Chapter __. Peripheral Artery Disease

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Abstract
Peripheral artery disease (PAD) is a global problem characterized by increased disability and mortality over the past two decades, and higher relative increase in disease burden in developing regions, compared with developed nations. The disease burden is significant among women and young adults, and not restricted to men or the elderly. There is rising worldwide prevalence of the modifiable risk factors for PAD, including smoking, cardiovascular disease (CVD), diabetes, hypertension, and hypercholesterolemia. These realities call for coordinated targeted cost-effective response centered on prevention and risk factor control for overall reduction of CVD burden, especially in low-resource settings.

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Introduction

Lower extremity peripheral artery disease (PAD) is a leading cause of atherosclerotic vascular morbidity and is only surpassed by coronary artery disease and stroke (Criqui, Langer et al. 1992, Dormandy and Rutherford 2000, Caro, Migliaccio-Walle et al. 2005). The global importance of PAD is rising because the number of people living with PAD has increased in the past decade in association with an aging populations and increased exposure to risk factors, particularly in low- and middle-income countries (LMICs).(Fowkes, Rudan et al. 2013) Consequently, it is important to assess the need for coordinated and cost-effective responses to the burden of PAD.

This chapter discusses the global epidemiology of PAD based on recent evidence that provides updated comparisons of age- and gender-specific prevalence of PAD between high-income countries (HICs) and LMICs; risk factors for PAD in HICs and LMICs; and robust estimates of the number of people living with PAD regionally and globally, PAD deaths, disability-adjusted life years (DALYs), years of life lost (YLLs), and years lived with disability (YLDs). We provide insights on the implications of current PAD epidemiology on potential cost effective approaches to prevention and treatment in LMICs.

Cause and Diagnosis

PAD is caused by atherosclerosis (plaque buildup in the arteries), which leads to stenosis (narrowing or blockage) of the vessels that deliver blood from the heart to the legs. Although some patients may be asymptomatic, the classic symptom is claudication, defined as pain, cramp, or ache in the legs (hip, buttock, thigh, or calf) due to exertion and relieved by rest. Patients may also present with critical limb ischemia or, occasionally, acute limb ischemia. Potential findings on examination include the presence of non-healing wounds, decreased or absent pulses, hair loss, and muscle atrophy.

Diagnosis in patients with suspected PAD employs use of the resting ankle-brachial index (ABI), a non-invasive test that measures the systolic blood pressure (SBP) in the ankle and compares it with the SBP in the arm. The SBP is determined with a pneumatic cuff, which is first inflated until flow ceases and then deflated slowly until there is reappearance of the flow signal, which is

usually detected by Doppler ultrasound or oscillometric methods (Rooke, Hirsch et al. 2011, Aboyans, Criqui et al. 2012). Normal ABI ranges between 1.00 and 1.40; abnormal values are defined as those less than 0.90. ABI values of 0.91 to 0.99 are considered borderline; values greater than 1.40 indicates stiff or non-compressible arteries (Rooke, Hirsch et al. 2011).

Additional information for the assessment of PAD may be derived from examination of treadmill exercise testing with and without ABI assessments; a six-minute walk test; and imaging tests, such as ultrasound, magnetic resonance angiography (MRA), contrast angiography, and computed tomographic (CT) angiography (Rooke, Hirsch et al. 2011). In patients with PAD, there is high co-prevalence of other atherosclerotic conditions, such as coronary and carotid artery disease. Consequently, patients with PAD have a high risk of adverse cardiovascular events, particularly myocardial infarctions. Death among PAD patients is usually not a direct effect of PAD but due to associated atherosclerotic complications, such as myocardial infarction or stroke, or attendant problems, such as infectious or surgical complications.

The prevention of PAD has not been formally evaluated, but PAD is likely to be ameliorated by typical cardiovascular prevention strategies. Recommendations for the management of patients with PAD focus on cardiovascular risk reduction and treatment of claudication and critical limb ischemia. Recommended cardiovascular risk reduction strategies include the use of lipid-lowering drugs such as statins; antihypertensives, such as angiotensin-converting enzyme inhibitors and beta blockers; antiplatelet and antithrombotic drugs, such as aspirin and clopidogrel; and smoking cessation efforts aided by pharmacological agents, such as nicotine and bupropion therapy. Interventions for claudication include exercise rehabilitation, the use of medical and pharmacological agents, and endovascular or surgical treatment for lifestyle-limiting disability. The main approaches to the treatment of limb ischemia include thrombolysis for acute cases and endovascular and surgical interventions.

Epidemiology

Prevalence (Fowkes, Rudan et al. 2013)

According to a recent study of the global estimates of prevalence and risk factors for PAD, the prevalence has increased across all ages in HICs and LMICs. Four models of PAD prevalence by age for each gender in HICs and LMICs are shown in figure __.1. The prevalence (95% CI) of PAD in HICs is not meaningfully different between men and women. Prevalence at ages 40-44 years was 4.6 percent (2.6 to 7.9 percent) in men and 4.5 percent (2.6 to 7.6 percent) in women; at ages 80-84 years, the prevalence was 16.3 percent (11.2 to 23.2 percent) in men and 15.9 percent (10.4 to 23.6 percent) in women.

Figure __.1: Prevalence of Peripheral Artery Disease by Age in Men and Women in High-Income and Low- and Middle-Income Countries

a. **Men, high-income countries**
b. **Men, low- and middle-income countries**
c. **Women, high-income countries**
d. **Women, low- and middle-income countries**

(Insert figure after permission is obtained)

Source: Fowkes et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet 2013.

In LMICs, the prevalence of PAD was consistently higher in women than men, although there was attenuation of the differences with increasing age. At ages 40-45 years, the prevalence was 5.6 percent (4.1 to 7.7 percent) in women and 2.3 percent (1.5 to 3.5 percent) in men; at ages 80-84 years, it was 13.7 percent (10.2 to 18.1 percent) in women and 12.3 percent (8.4 to 17.7 percent) in men. At all ages up to 60-64 years, the prevalence was consistently higher in HICs, compared to LMICs, across all age groups.

The number of people with PAD increased by 23.5 percent from 164 million in 2000 to 202 million in 2010. The proportional increase was higher in LMICs than HICs (28.7 percent versus 13.1 percent). In LMICs, gender differences in the increase in PAD cases paralleled noted differences in prevalence. In Sub-Saharan Africa, more women had PAD in 2010 than men (9.9 versus 4.4 million); the estimated PAD prevalence in women was twice the prevalence in men for all ages younger than 60 years. Overall, in 2010, the largest number of people with PAD was in the Western Pacific and South-East Asia; most cases in these regions were in people younger than age 55 years (online annex figure __.1).

Online Annex Figure __.1: Estimate of the Number of Cases and Contributing Age Groups in Eight High-Income and Low- and Middle-Income Regions, 2010

(Insert figure after permission is obtained)

Source: Fowkes et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet 2013.

Risk Factors for PAD (Fowkes, Rudan et al. 2013)

In addition to age, the risk factors significantly associated with PAD in HICs and LMICs were smoking and history of cardiovascular disease, diabetes, hypertension, and hypercholesterolemia.

- **Current smoking**: The estimates [meta-OR (95% CI)] were 2.7 (2.4 to 3.1) in HICs and 1.4 (1.3 to 1.6) in LMICs; those for former smoking were 2.0 (1.7 to 2.4) and 1.5 (1.1 to 1.9), respectively.
- **History of cardiovascular disease**: The estimates were 2.6 (2.2 to 3.0) and 1.8 (1.4 to 2.2) in HICs and LMICs, respectively;
- **Diabetes**: The corresponding estimates for diabetes were 1.9 (1.7 to 2.1) and 1.5 (1.3 to 1.7).
- **Hypertension**: The meta-OR in HICs was 1.6 (1.4 to 1.7) and 1.4 (1.2 to 1.5) in LMICs.
- **Hypercholesterolemia**: The estimates of 1.2 (1.1 to 1.3) and 1.1 (1.0 to 1.3) were in HICs and LMICs, respectively.

Globally, there was a statistically significant association between gender and PAD, with observed decreased risk for men compared to women (0.8 (0.7 to 0.9)). However, men were at increased risk in HICs but at much decreased risk in LMICs: meta-OR 1.4 (1.2 to 1.7) versus 0.5 (0.4 to 0.6).

Trends in Burden by Age and Gender (Sampson, Fowkes et al. 2014)

The age-specific death rates per 100,000 population associated with PAD in 1990 ranged from 0.05 (95% CI, 0.03 to 0.09) among ages 40-44 years to 16.6 (10.5 to 25.3) in ages 80 years and older. The corresponding estimates in 2010 were 0.07 (0.04 to 0.13) and 28.7 (18.3 to 43.1). In 1990 and 2010, there was consistent increase in death rate with increasing age; in all age categories, the 2010 rates exceeded the 1990 rates.

Regional estimates of PAD death rates are shown in figure __.2. The highest death rates in 1990 and 2010 were in Australasia, North America-High Income, and Western Europe. The Caribbean, Central Europe, southern Sub-Saharan Africa, Tropical Latin America, and East Asia were regions that ranked high. The death rates increased from 0.07 (0.04 to 0.13) in 1990 to 0.4 (0.2 to 0.7) in 2010 in the Asia Pacific-High Income region (figure __.2a). However the relative change in median death rate was +6.03 (1.5 to 11.8) and was largely driven by women: +17.4 (1.8 to 32.0) versus +1.3 (0.1 to 2.4) in men. Similarly, a remarkable relative change in median death rate of +3.7 (1.7 to 7.6) was observed in Oceania and was driven by a relative change of +4.8 (2.1 to 9.7) in women versus +1.6 (0.7 to 3.6) in men. The overall relative change in median death rate in HICs was higher in women than men (figure __.2b).

Generally, there were more striking changes in regional death rates among women, compared with men, between 1990 and 2010 (figures __.3a and __.3b). Figure __.4 shows the relationship between death rates and age, which provides estimates of age-specific death rates due to PAD for all regions and demonstrates increases in death rates by age in all regions in 1990 and 2010.

Figure __.2a Death Rates Attributed to Peripheral Artery Disease and Relative Change in Median Death Rates, by GBD 2010 Region, 1990 and 2010

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Note: The dots denote estimates of mean death rates due to PAD in all GBD regions. The bars around the estimates are the corresponding 95% Confidence Intervals (CI). The rates are Per 100,000 population.

Figure __.2b Relative Change in Median Death Rates, by Country Development Status, 1990 and 2010

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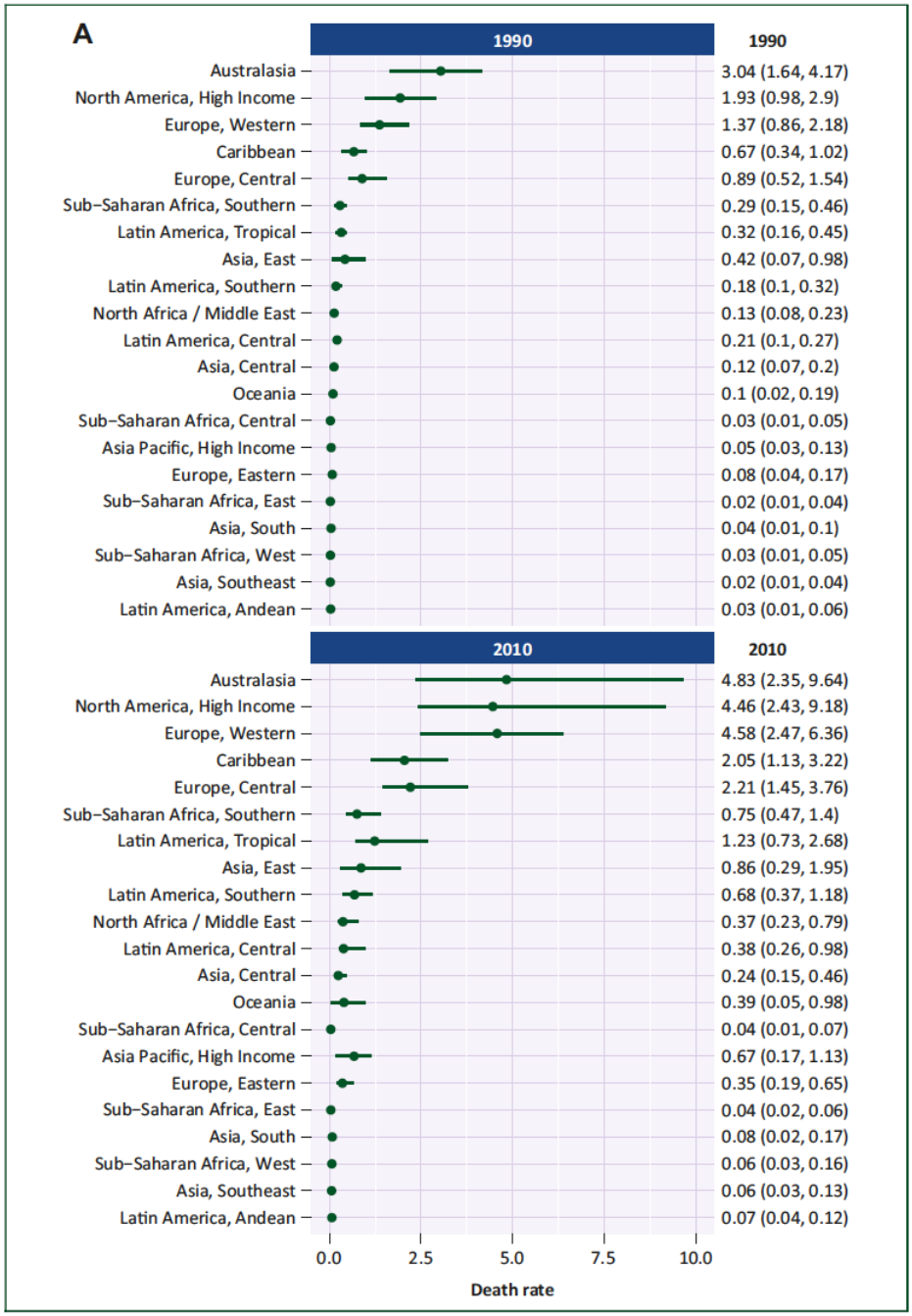
Note: The dots denote the relative change in median death rates due to PAD in developed and developing countries by sex. The bars around the estimates are the corresponding 95% CI. The rates are per 100,000 population.

Figure __.3 Death Rates Attributed to Peripheral Artery Disease, by GBD 2010 Region, 1990 and 2010

__.4a Death Rates among Women

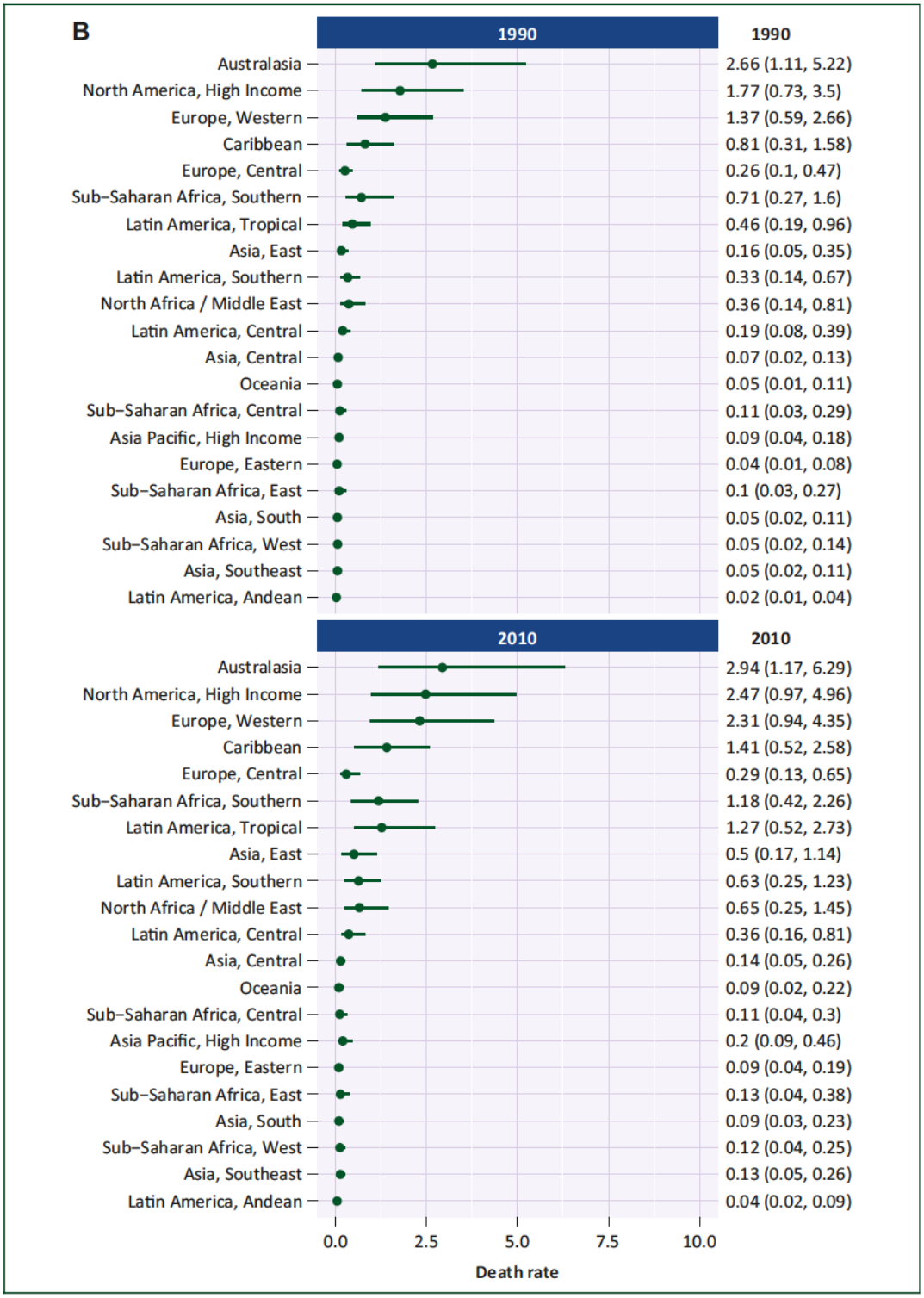
Insert figure after permission is obtained)



Source:

Note: The dots denote estimates of mean death rates due to PAD in all GBD regions. The bars around the estimates are the corresponding 95% confidence intervals (CI). The rates are per 100,000 population.

__.b Death Rates among Men



Source:

Note: The dots denote estimates of mean death rates due to PAD in all GBD regions. The bars around the estimates are the corresponding 95% confidence intervals (CI). The rates are per 100,000 population.

Figure __.4 Death Rates Due to PAD by GBD Region and Age Group, 1990 and 2010

(Insert figure after permission is obtained)

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Note: The chart provides estimates of age-specific death rates due to PAD for all GBD regions. Each color-coded box represents a range of age-specific death rates for a GBD region. Color gradations (also delineated by numbers within the color-coded boxes) represent different tiers of death rates. The color gradient from green to blue to purple to gray (or increasing numbers) observed with increasing age indicates increases in death rates by age in all regions in 1990 and 2010. Age groups are in years, and the rates are per 100,000 population.

Effectiveness of Interventions

Patients with atherosclerotic peripheral artery disease in the lower limbs typically present to clinicians with intermittent claudication. Less commonly, they may present with critical limb ischemia, which is more severe and involves pain at **rest**, ulceration, or gangrene. The management of intermittent claudication and critical limb ischemia may be quite different, and the effectiveness of treatments needs to be considered separately.

In assessing the effectiveness of treatments for intermittent claudication, the main outcome measure is the additional distance that patients can walk. This measure may be pain-free walking distance (PFWD) until the onset of claudication or maximum walking distance (MWD) until stopping walking due to pain. For many years, a large number of medications was advocated for improving walking distance. Now, however, only three—cilostazol, naftidrofuryl and pentoxifylline—tend to be used in clinical practice; this approach may vary by country due to guidelines, availability, and/or resource limitations. In recent Cochrane reviews, cilostazol compared to placebo was found to increase PFWD by a mean of 31 (95% CI 22-40) meters, (Syed and Mayosi 2014) (Syed and Mayosi 2014) and naftidrofuryl increased PFWD by 48 (95% CI 36-61) meters. (Karthikeyan and Mayosi 2014) (Karthikeyan and Mayosi 2014) A meta-analysis of trials of pentoxifylline showed an increase in MWD of 59 (95%CI 37-81) meters (Momsen, Jensen et al. 2009).

Regular exercise, in which patients undergo a supervised training program, has been evaluated as a method of improving walking distance (Fakhry, van de Luijtgaarden et al. 2012). The training programs and methods of supervision vary in approach and intensity. A recent meta-analysis of trials found a mean improvement of 109 (95% CI 38-180) meters, (Lemmer Hunsinger, Engel et al. 2014) (Lemmer Hunsinger, Engel et al. 2014) suggesting that exercise therapy is more effective than pharmacotherapy. However, such programs are resource-intensive. Unsupervised exercise regimes have been evaluated, but they were not as effective as supervised programs (Fokkenrood and others 2013). (Dzudie, Milo et al. 2014) (Dzudie, Milo et al. 2014)

In specialist vascular centers, endovascular therapy may be utilized for more intractable cases of claudication. There are many techniques of endovascular therapy; balloon angioplasty is one of the simplest and most commonly used. The results are comparable to exercise therapy (Liu, Wu et al. 2014); however, following angioplasty, re-stenosis is a frequent occurrence within a few years. Open bypass surgery is not commonly used for the treatment of claudication, and its effectiveness compared to endovascular therapy is not clearly known.

Critical limb ischemia is a very serious condition, which, if untreated, can lead to death. The principal outcomes of treatment are survival and limb salvage to avoid amputation. The two treatment options are bypass surgery or endovascular therapy; to date, only one major comparative trial has been conducted in HIC (Adam, Beard et al. 2005). Amputation-free survival did not differ significantly between the two approaches after six months of follow-up, hazard ratio 0.73 (95%CI 0.49-1.07). If open surgery or endovascular therapy is unavailable, primary amputation may be the preferred treatment. In patients deemed high risk for endovascular therapy or surgery, prostanoid medications may be tried. A systematic review of

trials of prostanoids, compared to other pharmacological preparations or placebo, found no differences in rates of amputation or mortality; it did find some improvements in pain relief, relative risk (RR) 1.3 (95%CI 1.1-1.6), and ulcer healing, RR 1.5(95% CI 1.2-2.0). (Mayosi 2014) (Mayosi 2014)

Cost-Effectiveness of Interventions

Very little research has been conducted on the cost-effectiveness of treatments for PAD; the research conducted has primarily focused on HICs. In treating claudication, medications to improve walking distance are moderately expensive in LMICs (approximately US$3 per day), have limited effectiveness, and need to be continued throughout life. Exercise therapy has been shown to be more cost-effective than endovascular treatment; however, the cost per quality-adjusted life year (QALY) gained of approximately US$8,000 in 2013 (Mazari, Khan et al. 2013) makes it too expensive for most LMICs. Furthermore, the feasibility of establishing suitable programs is difficult. For LMICs, the treatment of claudication needs to rely instead on the simple, well-established advice to patients of "stop smoking and keep walking" (Housley 1988).

In treating critical limb ischemia, the cost-effectiveness of the two key treatments of bypass surgery and angioplasty have been compared in one randomized controlled trial, in which the cost per QALY of angioplasty was found to be less than for bypass surgery (Forbes, Adam et al. 2010). However, the two treatments need to be carried out in specialized vascular centers, which are not available in most LMICs. The high costs of the procedures (US$25,000–US$35,000 in the United Kingdom in 2010) does not justify their use in most LMICs.

The range of treatments in HICs for PAD cannot be justified for most LMICs. What is more appropriate in these settings, if the critical limb ischemia is life-threatening, is amputation, which can normally be carried out in a first-level hospital. Otherwise, conservative medical therapy to relieve pain and infection is likely to be the most feasible approach. The high cost of prostanoid drugs and their limited benefits make them inappropriate in this setting. The emphasis needs to be placed instead on secondary prevention of major cardiovascular events. Smoking cessation, lipid lowering, diabetic control, antihypertensives, and antiplatelets are relatively inexpensive; the costs and substantial benefits in patients with PAD are similar to those for other cardiovascular diseases (See chapter XX on cardiovascular prevention).

Rationale of Interventions

The observed trends in global PAD epidemiology indicate a rising burden in LMICs with increasing involvement of younger adults and women thereby raising concerns and calling for targeted cost-effective responses. An array of interventions for PAD is available, including comprehensive control of risk factors and resource-intensive interventions, such as endovascular and other surgical treatments for claudication and critical limb ischemia. The resource challenges in LMICs negates reliance on surgical and emergency services to handle the increase in number of patients with chronic claudication, who may require elective or emergency revascularization procedures or limb amputation. In these settings, prevention and early disease management via risk factor control may be the most realistic strategies. The observed trends suggesting that increased exposure to PAD risk factors is occurring at relatively young ages underscores the merits of risk factor control (Fowkes, Rudan et al. 2013).

Targeting risk factors may be the most cost-effective approach for both prevention and early disease management and may yield good return on investment. The potential gain from this approach is heightened by the fact that the risk factors for PAD are common to other cardiovascular diseases that have emerged as leading causes of morbidity and mortality in both HICs and LMICs.

Conclusions

PAD is a global problem, evidenced by increased associated disability and mortality and a striking relative increase in the burden of disease in LMICs. The rising disease burden among women and increased involvement of young adults indicate that PAD is no longer limited to men or the elderly.

Governments, nongovernmental organizations, and private sectors in LMICs need to address the social and economic impacts and evaluate the best strategies for optimal treatment and prevention. Risk factor control should be a key part of a coordinated response to the problem of increased PAD burden, especially in LMICs where the health systems are not sufficiently robust to handle an increased number of patients with chronic claudication. In these settings, the scarcity of surgical services, especially emergency services, will lead to unmet needs for elective or emergency peripheral artery revascularization procedures or limb amputations. Potential response approaches may include the combination of environmental, policy, and legislative interventions for health promotion and primary prevention, coupled with improved access to evaluation, diagnosis, treatment, as well as control of major risk factors using evidence-based treatments that are affordable in low-resource settings.

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