total PAD event rate of 13.9 per 1000 person-years [110].

The ARIC study is a geographically diverse, bi-ethnic cohort, providing distinct advantages over similar cohort studies, such as the FHS, that were from single centers or examined only one ethnicity. There are some disadvantages to the ARIC cohort study. ABI was

measured in only one leg at baseline and only in segments of the cohort at subsequent visits. Follow-up ABI testing was completed for 4,575 participants at the third clinic visit (1993-1995) and in 6,404 participants at the fourth clinic visit (1996-1998). Thus, estimates from this study likely underestimate PAD burden in this population.

3.6.2.1.4 Women's Health Initiative (WHI)

The Women's Health Initiative (WHI) is a clinical trial (n=16,608) and observational study (n=69,000) designed to delineate causes of morbidity and mortality among postmenopausal women 50-79 years of age [111]. The study was initiated in 1992 and follow-up is ongoing. The clinical trial component, the Women's Health Initiative Estrogen Plus Progestin trial, randomized women to placebo or estrogen therapy. Peripheral artery disease, measured by self-reported history of carotid or lower extremity surgery, was exceedingly rare (0.5%) at baseline exam.

Hsia et al (2003) reported on incident lower extremity events, defined as overnight hospitalization with either symptoms or intervention and confirmed by procedure, absence of pulses, or non-invasive vascular studies [112]. Over 5.6 years of follow-up, the incidence proportion of PAD was 0.14% per year. Incident PAD events occurred more frequently among women with a history of coronary artery disease (CAD) or PAD (13 per 1000 person-years) than women with no history of arterial disease (1 per 1000 person-years).

The WHI is a large study that provides valuable data on PAD in women across the country at forty sites. The sample was not, however, random, and the healthy volunteer effect may be leading to lower PAD event rates than would be expected in the general population. The study is limited to women and estimates are not generalizable to men.

3.6.3 PAD Risk Factors Identified from Reviewed Literature

In the following section, traditional and sociodemographic risk factors for PAD will be discussed to further place PAD in the context of overall atherosclerotic disease burden. As PAD has a shared risk factor profile with coronary and cerebral atherosclerosis, the implication of reducing the prevalence of PAD risk factors extends to benefits in delaying or preventing myocardial infarction, stroke, and other major circulatory system disorders [25, 35, 113].

3.6.3.1 Traditional Risk Factors

Risk factors for PAD are identical to traditional cardiovascular disease risk factors, with diabetes [109, 110, 114, 115] and smoking [116-118] particularly predictive of PAD. Other important risk factors include hypertension [119-121], dyslipidemia [122-124], renal insufficiency [125, 126], poor diet [127-129], and lower levels of physical activity [130-132]. Risk factor profiles are similar for all stages of PAD severity, although diabetes may have a stronger association with CLI as compared to claudication [133].

3.6.3.1.1 Diabetes Mellitus/Impaired Glucose Tolerance as a PAD Risk Factor

Diabetes Mellitus (DM) causes an abnormal metabolic state which increases the susceptibility to atherosclerotic diseases in the three primary vascular beds: the coronary arteries, the lower extremity arteries and the extracranial arteries [134]. Diabetes is more predictive of PAD than of MI and stroke, and is considered one of the most prominent risk factors for PAD [120, 135]. The predictive ability of DM is so substantial that the American Diabetes Association has recommended ABI measurement, the most common test for PAD, every five years, for life, among diabetics [136].

In the CHS, the relative risk of PAD (ABI <0.90) among diabetics was 4.1 (95% CI: 2.8-5.9) compared to non-diabetics [72]. Research suggests that hyperglycemia, glucose intolerance, and glycosuria are all associated with an increased risk of claudication [121]. The risk of

claudication among women with glycosuria was 8.6 times the risk of claudication among women without glycosuria [121].

Diabetic patients are more likely to have disease in their distal (below the knee) arterial tree where vessels are smaller [134]. Disease in the popliteal and tibial arteries is associated with the more severe PAD sequelae [137]. Diabetic patients are at an increased risk of foot ulcers because of neuropathic complications and poor infection response [134]. As a result of these complicating factors, DM is associated with an increased risk of CLI and limb amputation [25, 138]. The risk of amputation is five-fold greater among diabetics as compared to non-diabetics, and DM is implicated in the majority of non-traumatic limb amputations [139, 140]. Diabetes represents a modifiable risk factor that, if appropriately managed, could reduce the overall burden of PAD.

3.6.3.1.2 Smoking as a PAD Risk Factor

While diabetes is largely associated with small vessel PAD, smoking is associated with progression of large vessel PAD [137] and is considered a well-known and significant risk factor for intermittent claudication [141, 142]. The first prospective study that identified smoking as a risk factor for PAD was the Framingham Study, which reported on the association between baseline number of cigarettes smoked daily (none, <20, 20, or >20) and incidence of intermittent claudication over a sixteen year period [117]. All levels of smokers had a higher incidence of IC at all age groups, although heavy smokers (>20 per day) were three times as likely as never smokers to develop IC over 16 years [117]. Association of smoking with PAD observed in FHS is similar to the relationship seen in the Cardiovascular Health Study (CHS). In CHS, the relative risk of PAD (defined as ankle-brachial index <0.90) among current smokers was 2.55 (95% CI: 1.76-3.68) compared to never smokers [72]. Other studies confirm a similar dose-

response relationship [116, 122, 143]. Smoking is associated with CLI [25] but does not confound the relationship of CLI to outcomes such as mortality and limb amputation [144, 145].

3.6.3.2 Sociodemographic Traits as PAD Risk Factors

Prior studies have shown that important sociodemographic traits such as age, gender, race, and socioeconomic status are associated with PAD [41, 64, 66, 67, 69]. Disease prevalence increases significantly with age and the American Heart Association recommends all individuals over the age of 65 be screened for PAD via the ABI test [60, 64, 86]. Selvin et al (2004) studied 2,174 participants aged 40 and older with ABI measurements in the National Health and Nutrition Examination Survey (NHANES I), conducted from 1999-2000 to estimate PAD prevalence [64]. Overall prevalence (ABI <0.90) was 4.3% (95% CI: 3.1%, 5.5%) among those 40-49 years of age, 2.5% (95% CI: 0.5%-4.5%) among those 50-59 years of age, 4.7% (95% CI: 2.5%-6.9%) among those 60-69 years of age and 14.5% (95% CI: 10.8%, 18.2%) among those 70 years of age and older. Overall, the investigators estimated that during the period of observation more than 5 million individuals in the US had PAD, including at least 4 million among those over 70 years of age [64].

The majority of population-based studies stratify estimates by gender, although evidence concerning differences in PAD prevalence between men and women is conflicting. The NHANES study identified no differences in PAD prevalence among men (4.5%, 95% CI: 2.9%-6.1%) as compared to women (4.2%, 95% CI: 2.8%-5.6%) [64]. The ARIC study did find a slightly greater prevalence of PAD (ABI <0.90) among women as compared to men [41]. Results from the FHS indicate a higher incidence rate of PAD among men (26 per 10,000 person-years) as compared to women (12 per 10,000 person-years) while information from the Limburg Peripheral Artery Occlusive Disease Study found higher incidence rate of PAD among women (14.2 per 1000 person-years) as compared to men (8.2 per 1000 person-years) [107, 146].

PAD burden estimates stratified by race in the US have consistently found that PAD prevalence is typically higher among blacks as compared with whites. Blacks had a higher prevalence (7.9%, 5.2%-10.6%) than whites (4.4%, 95% CI: 2.8%-6.0%) in NHANES [64]. Baseline PAD prevalence (ABI <0.90), among 2,343 participants of the San Diego Population Study (SDPS) of randomly selected population of former/current employees, was 7.8% in blacks and 4.9% in whites [69]. Prevalence is generally lower among Hispanics as compared to blacks and is sometimes lower than prevalence in whites. Less than 2% of Hispanics in the SDPS had PAD at baseline [69]. Three percent (95% CI, 1.4%-4.6%) of Mexican Americans in NHANES had prevalent PAD [64]. Prevalence of PAD (ABI<0.90) among 6,653 participants in the Multi-Ethnic Study of Atherosclerosis (MESA) was 7.2% in African Americans, 3.6% in whites, and 2.4% in Hispanics [147]. Results for race and gender are summarized in Table 3, below. Each of the studies described in Table 3 use homogeneous measurement methods (ABI < 0.90) to quantify PAD prevalence. The ages of the population eligible for inclusion of the study, however, are significantly different. The CHS Study enrolled only those 65 years of age and older. Estimates were similar among ARIC, NHANES, MESA, and San Diego, studies that included predominantly middle-aged individuals.

Table 3. PAD prevalence estimates by gender and race

	Gender		Race	
Study Population	Female (%)	Male (%)	Black (%)	White (%)
ARIC	3.5	2.5	3.7	2.8
CHS	12.4	14.8	21.5	11.9
NHANES	4.2	4.5	7.9	4.4
MESA	3.7	3.7	7.1	2.7
San Diego	3.6	6.1	7.8	4.9

Reports on the association between socioeconomic status (SES) and PAD are limited. In the population-based Heinz Nixdorf Recall Study in Germany, PAD prevalence (ABI<0.90) was inversely related to education and income among 4,738 individuals [67]. PAD prevalence among low ($\leq$ 10 years), medium (11-13 years), and high education ($\geq$ 14 years) was 8.1%, 7.5%, and 5.3%, respectively. Among 6,791 participants in the NHANES study, SES, defined by income, was inversely associated with prevalent PAD (ABI<0.90). Individuals with low SES had the highest PAD prevalence (8.4%, 95% CI: 7.3%-9.5%), while individuals in the highest SES category had the lowest PAD prevalence (3.4%, 95% CI: 1.8%-3.6%) [148]. Other studies only found weak associations between SES and PAD [149, 150].

Sociodemographic disparities in PAD extend to variations in rates of procedures. Several studies of revascularization procedures for PAD report lower procedure rates among blacks, women, and individuals of low SES in comparison with whites, men, and those of high SES, respectively [151, 152]. Numerous studies have reported disparities in surgery for lower extremity amputation [6, 153, 154]. Research relevant to sociodemographic procedure variations implicates poor access to care among these higher risk groups.

3.6.4 Literature Summary for PAD Epidemiology

PAD is an arterial disease that has significant consequences, both to the individual and to the health care system, if it is not identified and aggressively managed. Total all-cause hospitalizations for PAD are in excess of $21 billion with 57% of those due to revascularization procedures and amputations [15]. PAD can cause life-altering physical limitations with limb- and life-threatening consequences. More than 50% of individuals with critical limb ischemia, the most severe PAD, will be deceased or have experienced a limb amputation within one year of diagnosis. As such, early detection and management is critical. Furthermore, as PAD is associated with disease in other vascular beds, increasing awareness of PAD could have benefits in the prevention of myocardial infarction, stroke, and cardiovascular-related death. One of the primary hopes of the proposed research, therefore, is simply to raise awareness of PAD and to provide information that will allow PAD to be placed in context with other more well-known atherosclerotic conditions.

A thorough review of existing of PAD prevalence and incidence literature reveals widely varying estimates. Population bases and detection methods to assess PAD differ, making cross-study comparisons difficult. Differences among characteristics of PAD incidence studies include single gender representation, race-specific population studies, population-based versus clinic-based samples, differing questionnaires, and adjudicated versus non-adjudicated events among others. In the majority of population-based studies where PAD is an endpoint, it is synonymous with intermittent claudication to the exclusion of more severe sequelae, such as critical limb ischemia. Current estimates do not contain information on outpatient visits and procedures where the majority of encounters likely occur.

One method to address these methodological concerns is to use an administrative claims data source as a research study population. Medicare claims data are limited to those ages 65

years and older which is a limitation of this data source. Other administrative sources, such as

Medicaid and commercially available claims databases, include information on younger

populations. These sources are, however, not linked with the ARIC study. Further, the

Medicare-eligible population is a reasonable population to study PAD because it is a disease of

aging primarily found in the elderly. The next section will detail the use of administrative claims

as a research tool to quantify PAD.

3.6.5 Identification of PAD Events from Administrative Claims Data

Administrative claims originating from federal and private insurers are increasingly used

for research purposes. Claims are created by health care providers for payers and indicate what

services a provider billed for during a particular visit. The *International Classification of*

Diseases, Clinical Modification, version 9 (ICD-9-CM), *Current Procedural Terminology*, 4th

edition (CPT-4) codes, Healthcare Common Procedure Coding System (HCPCS) codes, and

Federally Qualified Healthcare Center codes (FQHC) are used to identify clinical events and

procedures in claims data. A description of these codes is found below in Table 4 (p.41).

Administrative claims data frequently are examined in Medicare Fee-for-Service (FFS) and

Managed Care Programs, which are discussed below.

3.6.5.1 Medicare Fee-for-Service and Medicare Advantage Programs

Medicare FFS is the program that provides hospital and ambulatory care to persons 65

years and older in the United States. FFS includes Part A (hospital insurance) and Part B

(supplemental insurance that covers physician and outpatient services). Medicare beneficiaries,

with the exception of those with end-stage renal disease and those on hospice care, also have the

option to enroll in a MA program where individuals can attain supplemental insurance to cover

the costs of their health care services [155]. Medicare Advantage receives capitated monthly

payments to provide health services to their clients and are at an advantage to enroll low-risk

individuals who are likely to have low medical care costs [156]. Significantly, MA is not required to submit claims information to Medicare for their enrollees; therefore health care utilization is not quantifiable for beneficiaries enrolled in MA using Medicare claims and researchers must note this study design limitation. The percentage of Medicare beneficiaries enrolled in MA varies significantly across states and geographic regions. An example of this variation (and significant to the proposed research) is the ARIC study, where penetrance ranges from <10% (Washington County, Jackson from 2003-2005) to >40% (Forsyth County, 2005-present). Figure 5, below, is a representation of penetrance among the four ARIC regions from 2001-2008.
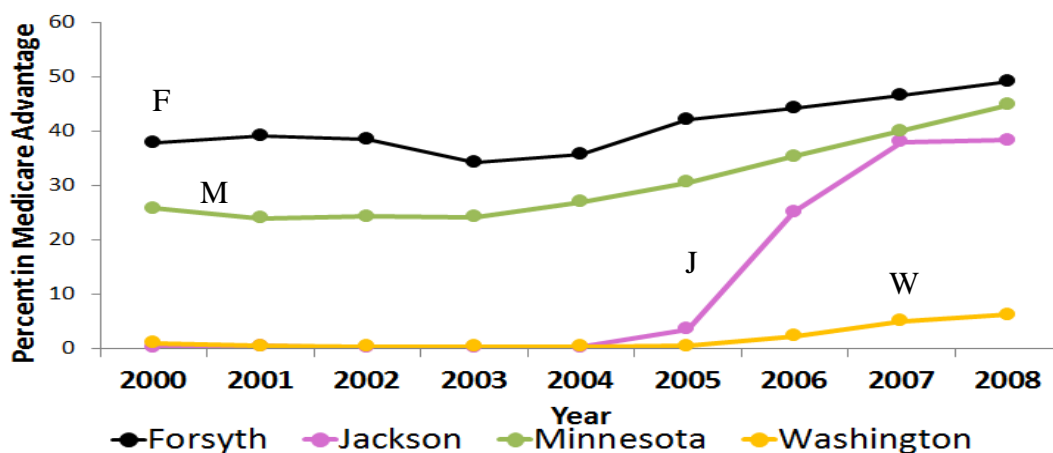
Figure 5. Percent managed care penetrance by ARIC community from 2001-2008; adapted from ARIC website

3.6.5.2 Validation of Administrative Claims Data

Administrative data studies examining the validity of ICD-9 and CPT codes to identify PAD are rare and only three studies on the validation of PAD related codes from claims data were identified for review [157-159].

The Mayo Clinic has developed the Mayo Clinic algorithm (MCA), a billing code-based algorithm for identifying PAD patients from an electronic medical record (EMR). The MCA, originally used to identify the PAD phenotype in genomics research, contains an exhaustive list

of ICD-9-CM and CPT-4 codes relevant to PAD [160]. Recently published work examined the application of the MCA in a community-based sample of 4420 Olmstead County residents seen at the Mayo Clinic with a PAD-related billing code [161]. Of these patients, 225 patient records were randomly selected for manual record abstraction by an experienced cardiologist. Results included: sensitivity, 68.0% (95% CI: 56.2-78.3); specificity, 87.6% (95% CI: 80.9-92.6); positive predictive value (PPV), 75.0% (95% CI: 63.0-84.7), and negative predictive value (NPV), 83.3% (95% CI: 76.2, 89.0). An additional study of 22,000 individuals at the Mayo clinic used billing codes and the ABI test to ascertain PAD. Area under the operating-receiver was 0.86, indicating sufficient PAD identification ability of the algorithm [159]. Appendix Table 7 provides a detailed report of these studies.

The Women's Health Initiative (WHI) study investigators validated ICD-9-CM codes in comparison with reviewer diagnosis and adjudication of 470 potential PAD events and found a sensitivity of 0.61 (95% CI: 0.54,0.68) and a positive predictive value of 0.31 (95% CI: 0.26,0.36; ICD-9-CM codes 443.9, 440.2) [158]. A second study by Fisher et al (1992) examined 217 hospitalized PAD events abstracted from a hospital record to assess agreement/reliability as compared to reabstraction, completed by the Office of the Inspector General [157]. The sensitivity of ICD-9-CM codes (in any position) to identify PAD was 0.58 (95% CI: 0.51, 0.64) with a PPV of 0.53. This study also examined a PAD diagnosis based on ICD-9-CM codes in the primary or secondary position and found that sensitivity and PPV were much higher at 0.76 and 0.69, respectively [157].

To date, no published report has examined the validity of using claims to quantify outpatient events. As such, a validation study of PAD ICD-9-CM codes, to include both inpatient and outpatient, would be a valuable contribution to the literature.

3.6.5.3 Estimates of PAD Burden Based on Administrative Claims

A small body of literature quantifies PAD prevalence and incidence using ICD-9-CM and/or CPT-4 codes obtained from administrative databases, with source populations originating from Medicare and managed care. The majority of those studies were completed for the purpose of assessing PAD-related costs [1, 15, 102, 162-165]. Each of the salient studies is discussed below. Appendix Table 8 lists the diagnostic codes used to define PAD in each study.

For the purposes of this review, the term PAD prevalence is used to describe the occurrence of PAD among individuals eligible for inclusion in administrative claims-based data sources. Thus, estimates are representative of individuals who have had medical encounters (i.e. the source of a claim) and do not reflect a true population-based denominator. PAD estimates from claims sources are unique in comparison to the previous literature discussed because asymptomatic disease, defined by ABI or questionnaire in the literature reviewed, cannot be quantified using administrative claims. Further, administrative claims allow outpatient PAD, for which there is limited information available otherwise, to be quantified. Estimates from administrative claims are, therefore, a reflection of the burden of clinically diagnosed PAD.

3.6.5.3.1 Estimates of PAD Burden Based on CMS Medicare Claims

The 5% Surveillance, Epidemiology, and End Results (SEER) non-cancer data for calendar year 2001 was used to determine PAD-related national health care expenditures in the US [162]. The SEER registry is a population-based cancer registry that collects information on about 28% of the US population. SEER includes information on Medicare enrollment and utilization. Hospitalized PAD events were identified on the basis of a PAD-related ICD-9-CM code in the primary or secondary position as well as a PAD-specific diagnosis-related group (DRG), as shown in Appendix Table 8. This study also included outpatient events, although the method of ascertainment was not described. Approximately 7% of the more than 150,000

beneficiaries studied had a PAD-related claim. PAD-related hospitalizations accounted for nearly 90% of expenditures among those with PAD, although only 6.4% (n=668) of those with PAD had an inpatient claim with a PAD-related diagnostic code. This study indicates that majority of PAD events occur in the outpatient setting, although the study investigators only present outpatient costs and do not present detailed burden information for outpatient claims. This study underscores the need to further examine PAD events occurring in the outpatient setting.

A 5% random sample of Medicare beneficiaries from the Medicare Standard Analytic Files (Medicare Part A and Part B) was used to quantify PAD costs and to assess clinical outcomes following invasive management [163]. PAD was defined using pre-specified ICD-9-CM and CPT code algorithms, as shown in Appendix Table 8. A range of 2.1 to 2.4 million beneficiaries were enrolled in the data set, depending on the year. Of these, 57,043 beneficiaries receiving PAD-related treatment were identified. Inpatient PAD prevalence increased during the period of observation from 8.2% in 1999 to 9.5% in 2005. Projected estimates for the full Medicare beneficiary population indicate prevalence of 4.3 million in 2005. Prevalence increased incrementally with age with the highest rates (19.3%) seen among those $\geq$ 85 years of age. Prevalence was comparable among men (9.3%) and women (9.7%). Among individuals treated for PAD less than 6% underwent limb amputation procedures and 27% died during the six years of follow-up. This is an important study that provides useful information on inpatient PAD-related care. The study, however, excludes outpatient data and does not provide information on PAD subtypes.

The PAD estimates above are presented to establish precedence for using Medicare claims to quantify clinically diagnosed PAD and to identify limitations in the existing literature.

The notable exclusion of outpatient data likely underreports PAD burden and, as such, is an important scientific need to be addressed by this proposal.

3.6.5.3.2 Administrative Claims from Managed Care Database to Estimate PAD

Administrative claims from a managed care database of 6.67 million members of two health plans in the western and southeastern US were used to examine PAD-related costs [14]. Those meeting inclusion criteria, 18 years of age and continuous plan eligibility from January 1st, 1999 to August 31st, 2003, were enrolled in the study. PAD was defined by ICD-9-CM codes (diagnosis and procedure) in the primary or secondary position, CPT codes, or by a pharmacy claim for PAD-specific medications, Cilostazol or Pentoxifylline. Of the total population of managed care participants examined, 30,561 (1.2%) had a PAD-related claim. PAD prevalence was 10.8 per 1000 plan members and increased significantly with age.

This study was limited to managed care participants, a traditionally healthier and younger group of individuals as compared to those with federally provided insurance [166]. Thus, while this study provides valuable information on those with private insurance, limited inferences can be made as to the prevalence and incidence of PAD among a more elderly population with greater prevalence of comorbidities.

3.6.5.4 Summary of PAD Estimates Based on Administrative Claims

Administrative claims present an opportunity to estimate the burden of PAD in defined populations and have several strengths over other types of data sources. Clinically diagnosed symptomatic PAD is an understudied problem and claims data are capable of assessing the magnitude of the disease in a particular population (65 years of age and older) that represents the most significant risk for this disease. In addition, while burden estimates from the literature largely exclude outpatient events making it difficult to quantify the full spectrum of PAD-related care, claims data present the ability to quantify PAD events in the outpatient setting.

Administrative data have several limitations and the limitations specific to CMS

Medicare claims are discussed next. CMS claims data do not provide detailed information on

comorbidities or illness severity. Coding inconsistencies and missing data, specifically missing

information on self-reported race, are also problematic. Additionally, enrollment of Medicare

beneficiaries in the MA programs or with other private insurers (i.e. health maintenance

organization (HMO) penetrance) effectively creates study populations with additional insurance

which may differ on health status as compared to those with only Medicare fee-for-service [167].

Information concerning health care encounters for those with MA plans and those with other

private insurance is not available from Medicare claims, thus making it impossible to collect all

relevant data for these individuals. This selective loss in our population base impacts the

generalizability of our findings, which will be specific only to those with continuous FFS

Medicare coverage. The findings will not be generalizable to the broader Medicare population or

to those enrolled in a managed care program.

3.6.5.5 Relevance of Administrative Claims to Proposed Research

The previously discussed PAD estimates based on administrative claims are presented

because this data source is relevant to the proposed study, which will use CMS Medicare claims

linked to the population-based surveillance database for the ARIC study. Claims are available as

a 100% sample of health care claims among those that live in the four geographically defined

areas of the ARIC study. These claims are available over multiple consecutive years and are

managed by the ARIC Study Coordinating Center here at UNC. By placing the proposed study

in the context of geographic regions we have the ability to examine clinically diagnosed PAD in

relationship to other clinically diagnosed cardiovascular conditions, such as heart failure, stroke,

and acute myocardial infarction, which have been the subject of other claims-based research in

ARIC. The ARIC study population is well-characterized in demographic and comorbid traits,

which will further help contextualize the importance of PAD in these particular communities. While the ARIC study regions were not chosen because they are nationally representative estimates, attained estimates could reflect PAD burden in communities with similar population traits.

3.7 Public Health Significance

PAD remains an understudied problem of public health significance for which there is poor awareness compared to other cardiovascular diseases [11]. The proposed research addresses important gaps in the literature by contributing to: sparse information for PAD in the outpatient setting, the longitudinal evaluation of post-diagnosis care, limited information for incidence, and PAD data by sociodemographic traits. By attaining age-, race-, and gender-specific estimates of PAD burden and post-diagnosis care, and with the knowledge that atherosclerotic diseases share risk profiles, results of this study could be used to implement more targeted and effective prevention efforts. These prevention efforts could have significant downstream benefits at delaying myocardial infarction, stroke, and other circulatory system disorders. Results of the proposed research will create a foundation for future studies aimed at comparing, by demographics and comorbid conditions, the different trajectories associated with clinically manifest PAD diagnosed in the inpatient or outpatient setting. Future work could also include examination of the relationship between PAD and other cardiovascular diseases, such as heart failure, on which similar research is being conducted.

CHAPTER 4: RESEARCH METHODS

4.1 Study Population

The study population for Specific Aims 1 and 2 will include Black and White ARIC

cohort participants ages 65 years and older enrolled in the Center for Medicare and Medicaid

Medicare fee-for-service program.

4.1.1 The ARIC Study <u>Cohort</u> Data Linked to CMS Medicare Claims

The ARIC cohort includes 15,792 participants (ages 45-64 at baseline) selected by

probability sampling from four US communities: Jackson, MS; Forsyth County, NC;

Washington County, MD; and Minneapolis, MN (Figure 6). Participants from Forsyth County

were selected from area sampling of households. Participants were also selected from drivers

licenses (MS, MD, MN), identification cards (MS, MN), voter registration cards (MN), and

individuals listed in a 1975 private county health census (MD). Of note, blacks were

oversampled in Forsyth County (NC) and constitute 100% of individuals sampled from the

Jackson (MS) site.
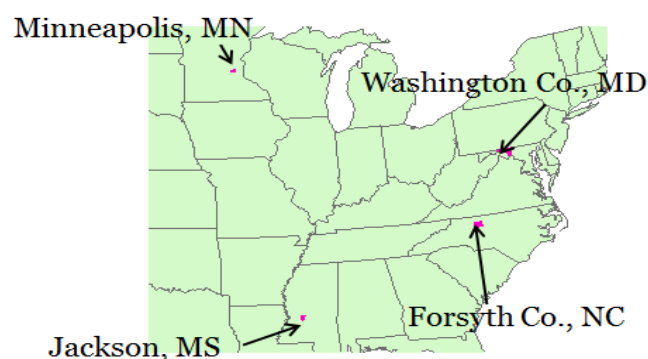
Figure 6. Map of the four ARIC communities

Potential cohort members were interviewed in their homes and then invited to a clinical examination. Overall, sixty percent of invitees chose to participate in the study including 49% of black females, 42% of black males, 68% of white females, and 67% of white males. Differences in comorbid conditions between respondents and non-respondents were more pronounced for men and women than for blacks and whites [168]. The ARIC cohort contains a limited number of Asian (n=44) and American Indian/Alaskan (n=14) persons who are traditionally excluded from analyses due to the lack of representation of these race groups. Twenty-seven percent (n=4266) of the baseline ARIC cohort population are black, 55% (n=8695) are female, and 24% (n=3754) have less than a high school education.

The cohort began enrollment in 1987 and recruited its final participant in 1989. There have been five clinic examinations with the fifth visit concluding in 2013. All hospitalizations associated with the ARIC Cohort are available through discharge data and from CMS claims. These inpatient data sources will be used estimate calibration factors associated with inpatient PAD.

Data from the ARIC cohort study does not include participants' outpatient visits. Instead, each participant agreed to annual follow-up (AFU) questionnaires in the form of a telephone interviews conducted by ARIC-trained representatives. The AFU questionnaires are used to capture non-hospitalized medical encounters that occur between the clinical examinations. Data from AFU questionnaires will be used to estimate calibration factors relevant to outpatient PAD. Notably, response rates are excellent (>85%) throughout study follow-up at all centers. All participants will be >65 years of age during the years sample for this study.

Our study will use FFS Medicare claims <u>specifically linked</u> to extant data for participants of the ARIC cohort study. The ARIC cohort participants are matched to CMS Medicare data on three factors: social security number, sex, and date of birth.

The CMS data are provided to the ARIC Study as part of the Interagency Agreement between the National Heart Lung and Blood Institute and the Centers for Medicare and Medicaid Services. The CMS data are curated and managed on an ongoing basis by the ARIC Study Coordinating Center.

4.1.1.1 Centers for Medicare and Medicaid Services Medicare Fee-for-Service Claims Data

The study will use claims from the Medicare FFS program, which provides hospital insurance (Part A) and supplemental insurance that covers physician and outpatient services (Part B) to persons ages 65 years and older in the United States.

4.1.1.2 Organization of Center for Medicare and Medicaid Services Data

The CMS data are organized into various files containing pertinent health care information including: the Master Beneficiary Summary File, Outpatient claim file, Carrier claim file, and the Medicare Provider Analysis and Review (MedPAR) file. Each of these CMS files is linked by a unique beneficiary identification number. A brief description of the contents of these files follows. The information is summarized in Table 4, which follows this section.

4.1.1.3 The Master Beneficiary Summary File

The Master Beneficiary Summary File includes beneficiary demographic traits including age, race, gender, and date of birth. The file includes information about beneficiary enrollment in: Medicare Parts A and B, MA, or Medicaid. This file contains information about beneficiary residence including: zip code, state and county codes. Files are provided monthly and are "frozen" in March of each subsequent calendar year.

4.1.1.4 Outpatient and Carrier Claim Files

The Outpatient claim file contains claims from institutional outpatient providers including: the outpatient department of hospitals, rural health clinics, outpatient rehabilitation centers, and other federally qualified health care centers. Emergency room visits that do not result in hospitalization are found in the Outpatient file.

The Carrier claim file (Part B) contains claims from non-institutional providers including: ambulatory surgery centers, clinical laboratories, nurse practitioners, physicians, and physician assistants.

4.1.1.5 MedPar File

The MedPar File contains records for inpatient hospital stays and skilled nursing facility visits. Emergency room visits that result in hospitalization are identified in the MedPar File.

4.1.2 Event Ascertainment in Claims

4.1.2.1 PAD Event Ascertainment in Center for Medicare and Medicare Services Fee-for-Service Population

The following sections will present the specifics on the identification of encounters in the proposed study, including the definition of clinical encounters and the definition of PAD. Table 4 lists the codes used to identify PAD encounters by the various setting where these encounters occur.

4.1.2.2 Identification of Clinical Encounters in our Fee-for-Service Medicare Population

Medicare enrollment information will be obtained from the Medicare Beneficiary Summary file. The MedPAR file will be used to identify hospitalized encounters and Emergency Department visits which resulted in a hospitalization. Time in a skilled nursing facility and home visits will be excluded from analyses because these encounters do not classify within traditional definitions of hospitalizations or of outpatient clinical care. Ambulatory care encounters and

Emergency Department visits that did not result in a hospitalization will be identified using the Carrier and Outpatient files.

4.1.2.3 Identification of Codes Used to Define PAD within Fee-for-Service Medicare Population

Peripheral artery disease will be identified from a thorough review of available literature. An exhaustive list of the codes proposed for this study and the definition of each code is included in Appendix 1.

Peripheral artery disease subtypes including intermittent claudication and critical limb ischemia will also be defined. Intermittent claudication will be defined by ICD-9-CM code 440.21 (Atherosclerosis of native arteries of the extremities with intermittent claudication) as per prior literature on this topic [1]. Critical limb ischemia will include the following ICD-9-CM codes per prior literature [1]: 440.22 (Atherosclerosis of native arteries of the extremities with rest pain), 440.23 (Atherosclerosis of native arteries of the extremities with ulceration), 440.24 Atherosclerosis of native arteries of the extremities with gangrene), 707.1* (ulcer of lower limb), and 785.4 (gangrene). Included will be codes relevant to open vascular surgical management and endovascular management, including bypass grafting and limb amputation procedures. For hospitalized encounters, only codes that appear in the primary or secondary position will be counted as a PAD event in accordance with prior literature on the topic [162]. Codes that appear in any position will be counted as a PAD event in the outpatient setting.

Table 4. Classification of clinical encounters from CMS Medicare claims

Encounter Type	Code Source	Code Type	Code
Ambulatory Care Visits			
New office visit	Carrier	HCPCS*	99201-99205
Established office visit	Carrier	HCPCS	99211-9215
Consultation	Carrier	HCPCS	99241-99245
New preventive medicine visit	Carrier	HCPCS	99385-99387
Established preventive medicine visit	Carrier	HCPCS	99395-99397
FQHC*	Outpatient	Revenue Center Code	See appendix
Inpatient Visits	MedPAR	ICD-9-CM	See Appendix
Emergency Department Visits			
ED visit, admitted to hospital	MedPAR	Emergency Room Charge Amount field where the amount is > $0	
ED visit, not admitted to hospital			
ED charge	Outpatient	Revenue Center Code	0450-0459
ED, professional fee	Outpatient	Revenue Center Code	0981

*HCPCS: Healthcare Common Procedure Coding System

*FQHC: Federally Qualified Healthcare Center

4.2 Research Approach for Assessment of Prevalence and Incidence of PAD (Specific Aim 1)

4.2.1 Analytic Sample

The analytic sample for Specific Aim 1 will exclude 1) participants enrolled in MA programs (N=4837), race other than black or white (N=45), and participants that were <65 years of age at time of fee-for-service enrollment (N=429). After applying these exclusion criteria, the final analytic sample included 10,481 ARIC participants.

4.2.2 Demographic and Comorbidity Assessment

Information on demographics of age, race and gender were obtained from annual Medicare beneficiary summary files. A version of the Charlson Comorbidity Index, modified to include outpatient codes, was used to identify comorbidity burden in our population. All claims (inpatient and outpatient) present in each calendar year were used to calculate an annual comorbidity score (Chapter 5, Table 1).

4.2.3 PAD Event Ascertainment

PAD was identified from the MedPAR records and the Carrier and Outpatient claims files using ICD-9-CM, CPT-4, HCPCS, and FQHC codes to ascertain PAD-related outpatient office visits, outpatient diagnostic tests, inpatient visits, and procedures. PAD codes were chosen from a review of available literature (See Chapter 5, Supplemental Table 2) [169].

4.2.4 Prevalence of PAD

Annual PAD prevalence was estimated for 2003-2012 using information on PAD encounters in the inpatient and outpatient setting. The denominator for annual prevalence estimates included cohort participants with continuous enrollment in FFS for the entire year of observation or until death. Prevalent *inpatient* PAD was defined as a record of ≥ 1 hospitalization with at least one of the selected PAD codes in any position during each calendar year of

observation. Prevalent *outpatient* PAD was defined as ≥ 1 claim with at least one of the selected PAD diagnostic or procedure codes identified in claims for outpatient services during each calendar year of observation. A sensitivity analysis was conducted using ≥ 2 outpatient claims to identify PAD (Chapter 5, Supplemental Table 3).

The table below describes the operational definitions to be used for prevalence calculations. Included are details relevant to event identification (numerator) and to the population being studied (denominator). Prevalence proportions will be calculated.

Table 5. Operational definitions for numerators and denominators used in prevalence calculations

	Numerator		Denominator
	Inpatient	**Outpatient**	**Denominator**
Prevalence	Occurrence of PAD-related hospitalization; If one outpatient event precedes an inpatient event, the event date will be the inpatient discharge date	One occurrence of the selected PAD-specific ICD-9-CM, CPT-4, HCPCS, and FQHC codes	Medicare beneficiaries with continuous fee-for-service Part A and Part B coverage during year of observation (2003-2012).
File source	MedPAR File	Carrier and Outpatient Files	Master Beneficiary Summary File

4.2.5 Incidence of PAD

A two-year look back period was chosen to minimize misclassification of prevalent events as incident events [170]; ARIC participants with a PAD-related inpatient or outpatient code occurring any time within the previous two years of initial FFS enrollment were excluded from annual analyses moving forward. Annual incidence rates (IR) are presented for the years 2005-2012. The denominator for annual incidence estimates included cohort participants' time in

continuous enrollment during the year of observation or until death if it occurred during the year of observation.

The table below describes the operational definitions to be used for incidence calculations. Included are details relevant to event identification (numerator) and to the population being studied (denominator). Person-time will be used to calculate incidence rates.

Table 6. Operational definitions for numerators and denominators used for incidence analyses

	Inpatient	**Outpatient**	**Denominator**
Incidence	Initial occurrence of PAD-related hospitalization with no PAD hospitalization in the preceding 365 days; If one outpatient event precedes an inpatient event, the initial event date will be the inpatient discharge date	Two consecutive occurrences of the selected PAD-specific codes occurring within 365 days of each other and at least one day apart	Person-time for beneficiaries described for incidence proportions
Source	MedPAR File	Carrier and Outpatient Files	Master Beneficiary Summary File

4.2.6 Statistical Analysis

The ARIC cohort is generally not reflective of the demographic distribution of the United States and, as such, several methods of estimate adjustment were considered. Methods considered but not pursued included adjusting to the mean age of PAD event and adjusting to the internal demographic distribution during a particular year. The method used was direct standardization to the age, sex, and race distribution of the 2005 Medicare population.

Age-standardized annual period prevalence (2003-2012) of PAD with 95% confidence intervals was estimated using direct standardization to the demographic distribution of the 2005 Medicare population ages $\geq$ 65. The following age categories were used to standardize the prevalence estimates: 65-69, 70-74, 75-79, and $\geq$ 80 years of age. Age-standardized incidence

(2005-2012) of PAD with 95% confidence intervals was estimated using direct standardization to the demographic distribution of the 2005 Medicare population ages ≥ 67. The following age categories were used to standardize the prevalence estimates: 67-69, 70-74, 75-79, and ≥ 80 years of age. All estimates were attained as overall, by health care setting (inpatient versus outpatient setting) and by age, race, gender, and race/gender subgroups. All analyses are performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC).

4.2.7 Strengths and Limitations

The proposed study has important strengths that will lead to a contribution in the comprehensive understanding of PAD burden. PAD remains an understudied problem of public health significance for which there is poor health care practitioner and public awareness compared to other cardiovascular diseases [11, 171]. Estimates obtained in this study could indicate that PAD is a relatively common disease in the Medicare Fee-for-Service population and, as such, could help to increase PAD awareness among practitioners who treat elderly populations. Further, by using an administrative data source, this study will provide estimates of PAD in the outpatient setting where information in the extant literature concerning prevalence and incidence is scarce. Finally, stratifying PAD estimates by race and gender could identify high burden groups that could be useful in establishing secondary prevention goals.

The study has also several limitations, the strongest of which is its reduced generalizability due to exclusion of Medicare beneficiaries enrolled in MA programs. MA organizations are not required to provide encounter- or person-level data to CMS Medicare. Information concerning health care encounters for MA participants is, therefore, not available from Medicare claims. An additional limitation related to the ARIC study is a varying and changing level of MA enrollment across the ARIC geographic regions over time; MA enrollment

varies from less than 10% in Washington County to greater than 40% in Forsyth. As our analyses were limited to Medicare beneficiaries not enrolled in MA plans, we acknowledge that we will have missed events among MA enrollees. Studies have reported that individuals with MA are typically a healthier population than an exclusive FFS population [166]; Thus, we are limited to making inferences only to individuals exclusively enrolled in Medicare FFS.

Other study limitations are specific to the use of administrative claims data. Illness severity is not possible to obtain from claims data. It would be helpful, for example, to examine prevalence and incidence by severity of claudication, a level of detail that is unobtainable in claims. Also related to claims limitations, coding inconsistencies are well documented. It is possible that PAD-related diagnosis codes were added to inpatient claims to generate more financial profit, a level of upcoding that could lead to falsely elevated estimates.

4.3 Research Approach for Assessment of Post-Diagnosis Encounters and Case Fatality Following a PAD Diagnosis (Specific Aim 2)

4.3.1 Analytic Sample

The analytic sample for Specific Aim 2 will exclude 1) participants enrolled in MA programs (N=3677), race other than black or white (N=45), and participants that were <65 years of age at time of fee-for-service enrollment (N=418). After applying these exclusion criteria, the final analytic sample included 11,652 ARIC participants.

4.3.2 Cohort Construction

CMS Medicare data linked with the ARIC cohort from 2000-2012 was used for this study. A synthetic cohort of Medicare FFS beneficiaries with an initial inpatient or outpatient PAD event was constructed to investigate the frequency of inpatient and outpatient encounters following a PAD diagnosis. A two-year look back period was chosen to minimize misclassification of incident events and the potential for at least two years of follow-up were

required. Therefore, our enrollment included participants with a PAD diagnosis from 2002 to 2010, with follow-up extending through an administrative censoring date of December 31st, 2012.

Inpatient PAD incidence was defined as a hospitalization for PAD at any time during the study period. Outpatient PAD was defined as at least two claims for outpatient visits (at least 1 day apart) with a PAD code listed on the claim within 12 consecutive months (outpatient PAD diagnosis). If a singular outpatient event preceded an inpatient event within 365 days, the incident event date was the inpatient date of service. Singular outpatient events occurring with no hospitalizations or outpatient events within 365 days were not considered incident PAD events.

4.3.3 Demographic and Comorbidity Assessment

Relevant demographic information (race, gender, education level, and family income) were self-reported at baseline. Age was calculated at the time of the incident PAD diagnosis. Four clinic visits and annual telephone follow-up surveys were used to assess comorbidities of income, education, diabetes, smoking history, hyperlipidemia, hypertension, obesity, coronary heart disease, stroke, heart failure, end stage renal disease, self-rated health, and adequate access to care.

Income was defined as the highest level of family income prior to a PAD diagnosis. The highest level of education completed prior to PAD diagnosis was used to define the education variable. Diabetes mellitus was defined as self-reported history of diabetes at any of the four clinic visits, usage of diabetes medication during the two weeks prior to a visit, a fasting blood glucose level of $\geq$ 126 mg/dl, or a non-fasting blood glucose $\geq$ 200 mg/dl. Hypertension was defined as systolic blood pressure $\geq$ 140 mm Hg or diastolic blood pressure $\geq$ 90 mm Hg at any of the four clinic visits or by antihypertensive medication usage during the two weeks prior to any of the clinic visits. Hyperlipidemia was defined as a total cholesterol $\geq$ 240 mg/dl at any of

the four clinic visits. Smoking status was self-reported at each clinic visit and is defined as any

history or no history for the purposes of this study. Trained technicians measured height and

weight at each clinic visit. Body mass index was calculated as weight in kilograms divided by

height squared (in meters). Obesity was defined as BMI $\geq$ 30.0 kg/m^2. History of coronary heart

disease (CHD), stroke, and heart failure prior to incident PAD diagnosis was based on self-report

at baseline and adjudication of hospitalized events occurring in follow up through the PAD

diagnosis date. End-stage renal disease was defined as estimated glomerular filtration rate

(eGFR) <15.0 mL/min/m^2 using creatinine measurements from the four clinic visits and

employment of the CKD-EPI equation. Self-rated health was defined as poor, fair, good, or

excellent. Adequate access to care was defined as any outpatient encounter within one year of the

incident PAD diagnosis date.

4.3.4 Event Ascertainment

PAD-related outpatient office visits, outpatient diagnostic tests, and inpatient visits and

procedures were identified from the MedPAR records and the Carrier and Outpatient claims files

using ICD-9-CM, CPT-4, HCPCS, and FQHC codes. The particular codes chosen were based on

recommendations from the current literature (See Supplemental Table, Citations). Non PAD-

related outpatient encounters were determined by provider specialty codes including primary

health care visits, cardiology visits, and podiatry visits (Chapter 6, Supplemental Table).

4.3.5 Statistical Analysis

Specific Aim 2 is designed to estimate the frequency of care and outcomes associated

with an incident PAD diagnosis in the outpatient or inpatient settings. Analytically the aim will

be subdivided into: 1) the calculation of age-standardized rates of encounters using direct

standardization methods and 2) time-to-event using product-limit estimation methods, the

subdistribution cumulative incidence function, and propensity score modeling.

In the proposed research, Poisson regression models were to be used to calculated age-adjusted rates of encounters. After careful consideration, an alternative method was suggested. Direct standardization was used to estimate age-standardized rates of inpatient and outpatient encounters with 95% confidence intervals (CI) following a PAD diagnosis. Rates were calculated for PAD and non PAD-related encounters. The denominator for rate estimates included cohort participants' time in continuous FFS enrollment following a PAD diagnosis. Estimates were age-standardized to reflect the age, race, and sex distribution of the 2005 Medicare population ages 67 years and older. Age categories for standardization included 67-69, 70-74, 75-79 and $\geq$ 80 years of age. Estimates were calculated by diagnosis location (inpatient, outpatient) and within diagnosis location in strata of race and gender.

Time to PAD-related encounters (first hospitalization, first re-hospitalization, and first outpatient visit) were calculated based on diagnosis location (outpatient vs. inpatient) from the date of the initial PAD encounter using product limit estimation methods. Product limit methods were chosen over life-table methods because the event times are measured with precision in CMS claims [172]. Encounters were censored at the end of follow-up, as determined by death, enrollment in MA or at December 31st, 2012 (end of our observation period). Analyses accounted for competing risk of death, as opposed to censoring for death. Patient death and death dates were obtained from the Master Beneficiary File.

There are several assumptions related to product limit estimation methods, also called Kaplan-Meier estimation methods [172]. Product limit methods assume the population is closed and that there are no competing risks. This cohort will not be closed and there will be competing risks. As such, I will use a competing risks modeling strategy.

In this study, we have a competing risk of death. It is common in the outcomes literature to treat death as a censored event. An assumption of censoring is that it is non-informative, which means that subsequent hazard of death and the outcome of interest are independent conditional on covariates [172]. In studies where <5% censoring is expected, these competing risks might be negligible resulting in negligible bias. However, in our study we expect substantial mortality (>25%) among the study population and hypothesize that the censoring is informative. Therefore, death should not be treated as a censored event to avoid inducing selection bias in our study. This selection bias can result in underestimation of the outcome being measured.

Analyses, therefore, accounted for death as a competing risk using the cumulative incidence function, a method that computes the hazard of failure associated directly with the event of interest (i.e. hospitalization) along with the hazard of failure associated with the competing risk (i.e. death)[173, 174]. Formula 14 demonstrates the principle used to calculate the cumulative incidence function. Median survival times were estimated in race and gender strata.

$$\text{Formula 14: Cumulative Incidence(t)} = \sum_{j=1}^{s} \frac{e_j}{n_{j-1}} KM_{12}(t_j)$$

where e_j = the number of patients who fail from the event of interest at time t_j

where n_j = the number of patients known to be at risk of failure beyond time t_j

where KM_{12} = the Kaplan-Meier estimate of survival

Propensity score models were used to estimate case fatality by diagnosis setting. The following directed acyclic graph (DAG), shown below in Figure 7, shows the conceptual framework used to determine confounders of the relationship between setting of diagnosis and case fatality. The following DAG is designed to depict the possible measured and unmeasured

confounding in our study. DAGs are informed by subject matter knowledge and literature review

[175]. The minimally sufficient adjustment set for this analysis includes all covariates listed

above (4.3.3).
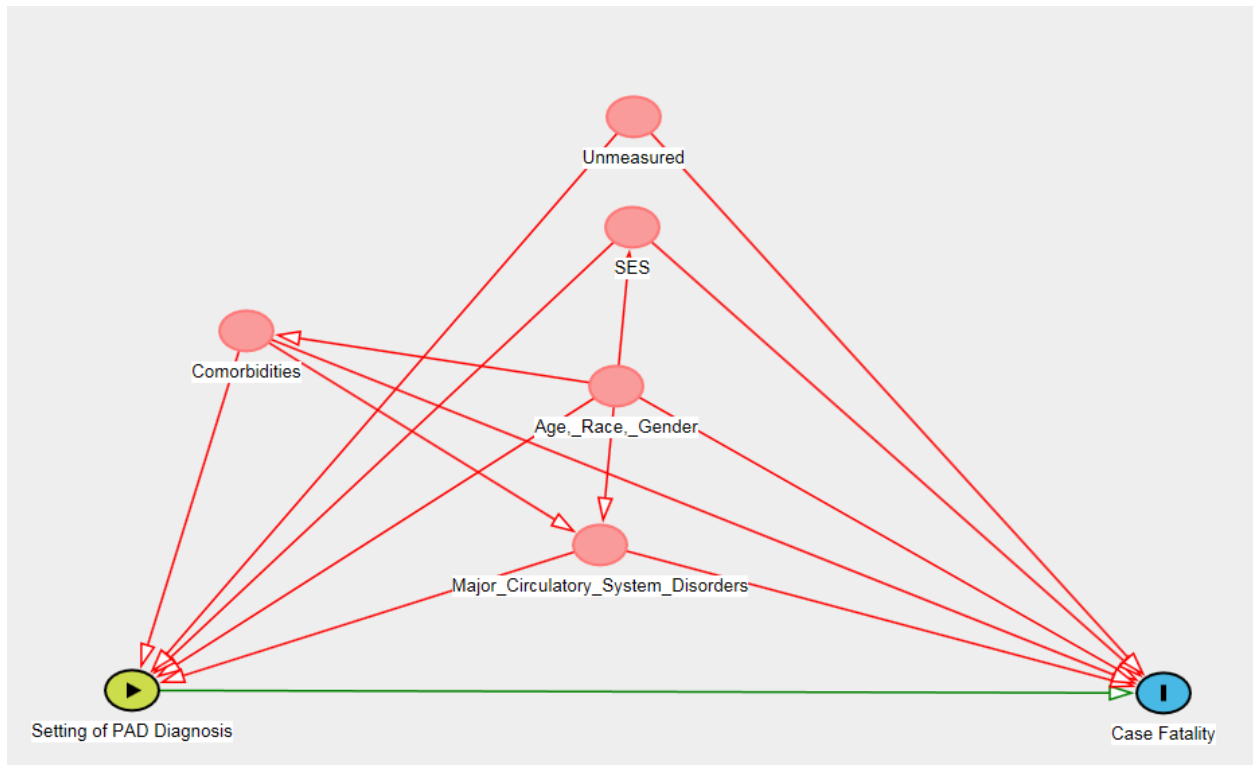
Figure 7. Directed acyclic graph showing the relationship between race and time-to-PAD event

4.3.6 Strengths and Limitations

This study is the first, to our knowledge, that provides information on the post-diagnosis

care following a PAD diagnosis in the outpatient setting. This study could find that participants

with PAD are frequent utilizers of health care services and, as such, could contribute to PAD

awareness. Differences in post-diagnosis care observed by race and gender groups will confer

important information to be used in understanding prevention needs. Finally, this study is a

methodologically replicable study that uses age-standardization techniques and the most recent

recommendations to define chronic disease events.

Limitations were similar to those anticipated for Specific Aim 1. Our exclusion of MA participants means that our findings are not generalizable to individuals with this type of care. Our cohort includes participants who survived until at least 2000 and, thus, could be biased toward healthier individuals with longer survival. As mentioned before, claims are suggest to the biases that arise from using data that reflects billing practices.

4.4 Calibration and Sensitivity Analyses

Administrative claims data reflect billing practices; therefore, diagnostic coding found in claims data is not always accurate in relation to documented diagnoses or procedures. To assess the performance of using claims to quantify inpatient and outpatient PAD, we used hospitalization data and annual follow-up questionnaires.

A hospital record abstraction form was developed to evaluate incident hospitalized PAD events obtained from discharge data available for ARIC cohort participants. We chose one year (calendar year 2007) for our hospitalization sample due to time and resource concerns. PAD codes in any position on the discharge summary were evaluated. Two reviewers performed medical record abstraction and review, with classification and adjudication for disagreement when needed, according to a previously established protocol. Events were classified as definite, probable, or unlikely PAD.

Table 7. ICD-9-CM hospitalizations and adjudication to identify hospitalized PAD

Test Result	Validated PAD (Adjudication)		
	Yes	No	Row sum
ARIC PAD hospitalization	a	b	r_1
Non-PAD hospitalization	c	d	r_2
Column sum	c_1	c_2	N

Comparability ratios (CR) were calculated as an estimate of validity that reflects the overall effect of misclassification from using different data sources to calibrate our inpatient PAD estimates [176]. Comparability ratios (r_1 / c_1) and 95% confidence intervals were calculated based on the 2x2 table shown below (Table XX). A range of comparability ratios were calculated given a range of sensitivity estimates found in the literature [157, 158, 161]. This range of comparability ratios is presented as the range of misclassification associated with using ICD-9-CM codes to estimate PAD prevalence and incidence.

Calibration factors associated with outpatient PAD occurrence were calculated by estimating concordance between information on self-reported PAD events available from the ARIC AFU and outpatient PAD identified from the CMS claims. Information concerning outpatient encounters is available in the ARIC cohort study from annual telephone surveys, during which study participants are asked the following targeted question: "Since we last contacted you has a doctor said that you have peripheral vascular disease or intermittent claudication?" Concordance was assessed by comparing the presence of a PAD outpatient claim with a positive answer to this AFU question from 2007-2010.

Table 8. Agreement between CMS outpatient claims and ARIC cohort outpatient events

ARIC Questionnaire	CMS Claims		
	Yes	No	Row sum
Yes	a	b	r_1
No	c	d	r_2
Column sum	c_1	c_2	N

Prevalence and $Bias\ Adjusted\ Kappa$ (PABAK) $= \dfrac{\sqrt{ad} - \sqrt{bc}}{\sqrt{ad} + \sqrt{bc}}$

Concordance was estimated using prevalence and bias adjusted kappa statistics with 95% confidence intervals to calibrate our outpatient estimates [177]. The 2x2 table shown below (Table XX) was used to calculate PABAK, presented with the unadjusted estimates. A kappa of >0.80 was considered excellent agreement [178].

4.5 Study Power

Using the 2000 census data, approximately 103,000 individuals who were 65 years of age and older are estimated to have been living in the four catchment areas of ARIC in the year 2000. Based on estimates of the MA program penetrance in the ARIC regions, 60% of the 103,000 people (n=62,000) will be fee-for-service Medicare beneficiaries and eligible for inclusion in our study. Further examination of the 2000 census data showed that in that year among those 65 years of age and older in the study population, 51% were 65-74 years of age, 36% were 75-84 years of age, and 14% were ≥ 85 years of age. Additionally, 57% were female and 16% were black.

4.5.1 Specific Aim 1

Specific Aim 1 is a descriptive analysis and, as such, the focus of this aim should be in attaining precise estimates of prevalence and incidence. Based on prior literature, we conservatively estimate 10% (n=6200) of individuals in this Medicare FFS population will have

prevalent PAD each year. Expected annual prevalent events by race-gender strata are shown

below in Table 9.

Table 9. Expected annual prevalent PAD by race-gender groups

	Race-Gender Groups			
	Black Male (7%)	Black Female (9%)	White Male (36%)	White Female (48%)
Individuals with PAD	434	558	2,232	2,976
Individuals with no PAD	3,906	5,022	20,088	26,784
Total population	4,340	5,580	22,320	29,760
Prevalence with 95% CI	10.0 (9.2, 10.9)	10.0 (9.3, 10.8)	10.0 (9.6, 10.4)	10.0 (9.7, 10.3)
Individuals with new* PAD	23	29	116	155

Based on prior work in which I used ARIC cohort data and ICD-9-CM codes to estimate

incident hospitalized PAD events from 1987-2010, I conservatively estimate the incidence of

hospitalized PAD is 2.6 per 1000 persons per year. Extrapolating this estimate to the study

population of 62,000 beneficiaries, 161.2 annual hospitalized PAD events are expected in the

four ARIC communities. A conservative estimate is that the incidence of non-hospitalized PAD

will be the same as the incidence of hospitalized PAD (2.6 per 1000; 161 annual outpatient

events). Therefore, an annual incidence of 322 clinically diagnosed PAD events is expected.

Over the six years of enrollment in the study, 1932 events are expected. This information is

reflected below in Table 10.

Table 10. Study population estimates for four ARIC communities

Population of the ARIC Study catchment areas	Residents >65 years of age	Fee-for-service Medicare beneficiaries*	Incident inpatient events (annual)**	Incident outpatient events (annual)	Total PAD events (annual)**	Total PAD events in years 2004-2009
450,000	103,000	62,000	161	161	322	1,932

* Estimate assumes an overall 40% participation in Medicare Advantage plans across all four ARIC geographic regions
** Estimate assumes an equal annual incidence of PAD in the outpatient and inpatient setting

Table 11 shows the number of PAD events expected among race-gender strata if the PAD event distribution is directly correlated to demographic trait distribution.

Table 11. Expected annual incident PAD by race-gender groups

	Race-Gender Groups			
	Black Male (7%)	Black Female (9%)	White Male (36%)	White Female (48%)
Individuals with new* PAD	23	29	116	155
Individuals with no new PAD	4,805	6,178	24,711	32,948
Total population	4,830	6,210	24,840	33,120
Incidence with 95% CI	0.5 (0.3, 0.7)	0.5 (0.3, 0.7)	0.5 (0.4, 0.6)	0.5 (0.4, 0.6)

* New implies incident PAD

4.5.2 Specific Aim 2

I expect 1,932 initial encounters over the duration of enrollment. Table 12 reflects the number of expected initial encounters in each of the gender/race strata over the entire enrollment period (2004-2009).

Table 12. Expected PAD events by race-gender strata

Black (n=309)		White (n=1,623)	
Male	Female	Male	Female
133	176	698	925

I expect our data will also not be normally distributed. As such, it is appropriate to perform non-parametric tests and to calculate medians with interquartile range (IQR) in place of means and 95% confidence intervals. Table 13, below, shows expected medians and IQRs for a sample of the outcomes under study. The number of events at one year is chosen to provide an appropriate timeframe to measure events.

Table 13. Expected median and IQR values for race-gender strata following inpatient encounter

	Black Females	Black Males	White Females	White Males
	Median (IQR)	Median	Median	Median
Number hospitalizations Within one year	2 (1, 2)	2 (1, 2)	1 (0-1)	1 (0, 1)
Number outpatient visits Within one year	3 (1, 4)	3 (1, 4)	2 (1-3)	2 (1, 3)
Time to first event (days) Re-hospitalization	150 (30, 750)	160 (25, 800)	180 (20, 825)	175 (25, 800)

I hypothesize that the time-to-event analyses will reveal differences by diagnosis location and among gender, race, and race/gender substrata. Power is reported for individuals expected to have the worst outcomes (black females) compared to a referent group projected to have the best outcomes (white males). Using the SAS procedure Proc Power, a cumulative event rate of 50% with differential dropout (20% for white men vs. 40% for black women) over three years, I estimate 80% power with a 2-sided test and alpha=0.05 to detect a hazard ratio of hospitalization of 1.35 when comparing black females to white males. The following figure describes the relationship between power (y-axis) and hazard ratio (x-axis) of hospitalization.
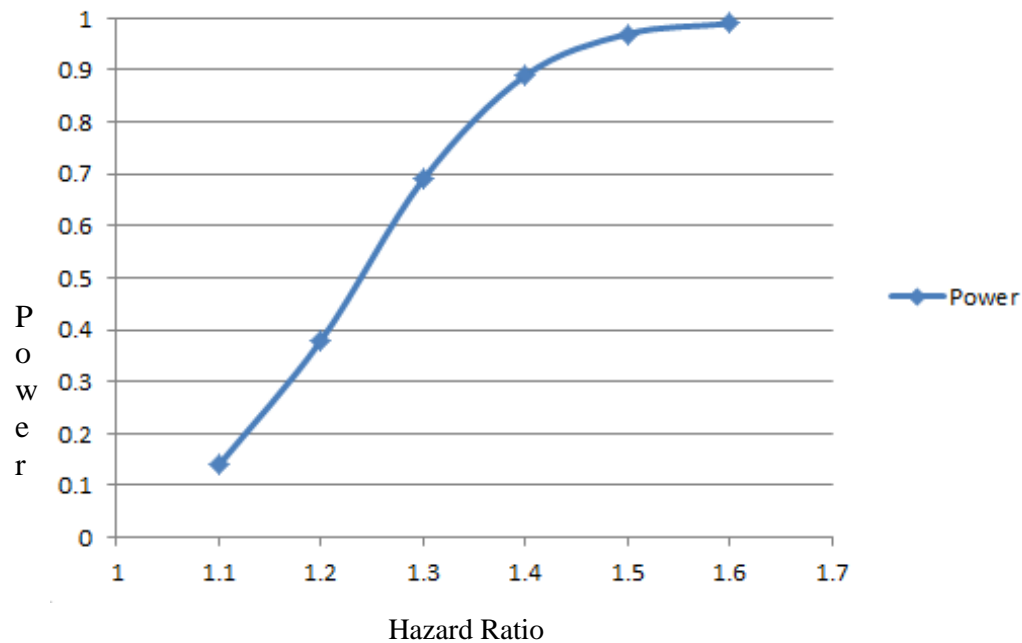
Figure 8. Estimates of hazard ratios of hospitalization by power

Using the same inputs with a cumulative event rate of 25%, I estimate 80% power to detect a hazard ratio of surgical intervention of 1.50 for black females compared to white males. The following figure describes the relationship between power (y-axis) and hazard ratio (x-axis) of surgical intervention.
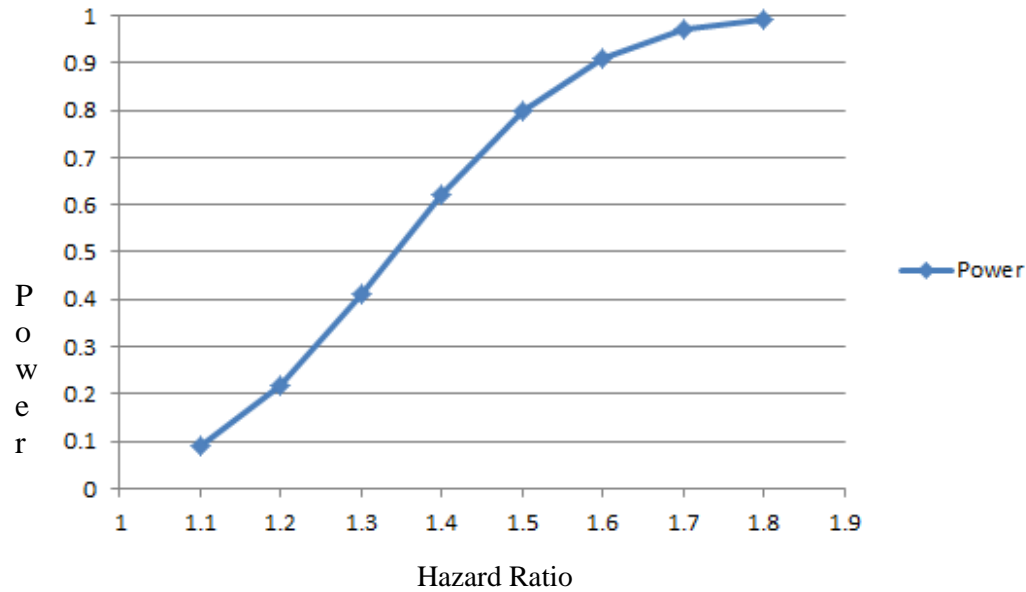
Figure 9. Estimates of hazard ratios of procedure by power

Overall, I expect to have adequate power to complete the proposed aims. Estimates of incidence are expected to be conservative compared to what will actually be seen in the data. Thus, these power curves represent worst case scenarios for detecting hazard ratios. As the expected sample size increases, the power to detect differences in outcomes is expected to increase.

CHAPTER 5. MANUSCRIPT #1: PERIPHERAL ARTERY DISEASE PREVALENCE AND INCIDENCE ESTIMATED FROM BOTH OUTPATIENT AND INPATIENT SETTINGS AMONG MEDICARE FEE-FOR-SERVICE BENEFICIARIES IN THE ATHEROSCLEROSIS RISK IN COMMUNITIES (ARIC) STUDY

5.1 Introduction

Peripheral artery disease (PAD) is a progressive atherosclerotic disorder that can lead to poor quality of life [13], an increased risk of hospitalization and limb amputation [14], high mortality [16] and high costs of care [12]. Early PAD detection in the outpatient setting combined with ambulatory follow-up care could help slow the disease progression and reduce PAD-related hospitalizations and sequelae [15]. However, the extent to which PAD is managed in the outpatient setting is not well documented.

Reported estimates of clinical PAD prevalence and incidence tend to focus on only hospitalized cases [11, 59, 64, 72, 81, 105, 146]. Estimates of disease occurrence both in the inpatient and outpatient setting could provide a broader, more comprehensive understanding of PAD and could lead to improved resource allocation to prevent PAD-related complications. Administrative claims data capture comprehensive services across the spectrum of health care settings, and provide an opportunity for a more inclusive assessment of PAD burden.

We estimated the age-standardized annual period prevalence and incidence of PAD in the inpatient and outpatient setting over a ten-year period (2003-2012), using data from the biracial Atherosclerosis Risk in Communities (ARIC) study cohort [8] linked with the Centers for Medicare and Medicaid Services (CMS) claims information for Medicare fee-for-service (FFS) beneficiaries ages 65 years and older. To further inform prevention efforts, we examined

differences in estimates of annual PAD period prevalence and incidence across strata of age, gender, and race.

5.2 Methods

5.2.1 Study Population

5.2.1.1 The Atherosclerosis Risk in Communities (ARIC) Cohort Study

The biracial ARIC cohort, established to examine the etiology of atherosclerosis and its clinical manifestations, includes 15,792 participants (45-64 years of age at baseline) enrolled between 1987 and 1989. The ARIC cohort was selected by probability sampling from four US communities: Washington County, Maryland (MD), Forsyth County, North Carolina (NC), the city of Jackson, Mississippi (MS), and the suburb cities of Minneapolis, Minnesota (MN) [8]. ARIC participants enrolled continuously for at least one year in Medicare Parts A and B through a fee-for-service plan from 2003-2012 were eligible for inclusion. Data were collected on cohort participants at five clinic examinations and through annual follow-up telephone interviews.

5.2.1.2 Linkage of ARIC Cohort Data with CMS Claims

An interagency agreement between the National Institute for Heart Lung and Blood Disorders (NHLBI) and CMS has enabled Medicare claims information to be obtained for the 14,899 ARIC cohort participants who were Medicare eligible between the years 1991 and 2012. Data for ARIC cohort participants were linked with CMS claims data, matching on participants' social security numbers, gender and date of birth. Of the 14,899 Medicare eligible participants, 14,702 ARIC cohort IDs (98.7%) were matched successfully.

Participant information on enrollment in Medicare FFS was obtained from monthly enrollment indicators for Part A, Part B, and MA buy-in available through annual CMS Medicare Beneficiary Summary files. Continuous enrollment periods were created to indicate uninterrupted CMS Medicare FFS coverage, defined as enrollment in CMS Medicare Part A and

Part B and lack of enrollment in a MA plan. Participants contributed data to calendar years in which they had uninterrupted FFS coverage. Participants were excluded if they had continuous MA enrollment or gaps in FFS coverage due to: 1) missing enrollment information, 2) discontinuation of enrollment, or 3) enrollment in a MA plan at any month in the observation year. Participants <65 years of age and those of race other than black or white were also excluded (see Supplemental Table 1). For those with multiple enrollments periods, the longest enrollment period was selected to give the best opportunity to capture relevant claims. The enrollment period selected was the first enrollment period in 10,144 participants (97%). The final analytic sample included 10,481 ARIC participants with 67,492 person-years of fee-for-service enrollment time.

5.2.1.3 Demographics and Comorbidities

Demographic information on age (at beginning of enrollment year), race and gender was obtained from annual Medicare beneficiary summary files. Age was categorized as: 65-74 years of age and ≥ 75 years of age. The Klabunde adaptation of the Charlson Comorbidity Index (CCI) was used to identify comorbidity burden using claims from the inpatient and outpatient settings [179, 180]. All claims present in each calendar year (prior to a PAD case) were used to calculate an annual CCI score.

5.2.1.4 Ascertainment of PAD

PAD-related outpatient office visits, outpatient diagnostic tests, inpatient visits, and procedures were identified from the Medicare Provider Analysis and Review (MedPAR) records and the Carrier and Outpatient claims files using International Classification of Diseases, Ninth Revision (ICD-9-CM), Current Procedural Terminology, 4th edition (CPT-4), Healthcare Common Procedure Coding System (HCPCS), and Federally Qualified Healthcare Center (FQHC) codes (See Supplemental Table 2) [169].

5.2.1.5 Prevalence of PAD

Annual PAD period prevalence was estimated for 2003-2012 using information on any PAD encounters in the inpatient and outpatient setting, including both prevalence cases from prior years and new incident cases during the year of observation. Overall mean annual prevalence, weighted to reflect the distribution of cases each year, also was estimated. The denominator for annual period prevalence estimates included cohort participants alive at the beginning of the year with continuous enrollment in FFS for the entire year of observation or until death. For each year of observation, prevalent *inpatient* PAD was defined as ≥ 1 hospitalization with a PAD code in any of the twenty-five diagnosis or procedure positions; prevalent *outpatient* PAD was defined as ≥ 1 claim with PAD diagnosis or procedure codes in any of the twelve diagnosis positions or six procedure positions. A sensitivity analysis using ≥ 2 outpatient claims was conducted to address the possibility of rule-out diagnoses (Supplemental Table 3).

5.2.1.6 Incidence of PAD

A two-year look back period was chosen to minimize misclassification of prevalent events as incident events [170]; therefore, the shortest enrollment window of ARIC participants was >24 months. ARIC participants with a prevalent PAD-related inpatient or outpatient code occurring any time within two years of the year in question were excluded from annual incidence analyses. Annual incidence rates (IR) are presented for the years 2005-2012. Overall mean incidence, weighted to reflect the distribution of events each year, was also estimated. The denominator for annual incidence estimates included cohort participants' time at risk in continuous enrollment during the year of observation or until death if it occurred during the year of observation.

Annual inpatient PAD incidence was defined as ≥ 1 hospitalization with a PAD-related ICD diagnosis or procedure code during each year of observation. Annual outpatient PAD incidence was defined as ≥ 2 claims within 12 consecutive months with a PAD-related ICD, CPT, HCPCS, or FQHC code; the claims had to occur ≥ 1 day apart and the incident date was defined as the date of the second claim. If a singular outpatient encounter preceded an inpatient encounter within 365 days, the incident date was the inpatient date of discharge. Singular outpatient encounters occurring with no hospitalizations or outpatient encounters within 365 days were not considered incident PAD. Each individual contributed between 1 to 12 months to each yearly estimate of incidence. Time contributed to the study for each ARIC participant was converted to and reported in person-years.

5.2.2 Statistical Analysis

Direct standardization was used to estimate age-standardized overall and annual prevalence of PAD with 95% confidence intervals (CI) from 2003 to 2012. Direct standardization was used to estimate age-standardized overall and annual incidence of PAD (per 1000 person-years) with 95% CI from 2005 to 2012. Prevalence estimates were age-standardized to reflect the age, race, and sex distribution of the 2005 Medicare population ages 65 years and older. Age categories for standardization of prevalence estimates included 65-69, 70-74, 75-79, and ≥ 80 years of age. Incidence estimates were age-standardized to reflect the age, race, and sex distribution of the 2005 Medicare population ages 67 years and older given a two-year look back period for excluding prevalence cases. Estimates were calculated overall, by health care setting (inpatient versus outpatient setting) and by age, race, gender, and race/gender subgroups. Age categories for incidence estimate standardization included 67-69, 70-74, 75-79, and ≥ 80 years of age. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Written

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informed consent was obtained from participants and all institutional review boards approved the study.

5.3 Results

The 10,481 ARIC cohort members who met eligibility requirements generally reflected the demographic distribution in the original ARIC cohort at baseline. The majority were female (58%) and white (76%) with black males (8%) as the least represented group (Table 14). Mean comorbidity scores were similar across race, gender, and race/gender strata. Mean comorbidity score differed by age categories, such that participants 75 years of age and older had higher mean comorbidity scores as compared to participants 65 to 74 years of age (Table 14).

5.3.1 Age-standardized Annual Prevalence and Weighted Mean Annual Prevalence of PAD

Age-standardized annual and weighted mean annual estimates of the prevalence of PAD across all study years (2003-2012), overall and stratified by health care setting are provided in Table 15. The weighted mean annual PAD period prevalence was 12.4% (95% CI: 12.2%, 12.8%). Overall age-standardized prevalence varied modestly from year to year, ranging from 10.3% (95% CI: 8.6%, 12.0%) to 13.5% (95% CI: 12.4%, 14.6%).

Higher annual PAD period prevalence was identified in the outpatient setting as compared to the inpatient setting (11.8% vs. 1.6%; Table 15). The majority of all unique PAD claims (>70%) identified were from outpatient settings. Prevalence of outpatient PAD claims ranged across years of observation from 9.5% (95% CI: 7.9%, 11.2%) in 2003 to 12.9% (95% CI: 11.9%, 14.0%) in 2012. By comparison, prevalence of inpatient PAD ranged across years of observation from 1.4% (95% CI: 1.1%, 1.7%) in 2005 to 1.8% (95% CI: 1.4%, 2.1%) in 2012.

Estimates of annual PAD period prevalence were further stratified by demographic groups. Age-standardized annual PAD period prevalence and mean annual prevalence was consistently higher among those 75 years and older as compared to those 65 to 74 years (Figure

10). Weighted mean annual PAD prevalence among those 75 years and older and those 65 to 74 was 16.8% and 8.4%, respectively. From 2003 to 2012, annual PAD prevalence in the age group 75 years and older ranged from 12.5% (95% CI: 9.0%, 15.9%) in 2003 to 18.5% (95% CI: 17.1%, 20.0%) in 2012. Annual PAD prevalence among those ages 65 to 74 years ranged from 8.0% (95% CI: 7.2%, 8.8%) to 9.0% (95% CI: 8.0%, 10.0%) over the same time frame.

Blacks had a higher mean annual prevalence of PAD compared to whites (15.6% vs. 11.4%), and had a higher annual prevalence of PAD across most years of the observation period (Figure 11). From 2003 to 2012, PAD prevalence among blacks ranged from 13.8% (95% CI: 10.4%, 17.2%) to 17.3% (95% CI: 15.0%, 19.7%) while PAD prevalence among whites ranged from 9.0% (95% CI: 7.1%, 10.9%) to 12.8% (95% CI: 11.6%, 14.0%). Regarding race/gender stratification, black females had the highest weighted mean annual PAD prevalence (16.9%), followed by black males (13.2%), white males (12.1%), and white females (10.9%; Supplemental Table 4).

Age-standardized prevalence of PAD did not differ significantly by gender alone in any year of observation (2003 to 2012). Overall, females had a higher prevalence of PAD although not statistically significant across all years of this study (Supplemental Table 5).

5.3.2 Age-standardized Annual Incidence and Weighted Mean Annual Incidence of PAD

Overall and age-standardized annual estimates of the incidence of PAD across all observation years (2005-2012), stratified by health care setting are provided in Table 16. The mean age-standardized PAD incidence rate (IR) across all observation years (2005-2012) was 26.8 (95% CI: 25.1, 28.6) per 1000 person-years. The age-standardized incidence of PAD remained relatively consistent across the study period (2005 to 2012), ranging from 25.6 (95% CI: 21.0, 30.4) per 1000 person-years in 2007 to 30.3 (95% CI: 24.9, 35.7) per 1000 person-years in 2012 (Table 16).

The first PAD-related claim most commonly was found in the outpatient setting (83%), at more than 5 times the incidence in the inpatient setting (Table 16). Rates of PAD incidence in the outpatient setting per 1000 person-years ranged from 20.0 (95% CI: 15.2, 24.8) to 26.0 (95% CI: 21.0, 30.9). Records of PAD-related hospitalizations were rare; for the years 2005-2012, the annual age-standardized incidence rates per 1000 person-years ranged from 3.2 (95% CI: 1.5, 4.8) in 2011 to 6.4 (95% CI: 3.4, 9.3) in 2005.

Annual estimates of PAD incidence were stratified by demographic groups. Age-standardized annual PAD incidence was different by age strata at all years examined except 2009 and 2012 (Figure 12). Incidence of PAD was significantly higher among those 75 years and older compared to those 65 to 74 years of age. From 2005 to 2012, estimates of annual PAD incidence among those 75 years and older ranged from 31.6 (95% CI: 24.1, 39.2) in 2009 to 37.2 (95% CI: 29.5, 45.0) per 1000 person-years in 2012. Estimates among those 65-74 years of age ranged from 16.2 (95% CI: 12.3, 20.1) per 1000 person-years to 21.7 (95% CI: 14.3, 29.1) per 1000 person-years over the same time period.

PAD incidence rates were different by race (Figure 13), with a higher mean annual (2005-2012) PAD incidence among blacks (31.3; 95% CI: 27.3, 35.4) compared to whites (25.4; 95% CI: 23.5, 27.3). Blacks had a higher incidence rate of PAD than whites across most observation years, although annual differences were attenuated due to low precision resulting from a small sample size among blacks (Figure 13). Incidence rates of PAD among blacks ranged from 28.4 (95% CI: 16.4, 40.3) to 32.7 (95% CI: 21.3, 44.1) per 1000 person-years, while incidence of PAD among whites ranged from 23.2 (95% CI: 17.1, 29.4) to 29.6 (95% CI: 23.7, 35.6) per 1000 person-years.

The age-standardized annual incidence of PAD did not differ significantly by gender (Supplemental Table 6). Mean annual incidence of PAD (2005-2012) was higher among black males and black women (31.8 and 30.9 per 1000 person-years, respectively) than among white males and white females (25.5 and 25.3 per 1000 person-years, respectively), although results were not statistically significant. Small sample sizes precluded *annual* assessment of PAD incidence across race/gender groups (Supplemental Figure 1).

5.4 Discussion

We found that the majority of all clinical PAD encounters occurred in the outpatient setting among a biracial, probability-based sample of four US communities including men and women 65 years of age and older with enrollment in a Medicare fee-for-service program. Studies which focus exclusively on hospitalized events underreport burden and provide a perspective of PAD skewed toward more severe manifestations occurring later in the course of the disease. Blacks had a significantly higher prevalence of PAD prevalence than whites, including both men and women. Incidence of PAD was also higher among blacks, although the relatively small proportion of blacks in our study (24%) limited our ability to make inferences in race- and race/gender- stratified analyses of PAD incidence.

While sources of administrative claims are increasingly used to study PAD burden, methodologic and source population differences make it difficult to compare PAD estimates across studies. In particular, it is well-documented that PAD prevalence increases with age [163, 169]; however, prior claims-based work did not report age-adjusted estimates of PAD prevalence, thus limiting comparisons across populations with differing age groups. For example, a recent study using the MarketScan database reported higher annual PAD prevalence among Medicare beneficiaries than the present study (14-21% vs. 10%-14%) [169]; however, the

population in the MarketScan study was older and had greater comorbidity. Conversely, a study of a healthier group of managed care enrollees found a lower prevalence of PAD (2%) than what was observed here [14]. In context of these other studies, age-standardized estimates of PAD prevalence (overall: 12.4%) in the present study are within the expected range given the estimates from younger and older populations.

Estimates of PAD incidence are rare in the literature and, as with prevalence studies, are difficult to compare due to differing study populations and inconsistency in the definition of PAD. Important in using administrative claims data for the estimation of disease incidence is the use of an appropriate look-back period for the correct identification of index events. Recent analyses suggest that for most chronic diseases a two year look-back period is necessary for the exclusion of pre-existing conditions [170]. Studies that do not include a sufficiently long look-back period have the potential to reflect prevalent disease that is misclassified as incident (up to 30%) [170]. Results of the current study, in which we employed a two-year look back period, suggest that 2-3% (26.8 per 1000 person-years) of Medicare beneficiaries had an incident PAD occurrence within any particular observation year (2005-2012). While our incidence estimates are lower, they are comparable to existing studies [169].

A significant body of evidence suggests differences in PAD burden by race [181]. Blacks were observed to have a higher PAD prevalence than whites in the NHANES, San Diego Population, Multi-Ethnic Study of Atherosclerosis (MESA), and Cardiovascular Health (CHS) studies [64, 69, 72, 147]. In the current study, we found that the mean annual prevalence and incidence of PAD was significantly higher among blacks as compared to whites, which confirms these prior observations. The current study adds the finding that PAD burden is higher among blacks despite a known access to care issue in this population. This study further adds to

estimates of PAD burden by providing race-gender analyses. We observed that black females consistently had the highest PAD prevalence while white females had the lowest PAD prevalence across all years of observation (2003-2012; Supplemental Table 4). Black males had the highest mean PAD incidence followed by black females (Supplemental Figure 1). Findings from this study suggest that blacks ages 65 years and older have a higher burden of PAD and could, therefore, benefit from prevention efforts targeting individuals well before they become age-eligible for Medicare.

The American Heart Association (AHA) recently identified gender-specific estimates of PAD, particularly for women, as a knowledge gap in the literature. The present study answers a challenge from the AHA to produce age-standardized, gender-specific estimates [182]. Males in this study had nearly identical age-standardized PAD estimates compared to females overall (mean annual prevalence: 12.4% vs. 12.5%; mean annual incidence: 26.9 vs. 26.8 per 1000 person-years) and at most years of observation. Findings from our study, which identified minimal differences in PAD burden by gender, are in accordance with the limited literature regarding gender-specific estimates of PAD prevalence and incidence and contribute important information to a perceived knowledge gap [105, 163].

5.4.1 Strengths and Limitations

The most important strength of this study is the inclusion of outpatient in addition to inpatient clinical encounters in the assessment of prevalent and incident PAD. Prior studies have provided limited information on the burden of PAD stratified by the setting of health care delivery (inpatient versus outpatient). Although a study by Hirsch et al (2008) found that inpatient visits represent up to 90% of PAD-related costs [162], more than 70% of *all* PAD claims in the current study were found in the outpatient records. In addition, more than 80% of all *incident* PAD events were found occurring in the outpatient setting. These estimates are age-

standardized and look back periods for incidence are in accordance with recent

recommendations, providing a further strength of this study.

As this study was based on inpatient and outpatient care among CMS Medicare enrollees

in FFS programs, our estimates are not generalizable to Medicare beneficiaries enrolled in MA,

who have been reported to be healthier than those in FFS [166]. Our estimates reflect cohort

survivors and we did not attempt to quantify PAD prior to enrollment in fee-for-service in 2003.

Administrative claims data reflect billing practices and, therefore, diagnostic coding found in

claims data is not always accurate in relation to documented diagnoses or procedures. Codes

selected were not independently validated, which could lead to misclassification of PAD

occurrence. Upcoding might increase billing by as much as 15% [183] and illness severity is not

readily obtainable from claims data.

5.4.2 Conclusions

This study addresses an important gap in the existing literature by providing estimates of

PAD in the outpatient setting where the majority of PAD burden was found. Individuals whose

PAD can be managed in the outpatient setting are an important subgroup for potentially targeted

interventions to prevent PAD-related hospitalizations and complications, such as limb

amputation. PAD estimates stratified by race corroborated other population-based studies that

reported a higher burden among blacks compared to whites; future work should focus on

identifying effective prevention of PAD and its sequelae in this group.

Table 14. ARIC* fee-for-service enrollees by year and demographic groups, 2003-2012

	2003 N=7,293	2004 N=7,678	2005 N=7,708	2006 N=7,372	2007 N=7,060	2008 N=6,995	2009 N=6,504	2010 N=6,183	2011 N=5,914	2012 N=5,546
Age, %										
65-74	72	69	66	63	60	57	54	49	44	40
≥ 75	28	31	34	37	40	43	46	51	56	60
Gender, %										
Female	57	57	58	57	58	58	59	60	60	61
Male	43	43	42	43	42	42	41	40	40	39
Race, %										
Black	26	26	26	23	21	22	23	24	24	24
White	74	74	74	77	79	78	77	76	76	76
Race/gender, %	17	17	18	15	14	14	15	16	16	16
Black Female	9	9	9	8	7	7	8	8	8	8
Black Male	40	40	40	42	44	44	45	44	44	44
White Female	34	34	33	35	35	34	32	32	32	32
White Male										
Overall mean comorbidity score[†] (standard deviation)	1.7 (2.2)	1.8 (2.3)	1.9 (2.2)	1.9 (2.2)	2.1 (2.3)	2.1 (2.3)	2.3 (2.5)	2.4 (2.5)	2.5 (2.5)	2.6 (2.6)
Overall median comorbidity score[+] (IQR)	1 (0, 3)	1 (0, 3)	1 (0, 3)	1 (0, 3)	2 (0, 3)	2 (0, 3)	2 (0, 3)	2 (0, 3)	2 (0, 4)	2 (1, 4)

*Atherosclerosis Risk in Communities (ARIC) cohort study; [†] Klabunde adaptation of Charlson comorbidity index

Table 15. Age-standardized* overall and annual prevalence (%) of peripheral artery disease claims, overall and by health care setting. The ARIC† study (2003-2012)

	Prevalence % (95% CI)		
	Overall	Outpatient Setting	Inpatient Setting
2003	10.3 (8.6, 12.0)	9.5 (7.9, 11.2)	1.5 (1.0, 1.9)
2004	11.2 (10.0, 12.4)	10.4 (9.3, 11.6)	1.8 (1.3, 2.3)
2005	11.4 (10.5, 12.4)	10.8 (9.8, 11.7)	1.4 (1.1, 1.7)
2006	12.1 (11.1, 13.0)	11.5 (10.6, 12.4)	1.8 (1.4, 2.1)
2007	12.3 (11.4, 13.2)	11.5 (10.7, 12.4)	1.4 (1.1, 1.7)
2008	11.8 (10.9, 12.6)	11.2 (10.4, 12.0)	1.6 (1.3, 1.9)
2009	12.6 (11.7, 13.4)	12.0 (11.1, 12.8)	1.4 (1.1, 1.7)
2010	13.2 (12.3, 14.1)	12.7 (11.8, 13.5)	1.4 (1.1, 1.7)
2011	13.1 (12.2, 14.0)	12.7 (11.7, 13.5)	1.6 (1.3, 1.9)
2012	13.5 (12.4, 14.6)	12.9 (11.9, 14.0)	1.8 (1.4, 2.3)
Weighted Mean	12.4 (12.2, 12.8)	11.8 (11.5, 12.1)	1.6 (1.5, 1.7)

* Standardized to reflect age distribution of 2005 Medicare population; † Atherosclerosis Risk in Communities (ARIC) cohort study

Table 16. Age-standardized* overall and annual incidence (per 1000 person-years) of peripheral artery disease claims, overall and by health care setting of incident claim. The ARIC† study (2005-2012)

	Overall	Outpatient	Inpatient
	Age-standardized rate[‡]	Age-standardized rate [‡]	Age-standardized rate [‡]
2005	26.6 (20.7, 32.6)	20.3 (15.1, 25.4)	6.4 (3.4, 9.3)
2006	25.8 (20.3, 31.3)	20.0 (15.2, 24.8)	5.8 (3.1, 8.5)
2007	25.6 (20.8, 30.4)	21.5 (17.2, 25.9)	4.0 (2.0, 6.1)
2008	26.0 (21.0, 31.0)	21.2 (16.7, 25.7)	4.8 (2.7, 6.9)
2009	25.6 (20.9, 30.3)	20.6 (16.4, 24.8)	5.0 (2.9, 7.1)
2010	29.3 (24.2, 34.4)	25.9 (21.1, 30.7)	3.4 (1.7, 5.0)
2011	26.5 (21.7, 31.4)	23.3 (18.8, 27.9)	3.2 (1.5, 4.8)
2012	30.3 (24.9, 35.7)	26.0 (21.0, 30.9)	4.3 (3.7, 5.1)
Weighted Mean	26.8 (25.1, 28.6)	22.4 (20.8, 24.0)	4.4 (3.7, 5.1)

[*] Standardized to reflect age distribution of 2005 Medicare population; [†] Atherosclerosis Risk in Communities (ARIC) cohort study; [‡] rates are per 1000 person-years
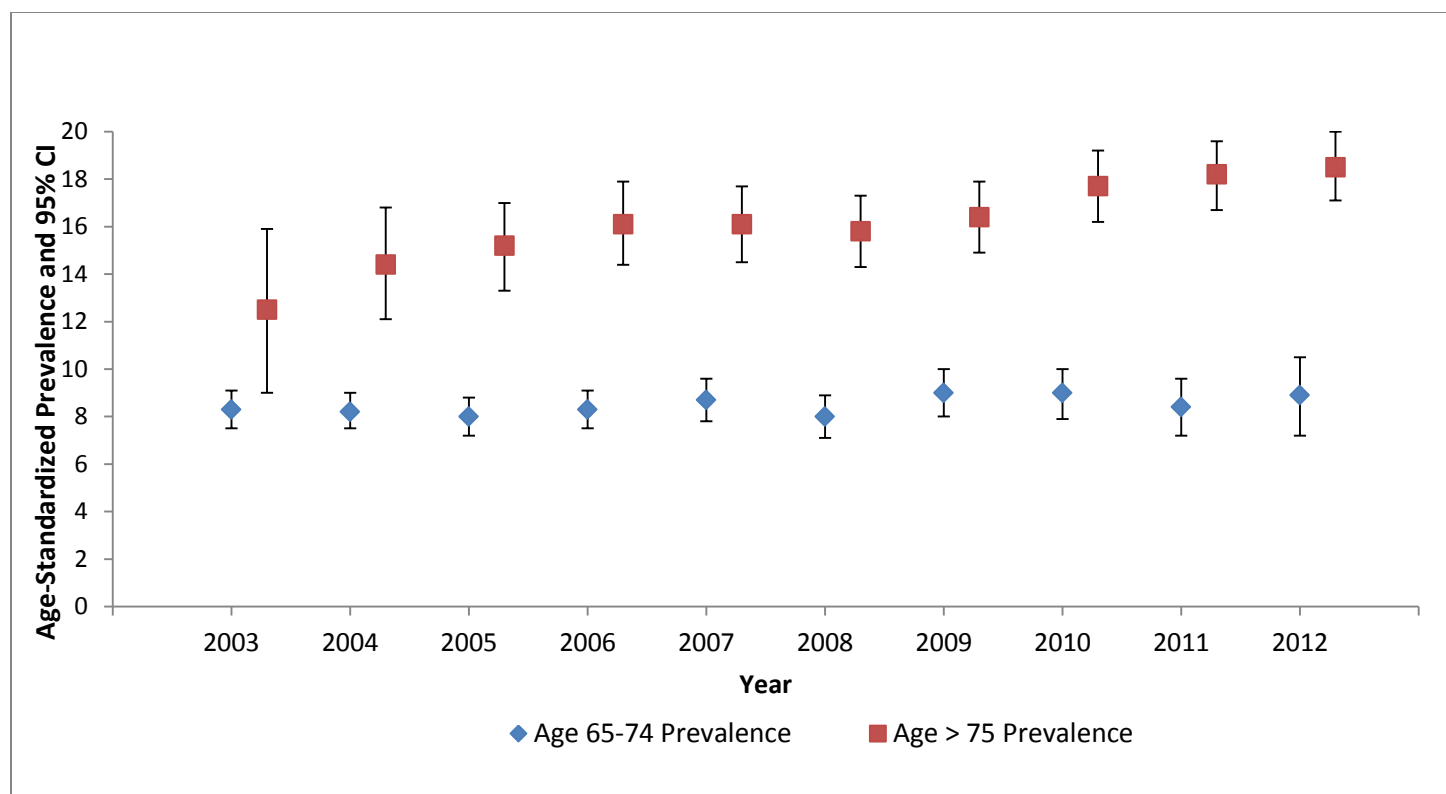
ARIC= Atherosclerosis Risk in Communities; Estimates are standardized to 2005 Medicare population

Figure 10. Age-standardized annual prevalence of PAD, by age groups. The ARIC Study, 2003-2012
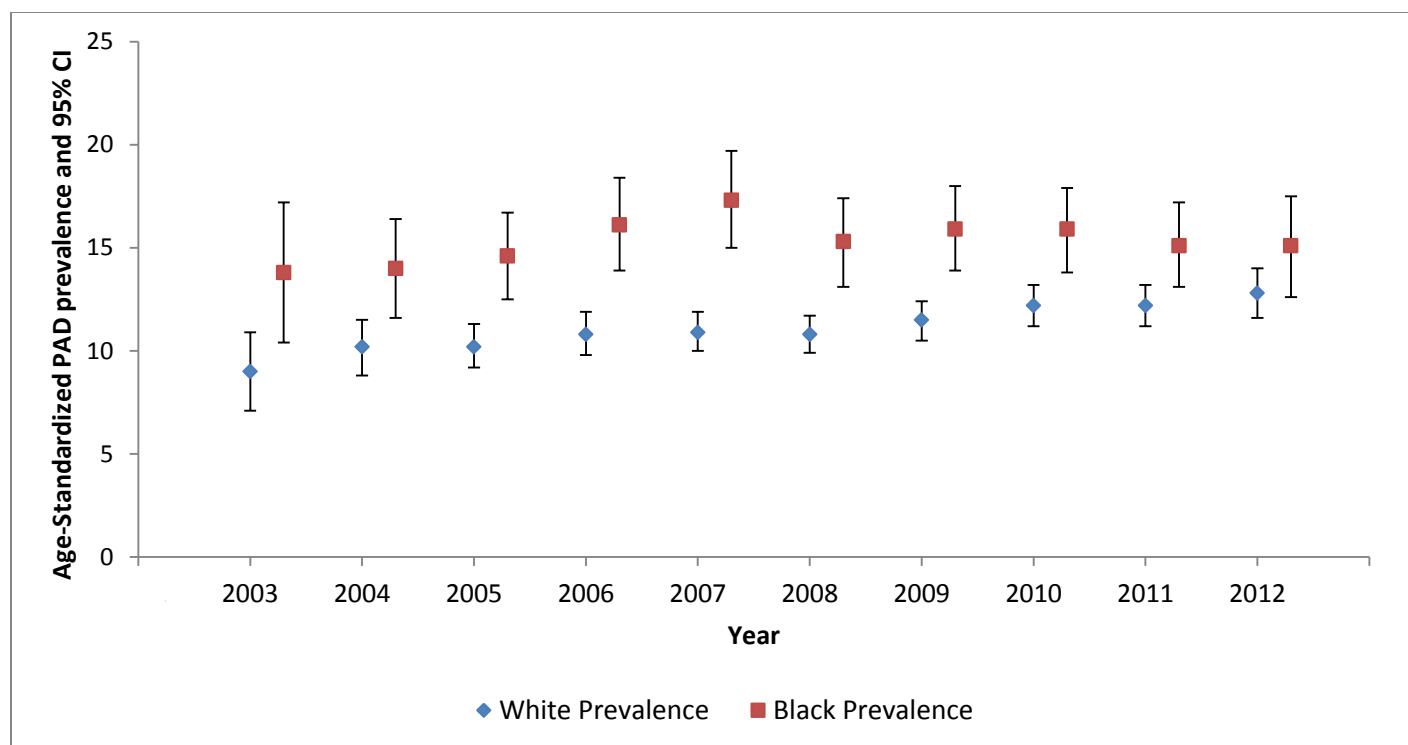
ARIC= Atherosclerosis Risk in Communities; Estimates are standardized to 2005 Medicare population

Figure 11. Age-standardized annual prevalence (%) of PAD, by race groups. The ARIC Study, 2003-2012

ARIC= Atherosclerosis Risk in Communities; Estimates are standardized to 2005 Medicare population; rates are per 1000 person-years

Figure 12. Age-standardized annual incidence (per 1000 person-years) of PAD, by age groups. The ARIC Study, 2005-2012

ARIC= Atherosclerosis Risk in Communities; Estimates are age-standardized to 2005 population; rates are per 1000 person-years

Figure 13. Age-standardized annual incidence of PAD (per 1000 person-years), by race groups. The ARIC study, 2005-2012

Supplemental Table 1. Exclusion criteria to arrive at final dataset. The ARIC Study, 2003-2012

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Total in dataset	9,948	10,380	10,821	11,250	11,563	11,657	11,440	11,085	10,718	10,355
Exclusions for HMO	2,013	2,140	2,640	3,478	4,200	4,495	4,863	4,856	4,759	4,670
race	39	44	44	45	41	40	41	41	40	37
age <65	603	518	429	355	262	127	32	5	5	2
Final Enrollees	**7,293**	**7,678**	**7,708**	**7,372**	**7,060**	**6,995**	**6,504**	**6,183**	**5,914**	**5,546**

ARIC= Atherosclerosis Risk in Communities

Supplemental Table 2. International Classification of Diseases, Ninth Revision (ICD-9-CM), Current Procedural Terminology, 4th edition (CPT-4), Healthcare Common Procedure Coding System (HCPCS), and Federally Qualified Healthcare Revenue Center (FQHC) codes used to identify peripheral artery disease in claims

Code Type	Codes
ICD-9-CM	249.70, 249.71, 250.70, 250.71, 250.72, 250.73, 440.20, 440.21, 440.22, 440.23, 440.24, 440.29, 440.30, 440.31, 440.32, 440.4, 440.8, 440.9, 443.1, 443.22, 443.81, 443.89, 443.9, 444.22, 444.81, 445.02 * 38.08, 38.16,, 38.18, 38.38, 38.48, 39.25, 39.29, 39.49, 39.50, 39.56, 39.57, 39.58, 39.90, 84.10, 84.12, 84.13, 84.14, 84.15, 84.16, 84.17, 84.18, 84.3, 84.91
HCPCS/ CPT-4	27295, 27590, 27591, 27592, 27594, 27596, 27598,27599,27880, 27881, 27882, 27888, 27889, 28800, 28805, 28810, 28820, 28825, 35221, 35226, 35256, 35286, 35302, 35303, 35304, 35305, 35306, 35331, 35351, 35355, 35361, 35363, 35371, 35372, 35381, 35452, 35454, 35456, 35459, 35470, 35472, 35473, 35474, 35480, 35481, 35482, 35483, 35485, 35490, 35491, 35492, 35493, 35495, 35500, 35521, 35533, 35537, 35538, 35539, 35540, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35583, 35585, 35587, 35621, 35623, 35646, 35647, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 35681, 35682, 35700, 35875, 35876, 35879, 35881, 35883, 35884, 35903 * 35683, 35686, 35571, 72191, 72198, 73706, 73725, 74175, 74185, 75630, 75631, 75635, 75710, 75711, 75712, 75716, 75717, 75718, 93922, 93924, 93925, 93926, 93978, 99201, 99202, 99203, 99204, 99205, 99211, 99212, 99213, 99214, 99215, 99216, 99241, 99242, 99243, 99244, 99245, 99385, 99386, 99387, 99395, 99396, 99397
Revenue Center Codes	*0320,0321,0322,0323,0324,0329,0360,0361,0370,0371,0372,0379,0402,0490,0499,0510,0517,0519,0520,0521,0610,0616,0710,0760, 0761,0762,0769,0921

* Must be accompanied with a PAD-related ICD-9-CM code

Supplemental Table 3. Sensitivity analysis comparing requiring two outpatient claims versus

	Outpatient PAD Prevalence[+] % (95% CI)	Outpatient PAD Prevalence[*] % (95% CI)
2003	4.0 (3.1, 4.9)	9.5 (7.9, 11.2)
2004	6.7 (5.7, 7.6)	10.4 (9.3, 11.6)
2005	6.7 (5.9, 7.4)	10.8 (9.8, 11.7)
2006	7.2 (6.5, 7.9)	11.5 (10.6, 12.4)
2007	7.3 (6.6, 7.9)	11.5 (10.7, 12.4)
2008	7.6 (6.9, 8.2)	11.2 (10.4, 12.0)
2009	8.0 (7.4, 8.8)	12.0 (11.1, 12.8)
2010	8.7 (8.0, 9.5)	12.7 (11.8, 13.5)
2011	9.5 (8.7, 10.3)	12.7 (11.7, 13.5)
2012	10.0 (9.1, 10.9)	12.9 (11.9, 14.0)
Weighted Mean	7.9 (7.7, 8.2)	11.8 (11.5, 12.1)

[+] Requires two outpatient claims in a year for prevalence estimates; [*] Requires one outpatient claim for prevalence estimates; ARIC= Atherosclerosis Risk in Communities; Estimates are standardized to 2005 Medicare population

Supplemental Table 4. Age-standardized annual prevalence of peripheral artery disease in the inpatient and outpatient setting by race-sex groups. The ARIC Study, 2003-2012

	White Males		White Females		Black Males		Black Females	
	Prevalence %	95% CI	Prevalence %	95% CI	Prevalence %	95% CI	Prevalence %	95% CI
2003	9.6	7.4, 11.8	8.8	5.6, 12.0	10.1	6.6, 13.6	16.2	10.8, 21.6
2004	10.9	9.1, 12.8	9.4	7.4, 11.3	10.5	7.8, 13.3	16.6	12.7, 20.4
2005	11.2	9.7, 12.8	9.4	7.9, 10.8	13.5	10.5, 16.4	15.4	12.3, 18.4
2006	12.6	11.0, 14.1	9.2	7.9, 10.5	14.1	10.9, 17.3	16.7	13.7, 19.8
2007	12.0	10.6, 13.4	10.2	8.9, 11.4	15.0	11.5, 18.5	18.7	15.5, 21.9
2008	11.7	10.3, 13.1	10.0	8.8, 11.2	15.3	11.8, 18.8	15.0	12.3, 17.7
2009	12.2	10.7, 13.7	10.9	9.6, 12.1	14.6	11.3, 17.9	16.5	13.8, 19.1
2010	13.0	11.4, 14.6	11.7	10.4, 13.0	12.9	9.8, 16.1	17.8	15.1, 20.6
2011	12.1	10.5, 13.8	12.4	11.0, 13.7	11.6	8.4, 14.8	17.2	14.4, 19.9
2012	12.3	10.4, 14.2	13.3	11.7, 14.8	13.6	9.3, 17.9	16.2	13.1, 19.2
Weighted Mean	12.1	11.6, 12.5	10.9	10.4, 11.3	13.2	12.2, 14.2	16.9	16.0, 17.8

ARIC= Atherosclerosis Risk in Communities; Estimates are standardized to 2005 Medicare population

Supplemental Table 5. Age-standardized annual prevalence of peripheral artery disease in the inpatient and outpatient setting by gender. The ARIC Study, 2003-2012

	Male		Female	
	Prevalence %	95% CI	Prevalence %	95% CI
2003	9.7	7.8, 11.7	11.1	8.2, 13.9
2004	10.8	9.2, 11.7	11.6	9.8, 13.4
2005	11.8	10.4, 13.2	11.1	9.8, 12.5
2006	13.0	11.6, 14.4	11.1	10.9, 12.3
2007	12.6	11.3, 13.9	12.1	10.1, 13.3
2008	12.4	11.1, 13.7	11.2	11.2, 13.6
2009	12.7	11.4, 14.1	12.4	12.1, 14.6
2010	13.1	11.7, 14.5	13.4	12.5, 15.0
2011	12.2	10.7, 13.6	13.8	12.5, 15.0
2012	12.8	11.0, 14.5	14.2	12.8, 15.6
Weighted Mean	12.4	12.0, 12.8	12.6	12.1, 12.9

ARIC= Atherosclerosis Risk in Communities; Estimates are standardized to 2005 Medicare population

Supplemental Table 6. Age-standardized annual incidence of peripheral artery disease in the inpatient and outpatient setting by gender. The ARIC Study, 2005-2012

	Male			Female		
	Events	Person-time	Age-standardized rate	Events	Person-time	Age-standardized rate
2005	66	2,667	31.5 (22.0, 41.0)	72	3,702	22.1 (15.0, 29.2)
2006	57	2,530	31.1 (22.0, 40.1)	63	3,512	20.5 (14.2, 26.8)
2007	64	2,391	28.7 (21.1, 36.3)	70	3,382	23.4 (17.3, 29.5)
2008	51	2,319	25.2 (18.0, 32.4)	70	3,352	26.6 (19.7, 33.5)
2009	57	2,096	28.0 (20.6, 35.4)	66	3,106	24.2 (18.0, 30.5)
2010	50	1,949	26.2 (18.9, 33.5)	84	2,944	31.6 (24.6, 38.7)
2011	41	1,817	23.2 (16.0, 30.4)	76	2,786	29.0 (22.4, 35.7)
2012	48	1,655	27.4 (19.2, 35.6)	82	2,561	32.8 (25.5, 40.1)
Weighted Mean	434	17,423	26.9 (24.3, 29.5)	583	25,346	26.8 (24.5, 29.2)

ARIC= Atherosclerosis Risk in Communities; Estimates are standardized to 2005 Medicare population

Age-standardized Incidence for Blacks, 2005-2012

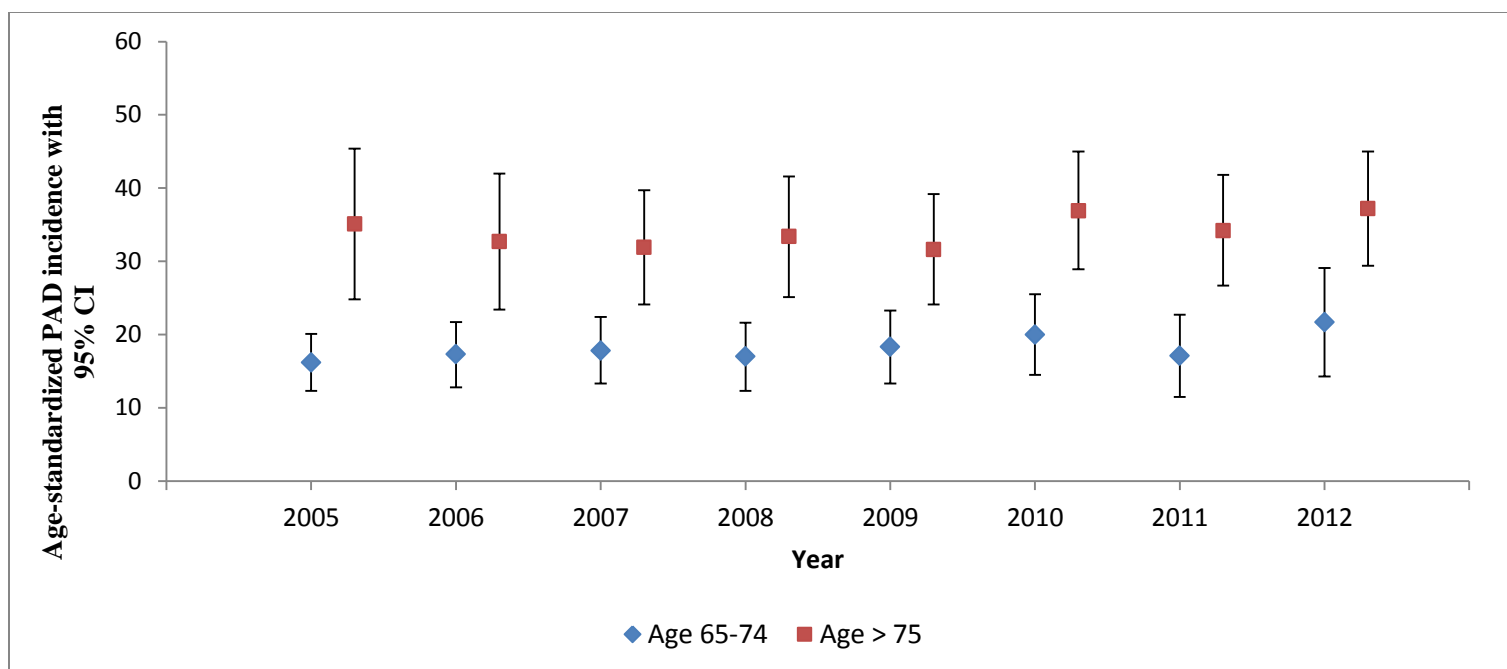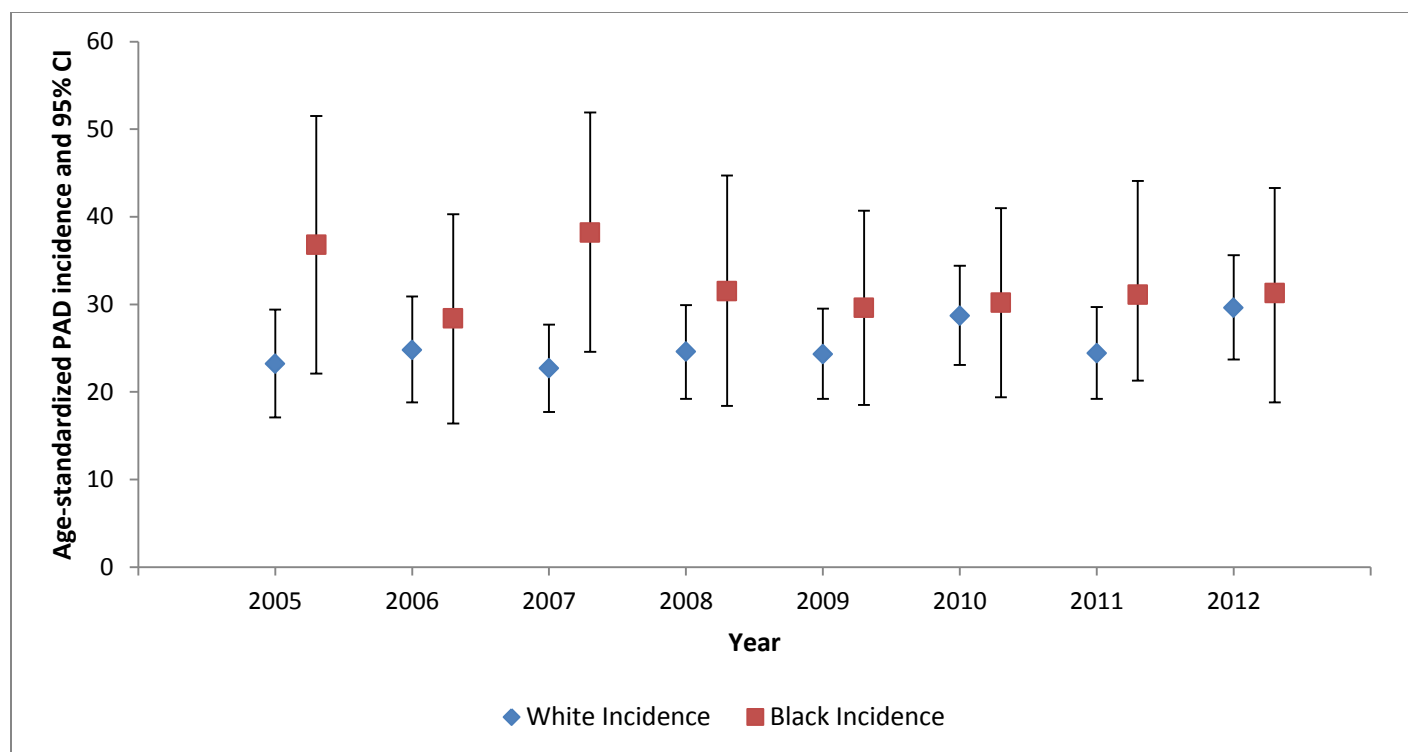Age-standardized Incidence for Whites, 2005-2012
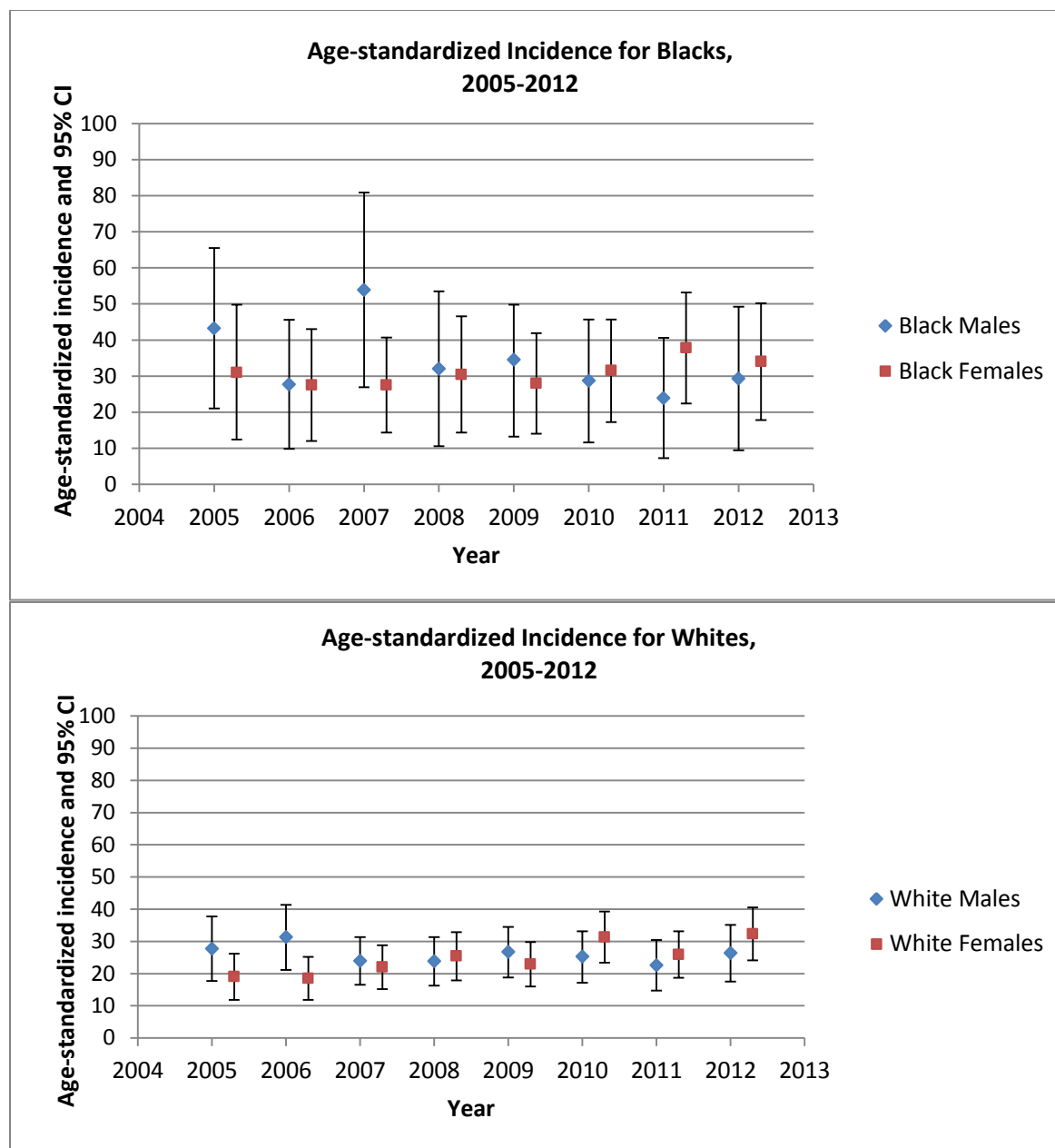
ARIC= Atherosclerosis Risk in Communities; Estimates are standardized to 2005 Medicare population

Supplemental Figure 1. Age-standardized annual incidence of peripheral artery disease in the inpatient and outpatient setting among four race/gender groups. The ARIC Study, 2005-2012

CHAPTER 6. MANUSCRIPT #2: FREQUENCY OF CARE AND MORTALITY
FOLLOWING AN INCIDENT DIAGNOSIS OF PERIPHERAL ARTERY DISEASE IN THE
INPATIENT OR OUTPATIENT SETTING. THE ARIC STUDY.

6.1 Introduction

Peripheral artery disease (PAD) is a prevalent and disabling atherosclerotic disorder that

disproportionately affects the elderly and minority populations in the United States [64, 147]. Up

to 25% of patients with symptomatic PAD may progress to limb-threatening clinical

manifestations that are associated with high health care costs and frequent PAD-related

procedures [15, 184]. In particular, hospitalization costs associated with PAD-related

revascularization and limb amputation procedures are more than $11 billion annually in the

United States. Long-term health status following these procedures is poor [15].

While prognosis for patients following a PAD-related procedure is well described [5, 7],

little is known about the outpatient and inpatient clinical care and outcomes following an *initial*

PAD diagnosis. In particular, the post diagnosis care for individuals with PAD, from initial

diagnosis in the outpatient setting - through clinic visits, admissions, and procedures – has not

been characterized. Administrative claims data, which contain diagnostic and procedure codes

from inpatient and outpatient encounters, provide an opportunity to estimate the frequency of

care of PAD from the health care setting of first diagnosis through follow-up care at both the

outpatient and inpatient levels.

The first objective of this study was to characterize the frequency of care for study

participants overall and by gender and race following an incident PAD diagnosis in the

outpatient or inpatient setting. Our second objective was to estimate 30-day, 1-year, and 2-year

mortality associated with an initial PAD diagnosis, by diagnosis setting. To accomplish these aims, we used data from the biracial Atherosclerosis Risk in Communities (ARIC) study cohort [8] linked with Center for Medicare and Medicaid Services (CMS) claims data.

6.2 Methods

6.2.1 Study Population

6.2.1.1 The Atherosclerosis Risk in Communities (ARIC) Cohort Study

The biracial ARIC cohort, established to examine the etiology of atherosclerosis and its clinical manifestations, includes 15,792 participants (45-64 years of age at baseline) enrolled between 1987 and 1989. The ARIC cohort was selected by probability sampling from four US communities: Washington County, Maryland (MD), Forsyth County, North Carolina (NC), the city of Jackson, Mississippi (MS), and the suburb cities of Minneapolis, Minnesota (MN) [8]. Eligible for inclusion in this study were ARIC participants enrolled continuously for at least two years in Medicare Parts A and B through a fee-for-service plan from 2000-2012. Data were collected on cohort participants at five clinic examinations and through annual follow-up telephone interviews. Information from visits 1-4, which occurred at three year intervals and concluded in 1999, is included in the present study.

6.2.1.2 Linkage of Cohort Data with Administrative Claims

Data for ARIC cohort participants were linked with the Centers for Medicare and Medicaid Services (CMS) claims data for the years 1991-2012 using a finder file that included participants' social security numbers, gender and date of birth. A total of 14,899 Medicare eligible ARIC study participants were identified, of which 14,702 ARIC cohort IDs (98.7 % match) were matched successfully indicating eligibility for CMS Medicare coverage.

Information concerning ARIC study participant enrollment in fee-for-service (FFS) Medicare was obtained from monthly indicators of enrollment in Part A, Part B, and Medicaid

buy-in available from annual CMS Medicare Beneficiary Summary files. Continuous enrollment periods were created to indicate uninterrupted CMS Medicare FFS coverage, defined as enrollment in CMS Medicare Part A and Part B and lack of enrollment in a Medicare Advantage (HMO) plan. Enrollment status prior to 2000 was not considered for this analysis. Study participants with missing enrollment information and those with continuous and exclusive Medicare Advantage enrollment were excluded from the study. Also excluded from analyses were participants <65 years of age and those of race other than black or white. For each study participant the longest enrollment period was selected to give the best opportunity to capture relevant claims.

6.2.1.3 Demographics and Comorbidities

Participant race, gender, education level and family income were self-reported at baseline. Age was calculated at the time of incident PAD event. Participant information regarding comorbid conditions was available from four clinic visits and annual telephone follow-up surveys. Diabetes mellitus was defined as self-reported history of diabetes at any of the four clinic visits or self-report questionnaire, usage of diabetes medication during the two weeks prior to a visit, a fasting blood glucose level of $\geq$ 126 mg/dl, or a non-fasting blood glucose $\geq$ 200 mg/dl. Hypertension was defined as systolic blood pressure $\geq$ 140 mm Hg or diastolic blood pressure $\geq$ 90 mm Hg at any of the four clinic visits or by antihypertensive medication usage during the two weeks prior to any of the clinic visits or via self-report questionnaire. Hyperlipidemia was defined as a total cholesterol $\geq$ 240 mg/dl at any of the four clinic visits or via self-report questionnaire. Smoking status was self-reported at each clinic visit and is defined as any history or no history for the purposes of this study. Trained technicians measured height and weight at each clinic visit. Body mass index was calculated as weight in kilograms divided by height squared (in meters). Obesity was defined as BMI $\geq$ 30.0 kg/m^2. History of coronary

heart disease (CHD), stroke, and heart failure prior to incident PAD diagnosis was based on self-report at baseline and adjudication of hospitalized events occurring in follow up from 2005 through the PAD diagnosis date. End-stage renal disease was defined as estimated glomerular filtration rate (eGFR) <15.0 mL/min/m^2 using creatinine measurements from the four clinic visits and employment of the CKD-EPI equation. Self-rated health (via self-report questionnaire) was defined as poor, fair, good, or excellent, and the lowest rating was used. Adequate access to care was defined as any outpatient encounter within one year of the incident PAD diagnosis date.

6.2.1.4 Ascertainment of Encounters in the Claims

PAD-related outpatient office visits and outpatient diagnostic tests were identified from: 1) the physician claims (Carrier) files as claims with PAD-related diagnostic and billing codes for new and established office visits and preventive medicine visits and 2) from facility claims (Outpatient) files as claims with PAD-related codes for visits to Federally Qualified Healthcare centers. Hospitalizations (e.g. inpatient visits and procedures) were identified from the Medicare Provider Analysis and Review (MedPAR) records. PAD occurrence was defined using International Classification of Diseases, Ninth Revision (ICD-9-CM) and Healthcare Common Procedure Coding System (HCPCS) codes selected based upon a review of the current literature [185]. Codes in any position on the records were considered for both inpatient and outpatient visits. Provider specialty codes were used to identify outpatient visits to primary care providers, cardiology visits, and podiatry visits. All discharge ICD-9 codes for the incident PAD hospitalizations were grouped into categories of comorbid conditions using definitions provided by Centers for Medicare and Medicaid Services Chronic Conditions Data Warehouse (Supplemental Table 7).

6.2.1.5 Cohort Construction

A synthetic cohort of ARIC participants enrolled in Medicare FFS beneficiaries who had an incident inpatient or outpatient PAD diagnosis was constructed to investigate the frequency of inpatient and outpatient encounters following a PAD diagnosis. A two-year look back period from the date of first PAD occurrence was chosen to minimize misclassification of incident events [170]. This two-year look back has been shown to reduce misclassification of incidence among chronic diseases to less than 10% [170]. In addition, FFS eligibility for at least two years of follow-up after the incident diagnosis was required. Therefore, the analytical study population included ARIC study participants with a PAD diagnosis from 2002 to 2010, with follow-up extending through an administrative censoring date of December 31st, 2012.

An incident inpatient PAD diagnosis was defined as a hospitalization for PAD at any time during the study period. An outpatient PAD diagnosis was defined as at least two outpatient claims with a PAD-related code for events at least 1 day apart occurring within 12 consecutive months. If a singular outpatient event preceded an inpatient event within 365 days, the event was classified as an inpatient PAD diagnosis with the incident event date as the inpatient date of discharge. Single PAD-related outpatient events occurring with no PAD-related hospitalizations or PAD-related outpatient events within 365 days were not considered incident PAD events.

6.2.2 Statistical Analysis

Direct standardization was used to estimate age-standardized rates of inpatient and outpatient encounters with 95% confidence intervals (CI) following an initial PAD diagnosis. The denominator for rate estimates included cohort participants' time in continuous FFS enrollment following an initial PAD diagnosis. Estimates were age-standardized to reflect the age, race, and sex distribution of the 2005 Medicare population ages 67 years and older. Age categories for standardization included 67-69, 70-74, 75-79 and $\geq$ 80 years of age at the time of

PAD diagnosis. Estimates were calculated by diagnosis location (inpatient, outpatient) and within diagnosis location in strata of race and gender.

Analyses for time to initial hospitalization or rehospitalization accounted for death as a competing risk using the cumulative incidence function, a method that computes the incidence of failure associated directly with the event of interest (i.e. hospitalization) along with the incidence of failure associated with the competing risk (i.e. death) [173, 174]. Estimates were calculated by initial diagnosis location and within diagnosis location in strata of race and gender. The end of follow-up was determined by death, enrollment in Medicare Advantage or at December 31st, 2012 (end of study observation period). Beneficiaries' death dates were obtained from the Master Beneficiary File. Propensity score models were used to adjust for confounding in estimates of mortality by using standardized mortality ratio weighting [186]; individuals diagnosed with PAD in the inpatient setting were weighted to reflect the distribution of covariates among individuals diagnosed with PAD in the outpatient setting. Covariates included age, gender, race, income, education, diabetes, smoking history, hyperlipidemia, hypertension, obesity, coronary heart disease, stroke, heart failure, end stage renal disease, self-rated health, and adequate access to care. The distribution of propensity scores was examined and non-overlapping propensity scores were trimmed from mortality analyses (n=21). All analyses were completed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Written informed consent was obtained from all participants and all institutional review boards approved the ARIC study. This study includes secondary data analysis of existing data and was approved by the institutional review board of UNC.

6.3 Results

The final analytic sample included 11,652 ARIC participants with 86,228 person-years of fee-for-service enrollment time. Median enrollment time was 6.3 years. We observed 1,086 incident diagnoses of PAD during the study period (2002-2010) including 873 (80.4%) incident

PAD cases diagnosed in the outpatient setting and 213 (19.6%) incident PAD cases diagnosed in the inpatient setting. Table 17 describes demographic and comorbid traits, stratified by initial PAD diagnosis location (outpatient vs. inpatient). Also included in Table 17 are demographic and comorbid traits among fee-for-service participants who did not have a PAD diagnosis during the study observation period (N=10,566). Compared to those with incident outpatient PAD, a larger proportion of study participants with incident inpatient PAD reported a history of major circulatory system disorders including CHD, stroke, and heart failure. Those with incident outpatient PAD were more likely to be female and have a history of diabetes and hypertension compared to those with incident inpatient PAD.

Among the 213 participants diagnosed with PAD in the inpatient setting, 37 (17.4%) were hospitalized with a primary diagnosis of PAD (Table 18). A PAD-related code was present in the first three or five positions, respectively, in 71 (33.3%) and 110 (51.6%) of the 213 incident hospitalizations. Participants diagnosed with PAD in the inpatient setting frequently had a concomitant code for ischemic heart disease (39.0%), diabetes (23.9%), chronic kidney disease (17.4%), heart failure (16.9%), and atrial fibrillation (12.2%). For 38% (81/213) of the incident PAD hospitalizations the primary discharge diagnosis was a circulatory system related condition (including PAD). Respiratory conditions (10.3%), digestive system diseases (8.9%), musculoskeletal diseases (7.0%), and neoplasms (6.6%) were the most common non-cardiovascular disease primary discharge diagnoses.

6.3.1 Age-standardized Rates of Post-Diagnosis Outpatient and Inpatient Encounters

Among individuals diagnosed with PAD in the outpatient setting, we observed an age-standardized rate of 2.15 (95% CI: 2.10, 2.21) PAD-related outpatient encounters per person year over the course of study follow-up (2002-2012; Table 17). There were no race or gender differences in rates of PAD-related outpatient encounters per person-year (Figure 14). The

highest rates of all-cause outpatient encounters were for primary care provider visits (PCP; age-standardized rate: 6.36 per person-year; 95% CI: 6.26, 6.45; Figure 15). Age-standardized rates of outpatient cardiology encounters were 1.94 (95% CI: 1.89, 2.0) encounters per person-year. Cardiology encounters per person-year were lower among blacks (1.20; 95% CI: 1.12, 1.28) as compared to whites (2.18; 95% CI: 2.12, 2.25) and among females (1.48; 95% CI: 1.43, 1.55) as compared to males (2.27; 95% CI: 2.21, 2.35; Figure 16). Individuals with PAD diagnosed in the outpatient setting had an age-standardized rate of 0.10 (95% CI: 0.09, 0.11) PAD-related hospitalizations and 0.17 (95% CI: 0.16, 0.19) all-cause hospitalizations per person-year over the course of follow-up from 2002 to 2012.

Individuals with PAD diagnosed in the inpatient setting had an age-standardized rate of 1.02 (95% CI: 0.94, 1.10) PAD-related outpatient encounters per person year following a PAD diagnosis (Figure 14). Age-standardized rates of PAD-related outpatient encounters per person-year among blacks and whites were 1.52 (95% CI: 1.28, 1.74) and 0.90 (95% CI: 0.82, 0.99), respectively. Among gender strata, males had 1.04 (95% CI: 0.93, 1.16) and females had 1.03 (95% CI: 0.92, 1.14) PAD-related outpatient encounters per person-year. The highest rates of outpatient encounters were to primary care providers (7.43 per person-year; 95% CI: 7.21, 7.64; Figure 15). Age-standardized rates of cardiology care were 2.29 (95% CI: 2.17, 2.40) encounters per person-year. Outpatient cardiology encounters per 1.76 (95% CI: 1.53, 2.0) person-year among blacks (1.76; 95% CI: 1.53, 2.0) and 2.32 (95% CI: 2.20, 2.45) among whites and were similar among females (2.41; 95% CI: 2.23, 2.59) and males (2.14; 95% CI: 1.99, 2.28; Figure 16). Individuals with PAD diagnosed in the outpatient setting had an age-standardized rate of 0.17 (95% CI: 0.14, 0.21) PAD-related hospitalizations and 0.30 (95% CI: 0.26, 0.34) all-cause hospitalizations per person-year after the PAD diagnosis.

6.3.2 Hospitalization and Re-Hospitalization Following an Incident PAD diagnosis

Cumulative one-year incidence of first PAD-related and first all-cause hospitalization among those with PAD diagnosed in the outpatient setting was 6.4% (95% CI: 4.8, 8.1) and 32.2% (95% CI: 29.0, 35.2), respectively (Table 19). Incidence of first PAD-related hospitalization was similar among blacks (7.6%; 95% CI: 4.2, 10.9) as compared to whites (6.0%; 95% CI: 4.1, 7.8) and among males (9.0%; 95% CI: 6.0, 11.8) as compared to females (4.6%; 95% CI: 2.7, 6.4). Incidence of first all-cause hospitalization was also similar among blacks (38.3%; 95% CI: 31.8, 44.2) as compared to whites (29.8%; 95% CI: 26.2, 33.3) and among males (35.3%; 95% CI: 30.2, 40.0) as compared to females (29.9%; 95% CI: 25.8, 33.8).

Cumulative incidence of first PAD-related and first all-cause hospitalization among those with PAD diagnosed in the inpatient setting was 14.2% (95% CI: 9.3, 18.7) and 43.4% (95% CI: 36.3, 49.7) at one year, respectively (Table 20). Incidence of PAD-related rehospitalization at one year was higher among blacks (21.4%; 95% CI: 9.9, 31.5) as compared to whites (11.6%; 6.4, 16.5), although estimates were imprecise. Incidence of PAD-related rehospitalization at one year was similar among males (14.3%; 95% CI: 7.6, 20.6) and females (13.9%; 95% CI: 6.9, 20.4). All-cause hospitalization at one year was higher, although not statistically significant, among blacks (55.1%; 95% CI: 40.0, 66.4) as compared to whites (38.7%; 95% CI: 34.6, 53.1). There were no differences detected in all-cause hospitalization at one year when comparing males (44.6%; 95% CI: 34.6, 53.1) to females (41.8%; 95% CI: 31.3, 50.6).

6.3.3 Mortality Following an Incident PAD Diagnosis

Overall age-standardized mortality was 1.8% (95% CI: 1.0, 2.5), 8.9% (95% CI: 7.2, 10.5), and 16.6% (95% CI: 14.4, 18.7) at 30 days, one year and two years after PAD diagnosis in any setting (Table 21). Thirty day, one-year and two-year age-standardized mortality was 0.8% (95% CI: 0.2, 1.4), 7.1% (95% CI: 5.4, 8.7) and 15.3% (95% CI: 12.9, 17.6), respectively, among

those with incident outpatient PAD diagnosis. Thirty-day, one-year and two-year age-standardized mortality was 5.7% (95% CI: 2.6, 8.7), 16.0% (11.0, 21.1) and 21.5% (15.8, 27.2) respectively, among those with incident inpatient PAD diagnosis. Propensity score adjusted mortality at one-year and two years (Figure 17) was 6.3% (95% CI: 4.8, 7.7) and 13.7% (95% CI: 11.4, 15.9) among those with incident outpatient PAD diagnosis. Propensity score adjusted mortality at one-year and two years was 14.7% (95% CI: 9.9, 19.3) and 19.9% (95% CI: 14.3, 25.5), among those with incident inpatient PAD diagnosis.

6.4 Discussion

The present study is among the first to examine the incidence of PAD diagnosis across different care settings and to examine frequency of health care encounters following a PAD diagnosis. Of 1,086 study participants enrolled in FFS CMS Medicare who had an incident PAD diagnosis, we found that 80% (873/1086) were initially diagnosed with PAD in the outpatient setting. PAD-related hospitalizations at one year were rare (6.4%) among those with an incident outpatient PAD diagnosis, although outpatient encounters with primary care providers, cardiologists, podiatrists, as well as encounters with PAD-related codes were relatively frequent compared to national rates [187]. Minimal differences for follow-up encounters were observed in analyses stratified by race and gender, although blacks experienced lower rates of follow-up cardiology encounters as compared to whites. Participants with an incident inpatient PAD diagnosis had a poor short-term prognosis, with a 30-day mortality of nearly 6% and a rate of all-cause rehospitalization which was close to 50% within one year. Our findings suggest a poor overall prognosis, including high mortality and high incidence of rehospitalization for participants diagnosed with incident PAD in the inpatient setting as compared to participants diagnosed with incident PAD in the outpatient setting.

Characteristics and pre-diagnosis comorbid conditions of ARIC Study participants with PAD identify similar risk factors as other studies of PAD [12, 25]. Diabetes (43%) and hypertension (84%) were more common in the current study population than among Medicare beneficiaries in a recent study based on the MarketScan database (Diabetes: 16%; Hypertension: 54%); however, the MarketScan-based analyses was not limited to fee-for-service participants and relied only on claims to describe prevalence of comorbid conditions [185]. The rich covariate detail available in the ARIC study from clinic visits and self-report questionnaires provided supplemental data that is unavailable in claims and, as such, could explain some of the difference in the prevalence of comorbid conditions. Participants with an incident PAD diagnosis in the inpatient setting were particularly likely to have coexisting circulatory system diseases (45%), a finding that is in accordance with estimates from the REACH registry in which 65% of individuals with PAD had <u>clinical</u> evidence of either coronary or cerebrovascular disease [17]. The estimated proportion of participants with of CHD, stroke, and heart failure from the current study represent major circulatory system events and are likely an underestimation of the actual number of participants with circulatory system diseases. Kroger et al (2009) observed an inverse relationship between education and income and PAD in a population-based study using ankle-brachial index <0.9 to define PAD [67]. Our study, which confirms these observations and extends them to the care of PAD in the inpatient or outpatient setting, further underscores disparities in the development of PAD which are similar to disparities observed in the development of other cardiovascular diseases [188].

We found that individuals diagnosed with PAD in the outpatient setting had more than twice the number of <u>PAD-related</u> post-diagnosis outpatient encounters per person-year than individuals diagnosed with PAD in the inpatient setting. While guidelines concerning appropriate

timing of healthcare encounters following an incident PAD diagnosis have not been established, most guideline recommendations for care following a hospitalized CVD event suggest contact with a provider within six weeks [189, 190]. The very long median time to first PAD-related outpatient visit following an incident diagnosis in the inpatient setting (849 days), which we observed in this study, suggests that those with an inpatient PAD diagnosis may constitute a population of individuals who are not receiving appropriate PAD-related care [191].

While our observations regarding differences in post-diagnosis PAD-related follow-up care by diagnosis setting are meaningful, there are several factors to consider that could influence these findings. First, nearly half of the incident inpatient PAD diagnoses included a PAD code in the eleventh position or beyond implying that PAD was only a distal cause of the hospitalization or that the PAD code represented prevalent disease. Participants diagnosed with PAD in the inpatient setting, therefore, might be less likely to have PAD severe enough to require follow-up care as compared to participants diagnosed with PAD in the outpatient setting; only four code positions are included in outpatient records, thus reducing the opportunities for inappropriate inclusion of a PAD code. Second, the greater prevalence of comorbid conditions that may necessitate frequent outpatient follow-up – such as diabetes and hypertension – identified among participants diagnosed with PAD in the outpatient, as compared to the inpatient setting, suggests that the two groups of study participants with a PAD diagnosis may utilize health care differently. Individuals with diabetes, who are frequent utilizers of outpatient services, are more likely to be screened for PAD in the outpatient setting and might be more likely to have PAD-related outpatient follow-up given a positive finding [136]. Finally, our assessment of post-diagnosis follow-up care was constrained for the inpatient setting by a

relatively high proportion of participants discharged to a nursing home (13%), where follow-up specialty care is unlikely.

Although we observed that study participants with inpatient PAD diagnosis had few post-diagnosis PAD-related outpatient encounters, our findings suggest that participants with an incident PAD diagnosis in either setting are high utilizers of all-type outpatient health care services. In comparison with a census-based Medicare-aged general population (including all diagnoses) derived from a national ambulatory health care survey (NAMCS), participants with a PAD diagnosis, identified in the present study, had, on average, 5 times the number of post-diagnosis outpatient encounters per person-year (31.6 vs 5.9) [187]. The ARIC study participants with a PAD diagnosis also experienced more than twice the rate of encounters per person-year with primary care providers than the general population of the NAMCS survey, possibly due to the coexisting comorbidity burden. Our overall outpatient encounter estimates were also slightly higher than estimates obtained from a recent claims-based study of working-aged Japanese patients with PAD that identified 25 all-cause outpatient encounters in the first year following a PAD diagnosis [192].

Examination of follow-up outpatient encounters with different types of providers revealed few differences in rates of care by race and gender. This study contributes information toward a knowledge gap in incidence and rates of post PAD diagnosis care, especially among women [182]. Differences in gender-specific estimates, which found that women were less likely to have follow-up cardiology care after an incident outpatient PAD diagnosis, concurs with previous literature not specific to PAD patients [193]. We also found that blacks were less likely than whites to have outpatient cardiology encounters following a PAD diagnosis, a finding that

complement data from extant literature suggesting race disparities in receipt of appropriate inpatient cardiology care [193].

Previous studies have suggested that diagnosis of CVD in the inpatient setting, as compared to the outpatient setting, portends worse outcomes [194, 195]. Results of the current study extend this observation to PAD. We found that five-year mortality was higher among participants with a PAD diagnosis in the inpatient setting (51.3%; 95% CI: 44.4, 58.3) as compared to the outpatient setting (34.4%; 95% CI: 31.1, 37.8). We used propensity score methods to adjust for demographic characteristics, comorbidities, disease severity, access to care, and health status observed for participants diagnosed with PAD in the inpatient and outpatient settings, and differences in survival between the two groups persisted. However, our comparison of mortality by setting is limited by the observational nature of our study and our inability to control for residual confounding. It is also important to note that participants from these two settings of diagnosis differ significantly by a variety of comorbid conditions and their respective risk profiles likely drive much of the mortality gap we observed. For example, the overall frequency of concomitant conditions associated with high mortality including ischemic heart disease, diabetes, chronic kidney disease, heart failure, and atrial fibrillation was much higher among those diagnosed with PAD in the inpatient setting (Table 18). While the intention of our study is to present descriptive information concerning mortality and hospitalizations by setting of diagnosis, findings from our study do suggest that identification of PAD in the outpatient setting, which presumably occurs at an early stage of the disease, is favorable.

6.4.1 Strengths and Limitations

An important strength of this study is the inclusion of outpatient in addition to inpatient clinical encounters in the assessment of the frequency of encounters following an incident PAD diagnosis. Furthermore, prior studies have provided limited information on the health care

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encounters for individuals with PAD, stratified by the setting of health care delivery (inpatient vs. outpatient). These estimates are age-standardized and look back periods for incidence are in accordance with recent recommendations [170], providing a further strength to this study.

As this analysis was based on inpatient and outpatient are among CMS Medicare enrollees in FFS programs, our estimates are not generalizable to Medicare beneficiaries enrolled in managed care programs and who have been reported to be healthier than those in FFS [166]. Generalizability of this study is further limited because our estimates reflect cohort survivors in a closed cohort. We did not attempt to quantify PAD prevalence prior to enrollment in fee-for-service in 2000 and it is possible that we did not capture the true PAD incidence. Administrative claims data reflect billing practices and, therefore, diagnostic coding found in claims data is not always accurate in relation to documented diagnoses or procedures. Diagnostic and procedure codes selected for the identification of PAD events were not independently validated, which could lead to misclassification of PAD occurrence. Lastly, PAD was the primary diagnosis code in only 17% of these hospitalizations. With a larger sample size, our definition of PAD hospitalization could have been limited to include only those where PAD was listed in the top three code positions.

6.4.2 Conclusions

This study addresses an important gap in existing literature by providing an assessment of the frequency of care following a PAD diagnosis in the outpatient or inpatient setting. Individuals with PAD, regardless of the setting of diagnosis, have frequent outpatient encounters with a variety of health care providers following the incident disease diagnosis. We found few differences in race- and gender-specific estimates of post-diagnosis care, although we did find that blacks and women were less likely than whites and men, respectively, to have post-diagnosis cardiology care. Lastly, we found a higher mortality among individuals diagnosed with PAD in the inpatient setting.

Table 17. Characteristics of fee-for-service participants without an incident PAD diagnosis (N=10,566) and those with an incident PAD diagnosis in the outpatient (N=873) or inpatient setting (N=213). The Atherosclerosis Risk in Communities Study, 2002-2010.

	PAD status		
	No PAD (N=10,566)	Incident Outpatient PAD (N=873)	Incident Inpatient PAD (N=213)
Mean Age at Diagnosis, SD	NA	74.9 (4.9)	74.4 (4.6)
Gender, % Female	57.4 (56.4, 58.3)	57.6 (54.3, 60.9)	47.0 (40.1, 53.9)
Race, % Black	27.9 (27.1, 28.8)	27.3 (24.3, 30.4)	26.4 (20.6, 32.9)
Income, %			
Low (<$35,000)	34.5 (33.6, 35.4)	53.8 (50.4, 57.2)	55.2 (48.2, 62.0)
Mid ($35,000-$49,999)	19.4 (18.7, 20.2)	19.2 (16.6, 22.0)	17.5 (12.6, 23.2)
High ($\geq$ $50,000)	46.1 (45.2, 47.1)	27.0 (24.1, 30.1)	27.3 (21.5, 33.9)
Education, < High School, %	22.2 (21.4, 23.0)	28.2 (25.2, 31.3)	28.3 (22.3, 34.9)
Diabetes*, %	20.0 (19.2, 20.7)	47.1 (43.7, 50.5)	26.3 (20.5, 32.7)
Smoking History[†], %	66.4 (65.5, 67.3)	67.1 (63.9, 70.2)	74.7 (68.3, 80.3)
Hyperlipidemia[‡], %	70.9 (70.1, 71.8)	75.8 (72.9, 78.6)	73.2 (66.8, 79.1)
Hypertension[§], %	52.4 (51.4, 53.4)	87.5 (85.1, 89.6)	70.0 (63.3, 76.0)
Obesity[#], %	39.8 (38.8, 40.7)	50.2 (46.8, 53.5)	50.0 (42.9, 56.7)
History of CHD[**], %	11.6 (11.0, 12.2)	15.4 (13.0, 17.9)	24.9 (19.2, 31.3)
History of Stroke[††], %	8.3 (7.8, 8.9)	9.4 (7.5, 11.5)	17.4 (12.5, 23.1)
History of Heart Failure[‡‡] %	16.2 (15.5, 16.9)	17.4 (15.0, 20.0)	35.7 (29.3, 42.5)
End Stage Renal Disease[§§]	0.7 (0.5, 0.9)	0.2 (0.0, 0.8)	0.9 (0.1, 3.4)
Self-Rated Health, Poor[##]	27.0 (26.1, 27.8)	27.6 (24.7, 30.7)	35.2 (28.8, 42.0)

*Diabetes defined as self-reported history of diabetes at any of the four clinic visits or diabetes medication during two weeks prior to visit or fasting glucose $\geq$ 126 mg/dl fasting or a nonfasting blood glucose $\geq$ 200 mg/dl; [†] Smoking History is defined as any history or

no history; ‡ Hyperlipidemia defined as total cholesterol $\geq$ 240 mg/dl ; § Hypertension defined as systolic blood pressure $\geq$ 140 mm Hg or diastolic blood pressure $\geq$ 90 mm Hg or antihypertensive medication usage during two weeks prior to any of the four clinic visits; # Obesity defined as body mass index $\geq$ 30 kg/m^2 ; ** History of CHD (coronary heart disease) defined as history of myocardial infarction, coronary revascularization during any time during follow-up but prior to incident PAD diagnosis date; ††History of stroke defined as prevalent or incident stroke prior to incident PAD diagnosis date; ‡‡ History of Heart Failure defined as prevalent or incident heart failure prior to incident PAD diagnosis date; §§ End-stage renal disease defined as eGFR <15.0 mL/min/m^2 using the CKD-EPI equation; ## Self-rated health defined as poor, fair, good, excellent

Table 18. Primary diagnoses and comorbid conditions for incident PAD hospitalizations. The Atherosclerosis Risk in Communities Study, 2002-2010 (N=213)

Primary Discharge Diagnosis Grouped by ICD-9-CM Chapter	Incident Inpatient PAD
Diseases of the circulatory system (390–459)	38.0%
PAD-related code in primary position	17.4%
Non-circulatory system disorders (001-389, 580-999, V01-V89, E800-E999, Procedures 00-99)	62.0%
Comorbid conditions and procedures* (ICD-9-CM code(s))	
Ischemic heart disease	39.0%
Acute myocardial infarction	3.3%
Atrial fibrillation	12.2%
Heart Failure	16.9%
Stroke	6.1%
Chronic Kidney Disease	17.4%
Diabetes	23.9%

Table 19. Age-standardized* cumulative incidence of first PAD and all-cause hospitalizations (95% CI) at 1 year and 2 years following incident PAD diagnosis among participants diagnosed in the outpatient setting. The ARIC study (2002-2012).

	Incident Outpatient PAD (n=873)			
	First PAD Hospitalization at One Year	First PAD Hospitalization at Two Years	First All-Cause Hospitalization at One Year	First All-Cause Hospitalization at Two Years
Overall	6.4	9.5	32.2	48.4
	(4.8, 8.1)	(7.6, 11.5)	(29.0, 35.2)	(44.9, 51.6)
Black	7.6	10.7	38.3	52.6
	(4.2, 10.9)	(6.7, 14.6)	(31.8, 44.2)	(45.7, 58.6)
White	6.0	9.1	29.8	46.8
	(4.1, 7.8)	(6.8, 11.3)	(26.2, 33.3)	(42.7, 50.5)
Males	9.0	11.8	35.3	49.4
	(6.0, 11.8)	(8.4, 15.0)	(30.2, 40.0)	(44.0, 54.3)
Females	4.6	7.9	29.9	47.6
	(2.7, 6.4)	(5.5, 10.2)	(25.8, 33.8)	(43.0, 51.8)

*Standardized to reflect age, race and sex distribution of 2005 Medicare population; Age strata included 67-69, 70-74, 75-79, and ≥ 80.

Table 20. Age-standardized* cumulative incidence of first PAD and all-cause hospitalizations (95% CI) at 1 year and 2 years following incident PAD diagnosis among participants diagnosed in the inpatient setting. The ARIC study (2002-2012).

	Incident Inpatient PAD (n=213)			
	First PAD Rehospitalization at One Year	First PAD Rehospitalization at Two Years	First All-Cause Rehospitalization at One Year	First All-Cause Rehospitalization at Two Years
Overall	14.2 (9.3, 18.7)	20.0 (14.4, 25.2)	43.4 (36.3, 49.7)	61.3 (54.1, 67.4)
Black	21.4 (9.9, 31.5)	30.7 (17.4, 41.9)	55.1 (40.0, 66.4)	75.4 (60.9, 84.5)
White	11.6 (6.4, 16.5)	16.2 (10.2, 21.9)	38.7 (30.5, 45.9)	55.8 (47.2, 63.0)
Males	14.3 (7.6, 20.6)	21.7 (13.6, 29.0)	44.6 (34.6, 53.1)	60.5 (50.2, 68.7)
Females	13.9 (6.9, 20.4)	18.1 (10.1, 25.3)	41.8 (31.3, 50.6)	61.8 (51.0, 70.2)

*Standardized to reflect age, race and sex distribution of 2005 Medicare population; Age strata included 67-69, 70-74, 75-79, and $\geq$ 80.

Table 21. Mortality at 30-days, 1-year, and 2-years after incident PAD diagnosis in the outpatient (N=873) or inpatient (N=213) setting. The Atherosclerosis Risk in Communities Study, 2002-2010.

	30-day mortality (95% CI)		1-year mortality (95% CI)		2-year mortality (95% CI)	
	Age-standardized model[*]	Full model[+]	Age-standardized model[*]	Full model[+]	Age-standardized model[*]	Full model[+]
Overall (N=1086)	1.8 (1.0, 2.5)	1.5 (0.8, 2.1)	8.9 (7.2, 10.5)	7.8 (6.1, 9.2)	16.6 (14.4, 18.7)	15.1 (13.0, 17.2)
Incident Outpatient (N=873)	0.8 (0.2, 1.4)	0.7 (0.2, 1.2)	7.1 (5.4, 8.7)	6.3 (4.8, 7.7)	15.3 (12.9, 17.6)	13.7 (11.4, 15.9)
Incident Inpatient (N=213)	5.7 (2.6, 8.7)	4.7 (2.0, 7.3)	16.0 (11.0, 21.1)	14.7 (9.9, 19.3)	21.5 (15.8, 27.2)	19.9 (14.3, 25.5)

[*] Standardized to reflect age, race and sex distribution of 2005 Medicare population; Age strata included 67-69, 70-74, 75-79, and $\geq$ 80.

[+] Full adjusted model includes age, race, sex, income, education, diabetes, smoking, hyperlipidemia, hypertension, obesity, CHD, stroke, heart failure, ESRD, disease severity, self-rated health, and any-cause office visit in 1 year prior to diagnosis; Propensity models use 202 incident inpatient PAD events and 862 incident outpatient PAD events due to nonoverlap of 22 observations.
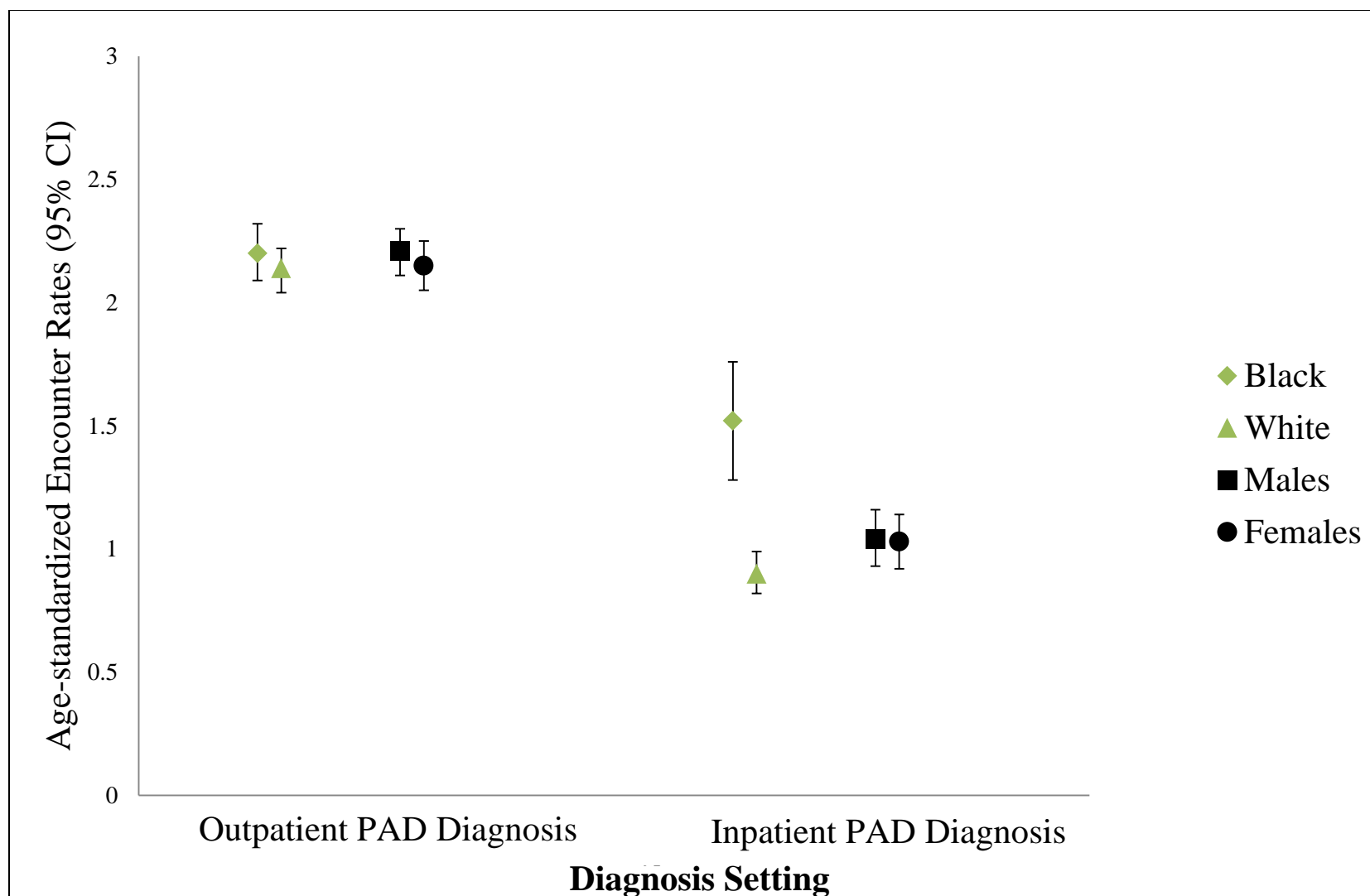
Figure 14. Age-standardized rates of race- and gender-specific PAD-related outpatient encounters (per person-year) following a PAD diagnosis, by diagnosis setting. The ARIC study, 2002-2012
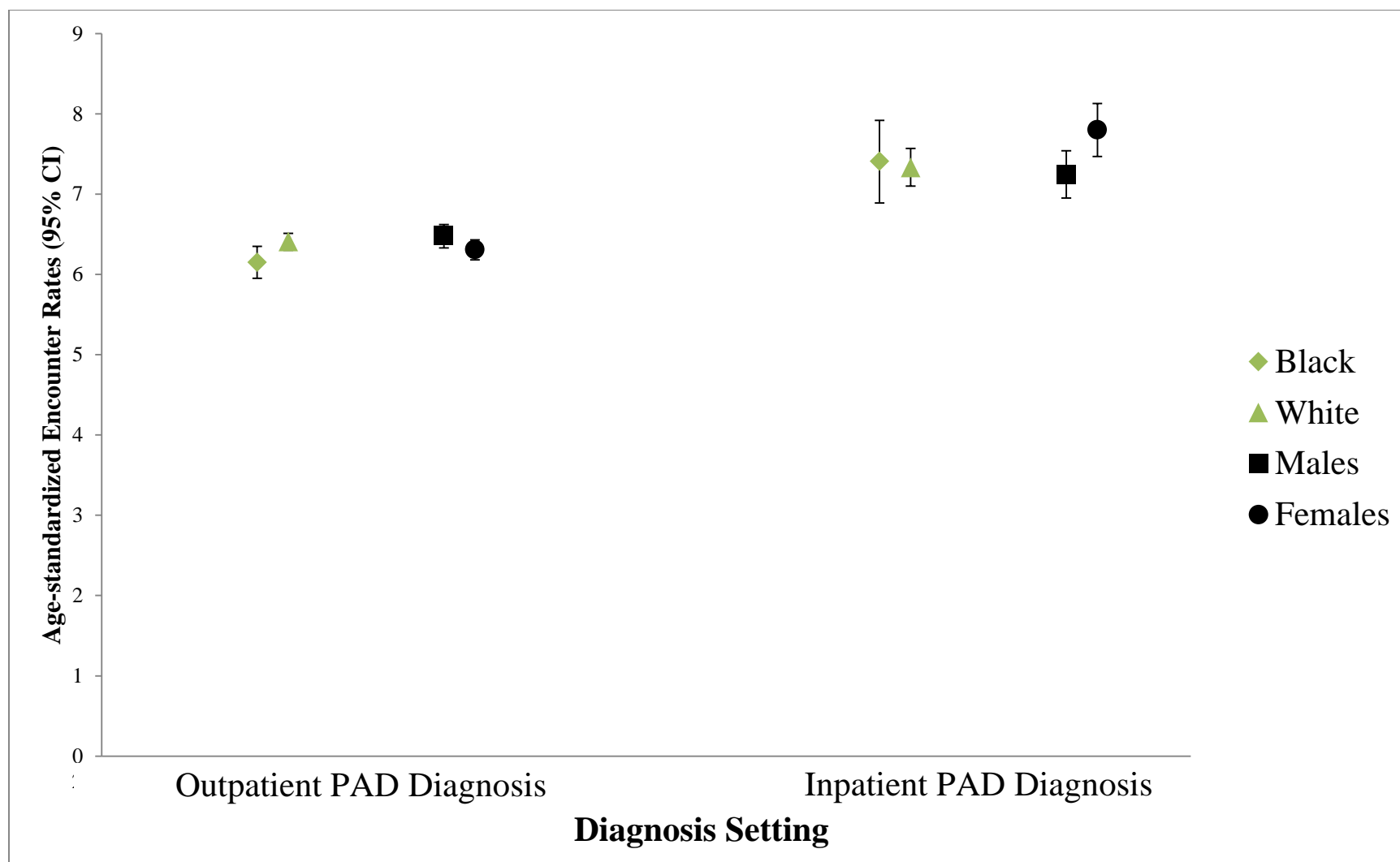
Figure 15. Age-standardized rates of race- and gender-specific outpatient primary care encounters (per person-year) following a PAD diagnosis, by diagnosis setting. The ARIC study, 2002-2012
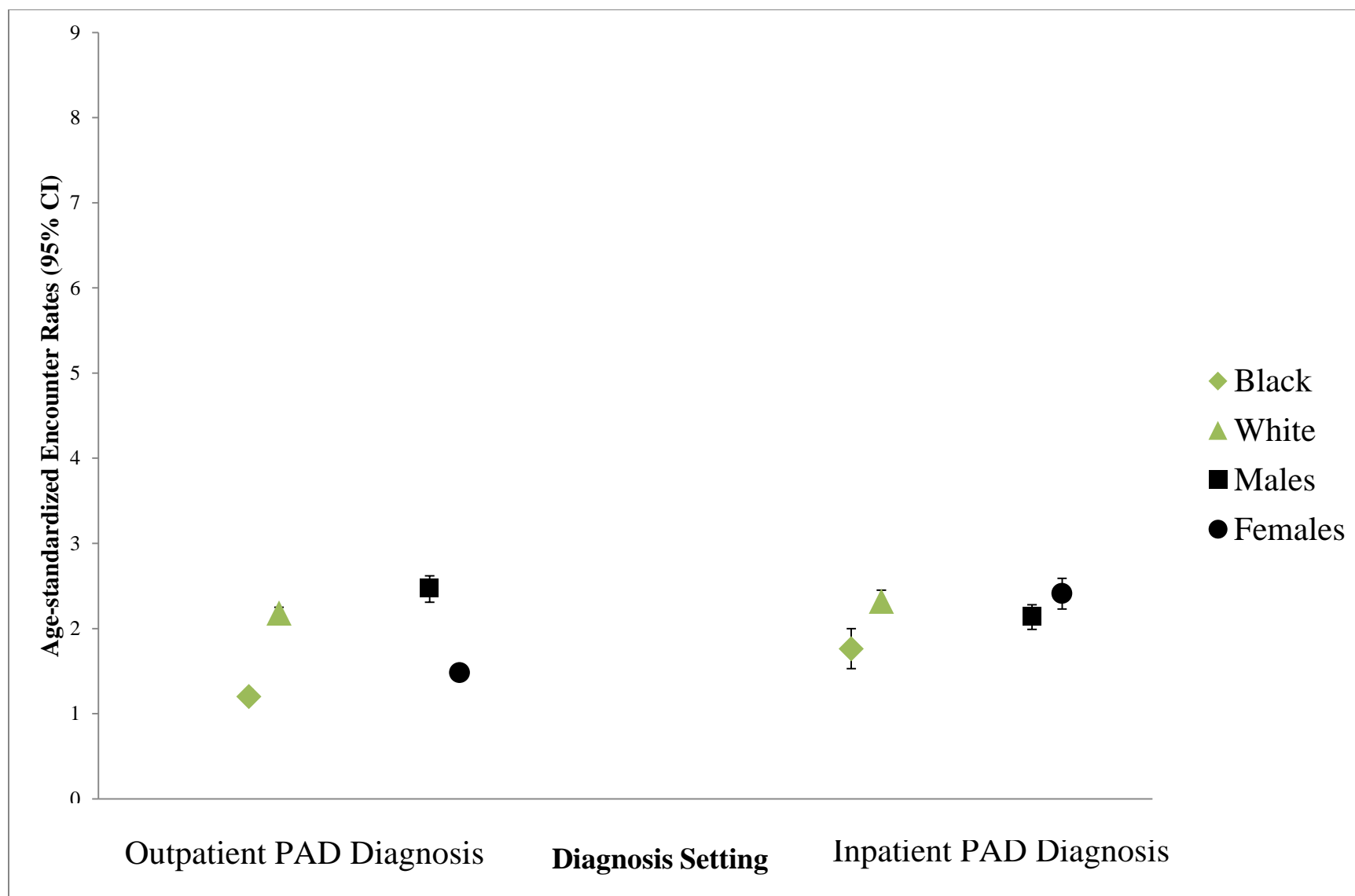
Figure 16. Age-standardized rates of race- and gender-specific outpatient cardiology encounters (per person-year) following a PAD diagnosis, by diagnosis setting. The ARIC study, 2002-2012
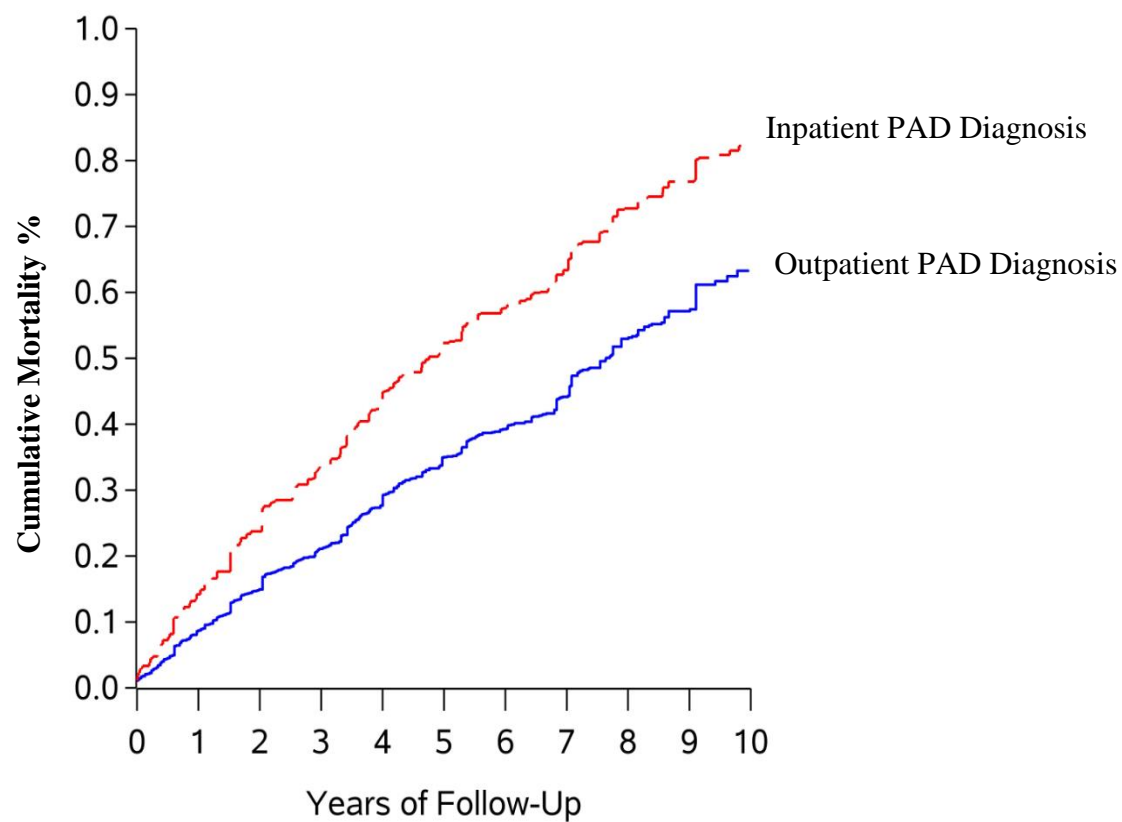
Figure 17. Propensity Score-Adjusted* Cumulative Mortality, by setting

* Propensity model includes age, race, sex, income, education, diabetes, smoking, hyperlipidemia, hypertension, obesity, CHD, stroke, heart failure, ESRD, disease severity, any-cause office visit in 1 year prior to diagnosis, and self-rated health

Supplemental Table 7. International Classification of Diseases, Ninth Revision (ICD-9-CM), Current Procedural Terminology, 4th edition (CPT-4), Healthcare Common Procedure Coding System (HCPCS), and Federally Qualified Healthcare Revenue Center (FQHC) codes used to identify peripheral artery disease and provider specialty visits in claims.

Code Type	Codes
ICD-9-CM	249.70, 249.71, 250.70, 250.71, 250.72, 250.73, 440.20, 440.21, 440.22, 440.23, 440.24, 440.29, 440.30, 440.31, 440.32, 440.4, 440.8, 440.9, 443.1, 443.22, 443.81, 443.89, 443.9, 444.22, 444.81, 445.02
	* 38.08, 38.16,, 38.18, 38.38, 38.48, 39.25, 39.29, 39.49, 39.50, 39.56, 39.57, 39.58, 39.90, 84.10, 84.12, 84.13, 84.14, 84.15, 84.16, 84.17, 84.18, 84.3, 84.91
HCPCS/CPT-4	27295, 27590, 27591, 27592, 27594, 27596, 27598,27599,27880, 27881, 27882, 27888, 27889, 28800, 28805, 28810, 28820, 28825, 35221, 35226, 35256, 35286, 35302, 35303, 35304, 35305, 35306, 35331, 35351, 35355, 35361, 35363, 35371, 35372, 35381, 35452, 35454, 35456, 35459, 35470, 35472, 35473, 35474, 35480, 35481, 35482, 35483, 35485, 35490, 35491, 35492, 35493, 35495, 35500, 35521, 35533, 35537, 35538, 35539, 35540, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35583, 35585, 35587, 35621, 35623, 35646, 35647, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 35681, 35682, 35700, 35875, 35876, 35879, 35881, 35883, 35884, 35903
	* 35683, 35686, 35571, 72191, 72198, 73706, 73725, 74175, 74185, 75630, 75631, 75635, 75710, 75711, 75712, 75716, 75717, 75718, 93922, 93924, 93925, 93926, 93978, 99201, 99202, 99203, 99204, 99205, 99211, 99212, 99213, 99214, 99215, 99216, 99241, 99242, 99243, 99244, 99245, 99385, 99386, 99387, 99395, 99396, 99397
Revenue Center Codes	*0320,0321,0322,0323,0324,0329,0360,0361,0370,0371,0372,0379,0402,0490,0499,0510,0517,0519,0520,0521,0610,0616,0710,0760, 0761,0762,0769,0921
Provider Specialty Codes	
Primary Care Provider	01, 08, 11, 50, 70
Cardiology	06
Podiatry	48

* Must be accompanied with a PAD-related ICD-9-CM code

Supplemental Table 8. Median count of PAD-related encounters following a diagnosis of PAD in the outpatient or inpatient setting. The Atherosclerosis Risk in Communities Study, 2002-2010.

	Incident Outpatient PAD (N=873)	Incident Inpatient PAD (N=213)
Median number of PAD-related outpatient visits (Q1, Q3)		
Within six months of diagnosis	1 (0, 2)	0 (0, 1)
Within a year of diagnosis	2 (0, 3)	1 (0, 2)
Within two years of diagnosis	3 (1, 6)	1 (0, 3)
Median number of primary care outpatient visits (Q1, Q3)		
Within six months of diagnosis	2 (1, 4)	2 (1, 4)
Within a year of diagnosis	4 (2, 8)	4 (1, 7)
Within two years of diagnosis	9 (4, 14)	8 (3, 13)
Median number of cardiology outpatient visits (Q1, Q3)		
Within six months of diagnosis	0 (0, 1)	0 (0, 1)
Within a year of diagnosis	0 (0, 2)	0 (0, 2)
Within two years of diagnosis	1 (0, 3)	1 (0, 4)
Median number of podiatry outpatient visits (Q1, Q3)		
Within six months of diagnosis	0 (0, 2)	0 (0, 0)
Within a year of diagnosis	1 (0, 3)	0 (0, 0)
Within two years of diagnosis	1 (0, 6)	0 (0, 1)

CHAPTER 7. CONCLUSIONS AND PUBLIC HEALTH IMPLICATIONS

Peripheral artery disease is a disabling atherosclerotic disorder that is expected to increase in prevalence as the population ages. Current estimates of PAD burden have not considered the setting of clinical encounter (inpatient versus outpatient setting) and estimates of outpatient burden are rare. The limited information regarding outpatient PAD clinical encounters has been a barrier to our understanding of the post-diagnosis health care associated with PAD, from initial diagnosis through clinic visits, admissions, and procedures. The specific aims of this dissertation, therefore, were to 1) estimate the prevalence and incidence of peripheral artery disease in the outpatient and inpatient settings; and 2) to estimate the frequency of health care encounters and mortality following an incident PAD diagnosis in the outpatient or inpatient setting.

7.1 Methodologic Challenges Addressed

The existing literature regarding PAD burden contains widely varying estimates obtained using a variety of detection methods, including ankle-brachial index measurement [41, 64] and self-report questionnaires [11, 67]. Administrative claims data sources are increasingly being used for research purposes and offer an opportunity to apply consistent disease definitions across studies [185]. Our study, in which we used PAD-related diagnostic codes identified from extant claims-based research, improves on the methodological sophistication of claims-based PAD research by providing burden estimates stratified by setting of diagnosis and by presenting data on the post-diagnosis care associated with a PAD diagnosis. Further methodologic improvements in our work apply to: 1) age standardizing to the age, race, and sex distribution of the Medicare

population, 2) reducing misclassification bias through the use a washout (look-back) period according to current recommendations (2 years) to distinguish incident from prevalent cases of PAD [170], and 3) the use of codes from prior claims-based studies [169]. This study, therefore, represents reproducible and rigorous methodology and is accessible to the wider community of investigators.

As a further methodologic point of significance, the literature commonly treats death as a non-informative censored event, meaning that subsequent hazard of death and the outcome of interest are independent conditional on covariates. We expected substantial mortality associated with a diagnosis of PAD, as well as informative censoring. Therefore, death was not treated as a censored event to avoid selection bias that could have led to mis-estimation of the outcome, and our analyses accounted for death as a competing risk using the cumulative incidence function. This analytic approach appears to be unique in the study of PAD.

7.2 The Advantage of Linkage with the ARIC Cohort

We further contribute to the extant claims-based assessments of PAD outcomes by our inclusion of comorbidity data. Prior claims-based studies of PAD have been based on information available in the claims data to estimate comorbid conditions [185], and as such, often lacked critical information on covariates related to PAD. Because our study linked a well characterized longitudinal cohort study (ARIC) to CMS Medicare claims data we were able to draw on the rich level of information available for covariates from cohort examination visits and annual follow-up questionnaires [8]. As examples, we were able to include in this analysis important demographic traits, such as race, which are frequently missing in claims data [196], as well as information on the relationship of socioeconomic status to PAD, as we found that more than half of individuals with PAD had a low family income (<$35,000/year) and about 30% had less than a high school education. We were also able to use as study outcomes heart failure,

stroke, and coronary heart disease events from the cohort, classified according to a standardized protocol and reviewed by a panel of clinical experts, which increased the validity of our estimates relative to the use of ICD codes to define events, as often done with claims data. Lastly, the linkage of the ARIC cohort to the CMS claims data provided the opportunity to ascertain key differences between individuals diagnosed with PAD in the inpatient versus outpatient settings that would not have been possible from claims data alone.

7.3 High Estimates of Burden and Frequency of Care Could Raise Awareness about PAD

Despite the known coexistence of PAD with other major circulatory system disorders [17, 34], health professional and public awareness of PAD is low in comparison with the awareness of diseases such as stroke, CHD, heart failure, and atrial fibrillation [11, 171]. Interestingly, our PAD prevalence estimates are similar to recent assessments of prevalence of stroke (5-6% in 60-79 year olds; 14-16% in 80+ year olds) and CHD (10-20% in 60-79 year olds, 19-32% in 80+ year olds) [181]. These findings support the National Cholesterol Education Program guidelines from the Adult Treatment Panel III, which considers the risk of ischemic events in those with PAD to be equivalent to the risk among those with CHD [197]. Still, while these estimates suggest a significant PAD burden, clinicians often do not evaluate for the presence of PAD. Furthermore, up to 50% of individuals with PAD are asymptomatic and might not be actively seeking PAD-related care [11]. Our claims-based estimates, which capture PAD in a clinical setting and would be unlikely to include asymptomatic PAD, therefore, are likely an underestimation of the prevalence and incidence of PAD in the Medicare-aged population. While we found an overall mean age-standardized prevalence of 12.4% in those 65 years of age and older, the prevalence of PAD could be much higher if asymptomatic disease had been identified. Still, participants with known PAD in our study were frequent utilizers of health care and had high mortality rates, particularly following an inpatient diagnosis. By pointing to

the burden, utilization and mortality associated with PAD, we hope that the publications based on this dissertation work will bring increased awareness of PAD and that our work could lead to better identification and management of this important disease.

7.4 High Mortality and Frequent Hospitalizations Following Inpatient PAD Diagnosis Highlights the Potential Importance of Early Identification, Screening, and Risk Factor Modification

Participants with PAD frequently have coexisting symptomatic coronary or cerebrovascular disease and up to half could have underlying asymptomatic CVD [17]. These coexisting diseases share a risk factor profile, thus, controlling modifiable risk factors among participants with PAD can not only help prevent PAD progression, but could be beneficial in delaying myocardial infarction, stroke, and reducing cardiovascular-related mortality [35]. Despite the significance of PAD to individuals (reduced quality of life, frequent hospitalizations, high risk of death) and to the health care system, particularly if not identified early, the US Task Preventive Services Task Force (USPSTF) has recommended against routine screening for PAD [198]). The USPSTF concluded that screening led to marginal benefits to those with PAD while inducing unnecessary harms to the individual. We (and others) take issue with the Task Force recommendation, which uses improvement in leg symptoms as its benefits measure [199]. We would argue that screening for PAD, which requires a simple (and largely risk-free) ABI test (section 3.4), could lead to early identification of these atherosclerotic diseases and patients could be placed into a lifestyle intervention program and managed with guideline recommended medications, to reduce the risk of these major cardiovascular adverse events [200]. While we agree with the USPSTF that routine screening on the entire population would produce little benefit, at a minimum, we concur with the American Diabetes Association's recommendation that all diabetics be screened for PAD every five years for life [136]. In addition, when paired with other recent PAD studies our results suggest the potential benefit of periodic screening for

PAD of high risk individuals 65 years of age and older, including smokers and those with a history of CVD, particularly given the increased risk of adverse cardiovascular events that individuals with PAD are known to have [35]. We note however that our data do not directly address the pros and cons of screening strategies of this kind.

7.5 Limitations Leading to Future Work

Limitations we experienced in our research point to areas of future work. Our original aims included consideration of burden and post-diagnosis care estimates by PAD subtypes, including lifestyle-limiting claudication and critical limb ischemia. Were however limited to claims data for the ARIC cohort, to the exclusion of the broader epidemiologic community surveillance data, resulting in a study size too small to stratify by subtype. CLI remains a disease for which there is a significant need for research regarding incidence and outcomes, particularly as the locus of PAD management is shifting to outpatient settings.

We encountered similar sample size issues in our estimates stratified by race-gender groups, limiting our ability to draw conclusions regarding disparities in PAD and PAD-related care. Our overall findings do point to racial differences in the prevalence and incidence of PAD, with blacks having higher burden as compared to whites. Blacks had a lower time to first hospitalization as compared to whites, although confidence intervals were imprecise. The analysis we conducted should be replicated in other settings and with larger sample sizes.

7.6 Validation Studies and PAD Misclassification

To date there have been no studies that validate a full range of diagnostic codes used to quantify inpatient and outpatient PAD, an important gap in the current literature [158]. As part of this dissertation research the classification of PAD based on claims records was compared to information from hospitalization record abstraction and self-reported PAD on annual telephone interviews of the ARIC cohort members. We developed a hospital record abstraction form (see

Appendix 1) to evaluate incident hospitalized PAD events obtained from hospital discharge data available for ARIC cohort participants. Comparability ratios were calculated from these data as a direct estimate of the bias from using ICD-9-CM codes to define inpatient PAD events (under the assumption that our validation protocol is the gold standard). We found that misclassification of PAD using ICD-9-CM codes, particularly those in the primary or second position, is minimal. We also estimated calibration factors associated with outpatient PAD occurrence by estimating concordance between information on self-reported PAD events available from the ARIC annual follow-up (AFU) and outpatient PAD identified from the CMS claims. Poor agreement was found between claims-based outpatient PAD and the self-reported, physician-diagnosed PAD and/or lower extremity revascularization, suggesting the need for a more comprehensive evaluation of the reproducibility and accuracy of self-report to identify PAD recorded in CMS Medicare claims records.

7.7 Conclusion

Individuals aged 65 years and older enrolled in CMS claims for fee-for-service program experience high prevalence and incidence of PAD, particularly for PAD identified in the outpatient setting: the mean age-standardized prevalence and incidence of outpatient PAD were 11.8% and 22.4 per 1000 person-years, respectively. Black individuals have higher mean age-standardized prevalence and incidence compared to whites, 15.6% vs. 11.4%, and 31.3 vs. 25.4 per 1000 person-years, respectively. Individuals diagnosed in the outpatient setting have lower mortality than individuals diagnosed in the inpatient setting. Individuals who are initially managed in the outpatient setting represent a group that could be targeted to prevent expensive hospitalizations, PAD-related complications such as limb amputation, and major cardiovascular events. Effective prevention of PAD and its sequelae in blacks represents an important area of persisting disparities to be addressed. Finally, up to half of individuals with PAD remain asymptomatic, a group with subclinical disease for whom early detection via screening could lead to preventive care and management to lower risks of long-term adverse health outcomes.

APPENDIX 1: CALIBRATION ANALYSES

Inpatient Calibration

All incident hospitalized PAD events (n=71) that took place during the calendar year 2007 among ARIC cohort participants were eligible for review. Sixty-four (90.1%) of the 71 requested records were located at the ARIC field centers and sent securely to the investigators. Records for two events were incomplete and were excluded from this analysis. Five additional records were excluded from this analysis because they were part of the training/calibration of reviewers. The remaining fifty-seven records were examined and classified by two reviewers. Forty events were classified as definite/probable PAD, establishing a positive predictive value of 70.2% (40/57).

Appendix Table 1. Adjudication of PAD-related hospitalizations

	Validated PAD (Adjudication)		
Test Result	Yes	No	Row sum
ARIC PAD hospitalization	$a = 40$	$b = 17$	$r_1 = 57$
ARIC Non-PAD hospitalization	$c = 20$	$d = 523$	$r_2 = 543$
Column sum	$c_1 = 60$	$c_2 = 540$	$N = 600*$

* N can vary depending on prevalence assumption

Given a sensitivity of 0.67 we calculate an expected specificity of 0.97 and a comparability ratio of 0.95. The comparability ratio is a direct estimate of the bias found in using ICD-9-CM codes to define PAD events (under the assumption that our validation protocol is the gold standard and correct). With a comparability ratio of 0.95 (for sensitivity=0.67), inpatient PAD defined by ICD-9-CM codes (as they are in CMS claims) *underestimates* events by 5% in our ARIC population.

Appendix Table 2. Comparability ratios based on empirical estimates of sensitivity from literature

Given estimated sensitivity	a	b	c	d	Calculated specificity	Calculated comparability ratio
0.40	40	17	60	483	0.97	0.57 (57/100)
0.50	40	17	40	503	0.97	0.71 (57/80)
0.60	40	17	27	516	0.94	0.85 (57/67)
0.70	40	17	17	526	0.93	1.0 (57/57)
0.80	40	17	10	533	0.91	1.14 (57/50)

Outpatient Calibration

We estimated the concordance between PAD events in the CMS claims and a positive answer to the PAD-related question in the self-reported ARIC annual follow-up questionnaire. Among 7136 participants, we found 183 positive PAD events in the AFU. Of those 183 events, 76 were simultaneously identified in the claims. Another 717 events were identified in claims that were not found in ARIC AFU responses. Overall, we found a prevalence and bias adjusted kappa (PABAK) of 0.42. We found poor agreement between claims and the self-report AFU to identify PAD events.

Appendix Table 3. Agreement between self-report PAD and PAD identified in claims

	PAD Event in Claims		
Questionnaire	Yes	No	Row sum
Positive	a = 76	b =107	r_1 = 183
Negative	c = 717	d = 6236	r_2 = 6953
Column sum	c_1 = 793	c_2 = 6343	N = 7136

PABAK=0.42

PERIPHERAL ARTERY DISEASE DIAGNOSIS (PADX) FORM

a. Reviewer initials: ☐☐☐   b. Event ID: ☐☐☐☐☐☐☐☐

	Yes, current	Yes, history	No/ NR
1. Did the patient **ever have any of the following diagnoses/symptoms**:			
1a. Claudication (LE pain with walking)?			
1b. Critical limb ischemia, gangrene, ulcer due to ischemia?			
1c. Lower extremity wound or ulcer?			
1d. IF YES, Was this diagnosed as a diabetic ulcer?			
1e. Diabetes?			
1f. Peripheral neuropathy?			
1g. Edema?			
1h. Diminished pulses?			
1i. Peripheral arterial disease?			
If YES, was PAD only documented as due to:			
1j. Carotid/cerebrovascular			
1k. Abdominal Aortic Aneurysm (AAA)			
1l. Renal artery disease			

Diagnostic Tests

	Yes, current	Yes, history	No/ NR
2a. Was an exercise test performed?			
2b. If YES, was test positive for claudication?			
3a. Was an ankle brachial index (ABI) performed?			
3b. If YES, was ABI ≤ 0.90?			
4a. Was LE angiography/CT angiography performed?			
4b. If YES, did angiography show a blockage or plaque?			

Procedures

	Yes, current	Yes, history	No/ NR
5. Ever had LE angioplasty or stent?			
6. Ever had LE surgical revascularization?			
7. Ever had LE amputation?			

Reviewer Classification	Definite	Probable	PAD unlikely	Unclassifiable
8a. Does the patient have PAD?				
8b. If definite or probable, is it CLI?				

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Question-by-Question Instructions for Peripheral Artery Disease Final Diagnosis Form

A Peripheral Artery Disease Diagnosis Form (PADX) is completed for each ARIC PAD hospitalization. The goal of this review is to be specific rather than too sensitive. Events are hospitalized events only. Your materials for each case will include: the PADX form, medical record documents such as a discharge summary, history and physical exam, and consults. PAD diagnosis refers to atherosclerotic disease in the iliac arteries or below; PAD includes a variety of diagnoses including (but not limited to) intermittent claudication, ischemic ulcers, gangrene and treatments including angioplasty, surgery, or amputation.

Complete only one PADX for each event.

Items: Review of PAD Diagnosis

Review information provided to determine if this event meets criteria for PAD event. PAD will be classified as definite PAD, probable PAD, no PAD, or unclassifiable based on the following criteria:

Based on your review of the medical record documents provided, indicate either Yes or No/Unknown for this criteria.

SECTION I: DIAGNOSES/SYMPTOMS

This section includes symptoms/physical exam findings or diagnoses associated with peripheral artery disease that may be present in the admission history and physical or the physician consult notes.

1. Did the patient ever have any of the following diagnoses or symptoms/findings?

1a. Claudication

Review the medical record for statements regarding claudication when walking any distance. Alternative wordings that are sufficient to record 'YES' include: tired legs after walking, complains of leg weakness after walking, exertional leg pain relieved at rest, lower extremity cramping. Record 'YES, current' if this is an active problem. Record 'Yes, history' if this is a historical problem. Record 'No/NR' if only weak legs are described or if the claudication is neurogenic or if a spinal stenosis is mentioned.

1b. Critical limb ischemia, gangrene, ulcer due to ischemia

Review the medical record for statements regarding critical limb ischemia. Synonyms include: limb threatening ischemia. Other diagnoses that are relevant to record 'YES' include: rest pain, pain at rest, tingling in the foot/toes relieved with dangling the extremity, tissue loss of the lower extremities, ulceration of the toe/foot/leg/calf/shin/thigh/heel, diabetic foot ulcer, open leg wound, lower extremity necrosis, gangrene. Record 'YES, current' if this is an active problem.

Record 'Yes, history' if this is a historical problem. Record 'No/NR' if upper extremity mentioned or if there is no mention of the above terms.

1c. <u>Lower extremity wound or ulcer</u>

Review the medical record for statements regarding lower extremity wounds or lower extremity ulcers. Record 'YES, current' if this is an active problem. Record 'Yes, history' if this is a historical problem. Record 'No/NR' if there is no mention of LE wounds or ulcers. Record no if wound is due to trauma.

1d. <u>If 'YES', was this diagnosed as a diabetic foot ulcer?</u>

Review the medical record for statements regarding diabetic foot ulcers Record 'YES, current' if this is an active problem. Record 'Yes, history' if this is a historical problem. Record 'No/NR' if there is no mention of diabetic foot ulcer.

1e. <u>Diabetes</u>

A history of diabetes includes a history of previous hospitalizations for ketoacidosis, hyperosmolar coma, or out of control glucose levels and those with juvenile onset diabetes, brittle diabetes, or diabetes treated with insulin or oral hypoglycemic drugs, a history of type I diabetes, a history of type II diabetes and current treatment with an oral hypoglycemic or insulin. If newly diagnosed during this hospitalization, consider this as a current problem and record 'Yes, current'. Record 'YES, current' if this is an active problem. Record 'Yes, history' if this is a historical problem. Record 'No/NR' if there is no mention of diabetes.

Synonyms: insulin dependent diabetes (IDDM), non-insulin dependent diabetes (NIDDM), diabetes mellitus (DM).

1f. <u>Peripheral neuropathy</u>

Review the medical record for statements regarding peripheral neuropathy. Synonyms include lower extremity neuropathy, diabetic neuropathy, and neuropathy. Record 'YES, current' if this is an active problem. Record 'Yes, history' if this is a historical problem. Record 'No/NR' if there is no mention of neuropathy.

1g. <u>Lower extremity edema</u>

Review the medical record for statements regarding lower extremity edema. Synonyms include: LE edema, peripheral edema, swollen ankles, 1+, 2+, 3+, 4+ pitting, nonpitting edema, trace, brawny edema. Record 'YES, current' if this is an active problem. Record 'Yes, history' if this is a historical problem. Record 'No/NR' if there is no mention of edema.

1h. <u>Does the patient have diminished or absent pulses?</u>

Review the "EXTREMITIES" section of the review of symptoms within the H&P for statements regarding diminished or absent pulses in the lower extremity arteries including: femoral, popliteal, tibial (posterior, anterior), peroneal, and dorsalis pedis. If pulses noted as 1+, 2+, 3+ pulses then they are not diminished and you should record 'No/NR'. Record 'YES, current' if this is an active problem. Record 'Yes, history' if this is a historical problem. Record 'No/NR' if there is no mention of diminished pulses.

1i. Peripheral arterial disease

Record 'YES' if the patient has a history of peripheral artery disease (PAD). This condition may also be referred to as peripheral vascular disease (PVD), which includes atherosclerotic disease of the arteries in the legs and arms. Synonyms include intermittent claudication, lower extremity arterial disease (LEAD). PVD does NOT include carotid or renal disease, however sometimes people refer to such disease as PAD. If stated to have PAD due to carotid, renal, or AAA then answer YES, then answer questions below. Record 'YES, current' if this is an active problem. Record 'Yes, history' if this is a historical problem. Record 'No/NR' if there is no mention of PAD.

If 'YES', was PAD only documented due to:

1j. Carotid/cerebrovascular disease?

Only answer YES here if the person does not have PAD in a peripheral location, but only the carotids or cerebrovascular area that is likely the source of the PAD diagnosis. Record 'YES, current' if this is an active problem. Record 'Yes, history' if this is a historical problem. Record 'No/NR' if there is no mention of this.

1k. Abdominal Aortic Aneurysm (AAA)?

Only answer YES here if the person does not have PAD in a peripheral location, but only has an AAA that is likely the source of the PAD diagnosis. Looking for PAD mentioned with an AAA manifestation. Record 'YES, current' if this is an active problem. Record 'Yes, history' if this is a historical problem. Record 'No/NR' if there is no mention of AAA.

1l. Renal artery disease?

Only answer YES here if the person does not have PAD in a peripheral location, but only in renal vasculature that is likely the source of the PAD diagnosis. Record 'YES, current' if this is an active problem. Record 'Yes, history' if this is a historical problem. Record 'No/NR' if there is no mention of renal artery disease or if this manifestation is only end-stage renal disease (ESRD).

SECTION II: DIAGNOSTIC TESTS

The purpose of this section is to determine if any diagnostic tests were completed relating to the lower extremity arteries.

2a. <u>Was an exercise test performed?</u>

Record 'YES, current' if there is evidence that an exercise test was performed during this admission/hospitalization. Record 'Yes, history' if there is evidence that an exercise test was performed from a prior office visit/hospitalization.

2b. <u>If 'YES', was the test positive for claudication?</u>

Record 'YES' if the test results indicate claudication.

3a. <u>Was an ankle brachial index test performed?</u>

Record 'YES, current' if there is evidence that an ankle brachial index test was performed during this admission/hospitalization. Record 'YES, history' if there is evidence that an ABI was performed during a prior office visit/hospitalization.

3b. <u>If 'YES', was the ankle-brachial systolic blood pressure ratio < 0.90?</u>

Record 'YES' if the test revealed an ABI of ≤ 0.90 in either leg.

4a. <u>Was angiography of the lower extremity performed?</u>

A lower extremity angiogram is a test of the lower extremity arteries where a catheter is inserted into an artery and advance to the lower extremity arteries to assess for blockages. Synonyms include: lower extremity catheterization, arteriography. Record 'YES, current' if there is evidence that angiography of the lower extremity was performed during this admission/hospitalization. If a person had a percutaneous transluminal angioplasty (PTA) record 'YES'. If a person had CT angiography of the lower extremities, record 'YES'. Record 'Yes, history' if there is evidence of lower extremity angiography performed in a prior admission/hospitalization. Record 'No/NR' if there is no mention of this procedure.

4b. <u>If 'YES', did the angiography demonstrate a plaque > 50% diameter or > 75% of cross-section of artery)</u>

Record 'YES' if the angiography demonstrates a plaque $\geq 50\%$ diameter or $\geq 75\%$ of cross-section of artery).

SECTION III: THERAPEUTIC PROCEDURES

5. <u>Has the patient ever had a percutaneous transluminal angioplasty/stent procedure performed on a lower extremity artery?</u>

Angioplasty is a procedure used to dilate (widen) narrowed arteries. A catheter with a deflated balloon angioplasty on its tip is passed into the narrow artery segment, the balloon inflated, and the narrow segment widened. Angioplasties can now also be done by laser. To keep arteries from collapsing, stents (stainless steel supports) can be inserted into the artery during angioplasty. This interventional procedure is often performed electively when the presence of severe blockages that needs to be treated. PTA may also include thrombolysis which involves injecting clot-busting medicine directly into the artery. An unsuccessful PTA or stent procedure in the past should be recorded as 'YES' for history of PTA. Synonyms include percutaneous angioplasty, balloon dilation, balloon test.

Lower extremity arteries include the abdominal aorta, iliac (common, external, internal), femoral (superficial, deep, profunda), popliteal (above knee, below knee), tibial (anterior, posterior), tibioperoneal trunk, or the dorsalis pedis. Record 'YES' if there is evidence that this treatment was performed.

Record 'YES, current' if this is procedure occurred during this admission/hospitalization. Record 'Yes, history' if this is a historical procedure. Record 'No/NR' if there is no mention of a procedure.

6. <u>Has the patient ever had a surgical revascularization performed on a lower extremity artery?</u>

Surgical revascularization includes lower extremity bypass or endarterectomy. Endarterectomy is surgery to take out plaque from an artery. Locations include: Aortic/Iliac endarterectomy, Femoral endarterectomy, Popliteal/Tibial endarterectomy. Bypass is a procedure where additional blood flow is brought to an artery via a bypass from a location elsewhere in the body. Bypass possibilities include: Aorto-iliac, Aorto-femoral, Femoral to popliteal, Femoral-tibial, Popliteal-tibial, and Tibial to tibial). Record 'YES, current' if there is evidence that this treatment was performed during this admission/hospitalization. Record 'YES, history' if there is evidence that this treatment was performed during a prior admission/hospitalization. Record 'No/NR' if there is no mention of a procedure.

7. <u>Has the patient ever had an amputation?</u>

Amputation is a procedure in which part of the extremity is removed. Options include: toe(s), transmetatarsal, forefoot, chopart, below-knee (BKA), through-knee (TKA), above-knee (AKA), or hip disarticulation. Record 'YES, current' if there is evidence that this treatment was performed. Record 'YES, history' if there is evidence that this treatment was performed during a prior admission/hospitalization. Record 'No/NR' if there is no mention of a procedure.

SECTION IV: REVIEWER CLASSIFICATION

8a. <u>Does the patient have PAD?</u>

Classification is: DEFINITE, PROBABLE, PAD UNLIKELY, or UNCLASSIFIABLE.

If recorded 'Yes, current' or 'Yes, history' for any of the following: 1a, 1b, 1c, 2b, 3a, 4a classification is DEFINITE. If recorded 'Yes, current' or 'Yes, history' for 5, 6, or 7 AND any of the following: 1a, 1b, 1c, 2b, 3a, 4a classification is DEFINITE. If recorded 'Yes, current' or 'Yes, history' for 1i <u>AND</u> 'No/NR' for 1j, 1k, 1l, classification is DEFINITE.

If recorded 'Yes, current' or 'Yes, history' for 1g or 1h, classification is PROBABLE. If recorded 'Yes, current' or 'Yes, history' for 5, 6, or 7 and 'No/NR' for all of the following: 1a, 1b, 1c, 2b, 3a, 4a, classification is PROBABLE.

If recorded 'No/NR' for 1a, 1b, 1c, 1i, 2b, 3a, 4a, 5, 6, <u>AND</u> 7, classification is PAD UNLIKELY. If recorded 'Yes, current' or 'Yes, history' for 1j, 1k, 1l then classification is PAD UNLIKELY.

Otherwise classification is UNCLASSIFIABLE.

8b. <u>If definite or probable, is it CLI?</u>

Classification is: DEFINITE, PROBABLE, CLI UNLIKELY, or UNCLASSIFIABLE.

If recorded 'Yes, current' or 'Yes, history' for 1b <u>OR</u> "1c or 1d AND 1i" <u>OR</u> "5, 6, or 7 <u>AND</u> 1b, 1c, or 1d", classification is DEFINITE.

If recorded 'No/NR' for 1b, 1c then CLI UNLIKELY.

Otherwise classification is UNCLASSIFIABLE

APPENDIX 2: DEFINITIONS OF PAD CODES

CD-9-CM Diagnosis Codes for PAD: Definitions	
Description	**Code**
Atherosclerosis:	
of native arteries of the extremities	440.2x
of bypass graft of the extremities	440.3x
of other specified arteries	440.8x
Generalized and unspecified atherosclerosis:	
arteriosclerotic vascular disease NOS	440.9×
Peripheral vascular disease, unspecified	443.9x

ICD-9-CM Surgical/Intervention Procedure Codes for PAD: Definitions	
Description	**Code**
Amputation of lower limb	84.1x
Amputation not otherwise specified	84.91
Aorta-iliac-femoral bypass	39.25
Other (peripheral) vascular shunt or bypass	39.29
Incision of lower limb arteries	38.08
Endarterectomy, lower limb arteries	38.18
Resection of vessel with anastomosis, lower limb arteries	38.38
Resection of vessel with replacement, lower limb arteries	38.48
Other excision of vessels, lower limb arteries	38.68
Other revision of vascular procedure	39.49
Angioplasty or atherectomy of other non-coronary vessel(s) Insertion of non-drug-eluting peripheral vessel stent(s)	39.50 39.90
Repair of blood vessel with tissue patch graft	39.56
Repair of blood vessel with synthetic patch graft	39.57
Repair of blood vessel with unspecified type of patch graft	39.58

ICD-9-CM Diagnostic Procedure Codes for PAD: Definitions	
Description	**Code**
Other diagnostic procedures on blood vessels	38.29
Aortography	88.42
Arteriography of femoral and other lower extremity arteries Diagnostic ultrasound	88.48
of peripheral vascular system	88.77

CPT-4 codes for PAD-related surgical or intervention procedures: Definitions	
Description	**Code**
Repair blood vessel lower extremity;	
direct	35226
with vein graft	35256
with graft other than vein	35286
Thromboendarterectomy, including patch graft, if performed; superficial femoral artery	
popliteal artery	35302
tibioperoneal trunk artery	35303
tibial or peroneal artery, initial vessel	35304
each additional tibial or peroneal artery	35305
	35306
Thromboendarterectomy, with or without patch graft;	

abdominal aorta (35331);	35331
iliac (35351);	35351
iliofemoral (35355);	35355
combined aortoiliac (35361);	35361
combined aortoiliofemoral (35363);	35363
common femoral (35371);	35371
deep (profunda) femoral (35372);	35372
femoral and/or popliteal, and/or tibioperoneal (35381)	35381
In-situ vein bypass;	
aortofemoral-popliteal (only femoral-popliteal portion in-situ)	35582
femoral-popliteal	35583
femoral-anterior tibial, posterior tibial, or peroneal artery	35585
popliteal-tibial, peroneal	35587
Bypass graft, with vein;	
axillary-femoral	35521
axillary-femoral-femoral	35533
aortoiliac	35537
aortobi-iliac	35538
aortofemoral	35539
aortobifemoral	35540
aortoiliac or bi-iliac	35541
aortofemoral or bifemoral	35546
aortoiliofemoral, unilateral	35548
aortoiliofemoral, bilateral	35549
aortofemoral-popliteal	35551
femoral-popliteal	35556
femoral-femoral	35558
ilioiliac	35563
iliofemoral	35565
femoral-anterior tibial, posterior tibial, peroneal artery or other distal vessels	35566
popliteal-tibial,-peroneal artery or other distal vessels	35571
Percutaneous:	
aortic	35491
iliac	35492
femoral-popliteal	35493
tibioperoneal trunk and branches	35495
Transluminal peripheral atherectomy, Open:	
aortic	35481
iliac	35482
femoral-popliteal	35483
tibioperoneal trunk and branches	35485
Transluminal balloon angioplasty, percutaneous;	
tibioperoneal trunk and branches, each vessel	35470
aortic	35472
iliac	35473
femoral-popliteal	35474
Transluminal balloon angioplasty, open;	
aortic (35452);	35452
iliac (35454);	35454
femoral-popliteal (35456);	35456

tibioperoneal trunk and branches (35459);	35459
Bypass graft, with other than vein;	
axillary-femoral	35621
axillary-popliteal or –tibial	35623
aortoiliac	35637
aortobi-iliac	35638
aortoiliac or bi-iliac	35641
aortofemoral or bifemoral	35646
aortofemoral	35647
aortofemoral-popliteal	35651
axillary-femoral-femoral	35654
femoral-popliteal	35656
femoral-femoral	35661
ilioiliac	35663
iliofemoral	35665
femoral-anterior tibial, posterior tibial, or peroneal artery	35666
popliteal-tibial or -peroneal artery	35671
Exploration, reoperation, femoral-popliteal or femoral (popliteal) -anterior tibial, posterior tibial, peroneal artery or other distal vessels, more than one month after original operation (List separately in addition to code for primary procedure)	35700
Exploration (not followed by surgical repair), with or without lysis of artery;	
femoral artery	35721
popliteal artery	35741
Thrombectomy of arterial or venous graft, with revision of arterial or venous graft	35876
Revision, lower extremity arterial bypass, without thrombectomy, open;	
with vein patch angioplasty	35879
with segmental vein interposition	35881
Revision, femoral anastomosis of synthetic arterial bypass graft in groin, open;	
with non autogenous patch graft (e.g., Dacron, ePTFE, bovine pericardium)	35883
with autogenous vein patch graft	35884
Primary percutaneous transluminal mechanical thrombectomy, noncoronary, arterial or arterial bypass graft, including fluoroscopic guidance and intra procedural pharmacological thrombolytic injection(s);	
initial vessel	37184
second and all subsequent vessel(s) within the same vascular family (List separately in addition to code for primary mechanical thrombectomy procedure)	37185
Secondary percutaneous transluminal thrombectomy (e.g., non primary mechanical, snare basket, suction technique), noncoronary, arterial or arterial bypass graft, including fluoroscopic guidance and intra procedural pharmacological thrombolytic injections, provided in conjunction with another percutaneous intervention other than primary mechanical thrombectomy (List separately in addition to code for primary procedure)	37186
Transcatheter placement of an intravascular stent(s), (except coronary, carotid, and vertebral vessel), percutaneous;	
initial vessel (37205)	37205
each additional vessel (List separately in addition to code for primary procedure)	37206
Transcatheter placement of an intravascular stent(s), (except coronary, carotid, and vertebral vessel), open;	
each additional vessel (List separately in addition to code for primary procedure)	37208
Disarticulation;	
of hip	27295

at knee	27598
of ankle	27889
Amputation, thigh, through femur, any level	27590
immediate fitting technique including first cast	27591
open, circular (guillotine)	27592
leg, through tibia and fibula	27880
with immediate fitting technique including application of first cast	27881
open, circular (guillotine)	27882
ankle, through malleoli of tibia and fibula (e.g., Syme, Pirogoff type procedures), with plastic closure and resection of nerves	27888
foot; midtarsal (e.g., Chopart type procedure)	28800
transmetatarsal	28805

CPT-4 codes for PAD-related diagnostic procedures: Definitions	
Description	**Code**
Aortography: abdominal plus bilateral iliofemoral lower extremity, catheter, by serialography, radiological complete procedure	75630
	75631
Angiography, extremity, unilateral, radiological supervision and interpretation	75710
complete procedure	75711
bilateral; by serialography, complete procedure	75712
radiological	75716
without serialography; complete procedure	75717
by serialography, complete procedure	75718
Arterial duplex of the lower extremities,	
unilateral	93925
bilateral	93926
aorta	93978
CT Angiogram Abdomen with & w/o contrast	74175
Pelvis	72191
Lower Extremity	73706
abdominal aorta and bilateral iliofemoral lower extremity runoff	75635
MRA abdomen images from the diaphragm to the umbilicus or iliac crest	74185
Pelvis	72198
Lower extremity w/ or w/o contrast	73725
Non-invasive physiologic studies of lower extremity arteries, single level, bilateral	93922
at rest and following treadmill stress testing, complete bilateral study	93924

Other PAD-related codes not included in the Mayo algorithm: Definitions	
Description	**Code**
Atherosclerosis of aorta	440.0
Chronic total occlusion of artery of the extremities	440.4
Arterial embolism and thrombosis of lower extremity	444.22
Embolism and thrombosis of iliac artery	444.81
Atheroembolism of lower extremity	445.02
Diabetes with peripheral circulatory disorders, Type II or unspecified type, not stated as uncontrolled	250.70
Diabetes with peripheral circulatory disorders, Type I (Juvenile type), not stated as uncontrolled	250.71

Diabetes with peripheral circulatory disorders, Type II or unspecified type, uncontrolled	
Diabetes with peripheral circulatory disorders, Type I (Juvenile type), uncontrolled	250.72
	250.73
Unspecified ulcer of lower limb:	707.10
of thigh	707.11
of calf	707.12
of ankle	707.13
of heel and midfoot	707.14
of other part of foot	707.15
of other part of lower limb	707.19
Gangrene	785.4
Endarterectomy, abdominal arteries	38.16
Other surgical occlusion of vessels, lower limb arteries	38.88

Exclusion codes for non-atherosclerotic vascular disease: Definitions	
Description	Code
Neurofibromatosis	237.7
Buerger's disease	443.1
Polyarteritis nodosa	446.0
Wegener's granulomatosis	446.4
Giant cell arteritis	446.5
Thrombotic microangiopathy	446.6
Takayasu's disease	446.7
Arteritis, unspecified	447.6
Systemic sclerosis	710.1
Coarctation of the aorta	747.1
Lower limb vessel anomaly	747.64
Atresia and stenosis of aorta	747.22

Exclusion codes for lower extremity trauma/injury and others: Definitions	
Description	Code
Acquired deformities of hip	736.3x
Genu valgum or varum (acquired)	736.4x
Genu recurvatum (acquired)	736.5
Other acquired deformities of knee	736.6
Other acquired deformities of ankle and foot	736.7x
Acquired deformities of other parts of limbs	736.8x
Acquired deformity of limb, site unspecified	736.9
Acquired deformities of toe	735.x
Congenital dislocation of hip	754.3x
Congenital genu recurvatum and bowing of long bones of leg	754.4x
Varus deformities of feet	754.5x
Valgus deformities of feet	754.6x
Other deformities of feet	754.7x
Other congenital anomalies of toes	755.02
Syndactyly of toes without fusion of bone	755.13
Syndactyly of toes with fusion of bone	755.14
Reduction deformities of lower limb	755.3
Reduction deformities, unspecified limb	755.4
Other anomalies of lower limb, including pelvic girdle	755.6x
Other specified anomalies of unspecified limb	755.8
Multiple congenital anomalies, so described	759.7
Other and unspecified congenital anomalies	759.89
Fracture of lower limb	820.xx - 829.xx
Dislocation;	
of hip	835.xx
of knee	836.xx
of ankle	837.xx
of foot	838.xx
Traumatic amputation;	
of toe(s), complete/partial	895.xx
of foot, complete/partial	896.xx
of leg(s) complete/partial	897.xx
Injury to blood vessels of lower extremity and unspecified sites	904.xx
Crushing injury;	
of lower limb	928.xx
of multiple and unspecified sites	929.xx
Injury, hip and thigh	959.6
Injury, knee, leg, ankle, and foot	959.7
Mechanical complication of internal orthopedic device, implant, and graft	996.4
Complications peculiar to certain specified procedures due to internal joint prosthesis	
Complications due to other internal orthopedic device, implant and graft	996.66
Other complications of internal (biological) (synthetic) prosthetic device, implant, and graft (due to internal joint prosthesis)	996.67
Complications due to other internal orthopedic device, implant, and graft	996.77
	996.78

Exclusion codes for non-PAD indication of amputation: Definitions	
Description	**Code**
Malignant neoplasm of pelvic bones, sacrum, and coccyx	170.6
Malignant neoplasm of bone and articular cartilage;	
long bones of lower limb	170.7
short bones of lower limb	170.8
Malignant neoplasm of bone and articular cartilage	170.9
Malignant neoplasm of connective and other soft tissue (lower limb, including hip)	171.3
Malignant melanoma of skin; lower limb, including hip	172.7
Other malignant neoplasm of skin; skin of lower limb, including hip	173.7
Secondary malignant neoplasm of other specified sites (bone and bone marrow)	198.5
Paraplegia	344.1
Pyogenic arthritis	711.0
Necrotizing fasciitis	728.86
Cyst of bone	733.2
Acquired deformities of hip	736.3x
Genu valgum or varum (acquired)	736.4x
Genu recurvatum (acquired)	736.5
Other acquired deformities of knee	736.6
Other acquired deformities of ankle and foot	736.7
Acquired deformities of other parts of limbs	736.8
Acquired deformity of limb, site unspecified	736.9
Acquired deformities of toe	735.x
Congenital dislocation of hip	754.3x
Congenital genu recurvatum and bowing of long bones of leg	754.4x
Varus deformities of feet	754.5
Valgus deformities of feet	754.6x
Other deformities of feet	754.7x
Other congenital anomalies of toes	755.02
Syndactyly of toes without fusion of bone	755.13
Syndactyly of toes with fusion of bone	755.14
Reduction deformities of lower limb	755.3
Reduction deformities, unspecified limb	755.4
Other anomalies of lower limb, including pelvic girdle	755.6x
other specified anomalies of unspecified limb	755.8
Multiple congenital anomalies, so described	759.7
Other and unspecified congenital anomalies	759.89
Fracture of lower limb	820.xx-829.xx
Dislocation;	
of hip	835.xx
of knee	836.xx
of ankle	837.xx
of foot	838.xx
Open wound of hip and thigh	890
Open wound of knee, leg (except thigh), and ankle	891
Traumatic amputation; of toe(s), complete/partial	895.xx
of foot, complete/partial	896.xx
of leg(s) complete/partial	897.xx
Injury to blood vessels of lower extremity and unspecified sites	904.xx

Late effect of fracture of lower extremities	905.4
Crushing injury; of lower limb	928.xx
of multiple and unspecified sites	929.xx
Injury, hip and thigh	959.6
Injury, knee, leg, ankle, and foot	959.7
Mechanical complication of internal orthopedic device, implant, and graft	996.4x
Complications peculiar to certain specified procedures due to internal joint prosthesis	996.66
Complications due to other internal orthopedic device, implant and graft	996.67
Other complications of internal (biological) (synthetic) prosthetic device, implant, and graft (due to internal joint prosthesis)	996.77
Complications due to other internal orthopedic device, implant, and graft	996.78

Appendix Table 4. PAD prevalence from population-based studies with assessment based on ABI measurement

Author, year Country N= Age range in years	Study Population	PAD Prevalence Estimates	Limitations
Selvin, 2004 United States N=2,174 Ages ≥ 40	National Health and Nutrition Examination Survey (NHANES); cross-sectional	4.3% (95% CI: 3.1, 5.5)	
McDermott, 2005 United States N=6,570 Ages 45-84	Multi-Ethnic Study of Atherosclerosis (MESA); cross-sectional	3.7%	Those with clinically evident cardiovascular disease were excluded
Fabsitz, 1999 United States N=4,276 Ages 45-74	The Strong Heart Study; 13 tribes across 3 diverse centers in the Dakotas, Oklahoma, and Arizona;	5.3%	
Criqui, 2005 United States N=2,343 Ages 29-91	The San Diego Population Study; randomly selected defined population of employees and retirees of UCSD in SoCal including 4 ethnic groups	4.4%	Women over-sampled
Zheng, 1997 United States N=15,106 Ages 45-64	Atherosclerosis Risk in Communities Study (1987-1989) in four US communities (NC, MD, MS MN)	3.0%	ABI in only one leg African Americans over-sampled in two centers
Newman, 1999 United States N=5,714 Ages ≥ 65	Cardiovascular Health Study in Medicare eligible participants	13.4%	

Appendix Table 5. PAD prevalence among clinic-based studies with assessment based on ABI measurement

Author, year Country N= Age range in years	Study Population	PAD Prevalence Estimates	Limitations
Alzamora, 2010 Spain N=3,786 Ages >49	PERART; Barcelona, Spain; randomly selected from 28 primary care centers, cross-sectional	7.6% (95% CI: 6.7, 8.4)	Women over-sampled
Diehm, 2004 Germany N=6,880 Ages ≥ 65	Observational German Epidemiological Trial on Ankle Brachial Index (getABI) Study; 344 general practitioners throughout Germany	18.0%	
Garofolo, 2007 Brazil N=1,008 Ages ≥ 30	Survey of first and second-generation Japanese-Brazilian participants from Baurau, Sao Paulo, Brazil	20.4%	Persons with chronic kidney disease were excluded
Collins, 2005 United States N=403 Ages ≥ 50	Participants screened from DeBakey VA and 3 primary care clinics in Harris County (Houston, TX)	16.7%	Small sample size suggesting low power to detect differences

Appendix Table 6. PAD prevalence studies with assessment based on both ABI and Questionnaire

Author, year Country N= Age range in years	Study Population	PAD Diagnostic Criteria	PAD Burden Estimates	Limitations
Meijer, 1998 Netherlands N=7,715 Ages ≥55	The Rotterdam Study; invited to participate	ABI < 0.90 and Rose Questionnaire	PAD prevalence = 19.1%; IC prevalence = 1.6% overall	Poor response rate in elderly; WHO/RQ has sensitivity of 60%
Fowler, 2002 Perth, Australia N= 4,470 Ages 65-83	Cross-sectional survey of randomly selected urban men from the Western Australia State Electoral Roll	ABI <0.90 and/or positive Edinburgh Questionnaire	Prevalence = 15.6% (14.5,16.6)	
Sigvant, 2007 Sweden N=5,080 Ages 60-90	Population-based in four different regions of Sweden	Any PAD (ABI<0.9; asymptomatic PAD, ABI <0.9 and negative questionnaire); IC, ABI <0.9 and positive questionnaire;	Any PAD prevalence=18.0%, Asymptomatic PAD = 11.1% IC = 6.8%	Low response rate (64%) Underestimate severe limb ischemia because of particularly low response rate in most elderly (≥ 80)
He, 2006 China N=2,334 Ages ≥ 60	Population-based study in Wanshoulu Community of Haidian District in Beijing, China	ABI < 0.90 and/or symptoms of IC measured by the WHO/RQ	ABI <0.90 prevalence = 15.3% IC prevalence = 11.3% Both IC and ABI <0.90 = 19.8%	WHO/RQ has sensitivity of 60%

Appendix Table 7. PAD prevalence among clinic-based studies with assessment based on self-report with/out ABI or questionnaire

Author, year Country N= Age range in years	Study Population	PAD Diagnostic Criteria	PAD Prevalence Estimates	Limitations
Hirsch, 2001 United States N=6,979 Ages ≥ 50	The PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) program, 27 sites and 25 cities and 350 primary care practices; aged ≥70 or 50-69 if had a history of DM or smoking	ABI <0.90 or PAD documented in medical record, or history of limb revascularization	29%	Not a population-based study; inclusion criteria leads to higher prevalence
Criqui, 1985 United States N=613 Ages 38-82	Lipid Research Clinics, half of subjects from random sample, half from high-risk cholesterol groups	IC measured by WHO/RQ; Self-report surgery, NIVS, pulses	27.7% (large or small vessel PAD) 16% isolated small-vessel PAD	Study in predominantly white, upper-middle class in S. Cal, higher risk population

Appendix Table 8. PAD prevalence among population-based studies with assessment based on self-report with/out ABI or questionnaire

Author, year Country N= Age range in years	Study Population	PAD Diagnostic Criteria	PAD Prevalence Estimates	Limitations
Kroger, 2009 Germany N=4,738 Ages 45-75	Heinz Nixdorf Recall Study of individuals in Bochum, Essen, and Mulheim/Ruhr, industrialized urban regions of W. Germany	ABI <0.90 and/or self-reported doctor-diagnosed PAD	6.8%	Poor response rate (55.8%)
Sritara, 2007 Thailand N=2,305 Ages 52-73	Cross-sectional study at Electric Generating Authority of Thailand's head plant (Nonthaburi) on all former and current employees who had participated in original survey to assess CVDs	ABI < 0.90 or had amputation, surgery, angioplasty because of DM but no hx of trauma	5.2%	Survivor bias Study completed in middle-class, urban population Only considered PAD if procedures related to DM

Appendix Table 9. PAD incidence studies with assessment based on various methodologies

Author, year Country N= Age range in years	Study Population	PAD Diagnostic Criteria	PAD Incidence Estimates	Limitations
Leng, 1996 Scotland n=1592 Ages 55-74	Edinburgh Artery Study; 1592 men and women aged 55-74 randomly selected from 10 general practices in 1987; cohort followed for five years	WHO/RQ, ABI, reactive hyperemia test	116 incident cases of claudication (cum inc=9%, IR=15.5 per 1000 person-years), 4.5% baseline prevalence of claudication.	Not true population-based study because sampled from GPs, only looked at claudication, Self-report
Hooi, 2001 Netherlands n=2589 Ages 40-78	Limburg PAOD Study (1998-1997) with source population from 18 general practice centers	ABI <0.95 for at least one leg measured twice at weekly intervals; Defined symptomatic IC by questionnaire	Overall incidence = 11.0 per 1000 person-years	Non-traditional cut-point for ABI Unvalidated questionnaire
Murabito, 2005 United States n=5209 Ages 29-62	Framingham Study, general population study in Mass 1950-1999	Unequivocal symptoms of IC, cases were adjudicated by panel	Incidence by decade (per 100,00 person-years): 1950-1969 (282), 1970-1979 (345), 1980-1989 (243), 1990-1999 (225)	All white population
Merino, 2010 Spain n=699 Ages 55-74	Pubilla Casas Artery Study in Barcelona, Spain identified via Pubilla Casas Primary Care Centre	ABI < 0.90	Baseline prevalence = 13.4% Incidence = 23.8 per 1000 person-years	All male population

Author, year Country N= Age range in years	Study Population	PAD Diagnostic Criteria	PAD Incidence Estimates	Limitations
Hsia, 2003 United States n=16,608 Ages 50-79	The Women's Health Initiative Estrogen Plus Progestin trial	Overnight hospitalization with either symptoms or intervention; confirmed by NIVS, revascularization, absence of pulses	Baseline prevalence=0.5%; Overall incidence = 13 per 1000 person-years among those with history of CHD or PAD; 1 per 1000 woman-years among those with no history of CHD or PAD	All female population

Appendix Table 10. PAD validation studies using ICD-9-CM or CPT-4 codes

Author, year N=	Study Population	Codes	Outcome (95% CI)
Heckbert, 2004 N=34,016	Women's Health Initiative; January 1994–November 2000	440.2 443.9	PPV = 31 (26,36) Sensitivity = 61 (54,68) Kappa = 0.40 (0.35,0.46)
Fisher, 1992 N=7,050	The National Diagnosis Related Group (DRG) Validation Study; The Office of the Inspector General, US Department of Health and Human Services, randomly sampled hospitals from each of three bed-size strata, excluding specialty hospitals and those in states not using prospective payment during the study period (1985)	38.18, 38.38, 38.48, 38.68, 39.25, 39.29 440-442.9, 433.9	**In any position (n=34):** PPV = 0.97 (0.84,1.0) Sensitivity = 0.94 (0.80,0.99) **In primary position (n=29):** PPV = 0.92 (0.75,0.99) Sensitivity = 0.83 (0.64,0.94) **In any position (n=217):** PPV = 0.53 (0.47,0.60) Sensitivity = 0.58 (0.51,0.64) **In primary position (n=38):** PPV = 0.69 (0.53,0.82) Sensitivity = 0.76 (0.60,0.89)
Kullo, 2010 N=11,644	Northwestern University, Mayo Clinic – Rochester, Marshfield Clinic Research Foundation	Mayo clinic algorithm codes	**Northwestern:** PPV=95% Sensitivity = 100% **Mayo Clinic – Rochester:** PPV = 90.7% Sensitivity = 85.5% **Marshfield Clinic Research Foundation:** PPV = 87.5% Sensitivity = 97.2%

Appendix Table 11. ICD-9-CM and CPT-4 codes used in administrative claims studies to identify PAD

Author, year	Study Population	PAD Identification Methodology	ICD-9 Codes	CPT Codes
Jaff, 2008	5% random sample of Medicare beneficiaries from 1999-2005	PAD diagnosis and/or procedures using ICD-9-CM and CPT coding	440.2, 440.3, 440.9, 443.9, 444.2, 444.22, 444.8, 444.81, 447.1, 445.0, 445.02, 250.7, 707.1, 00.40, 00.41-3, 00.44, 99.10, 39.50, 39.29, 39.25, 38.18, 38.08, 38.38, 38.48, 38.68, 00.45, 00.46-8, 39.90, 86.22, 86.27, 86.28, 77.65-77.68, 440.21, 440.22, 440.23, 785.4, 440.24, 84.17, 84.10, 84.13, 84.14, 84.16, 84.18, 84.12	35450, 35470, 37184-6, 35470, 35473, 35474, 35492, 35493, 35495, 35482, 35483, 35485, 35563, 35556, 35558, 35566, 35571, 35903, 35351, 35355, 35302, 35371, 35303, 35304-6, 37205-8, 97597-606, 11040-4, 27590-2, 27880-2, 27884, 27886, 27888-9, 28820, 28825, 28800, 28805, 28810
Hirsch, 2008	5% Medicare sample of the non-cancer SEER Registry, 2001	PAD diagnosis in primary or secondary position, discharge categorized with PAD DRG	440.0, 440.0-440.24, 440.31, 440.9, 442.3, 443.9, 444.2, 444.81 DRGs: 5, 110, 111, 113, 114, 124, 130-133, 213, 271, 285, 287, 478, 479	Not specified
Margolis, 2005	Managed care database, 1999-2003	PAD diagnosis in primary or secondary position, pharmacy claim for Cilostazol or Pentoxifylline	440.xx, 443.9, 38.08, 38.13, 38.18, 39.25, 39.26, 39.29, 39.50, 39.90	Not specified – 30 codes available upon request
Tunis, 1991	Maryland Health Services Cost Review Commission	PAD-related diagnosis in first five positions, PAD-related procedure	39.25, 39.29, 84.12, 84.15, 84.17, 39.59	Not utilized

Author, year	Study Population	PAD Identification Methodology	ICD-9 Codes	CPT Codes
	database	in first three positions		
Goodney, 2009	100% sample of Part B claims from all insurance carriers	PAD-related CPT code	Not utilized	35646, 35661, 35556, 35583, 35656, 35566, 35585, 35666, 27590-27592, 27880-27882, 35492, 35493, 35495, 35473, 35474, 35470
O'Brien-Irr, 2012	Statewide Planning and Research Cooperative System in New York State, 2001-2008	PAD-related code	440.21-440.24, 707.10, 707.13-707.15, 785.4, 39.25, 39.29, 38.38, 38.48, 39.50, 39.90, 0.48-00.48, 84.15, 84.17	Not utilized

Appendix Table 12. PAD Prevalence studies based on administrative data assessment

Author, year Country N= Age range in years	Study Population	PAD Identification Methodology	Burden Estimates	Limitations
Hirsch, 2008 United States n=152,381 Ages ≥ 65	5% Medicare sample of the non-cancer SEER Registry in 2001	PAD-related diagnosis code in first or second position and for discharge to be categorized in PAD DRG	Overall prevalence = 6.8%; Age 65-74, 4.5% Age 75-84, 7.5% Age ≥ 85, 11.8%	Sampling strategy using 5% of SEER registry is not common and is poorly generalizable
Jaff, 2008 United States n=43,000-57,000	5% random sample of Medicare beneficiaries from 1999-2005	PAD diagnosis and/or procedures using ICD-9-CM and CPT coding	Overall prevalence in 1999 and 2005: 1999: 8.2% 2005: 9.5%	5% sample, no regional stratification
Margolis, 2005 United States n=30,561 Ages ≥ 18	Managed care database with medical, hospital, outpatient, and pharmacy claims from Jan 1, 1999- August 31, 2003;	Primary of secondary ICD-9-CM listing, CPT codes, or pharmacy claim for Cilostazol or Pentoxifylline	Overall prevalence = 1.2%	Managed care only population Did not stratify results by gender, race, age

APPENDIX 4: CONSTRUCTING A COMORBIDITY SCORE USING ADMINISTRATIVE
CLAIMS

Several summary scores have been identified and validated to overcome the challenges

associated with accurately identifying comorbidity burden from claims data. Charlson et al

(1987) identified 19 conditions that they included in a summary score that is commonly used in

administrative claims data [179]. Klabunde et al (2000) adapted and validated the score for use

with physician claims data as well as inpatient claims [180]. Klabunde assigned new weights to

each comorbidity based on the strength of associated hazard ratios, concluding that a large

comorbidity burden can be found in the outpatient setting that is not found through inpatient

claims [179, 180]. Table 16 shows the adapted comorbidity score that will be used in the

proposed research along with the codes for each comorbid condition and their associated

weights.

Appendix Table 13. ICD-9-CM codes to identify comorbidities with associated weights

Comorbid condition	ICD-9-CM	Assigned weights
Myocardial infarction	410.xx, 412	3
Congestive heart failure	402.01, 402.11, 402.91, 425.x, 428.x, 429.3	2
Cerebrovascular disease	430-437.x	3
Dementia	290.x	3
Chronic pulmonary disease	490-496, 500-505, 506.4	2
Rheumatologic disease	710.0-710.1, 710.4, 714.0-714.2, 714.81, 725	3
Mild liver disease	571.2, 571.4, 571.5, 571.6x	3
Diabetes	250.0x-250.3x, 250.7x	2
Diabetes with end stage disease	250.4x-250.6x	2
Hemiplegia or paraplegia	342.x, 344.x	3
Renal disease	582.x, 583.0-583.7, 585, 586, 588.x	4
Any malignancy including lymphoma and leukemia	140.x-172.x, 174.x-195.x, 200.xx-208.xx	2
Moderate or severe liver disease	572.2-582.8, 456.0-456.2x	4

* Table adapted from Romano et al (1993)[201]

The weights for each condition are summed to form a comorbidity score. For example, an individual with heart failure (2), dementia (3), and diabetes (2) would receive a score of 7. Mean comorbidity scores will be presented for each demographic stratum. A one year period prior to the PAD occurrence will be used to calculate comorbidities.

Formula 1: Annual Prevalence $= \dfrac{\text{\# PAD events}_{\text{year i,age,gender,race,race-gender}}}{\text{population at risk}_{\text{year i,age,gender,race,race-gender}}}$

Formula 2: Incidence proportion $= \dfrac{\text{\# new PAD events}_{\text{year i,age,gender,race,race-gender}}}{\text{population at risk}_{\text{year i,age,gender,race,race-gender}}}$

Formula 3: Incidence rate $= \dfrac{\text{\# new PAD events}_{\text{year i,age,gender,race,race-gender}}}{\text{person years at risk}_{\text{year i,age,gender,race,race-gender}}}$

Formula 4: Sensitivity $= \dfrac{a}{c_1}$

Formula 5: Specificity $= \dfrac{d}{c_2}$

Formula 6: Positive predictive value $= \dfrac{a}{r_1}$

Formula 7: Negative predictive value $= \dfrac{d}{r_2}$

Formula 8: Kappa (K) $= \dfrac{p_0 - p_e}{1 - p_e}$ Where: $p_0 = (a+d)/N$

$\qquad\qquad\qquad\qquad\qquad\qquad\quad p_e = ((a+c)(a+b) + (b+d)(c+d))/N^2$

Formula 9: Bias Adjusted Kappa (Y) $= \dfrac{\sqrt{ad} - \sqrt{bc}}{\sqrt{ad} + \sqrt{bc}}$

Formula 10: Comparability Ratio$_{\text{Hospitalization,Outpatient}}$ $=> c_{PAD} = \dfrac{E_{\text{PAD,ARIC}}}{E_{\text{PAD,Claims}}}$

Formula 11: Adjusted Annual Prevalence $= c_{PAD} * \dfrac{\text{\# PAD events}_{\text{year i,age,gender,race,race-gender}}}{\text{population at risk}_{\text{year i,age,gender,race,race-gender}}}$

Formula 12:   Poisson formula: $\lambda_k = \exp(\alpha + \beta X + \gamma Z)$

Formula 13:   Negative binomial formula: $\lambda_k = \exp(\alpha + \beta X + \gamma Z + \eta \varepsilon_k)$

Formula 14: $R = 1 - \sum_{k=1}^{k} I_k * \Delta t_k$

Formula 15: Cumulative Incidence(t) $= \displaystyle\sum_{j=1}^{s} \dfrac{e_j}{n_{j-1}} KM_{12}(t_j)$

where e_j = the number of patients who fail from the event of interest at time t_j

where n_j = the number of patients known to be at risk of failure beyond time t_j

where KM_{12} = the Kaplan-Meier estimate of survival

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