Title
A Cost Effectiveness Analysis of Using the Ankle-Brachial Index to Screen for Peripheral Artery Disease

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Publication Date
2012

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

A Cost Effectiveness Analysis of Using the Ankle-Brachial Index to Screen for Peripheral Artery Disease

A dissertation submitted in partial satisfaction of the

requirements for the degree of Doctor of Public Health

by

Nell Justine Marshall

2012

ABSTRACT OF THE DISSERTATION

A Cost Effectiveness Analysis of Using the

Ankle-Brachial Index to Screen for Peripheral Artery Disease

by

Nell Justine Marshall

Doctor of Public Health

University of California, Los Angeles, 2012

Professor Robert M. Kaplan, Chair

Peripheral artery disease (PAD), a common circulatory problem in which narrowed arteries reduce blood flow to limbs, is a major public health problem. A robust epidemiologic literature shows that patients with PAD have up to three times the risk of all cause mortality. The risks of death from coronary artery disease are up to six times greater for PAD patients in comparison to those without the disease. PAD, however, is usually not recognized as a major public health threat and motivation to evaluate patients for PAD is much lower than it is for other cardiovascular conditions. Peripheral artery disease is a serious health condition that increases an individual's risk for heart attack, stroke, and leg amputation. While PAD is highly prevalent in primary care settings and is easily detected with the ABI during a routine office visit, the procedure is underutilized and without a pulse volume recording or Doppler waveform tracings,

it is not reimbursable by healthcare payers. Demonstration that the ABI is a low cost and effective screening technique for identifying PAD in patients with cardiovascular risk factors would support its adoption into primary care and specialty care settings. Furthermore, newly identified PAD patients could be targeted for prevention measures such as treatment with antiplatelet drugs, ACE inhibitors, and statins, decreasing their overall risk of cardiovascular events while increasing functionality and quality of life. With the combined high risk that PAD represents and the availability of effective treatment, systematic use of screening using the ABI to identify patients with asymptomatic PAD is warranted in patients with cardiovascular risk, and is critical to reduce overall morbidity and mortality.

The dissertation of Nell Justine Marshall is approved.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

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Background and Significance

Peripheral artery disease (PAD), a common circulatory problem in which narrowed arteries reduce blood flow to limbs, is a major public health problem. [1-3] A robust epidemiologic literature shows that patients with PAD have up to three times the risk of all cause mortality.[4] The risks of death from coronary artery disease are up to six times greater for PAD patients in comparison to those without the disease[5]. PAD, however, is usually not recognized as a major public health threat and motivation to evaluate patients for PAD is much lower than it is for other cardiovascular conditions.

Peripheral artery disease is a serious health condition that increases an individual's risk for heart attack, stroke, and leg amputation. PAD affects 8-12 million men and women over 40 years of age in the United States, including 12-20 percent of Americans over 65 [6-8]. The overall prevalence of PAD is slightly higher in men than in women, although prevalence rates among women increase later in life. African Americans are disproportionally affected, where the likelihood of PAD is 50 percent greater than in non-Hispanics whites [6, 9], while the prevalence of PAD in people of Hispanic origin is similar to non-Hispanic whites [6, 10].

Individuals with symptomatic PAD classically present with intermittent claudication [11]. However, studies have shown that when the ankle-brachial index (ABI) is used to diagnose PAD, approximately 33-90 percent of individuals with PAD are asymptomatic (report no exertional leg symptoms)[12, 13]. Recent research also suggests that the functionality of those with asymptomatic PAD may be lower than those with intermittent claudication using standard walking performance measures and physical functional scoring [3], measures shown to be

significantly and independently associated with higher all-cause mortality and cardiovascular disease mortality rates [5].

Because of the importance of PAD, there have been calls for national screening programs. In particular, it has been suggested that it might be valuable for the entire "at risk" population to be screened using the Ankle-Brachial Index ("ABI")[14].

Significance

While PAD is highly prevalent in primary care settings and is easily detected with the ABI during a routine office visit [13], the procedure is underutilized and without a pulse volume recording or Doppler waveform tracings, it is not reimbursable by healthcare payers[15]. Demonstration that the ABI is a low cost and effective screening technique for identifying PAD in patients with cardiovascular risk factors would support its adoption into primary care and specialty care settings. Furthermore, newly identified PAD patients could be targeted for prevention measures such as treatment with antiplatelet drugs, ACE inhibitors, and statins, decreasing their overall risk of cardiovascular events while increasing functionality and quality of life.

Despite its prevalence and cardiovascular risk implications, only about 70 percent to 80 percent of patients with PAD undergo recommended antiplatelet therapy or lipid-lowering therapy[16]. A recent study using the same NHANES data, estimated that approximately 5.4 million adults with PAD are not receiving guideline recommended secondary prevention; therapies that are associated with 65 percent reduced risk of all-cause mortality in that cohort[17]. Another study by Hackam et al, modeled randomized trial data and meta-analysis' of

RCTs, to look at the effectiveness of antiplatelet agents, statins, and angiotensin-converting enzyme inhibitors, and found reduced risk with all three: antiplatelet agents (pooled RRR 26%, 95% CI 10 to 42), statins (pooled RRR 26%, 95% CI 18 to 33), and angiotensin-converting enzyme inhibitors (individual trial RRR 25%, 95% CI 8 to 39), with an estimated cumulative relative risk reduction of 59 percent (CI 32 to 76)[18].

With the combined high risk that PAD represents and the availability of effective treatment, systematic use of screening using the ABI to identify patients with asymptomatic PAD is warranted in patients with cardiovascular risk, and is critical to reduce overall morbidity and mortality. In some respects, it is surprising that with the combined high risk that PAD represents and the availability of effective treatment, that systematic screening using a low cost procedure such as measuring the ABI, hasn't already been adopted. Addressing the education and awareness gap for both at risk patients and providers on the cardiovascular risk associated with PAD, and the value of screening with the ABI, could increase its demand[19]. However, a significant change in reimbursement policy is also needed. To achieve this, we need to explore the effectiveness and cost-effectiveness of screening using the ABI at the population level. This kind of study would contribute an important element to the body of knowledge that already exists in support of ABI screening to reduce PAD morbidity and mortality at a population health level.

Dissertation Outline

This dissertation is divided into two main studies that will attempt to answer key questions around population-based screening for PAD using the ABI. The first study will

generate a preference based utility measure for patients with PAD and examine how this measure correlates with the ABI. The second study will examine the cost-effectiveness of screening and early treatment of high-risk individuals for PAD using the ABI, versus standard symptomatic diagnosis and treatment.

Chapter 1: Peripheral Artery Disease

The most common cause of peripheral artery disease (PAD) is atherosclerosis, a systemic disease process in which fatty deposits, inflammation, cells, and scar tissue build up within the walls of arteries, narrowing the arteries, restricting the supply of blood to the extremities. PAD progresses gradually and often silently over many years, and can lead to loss of functional capacity and quality of life, limb amputation, and an increased risk of death.

The general term "peripheral artery disease" refers to arterial disease outside or beyond the coronary arteries, namely disorders of the abdominal aorta, renal and mesenteric arteries, and lower extremity arteries. The scope of this study, however, is limited to the lower extremity arteries and all references to PAD are made according to this definition.

Peripheral artery disease (PAD) is characterized by symptoms of intermittent claudication or critical limb ischemia. The common symptoms of intermittent claudication are pain, achiness, fatigue, or discomfort in the muscles of the legs, predominately the, calves. Symptoms usually appear during walking or exercise and go away after several minutes of rest. Symptoms may initially appear only when walking uphill, walking at a faster pace, or walking for longer distances. As the disease progresses these symptoms come on more quickly and with less exercise. Critical limb ischemia occurs from prolonged restricted blood flow and is characterized by severe pain at rest. Complications of critical limb ischemia are ulcers or wounds on the legs and feet that won't heal, and critical limb ischemia can result in limb amputation. Only about 10 percent of people with PAD have the classic symptoms of

intermittent claudication. Approximately 40 percent do not complain of leg pain, and the remaining 50 percent have a variety of leg symptoms different from classic claudication[12, 13].

The presence of PAD is also an indicator of atherosclerotic disease in other vascular areas, often referred to as "polyvascular disease". Due to its systemic nature, individuals with PAD often also have atherosclerotic disease in the arteries that supply blood to the heart and to the brain. In the *RE*duction of *A*therothrombosis for Continued *H*ealth (REACH) Registry, greater than 60 percent of patients with PAD had polyvascular disease: 40 percent had coronary artery disease (CAD), 10 percent had cerebral vascular disease (CVD), and 13 percent had both CAD and CVD. REACH Registry outcomes also showed that compared with CAD or CVD patients; patients with PAD had the highest rates of all-cause mortality and cardiovascular death[16].

PAD is also a significant independent predictor of ischemic stroke. In a 5-year prospective study of 6800 patients in a primary care setting, patients with PAD compared to those without PAD had 1.6 times the risk of total stroke, 1.7 times the risk for ischemic stroke, and 2.5 times the risk for fatal stroke[20].

Among patients with diabetes, having PAD further increases their risk of morbidity and mortality from cardiovascular diseases and presents additional challenges. In diabetic patients, PAD presents at an earlier age and progresses more rapidly than in non-diabetic patients. It may be asymptomatic longer, increasing the risk of going undiagnosed until it reaches an advanced stage. And the extent of disease is usually more severe, and often not all patients may be offered

a revascularization procedure when needed. Furthermore, the outcome after revascularization procedures is poorer and many patients progress to a major amputation [21].

Risk Factors

Multiple studies have demonstrated that the prevalence of PAD increases with age[9, 13, 22]. One study that looked specifically at a defined older population, found a prevalence of 2.5 percent in people aged <60 years old, this increased to 8.3 percent for those 60-69 years old, and was 18.8 percent in people >70 years old[23]. Having a parent with PAD is associated with a 3-fold increase in PAD risk, and any first-degree relative is associated with a 2.4-fold increase[24]. Other risk factors for PAD are similar to those associated with other atherosclerotic vascular diseases, although the strength of their association may vary. Diabetes and smoking are considered the most prominent risk factors for PAD[15, 25]. Cigarette smoking is a very powerful predictor of PAD. Current smokers have as much as a 6-fold greater risk of developing PAD than those who do not smoke[13, 26]; although the risk for former smokers is not as high as that of current smokers, it remains significant. Current smoking is also a significant predictor of PAD progression [26].

Hypertension and dyslipidemia are also associated with PAD, but to a lesser extent than with CAD and CVD. Individuals with hypertension (blood pressure ≥ 140/90 mm Hg) and dyslipidemia have approximately a 2-fold greater risk of developing PAD than those without these conditions[13]. While obesity is a well-established risk factor for CVD and CAD, it has not been associated with an increased risk of PAD [26].

Diabetes is also a strong predictor of PAD. The risk of developing PAD in diabetic patients is 2- to 4-fold greater than in the non-diabetic population [13]. For every 1 percent increase in HbA1C, there is approximately a 26 percent increased risk of PAD, independent of other risk factors[9]. Poor glycemic control is also associated with PAD progression and increased amputation and mortality [15], where even insulin resistance in the absence of diabetes increases PAD risk by 40-50 percent[27]. Considering that between 120 and 140 million people suffer from diabetes worldwide and that diabetic patients are at excess risk of developing PAD[28], the implications of the problem are potentially enormous.

Detection and Awareness

Despite the importance of early detection of PAD, and the associated increased morbidity and mortality, PAD remains underdiagnosed and undertreated [13, 29-31]. Underdiagnosis in part can be attributed to the lower percentage of patients who display the classic symptoms of intermittent claudication, and as a result are not diagnosed during a standard physical exam. Since PAD is often asymptomatic for many years before progressing to the stages of intermittent claudication or more advanced critical limb ischemia, early diagnosis during this period becomes vitally important.

Supporting underdiagnosis and undertreated PAD is low provider awareness. In a study conducted in primary care clinics, 83 percent of patients with prior PAD were aware of their diagnosis, but only 49 percent of physicians were aware of this diagnosis[13]. Public awareness studies also show that the public continues to demonstrate "a profound lack of awareness of PAD"[32]. In a study by Hirsch et al., with a random sample of 2501 adults found that 3 of 4

adult Americans had no awareness of PAD, and almost half were unaware that smoking and diabetes were strong risk factors for PAD[29]. Media sources were the primary source of information (broadcast or cable television 26 percent, magazines 15 percent, and newspaper 5 percent). In a Canadian study of 500 adults over 50 years of age, 2 of 3 adult Canadians had no awareness of PAD[33]. A smaller cross-sectional study in a Veteran Affairs ambulatory clinic reported similar poor rates of PAD awareness among women at risk for cardiovascular disease[34].

While the ABI is widely used in specialty vascular clinics, several factors contribute to limited usage in routine clinical practice. In one survey of primary care physicians who were trained on how to use the ABI, 50 percent cited time constraints, lack of reimbursement, and lack of available staff as barriers to adopting the ABI into routine practice[35]. Beyond logistics, there are clinical reasons why ABI usage in routine practice is low as well. Providers lack awareness that a low ABI is an indicator of cardiovascular risk. They hold a mis-perception that vascular specialists only should measure the ABI, and providers lack knowledge on how to accurately measure the ABI[36].

The Ankle-Brachial Index

The Ankle-Brachial Index (ABI) is a highly accepted and practical option for PAD screening[13]. The ABI is the ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm. Pressures are obtained using blood pressure cuffs and a hand-held Doppler ultrasound. The ABI is measured by taking the systolic blood pressure in the bilateral brachial, dorsalis pedis (DP) and posterior tibial pedis (PT) arteries. The higher of the two

brachial measures is used in the denominator, while the right and left ABI values are determined by dividing the higher of DP or PT pressure in each leg by the higher brachial artery pressure[15].

The ABI is simple, inexpensive, and noninvasive [36, 37]. The ABI is useful for two important purposes; one is that the ABI can detect individuals who are asymptomatic for PAD and might otherwise go undiagnosed during a standard physical exam. The ABI level can both diagnose PAD and quantify the severity of disease, so asymptomatic patients can be managed and prevented from progressing to intermittent claudication or critical limb ischemia. The second useful purpose is in the ability of the ABI to predict future cardiovascular events. The relative simplicity of the test combined with its effectiveness at both diagnosing PAD and predicting future cardiovascular events, make the ABI the most reasonable option for PAD screening on a population basis[14].

An ABI score of 1.00-1.40 is considered normal, 0.91-1.00 indicates possible borderline PAD, an ABI<= 0.90 is diagnostic of PAD, and <0.70 indicates moderate to severe PAD. Individuals with an ABI>1.40 are classified as having stiff and presumably calcified arteries, in some cases completely non-decompressable, often seen in those with advanced or long term diabetes. With treadmill testing, functional capacity can also be assessed. The distance walked can be recorded as a baseline measure for future comparisons after risk-modifying interventions or treatment.

The ABI is an accurate and reliable test of PAD. The sensitivity, specificity and accuracy of the ABI as a PAD diagnostic tool is well documented. Using a receiver-operating characteristic with an ABI diagnostic threshold of .90, Lijmer et al. demonstrated a sensitivity of 79 percent and specificity of 96 percent[37]. Anther study compared the ABI to angioplasty and using a slightly higher cut-off of .91, found the ABI was 89-95 percent sensitive and 99-100 percent specific[38, 39], illustrating a positive predictive value of 90 percent, a negative predictive value of 99 percent, and an overall accuracy of 98 percent. However, this study did not include persons with borderline ABI values.

In a survey of primary care physicians, the majority found the ABI useful and feasible for the diagnosis and management of PAD[35]. A nurse or nurse practitioner can obtain the ABI; it takes physicians on average 15 minutes to perform the ABI test[30]. Yet, while PAD is highly prevalent in primary care settings and is easily detected with the ABI during a routine office visit, the procedure is underutilized and non-reimbursable by healthcare payers without a Doppler waveform tracing or pulse volume recording[15].

The ABI as marker for cardiovascular risk

A low ABI is not only diagnostic of PAD, but is also an effective biomarker or measure of more systemic atherosclerotic disease. A recent meta-analysis of 24 955 men and 23 339 women demonstrated that the association of the ankle brachial index (ABI) with mortality has a reverse J-shaped distribution in which participants with an ABI of 1.11 to 1.40 are at lowest risk for mortality[36]. Among 508 patients identified from 2 vascular laboratories in San Diego, CA, a decline in ABI of 0.15 within a 10-year period was associated with a 2.4 times greater risk of

all-cause mortality, and a 2.8 times greater risk of CVD mortality[1] beyond the increased risk associated with the baseline ABI. When the Ankle-Brachial Index Collaboration completed a meta-analysis using nearly a half million-person years of follow-up, they reported that the hazard ratio for cardiovascular deaths among men with a low ABI was more than four times greater than for men with a normal ABI. For women, it was three and half times greater[40].

The ABI has demonstrated effectiveness at identifying asymptomatic individuals at increased risk of cardiovascular events. In a study that pooled data from 11 studies in 6 countries looking at participants from the general population with no pre-existing disease, the findings were remarkably consistent in demonstrating an increased risk of clinical cardiovascular disease associated with a low ABI. A low ABI (<0.9) was significantly associated with an increased risk of all cause mortality (pooled RR 1.60, 95% CI 1.32-1.95), cardiovascular mortality (pooled RR 1.96, 95% CI 1.46-2.64), coronary heart disease (pooled RR 1.45, 95% CI 1.08-1.93) and stroke (pooled RR 1.35, 95% CI 1.10-1.65) after adjustment for age, sex, cardiovascular risk factors and cardiovascular disease[41].

Improves Accuracy of the Framingham Risk Score

Risk scoring systems such as the Framingham Risk Score (FRS) are commonly used to estimate an individual's risk of developing cardiovascular disease or having a major cardiovascular event within the next 5 or 10 years. This type of risk prediction model relies on traditional risk factors and scoring equations to predict if an individual is at low risk (<10 percent), intermediate risk (10-20 percent), or high risk (20 percent or more). While commonly used to estimate CHD risk in the United States, the FRS is known to overestimate the risk in

low-risk populations, and underestimated the risk in high-risk populations[42]. To improve on the accuracy of the Framingham Risk Score, other biomarkers such as C-reactive protein (an indicator of inflammation), and measures of asymptomatic atherosclerosis such as coronary artery calcium levels, carotid intima media thickness and the ankle-brachial index have been tested to see if incorporating them improves the risk score.

One such study was done by the ABI collaborative that looked at 16 studies worldwide from the general population to determine if the ABI provided information on the risk of cardiovascular events and mortality independent of the Framingham Risk Score, improving on the accuracy of its prediction[36]. During a cumulative 480,325 person years of follow up of 24,955 men and 23,339 women, the study found that the ABI provided independent risk information beyond the FRS and, when combined with the FRS, a low ABI <=0.90 predicted approximately doubled the 10-year total mortality, cardiovascular mortality, and major coronary event rates across all risk categories compared to the FRS alone. Including the ABI in the risk model resulted in a risk category reclassification of approximately 19 percent of men, and 35 percent of women. For men, the greatest effect was in high-risk individuals (FRS>=20%) with a normal ABI (1.11-1.40) in who the risk level would be reduced to intermediate risk (FRS 10%-19%). All men with a low ABI (<=0.90) had a relatively high risk but their clinical risk level did not change from what was predicted by the FRS alone. In women, including the ABI had the greatest effect on those in the lowest FRS category (FRS 10%) who had an abnormal ABI (<=0.90 or 0.91 -1.10 or >1.40) where all women in this category were reclassified to a higher risk level. In addition, all women in the intermediate FRS category (FRS 10%-19%) with a low ABI (<=0.90) were reclassified to high risk (FRS >=20%). A change from a higher to a lower

risk category, the main effect for men, would likely have an effect on decisions to start preventive therapy such as lipid lowering drugs as recommended by the Adult Treatment Panel III guidelines (cite). In contrast, including the ABI resulted in approximately 1 in 3 women reclassified from low to high risk. Results of this study confirmed two things, one is that the ABI has added value from a clinical perspective in that its inclusion can be used to reclassify cardiovascular risk at the individual level[43]. Second, it confirmed that a new risk equation adding the ABI to the Framingham risk variables could more accurately predict risk, a position that has been adopted by the American Heart Association and the American College of Cardiology[15], the Transatlantic Inter-Society Consensus Working Group[44], and the Fourth Joint European Task Force[45].

Use of ABI screening can lead to an increased diagnosis and awareness of PAD, and the opportunity for early intervention. A recent study using NHANES data, estimated that 4.6 percent of Americans over 40 have mild PAD[7]. Mild PAD is typically asymptomatic and at a level where interventions may be most effect at slowing or preventing disease progression.

Despite its prevalence and cardiovascular risk implications, only about 70 percent to 80 percent of patients with PAD undergo recommended antiplatelet therapy or lipid-lowering therapy[16]. A recent study using the same NHANES data, estimated that approximately 5.4 million adults with PAD are not receiving guideline recommended secondary prevention; therapies that are associated with 65 percent reduced risk of all-cause mortality in that cohort[17]. Another study by Hackam et al, modeled randomized trial data and meta-analysis' of RCTs, to look at the effectiveness of antiplatelet agents, statins, and angiotensin-converting

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With the combined high risk that PAD represents and the availability of effective treatment, systematic use of screening using the ABI to identify patients with asymptomatic PAD is warranted in patients with cardiovascular risk, and is critical to reduce overall morbidity and mortality.

Chapter 2: Estimation of a Preference Based Utility and Quality Adjusted Life Expectancy for Patients with Peripheral Artery Disease

The purpose of the first study was to derive a preference-based utility score for individuals with PAD using SF-36 health status scores, and to describe the relationship between quality-adjusted life years (QALYs) and the ankle-brachial index (ABI), a clinical indicator used to screen an individual for PAD. A second aim was to examine the relationships between QALYs and levels of PAD co-morbidities and PAD risk factors, and test the hypothesis that as the ABI level decreased, and PAD risk factors increased, there would be a corresponding decrease in QALYs. Knowing how QALYs correspond to the ABI adds to the armament of information available to doctors and patients, may increase the awareness of PAD risk, and emphasize the importance of managing and decreasing a patient's overall CVD risk. The translation will also provide the utility needed to estimate the cost per quality adjusted life years in the economic model constructed in the second study.

Health related quality of life (HRQoL) data on the outcomes and long-term survival of patients with cardiovascular diseases (CVD) [46-49] coronary artery disease (CAD)[46-48], and peripheral artery disease (PAD) [50, 51] firmly supports that a lower HRQoL is associated with lower survival rates independent of other established risk factors. However, HRQoL measures, whether generic or disease specific, cannot be used to make comparisons of the relative burden of illness across different diseases. Utility measures, on the other hand, widely used in medical decision-making and health economics as an outcome measure, incorporate both length of life and quality of life into a single metric and can be used to estimate the total burden of disease and

disability at both an individual and population-based level. Current studies in the literature that have applied preference-based utility measures to patients with PAD are limited to studies of patients with severe intermittent claudication who are underwent vascular surgery[52, 53], or who participated in 6-month exercise program[54]. No studies have been done to measure preference-based utility for patients with PAD who are not in an advanced stage of disease. This study will contribute to the literature by creating an index of QALYs based on health related quality of life scores obtained in primary care clinic settings in the United States.

Health-related Quality of Life

Quality of life or health related quality of life (HRQoL) is increasingly an important outcome measure in the evaluation of the effectiveness of healthcare. The World Health Organization (WHO) has defined health as a state of complete physical, mental and social well-being, beyond the absence of disease[55]. Health status measures, an important objective measure of functional limitations as a result of disease on physical, mental and social well-being, lack the individual patients perception of those limitations. Quality of life measurements evaluate the functional restrictions of health status with the added subjective appraisal of the limitations. A measurement of quality of life by the WHO definition includes "an individuals perception of his/her position in life in the context of culture and value systems in which he/she lives and in relation to his/her goals, expectations, standard and concerns." HRQoL can be useful when measuring an intervention affect [56], or for comparing the relative burden of a particular disease among patients. For patients with PAD, it has also become important to incorporate HRQoL into day-to-day clinical practice, where treatment plans should focus on the patient and not just the disease[57].

Patients with symptomatic PAD typically experience a multitude of problems, such as claudication, ischemic rest pain, ischemic ulcerations, repeated hospitalizations, revascularizations, and limb loss, leading to a poorer quality of life and a higher rate of depression. Analysis has shown that in comparison with the general population, the quality of life in patients with PAD is considerably impaired, in particular by pain, anxiety, general complaints and reduced physical mobility[58]. Lack of physical fitness, which is a strong predictor of cardiovascular and all-cause mortality, may partially explain why individuals with PAD have poor outcomes. However, even those patients who are asymptomatic, experience impaired function and quality of life [5, 59].

Patients with established PAD have shown that higher physical activity levels during daily life are associated with better overall survival rate, a lower risk of death because of CVD, and slower rates of functional decline[59, 60]. In addition, better 6-minute walk performance and faster walking speed are associated with lower rates of all-cause mortality, cardiovascular mortality, and mobility loss[5, 61].

McDermott and colleagues have shown that patients with PAD experience a greater functional decline than those without PAD[5, 59, 60]. Asymptomatic patients with PAD have poorer functional performance (measured as slower walking speed, poorer balance, slower getting out of a chair, and decreased walking distance), poorer quality of life, and a smaller calf muscle area, than age match, sedentary, individuals without PAD[3].

Counter to what we might expect, selected clinical patients with PAD who are considered "asymptomatic" have poorer functional outcomes when compared to those with classic intermittent claudication[3]. These asymptomatic patients had significantly lower 6-minute walk performance, physical fitness and quality of life, compared to those who exhibited symptoms of classic intermittent claudication[3]. In a cross-sectional study comparing PAD patients with IC versus those who were "always" asymptomatic (have never experienced exertional leg pain even during the 6-minute walk), found that always asymptomatic PAD participants had significantly smaller calf muscle area ($P<0.001$), higher calf muscle percent fat ($P<0.001$), poorer 6-minute walk performance ($P=0.0002$), slower usual-paced walking speed ($P=0.0019$), slower fast-paced walking speed ($P<0.001$), and a poorer SF-36 Physical Functioning score ($P=0.016$). The findings persisted even when compared with an age-matched, sedentary, non-PAD cohort, where always-asymptomatic PAD participants had smaller calf muscle area ($P=0.009$), poorer 6-minute walk performance ($P<0.001$), and poorer Walking Impairment Questionnaire speed scores ($P=0.001$)[3]. A more recent prospective study with the WALCS cohort has further confirmed these findings. The Walking and Leg Circulation Study (WALCS) has been enrolling participants in a series of prospective studies to identify characteristics associated with function decline and mortality in PAD. Four hundred fifteen patients with PAD were classified into symptom categories including intermittent claudication; those with leg pain on exertion and rest (atypical leg symptoms); those who could walk through the pain (pain/carry on); and those who were always asymptomatic. Always asymptomatic participants, and those with atypical leg symptoms, both had almost three times the mobility loss of participants with IC. The authors were unable to fully explain why some participants with PAD never had exertional leg

symptoms. One possible explanation is that always-asymptomatic PAD participants may slow their walking speeds naturally to avoid experiencing leg pain[62].

The Walking and Leg Circulation Study WALCS II cohort enrolled participants who were newly identified with PAD and followed them annually for up to four years. A greater decline in six-minute walk performance and four-meter walking velocity were associated with a significant increased all-cause mortality, compared to those who had lesser declines[63]. Within the same cohort, women compared to men were more than twice as likely to become unable to walk for six minutes continuously, had greater mobility loss, and had greater average annual declines in 6-minute walk distance and usual-paced 4-m walking velocity, adjusting for age, race, ABI, risk factors and comorbidities. When the differences between sexes were adjusted for baseline difference in calf muscle area and knee extension strength, the findings were no longer significant, suggesting that weaker leg muscles at baseline likely explains the faster rates of functional decline seen in women[64].

The Study to Improve Leg Circulation (SILC) enrolled PAD participants with and without symptoms of intermittent claudication, to examine whether the ABI was associated with functional decline. In models full adjusted for age, sex, race, risk factors, comorbidities and leg symptoms, a lower ABI was significantly associated with a shorter maximal treadmill walking time ($p=0.001$) and a shorter 6-minute walk distance ($p<0.001$)[65]. Because the exclusion criteria of the study included those who engage in routine exercise or had other measures of higher functional performance, application of the findings may be limited to more sedentary or unfit individuals.

Quality-Adjusted Life Year (QALY)

The purpose of a preference-based summary measure of health-related quality of life is to summarize an individual's life expectancy adjusting for preferences and quality of life. While an imperfect but useful proxy measure of value or utility in healthcare, QALYs are widely used in medical decision-making and health economics because as an outcome measure it incorporates both length of life and quality of life into a single metric, calculated by summing the time periods individuals spend in different health states, weighted by the qualities of the health states [66]. A gain in QALYs represents an increase in survival time, an improvement in quality of life, or both.

Currently there are a number of indexes that measure self-reported generic health-related quality of life using preference-based scoring. Such measures include the EuroQol (EQ-5D), the Health Utilities Index Mark 2 (HUI2) and Mark 3(HUI3), the SF-6D, the Quality of Well-being scale self-administered form (QWB-SA), and the Health and Activities Limitations index (HALex), all of which are widely used in population surveys and clinical studies in the United States[67]. Equivalent to a Quality-Adjusted Life Year (QALY), these six generic HRQoL indexes score health using standardized weights to represent community preferences for health states on a scale of 0 (dead) to 1 (full health).

The calculation of a preference-based utility score for patients with PAD is important. Having this utility measure would allow the level of disability of PAD to be quantified on a continuum of 0-1.0, which would provide an estimate of the level and seriousness of disability

caused by PAD in relation to others diseases. Knowing the relative seriousness of a disease can inform treatment choices, individual lifestyle choices, and have policy implications on how resources are directed in prevention and screening. For example, the information could inform providers and patients about when initiating treatment may yield an adequate marginal benefit, or when initiating treatment may yield diminishing returns in terms of quality of life gained. Finally, QALYs can be used in cost-utility evaluations of screening and treatment options for patient with PAD.

Quality adjusted survival

Quality and quantity of life can be combined into a single endpoint by weighting periods of survival time according to the quality of life experienced. The resulting outcome measures are generally referred to as QALYs (quality-adjusted life years). Presented here is a method for consistently estimating quality-adjusted life, recognizing that there is still debate on the use of such a simple measure. Quality adjusted life has been studied by Glasziou [68], Goldhirsch et al.[69], and Glasziou, Simes & Gelber [70].

The use of standard survival analysis techniques on the QALY endpoint will generally give biased results because individuals with a worse quality of life will be censored earlier than those with a good quality of life, resulting in informative censoring. Methods of overcoming this problem, including partitioned survival analysis, are discussed. Quality-adjusted survival analysis overcomes problems of informative drop-out due to death and has the potential to be extended to deal with other disease- or treatment-related reasons for drop-out.

Methods

Translation methodology

The SF-36 is currently used in cardiovascular studies as a general measure of health status. While the SF-36 can be a measure of individual health status, and be used to profile a disease, it offers only a single numeric expression of health status. The SF-36 includes eight dimensions of health (physical functioning, role-physical, bodily pain, general health perception, vitality, social functioning, role-emotional, and mental health) plus two summary scores (physical and mental). Because the SF-36 is a general measure of health related quality of life, it can provide information on patient health status, including gains or losses in health status before and after an intervention. However, since preferences are not part of the SF-36, estimating trade-offs between dimensions of health, and between dimensions of health and survival is not possible [71]

To generate the preference-based utility score for individuals with PAD, SF-6D scores were imputed from Medical Outcomes Study SF-36 (MOS SF-36) scores using methodology developed by Brazier et al[71, 72]. The methodology translates the eight domains of the SF-36 into six domains known as the SF-6D (physical function, role limitation, social function, pain, mental health, and vitality) each of which has 5 to 6 levels, defining 18,000 health states. The elements of each health state are combined into a single number and transformed into a linear scale ranging from 0.26 (worst possible health) to 1 (best possible health) using preference scores to reflect the value assigned to that health state, which were obtain from a sample in the UK using a standard gamble technique. Combining SF-6D estimates with known mortality

effects can then be used to estimate QALYs. The SF-6D has been tested and validated for use in various patient groups[73] and is currently used in many health economics studies.

Quality adjusted survival

Quality adjusted survival estimates are a single health outcome measure of mortality and morbidity. By combining estimates of life expectancy (mortality) with health-related quality of life (morbidity) estimates, quality adjusted survival is more complete measure of survival.

Using the United States period life table with age-specific death rates for 2007[74], mortality rates and current of life expectancy were characterized for hypothetical males and female cohorts with and without PAD. Life tables, which use mortality estimates from a single point in time, allow these estimates to be extended to demonstrate the long-range implications of current age-specific mortality rates.

Hazard ratios of total mortality by gender and ABI level were estimated using a meta-analysis of population cohort studies that measured ABI at baseline and follow up in the general population. These analyses allowed an estimate of annual death by ABI level and gender[36]. Using a formula derived from the lifetime distribution function and cumulative hazard function, one-year mortality estimates were derived using hazard ratios:

[Adjusted one-year mortality probability=1-EXP(HR*(LN(1-annual mortality)))]

One-year and 10-year probabilities of mortality by gender and cardiovascular co-morbidity (PAD, CVD, and combine PAD/CVD) were also available[36, 75, 76], but due to being fixed across age groups, they were not adequate for estimating age-specific mortality rates.

Quality adjusted survival estimates were obtained from the product of quantity of life estimates (mortality estimates) with age specific quality of life estimates using SF-6D values by gender and ABI category.

Sample

The PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) program was a cross-sectional study of PAD patients identified in community-based primary care practices in the United States between June and October 1999. With primary study outcomes of PAD prevalence, awareness, and treatment, eligible patients aged 70 years or older, or aged 50-69 years with a history of cigarette smoking or diabetes were evaluated by patient history and by measurement of the ankle-brachial index (ABI)[13, 50]. The PARTNERS study included a total number of 7,155 patients[50], of which 5,313 provided evaluable HRQoL data on at least one of the survey instruments, and of which 5070 (71%) had sufficient SF-36 scores and associated demographic, risk factor and co-morbidities to be included in this analysis.

Statistical analyses

The output for the preference-based index was generated using a computer algorithm for deriving a preference-based index from SF-36 version 1 data using SAS version 8.12 (SAS Institute Inc, Cary, NC, 1990). The algorithm is copyrighted by Qualitymetric Inc. and is free of charge for non-commercial users[72]. All data were analyzed using STATA (StataCorp. 2011.

Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Basic demographics, risk factors, and comorbidities were summarized for all patients as a mean and standard deviation for continuous variables or number and percentage for categorical data. All variables were checked for normality using histograms and normality tests (Shapiro-Wilk). Parametric correlation (Pearson's) analysis was performed for utility scores and demographics, risk factors and comorbidities. To describe the strength of association, correlation categories of very weak (r=0.00-0.19), weak (r=0.20-0.39), moderate (r=0.40-0.59), strong (r=0.60-0.79, and very strong (r=0.80-1.00) were used. Multivariate regression was used to examine the effects of clinical risk factors and comorbidities on utility. Imputed mean SF6D scores by gender, age and ABI category (PAD <=0.90, borderline 0.91-1.10, normal 1.11-1.40, and high >1.40) were compared to SF6D scores by gender and age for healthy U.S. adults[67].

Results

The mean (SD) ABI was 0.984 (0.212) for all patients [Table 1] 1392 (27%) of patients had an ABI<=0.90 which by definition is classified as PAD. 2158 (43%) of patients with an ABI in the range of 0.91-1.10 are considered borderline PAD, while 1217 (24%) of patients had an ABI in the normal range of 1.11-1.40. 303 (6%) of patients had ABI levels >1.40 which is classified as calcified due to compromised compressibility in the arteries, often seen in diabetes and/or chronic kidney disease.

Patients had mean age of 70.85 (9.64), 1878 (37%). There were approximately equal proportions of men (49%) and women (51%) overall. Within the cohort, 3505 (74%) were

retired, 924 (20%) of the patients were employed, and 306 (6%) were unemployed. The majority of patients 4077 (83%) were non-Hispanic white, 493 (10%) black, 186 (4%) Hispanic, and 141(3%) other.

The majority of the cohort had hypertension 3270 (67%) and hyperlipidemia 2650 (56%), and 1846 (18%) had diabetes. The 37 percent of the cohort could be classified as overweight or obese, with an average BMI of 28.74 (6.24), and had either a history of smoking 2121 (48%) or were current smokers 787 (18%).

Patients were also classified into four clinical subgroups. The reference group was defined as no PAD or other CVD or other clinical history of CVD; PAD (defined as ABI of 0.90 or less, documentation of PAD in their medical record, or documentation of limb revascularization); other-CVD (defined as a history of myocardial infarction, angina, coronary revascularization, congestive heart failure, stroke, transient ischemic attack, carotid artery revascularization or aortic aneurysm repair); and combined PAD-other-CVD.

Under this classification, 642 (13%) of this cohort were classified as PAD only, 1288 (26%) had CVD, 868 (18%) had combined PAD/CVD, and 1890 (39%) had neither PAD nor CVD (reference group). These distributions are similar to those reported in the original study[13]. Although the categories are not mutually exclusive, the CVD group was classified primary by patients with coronary artery disease, with smaller percentages having had cerebrovascular disease, congestive heart disease or an aneurysm.

Table 1: Demographics

Age	70.85, SD 9.64, range 40.8-99.6
Age (years)	
35-44	2 (<1%)
45-54	358 (7%)
55-64	914 (18%)
65-74	1732 (34%)
Over 89	71 (1%)
Male	2408 (49%)
Race	
Non-hispanic, white)	4077 (83%)
Black	493 (10%)
Hispanic	186 (4%)
Other	141 (3%)
Education	
<=8th grade	443 (9%)
Some High school	606 (13%)
High school grad	1475 (32%)
Some college	1012 (22%)
College grad	630 (14%)
Graduate/Professional	447 (10%)
Residence	
Urban	1720 (36%)
Suburban	2155 (45%)
Rural	915 (19%)
Employment status	
Unemployed	306 (6%)
Part time employment	266 (6%)
Full time employment	658 (14%)
Retired	3505 (74%)
Other-CVD risk factors	
Never (yes/no)	1480 (34%)
Former smoker (yes/no)	2121 (48%)
Current smoker (yes/no)	787 (18%)
Hypertension (yes/no)	3270 (67%)
Hyperlipidemia (yes/no)	2650 (56%)
Diabetes (yes/no)	1846 (38%)
BMI	28.74, SD 6.24, 13.6-74.14
ABI	0.984, SD 0.212, 0.190-2.50
ABI Index Levels	
Normal 1.11-1.40	1217 (24%)
Borderline 0.91-1.10	2158 (43%)
PAD <=0.90	1392 (27%)
Calcified >1.40	303 (6%)
Co-Morbidities	
No PAD, No CVD	1890 (39%)
PAD	642 (13%)
CVD	1288 (26%)
PAD/CVD	868 (18%)
Calcification	196 (4%)

Correlation analysis

In pair wise correlation shown in Table 2, the analysis showed very weak but highly significant associations of the SF-6D index scores with PAD and CVD clinical subgroups, a diagnosis of hypertension or diabetes, ABI and BMI levels, sex and education. The variables most strongly correlated with SF-6D index scores were cardiovascular clinical subgroup and education. The clinical subgroup, PAD plus CVD, $r(4884) = -0.15.$, $p < .000$ had a very weak but highly significant negative association, indicating that as a patient moved from the reference category of no PAD and no CVD, to PAD plus CVD, it was associated with slight decline in SF-6D scores. The small decline may be due to the relatively small quality of life difference between each of the clinical subgroups. Means SF6D scores across the clinical subgroups also demonstrated this, where means SF-6D scores declined as the clinical category moved from no PAD and no CVD (0.721, SD 0.124) to PAD only (0.699, SD 0.122), CVD only (0.690, SD 0.121, and PAD plus CVD (0.668, SD 0.120). Education was similar, $r(4613) = 0.15.$, $p < .000$ however the association was positive indicating that a higher education had a positive association with SF6D index scores. Mean SF-6D scores increased as education level increased, from 0.679 (SD0.124) for some high school, 0.695 (SD 0.120) for high school graduates, 0.702 (SD 0.116) for some college, 0.724 (SD 0.124) for college graduates, and 0.737 (SD0.111) for those with some graduate or professional education. BMI $r(4913) = -0.13.$, $p < .000$, was also very weak but highly significant, and showed that being overweight or obese has a negative association with quality of life. Being male, sex $r(4936) = -0.12.$, $p < .000$, had a very weak but highly significant inverse association with the SF6D. Males had slightly higher mean SF6D scores 0.715 (SD .122) compared with females, 0.686 (SD .121). The ABI $r(4836) = 0.10$, $p < .000$, had a very weak but highly significant association with the SF6D. This association would

indicate that as a patient moved from a lower ABI score where <=0.90 indicates having PAD, to a higher ABI score, there is an associated positive increase in SF6D index scores. Mean SF6D scores also increased as the ABI moved from a low ABI <=0.90, 0.681, (SD .118), to ABI >1.40 0.689, (SD .121) to borderline ABI, 0.704 (SD 0.12), to normal ABI, 0.713 (SD 0.123).

Table 2: Pearson Correlation with SF6D index scores

(Coef, p-value, observations)

	CVD co morbidity?	Education?	BMI**	Sex*	Age*	ABI**	Hypertension*
r	-0.147*	0.146*	-0.128*	-0.118*	-0.016	0.099*	-0.0696*
p	0.000	0.000	0.000	0.000	0.272	0.000	0.000
N	4884	4613	4913	4936	4955	4836	4851
	Diabetes*	Cholesterol**	Employ?	Smoked*	Location?	Race?	Hyperlipidemia*
r	-0.066*	-0.057*	0.046*	-0.034*	-0.024	0.011	-0.010
p	0.000	0.000	0.002	0.023	0.097	0.436	0.475
N	4861	3822	4735	4388	4790	4897	4742

* Binary variable
** Continuous variable
? Categorical variable

Regression models

A single-sample t-test shown in Table 3, comparing the mean values for U.S. normal SF6D index values for men and women aged 35-89[67], found on average a statistically significant mean difference between males, females, and the overall sample mean.

Table 3: SF6D index one-sample t-test compared to US mean scores for males (0.79), females (0.76), and the average of males and females (0.78)

Variable	Mean	Std. Err	Std. Dev.	[95% Conf. Interval]		t-statistic	df	p value
SF-6D females	0.686	0.002	0.121	0.681	0.690	-30.998	2527	p<0.000
SF-6D males	0.714	0.002	0.122	0.710	0.719	-30.244	2407	p<0.000
SF-6D combined	0.699	0.002	0.122	0.696	0.703	-47.040	5069	p<0.000

In bivariate analysis using ABI as a continuous variable, when a patients ABI score increased by 1.0 point, on average their SF6D score increased by 5.7 percent (b=.057, $p < 0.000$). In the multivariate model shown in Table 4, this effect was reduced where in comparison to those with a normal ABI (1.11-1.40), having a low ABI score (<=.90) resulted in a highly significant 2-3 percent decline in SF6D scores (b=-.02, $p<0.003$; b=-.03, $p<0.000$). A low ABI also explained a significant but very small proportion of variance in SF6D scores, $R^2 = .01$, $F(3, 5066) = 16.40$, $p < .000$. When combined with other demographic and risk factor variables, the coefficients for low ABI were reduced but remained significant, with the exception of the final model that included clinical subgroups. The addition of clinical subgroups likely over adjusts the model since the clinical subgroups are defined in part by ABI levels, thereby diminishing the effect of being in the low ABI group due to covariance with the clinical subgroup PAD and PAD/CVD.

In the multivariate analysis, there was about a 2.5-3.0 percent significant ($p < 0.000$) difference between males and female SF6D scores, with males scoring slightly higher than females, holding all other variable constant. Completing a higher education accounted for on average a 4.5 percent higher utility score ($p < 0.000$). Current smokers had significantly decreased utility scores by 3 percent, $p < 0.000$, whereas being a diabetic decreased utility scores by 1 percent, $p < 0.001$. There was a highly significant 6 percent decline (b=-0.06, $p<0.000$) in SF6D scores for patients diagnosed with combined PAD and CVD disease versus no PAD and no CVD (reference). For those diagnosed with just CVD there was 3.5 percent decline (b=-.035, $p < 0.000$) and for those diagnosed with PAD a 2.8 percent decline (b=-.028, $p < 0.000$), compared to those with no PAD and no CVD.

Overall, the final model (r^2 = .082, F(20, 3685) = 16.36, p < .000) explained only a modest amount of variance in the utility score.

Table 4: Effect of risk factors and comorbidities on utility

Effect of risk factors and comorbidities on utility								
	Model 1		**Model 2**		**Model 3**		**Model 4**	
ABI								
0.91-1.10	-0.008		-0.001		-0.002		-0.002	
	(0.00)		(0.00)		(0.00)		(0.00)	
Low <=0.90	-0.031	***	-0.023	***	-0.016	**	-0.013	
	(0.00)		(0.00)		(0.01)		(0.00)	
>1.40	-0.023	*	-0.013		-0.023	*	-0.012	
	(0.01)		(0.01)		(0.01)		(0.01)	
Female			-0.024	***	-0.025	***	-0.028	***
			(0.00)		(0.00)		(0.00)	
Age			0.000	**	-0.001	***	0.000	**
			(0.00)		(0.00)		(0.00)	
BMI			-0.003	***	-0.003	***	-0.003	***
			(0.00)		(0.00)		(0.00)	
Education								
some high school			0.007		0.003		0.002	
			(0.01)		(0.01)		(0.01)	
completed high school			0.023	**	0.019	**	0.018	**
			(0.01)		(0.01)		(0.01)	
some college			0.027	***	0.020	**	0.018	**
			(0.01)		(0.01)		(0.01)	
completed college			0.045	***	0.043	***	0.041	***
			(0.01)		(0.01)		(0.01)	
graduate/professional			0.053	***	0.047	***	0.045	***
			(0.01)		(0.01)		(0.01)	
Former smoker					-0.003		-0.001	
					(0.00)		(0.01)	
Current smoker					-0.030	***	-0.032	***
					(0.01)		(0.01)	
Hypertension					-0.005		-0.001	
					(0.00)		(0.00)	
Hypercholesterolemia					0.001		0.007	
					(0.00)		(0.00)	
Diabetic					-0.014	**	-0.013	**
					(0.00)		(0.00)	
Clinical subgroup								
PAD							-0.028	**
							(0.01)	
CVD							-0.035	***
							(0.01)	
PAD/CVD							-0.060	***
							(0.01)	
CALC							-0.042	***
							(0.01)	
Constant	0.713	***	0.798	***	0.850	***	0.846	***
	(0.00)		(0.02)		(0.02)		(0.02)	
R-sqr	0.010		0.056		0.062		0.082	
dfres	5066		4516		3714		3685	
BIC	-6938.2						-5282.2	
*p<0.05, **p<0.01, ***p,0.001								

SF-6D utility scores

The estimated SF6D mean scores by gender, age and ABI category (PAD <=0.90, borderline 0.91-1.10, normal 1.11-1.40, and high >1.40) compared to SF6D scores by gender and age, for a sample of U.S. adults aged 35-89, weight adjusted to the U.S. adult population, are shown in Table 5.

Table 5: Mean SF6D scores by age, gender and ABI level compared to U.S. Norms

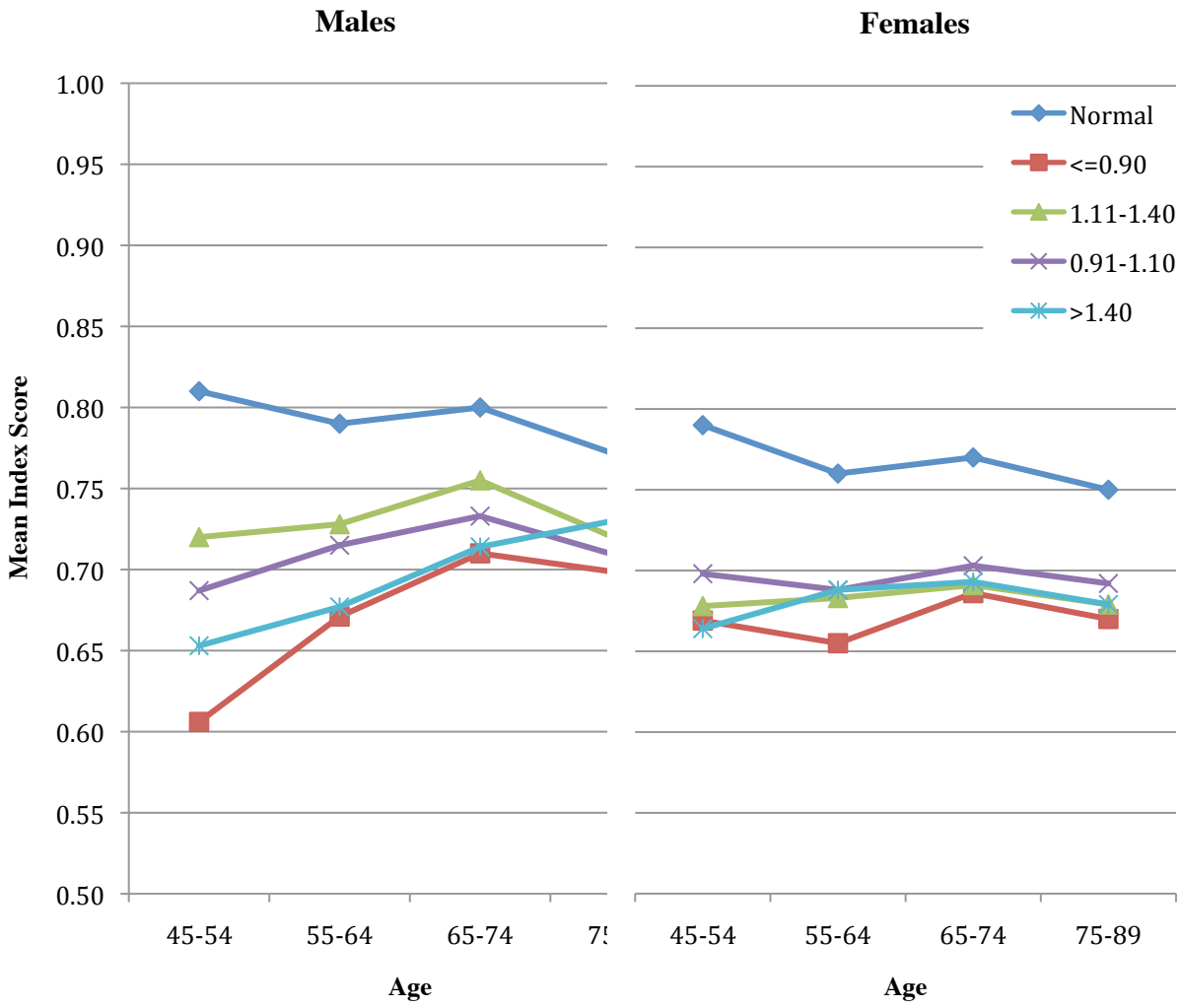
	Normal*	<=0.90	1.11-1.40	0.91-1.10	>1.40
Males					
45-54	0.81	0.61	0.72	0.69	0.65
55-64	0.79	0.67	0.73	0.72	0.68
65-74	0.80	0.71	0.76	0.73	0.71
75-89	0.77	0.70	0.72	0.71	0.73
Females					
45-54	0.79	0.67	0.68	0.70	0.66
55-64	0.76	0.66	0.68	0.69	0.69
65-74	0.77	0.69	0.69	0.70	0.69
75-89	0.75	0.67	0.68	0.69	0.68
Total	0.78	0.67	0.71	0.70	0.69

*Fryback, D.G., et al., *US norms for six generic health-related quality-of-life indexes from the National Health Measurement study.* Med Care, 2007. **45**(12): p. 1162-70.

All index scores for males, for both the U.S. norms and Partners sample, demonstrate a similar general relationship with age, displayed in Figure 1. At age 65-74, males showed a slight increase in utility score compared to those age 55-64, a "bump" previously observed in the healthy population. Males with a low ABI <=0.90 aged 45-54 had on average an SF6D score of 0.61 (SD .110), lower than reported for any other age category. For subsequent age categories, utility scores for males with a low ABI was consistently lower than the other ABI categories.

Utility scores for males age 45-54 in all ABI categories was less than those of healthy males in the same age group.

Figure 1: Mean Utility Scores by Gender and ABI



Mean SF6D scores for females were overall slightly lower, across all age groups, than for men. Females with low ABI <=0.90 scores, had lower utility scores than men, with the exception of ages 45-54 where the score was slightly higher (0.67 vs. 0.61).

The difference in average mean utility scores between males with a low ABI <=0.90 and normal males ranged from a difference of 0.2 (age 45-54) to a difference of 0.07 (age 75-89). The difference in average mean utility scores between female with a low ABI <=0.90 and normal females ranged from a difference of 0.12 (age 45-54) to a difference of 0.08 (age 75-89). These differences while small, reflect a clinically meaningful difference, where on average, the clinically meaningful minimal difference between groups should be >=0.04 (Walters, Brazier).

Quality adjusted survival

Figures 2 and 3 summarize the life expectancy for males and females ages 45-89 using this 2007 life tables, comparing life expectancy across ABI level compared to healthy individuals. Starting at birth, healthy men a have cumulative life expectancy of 76 years, compared to health women who have a cumulative life expectancy of 81 years. When an individual is diagnosed with PAD (ABI <=.90) life expectancy is reduced to 65 years for males (11 year decline) and 71 years for females (10 year decline).

Weighting proportion alive at each age by utility scores produces quality-adjusted life expectancy estimates. Figures 4 and 5 demonstrate the quality-adjusted life expectancy (QALE) for males and females ages 45-89 by level of ABI compared to the general population. The QALE for males and females in the normal population were 69 years (7 year decline) and 72 years (9 year decline), respectively, due to an average reduced quality of life. For individuals with PAD, quality-adjusted life expectancy is further reduced 7 years to 58 years for males and

Figure 2: Adjusted Survival for Males by ABI Level

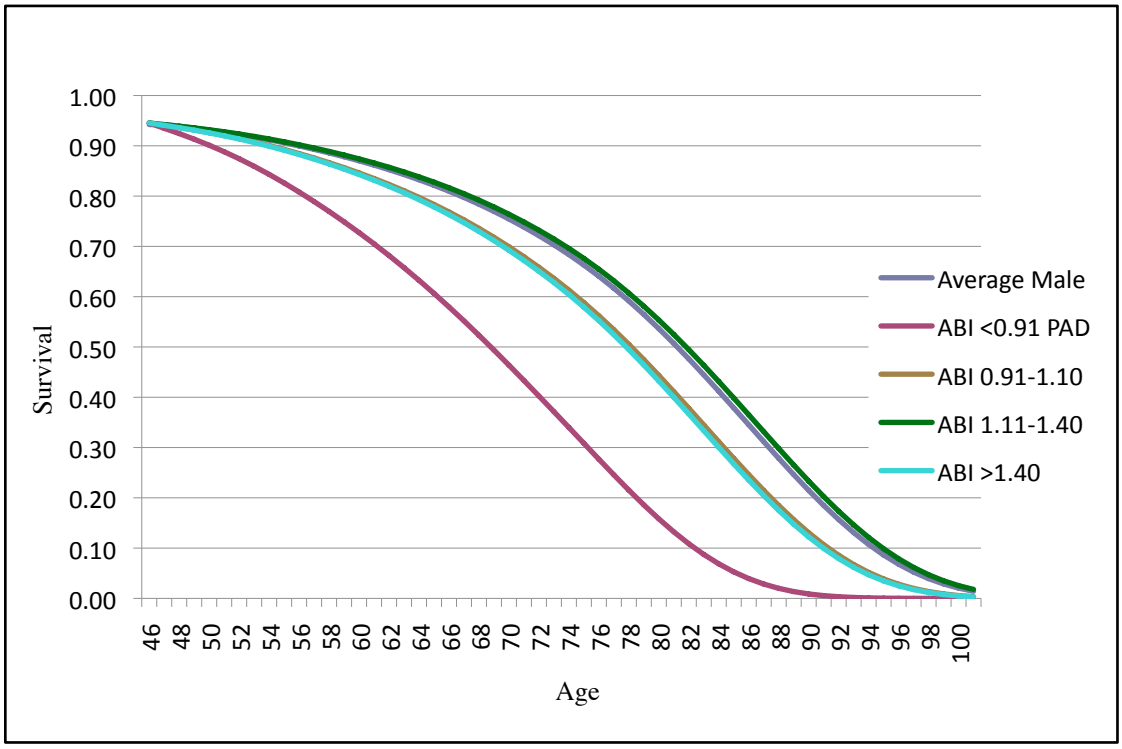


Figure 3: Adjusted Survival for Females by ABI Level

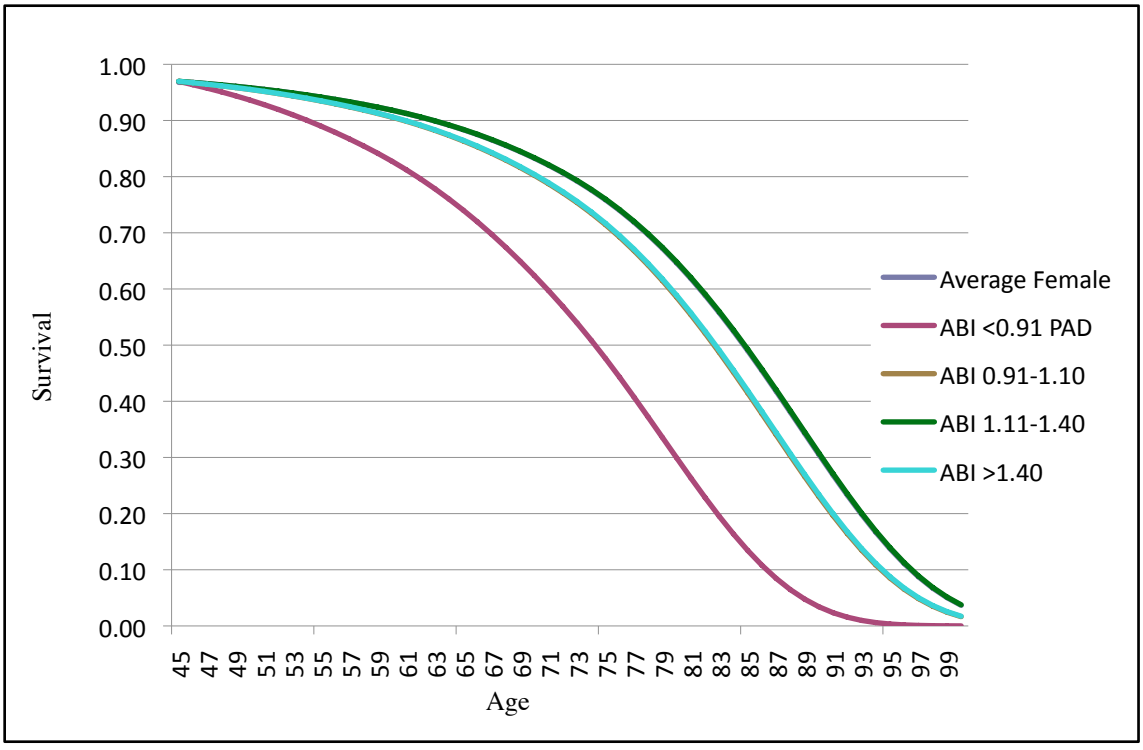


Figure 4: Quality Adjusted Life Expectancy for Males by ABI Level

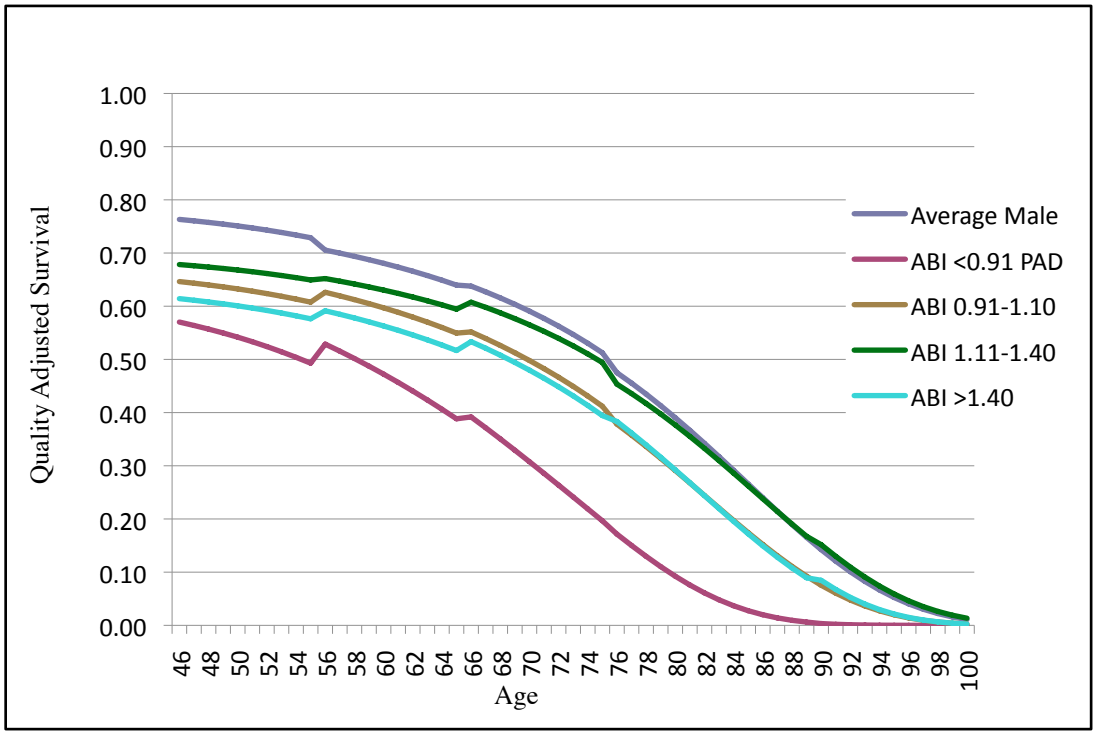
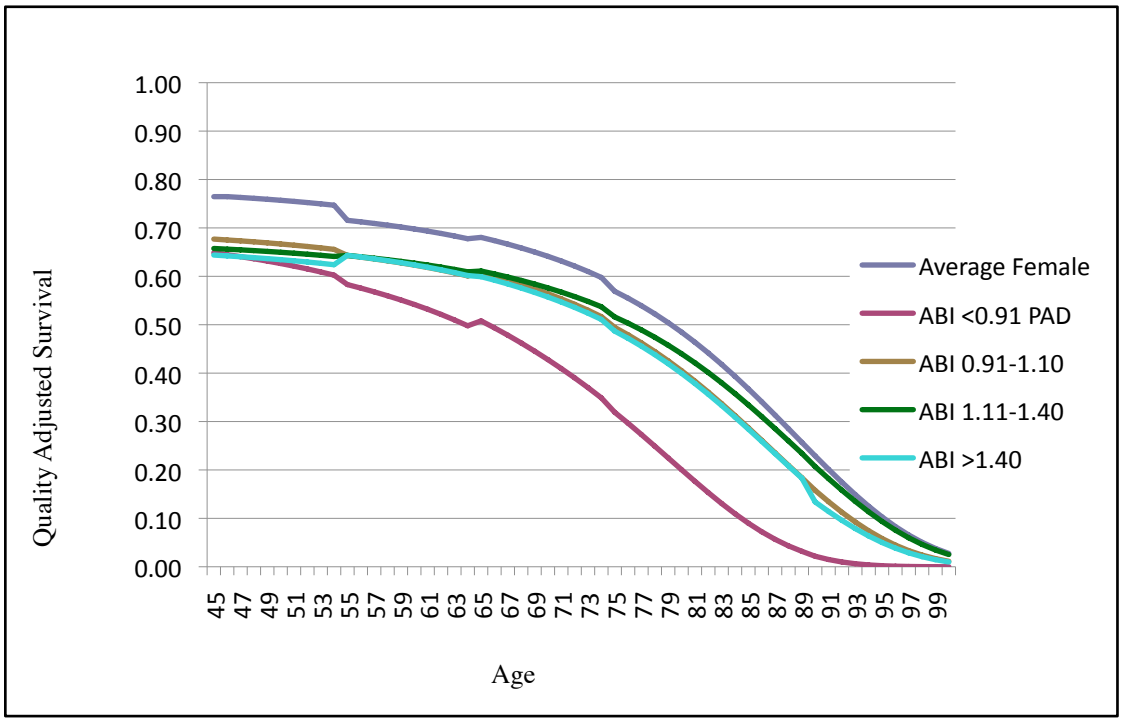


Figure 5: Quality Adjusted Life Expectancy for Females by ABI Level

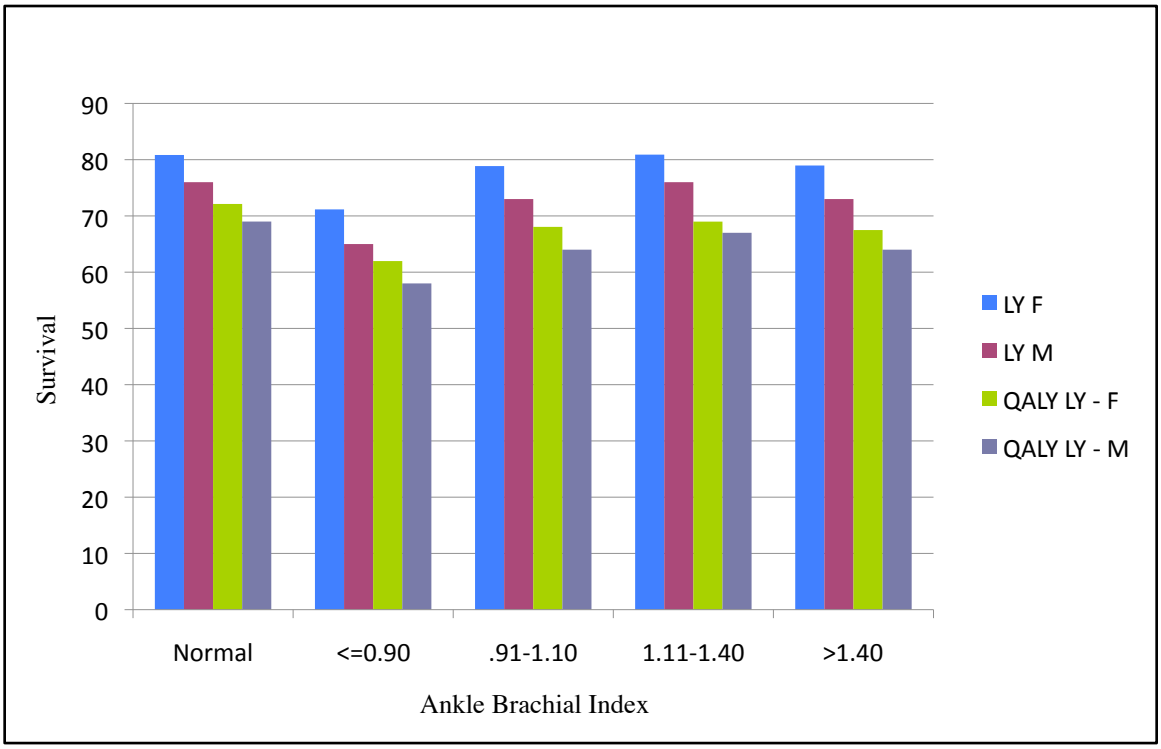


by 9 to 62 years for females, accounting for an additional decline of 15 years and 12 years, respectively. The total number of life years lost, summarized in Table 6 and Figure 6, is on average, 18 years for males and 19 years for females.

Table 6: Quality Adjusted Life Years Lost

	Predicted Life Years		Quality Adjusted Life Years	
	Females	Males	Females	Males
Normal	81	76	72	69
<=0.90	71	65	62	58
.91-1.10	79	73	68	64
1.11-1.40	81	76	69	67
>1.40	79	73	67	64

Figure 6: Total Life Years Lost by ABI Level and Reduced Utility



Discussion

Previous studies have demonstrated the correlation between quality of life and clinical indicators of patients with lower limb ischemia to be moderate at best, with disease-specific instruments showing a stronger correlation than those obtained from generic instruments[77, 78]. Furthermore, Mazari et al found the correlation between quality of life and resting ABI to be marginally superior to that with a post exercise ABI[79], while other studies have shown a weak association between level of ABI and HRQoL indices[52, 80]. Our findings confirm this.

When measuring quality of life, different instruments can lead to different health-related utility scores, however it is not always clear why these differences arise. In terms of sensitivity to clinical changes, studies have compared the SF-6D to the EQ-5D, another general health status instrument. In one study, Brazier et al. compared SF-6D and EQ-5D scores across seven patient groups with differing severity of illness and found that the SF-6D had a smaller range and lower variance in values[73]. In addition, a chronic disease case study found the inclusion of items such as "vitality" and "social functioning" included in the SF-6D, contributed to a difference in scores, suggesting the SF-6D index may be a stronger correlate to clinical indicators than the EQ-5D[73, 81]. In contrast, Mazari et al found that after measuring clinical changes post-revascularization for patients with intermittent claudication, the EQ-5D showed a stronger correlation, and thus was more sensitive, in measuring a change in quality of life compared to the SF-6D. Overall, weak correlations in the SF6D and clinical outcome measures suggests that while both outcomes are important for measuring effectiveness, changes in one should not presume a change in the other.

Additionally, in situations where changes in unobserved clinical differences may be small, subsequent changes in HRQoL indicators will likely be even smaller. Moreover, since

these indices are the basis for imputing QALYs, the true benefit gained by patients as a result of intervention, medical or functional, is likely underestimated. The result would be a higher cost per QALY, making these interventions or treatments more expensive and seemingly less attractive or cost effective.

Yet, despite the weak correlation to the ABI and other PAD clinical risk factors, the SF-6D remains a valid measure and valuable input for calculating quality adjusted life years used in economic analysis [71], and quality adjusted life expectancy, a tangible measure of life years lost due to PAD.

Limitations

The SF-6D creates an estimate of utility for the patient one point in time. While the patient will have a certain quality of life carried over so many years of life, the SF-6D assumes a static quality of life, and does not take into account the sequence of health states or length of time in each health state. Therefore, it does not factor in changes in quality of life, increases but also decreases, some of which are factored into survival years and the natural decrease in quality of life that occurs as one ages and approaches death. Utility scores were imputed using HRQoL data from a national population sample collected in the Partners study. While the study sample was taken from U.S. primary care practice settings, it may not be a true representative of PAD population prevalence.

Chapter 3: A Markov Simulation and Cost-Effectiveness Analysis of using the Ankle-Brachial Index to Screen and Treat Patients with Peripheral Arterial Disease

Introduction

In 2001, a total of $4.37 billion dollars was spent on PAD related treatment in the United States[82]. Of this, approximately $3.87 billion is billed to Medicare with an annual enrollee expenditure of $500 million, placing PAD treatment costs in line with Medicare expenditures for congestive heart failure ($3.9 billion) and cerebral vascular disease ($3.7 billion). In 2001, PAD treatment accounted for approximately 2.3 percent of the $167.8 billion spend for Medicare Part A and B, and 3.5 percent of the $97.8 billion spent for Part A[82].

Since PAD is particularly prevalent in the elderly, Medicare pays the majority of PAD related expense. The bulk of these expenditures are attributable to invasive inpatient care such as peripheral vascular shunt or bypass, angioplasty of non-coronary vessels, and amputations, procedures that would theoretically be decreased if PAD patients are identified and treated earlier.

Medicare patients treated for PAD have, on average, total annual healthcare cost of approximately $14,000 ($17,269, adjusted 2010), almost twice the average Medicare expenditure ($5833) for an elderly enrollee. The mean annual per patient expenditure for PAD specific treatments is $1868 ($2304, adjusted 2010), with the majority of the expense ($1653) billed to Medicare and the remaining ($215) billed to the patient through copays and deductibles[82]. The difference in total annual healthcare costs and PAD-specific expenditures reflects both the high number of high cost comorbidities associated with PAD, and the challenges in differentiating

PAD related costs from those of other related atherosclerotic conditions. For example, a patient may be diagnosed and treated for "cardiovascular disease" related to a myocardial infarction or stroke, but have underlying PAD that is the primary cause or contributing risk-factor for the event. For these reasons, Medicare costs are considered conservative estimates of the actual costs incurred due to PAD.

Screening

Individuals at high-risk for PAD and candidates for screening include those who are[15]:

- Age 50 years or less, with diabetes and one other atherosclerosis risk factor such as cigarette smoking, dyslipidemia, hypertension, and hyperhomocysteinemia;
- Age 50 to 69 years with a history of smoking or diabetes;
- Age 70 years and older;
- Leg symptoms with exertion (suggestive of claudication) or ischemic rest pain;
- Abnormal lower extremity pulse examination;
- Know atherosclerotic coronary, carotid, or renal artery disease.

Cigarette smoking in particular has a strong causal effect on PAD where it is 2 to 3 times more likely to cause PAD than coronary artery disease[83]. Those who smoke have a 2- to 6-fold increased risk for PAD, and 3- to 10-fold increased risk for intermittent claudication[84]. More than 80 percent of patients with PAD are former or current smokers, where a dose dependent relationship exists with the number of cigarettes smoked and number of years smoked[85, 86].

Diabetes mellitus increases the risk for PAD by 2- to 4-fold, and is present in 12 to 20 of patients with PAD[83, 87]. The risk of developing PAD is proportional to the severity and duration of diabetes, where the men have a 3.5-fold and women 8.6-fold increased risk of intermittent claudication[88]. Diabetic patients with PAD are also 7- to 15-fold more likely to develop critical limb ischemia and undergo a major amputation than nondiabetics with PAD[89, 90].

The risk of developing PAD increases by approximately 5 to 10 percent with each 10 mg per dL increase in total cholesterol[90]. Hypertension is associated with PAD, although the association is somewhat weaker than it is with cerebrovascular and coronary artery disease. Hypertension increased the risk of PAD in some studies but not in others[90, 91]. However, in the Framingham Health Study, hypertension increased the risk of intermittent claudication 2.5- to 4-fold in men and women, respectively, with the risk being proportional to the severity of high blood pressure[92].

There are seven vascular non-invasive diagnostic techniques to screen for PAD[15]. These tests include patient questionnaires, the ankle-brachial index, segmental pressure measurements, pulse volume recordings, duplex ultrasound imaging, Doppler waveform analysis, and exercise testing. Four of these tests, the Rose questionnaire, pulse examination, ABI and pulse wave velocity were used to determine the prevalence of PAD in a San Diego population study[23]. In that study, the Rose questionnaire severely underestimated the prevalence of PAD, while the ABI and pulse wave velocity increased the detection rate by 2 to 7 times, and pulse examination overestimated the prevalence by 2-fold.

Screening for PAD using the Ankle-Brachial Index

The Ankle-Brachial Index (ABI) is the most reasonable option for PAD screening on a population basis[14]. Current 2011 recommendations for screening for PAD using the ankle-brachial index indicate that "the resting ABI should be used to establish the lower extremity PAD diagnosis in patients with suspected lower extremity PAD, defined as individuals with 1 or more of the following: exertional leg symptoms, nonhealing wounds, age 65 years or older, or 50 years and older with a history of smoking or diabetes"[93]. Based on the results of the German Epidemiologic Trial on Ankle Brachial Index Group that included 6880 patients 65 years of age or older, and found that 21 percent of the cohort had PAD, earlier 2005 recommendations were modified to lower the age of screening from 70 to 65 years of age. While the modification represented a significant increase in the size of the at-risk population to be screened, the American College of Cardiology Foundation/American Heart Association Task Force (ACCF/AHA) felt the recommendation reflected their intent "to blunt the profound ongoing underdiagnosis and undertreatment of individuals with PAD until limb ischemic symptoms have become severe"[93]. The ACCF/AHA also noted, however, that the ABI recommendation was for office-based and vascular laboratory diagnostic use and was not intended to be a population based screening tool. The group further recognized that no other cardiovascular disease diagnostic test could be applied in an age-defined clinical population with such a high detection rate, low to no risk, and low cost. In addition to lowering the age of screening, the evidence based for the recommendation was upgraded from a C to a B.[1]

[1] A C-level of evidence is given when there is only consensus opinion of experts, case studies, or standard-of-care. A B-level of evidence is given for data derived from a single randomized trial or nonrandomized studies.

Acknowledging the need to accurately diagnosis PAD in order to provide systemic risk-lowering lifestyle and treatment interventions, the American College of Cardiology, the American Heart Association, and international vascular specialty societies have all endorsed the strongest Class 1A recommendation for measuring the ABI in "at-risk' populations[15, 44]. In contrast, the U.S. Preventive Task Force has recommended against routine screening for PAD[94, 95].

Grounds for the USPTF decision was that current evidence was insufficient to adequately determine the benefits and harms of using the ABI to screen asymptomatic patients with no history or risk of CHD[95]. Despite evidence found by Fowkes et al, that demonstrated that the ABI contributed significant cardiovascular prognostic information beyond the Framingham Risk Score[40], the USPTF rationale was that screening with the ABI would not provide information "beyond treatment based on standard cardiovascular assessment". Furthermore, the task force reasoned that screening asymptomatic adults could lead to increased harm due to "false positive results and unnecessary work-ups."

More specifically, the USPSTF review determined whether the ABI, as an added risk measurement, could reliably reassign individuals assessed using the Farmington risk model from the intermediated risk profile, to either the low-risk profile or the high-risk profile, thereby indentifying those who need to initiate risk modifying behavior and treatment that is more aggressive. The outcome of the USPSTF assessment of the ABI data using the risk model was inconclusive for men in the intermediate-risk category. For women, however, the data on the ABI indicated that approximately 10 percent of women with an intermediate-risk profile would

be reclassified to a high-risk profile for CHD. Insofar as determining the size of the reduction in CHD events associated with using the ABI, the USPSTF concluded that current evidence was insufficient to determine this but that the information represented a "critical gap in the evidence for benefit from screening" and furthermore, that once the evidence became clearer, evaluating the cost-effectiveness would be a research priority[95].

New Criteria for Screening

In addition to the USPTF perspective on screening, it is important to consider guidelines proposed by other groups for disease screening. On an international level, Wilson and Junger proposed the most commonly cited criteria[96]. According to these authors, 10 criteria should be met in order to justify a screening test. The World Health Organization (WHO) has adopted these criteria and they are summarized in Table 7. Within the table are comments on whether PAD screening meets each criterion. For example, PAD is clearly an important public health problem, and there is acceptable treatment for those recognized with the disease[97]. The natural history of disease progression has been described quantitatively[25, 26, 83]. Many studies focus only on the effects of PAD on the lower extremities. Although only about 5% of PAD patients eventually go to amputation, in part this may be a function of early mortality from other causes. Substantial evidence suggests that PAD has very general vascular effects[98]. There is a latent or early symptomatic stage prior to truly symptomatic expression of PAD symptoms[29, 83]. For example, there is a worsening of ABI followed by development of symptoms. Further, while it has not been established that there is a suitable screening test that is acceptable to the population, the ABI is a strong candidate because it is only a little more demanding than taking a blood pressure. As Table 1 suggests, most of the criteria proposed by the WHO are met for PAD

screening. However, the final criterion asks whether the cost of screening is economical in relation to total healthcare costs. In order to evaluate this question, a systematic cost-effectiveness model must be developed.

Table 7: Evaluation of the ABI as a Screening Tool for PAD using Wilson's Ten Criteria for Screening and Justification

Criterion	Met? Y/N	Comment	Reference
The conditions should pose an important health problem.	Y	PAD is an important health problem and is a predictor of morbidity and mortality.	[2, 99]
The natural history of the disease should be well understood.	Y	The natural history of PAD has been studied, risk of untreated PAD are documented.	[3, 14, 26, 98]
There should be a recognizable early, latent, pre-symptomatic stage.	Y	PAD may have a long asymptomatic period.	[25]
Treatment in the early stages should be of more benefit than treatment in a later stage.	Y		[100]
A suitable test exists.	Y	There are a variety of non-invasive diagnostic methods available to test for PAD (ABI, pulse volume recording, duplex ultrasound imaging, Doppler wave form analysis) however; the ABI is the most simple and accurate.	[14, 15, 40]
Test is acceptable to the population.	Likely but not known	The public is largely unaware of PAD. The ABI is simple, accurate, and painless.	[29]
There are adequate facilities for the diagnosis and treatment of abnormalities detected.	Not known	It is not know if there is the capacity to respond to a large increase in PAD cases.	
There is an agreed policy on who to treat.	Y	Guidelines are available.	[15, 101]
Case findings should be	Unclear	If screening were undertaken, it would need to	

continuous.		be repeated on a regular basis, although at what interval is not unclear.
The costs of screening should be economical in relation to total health care – all costs must be balanced against benefits.	No	It has not yet been demonstrated that the benefits outweigh the costs. This is the focus of the proposed study.

Research Aims

Despite the significant individual and population-based level health risks that PAD represents [1-3], increased screening and early treatment has not been a public health priority. Therefore, in order to address the research questions around the cost-effectiveness of using the ABI to screen and treat patients with PAD, the current CEA study was designed with the following aims:

1. To determine the cost per quality-adjusted life year (QALY) gained as a function of screening for PAD using the ABI and treatment of newly identified cases;
2. To compare the cost per quality-adjusted life year (QALY) gained as a function of screening and treatment of newly identified cases with those who initiate treatment when they become symptomatic;
3. To estimate the decreased PAD-specific morbidity or improved health outcomes from screening for PAD using the ABI and early treatment;
4. To estimate the harms from screening for PAD using the ABI, including over-treatment and over-diagnosis.

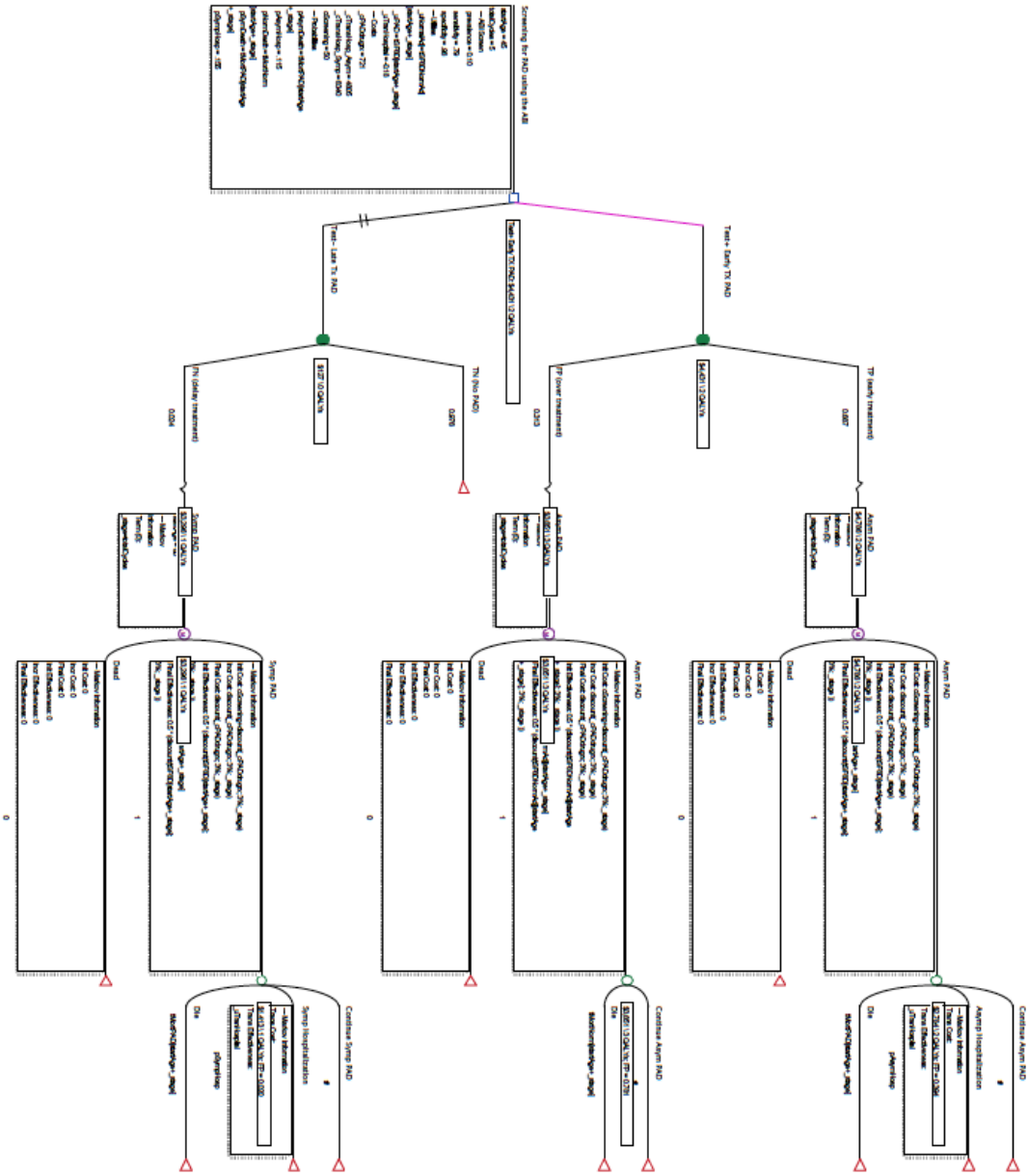
Methods

The model was constructed to measure the cost-utility of screening for PAD in an asymptomatic population using the ABI. At post-test screening, patients will be in one of four mutually exclusive categories, true positive, false positive, true negative or false negative. Patients in the true-positive category, those who test positive and have disease, progress to treatment. Patients in the false positive category, those who test positive but do not have disease, also progress to treatment. These two groups make up the "Early Treatment" arm or strategy. The second arm includes patients who are false negatives, those who have disease but do not test positive, and progress to treatment 20 years later after becoming symptomatic. True negatives, those without disease who test negative, are also included in this treatment arm, but did not progress to treatment. Those who test negative make up the "Late Treatment" arm, which also represents the comparison group and reflects current medical practice that treats patients once they become symptomatic for the disease. The model was developed from the payer perspective with a cycle length of one-year. Cost data were obtained from the literature. Quality-adjusted life years (QALYs) were imputed from SF-36 scores, and are used for the measure of health utility.

Model Specification

The decision model was created in TreeAge Pro(TM), version 2012, and is shown in Figure 7.

Figure 7: Decision Tree for Peripheral Artery Disease Screening Using the Ankle-Brachial Index



Estimating Post-Test Probabilities

Diagnostic and screening tests do not give perfect information, therefore understanding how a test performs is important when assessing the probability that a patient has a given disease. In other words, when deciding who should receive treatment, we are interested in the probability of disease conditional on the result of the test. In this model, we are specifically interested in the probability of PAD given a positive or negative ABI screen test.

Independent values such as sensitivity and specificity describe how often a test result is correct, based on the presence or absence of disease. Sensitivity is a measure of the proportion of patients with disease who have a positive test, or the probability of a positive test result given that the disease is present, called the true-positive ratio (TPR). Specificity is a measure of the proportion of patients without disease who have a negative test, or the probability of a negative test result given that the disease is not present, called the true-negative ratio (TNR). A highly sensitive test is good at identifying those with the disease, while a highly specific test is good at identifying those without the disease.

The complement of sensitivity and specificity are the false-negative ratio (FNR), those with disease who screen negative, and false-positive ratio (FPR), those without disease who screen positive. Both the FNR and FPR describe how often the test is in error.

Unlike sensitivity and specificity, which are independent variables, post-test probabilities are dependent on sensitivity, specificity and disease prevalence. To move from the probability of a test result given the presence or absence of disease (sensitivity and specificity) to the probability of disease given a test result (post-test probabilities), Bayes' formula for a dichotomous test with two disease states was used[102]. For example, the formula for determining the post-test probability is:

$$P(D+ \mid T+) = P(T+ \mid D+)\,P(D+) / P(T+ \mid D+)\,P(D+) + P(T+ \mid D-)\,P(D-)$$

Or, substituting "prevalence" for "pretest probability";

Sensitivity x Prevalence / (Sensitivity x Prevalence) + ((1-Specificity) x (1-Prevalence))

Or, Post-Test+ = TP/TP+FP Post-Test- = FN/FN+TN

Applying these formulas in a 2x2 table, the post-test probabilities for the ABI are shown in Table 8. In a hypothetical cohort of 10,000 with 10 percent PAD prevalence, the positive predictive value of the ABI is 0.6869, and the negative predictive value is 0.9763. The majority of screened patients will be true-negatives (8640), which is what we would expect with a high specificity of 0.96, and a corresponding low number of false-negatives (210). However, the estimation of true-positives is not quite as accurate, reflecting a lower value for sensitivity.

Table 8: Positive and Negative Predictive Values of the ABI

cohort	10000	
pre-test =	0.10	
sensitivity =	0.79	(Lijmer, 1996)
specificity =	0.96	(Lijmer, 1996)
	Diseased	Non-Diseased
positive	790	360
negative	210	8640
total	1000	9000
post-test +	0.686	
post-test -	0.976	

Positive Screen: Early Treatment and Over Treatment

In the model, patients who screen positive transition into one of two categories, true positives (TP) or false positives (FP) based on the ABI post-test probabilities. True positives labeled early treatment, and false positives labeled over treatment, progress to a Markov treatment and outcome sequence. In the first state of the Markov sequence, all patients progress to treatment. In the second state, true positives can 1) remain in the asymptomatic treatment phase, 2) experience a non-fatal PAD event that leads to hospitalization, or 3) die. Patients in treatment repeat the same cycle, while those in hospitalization or death end at those terminal nodes. Patients in the over treatment group progress through a similar sequence, with the option for hospitalization due to a PAD related event removed.

Negative Screen: No Treatment and Late Treatment

Patients who screen negative transition into one of two categories, true negatives (TN) or false negatives (FN) based on the ABI post-test probabilities. False negatives label late treatment, progress to a Markov treatment and outcome sequence identical to true positives. True negatives progress to a terminal node.

Cycle lengths were set at one-year increments and could be defined individually at each Markov node.

Termination Criterion

Two different termination criterions were used. Stages were defined numerically to terminate after 5-year and 10-year cycles. Or, a stop rule was entered to terminate the analysis

when 99.9 percent of the cohort was dead[2]. This stopping rule was evaluated at each of the cycles beginning from cycle 1. When 99.9 percent of the cohort was dead, the final stage rewards were assigned and the Markov model ended.

Half-cycle Correction

Markov models assume that transitions occur at the beginning or end of each cycle. This may not necessarily be true however; transitions can occur at any point in the cycle. When transitions are assumed to occur at the beginning of a cycle, the calculated life expectancy is underestimated. Conversely, the calculated life expectancy is overestimated when transitions are assumed to occur at the end of the cycle. Therefore, half-cycle corrections, where transitions are assumed to occur halfway through the cycle on average, are made to adjust for any overestimation or underestimation to the calculated life expectancies of the cohort.

Discounting

In accordance with guidelines for conducting cost-effectiveness studies, costs and benefits accruing after year 1 were discounted at an annual rate of 3 percent[66, 103].

Base Case Analysis

Probabilities, costs, utilities, and data sources, for screening using the ABI and treatment for PAD are shown in Table 9.

[2] 99.9% stopping rule by convention. See Hunink et al, 2001.

Table 9: Model Parameters - Probabilities, Costs, and Utilities

Name	Definition	Value ($ annual, adj 2010)c	Low	High	Reference
startAge	Age of Screening	45	40	75	
totalCycles	Total number of cycles (years) in simulation	5 - 40	5	20	
Ankle-Brachial Index					
prevalence	Disease Prevalence	0.1	0.05	0.2	Jaff/NHANES 8.2-9.5% 1999-2005 Ostchenga/NHANES 7% 60-69, 12.5% 70-79, 23.2% >=80 Pande/NHANES 4.7% ABI tested no CVD Selvin/NHANES 4.3% >=40, 14.5% >=70 Mahoney/REACH US cohort 10%
sensitivity	Sensitivity	0.79	0.5	0.99	(Lijmer, 1996)
specificity	Specificity	0.96	0.5	0.99	(Lijmer, 1996)
Bayes Revision					
_p7	Bayes revision: TP (early treatment)	0.687	-	-	(Hunick et al, 2006)
_p8	Bayes revision:	0.024	-	-	(Hunick et al, 2006)

	FN (delay treatment)				
_p9	Bayes revision: PAD		-	-	(Hunick et al, 2006)
_p10	Bayes revision: TN (no treatment)	0.976	-	-	(Hunick et al, 2006)
_p11	Bayes revision: FP(over treatment)	0.313	-	-	(Hunick et al, 2006)
_p12	Bayes revision: No PAD		-	-	(Hunick et al, 2006)
Probabilities					
pAsymDeath	Probability of Death with Asymptomatic PAD	tMortPAD[startAge+_stage]	-	-	CDC 2007 Life Tables adjusted with HR for PAD and QALY
pAsymHosp	Probability of Hosp for Asym PAD_Mahoney	0.115	-	-	(Mahoney, 2004) Half of 2-year rate of vascular-related hospitalization asymp patients
pSymDeath	Probability of Death with Symptomatic PAD	tMortPAD[startAge+_stage]	-	-	CDC 2007 Life Tables adjusted with PAD HR and QALY
pSympHosp	Probability of	0.155	-	-	(Mahoney, 2004) Half of

	Hosp for Symp PAD_Mahoney				2-year rate of vascular-related hospitalization symp patients
pNormDeath	Probability of Death for Normals/no-PAD	tMortNorm[startAge+_stage]			CDC 2007 Life Tables
Utilities					
_uPAD	Utility of PAD	tSF6D[startAge+_stage]	0.79	0.89	Imputed values from Partners Dataset
_uTranHospital	Disutility of Hospitalization	-0.18 QALY	-0.5	-0.01	(Sigvant, 2011) -0.10 MI, -0.26 stroke; average -0.18
_uNormalAdj	Utility of Normal Population adjusted down for drug AE	tSF6DNormAdj[startAge+_stage]			SF6D for normal population by age adjusted -0.02 for drug adverse events (FP Over Treatment)
Costs					
cScreening	Cost of ABI Screening	$50	50	250	CMS Physician Fee Schedule using National Average GCPI $42 increased to $50 to account for ($700 Hand Held Doppler fixed cost)
_cPADdrugrx	Annual cost for PAD Treatment	$721	500	1000	(Margolis, 2003) 610/annual cost, 2010

						$721
_cTransHosp_Asym	Cost of Hosp for Asym PAD_Mahoney	$4,805		4805	30000	(Mahoney, 2004) Mean Cost Asymp 4199, 2010 $4805
_cTransHosp_Symp	Cost of Hosp for Symp PAD_Mahoney	$6,340		6340	30000	(Mahoney, 2004) Mean Cost Symp (aver of claud, amp, revas) 5540, 2010 $6340

Formulas: TP=(prevalence*sensitivity)/((prevalence*sensitivity)+((1-prevalence)*(1-specificity)))

FN: (prevalence*(1-sensitivity))/((prevalence*(1-sensitivity))+((1-prevalence)*specificity))

PAD: ((prevalence*sensitivity)+((1-prevalence)*(1-specificity)))

TN: ((1-prevalence)*specificity)/((prevalence*(1-sensitivity))+((1-prevalence)*specificity))

FP: ((1-prevalence)*(1-specificity))/((prevalence*sensitivity)+((1-prevalence)*(1-specificity)))

No PAD: ((prevalence*(1-sensitivity))+((1-prevalence)*specificity))

The age when patients enter screening was defined as age 45 in this model. PAD prevalence is low in this age group, however in terms of prevention, early detection and treatment can maximize outcomes. Estimating costs and effectiveness of treatment starting at age 45 provides a high-end estimate representing the maximum period of time patients would be on treatment and incur costs. Sensitivity and specificity estimates for the ankle-brachial index were obtained from the literature. (Lijmer, 1996) Disease prevalence was estimated at 10 percent in the model and represents an average of estimates obtained from four studies using NHANES data (Jaff et al, 2010; Ostchenga et al; Pande et al, and Selvin et al) and one prospective cohort study using a US sample (Mahoney, 2010).

Bayes' Revision Probabilities

Post-test probabilities for the ABI were calculated according to Bayes' theorem using pre-test estimates of sensitivity and specificity, and disease prevalence.

Transition Probabilities

Transition probabilities were assigned at each chance node and correspond to a 1-year cycle. Probabilities for transitioning to a PAD-related hospitalization were obtained from the literature and are entered as numeric values. Mortality estimates for PAD are linked to CDC 2007 life tables adjusted for PAD risk (JAMA 2008); mortality estimates for false positives are linked to unadjusted CDC 2007 life tables. At each subsequent cycle of the model after cycle 0, a progressively higher probability of mortality is utilized because the values in the table increase with age. (Appendix 3)

Utility Estimates

Utility estimates were assigned at each Markov node and are accumulated by a patient until they reach a terminal node. The disutility of entering a hospital for a non-fatal PAD event was estimated based the average of the disutility of a stroke and the disutility of an MI[104] and entered as a numeric value. Utility estimates for PAD use estimates generated in the first study and are linked tables indexed by age group, 45-54 years, 55-64 years, 65-74 years, and >75 years. Utility estimates for patients in over treatment are based on estimates for the general population adjusted down 2 percent annually for treatment side effects.

Cost Estimates

The cost of screening was based on the cost of 15 minutes of physician time according to the CMS Physician Fee Schedule using the National Average GCPI of $42.00. The cost of a hand-held Doppler was estimated at $700 based on a current Internet search of medical equipment suppliers. To incorporate this fixed cost, the cost of a 15-minute ABI screen was rounded to $50.00. Treatment and hospitalization cost estimates are based on data from three key studies by Jaff, 2005; Mahoney, 2004; and Margolis, 2003; adjusted to 2010 USD. Recognizing that except for post-revascularization patients, PAD patients usually take either aspiring or another antiplatelet, but not both, the annual cost of drug treatment was based on estimates from claims data with an HMO managed care population for a regime that included aspirin, a statin, an ace-inhibitor, and a non-aspirin antiplatelet. (Margolis, 2003) The mean cost for hospitalization for asymptomatic patients was estimated at $4805 per event and $6340 for symptomatic patients. (Mahoney, 2004) (Appendix 4)

Data Analysis

A cost-effectiveness analysis model is proposed to evaluate the potential benefits of ABI screening. The analysis will use a societal perspective to determine the cost per quality-adjusted life year (QALY) gained as a function of ABI screening. To correct for lead-time bias associated with screening, the start age was defined independently at the root decision node, and Markov nodes.

Cost effectiveness ratios

Cost-effectiveness will be calculated as a ratio of the difference between costs divided by the difference in QALYs for patients who screen positive and negative for PAD, and will be projected for five, ten and fifteen years following screening.

One-Way Sensitivity Tornado Analysis

Sensitivity analysis is a means of assessing the extent to which a model's calculations are affected by uncertainty. Specifically, a sensitivity analysis can determine the extent to which varying the value of a parameter or group of parameters will result in the change of the optimal strategy, and the point or value where the change in strategy occurs. In a single variable or one-way sensitivity analysis, the expected value of each comparison strategy is plotted as a function of the increasing value of the variable. When plotted on a graph, deviations from a horizontal line indicate that the strategy is sensitive to that variable, as either an increasing or decreasing function. If two lines intersect on the graph, at the corresponding value of the variable the two alternatives have the same expected value. The crossing point represents a change in the optimal strategy and is called the threshold.

Monte Carlo Probabilistic Sensitivity Analysis and Micro-simulation

Monte Carlo Probabilistic Sensitivity Analysis (PSA) or second-order trials were combined with a micro-simulation for this model. Monte Carlo techniques were used to introduce a level of chance or randomness to the uncertainty estimates. Unlike one-way sensitivity analyses, which use a defined point estimate for each variable and set probability at

each chance node, Monte Carlo techniques can introduce randomness into the analysis through first- and second-order simulation.

A second-order simulation (PSA) was used to assess uncertainty around parameters in the model. Since parameters are often used across strategies in a model, second-order trials roughly correspond to the model or system uncertainty. For second-order trials, parameter values are samples taken from a variable's distribution rather than it's discrete numeric value or range of values. Using normal approximations, all the probabilities, costs and utilities were defined as distributions in the simulation. 1000 samples were taken from these distributions to calculate the expected value for each strategy; in general, sampling above 1,000, does not substantially improve the empirical distribution function as an estimate of the population distribution function.

In contrast, micro-simulation, first-order, or random walk, was used to assess the uncertainty around the chance nodes, which determine the future states of the modeled outcome. For the micro simulation, each trial used a random number to select a path through the decision tree, where higher probability events were more likely to occur. To ensure that even small probability paths would be selected, 10,000 trials were run and then averaged to produce the expected value calculation. By running the simulation at the decision node, each trial was repeated for both screening strategies, so values for early and late treatment could be compared.

Results

The mean expected value cost/effectiveness calculations of early and late treatment are shown in Table 10. The analysis assumes a PAD prevalence of 10 percent at 5, 10 and 15 year intervals. The mean expected cost of ABI screening ranges from $127 to $128 for a negative ABI screen test and subsequent late treatment, to $4,580 to $6,445 for a positive ABI screen test

and early treatment. Screening and late treatment accounts for a gain of <1 QALY, while early treatment accounts for a gain of 2.47 to 4.43 QALYs, for an additional cost of $4453 to $6317. The cost-effectiveness ratios for late treatment range from $5638/QALY to $5867/QALY; for early treatment the range is $1453/QALY to $1857/QALY, with improved cost-effectiveness as the time interval increases.

Table 10: Cost-effectiveness Ratios for Screening Plus Early Treatment vs. Late Treatment

Strategy	Cost	Incremental Cost	Effectiveness QALY	Incremental Effectiveness QALY	Cost-effectiveness Ratio (Cost/QALY)	Incremental Cost-effectiveness Ratio (ICER)
						Prevalence 10%
5-years						
Test- Late Tx	$127		0		$5867/QALY	
Test+ Early Tx	$4,580	$4453	2	2	$1857 /QALY	$1823/QALY
10-years						
Test- Late Tx	$128		0		$5638/QALY	
Test+ Early Tx	$5,954	$5826	4	4	$1578/QALY	$1554/QALY
15-years						
Test- Late Tx	$128		0		$5638/QALY	
Test+ Early Tx	$6,445	$6317	4	4	$1453/QALY	$1432/QALY

Markov State Probabilities

Markov state probability estimates for each treatment option were calculated at 5, 10, and 15-year intervals and are shown in Table 11 (For full stage calculations see Appendix 5). In order to calculate the individual probabilities of being in each state, and the number of hospitalizations and death per stage, individual Markov analysis were run for each of the treatment arms. Markov state probabilities represent for each state, the reward that was received

at each stage. In the first cycle of the Markov process, Stage O, the cohort was distributed among the Markov states according to the initial probabilities entered under the branches (the only time these probabilities are used); initial rewards are accumulated based on state membership; the members of a state traverse the transition subtree based on the transition probabilities, and the percentage of the cohort at a transition node are assigned the transition rewards in the path back to the state (before entering new states for the next cycle).

Positive Screen: Asymptomatic Early Treatment

For example, at Stage 0, the cohort has a probability of 1.0 for entering the state "Asymp PAD" labeled as "Prob Cohort in treatment". The cohort traverses the subtree based on transition probabilities; 1*0.115 progress to "Asymp Hospitalization", 1*0.043 (PAD mortality at age 45) progress to dead, and the remaining [1-(1*0.115) + (1*0.043)] continue to "Asymp PAD". The cohort that ends a stage in "Asymp PAD" enters the next stage.

The cost of Stage 0 is the sum of the cost of treatment (in Stage 0 this includes the cost of screening; Int Cost: cScreening+discount (_cPADrugrx; 3%; _stage)) and the sum of transition costs. Because in discrete-time Markov models the assumption is that, all state transitions occur simultaneously at the end of each cycle, a 0.5 cycle correction was applied at the initial and end stages. A 3 percent discount was applied to stage costs but not transition costs starting in Stage 1.

Stage 0 cost = [50+721] + [.115*4805] = 1324

The effectiveness of Stage 0 is the sum of the percent QALY gained in that stage plus any disutility acquired in hospitalization. In Stage 0, 11.5 percent of the cohort was hospitalized and 4.3 percent died.

Stage 0 = [0.638 (PAD utility at age 45) *1*0.50] + [0.115*-0.18] = 0.2981 QALY

Because the Markov analyses are downstream from the decision node, final costs and effectiveness calculations associated with the decision and first chance nodes, were adjusted based on the Bayes probabilities. Markov survival and transition probabilities, reported at the terminal nodes are unadjusted.

Markov state probability reward estimates for each treatment option were also calculated at 5, 10, and 20-year intervals and are shown in Table 12. Entering the 5th year, 39.4 percent of asymptomatic early treatment patients are in treatment, 41.6 percent will have been hospitalized, and 19 percent will have died. Of those alive, 0.3937*0.115 progress to "Asymp Hospitalization" and jump to dead, 0.3937*0.082 (PAD mortality at age 50) progress to dead, and the remaining [1-(0.3937*0.115) +(0.3937*0.082)] continue to "Asymp PAD".

The unadjusted cost for the first 5 years for an individual with a true positive screen and early treatment is $5003 [(((721*.40*.85) + (.0453*4805))+4541], or $3437 when adjusted by the post-test probability of 0.687, for an gain of 1.48 QALYs per individual screened with a positive test result[3]. (Figure 1)

At 10 years, 11.3 percent are still in treatment, 56.7 percent will have been hospitalized, and 32 percent will have died. The adjusted cumulative cost at 10 years is $4233, for a gain of 4 QALYS per individual screened with a true positive test result. At 20 years, 99 percent of early treatment patients will have experienced hospitalization (61 percent) or death (39 percent).

Negative Screen: Symptomatic Late Treatment

At 5 years, 2 percent of symptomatic late treatment patients are still in treatment, 30 percent will have been hospitalized, and 68 percent will have died. Of those alive, 0.0196*0.155

[3] The cost of 5 year screening for patients who screen positive is listed as $4786/2 QALYs on the "roll back" expected value for true positive screens "Asymp PAD" in Figure 1. This number should be $5003/2 QALYs. The cost of hospitalizations in stage 5 ($217) for asymptomatic patients in early treatment was left out in error.

progress to "Asymp Hospitalization" and jump to dead, 0.0196*0.47 (PAD mortality at age 70) progress to dead, and the remaining [1-(0.0196*0.155) +(0.0196*0.47)] continue to "Asymp PAD".

The unadjusted cost for the first 5 years for an individual with a negative screen and late treatment is $3315 [(((721*0.0196*.88) + (.0030*6340)) + 3284)*0.024], or $79.57 when adjusted by the post-test negative probability of 0.024, for a gain of .02 QALYs per individual screened. When the cost of screening alone $48.80 (50*.976) is added, the average total 5 year cost 5 for an individual with a negative screen is $120, for an average gain of .02 QALYs. The low adjusted cost of treatment is due to the low probability of a false negative screen (0.024) and the low probability that a 65 year old patient will be in treatment and incur costs.

At 10 years, 30 percent will have been hospitalized, and 70 percent will have died. The cost of screening and treatment 10 years is $3333 unadjusted, and $128 adjusted, for a gain of .02 QALYS per individual.

Positive Screen: Over Treatment

In patients who are otherwise healthy but screen positive for PAD, 78 percent, 56 percent, and 17.5 percent will continue treatment after 5, 10 and 20 years, respectively. The adjusted costs of over treatment range from $1143 to $1721, after 5 years and 10 years, for a gain of 1.8-1.97 QALYS. Costs of over treatment assume patients will continue treatment for the entire time period. However, since patients with a false positive diagnosis for PAD may have their diagnosis corrected at a subsequent doctors appointment, over treatment costs represent a conservative, high-end estimate.

Table 11: Markov State Probabilities by Stage

Stage	State	Node	Prob	Stage Cost	Total Cost	Stage QALY	Total QALY	Bayes Adjusted Total Cost	Bayes Adjusted QALY
									0.687
0	Asym ET	Prob Cohort In Tx	1.0000	$1,324	$1,324	0.2981	0.29805		
0	Asym ET	Continue Asym PAD	0.8420	$771		0.3188			
0	Asym ET	jump to: Asym PAD	0.8420						
0	Asym ET	Asym Hosp	0.1150	$553		-0.0207			
0	Asym ET	jump to: Dead	0.1150						
0	Asym ET	Die	0.0430						
0	Asym ET	jump to: Dead	0.0430						
0	Dead	Prob Hosp or Dead	0.0000						
5	Asym ET	Prob Cohort In Tx	0.3937	$462	$5,003	0.2429	2.1582	$3,437.40	1.48
5	Asym ET	Continue Asym PAD	0.3162	$245		0.2510			
5	Asym ET	jump to: Asym PAD	0.3162						
5	Asym ET	Asym Hosp	0.0453	$218		-0.0082			
5	Asym ET	jump to: Dead	0.0453						
5	Asym ET	Die	0.0323						
5	Asym ET	jump to: Dead	0.0323						
5	Dead	Prob Hosp or Dead	0.6063						
10	Asym ET	Prob Cohort In Tx	0.1130	$123	$6,162	0.0726	2.7931	$4,233.26	1.92
10	Asym ET	Continue Asym PAD	0.0836	$61		0.0749			
10	Asym ET	jump to: Asym PAD	0.0836						
10	Asym ET	Asym Hosp	0.0130	$62		-0.0023			
10	Asym ET	jump to: Dead	0.0130						
10	Asym ET	Die	0.0164						
10	Asym ET	jump to: Dead	0.0164						
10	Dead	Prob Hosp	0.8870						

		or Dead	0						
20	Asym ET		0.0018	$1	$6,442	0.0003	2.9647	$4,425.53	2.04
20	Dead		0.9982	$-		0			
									0.313
0	Asym OT	Prob Cohort In Tx	1.0000	$771	$771	0.390	0.390		
0	Asym OT	Continue Asym PAD	0.9570	$771		0.390			
0	Asym OT	jump to: Asym PAD	0.9570						
0	Asym OT	Asym Hosp		$-		0.000			
0	Asym OT	jump to: Dead							
0	Asym OT	Die	0.0430						
0	Asym OT	jump to: Dead	0.0430						
0	Dead	Prob Hosp or Dead	0.0000						
5	Asym OT	Prob Cohort In Tx	0.7811	$486	$3,651	0.609	3.781	$1,142.71	1.18
5	Asym OT	Continue Asym PAD	0.7358	$486		0.609			
5	Asym OT	jump to: Asym PAD	0.7358						
5	Asym OT	Asym Hosp		$-		0.000			
5	Asym OT	jump to: Dead							
5	Asym OT	Die	0.0453						
5	Asym OT	jump to: Dead	0.0453						
5	Dead	Prob Hosp or Dead	0.2189						
10	Asym OT	Prob Cohort In Tx	0.5557	$298	$5,498	0.420	6.286	$1,720.87	1.97
10	Asym OT	Continue Asym PAD	0.5113	$298		0.420			
10	Asym OT	jump to: Asym PAD	0.5113						
10	Asym OT	Asym Hosp		$-		0.000			
10	Asym OT	jump to: Dead							
10	Asym	Die	0.044						

	OT		5						
10	Asym OT	jump to: Dead	0.0445						
10	Dead	Prob Hosp or Dead	0.4443						
20	Asym OT		0.1752	$70	$7,062	0.037	8.702	$2,210.38	2.72
20	Dead		0.8248	$-		0.000			
									0.024
0	Sym LT	Prob Cohort In Tx	1.0000	$1,754	$1,754	0.3211	0.3211		
0	Sym LT	Continue Sym PAD	0.5090	$771		0.3490			
0	Sym LT	jump to: Sym PAD	0.5090						
0	Sym LT	Sym Hosp	0.1550	$983		-0.0279			
0	Sym LT	jump to: Dead	0.1550						
0	Sym LT	Die	0.3360						
0	Sym LT	jump to: Dead	0.3360						
0	Dead	Prob Hosp or Dead	0.0000						
5	Sym LT	Prob Cohort In Tx	0.0196	$31	$3,315	0.0131	0.9486	$79.57	0.02
5	Sym LT	Continue Sym PAD	0.0073	$12		0.0137			
5	Sym LT	jump to: Sym PAD	0.0073						
5	Sym LT	Sym Hosp	0.0030	$19		-0.0005			
5	Sym LT	jump to: Dead	0.0030						
5	Sym LT	Die	0.0092						
5	Sym LT	jump to: Dead	0.0092						
5	Dead	Prob Hosp or Dead	0.9804						
10	Sym LT		0.0001	$0.03	$3,333	0.0000	0.9559	$79.98	0.02
10	Dead		0.9999	$-		0.0000			

Definitions:

Prob Cohort In Treatment: Probability of entering that stage, which is equal to the sum of "jump to: Asym PAD" from the prior stage". This number is distributed between "Sum of Continue Asym", "Asym Hosp", and "Die" in the current stage.

Continue Asym PAD: Complement of prob Hosp + prob Dead (1-((Asym Hos + Die))

jump to: Asym PAD; also total number that go on to the next stage

Asym Hospitalization: Of the cohort alive, probability of entering Hospitalization
jump to: Dead: Termination node for Hospitalization; also number of Hosp at that stage
Die: Of the cohort in treatment probability of entering Dead
jump to: Dead: Termination node for Dead; also number of deaths for the stage
Prob Hosp or Dead: Probability of being at Hospitalized or Dead at beginning of stage (the complement of Prob Cohort In Treatment); also the sum of "jump to Dead" for Hospitalization and Death in the previous stage.

Table 12: Markov State Rewards by Stage

Stage	Prob In Treatment	Prob Hosp or Dead	Stage Hosp	Cumul Hosp	Stage Deaths	Cumul Deaths
Early Treatment						
4	0.484	0.516	0.0557	**0.4165**	0.0349	**0.1897**
5	**0.394**	0.606	0.0453	0.4618	0.0323	0.2220
9	0.150	0.850	0.0172	**0.5667**	0.0196	**0.3204**
10	**0.113**	0.887	0.0130	0.5796	0.0164	0.3368
19	0.003	0.997	0.0004	**0.6103**	0.0010	**0.3879**
20	**0.002**	0.998	0.9982	1.6086	0.9982	1.3862
Late Treatment						
4	0.049	0.951	0.0075	**0.2971**	**0**.0215	**0.6833**
5	**0.020**	0.980	0.0030	0.3001	0.0092	0.6925
9	0.000	1.000	0.0000	**0.3018**	0.0001	**0.6981**
10	**0.000**	1.000	0.0000	0.3018	0.0001	0.6981
Over Treatment						
4	0.826	0.174			0.0446	**0.2189**
5	**0.781**	0.219			0.0453	0.2642
9	0.601	0.399			0.0451	**0.4443**
10	**0.556**	0.444			0.0445	0.4887
19	0.205	0.795			0.0295	**0.8248**
20	**0.175**	0.825			0.8248	1.6496

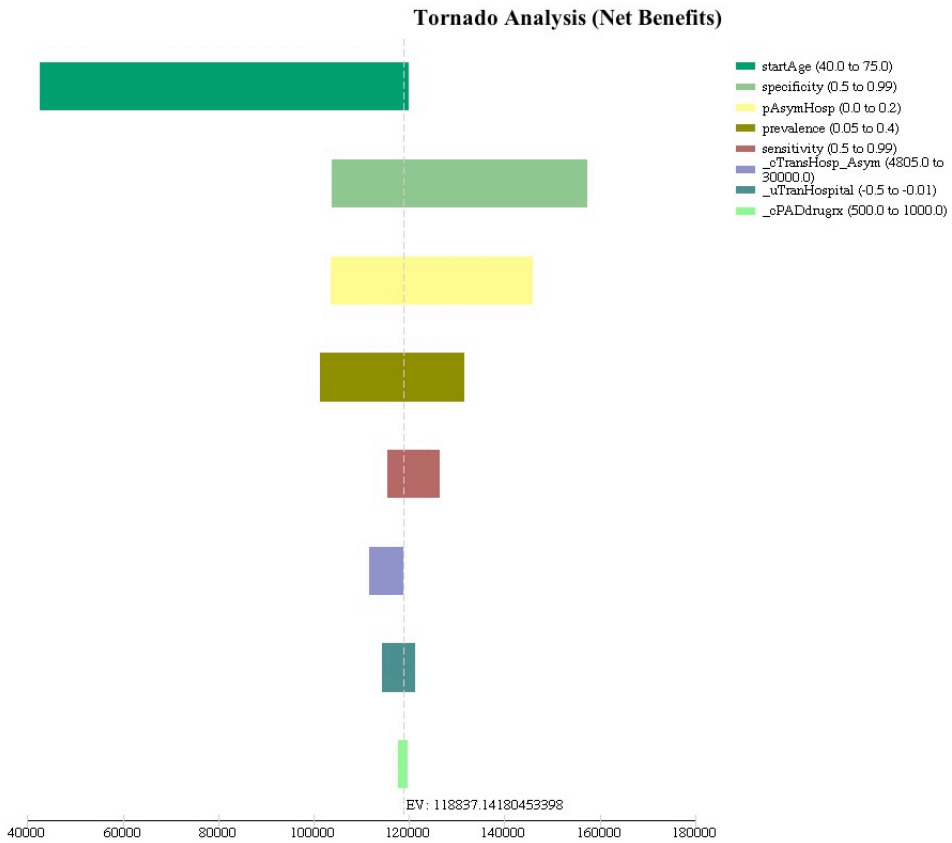
In a hypothetical cohort of 10,000 symptomatic patients who start treatment at age 65, it is estimated that there will be 3018 hospitalizations, and 6981 deaths, at the end of 10 years. In a similar cohort of early treatment asymptomatic patients starting treatment at age 45, we estimated 5796 hospitalizations, and 3368 deaths, at the end of 10 years. The increased number of hospitalizations and decreased number of deaths for asymptomatic patients are likely attributable to the relative difference in age and corresponding lower mortality rates that allow for patients to remain active in treatment longer, transitioning between treatment and hospitalization and then eventually death. Deaths experienced by patients with a false positive

screen attributed to non-PAD other causes of death, were estimated at 8248 after 20 years, while 1752 could hypothetically continue treatment.

One-Way Sensitivity Tornado Analysis

Using a tornado diagram for the one-way sensitivity analysis shown in figure 8, the uncertainty in multiple parameters defined as variables instead of numeric values were analyzed together in a single graph, and ranked by order of uncertainty.

Figure 8: Tornado Analysis



Each bar in the graph represents a one-way sensitivity analysis for the variables displaying the most uncertainty in the model. Costs are plotted on the x-axis, and the individual

variables are represented on the y-axis. The expected value (EV), represented by the vertical doted line, was calculated using the mean value of each variable, and weighting each branch or path based on its path probability. The placement of each bar relative to the vertical line indicates the relative impact that each variable has on the expected value. For example as shown in table 13, the start age when patients are first screened represents 50.8 percent of the total uncertainty in the expected value; specificity represents 24.4 percent, and prevalence 15.1 percent. Therefore, by addressing the uncertainty in these three variables, one could hypothetically account for 90.4 percent of the risk the model.

[The percentage of risk represented by each variable is equal to: $(\text{High EV-Low EV})^2$ /Net Risk]

Table 13: Accounting for Model Uncertainty Using Risk Percentages

Variable	Description	Range	Risk Percentage	Cumulative Percentage
startAge	Age of Screening	40.0 to 75.0	0.508	0.508
specificity	Specificity	0.5 to 0.99	0.244	0.753
prevalence	Disease Prevalance	0.05 to 0.4	0.151	0.904
pAsymHosp	Probability of Hosp for Asym PAD_Mahoney	0.0 to 0.115	0.077	0.981
sensitivity	Sensitivity	0.5 to 0.99	0.010	0.991
_cTransHosp_Asym	Cost of Hosp for Asym PAD_Mahoney	4805.0 to 30000.0	0.004	0.996
_uTranHospital	Disutility of Hospitalization	-0.5 to -0.01	0.004	1.000
_cPADdrugrx	Annual cost for PAD Treatment	500.0 to 1000.0	0.000	1.000

Monte Carlo Probabilistic Sensitivity Analysis and Micro-simulation

For the combined simulation in this model, 1000 samples were drawn for the parameter distributions (second-order, PSA) and 10,000 micro-simulation trials (first-order) were run with the sampled parameter values held constant. The final values of the 10,000 trials were averaged for each of the 1,000 sets of random distribution samples. The variations around the mean cost and effectiveness values of both 5-year and 10-year simulations are reported in Table 14.

The mean cost in 2010 US dollars for the individual in the positive ABI screen arm (the sum of early treatment and over treatment) is $4596 (std dev. $397; range $3355-$6035) for the first 10 years, with an average gain of 2 QALYs (std dev. 0.082; range 2.076-2.926). 10-year costs averaged about 30 percent higher at $5994 (std dev $549; range $3725-$7775), for an average gain of 3.337 QALYs (std dev. 0.189; range 3.00-4.74).

The mean cost in 2010 US dollars for the negative ABI screen arm (the sum of late treatment and no treatment) is $225 (std dev. $55; range $75-$431) per individual over 10 years, with an average gain in QALYs of 0.05 (std dev. 0.01; range 0-0.09). 10-year and 5-year costs were nearly equivalent for the same gain in QALYs.

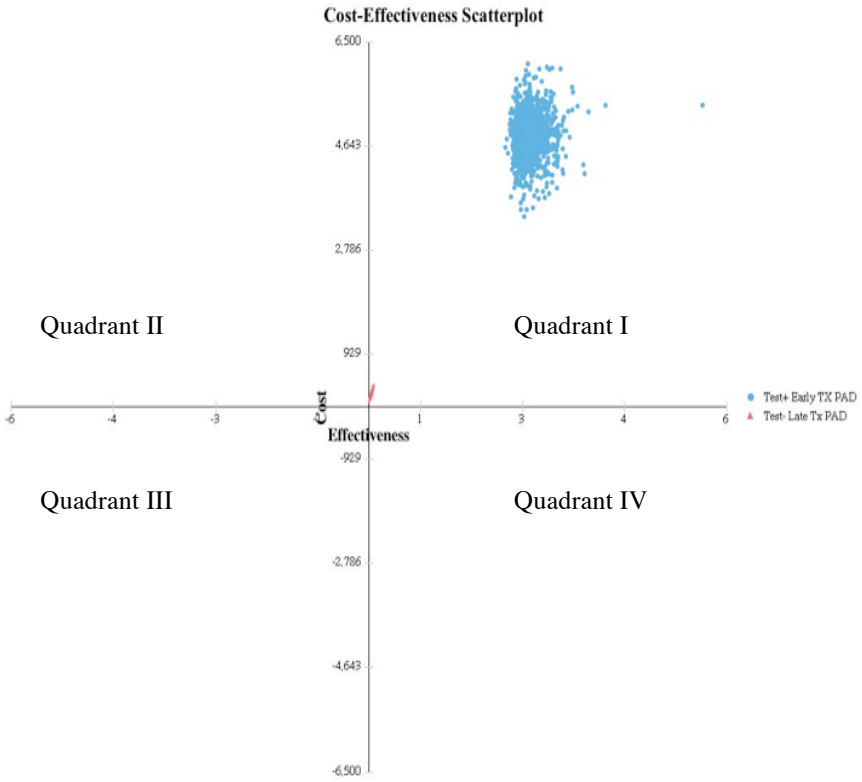
Table 14: Monte Carlo Cost-Effectiveness Variation Estimates

	5-year cycle		10-year cycle	
Test+ (Early and Over Treatment)	Cost (2010 US Dollars)	Effectiveness (QALY)	Cost (2010 US Dollars)	Effectiveness (QALY)
Mean	$4,596	2.270	$5,994	3.337
Std Deviation	$397	0.082	$549	0.189
Minimum	$3,355	2.076	$3,725	3.005
2.5%	$3,845	2.142	$4,974	3.079
10%	$4,062	2.182	$5,318	3.140
Median	$4,616	2.259	$5,988	3.304
90%	$5,092	2.370	$6,670	3.541
97.5%	$5,352	2.468	$7,082	3.772
Maximum	$6,035	2.926	$7,775	4.745
Test- (Late and No Treatment)				
Mean	$225	0.051	$221	0.050
Std Deviation	$55	0.015	$53	0.015
Minimum	$75	0.006	$67	0.008
2.5%	$128	0.023	$123	0.023
10%	$156	0.031	$154	0.032
Median	$222	0.050	$217	0.049
90%	$297	0.071	$291	0.069
97.5%	$340	0.082	$334	0.081
Maximum	$431	0.099	$381	0.102

Values calculated from 1,000 samples, 10,000 trials
Time elapsed 5.30 min

The distribution of incremental CE ratios (ICERs) is shown in a scatterplot in Figure 9. QALYs are plotted on the x-axis, and costs are represented on the y-axis. The distribution across the four quadrants [Quadrant I higher costs and higher effectiveness (trade-off), Quadrant II higher costs and lower effectiveness (inferior), Quadrant III lower costs and lower effectiveness (trade-off), and Quadrant IV lower costs and higher effectiveness (superior)], confirms that all ICERs are in Quadrant I (versus Quadrant III). The larger distribution of screen positives plus treatment, shown by the mass of blue dots in the upper right corner of Quadrant I, shows a somewhat uniform distribution around the mean. In contrast, the small red mark in the lower left corner of Quadrant I, representing screen negative plus treatment, show a very small distribution around the mean. The placement of screen positives plus treatment, relative to the origin, shows the relative added cost and added effectiveness of that strategy. While the cost is much lower for screen negative plus treatment, there is also little to no gain in QALY.

Figure 9: Distribution of Monte Carlo Analysis



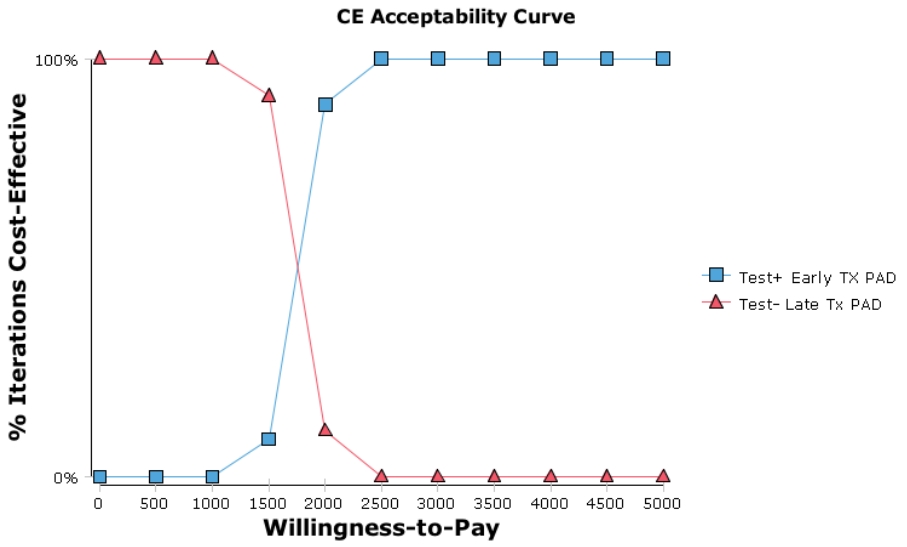
By extending the analysis to include a Willingness-to-pay (WTP) threshold of $50,000/QALY, all simulations, shown in table 15, favored the cost-utility of positive screens and treatment in Quadrant 1.

Table 15: The Relative Cost/Utility of Positive to Negative Screens and Treatment

Component	Quadrant	Incremental Effectiveness	Incremental Cost	CER	Number of Points	Percent
C1	IV	E>0	C<0	Superior	0	0
C2	I	E>0	C>0	CER<50000	1000	1
C3	III	E<0	C<0	CER>50000	0	0
C4	I	E>0	C>0	CER>50000	0	0
C5	III	E<0	C<0	CER<50000	0	0
C6	II	E<0	C>0	Inferior	0	0

Graphing the results of the probabilistic sensitivity analysis in figure 10, the cost-effectiveness acceptability curve shows that screening and early treatment has the highest probability of being the most effective option at all levels above $1800. This result is expected; both arms incur the cost of screening in the initial stage, early treatment has a cost of $2095 and 0.30 QALY, and late treatment is $1754 for the same effectiveness. However, in stage 1-2, the ratio shifts where the incremental cost of early treatment is $953 for 0.47 QALY, and late treatment while less expensive $756, gains less effectiveness, 0.30. As the stages progress, early treatment becomes increasingly cost-effective.

Figure 10: Screening and early treatment is the more cost-effective option above $1800



Model Validation

In order to test that the model did not have an obvious errors, extreme values such as 0 QALYs were inputted into the model to check the validity (results not shown). Monte Carlo

simulations were also performed with extreme values and the results supported the models to be valid (i.e., 0 QALYs was inputted as a constant value, producing the result of cost/0 QALY).

Discussion

Determining the optimal screening age and population prevalence will be central to any ABI screening policy. Since seventy-five percent of variation in the model is due to these two modifiable variables, age of screening and disease prevalence, it is conceivable that efficiencies could be gained by optimizing these two factors. Since screening patients before the age 45 is unlikely, CE ratios in this analysis represent the high-end estimate, where increasing the age of screening would primarily reduce costs with a small reduction in effectiveness.

When considering disease prevalence, it is important to understand how its impact is translated by Bayesian probabilities, in particular the post-test+ screening value. To maximize the effectiveness and efficiency of screening and treatment, we want to increase the post-test+ probability of the ABI in order to maximize the true positive to false positive ratio. This would provide early treatment to the highest number of true positives, and minimize over treatment to the false positives. For example, the impact of increasing disease prevalence to 15 percent is a 10 percent gain in post-test+ probability from 0.686 to 0.777; increasing to 20 percent prevalence, moves the post-test+ probability to 0.831.

Limitations

Missing data and confounding effects were the main limitations in the study. Assumptions made were based on current literature, and the model reflects clinical practices and outcomes that are typical of the patients, the disease and the associated costs incurred upon them.

The model makes several assumptions that limit the application of findings. First, the model assumes that patients continue on treatment based on the probability of hospitalization and probability of death, and assumes no other events occur. Second, rather than measuring the frequency of individual events such as a myocardial infarction or stroke, the model used 2-year estimates of patients having at least one vascular-related hospitalization, and captures only the time to the first hospital event. In reality, patients are likely to recover from vascular procedures such as angioplasty or stenting, and re-enter treatment with the possibility of experiencing additional hospitalizations. The model also does not factor in the prevalence of co-morbidities such as diabetes, high blood pressure and hypercholesterolemia, all of which are prevalent in patients with PAD and in the general population. In addition, hospitalization rates are taken from a study with an older and sicker population. Third, the measure of PAD prevalence is age invariant. The model represents outcomes based on screening done at one point in time based on an average prevalence. In this study, screening was based on an average disease prevalence of 10 percent, which is likely too high if the goal is to target only 45 year olds, and instead may be more representative of the average prevalence across 45-70 years olds.

Data on the effects of early drug treatment in asymptomatic patients with PAD is largely unknown and therefore was not included in the model. However, the study that measured hospitalization rates reported a high baseline medication use for both asymptomatic and symptomatic patients (81 percent antiplatelet therapy, 76 percent statin use) and this might capture some drug treatment effects. The model also does not include exercise and smoking cessation programs that are very important and effective in a long-term strategy.

The preference measure used in the model was imputed using UK-based preference weights. The implicit assumption in most studies is that there are minimal differences in

preferences for health states between UK and US populations, however this may not be accurate. US populations rate poor health states higher and thus, cost-effectiveness estimates would be more conservative using US preference weights. Use of a preference based measure with UK weights, could explain, in part, the difference in QALYs in the early treatment group compared with delayed symptomatic treatment group.

Some have suggested that including a range for the possible outcomes when reporting results may address some of the concern around differences in utility measurement methods. By reporting the range of possible outcomes through the Monte Carlo analysis and finding similar results to the base case analysis, this would suggest that the distribution of possible values, and hence uncertainty, is somewhat narrow. Most studies show that the small differences in preference weights from different populations have little effect on the conclusions of a cost-effectiveness analysis[105].

Finally, the model is based on 5-, 10- and 15-year time periods and is limited to the payor perspective that may not be the most appropriate. For example, a societal perspective that takes into account productivity gains from treatment and losses due to morbidity, while partially but not completely captured in the utility estimate, might be particularly relevant to a 45-year-old individual when a screening program may be initiated.

The outcomes of this cost-effectiveness model provide a starting point for additional more refined studies. For example, incorporating Medicare Part D claims data would be a potentially useful source of drug treatment rates and associated costs beyond hospitalizations. Modeling the effects of individual drugs could provide additional estimates on quality of life due to positive treatment effects and adverse events. Medicare Part D claims data could also capture variation important in any sub group analysis.

Policy Implications

A 2005 recommendation by the U.S. Preventive Services Task Force against routine screening for PAD was based on the rational that screening using the ABI would not provide information "beyond treatment based on standard cardiovascular risk assessment" and moreover that screening asymptomatic adults could lead to increased harm due to "false-positive results and unnecessary work-ups."[106] Published studies have refuted the first point[1, 107], including the 2009 USPTF follow up review, which concluded that individual data on the ABI did not yield a clear picture on the proportion of intermediate-risk men who would be reclassified to a different Framingham risk category, but did suggest that approximately 10 percent of women would be reclassified from intermediate risk to high risk for CHD[95]. If the current evidence in the 2009 review was "inconclusive to assess the benefits and the harms", the preliminary results of this study suggest that in terms of cost-effectiveness, the benefits could outweigh the added costs. Given the high specificity of the ABI, the percentage of false-positives is relatively low. Furthermore, the overall cost-effectiveness of early screening, which accounts for true and false positives, ranged from $1857/QALY over 5 years to $1453/QALY over 15 years, demonstrating that the cost impact of false negatives is very low. In terms of added quality adjusted life years, the negative impact of false-negatives was also very small. These results suggest that screening for PAD using the ankle-brachial index could be a highly cost-effective option for population based identification and treatment of high-risk individuals who have peripheral artery disease, and could be useful in weighing the balance between potential harms and benefits of a national screening policy.

Appendix 1: SAS Code To Translate SF36v1 scores into SF6D

```
/* May 2, 2002
Altered by Jenny Freeman, 2 July 2003; Altered by Jenny Freeman, 22 Feb 2008;
Altered by Donna Rowen, 5 Nov 2008; Revised by Donna Rowen in accordance with
changes agreed by Qualitymetric Inc., John Brazier and Dennis Fryback on 17th
January 2007;

Weighting of domain scores from Brazier JE, Roberts JR, (2004) The estimation
of a preference-based index from the SF-12. Medical Care, 42: 851-859.

The algorithm presented below is based on a consistent version of model 10 in
this paper.

***** VERY IMPORTANT! *****
This program is set up to work with SF-36 version 1 US data. Provided the
dataset you wish to analyze is the active dataset, all you need to do is run
the code below. If this is not the case then you will need to specify which
dataset, you wish to analyze in the set statement. The new values will be
written to a temporary file work.tmp ;

*/
options ls=78 ps=56 nocenter;

libname indata "E:\PARTNERS\Analysis Datasets";

data d; set "E:\PARTNERS\Analysis Datasets\sf36indx";
rename
gh1=sf1
ht=sf2
pf01=sf3
pf02=sf4
pf03=sf5
pf04=sf6
pf05=sf7
pf06=sf8
pf07=sf9
pf08=sf10
pf09=sf11
pf10=sf12
rp1=sf13
rp2=sf14
rp3=sf15
rp4=sf16
re1=sf17
re2=sf18
re3=sf19
sf1=sf20
bp1=sf21
bp2=sf22
vt1=sf23
mh1=sf24
mh2=sf25
mh3=sf26
vt2=sf27
mh4=sf28
vt3=sf29
mh5=sf30
```

```
vt4=sf31
sf2=sf32
gh2=sf33
gh3=sf34
gh4=sf35
gh5=sf36
;
run;

data tmp ; set d;

/*Converting version 1.0 SF24, SF27 and SF28 to version 2.0 */

rand1=uniform(-1);
rand2=uniform(-1);
rand3=uniform(-1);

sf24r=sf24;
If (sf24=2)                then sf24r=2 ;
If (sf24=3 and rand1 <0.5)  then sf24r=2 ;
If (sf24=3 and rand1>=0.5)  then sf24r=3;
If (sf24=4)                then sf24r=3 ;
If (sf24=5)                then sf24r=4 ;
If (sf24=6)                then sf24r=5 ;
if sf24<1 or sf24>6 then sf24=9 ;

sf27r=sf27;
If (sf27=2)                then sf27r=2 ;
If (sf27=3 and rand2 <0.5)  then sf27r=2 ;
If (sf27=3 and rand2>=0.5)  then sf27r=3;
If (sf27=4)                then sf27r=3 ;
If (sf27=5)                then sf27r=4;
If (sf27=6)                then sf27r=5 ;
if sf27<1 or sf27>6 then sf27=9 ;

sf28r=sf28;
If (sf28=2)                then sf28r=2 ;
If (sf28=3 and rand3 <0.5)  then sf28r=2 ;
If (sf28=3 and rand3>=0.5)  then sf28r=3 ;
If (sf28=4)                then sf28r=3 ;
If (sf28=5)                then sf28r=4 ;
If (sf28=6)                then sf28r=5 ;
if sf28<1 or sf28>6 then sf28=9 ;

*Physical functioning dimension*;

IF (sf3=3 and sf4=3 and sf12=3) then SFPhys = 1 ;
IF (sf3=1 or sf3=2) and (sf4=3) and (sf12=3) then SFPhys = 2 ;
IF (sf4=2 and sf12=3)  then SFPhys = 3 ;
IF (sf4=1 and sf12=3)  then SFPhys = 4 ;
IF (sf12=2) then SFPhys = 5 ;
IF (sf12=1) then SFPhys = 6 ;
if (sf3<1 or sf3>3) and (sf4<1 or sf4>3) and (sf12<1 or sf12>3) then SFPhys=9
;

*Role limitations dimension*;

IF (sf15=2 and sf18=2)  then SFRole = 1 ;
```

```
IF (sf15=1 and sf18=2)  then SFRole = 2 ;
IF (sf15=2 and sf18=1)  then SFRole = 3 ;
IF (sf15=1 and sf18=1)  then SFRole = 4 ;
if (sf15<1 or sf15>2) or (sf18<1 or sf18>2) then SFRole=9 ;

*Social functioning dimension*;

IF (sf32=5) then SFSocial = 1 ;
IF (sf32=4) then SFSocial = 2 ;
IF (sf32=3) then SFSocial = 3 ;
IF (sf32=2) then SFSocial = 4 ;
IF (sf32=1) then SFSocial = 5 ;
if sf32<1 or sf32>5 then SFSocial=9 ;

*Bodily pain dimension*;

IF (sf21=1 and sf22=1) then SFPain = 1 ;
IF (sf21=2 or
    sf21=3 or
    sf21=4 or
    sf21=5 or
    sf21=6)  and sf22=1 then SFPain = 2 ;
IF (sf22=2)             then SFPain = 3 ;
IF (sf22=3)             then SFPain = 4 ;
IF (sf22=4)             then SFPain = 5 ;
IF (sf22=5)             then SFPain = 6 ;
if (sf21<1 or sf21>6) and (sf22<1 or sf22>5) then sfPain=9 ;

*Mental health dimension*;

IF (sf24r=5 and sf28r=5) then SFMental=1 ;
IF (sf24r=4) and (sf28r=4 or sf28r=5) then SFMental=2 ;
IF (sf28r=4) and (sf24r=5) then SFMental=2 ;
IF (sf24r=3) and (sf28r=3 or
                  sf28r=4 or sf28r=5) then SFMental=3 ;
IF (sf28r=3) and (sf24r=4 or sf24r=5) then SFMental=3 ;
IF (sf24r=2) and (sf28r=2 or sf28r=3 or
                  sf28r=4 or sf28r=5) then SFMental=4 ;
IF (sf28r=2) and (sf24r=3 or
                  sf24r=4 or sf24r=5) then SFMental=4 ;
IF (sf24r=1) then SFMental=5 ;
IF (sf28r=1) then SFMental=5 ;
IF (sf24r<1 or sf24r>5) and (sf28r<1 or sf28r>5) then SFMental=9 ;

*Vitality dimension*;

If (sf27r=1) then SFVital = 1 ;
If (sf27r=2) then SFVital = 2 ;
If (sf27r=3) then SFVital = 3 ;
If (sf27r=4) then SFVital = 4 ;
If (sf27r=5) then SFVital = 5 ;
IF (sf27r<1 or sf27r>5) then SFVital = 9 ;

most=0;
if SFPhys=4   or SFPhys=5   or SFPhys=6 or
   SFRole=3   or SFRole=4   or
   SFSocial=4 or SFSocial=5 or
   SFPain=5   or SFPain=6   or
```

```
   SFMental=4 or SFMental=5 or
   SFVital=4  or SFVital=5
then most=1;

*Weighting of domain scores from Brazier JE, Roberts JR, (2004) The
estimation of a preference-based index from the SF-12. Medical Care, 42: 851-
859.*;

If (SFPhys=1) then pf1 =     0 ;
IF (SFPhys=2) then pf1 = -.035 ;
IF (SFPhys=3) then pf1 = -.035 ;
IF (SFPhys=4) then pf1 = -.044 ;
IF (SFPhys=5) then pf1 = -.056 ;
If (SFPhys=6) then pf1 = -.117 ;

If (SFRole=1) then rl1 =     0 ;
IF (SFRole=2) then rl1 = -.053 ;
IF (SFRole=3) then rl1 = -.053 ;
IF (SFRole=4) then rl1 = -.053 ;

IF (SFSocial=1) then sc1 =     0 ;
IF (SFSocial=2) then sc1 = -.057 ;
IF (SFSocial=3) then sc1 = -.059 ;
IF (SFSocial=4) then sc1 = -.072 ;
IF (SFsocial=5) then sc1 = -.087 ;

If (SFPain=1) then pn1 =     0 ;
IF (SFPain=2) then pn1 = -.042 ;
IF (SFPain=3) then pn1 = -.042 ;
IF (SFPain=4) then pn1 = -.065 ;
IF (SFPain=5) then pn1 = -.102 ;
If (SFPain=6) then pn1 = -.171 ;

If (SFMental=1) then mh1 =     0 ;
IF (SFMental=2) then mh1 = -.042 ;
IF (SFMental=3) then mh1 = -.042 ;
IF (SFMental=4) then mh1 = -.1 ;
IF (SFMental=5) then mh1 = -.118 ;

IF (SFVital=1) then v1 =     0 ;
IF (SFVital=2) then v1 = -.071 ;
IF (SFVital=3) then v1 = -.071 ;
IF (SFVital=4) then v1 = -.071 ;
IF (SFVital=5) then v1 = -.092 ;

if most=0 then mst1 =     0;
if most=1 then mst1 = -.061;

SFIndex = 1 + pf1+rl1+sc1+pn1+mh1+v1+mst1 ;
run;

TITLE "Statistics on Brazier index";
proc means maxdec=4 data=tmp ;
  var Sfindex;
run;

data "E:\PARTNERS\Analysis Datasets\sf36indx_new";
      set tmp;
```

```
run;

proc export data=tmp outfile="E:\PARTNERS\Analysis Datasets\sf36indx_new.dta"
dbms=dta replace;
run;
```

Appendix 2: One-year mortality estimates from hazard ratios - MALES

	NORMAL				ABI <0.91				
	Mean HRQoL Index Score SF-6D	Probablity of dying between ages x to x+1	Prob alive to age X	Quality-adjusted survival	Mean HRQoL Index Score SF-6D	Total Mortality Hazard Ratio:	HR*Probability of dying between x to x+1 ABI <0.91	Prob alive to age X	Quality-adjusted survival
Age		q\\x							
45	0.81	0.004	0.94	0.76	0.61	3.15	0.011	0.95	0.58
46	0.81	0.004	0.94	0.76	0.61		0.011	0.93	0.57
47	0.81	0.004	0.94	0.76	0.61		0.012	0.92	0.56
48	0.81	0.004	0.94	0.76	0.61		0.013	0.91	0.56
49	0.81	0.005	0.93	0.75	0.61		0.014	0.90	0.55
50	0.81	0.005	0.93	0.75	0.61		0.016	0.89	0.54
51	0.81	0.005	0.92	0.75	0.61		0.017	0.87	0.53
52	0.81	0.006	0.92	0.74	0.61		0.019	0.86	0.52
53	0.81	0.006	0.91	0.74	0.61		0.020	0.84	0.51
54	0.81	0.007	0.91	0.73	0.61		0.022	0.83	0.50
55	0.81	0.007	0.90	0.73	0.61		0.023	0.81	0.49
56	0.79	0.008	0.89	0.71	0.67		0.025	0.79	0.53
57	0.79	0.009	0.89	0.70	0.67		0.027	0.77	0.52
58	0.79	0.009	0.88	0.69	0.67		0.029	0.75	0.50
59	0.79	0.010	0.87	0.69	0.67		0.031	0.73	0.49
60	0.79	0.011	0.86	0.68	0.67		0.033	0.71	0.47
61	0.79	0.011	0.85	0.67	0.67		0.035	0.68	0.46
62	0.79	0.012	0.84	0.67	0.67		0.038	0.66	0.44
63	0.79	0.013	0.83	0.66	0.67		0.041	0.63	0.42
64	0.79	0.014	0.82	0.65	0.67		0.044	0.61	0.41
65	0.79	0.015	0.81	0.64	0.67		0.048	0.58	0.39
66	0.80	0.017	0.80	0.64	0.71		0.052	0.55	0.39
67	0.80	0.018	0.78	0.63	0.71		0.056	0.52	0.37
68	0.80	0.020	0.77	0.62	0.71		0.061	0.49	0.35
69	0.80	0.021	0.75	0.60	0.71		0.066	0.46	0.33
70	0.80	0.023	0.74	0.59	0.71		0.071	0.43	0.31
71	0.80	0.025	0.72	0.58	0.71		0.077	0.40	0.29
72	0.80	0.028	0.70	0.56	0.71		0.085	0.37	0.26
73	0.80	0.030	0.68	0.55	0.71		0.093	0.34	0.24
74	0.80	0.034	0.66	0.53	0.71		0.102	0.31	0.22
75	0.80	0.037	0.64	0.51	0.71		0.113	0.28	0.20
76	0.77	0.041	0.62	0.47	0.70		0.124	0.25	0.17
77	0.77	0.045	0.59	0.46	0.70		0.136	0.22	0.15
78	0.77	0.050	0.56	0.43	0.70		0.149	0.19	0.13
79	0.77	0.055	0.54	0.41	0.70		0.163	0.16	0.11
80	0.77	0.061	0.51	0.39	0.70		0.179	0.13	0.09
81	0.77	0.067	0.48	0.37	0.70		0.196	0.11	0.08
82	0.77	0.073	0.44	0.34	0.70		0.213	0.09	0.06
83	0.77	0.081	0.41	0.32	0.70		0.233	0.07	0.05
84	0.77	0.088	0.38	0.29	0.70		0.253	0.05	0.04
85	0.77	0.097	0.35	0.27	0.70		0.275	0.04	0.03
86	0.77	0.106	0.31	0.24	0.70		0.299	0.03	0.02
87	0.77	0.116	0.28	0.21	0.70		0.323	0.02	0.01
88	0.77	0.127	0.25	0.19	0.70		0.349	0.01	0.01
89	0.77	0.139	0.21	0.17	0.70		0.377	0.01	0.01
90	0.77	0.152	0.18	0.14	0.61		0.405	0.01	0.00
91	0.77	0.165	0.16	0.12	0.61		0.435	0.00	0.00
92	0.77	0.180	0.13	0.10	0.61		0.465	0.00	0.00
93	0.77	0.196	0.11	0.08	0.61		0.497	0.00	0.00
94	0.77	0.212	0.09	0.07	0.61		0.529	0.00	0.00
95	0.77	0.230	0.07	0.05	0.61		0.561	0.00	0.00
96	0.77	0.248	0.05	0.04	0.61		0.594	0.00	0.00
97	0.77	0.268	0.04	0.03	0.61		0.626	0.00	0.00
98	0.77	0.288	0.03	0.02	0.61		0.658	0.00	0.00
99	0.77	0.310	0.02	0.02	0.61		0.689	0.00	0.00
100	0.77	0.332	0.01	0.01	0.61		0.720	0.00	0.00

ABI 0.91-1.10					ABI 1.11-1.40				
Mean HRQoL Index Score SF-6D	Total Mortality Hazard Ratio:	HR*Probability of dying between x to x+1 ABI <0.91	Prob alive to age X	Quality-adjusted survival	Mean HRQoL Index Score SF-6D	Total Mortality Hazard Ratio:	HR*Probability of dying between x to x+1 ABI <0.91	Prob alive to age X	Quality-adjusted survival
0.69	**1.34**	0.005	0.95	0.65	0.72	**0.94**	0.003358	0.95	0.68
0.69		0.005	0.94	0.65	0.72		0.003358	0.94	0.68
0.69		0.005	0.94	0.64	0.72		0.003640	0.94	0.68
0.69		0.006	0.93	0.64	0.72		0.003954	0.94	0.67
0.69		0.006	0.93	0.64	0.72		0.004315	0.93	0.67
0.69		0.007	0.92	0.63	0.72		0.004723	0.93	0.67
0.69		0.007	0.91	0.63	0.72		0.005170	0.92	0.66
0.69		0.008	0.91	0.62	0.72		0.005637	0.92	0.66
0.69		0.009	0.90	0.62	0.72		0.006113	0.91	0.66
0.69		0.009	0.89	0.61	0.72		0.006584	0.91	0.65
0.69		0.010	0.88	0.61	0.72		0.007054	0.90	0.65
0.72		0.011	0.88	0.63	0.73		0.007551	0.90	0.65
0.72		0.011	0.87	0.62	0.73		0.008090	0.89	0.65
0.72		0.012	0.86	0.61	0.73		0.008669	0.88	0.64
0.72		0.013	0.85	0.60	0.73		0.009296	0.87	0.64
0.72		0.014	0.83	0.60	0.73		0.009984	0.87	0.63
0.72		0.015	0.82	0.59	0.73		0.010746	0.86	0.62
0.72		0.016	0.81	0.58	0.73		0.011583	0.85	0.62
0.72		0.018	0.80	0.57	0.73		0.012493	0.84	0.61
0.72		0.019	0.78	0.56	0.73		0.013484	0.83	0.60
0.72		0.021	0.77	0.55	0.73		0.014579	0.82	0.59
0.73		0.022	0.75	0.55	0.76		0.015843	0.80	0.61
0.73		0.024	0.74	0.54	0.76		0.017152	0.79	0.60
0.73		0.026	0.72	0.53	0.76		0.018594	0.78	0.59
0.73		0.028	0.70	0.51	0.76		0.020149	0.76	0.58
0.73		0.031	0.68	0.50	0.76		0.021867	0.75	0.57
0.73		0.034	0.66	0.48	0.76		0.023815	0.73	0.55
0.73		0.037	0.64	0.47	0.76		0.026095	0.71	0.54
0.73		0.040	0.61	0.45	0.76		0.028744	0.70	0.53
0.73		0.045	0.59	0.43	0.76		0.031754	0.68	0.51
0.73		0.049	0.56	0.41	0.76		0.035117	0.65	0.49
0.71		0.055	0.53	0.38	0.72		0.038849	0.63	0.45
0.71		0.060	0.51	0.36	0.72		0.042842	0.61	0.44
0.71		0.066	0.47	0.34	0.72		0.047224	0.58	0.42
0.71		0.073	0.44	0.31	0.72		0.052030	0.55	0.40
0.71		0.080	0.41	0.29	0.72		0.057295	0.52	0.38
0.71		0.088	0.38	0.27	0.72		0.063055	0.49	0.36
0.71		0.097	0.34	0.24	0.72		0.069351	0.46	0.33
0.71		0.106	0.31	0.22	0.72		0.076224	0.43	0.31
0.71		0.116	0.28	0.20	0.72		0.083714	0.40	0.29
0.71		0.127	0.25	0.17	0.72		0.091865	0.37	0.26
0.71		0.139	0.21	0.15	0.72		0.100720	0.33	0.24
0.71		0.152	0.18	0.13	0.72		0.110321	0.30	0.21
0.71		0.166	0.16	0.11	0.72		0.120712	0.27	0.19
0.71		0.181	0.13	0.09	0.72		0.131932	0.23	0.17
0.71		0.197	0.11	0.08	0.75		0.144020	0.20	0.15
0.71		0.215	0.09	0.06	0.75		0.157009	0.17	0.13
0.71		0.233	0.07	0.05	0.75		0.170930	0.15	0.11
0.71		0.252	0.05	0.04	0.75		0.185805	0.12	0.09
0.71		0.273	0.04	0.03	0.75		0.201651	0.10	0.07
0.71		0.294	0.03	0.02	0.75		0.218477	0.08	0.06
0.71		0.317	0.02	0.01	0.75		0.236280	0.06	0.05
0.71		0.341	0.01	0.01	0.75		0.255048	0.05	0.04
0.71		0.365	0.01	0.01	0.75		0.274756	0.04	0.03
0.71		0.391	0.01	0.00	0.75		0.295368	0.03	0.02
0.71		0.417	0.00	0.00	0.75		0.316834	0.02	0.01

ABI >1.40				
Mean HRQoL Index Score SF-6D	Total Mortality Hazard Ratio:	HR*Probability of dying between x to x+1 ABI <0.91	Prob alive to age X	Quality-adjusted survival
0.65	1.38	0.005	0.95	0.62
0.65		0.005	0.94	0.61
0.65		0.005	0.94	0.61
0.65		0.006	0.93	0.61
0.65		0.006	0.93	0.60
0.65		0.007	0.92	0.60
0.65		0.008	0.91	0.60
0.65		0.008	0.91	0.59
0.65		0.009	0.90	0.59
0.65		0.010	0.89	0.58
0.65		0.010	0.88	0.58
0.68		0.011	0.87	0.59
0.68		0.012	0.86	0.58
0.68		0.013	0.85	0.58
0.68		0.014	0.84	0.57
0.68		0.015	0.83	0.56
0.68		0.016	0.82	0.55
0.68		0.017	0.81	0.55
0.68		0.018	0.79	0.54
0.68		0.020	0.78	0.53
0.68		0.021	0.76	0.52
0.71		0.023	0.75	0.53
0.71		0.025	0.73	0.52
0.71		0.027	0.71	0.51
0.71		0.029	0.69	0.49
0.71		0.032	0.67	0.48
0.71		0.035	0.65	0.46
0.71		0.038	0.63	0.45
0.71		0.042	0.60	0.43
0.71		0.046	0.58	0.41
0.71		0.051	0.55	0.39
0.73		0.056	0.52	0.38
0.73		0.062	0.49	0.36
0.73		0.068	0.46	0.34
0.73		0.075	0.43	0.32
0.73		0.083	0.40	0.29
0.73		0.091	0.37	0.27
0.73		0.100	0.33	0.24
0.73		0.109	0.30	0.22
0.73		0.120	0.27	0.20
0.73		0.131	0.24	0.17
0.73		0.144	0.20	0.15
0.73		0.157	0.18	0.13
0.73		0.171	0.15	0.11
0.73		0.187	0.12	0.09
0.85		0.203	0.10	0.08
0.85		0.221	0.08	0.07
0.85		0.240	0.06	0.05
0.85		0.259	0.05	0.04
0.85		0.280	0.03	0.03
0.85		0.303	0.03	0.02
0.85		0.326	0.02	0.01
0.85		0.350	0.01	0.01
0.85		0.375	0.01	0.01
0.85		0.400	0.00	0.00
0.85		0.427	0.00	0.00

One-year mortality estimates from hazard ratios - FEMALES

Life table for females: United States, 2007

NORMAL					ABI <0.91				
Age	Mean HRQoL Index Score SF-6D	Probablity of dying between ages x to x+1	Prob alive to age X	Quality-adjuested Survival	Mean HRQoL Index Score SF-6D	Total Mortality Hazard Ratio:	HR*Probability of dying between x to x+1 ABI <0.91	Prob alive to age X	Quality-adjusted Survival
		q\\x							
45	0.79	0.002	0.97	0.76	0.67	**2.90**	0.006	0.97	0.65
46	0.79	0.002	0.97	0.76	0.67		0.006	0.96	0.64
47	0.79	0.002	0.97	0.76	0.67		0.007	0.96	0.64
48	0.79	0.003	0.96	0.76	0.67		0.007	0.95	0.64
49	0.79	0.003	0.96	0.76	0.67		0.008	0.94	0.63
50	0.79	0.003	0.96	0.76	0.67		0.009	0.94	0.63
51	0.79	0.003	0.96	0.75	0.67		0.009	0.93	0.62
52	0.79	0.003	0.95	0.75	0.67		0.010	0.92	0.62
53	0.79	0.004	0.95	0.75	0.67		0.011	0.91	0.61
54	0.79	0.004	0.95	0.75	0.67		0.012	0.90	0.60
55	0.76	0.004	0.94	0.72	0.66		0.012	0.89	0.58
56	0.76	0.005	0.94	0.71	0.66		0.013	0.88	0.58
57	0.76	0.005	0.93	0.71	0.66		0.014	0.87	0.57
58	0.76	0.005	0.93	0.71	0.66		0.015	0.85	0.56
59	0.76	0.006	0.92	0.70	0.66		0.017	0.84	0.55
60	0.76	0.006	0.92	0.70	0.66		0.018	0.83	0.54
61	0.76	0.007	0.91	0.69	0.66		0.020	0.81	0.53
62	0.76	0.008	0.91	0.69	0.66		0.022	0.80	0.52
63	0.76	0.008	0.90	0.68	0.66		0.024	0.78	0.51
64	0.76	0.009	0.89	0.68	0.66		0.026	0.76	0.50
65	0.77	0.010	0.88	0.68	0.69		0.028	0.74	0.51
66	0.77	0.011	0.87	0.67	0.69		0.031	0.72	0.49
67	0.77	0.012	0.87	0.67	0.69		0.033	0.70	0.48
68	0.77	0.013	0.86	0.66	0.69		0.036	0.67	0.46
69	0.77	0.014	0.84	0.65	0.69		0.040	0.65	0.45
70	0.77	0.015	0.83	0.64	0.69		0.043	0.62	0.43
71	0.77	0.016	0.82	0.63	0.69		0.047	0.60	0.41
72	0.77	0.018	0.81	0.62	0.69		0.052	0.57	0.39
73	0.77	0.020	0.79	0.61	0.69		0.057	0.54	0.37
74	0.77	0.022	0.78	0.60	0.69		0.064	0.51	0.35
75	0.75	0.025	0.76	0.57	0.67		0.071	0.48	0.32
76	0.75	0.028	0.74	0.55	0.67		0.079	0.44	0.30
77	0.75	0.031	0.72	0.54	0.67		0.088	0.41	0.27
78	0.75	0.035	0.70	0.52	0.67		0.097	0.37	0.25
79	0.75	0.039	0.67	0.50	0.67		0.108	0.34	0.22
80	0.75	0.043	0.65	0.48	0.67		0.120	0.30	0.20
81	0.75	0.048	0.62	0.46	0.67		0.133	0.26	0.18
82	0.75	0.053	0.59	0.44	0.67		0.147	0.23	0.15
83	0.75	0.059	0.56	0.42	0.67		0.162	0.20	0.13
84	0.75	0.066	0.52	0.39	0.67		0.179	0.16	0.11
85	0.75	0.073	0.49	0.37	0.67		0.197	0.13	0.09
86	0.75	0.081	0.45	0.34	0.67		0.216	0.11	0.07
87	0.75	0.089	0.42	0.31	0.67		0.238	0.08	0.06
88	0.75	0.099	0.38	0.29	0.67		0.260	0.06	0.04
89	0.75	0.109	0.34	0.26	0.67		0.285	0.05	0.03
90	0.75	0.121	0.31	0.23	0.64		0.311	0.03	0.02
91	0.75	0.133	0.27	0.20	0.64		0.338	0.02	0.01
92	0.75	0.146	0.23	0.17	0.64		0.368	0.02	0.01
93	0.75	0.161	0.20	0.15	0.64		0.398	0.01	0.01
94	0.75	0.176	0.17	0.13	0.64		0.430	0.01	0.00
95	0.75	0.193	0.14	0.10	0.64		0.463	0.00	0.00
96	0.75	0.211	0.11	0.08	0.64		0.497	0.00	0.00
97	0.75	0.230	0.09	0.07	0.64		0.531	0.00	0.00
98	0.75	0.251	0.07	0.05	0.64		0.566	0.00	0.00
99	0.75	0.272	0.05	0.04	0.64		0.601	0.00	0.00
100	0.75	0.295	0.04	0.03	0.64		0.636	0.00	0.00

ABI 0.91-1.10					ABI 1.11-1.40				
Mean HRQoL Index Score SF-6D	Total Mortality Hazard Ratio:	HR*Probability of dying between x to x+1 ABI <0.91	Prob alive to age X	Quality-adjusted Survival	Mean HRQoL Index Score SF-6D	Total Mortality Hazard Ratio:	HR*Probability of dying between x to x+1 ABI <0.91	Number surviving to age x	Prob alive to age X
								l\\x	
0.70	1.24	0.003	0.97	0.68	0.68	0.99	0.002166	96,976.99	0.97
0.70		0.003	0.97	0.68	0.68		0.002166	96,766.95	0.97
0.70		0.003	0.96	0.67	0.68		0.002355	96,557.37	0.97
0.70		0.003	0.96	0.67	0.68		0.002550	96,329.98	0.96
0.70		0.003	0.96	0.67	0.68		0.002754	96,084.39	0.96
0.70		0.004	0.96	0.67	0.68		0.002972	95,819.80	0.96
0.70		0.004	0.95	0.66	0.68		0.003211	95,535.00	0.96
0.70		0.004	0.95	0.66	0.68		0.003467	95,228.21	0.95
0.70		0.005	0.94	0.66	0.68		0.003735	94,898.02	0.95
0.70		0.005	0.94	0.66	0.68		0.004010	94,543.56	0.95
0.69		0.005	0.93	0.64	0.68		0.004298	94,164.41	0.94
0.69		0.006	0.93	0.64	0.68		0.004604	93,759.71	0.94
0.69		0.006	0.92	0.64	0.68		0.004944	93,328.05	0.93
0.69		0.007	0.92	0.63	0.68		0.005332	92,866.65	0.93
0.69		0.007	0.91	0.63	0.68		0.005782	92,371.53	0.92
0.69		0.008	0.91	0.62	0.68		0.006300	91,837.40	0.92
0.69		0.009	0.90	0.62	0.68		0.006890	91,258.84	0.91
0.69		0.009	0.89	0.61	0.68		0.007538	90,630.10	0.91
0.69		0.010	0.88	0.61	0.68		0.008231	89,946.94	0.90
0.69		0.011	0.87	0.60	0.68		0.008962	89,206.61	0.89
0.70		0.012	0.86	0.61	0.69		0.009752	88,407.18	0.88
0.70		0.013	0.85	0.60	0.69		0.010673	87,545.03	0.88
0.70		0.015	0.84	0.59	0.69		0.011604	86,610.68	0.87
0.70		0.016	0.83	0.58	0.69		0.012627	85,605.62	0.86
0.70		0.017	0.82	0.57	0.69		0.013727	84,524.69	0.85
0.70		0.019	0.80	0.56	0.69		0.014950	83,364.46	0.83
0.70		0.020	0.79	0.55	0.69		0.016361	82,118.17	0.82
0.70		0.023	0.77	0.54	0.69		0.018035	80,774.64	0.81
0.70		0.025	0.75	0.53	0.69		0.020001	79,317.88	0.79
0.70		0.028	0.73	0.52	0.69		0.022278	77,731.45	0.78
0.69		0.031	0.71	0.49	0.68		0.024870	75,999.78	0.76
0.69		0.035	0.69	0.48	0.68		0.027808	74,109.68	0.74
0.69		0.039	0.67	0.46	0.68		0.030984	72,048.83	0.72
0.69		0.043	0.64	0.44	0.68		0.034510	69,816.44	0.70
0.69		0.048	0.61	0.43	0.68		0.038421	67,407.06	0.67
0.69		0.053	0.59	0.41	0.68		0.042756	64,817.18	0.65
0.69		0.059	0.55	0.38	0.68		0.047556	62,045.84	0.62
0.69		0.066	0.52	0.36	0.68		0.052864	59,095.20	0.59
0.69		0.073	0.49	0.34	0.68		0.058729	55,971.17	0.56
0.69		0.081	0.45	0.31	0.68		0.065199	52,684.05	0.53
0.69		0.090	0.41	0.29	0.68		0.072327	49,249.11	0.49
0.69		0.099	0.38	0.26	0.68		0.080167	45,687.09	0.46
0.69		0.110	0.34	0.24	0.68		0.088775	42,024.51	0.42
0.69		0.121	0.30	0.21	0.68		0.098208	38,293.79	0.38
0.69		0.134	0.27	0.18	0.68		0.108524	34,533.02	0.35
0.69		0.148	0.23	0.16	0.67		0.119780	30,785.35	0.31
0.69		0.163	0.20	0.13	0.67		0.132029	27,097.88	0.27
0.69		0.179	0.16	0.11	0.67		0.145323	23,520.18	0.24
0.69		0.196	0.13	0.09	0.67		0.159709	20,102.15	0.20
0.69		0.214	0.11	0.07	0.67		0.175225	16,891.66	0.17
0.69		0.234	0.09	0.06	0.67		0.191904	13,931.81	0.14
0.69		0.255	0.07	0.04	0.67		0.209765	11,258.24	0.11
0.69		0.278	0.05	0.03	0.67		0.228817	8,896.65	0.09
0.69		0.302	0.04	0.02	0.67		0.249051	6,860.95	0.07
0.69		0.326	0.02	0.02	0.67		0.270445	5,152.22	0.05
0.69		0.352	0.02	0.01	0.67		0.292958	3,758.83	0.04

ABI >1.40				
Mean HRQoL Index Score SF-6D	Total Mortality Hazard Ratio:	HR*Probability of dying between x to x+1 ABI <0.91	Prob alive to age X	Quality-adjusted Survival
0.66	**1.23**	0.003	0.97	0.64
0.66		0.003	0.97	0.64
0.66		0.003	0.96	0.64
0.66		0.003	0.96	0.64
0.66		0.003	0.96	0.64
0.66		0.004	0.96	0.63
0.66		0.004	0.95	0.63
0.66		0.004	0.95	0.63
0.66		0.005	0.94	0.63
0.66		0.005	0.94	0.62
0.69		0.005	0.94	0.64
0.69		0.006	0.93	0.64
0.69		0.006	0.92	0.64
0.69		0.007	0.92	0.63
0.69		0.007	0.91	0.63
0.69		0.008	0.91	0.62
0.69		0.009	0.90	0.62
0.69		0.009	0.89	0.61
0.69		0.010	0.88	0.61
0.69		0.011	0.87	0.60
0.69		0.012	0.86	0.60
0.69		0.013	0.85	0.59
0.69		0.014	0.84	0.58
0.69		0.016	0.83	0.58
0.69		0.017	0.82	0.57
0.69		0.018	0.80	0.56
0.69		0.020	0.79	0.55
0.69		0.022	0.77	0.54
0.69		0.025	0.76	0.52
0.69		0.028	0.74	0.51
0.68		0.031	0.72	0.49
0.68		0.034	0.69	0.47
0.68		0.038	0.67	0.46
0.68		0.043	0.65	0.44
0.68		0.047	0.62	0.42
0.68		0.053	0.59	0.40
0.68		0.059	0.56	0.38
0.68		0.065	0.52	0.36
0.68		0.072	0.49	0.33
0.68		0.080	0.46	0.31
0.68		0.089	0.42	0.28
0.68		0.098	0.38	0.26
0.68		0.109	0.34	0.23
0.68		0.120	0.31	0.21
0.68		0.133	0.27	0.18
0.57		0.146	0.23	0.13
0.57		0.161	0.20	0.11
0.57		0.177	0.17	0.10
0.57		0.194	0.14	0.08
0.57		0.212	0.11	0.06
0.57		0.232	0.09	0.05
0.57		0.253	0.07	0.04
0.57		0.275	0.05	0.03
0.57		0.299	0.04	0.02
0.57		0.323	0.03	0.01
0.57		0.349	0.02	0.01

Appendix 3: Mortality and Utility Tables

Age	Mortality Table	PAD Mortality Table	PAD Utility table	Utility for Normals adj for Tx AE -0.020
	tMortNorm	tMortPAD	tSF6D	tSF6DNormAdj
	Value	Value	Value	Value
45	0.043	0.043	0.638	0.780
46	0.045	0.045	0.638	0.780
47	0.048	0.053	0.638	0.780
48	0.051	0.062	0.638	0.780
49	0.054	0.072	0.638	0.780
50	0.058	0.082	0.638	0.780
51	0.061	0.093	0.638	0.780
52	0.065	0.105	0.638	0.780
53	0.070	0.118	0.638	0.780
54	0.075	0.131	0.638	0.780
55	0.080	0.145	0.663	0.755
56	0.085	0.160	0.663	0.755
57	0.091	0.176	0.663	0.755
58	0.097	0.193	0.663	0.755
59	0.103	0.210	0.663	0.755
60	0.110	0.229	0.663	0.755
61	0.118	0.248	0.663	0.755
62	0.126	0.268	0.663	0.755
63	0.134	0.290	0.663	0.755
64	0.144	0.313	0.663	0.755
65	0.154	0.336	0.698	0.765

66	0.164	0.361	0.698	0.765
67	0.175	0.387	0.698	0.765
68	0.188	0.414	0.698	0.765
69	0.201	0.442	0.698	0.765
70	0.214	0.470	0.698	0.765
71	0.229	0.500	0.698	0.765
72	0.245	0.530	0.698	0.765
73	0.262	0.561	0.698	0.765
74	0.280	0.593	0.698	0.765
75	0.300	0.626	0.684	0.740
76	0.321	0.659	0.684	0.740
77	0.344	0.692	0.684	0.740
78	0.368	0.726	0.684	0.740
79	0.394	0.758	0.684	0.740
80	0.422	0.790	0.684	0.740
81	0.451	0.820	0.684	0.740
82	0.481	0.849	0.684	0.740
83	0.513	0.875	0.684	0.740
84	0.546	0.899	0.684	0.740
85	0.580	0.920	0.684	0.740
86	0.614	0.938	0.684	0.740
87	0.649	0.954	0.684	0.740
88	0.684	0.966	0.684	0.740
89	0.719	0.976	0.684	0.740
90	0.752	0.984	0.684	0.740
91	0.785	0.989	0.684	0.740
92	0.816	0.993	0.684	0.740

93	0.845	0.996	0.684	0.740
94	0.871	0.998	0.684	0.740
95	0.895	0.999	0.684	0.740
96	0.917	0.999	0.684	0.740
97	0.935	1.000	0.684	0.740
98	0.951	1.000	0.684	0.740
99	0.963	1.000	0.684	0.740
100	0.974	1.000	0.684	0.740

Appendix 4: Cost Variables

Annual Costs - NOT Adjusted for Inflation to 2010 costs (as reported in the journal article) Costs in the tree diagram are adjusted to 2010 and therefore do not match the numbers here, instead refer to the variable name/definition in the variable report for the reference.	Jaff		Mahoney		Margolis	Hirsch	Sigvant
	2005		2004		2003	2001	
	Medicare		US REACH		HMO	SEER data	Sweden
Aspirin							$26.00
Statin					$207.00		$35.00
Non-aspirin antiplatelet					$90.00		$145.00
ACE					$313.00		$33.00
Total					$610.00		$239.00
Annual cost first year PAD sym							$25,227.50
Subsequent year							$7,539.00
Annual cost MI							$20,217.00
Subsequent year							$5,387.00
Endovascular, revascularization - Symptomatic (PTA) (risk adj) (index qtr + 3 qtr fu)	$16,876.00	34%				1.4%	
Surgical - Symptomatic (bypass, endarterectom)y (risk adj) (index qtr + 3 qtr fu)	$25,950.00	22%				0.7%	
Combination endo + surgical (index qtr + 3 qtr fu) - Symptomatic	$31,078.00	10%					
Unadjusted mean PAD-related medical costs (index qtr + 3 qtr fu)	$19,540.00						
Amputation		6%			1%	0.6%	
Mean PAD related medical costs					$5,955.00	$1,868.00	
Mean PAD all cause hospitalization					$9,149.00		
Mean total PAD related health care costs, all in average PPPY					$10,662.00		
Mean Hospital Costs - Asymptomatic			$4,199.00	11.5%			

Mean Hospital Costs - claudication, Symptomatic		$4,463.00	13%			
Mean Hospital Costs - amputation, Symptomatic		$6,262.00	16%			
Mean Hospital Costs - Revascularization, Symptomatic		$5,895.00	18%			

Jaff, Medicare SAF data 1999, 2002 & 2005 (5% random sample), PAD claims data, n=45,000-75,000 depending on year, prevalance ranged from 8.2-9.5%, high prevalance of diabetes 1999 15.8%, 2005 30.2%. Risk-adjusted hospitalization rates and costs. Costs reported for index quarter of hospitalization, and 4 quarters following hospitalization. Calculated annual costs reported here are [index quarter + 3*follow up quarter].
PROS: Large sample, Medicare claims data, risk-adjusted costs seperated by index and quarters following hospitalization.
CONS: Costs appear very high.

Mahoney, n=2396 symp PAD, n=213 asym PAD, US cohort, hospitalization rates & costs (need to add drug costs)
2-year follow up data, separates sym & asym, claudication, amputation, revasularization
high-medication usage
broader population than Medicare data
2-year rate of vascular-related hosp, 23% asym, 31% symp
rates of claud, amp, revas for symp patients
PROS: Seperates mean costs for Asym & Symp hospitalizations, reports rates of hospitalization for Asym & Symp
CONS: Small sample, managed care not medicare

Margolis, n=30,561 (n=24,075 new PAD)
HMO managed care population, claims data, 2 year follow up
55% with heart disease, high co-morbidities
only study reporting annual drug costs for US
PROS: Annual drug costs for US, large sample, predominantly new PAD
CONS: few event rates, costs aggregated

Appendix 5: Markov State Transition Probabilities by Stage

Early Treatment

Stage	State	Node	Prob	Stage Cost	Stage Effect	Total Cost	Total Effect
0				$1,324	0.2981	$1,324	0.29805
0	Asym PAD	Prob Cohort In Treatment	1.0000	$771	0.3188		
0	Asym PAD	Continue Asym PAD	0.8420				
0	Asym PAD	jump to: Asym PAD	0.8420				
0	Asym PAD	Asym Hospitalization	0.1150				
0	Asym PAD	jump to: Dead	0.1150				
0	Asym PAD	Die	0.0430				
0	Asym PAD	jump to: Dead	0.0430				
0	Dead	Prob Hosp or Dead	0.0000	$553	-0.0207		
1				$1,055	0.5193	$2,378	0.8174
1	Asym PAD	Prob Cohort In Treatment	0.8420	$589	0.5368		
1	Asym PAD	Continue Asym PAD	0.7073				
1	Asym PAD	jump to: Asym PAD	0.7073				
1	Asym PAD	Asym Hospitalization	0.0968				
1	Asym PAD	jump to: Dead	0.0968				
1	Asym PAD	Die	0.0379				
1	Asym PAD	jump to: Dead	0.0379				
1	Dead	Prob Hosp or Dead	0.1580	$465	-0.0174		
2				$872	0.4363	$3,250	1.2536
2	Asym PAD	Prob Cohort In Treatment	0.7073	$481	0.4509		
2	Asym PAD	Continue Asym PAD	0.5885				
2	Asym PAD	jump to: Asym PAD	0.5885				
2	Asym PAD	Asym Hospitalization	0.0813				

2	Asym PAD	jump to: Dead	0.0813				
2	Asym PAD	Die	0.0375				
2	Asym PAD	jump to: Dead	0.0375				
2	Dead	Prob Hosp or Dead	0.2927	$391	-0.0146		
3				$713	0.3630	$3,963	1.6166
3	Asym PAD	Prob Cohort In Treatment	0.5885	$388	0.3751		
3	Asym PAD	Continue Asym PAD	0.4843				
3	Asym PAD	jump to: Asym PAD	0.4843				
3	Asym PAD	Asym Hospitalization	0.0677				
3	Asym PAD	jump to: Dead	0.0677				
3	Asym PAD	Die	0.0365				
3	Asym PAD	jump to: Dead	0.0365				
3	Dead	Prob Hosp or Dead	0.4115	$325	-0.0122		
4				$578	0.2987	$4,541	1.9153
4	Asym PAD	Prob Cohort In Treatment	0.4843	$310	0.3087		
4	Asym PAD	Continue Asym PAD	0.3937				
4	Asym PAD	jump to: Asym PAD	0.3937				
4	Asym PAD	Asym Hospitalization	0.0557				
4	Asym PAD	jump to: Dead	0.0557				
4	Asym PAD	Die	0.0349				
4	Asym PAD	jump to: Dead	0.0349				
4	Dead	Prob Hosp or Dead	0.5157	$268	-0.0100		
5				$462	0.2429	$5,003	2.1582
5	Asym PAD	Prob Cohort In Treatment	0.3937	$245	0.2510		
5	Asym PAD	Continue Asym PAD	0.3162				

5	Asym PAD	jump to: Asym PAD	0.3162				
5	Asym PAD	Asym Hospitalization	0.0453				
5	Asym PAD	jump to: Dead	0.0453				
5	Asym PAD	Die	0.0323				
5	Asym PAD	jump to: Dead	0.0323				
5	Dead	Prob Hosp or Dead	0.6063	$218	-0.0082		
6				$366	0.1950	$5,369	2.3532
6	Asym PAD	Prob Cohort In Treatment	0.3162	$191	0.2016		
6	Asym PAD	Continue Asym PAD	0.2504				
6	Asym PAD	jump to: Asym PAD	0.2504				
6	Asym PAD	Asym Hospitalization	0.0364				
6	Asym PAD	jump to: Dead	0.0364				
6	Asym PAD	Die	0.0294				
6	Asym PAD	jump to: Dead	0.0294				
6	Dead	Prob Hosp or Dead	0.6838	$175	-0.0065		
7				$285	0.1545	$5,654	2.5076
7	Asym PAD	Prob Cohort In Treatment	0.2504	$147	0.1596		
7	Asym PAD	Continue Asym PAD	0.1953				
7	Asym PAD	jump to: Asym PAD	0.1953				
7	Asym PAD	Asym Hospitalization	0.0288				
7	Asym PAD	jump to: Dead	0.0288				
7	Asym PAD	Die	0.0263				
7	Asym PAD	jump to: Dead	0.0263				
7	Dead	Prob Hosp or Dead	0.7496	$138	-0.0052		
8				$219	0.1205	$5,873	2.6281

8	Asym PAD	Prob Cohort In Treatment	0.1953	$111.17	0.1245		
8	Asym PAD	Continue Asym PAD	0.1498				
8	Asym PAD	jump to: Asym PAD	0.1498				
8	Asym PAD	Asym Hospitalization	0.0225				
8	Asym PAD	jump to: Dead	0.0225				
8	Asym PAD	Die	0.0230				
8	Asym PAD	jump to: Dead	0.0230				
8	Dead	Prob Hosp or Dead	0.8047	$107.93	-0.0040		
9				$165.56	0.0924	$6,039	2.7205
9	Asym PAD	Prob Cohort In Treatment	0.1498	$82.78	0.0955		
9	Asym PAD	Continue Asym PAD	0.1130				
9	Asym PAD	jump to: Asym PAD	0.1130				
9	Asym PAD	Asym Hospitalization	0.0172				
9	Asym PAD	jump to: Dead	0.0172				
9	Asym PAD	Die	0.0196				
9	Asym PAD	jump to: Dead	0.0196				
9	Dead	Prob Hosp or Dead	0.8502	$82.78	-0.0031		
10				$123	0.0726	$6,162	2.7931
10	Asym PAD	Prob Cohort In Treatment	0.1130	$61	0.0749		
10	Asym PAD	Continue Asym PAD	0.0836				
10	Asym PAD	jump to: Asym PAD	0.0836				
10	Asym PAD	Asym Hospitalization	0.0130				
10	Asym PAD	jump to: Dead	0.0130				
10	Asym PAD	Die	0.0164				
10	Asym PAD	jump to: Dead	0.0164				
10	Dead	Prob Hosp or Dead	0.8870	$62	-0.0023		

11				$90	0.0537	$6,252	2.8468
11	Asym PAD	Prob Cohort In Treatment	0.0836	$44	0.0554		
11	Asym PAD	Continue Asym PAD	0.0606				
11	Asym PAD	jump to: Asym PAD	0.0606				
11	Asym PAD	Asym Hospitalization	0.0096				
11	Asym PAD	jump to: Dead	0.0096				
11	Asym PAD	Die	0.0134				
11	Asym PAD	jump to: Dead	0.0134				
11	Dead	Prob Hosp or Dead	0.9164	$46	-0.0017		
12				$64	0.0389	$6,316	2.8857
12	Asym PAD	Prob Cohort In Treatment	0.0606	$31	0.0402		
12	Asym PAD	Continue Asym PAD	0.0430				
12	Asym PAD	jump to: Asym PAD	0.0430				
12	Asym PAD	Asym Hospitalization	0.0070				
12	Asym PAD	jump to: Dead	0.0070				
12	Asym PAD	Die	0.0107				
12	Asym PAD	jump to: Dead	0.0107				
12	Dead	Prob Hosp or Dead	0.9394	$33	-0.0013		
13				$45	0.0276	$6,361	2.9133
13	Asym PAD	Prob Cohort In Treatment	0.0430	$21	0.0285		
13	Asym PAD	Continue Asym PAD	0.0297				
13	Asym PAD	jump to: Asym PAD	0.0297				
13	Asym PAD	Asym Hospitalization	0.0049				
13	Asym PAD	jump to: Dead	0.0049				
13	Asym PAD	Die	0.0083				

13	Asym PAD	jump to: Dead	0.0083				
13	Dead	Prob Hosp or Dead	0.9570	$24	-0.0009		
14				$31	0.0191	$6,391	2.9324
14	Asym PAD	Prob Cohort In Treatment	0.0297	$14	0.0197		
14	Asym PAD	Continue Asym PAD	0.0201				
14	Asym PAD	jump to: Asym PAD	0.0201				
14	Asym PAD	Asym Hospitalization	0.0034				
14	Asym PAD	jump to: Dead	0.0034				
14	Asym PAD	Die	0.0062				
14	Asym PAD	jump to: Dead	0.0062				
14	Dead	Prob Hosp or Dead	0.9703	$16	-0.0006		
15				$20	0.0129	$6,412	2.9453
15	Asym PAD	Prob Cohort In Treatment	0.0201	$9	0.0133		
15	Asym PAD	Continue Asym PAD	0.0132				
15	Asym PAD	jump to: Asym PAD	0.0132				
15	Asym PAD	Asym Hospitalization	0.0023				
15	Asym PAD	jump to: Dead	0.0023				
15	Asym PAD	Die	0.0046				
15	Asym PAD	jump to: Dead	0.0046				
15	Dead	Prob Hosp or Dead	0.9799	$11	-0.0004		
16				$13	0.0085	$6,425	2.9537
16	Asym PAD	Prob Cohort In Treatment	0.0132	$6	0.0087		
16	Asym PAD	Continue Asym PAD	0.0084				
16	Asym PAD	jump to: Asym PAD	0.0084				
16	Asym PAD	Asym Hospitalization	0.0015				

16	Asym PAD	jump to: Dead	0.0015				
16	Asym PAD	Die	0.0033				
16	Asym PAD	jump to: Dead	0.0033				
16	Dead	Prob Hosp or Dead	0.9868	$7	-0.0003		
17				$8	0.0054	$6,433	2.9591
17	Asym PAD	Prob Cohort In Treatment	0.0084	$3.66	0.0056		
17	Asym PAD	Continue Asym PAD	0.0052				
17	Asym PAD	jump to: Asym PAD	0.0052				
17	Asym PAD	Asym Hospitalization	0.0010				
17	Asym PAD	jump to: Dead	0.0010				
17	Asym PAD	Die	0.0022				
17	Asym PAD	jump to: Dead	0.0022				
17	Dead	Prob Hosp or Dead	0.9916	$4.63	-0.0002		
18				$5.05	0.0033	$6,438	2.9624
18	Asym PAD	Prob Cohort In Treatment	0.0052	$2.19	0.0034		
18	Asym PAD	Continue Asym PAD	0.0031				
18	Asym PAD	jump to: Asym PAD	0.0031				
18	Asym PAD	Asym Hospitalization	0.0006				
18	Asym PAD	jump to: Dead	0.0006				
18	Asym PAD	Die	0.0015				
18	Asym PAD	jump to: Dead	0.0015				
18	Dead	Prob Hosp or Dead	0.9948	$2.86	-0.0001		
19				$2.97	0.0020	$6,441	2.9644
19	Asym PAD	Prob Cohort In Treatment	0.0031	$1.27	0.0020		
19	Asym PAD	Continue Asym PAD	0.0018				

19	Asym PAD	jump to: Asym PAD	0.0018				
19	Asym PAD	Asym Hospitalization	0.0004				
19	Asym PAD	jump to: Dead	0.0004				
19	Asym PAD	Die	0.0010				
19	Asym PAD	jump to: Dead	0.0010				
19	Dead	Prob Hosp or Dead	0.9969	$1.70	-0.0001		
20		null		$1	0.000340295	$6,442	2.964748246
20	Asym PAD	null	0.00176	$1	0.000340295		
20	Dead	null	0.99823	$-	0		

Prob Cohort In Treatment: Probability of entering that stage, which is equal to the sum of "jump to: Asym PAD" from the prior stage". This number is distributed between "Sum of Continue Asym", "Asym Hospitalization", and "Die" in the current stage.

Continue Asym PAD: Complement of prob Hosp + prob Dead (1-((Asym Hos + Die))			
jump to: Asym PAD; also total number that go on to the next stage			
Asym Hospitalization: Of the cohort in treatment probability of entering Hospitalization			
jump to: Dead: Termination node for Hospitalization; also number of Hosp at that stage			
Die: Of the cohort in treatment probability of entering Dead			
jump to: Dead: Termination node for Dead; also number of deaths for the stage			

Prob Hosp or Dead: Probability of being at Hospalized or Dead at beginning of stage (the complement of Prob Cohort In Treatment); also the sum of "jump to Dead" for Hospitalization and Death in the previous stage.

Over Treatment

Stage	State	Node	Prob	Stage Cost	Stage Effect	Total Cost	Total Effect
0				$771	0.390	$771	0.390
0	Asym PAD	Prob Cohort In Treatment	1.0000	$771	0.390		
0	Asym PAD	Continue Asym PAD	0.9570				
0	Asym PAD	jump to: Asym PAD	0.9570				
0	Asym PAD	Asym Hospitalization					
0	Asym PAD	jump to: Dead					
0	Asym PAD	Die	0.0430				
0	Asym PAD	jump to: Dead	0.0430				
0	Dead	Prob Hosp or Dead	0.0000	$-	0.000		
1				$670	0.746	$1,441	1.136
1	Asym PAD	Prob Cohort In Treatment	0.9570	$670	0.746		
1	Asym PAD	Continue Asym PAD	0.9139				
1	Asym PAD	jump to: Asym PAD	0.9139				
1	Asym PAD	Asym Hospitalization					
1	Asym PAD	jump to: Dead					
1	Asym PAD	Die	0.0431				
1	Asym PAD	jump to: Dead	0.0431				
1	Dead	Prob Hosp or Dead	0.0430	$-	0.000		
2				$621	0.713	$2,062	1.849
2	Asym PAD	Prob Cohort In Treatment	0.9139	$621	0.713		
2	Asym PAD	Continue Asym PAD	0.8701				
2	Asym PAD	jump to: Asym PAD	0.8701				
2	Asym PAD	Asym Hospitalization					
2	Asym PAD	jump to: Dead					

2	Asym PAD	Die	0.0439				
2	Asym PAD	jump to: Dead	0.0439				
2	Dead	Prob Hosp or Dead	0.0861	$-	0.000		
3				$574	0.679	$2,636	2.528
3	Asym PAD	Prob Cohort In Treatment	0.8701	$574	0.679		
3	Asym PAD	Continue Asym PAD	0.8257				
3	Asym PAD	jump to: Asym PAD	0.8257				
3	Asym PAD	Asym Hospitalization					
3	Asym PAD	jump to: Dead					
3	Asym PAD	Die	0.0444				
3	Asym PAD	jump to: Dead	0.0444				
3	Dead	Prob Hosp or Dead	0.1299	$-	0.000		
4				$529	0.644	$3,165	3.172
4	Asym PAD	Prob Cohort In Treatment	0.8257	$529	0.644		
4	Asym PAD	Continue Asym PAD	0.7811				
4	Asym PAD	jump to: Asym PAD	0.7811				
4	Asym PAD	Asym Hospitalization					
4	Asym PAD	jump to: Dead					
4	Asym PAD	Die	0.0446				
4	Asym PAD	jump to: Dead	0.0446				
4	Dead	Prob Hosp or Dead	0.1743	$-	0.000		
5				$486	0.609	$3,651	3.781
5	Asym PAD	Prob Cohort In Treatment	0.7811	$486	0.609		
5	Asym PAD	Continue Asym PAD	0.7358				
5	Asym PAD	jump to: Asym PAD	0.7358				

5	Asym PAD	Asym Hospitalization					
5	Asym PAD	jump to: Dead					
5	Asym PAD	Die	0.0453				
5	Asym PAD	jump to: Dead	0.0453				
5	Dead	Prob Hosp or Dead	0.2189	$-	0.000		
6				$444	0.574	$4,095	4.355
6	Asym PAD	Prob Cohort In Treatment	0.7358	$444	0.574		
6	Asym PAD	Continue Asym PAD	0.6909				
6	Asym PAD	jump to: Asym PAD	0.6909				
6	Asym PAD	Asym Hospitalization					
6	Asym PAD	jump to: Dead					
6	Asym PAD	Die	0.0449				
6	Asym PAD	jump to: Dead	0.0449				
6	Dead	Prob Hosp or Dead	0.2642	$-	0.000		
7				$405	0.539	$4,500	4.894
7	Asym PAD	Prob Cohort In Treatment	0.6909	$405	0.539		
7	Asym PAD	Continue Asym PAD	0.6460				
7	Asym PAD	jump to: Asym PAD	0.6460				
7	Asym PAD	Asym Hospitalization					
7	Asym PAD	jump to: Dead					
7	Asym PAD	Die	0.0449				
7	Asym PAD	jump to: Dead	0.0449				
7	Dead	Prob Hosp or Dead	0.3091	$-	0.000		
8				$368	0.504	$4,868	5.398
8	Asym PAD	Prob Cohort In Treatment	0.6460	$367.68	0.504		

8	Asym PAD	Continue Asym PAD	0.6008				
8	Asym PAD	jump to: Asym PAD	0.6008				
8	Asym PAD	Asym Hospitalization					
8	Asym PAD	jump to: Dead					
8	Asym PAD	Die	0.0452				
8	Asym PAD	jump to: Dead	0.0452				
8	Dead	Prob Hosp or Dead	0.3540	$-	0.000		
9				$331.99	0.469	$5,200	5.867
9	Asym PAD	Prob Cohort In Treatment	0.6008	$331.99	0.469		
9	Asym PAD	Continue Asym PAD	0.5557				
9	Asym PAD	jump to: Asym PAD	0.5557				
9	Asym PAD	Asym Hospitalization					
9	Asym PAD	jump to: Dead					
9	Asym PAD	Die	0.0451				
9	Asym PAD	jump to: Dead	0.0451				
9	Dead	Prob Hosp or Dead	0.3992	$-	0.000		
10				$298	0.420	$5,498	6.286
10	Asym PAD	Prob Cohort In Treatment	0.5557	$298	0.420		
10	Asym PAD	Continue Asym PAD	0.5113				
10	Asym PAD	jump to: Asym PAD	0.5113				
10	Asym PAD	Asym Hospitalization					
10	Asym PAD	jump to: Dead					
10	Asym PAD	Die	0.0445				
10	Asym PAD	jump to: Dead	0.0445				
10	Dead	Prob Hosp or Dead	0.4443	$-	0.000		

11				$266	0.386	$5,764	6.672
11	Asym PAD	Prob Cohort In Treatment	0.5113	$266	0.386		
11	Asym PAD	Continue Asym PAD	0.4678				
11	Asym PAD	jump to: Asym PAD	0.4678				
11	Asym PAD	Asym Hospitalization					
11	Asym PAD	jump to: Dead					
11	Asym PAD	Die	0.0435				
11	Asym PAD	jump to: Dead	0.0435				
11	Dead	Prob Hosp or Dead	0.4887	$-	0.000		
12				$237	0.353	$6,001	7.025
12	Asym PAD	Prob Cohort In Treatment	0.4678	$237	0.353		
12	Asym PAD	Continue Asym PAD	0.4252				
12	Asym PAD	jump to: Asym PAD	0.4252				
12	Asym PAD	Asym Hospitalization					
12	Asym PAD	jump to: Dead					
12	Asym PAD	Die	0.0426				
12	Asym PAD	jump to: Dead	0.0426				
12	Dead	Prob Hosp or Dead	0.5322	$-	0.000		
13				$209	0.321	$6,210	7.346
13	Asym PAD	Prob Cohort In Treatment	0.4252	$209	0.321		
13	Asym PAD	Continue Asym PAD	0.3840				
13	Asym PAD	jump to: Asym PAD	0.3840				
13	Asym PAD	Asym Hospitalization					
13	Asym PAD	jump to: Dead					
13	Asym PAD	Die	0.0412				
13	Asym PAD	jump to: Dead	0.0412				

13	Dead	Prob Hosp or Dead	0.5748	$-	0.000		
14				$183	0.290	$6,393	7.636
14	Asym PAD	Prob Cohort In Treatment	0.3840	$183	0.290		
14	Asym PAD	Continue Asym PAD	0.3444				
14	Asym PAD	jump to: Asym PAD	0.3444				
14	Asym PAD	Asym Hospitalization					
14	Asym PAD	jump to: Dead					
14	Asym PAD	Die	0.0396				
14	Asym PAD	jump to: Dead	0.0396				
14	Dead	Prob Hosp or Dead	0.6160	$-	0.000		
15				$159	0.260	$6,552	7.896
15	Asym PAD	Prob Cohort In Treatment	0.3444	$159	0.260		
15	Asym PAD	Continue Asym PAD	0.3066				
15	Asym PAD	jump to: Asym PAD	0.3066				
15	Asym PAD	Asym Hospitalization					
15	Asym PAD	jump to: Dead					
15	Asym PAD	Die	0.0379				
15	Asym PAD	jump to: Dead	0.0379				
15	Dead	Prob Hosp or Dead	0.6556	$-	0.000		
16				$138	0.231	$6,690	8.128
16	Asym PAD	Prob Cohort In Treatment	0.3066	$138	0.231		
16	Asym PAD	Continue Asym PAD	0.2704				
16	Asym PAD	jump to: Asym PAD	0.2704				
16	Asym PAD	Asym Hospitalization					
16	Asym PAD	jump to: Dead					

16	Asym PAD	Die	0.0362				
16	Asym PAD	jump to: Dead	0.0362				
16	Dead	Prob Hosp or Dead	0.6934	$-	0.000		
17				$118	0.204	$6,808	8.332
17	Asym PAD	Prob Cohort In Treatment	0.2704	$117.94	0.204		
17	Asym PAD	Continue Asym PAD	0.2363				
17	Asym PAD	jump to: Asym PAD	0.2363				
17	Asym PAD	Asym Hospitalization					
17	Asym PAD	jump to: Dead					
17	Asym PAD	Die	0.0341				
17	Asym PAD	jump to: Dead	0.0341				
17	Dead	Prob Hosp or Dead	0.7296	$-	0.000		
18				$100.08	0.178	$6,908	8.510
18	Asym PAD	Prob Cohort In Treatment	0.2363	$100.08	0.178		
18	Asym PAD	Continue Asym PAD	0.2046				
18	Asym PAD	jump to: Asym PAD	0.2046				
18	Asym PAD	Asym Hospitalization					
18	Asym PAD	jump to: Dead					
18	Asym PAD	Die	0.0317				
18	Asym PAD	jump to: Dead	0.0317				
18	Dead	Prob Hosp or Dead	0.7637	$-	0.000		
19				$84.15	0.155	$6,992	8.665
19	Asym PAD	Prob Cohort In Treatment	0.2046	$84.15	0.155		
19	Asym PAD	Continue Asym PAD	0.1752				
19	Asym PAD	jump to: Asym PAD	0.1752				

19	Asym PAD	Asym Hospitalization					
19	Asym PAD	jump to: Dead					
19	Asym PAD	Die	0.0295				
19	Asym PAD	jump to: Dead	0.0295				
19	Dead	Prob Hosp or Dead	0.7954	$-	0.000		
20		null		$70	0.037	$7,062	8.702
20	Asym PAD	null	0.175176995	$70	0.037		
20	Dead	null	0.824823005	$-	0.000		

Late Treatment

Stage	State	Node	Prob	Stage Cost	Stage Effect	Total Cost	Total Effect
0				$1,754	0.3211	$1,754	0.3211
0	Symp PAD	Prob Cohort In Treatment	1.0000	$771	0.3490		
0	Symp PAD	Continue Symp PAD	0.5090				
0	Symp PAD	jump to: Symp PAD	0.5090				
0	Symp PAD	Symp Hospitalization	0.1550				
0	Symp PAD	jump to: Dead	0.1550				
0	Symp PAD	Die	0.3360				
0	Symp PAD	jump to: Dead	0.3360				
0	Dead	Prob Hosp or Dead	0.0000	$983	-0.0279		
1				$856	0.3411	$2,610	0.6622
1	Symp PAD	Prob Cohort In Treatment	0.5090	$356	0.3553		
1	Symp PAD	Continue Symp PAD	0.2464				
1	Symp PAD	jump to: Symp PAD	0.2464				
1	Symp PAD	Symp Hospitalization	0.0789				
1	Symp PAD	jump to: Dead	0.0789				
1	Symp PAD	Die	0.1837				
1	Symp PAD	jump to: Dead	0.1837				
1	Dead	Prob Hosp or Dead	0.4910	$500	-0.0142		
2				$410	0.1651	$3,020	0.8273
2	Symp PAD	Prob Cohort In Treatment	0.2464	$167	0.1720		
2	Symp PAD	Continue Symp PAD	0.1128				
2	Symp PAD	jump to: Symp PAD	0.1128				
2	Symp PAD	Symp Hospitalization	0.0382				
2	Symp PAD	jump to: Dead	0.0382				

2	Symp PAD	Die	0.0953				
2	Symp PAD	jump to: Dead	0.0953				
2	Dead	Prob Hosp or Dead	0.7536	$242	-0.0069		
3				$185	0.0756	$3,205	0.9029
3	Symp PAD	Prob Cohort In Treatment	0.1128	$74	0.0788		
3	Symp PAD	Continue Symp PAD	0.0486				
3	Symp PAD	jump to: Symp PAD	0.0486				
3	Symp PAD	Symp Hospitalization	0.0175				
3	Symp PAD	jump to: Dead	0.0175				
3	Symp PAD	Die	0.0467				
3	Symp PAD	jump to: Dead	0.0467				
3	Dead	Prob Hosp or Dead	0.8872	$111	-0.0031		
4				$79	0.0326	$3,284	0.9355
4	Symp PAD	Prob Cohort In Treatment	0.0486	$31	0.0339		
4	Symp PAD	Continue Symp PAD	0.0196				
4	Symp PAD	jump to: Symp PAD	0.0196				
4	Symp PAD	Symp Hospitalization	0.0075				
4	Symp PAD	jump to: Dead	0.0075				
4	Symp PAD	Die	0.0215				
4	Symp PAD	jump to: Dead	0.0215				
4	Dead	Prob Hosp or Dead	0.9514	$48	-0.0014		
5				$31	0.0131	$3,315	0.9486
5	Symp PAD	Prob Cohort In Treatment	0.0196	$12	0.0137		
5	Symp PAD	Continue Symp PAD	0.0073				
5	Symp PAD	jump to: Symp PAD	0.0073				

5	Symp PAD	Symp Hospitalization	0.0030				
5	Symp PAD	jump to: Dead	0.0030				
5	Symp PAD	Die	0.0092				
5	Symp PAD	jump to: Dead	0.0092				
5	Dead	Prob Hosp or Dead	0.9804	$19	-0.0005		
6				$12	0.0049	$3,327	0.9535
6	Symp PAD	Prob Cohort In Treatment	0.0073	$4	0.0051		
6	Symp PAD	Continue Symp PAD	0.0025				
6	Symp PAD	jump to: Symp PAD	0.0025				
6	Symp PAD	Symp Hospitalization	0.0011				
6	Symp PAD	jump to: Dead	0.0011				
6	Symp PAD	Die	0.0037				
6	Symp PAD	jump to: Dead	0.0037				
6	Dead	Prob Hosp or Dead	0.9927	$7	-0.0002		
7				$4	0.0017	$3,331	0.9552
7	Symp PAD	Prob Cohort In Treatment	0.0025	$1	0.0018		
7	Symp PAD	Continue Symp PAD	0.0008				
7	Symp PAD	jump to: Symp PAD	0.0008				
7	Symp PAD	Symp Hospitalization	0.0004				
7	Symp PAD	jump to: Dead	0.0004				
7	Symp PAD	Die	0.0013				
7	Symp PAD	jump to: Dead	0.0013				
7	Dead	Prob Hosp or Dead	0.9975	$2	-0.0001		
8				$1	0.0005	$3,332	0.9558
8	Symp PAD	Prob Cohort In Treatment	0.0008	$0.45	0.0006		

8	Symp PAD	Continue Symp PAD	0.0002				
8	Symp PAD	jump to: Symp PAD	0.0002				
8	Symp PAD	Symp Hospitalization	0.0001				
8	Symp PAD	jump to: Dead	0.0001				
8	Symp PAD	Die	0.0004				
8	Symp PAD	jump to: Dead	0.0004				
8	Dead	Prob Hosp or Dead	0.9992	$0.78	0.0000		
9				$0.35	0.0002	$3,333	0.9559
9	Symp PAD	Prob Cohort In Treatment	0.0002	$0.13	0.0002		
9	Symp PAD	Continue Symp PAD	0.0001				
9	Symp PAD	jump to: Symp PAD	0.0001				
9	Symp PAD	Symp Hospitalization	0.0000				
9	Symp PAD	jump to: Dead	0.0000				
9	Symp PAD	Die	0.0001				
9	Symp PAD	jump to: Dead	0.0001				
9	Dead	Prob Hosp or Dead	0.9998	$0.22	0.0000		
10				$0.03	0.0000	$3,333	0.9559
10	Symp PAD		0.0001	$0.03	0.0000		
10	Dead		0.9999	$-	0.0000		

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