Chapter 14

Peripheral Artery Disease

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INTRODUCTION

The term *peripheral artery disease* (PAD) classically encompasses the various diseases that affect noncardiac, nonintracranial arteries. The most common cause of PAD is atherosclerosis; less common causes include inflammatory disorders of the arterial wall (vasculitis) and noninflammatory arteriopathies, such as fibromuscular dysplasia (Kullo and Rooke 2016). Lower extremity PAD is a leading cause of atherosclerotic vascular morbidity and is only surpassed by coronary artery disease and stroke (Caro and others 2005; Criqui and others 1992; Dormandy and Rutherford 2000).

The global importance of PAD is rising because the number of people living with PAD has increased in the past decade; causes of the increase include aging populations and increased exposure to risk factors, particularly in low- and middle-income countries (LMICs) (Fowkes and others 2013). Consequently, assessing the need for coordinated and cost-effective responses to the burden of PAD is important.

This chapter discusses the global epidemiology of PAD based on recent evidence that provides updated comparisons of age- and gender-specific prevalence between high-income countries (HICs) and LMICs, risk factors for PAD in HICs and LMICs, and robust estimates of PAD deaths and the number of people living with PAD regionally and globally. The chapter provides insights into the implications of current PAD epidemiology for potential cost-effective approaches to prevention and treatment in LMICs.

CAUSE AND DIAGNOSIS

Atherosclerosis is 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 most 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 nonhealing wounds, decreased or absent pulses, hair loss, and muscle atrophy.

The diagnosis of PAD is usually made in symptomatic patients using clinical signs alone, including appropriate typical symptoms, absence of peripheral pulses, presence of ischemic skin changes, and presence of necrosis. However, diagnosis is usually aided by the use of resting ankle-brachial index (ABI), particularly to quantify symptomatic disease, evaluate atypical symptoms, and find asymptomatic disease. ABI is a noninvasive test that measures the systolic blood pressure (SBP) in the ankle and compares it with SBP in the arm. SBP is determined with a pneumatic cuff, which is first inflated

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until flow ceases and then deflated slowly until the flow signal reappears, usually detected by Doppler ultrasound or oscillometric methods (Aboyans and others 2012; Rooke and others 2011). Normal ABI ranges between 1.00 and 1.40; abnormal values are defined as those less than 0.90. ABI values of 0.91–0.99 are considered borderline; values greater than 1.40 indicate stiff or noncompressible arteries (Rooke and others 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, contrast angiography, and computed tomographic angiography (Rooke and others 2011). Patients with PAD have high coprevalence of other atherosclerotic conditions such as coronary and carotid artery disease (getABI Study Group 2002; Saw and others 2006). Consequently, patients have a high risk of adverse cardiovascular events, particularly myocardial infarctions. Death among PAD patients is usually not a direct effect of the disease but is due to associated atherosclerotic complications such as myocardial infarction or stroke, or attendant problems such as infectious or surgical complications.

Recent evidence indicates that the risk of PAD progression is higher than previously expected (Sigvant, Lundin, and Wahlberg 2016). Therefore, although the prevention of PAD has not been formally evaluated, PAD is likely to be ameliorated by typical cardiovascular prevention strategies (Pande and others 2011). 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, 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

According to a study of the global estimates of prevalence and risk factors for PAD, prevalence has increased across all ages in HICs and LMICs (Fowkes and others 2013). Four models of PAD prevalence by age and gender in HICs and LMICs are shown in figure 14.1. The prevalence of PAD in HICs is not meaningfully different between men and women. Prevalence at ages 40–44 years was 4.6 percent (95 percent confidence interval [CI] 2.6–7.9 percent) in men and 4.5 percent (95 percent CI 2.6–7.6 percent) in women; at ages 80–84 years, prevalence was 16.3 percent (95 percent CI 11.2–23.2 percent) in men and 15.9 percent (95 percent CI 10.4–23.6 percent) in women.

In LMICs, the prevalence of PAD was consistently higher in women than in men, although the differences were attenuated with increasing age. At ages 40–45 years, prevalence was 5.6 percent (95 percent CI 4.1–7.7 percent) in women and 2.3 percent (95 percent CI 1.5–3.5 percent) in men; at ages 80–84 years, it was 13.7 percent (95 percent CI 10.2–18.1 percent) in women and 12.3 percent (95 percent CI 8.4–17.7 percent) in men. At all ages up to 60–64 years prevalence was consistently higher in HICs compared with LMICs.

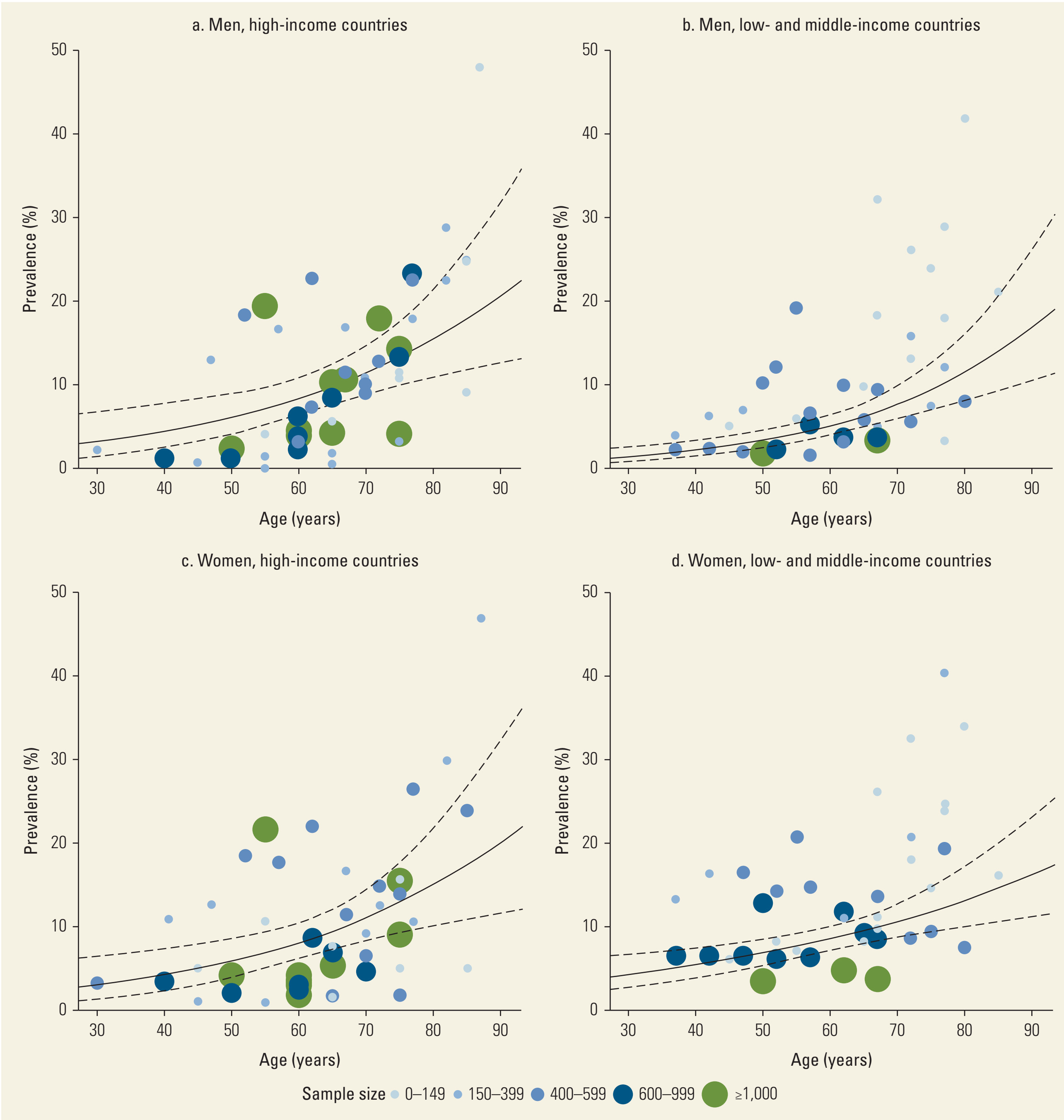
The number of people with PAD increased by 23.5 percent from 164 million in 2000 to 202 million in 2010. The proportional increase was higher in LMICs than in HICs (28.7 percent versus 13.1 percent). In LMICs, gender differences in the increase in PAD cases paralleled noted differences in prevalence. In Sub-Saharan Africa, more women in 2010 had PAD than did men (9.9 million versus 4.4 million); the estimated 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 were in the Southeast Asia and Western Pacific regions; most cases in these regions were in people younger than age 55 years (figure 14.2).

Risk Factors for PAD

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 (Fowkes and others 2013).

- *Current smoking*. The estimates were meta–odds ratio (meta-OR) 2.7 (95 percent CI 2.4–3.1) in HICs and 1.4 (1.3–1.6) in LMICs; those for former smoking were 2.0 (1.7–2.4) and 1.5 (1.1–1.9), respectively.
- *History of cardiovascular disease*. The estimates were 2.6 (2.2–3.0) and 1.8 (1.4–2.2) in HICs and LMICs, respectively.
- *Diabetes*. The estimates were 1.9 (1.7–2.1) and 1.5 (1.3–1.7) in HICs and LMICs, respectively.

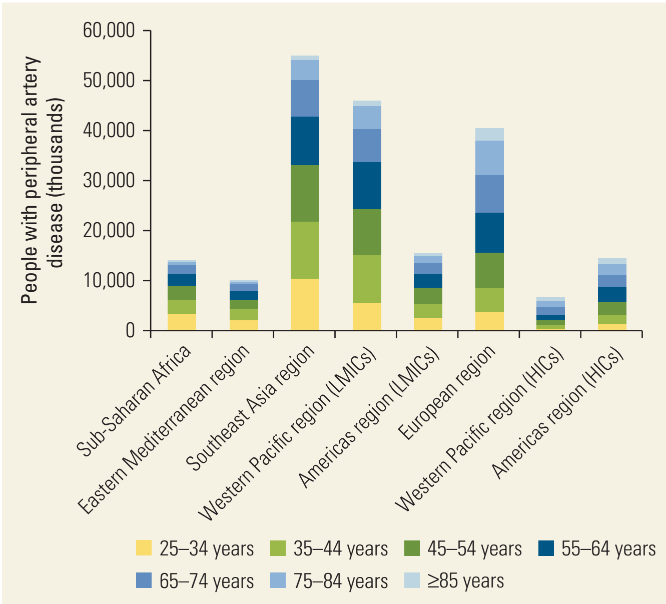
Figure 14.1 Prevalence of Peripheral Artery Disease by Age in Men and Women in High-Income and Low- and Middle-Income Countries



Source: Fowkes and others 2013.

Note: Size and color of circles equivalent to sample size of population from which datapoint was derived. At younger (< 40 years) and older (> 80 years) ages, regression lines are based on projection only or on very few datapoints. Akaike Information Criterion for model goodness of fit: male high-income countries 1,974.72; male low-income or middle-income countries 838.36; female high-income countries 1,971.59; female low-income or middle-income countries 1,115.09.

Figure 14.2 Estimate of the Number of Cases of PAD and Contributing Age Groups in Eight High-Income and Low- and Middle-Income Regions, 2010



Source: Fowkes and others 2013.
Note: HICs = high-income countries; LMICs = low- and middle-income countries; PAD = peripheral artery disease.

- *Hypertension*. The estimates were 1.6 (1.4–1.7) and 1.4 (1.2–1.5) in HICs and LMICs, respectively.
- *Hypercholesterolemia*. The estimates were 1.2 (1.1–1.3) and 1.1 (1.0–1.3) in HICs and LMICs, respectively.

Globally, there was a statistically significant association between gender and PAD, with observed decreased risk for men compared with women (meta-OR 0.8, 95 percent CI 0.7–0.9). However, men were at increased risk in HICs but at much decreased risk in LMICs: meta-OR 1.4 (95 percent CI 1.2–1.7) versus meta-OR 0.5 (95 percent CI 0.4–0.6).

Trends in Burden by Age and Gender

The age-specific death rates per 100,000 population associated with PAD in 1990 ranged from 0.05 (95 percent CI 0.03–0.09) among those ages 40–44 years to 16.6 (95 percent CI 10.5–25.3) in ages 80 years and older (Sampson and others 2014). The corresponding estimates in 2010 were 0.07 (95 percent CI 0.04–0.13) and 28.7 (95 percent CI 18.3–43.1). In both 1990 and 2010, the death rate consistently increased with increasing age; in all age categories, the 2010 rates exceeded the 1990 rates.

Regional estimates of PAD death rates are shown in figure 14.3. 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 regions also ranked high. The death rates increased from 0.07 (95 percent CI 0.04–0.13) in 1990 to 0.44 (95 percent CI 0.18–0.69) in 2010 in the Asia Pacific high-income region (figure 14.3). However the relative change in median death rate was +6.03 (95 percent CI 1.5–11.8) and was largely driven by women: +17.4 (95 percent CI 1.8–32.0) versus +1.3 (95 percent CI 0.1–2.4) in men. Similarly, a remarkable relative change in median death rate of +3.7 (95 percent CI 1.7–7.6) was observed in Oceania and was driven by a relative change of +4.8 (95 percent CI 2.1–9.7) in women versus +1.6 (95 percent CI 0.7–3.6) in men. The overall relative change in median death rate in HICs was higher in women than men (figure 14.4).

Generally, the changes in regional death rates were more striking among women compared with men between 1990 and 2010 (panels a and b of figure 14.5). Figure 14.6 provides estimates of age-specific death rates attributed to PAD for all regions, demonstrating increases in death rates by age in all regions between 1990 and 2010.

EFFECTIVENESS OF INTERVENTIONS

The main goals in treating patients with PAD are to reduce the risks of adverse cardiovascular outcomes, improve functional capacity, and preserve limb viability. Patients with atherosclerotic PAD 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. There are reasons for the different treatment approaches: The risk of limb loss in patients with functional ischemia is low, and the primary goal of treatment is the quality of life. In patients with critical ischemia, the primary goal is limb salvage.

Intermittent Claudication

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 until stopping walking because of pain. For many years, a large number of medications were 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 because of guidelines, availability, and resource limitations. In recent Cochrane reviews, cilostazol compared with placebo was found to increase PFWD by a mean of 31 meters (95 percent CI 22–40) (Bedenis and others 2014) and naftidrofuryl increased PFWD by 48 meters (95 percent CI 36–61) (de Backer and others 2012). A meta-analysis of trials of pentoxifylline showed an increase in maximum walking distance of 59 meters (95 percent CI 37–81) (Momsen and others 2009).

Regular exercise, in which patients undergo a supervised training program, has been evaluated as a method of improving walking distance (Fakhry and others 2012). The training programs and methods of supervision vary in approach and intensity. A meta-analysis of trials found a mean improvement of 109 meters (95 percent CI 38–180) (Lane and others 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). Although the long-term durability favors supervised exercise, the uptake for such exercise programs is variable and the drop-out rate is high.

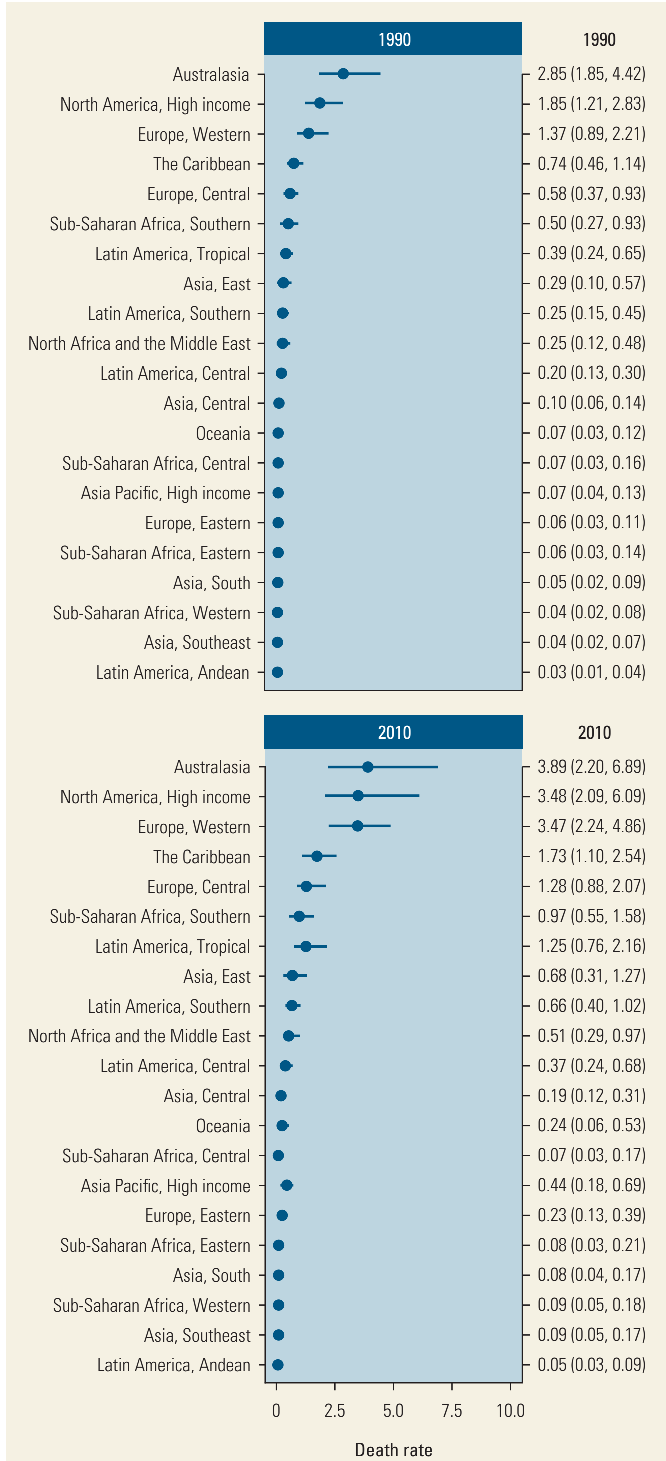
In specialist vascular centers, endovascular therapy may be used for more intractable cases of claudication. Among the many techniques of endovascular therapy, balloon angioplasty is one of the simplest and most commonly used. The results are comparable to exercise therapy (Liu and others 2014); however,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

Critical Limb Ischemia

Critical limb ischemia is a very serious condition, which, if untreated, can lead to limb loss with associated significant disabilities; it can also lead to death. The principal outcomes of treatment are survival and limb salvage to avoid amputation. The two treatment options are bypass surgery and endovascular therapy; to date, only one major comparative trial has been conducted in an HIC (Adam and others 2005). Amputation-free survival did not differ significantly between the two approaches after six months of follow-up (hazard ratio 0.73, 95 percent CI 0.49–1.07).

If open surgery or endovascular therapy is unavailable, primary amputation may be the preferred treatment.

Figure 14.3 Death Rates per 100,000 Population Attributed to Peripheral Artery Disease and Relative Change in Median Death Rates, by GBD 2010 Region, 1990 and 2010



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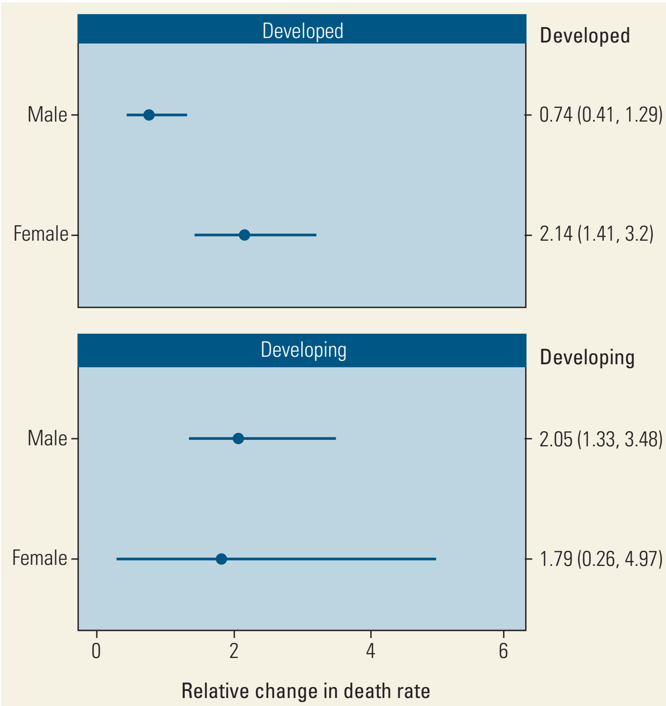
Note: GBD 2010 = Global Burden of Disease study 2010. The dots denote estimates of mean death rates attributed to peripheral artery disease in all GBD regions. The parenthetical numbers are the corresponding 95 percent confidence intervals.

Figure 14.4 Relative Change in Median Death Rates per 100,000 Population, by Country Development Status, 1990 and 2010



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Note: The dots denote the relative change in median death rates attributed to peripheral artery disease in developed and developing countries by gender. The parenthetical numbers are the corresponding 95 percent confidence intervals.

In patients deemed high risk for endovascular therapy or surgery, prostanoid medications may be tried. A systematic review of trials of prostanoids, compared with other pharmacological preparations or placebo, found no differences in rates of amputation or mortality; it did find some improvements in pain relief (relative risk 1.3, 95 percent CI 1.1–1.6) and ulcer healing (relative risk 1.5, 95 percent CI 1.2–2.0) (Ruffolo, Romano, and Ciapponi 2010).

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 gained of approximately US$8,000 in 2013 (Mazari and others 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 to "stop smoking and keep walking" (Housley 1988).

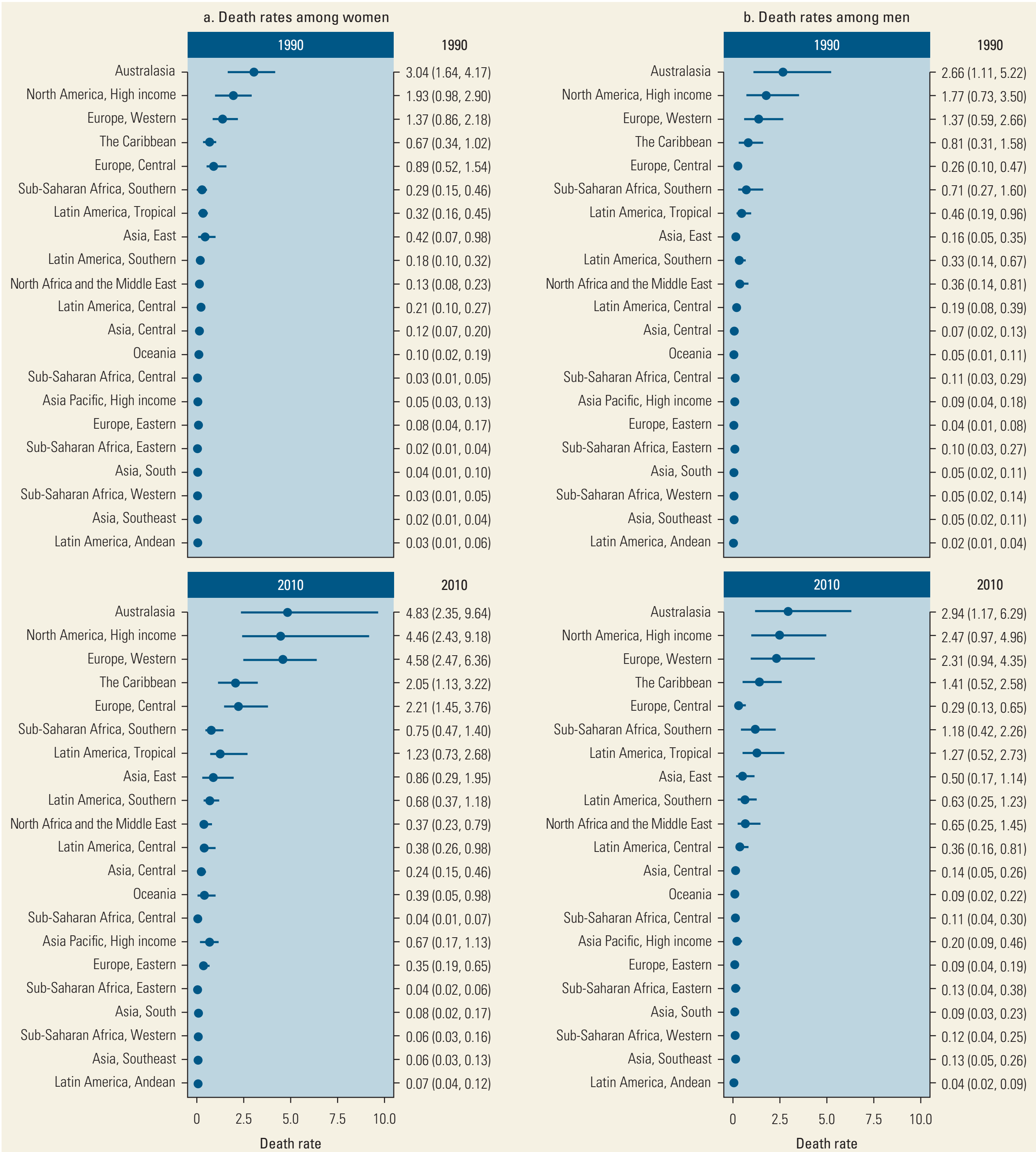
In treating critical limb ischemia, the cost-effectiveness of the two key treatments of bypass surgery and angioplasty have been compared in one randomized controlled trial; the cost of angioplasty per quality-adjusted life year gained was found to be less than for bypass surgery (Forbes and others 2010). 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—may not justify their use in most LMICs.

The range of PAD treatments in HICs may not be justified for most LMICs. If the critical limb ischemia is life threatening, amputation may be more appropriate in these settings; this procedure can usually be provided 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 is better 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 19 in this volume, Gaziano and others 2017).

Rationale of Interventions

The observed trends in global PAD epidemiology indicate a rising burden in LMICs with increasing involvement of younger adults and women, raising concerns and requiring 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 preclude reliance on surgical and emergency services to handle the increases in the 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 through 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

Figure 14.5 Death Rates per 100,000 Population Attributed to Peripheral Artery Disease, by GBD 2010 Region, 1990 and 2010



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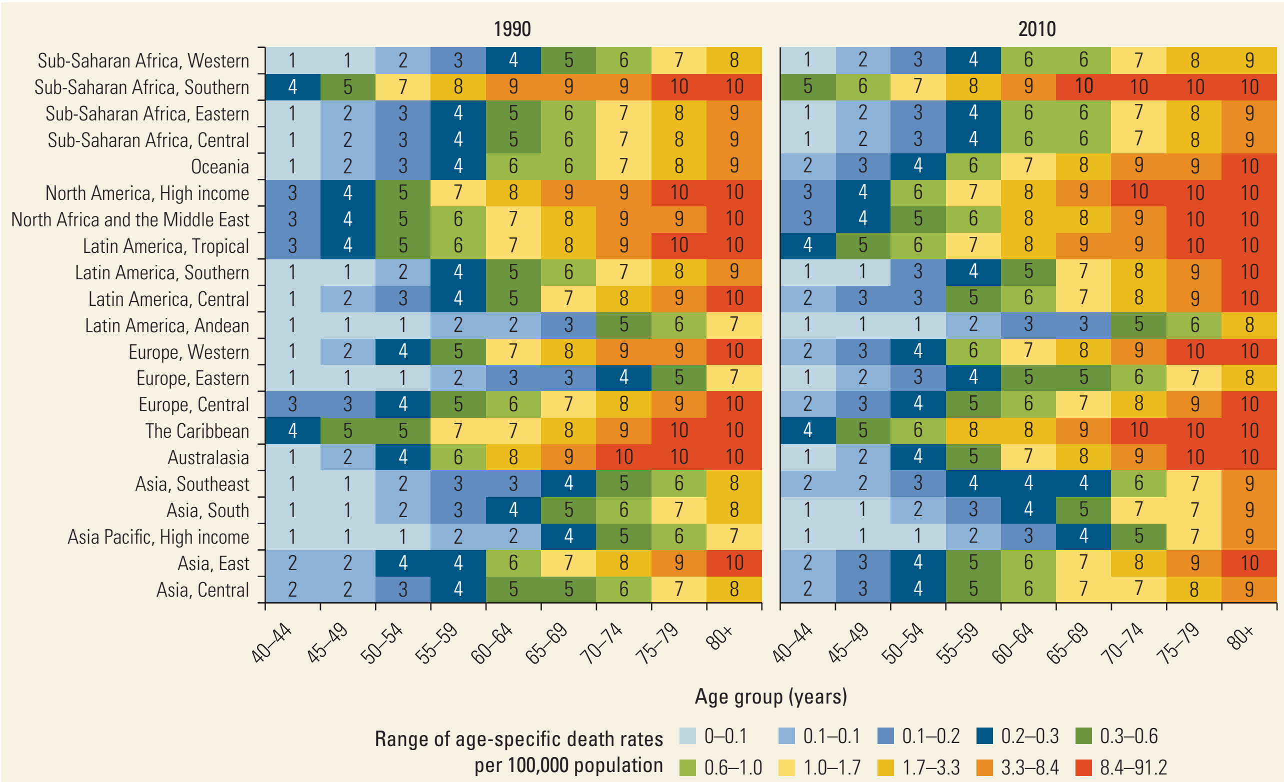
Note: GBD 2010 = Global Burden of Disease study 2010. The dots denote estimates of mean death rates attributable to peripheral artery disease in all GBD regions. The parenthetical numbers are the corresponding 95 percent confidence intervals.

Figure 14.6 Death Rates Attributed to Peripheral Artery Disease by GBD Region and Age Group, 1990 and 2010



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Note: GBD = Global Burden of Disease. The figure provides estimates of age-specific death rates attributed to peripheral artery disease 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 blue to green to orange to red (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.

underscores the merits of risk factor control (Fowkes and others 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 amplified 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 elderly persons.

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 (Papia and others 2015). Risk factor control could be a key part of a coordinated response to the increased PAD burden, especially in LMICs where health systems are not sufficiently robust to handle an increased number of patients with chronic PAD. In these settings, the scarcity of surgical services, especially emergency services, will lead to unmet need 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, and treatment, as well as control of major risk factors using evidence-based treatments that are affordable in low-resource settings.

NOTE

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US$1,045 or less
- Middle-income countries (MICs) are subdivided:
  (a) lower-middle-income = US$1,046 to US$4,125
  (b) upper-middle-income (UMICs) = US$4,126 to US$12,745
- High-income countries (HICs) = US$12,746 or more.

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