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

Running title: Owens et al.; Medical management of PAD: 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. The majority of patients with PAD are either asymptomatic or have atypical leg symptoms, with classical claudication in only 10-35%, therefore detection is elusive unless actively sought. Given shared risk factors, it is axiomatic that there exists a high co-prevalence of atherosclerosis in other vascular beds including the coronary arteries in PAD patients. However, PAD disproportionately affects the elderly, non-whites, and women compared with CAD alone. The actual co-prevalence of CAD in patients with established PAD depends on how closely it is searched for, with clinical history and ECG detecting only 20-40% of co-existing disease whereas cardiac catheterization detects CAD in as many as 90% of PAD patients.

There is a direct relationship between the severity of PAD (e.g. as measured by the ankle-brachial index) and cardiovascular and overall mortality, regardless of whether the PAD is symptomatic or not. In general, men and women with PAD have about a 5-fold greater risk of cardiovascular mortality and a 3-fold greater risk for all-cause mortality even after adjusting for known Framingham risk factors. Patients with PAD have worse outcomes following acute ischemic events and hospitalizations for acute coronary syndrome and after percutaneous coronary interventions.

Current guidelines for secondary prevention and risk reduction therapy in patients with PAD recommend anti-platelet 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 mmHg (or < 130 mmHg in diabetics and chronic renal disease). Despite these guidelines cross sectional studies, registries, and surveys
have consistently shown that utilization of proven cardioprotective medication for secondary prevention in patients with PAD significantly lags behind CAD.\textsuperscript{12,13} The reasons behind this gap in treatment aggressiveness for atherosclerosis in the periphery remain unclear. Cross sectional “snapshots” are limited by lacking incidence data, incomplete assessment of medication compliance, and 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 current report by Subherwal and colleagues of a longitudinal, population-based cohort study conducted in Denmark has given us a valuable insight.\textsuperscript{14}

Denmark’s latitude and longitude are 56° North and 10° East located on roughly the same latitude as Scotland, Canada, and Alaska. There are 3.4 physicians/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. (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, 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 health care 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,\textsuperscript{2} to determine utilization trends of cardioprotective medications in patients with PAD alone, combined PAD and CAD, and CAD alone.

As expected, the utilization of cardioprotective meds increased in all 3 groups over the
study period with a doubling in the use of anti-platelet agents and a 6-fold increase in the use of statins for the PAD 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. For all PAD patients, 41.9% were on antiplatelet therapy prior to diagnosis increasing to just 48.3% within the first 3 months subsequent to making a diagnosis of PAD. Statin use was also low, though increasing from 27.6% to 36.9% following 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, examining results of recently completed surgery trials suggests otherwise. The 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.\textsuperscript{15} In this study there was an improvement of aspirin therapy from the time of admission at 67% to 88% by the time of discharge following leg bypass surgery. Similar trends were also noted for β-blockers, 49% on admission to 60% at the time of discharge while statin usage 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 utilization of cardioprotective medications were observed in African Americans and at non-university 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 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 usage 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, underutilization 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 towards 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. Ninety-one percent of the 120 specialist queried responded and identified cognitive, physician attitude, and social and organizational barriers to
guideline implementation. Some of the most notable responses were that 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 didn’t like imposed activities.¹⁹

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 gm/dl is a class I 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
mg/dl 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.²⁰,²¹ The “lower is better” hypothesis is supported by the Heart
Protection Study (HPS) where evidence was provided that allocation to statin therapy in patients
with PAD produced a 25% risk reduction irrespective of baseline cholesterol levels at entry into
the study.²² These results are relevant as 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 and 74.9 for those not on statin therapy at the time of surgery).²³ 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
(hs-CRP) 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 hs-CRP 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 datasets such as the Denmark cohort have limitations. There are no
hemodynamic data on severity of PAD as assessed by ABI or other noninvasive testing. As the
authors admit, ICD-10 codes most likely capture patients who are symptomatic, in a hospital
setting, and are therefore more likely to be treated. Admittedly little data exists to guide us on
secondary prevention in asymptomatic PAD patients but 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. There is no data available on either cholesterol levels or blood pressure in the
Danish cohort, and we therefore cannot know if the non-medicated patients are already within
current guidelines. There is also no provider data. It is well documented that disparities exists in
knowledge and action gaps in the treatment of PAD between internal medicine, vascular
surgeons, and cardiologists.

The good news is that the gap between PAD and CAD is closing but we are not there 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 more than 70% of primary care providers whose patients were
screened were unaware of the presence of PAD. As an American TV commercial for one
large pharmaceutical company says, “ask your doctor about PAD.” Because they know your
doctor is probably not going to ask you about it!
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References:


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