Medical Management of Peripheral Arterial Disease
Bridging the “Gap”?

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Peripheral artery disease (PAD) is estimated to affect 27 million individuals in Europe and North America, and its prevalence is increasing in concert with recent demographic and risk factor trends.1 The majority of patients with PAD either are asymptomatic or have atypical leg symptoms, with classic claudication in only 10% to 35%; therefore, detection is elusive unless actively sought.2 Given shared risk factors, it is axiomatic that a high coprevalence of atherosclerosis in other vascular beds exists, including the coronary arteries in PAD patients. However, PAD disproportionately affects the elderly, nonwhites, and women compared with coronary artery disease (CAD) alone.3,4 The actual coprevalence of CAD in patients with established PAD depends on how closely it is searched for, with clinical history and ECG detecting only 20% to 40% of coexisting disease and cardiac catheterization detecting CAD in as many as 90% of PAD patients.5,6

There is a direct relationship between the severity of PAD (eg, as measured by the ankle brachial index) and cardiovascular and overall mortality, regardless of whether the PAD is symptomatic or not.7,8 In general, men and women with PAD have an ≈5-fold greater risk of cardiovascular mortality and a 3-fold greater risk for all-cause mortality even after adjustment for known Framingham risk factors.9 Patients with PAD have worse outcomes after acute ischemic events and hospitalizations for acute coronary syndrome and after percutaneous coronary interventions.1,10 Current guidelines for secondary prevention and risk reduction therapy in patients with PAD recommend antiplatelet therapy, lipid-lowering therapy with a statin to achieve a goal low-density lipoprotein (LDL; <100 mg/dL or <70 mg/dL in high-risk patients), and antihypertensive therapy to achieve a systolic blood pressure <140 mm Hg (or <130 mm Hg in diabetics and patients with chronic renal disease).2,11 Despite these guidelines, cross-sectional studies, registries, and surveys have consistently shown that the use of proven cardioprotective medication for secondary prevention in patients with PAD significantly lags behind treatment for CAD.12,13 The reasons behind this gap in treatment aggressiveness for atherosclerosis in the periphery remain unclear. Cross-sectional “snapshots” are limited by a lack of incidence data, an incomplete assessment of medication compliance, and an inability to capture practice trends over time. Importantly, they also fail to provide information on the impact of the incident diagnosis of PAD on subsequent medical management, reflecting the treating physician’s awareness and attitudes toward PAD and its treatment. It is here that the report by Subherwal and colleagues14 of a longitudinal, population-based cohort study conducted in Denmark has given us a valuable insight.

The latitude and longitude of Denmark are 56° north and 10[°east] east, roughly the same latitude as Scotland, Canada, and Alaska. There are 3.4 physicians per 1000 residents, and health expenditure is 7% of the $330.5 billion gross domestic product. Ninety-nine percent of Danish men and women are literate; unemployment is only 6%; and life expectancy is 78 years. By all metrics, Denmark is an affluent country (https://www.cia.gov/library/publications/the-world-factbook/geos/da.html). Each Dane is issued a personal identification number allowing individual-level linkage to all admissions to Danish hospitals and outpatient and specialty clinics. In addition, Danish pharmacies must register all filled prescriptions, including the date, strength, and number of tablets, in a National Prescription Register, and prescriptions are partially reimbursed by the healthcare system. It is in this unique setting that Subherwal and colleagues conducted a population-based cohort study from 2000 to 2009, a span of time in which PAD guidelines became available,2 to determine trends of use of cardioprotective medications in patients with PAD alone, combined PAD and CAD, and CAD alone.

As expected, the use of cardioprotective medications increased in all 3 groups over the study period, with a doubling in the use of antiplatelet agents and a 6-fold increase in the use of statins for the CAD alone group. After the diagnosis of PAD or CAD was made and the physician became aware of the disease, there was also an improvement of cardioprotective medications. However, the improvement was far less in both PAD subgroups compared with the CAD alone group. Among all PAD patients, 41.9% were on antiplatelet therapy before diagnosis, increasing to just 48.3% within the first 3 months after a diagnosis of PAD was made. Statin use was also low, although it increased from 27.6% to 36.9% after the diagnosis of PAD. One of the most startling observations was that the publication of PAD guidelines in 2005 made an almost imperceptible difference in the temporal prescribing patterns, suggesting that their impact was modest.

One might presume that the newly diagnosed patients in the Denmark cohort had mild PAD and therefore the diagnosing physicians were less likely to prescribe medications. However, an examination of the results of recently completed surgery trials suggests otherwise. Project of Ex-Vivo vein
grant ENgineering via Transfection III (PREVENT III) study, which was the largest prospective North American trial conducted in patients undergoing lower-extremity bypass surgery for critical limb ischemia, suggests that even the most vulnerable patients are undertreated. In this study, there was an improvement in aspirin therapy from 67% at the time of admission to 88% by the time of discharge after leg bypass surgery. Similar trends were also noted for β-blockers, 49% on admission to 60% at the time of discharge, whereas statin use was stable at 46% throughout the hospitalization. One of the salient findings from the PREVENT III study was that both racial and practice setting disparities existed in the use of evidence-based medical therapy. Reduced rates of use of cardioprotective medications were observed in blacks and at nonuniversity institutions. In the Bypass Versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial, a United Kingdom–based study comparing angioplasty-first to bypass surgery–first treatment in patients with severe limb ischemia, aspirin and statin use were 54% and 34%, respectively. So, even patients requiring surgical or endovascular interventions for advanced limb ischemia, in both Europe and the United States, are not receiving medical therapies within guidelines.

In general, all 3 Danish subgroups examined by Subherwal et al are out of compliance with evidenced-based, secondary prevention medications. The group with clinically evident PAD and CAD, a particularly vulnerable group with polyvascular disease, had just 65% antiplatelet and 48.3% statin use 3 months after incident diagnosis. It is reasonable to assume similar patterns of compliance in other affluent countries and far inferior compliance in lower-income countries, particularly in their rural areas. Hence, the underuse of cardioprotective medication in patients with PAD is a conspicuous example of a more generalized failure to embrace secondary preventive guidelines.

Cardiovascular practice guidelines for secondary prevention are designed to support decision-making processes to achieve treatment goals of blood pressure and lipid levels and are ultimately aimed at improving outcomes and quality of care. However, considerable clinical inertia exists in their implementation. General reasons include overestimation of care provided by other caregivers; lack of education and training, particularly among students and residents; and lack of systematic practice organization such as electronic medical records that reinforce compliance. Physician, institutional, and cultural (specialty) attitudes should not be underestimated. For example, internists specializing in diabetes care in general hospitals in the Netherlands were asked to indicate the perceived organizational and personal barriers to adherence to the diabetes guidelines. Of the 120 specialists queried, 91% responded and identified cognitive, physician attitude, and social and organizational barriers to guideline implementation. Most notably, 44% reported that the guidelines would not be read, 35% believed that there was insufficient evidence base, 56% reported that the guidelines were too rigid, and 50% simply did not like imposed activities.

Could it be that guidelines are too rigid and do not reflect the complexities of practice in the trenches? Evidence suggests otherwise. Treatment with a statin to lower LDL cholesterol <100 mg/dL is a Class 1, Level B recommendation in PAD patients. Given that the majority of patients with PAD who are on a statin will still die of cardiovascular disease, an LDL of 100 or even 70 mg/dL may be too high. Both the Reversal of Atherosclerosis and Aggressive Lipid Lowering (REVERSAL) and the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial also support targeting LDL to ≤70 mg/dL in high-risk patients to lower cardiovascular events. The “lower is better” hypothesis is supported by the Heart Protection Study (HPS), which provided evidence that allocation to statin therapy in patients with PAD produced a 25% risk reduction regardless of baseline cholesterol levels at entry into the study. These results are relevant because a recent prospective cohort study of 225 patients undergoing lower-extremity bypass had a mean LDL of 63.7 mg/dL (60.9 mg/dL for those on statin therapy and 74.9 for those not on statin therapy at the time of surgery). Thus, a good number of these advanced PAD patients had LDL levels within current guidelines, even without being on a statin at the time of their leg surgery. Yet, in the same cohort, high-sensitivity C-reactive protein levels were notably elevated, with a mean value of 12.0 mg/L (median, 3.0 mg/L). This begins to get at the nature of the persistent gap in evidence for PAD, which may also be at play. What are the most appropriate goals for statin therapy in the PAD patient? Is it LDL cholesterol, or should it be high-sensitivity C-reactive protein or a combination thereof? Unfortunately, the evidence base supporting treatment targets specific to PAD remains quite thin, and clearly we need more high-quality, randomized trials to determine optimal intensity of therapy in this population. Better-quality evidence is undoubtedly part of the problem in the persisting treatment gap between CAD and PAD.

Administrative data sets such as the Denmark cohort have limitations. There are no hemodynamic data on the severity of PAD as assessed by ankle brachial index or other noninvasive testing. As the authors admit, International Classification of Disease, 10th edition, codes most likely capture patients who are symptomatic, in a hospital setting, and therefore more likely to be treated. Admittedly, few data exist to guide us on secondary prevention in asymptomatic PAD patients, but it may be assumed that they would receive even less aggressive treatment. In fact, recent studies suggest that aspirin, the staple cost-effective drug of cardiovascular specialists, may be of no benefit in the asymptomatic PAD population. No data are available on either cholesterol levels or blood pressure in the Danish cohort; therefore, we cannot know whether the nonmedicated patients are already within current guidelines. There are also no provider data. It is well documented that disparities in knowledge and action gaps exist in the treatment of PAD among internal medicine, vascular surgeons, and cardiologists.

The good news is that the gap between PAD and CAD is closing, but it is not closed yet. It is well documented that physician and patient awareness of PAD is low, and this has not escaped the attention of pharmaceutical companies wishing to market to this patient population. In the PAD Awareness, Risk, and Treatment; New Resources for Survival (PARTNERS) national cross-sectional study, >70% of primary care providers whose patients were screened were unaware of the presence of PAD. An American television commercial for a large pharmaceutical company says, “Ask
your doctor about PAD.” The pharmaceutical company knows that the doctor probably is not going to ask the patient.

**Disclosures**

None.

**References**


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