Cardiovascular
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A Summary of Recent International Meetings

Optimal Risk Reduction in Diffuse Vascular Disease: Focus on Peripheral Arterial Disease

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REPORTED BY: Alan D. Bell, MD, MCFP
Humber River Regional Hospital
Toronto, Ontario

Introduction

Atherothrombosis can occur in the coronary, cerebral and peripheral arterial beds. The disease that is the leading cause of death worldwide is better characterized as diffuse vascular disease, as patients with symptomatic manifestations of atherothrombosis in one vascular bed are at great risk of developing and dying from the same pathology in a different bed. Widely available strategies can significantly reduce disease burden but are currently under-utilized. A real-world registry of how patients with diffuse vascular disease are typically managed in different countries has identified gaps in treatment care as reflected by significant event rates as early as one-year follow-up. Proven treatment strategies can improve the health of this patient population. In particular, physicians need to turn their collective attention to the diagnosis and management of peripheral arterial disease, currently the least well managed of all manifestations of diffuse vascular disease, despite the fact that it carries the greatest risk of cardiovascular morbidity and mortality.

Historically, atherosclerosis was believed to be a generalized and progressive disease during which the arteries narrowed to the point where they closed off, shutting down blood flow to critical organs and triggering an acute vascular event. We now know that this is only part of the pathology behind the greatest cause of mortality worldwide. Cardiovascular (CV) events occur as a result of acute thrombus formation triggered over ruptured arterial plaque. It is the combination of plaque rupture and the formation of a thrombus within the arterial bed that leads to clinical manifestations of vascular disease, including unstable angina, myocardial infarction (MI), ischemic stroke, and worsening of peripheral vascular disease. Studies investigating culprit lesions in the coronary arteries resulting in an MI indicate that lesions most likely to rupture typically occlude less than 50% of the artery: it is not the degree of narrowing that is responsible for the acute vascular event, it is the stability of the plaque.

Thus the aim of risk-reduction strategies in patients with diffuse vascular disease is to improve plaque stability and reduce thrombosis risk.

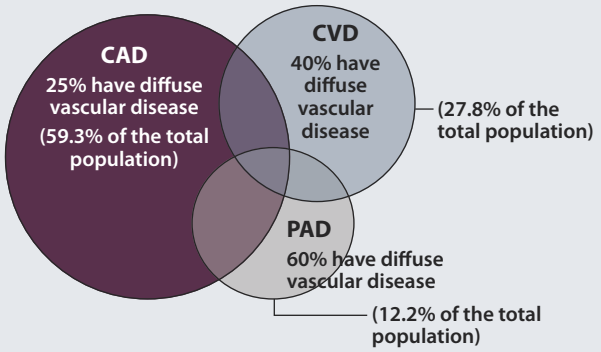
Currently, there are three distinct medical interventions that have been widely proven to achieve these goals: statins, inhibitors of the renin-aldosterone-angiotensin system (RAAS) and antiplatelet agents. As pointed out by the Canadian Cardiovascular Society (CCS) in their consensus guidelines on peripheral arterial disease (PAD) (*Can J Cardiol* 2005; 21:997-1006), strong evidence from randomized clinical trials indicates that antiplatelet therapy, ACE inhibitors and the statins reduce the risk of future vascular events by approximately one quarter each and their benefits appear to be independent and additive. It is therefore plausible to expect these medical interventions—together with lifestyle changes—could collectively reduce the risk of future vascular events by 75%, an observation that has enormous public-health repercussions if successfully implemented.

REACH Registry

The REACH (Reduction of Atherothrombosis for Continued Health) registry reveals that risk-reduction strategies are still not optimally utilized. Unlike a randomized clinical trial, a registry such as REACH tells us what real-world outcomes are in a specific patient population. REACH permits us to examine the natural history of diffuse vascular disease based on an enormous database of 68,000 patients worldwide.

To be eligible for REACH, patients had to be at least 45 years of age and have documented disease in one of the three vascular beds. Patients were also eligible for REACH if they had

Figure 1. **REACH Population Design Characteristics**



Patients with coronary artery disease (CAD)
- 59.3% of the REACH Registry population
- 25.5% of the 40,258 patients with CAD also have atherothrombotic diease in other arterial territories

Patients with cerebrovascular disease (CVD)
- 27.8% of the REACH Registry population
- 40% of the 18,843 patients with CVD also have atherothrombotic diease in other arterial territories

Patients with peripheral arterial disease (PAD)
- 12.2% of the REACH Registry population
- 60% of the 8,273 patients with PAD also have atherothrombotic diease in other arterial territories

Adapted from Bhatt et al. JAMA 2006; 295(2):180-9.

multiple CV risk factors. Approximately 80% of the REACH population had manifest disease in at least one vascular bed; the remaining 20% came into REACH on the basis of multiple risk factors alone. Sixteen percent of the symptomatic REACH registry had disease manifest in more than one vascular bed.

Coronary artery disease (CAD) was the most prominent manifestation of vascular disease in the REACH population, affecting some 59% of patients overall (Figure 1). Cerebrovascular disease affected approximately 28% of the population, while PAD affected the fewest at approximately 12%. One of the first lessons from REACH is that the distribution of CV risk factors is consistent across all disease subpopulations. In other words, it did not matter if patients had CAD, cerebrovascular disease (CVD) or PAD; known risk factors for CV disease including high blood pressure, high cholesterol levels, diabetes, obesity and smoking, were relatively evenly distributed across the three categories of disease (That said, the highest rates of hypertension were predictably among patients who had CVD, as was hypercholesterolemia among CAD patients and smoking among those with PAD). One quarter of over 40,000 patients with CAD in REACH also had atherothrombotic disease in other vascular beds, as did 40% of those with CVD and 60% of those with PAD.

At one year, 4.2% of all REACH participants had experienced a vascular event. This translates into a 42% 10-year risk, far greater than the 20% 10-year risk considered high by the Framingham risk score.

Thus, we as clinicians should reconsider how stable patients such as those in the REACH registry really are, as they are at significant risk for a vascular event even in the short term.

The high rate of manifestations in another vascular bed in the PAD population probably reflects two realities: patients with PAD are amongst our highest-risk CV patients and we tend not to recognize PAD until diffuse vascular disease has manifested in another bed. The annual rate of the triple endpoint of CV death, MI or stroke in the PAD population was 5.2%. This translates into an extraordinarily high 10-year risk of 54% of having a vascular event, well above the 20% 10-year risk Framingham categorizes as high.

Regarding only the multiple-risk-factor-population, REACH observed a 2.2% annual rate of the triple endpoint of CV death, MI or stroke. If we include hospitalization in the endpoint, the annual rate jumps to 5.3% of the same population.

Given that hospitalization for atherothrombotic events included unstable angina, a transient ischemic attack or coronary artery bypass with or without stents, REACH registry patients—and those like them who we all manage—are at very real risk for vascular events and should receive prompt aggressive therapy. For patients with disease in more than one bed, one-year CV event rates were significantly higher across all disease categories than they were for patients with disease confined to a single bed. Indeed, as patients accumulated disease in an additional bed, their risk for reaching the triple endpoint roughly doubled. PAD patients were at particularly high risk to experience a vascular event over the same one-year follow-up, rivaling those with CAD for cardiac vascular events, including unstable angina and congestive heart failure.

REACH data showed that the highest event rates occurred among those whose risk factors were the least well managed. This was most prevalent in countries of Eastern Europe.

Canadian Guidelines and PAD

REACH showed us that PAD patients are among the highest risk of all vascular patients. To mitigate this risk, the first thing we can do is diagnose PAD at a stage when risk-factor reduction will be more effective. Currently, approximately 27 million individuals in North America and Europe have PAD and of these, 16.5 million are asymptomatic. In other words, between 60% and 65% of PAD patients go undiagnosed as they do not present with symptomatic complaints until the disease is advanced.

To improve the diagnosis of PAD in symptomatic patients, the CCS recommends physicians take a directed history for symptoms of PAD. One very simple approach is to use the validated Edinburgh Questionnaire consisting of six questions which, when answered appropriately, can identify with 91.3% sensitivity and 99.3% specificity all patients with underlying PAD (Table 1).

Physicians should also carry out a directed physical exam of patients at high risk for PAD—smokers and those with diabetes being at highest risk—looking for arterial bruits or diminished peripheral pulses, both sensitive measures for PAD. Patients should also be sent for a simple and inexpensive ankle brachial index (ABI) test.

An ABI below 0.9 is diagnostic of PAD, with values below 0.4 indicative of severe disease. The lower the ABI, the lower

the survival as well, according to data presented by Diehm et al at the European Society of Cardiology last year.

Why Focus on PAD?

Patients with PAD are at very high risk for acute vascular events. In one study (*Circulation* 1996; 94:3026-49), 50% of PAD patients had fatal or non-fatal vascular events at five years. Another long-term follow-up of PAD patients by Criqui et al (*N Engl J Med* 1992; 326:381-6) showed that some 80% of patients with severe symptomatic PAD experienced fatal events by 12 years.

Given that PAD is associated with far more morbidity and mortality than is often appreciated, what can we as physicians do to reduce the risk of these hard clinical endpoints and improve the quality of life for our patients with PAD? Keeping in mind the diffuse nature of vascular disease, the same strategies used to reduce risk in CAD and CVD populations are entirely appropriate for those with PAD as well, with a special emphasis on smoking cessation.

The statins, RAAS inhibitors and antiplatelet therapy are the medical anchors of the overall strategy to reduce vascular risk and PAD patients should be taking all three classes of medication. For antiplatelet therapy, the CCS recommends either lifelong ASA therapy 75 to 325 mg/day or clopidogrel 75 mg/day.

There is considerable evidence supporting additional protective benefits of treating patients with diffuse vascular disease with clopidogrel over ASA alone to reduce the risk of thrombotic events. In the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) study, for example, there was a 22.7% relative risk reduction of ischemic stroke, MI or vascular death in patients with multi-bed disease who received clopidogrel over ASA. In CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events), clopidogrel plus ASA produced a 20% relative risk reduction in MI, stroke and CV death at the end of 12 months vs. ASA alone in acute coronary syndrome patients, a highly statistically significant result ($p = 0.00009$).

Although the risk of bleeding with ASA, at any given dose, plus clopidogrel is greater than with ASA alone, the actual bleeding risk is more dependent on the dose of ASA. Specifically, with regard to bleeding in the CURE trial, clopidogrel plus ASA 100 mg was safer than ASA alone at 200 to 325 mg (2.6% vs. 4% major bleeding rates).

In contrast, it is not recommended to give asymptomatic multiple-risk-factor patients dual antiplatelet therapy, as results from CHARISMA (Cardiac Arrhythmia and Risk Stratification after Myocardial Infarction) demonstrated. Patients in CHARISMA were similar to those included in the REACH registry—they had either manifest disease or multiple risk factors—all of whom received either ASA alone or ASA plus clopidogrel. Among those patients who had sustained a prior atherothrombotic event, CHARISMA showed a significant protective benefit from long-term dual antiplatelet therapy at a median follow-up of 27 months. In contrast, not only did multiple-risk-factor patients not benefit from the same dual antiplatelet strategy, but asymptomatic patients on the dual regimen had more MIs and strokes than those on ASA alone.

Table 1. Edinburgh Questionnaire

- Do you feel pain or discomfort in your leg(s) when you walk? (Yes)
- Does this pain ever begin when you are standing still or sitting? (No)
- Do you get it when you walk uphill or hurry? (Yes)
- Do you get it when you walk at an ordinary pace on level ground? (Yes)
- What happens to it when you stand still? (Pain usually disappears in 10 minutes or less)
- Where do you feel this pain or discomfort? (Calf and/or thigh and/or buttock)

Non-pharmacologic Intervention

Medical therapy may be the cornerstone of risk-reduction management but it must be accompanied by non-pharmacologic interventions. These include dietary therapy to optimize plasma lipids, regular exercise and smoking cessation. A supervised exercise program has been demonstrated to improve claudication symptoms in patients with PAD. Patients need to be encouraged to walk with moderate intensity to the point of discomfort and beyond, rest, and then resume walking. Such an approach can be expected to provide tangible clinical benefits in as little as four weeks, reinforcing patient motivation to continue with the regimen.

Smoking cessation is more likely to be successful if associated with physician counseling and the use of pharmacologic agents, including nicotine replacement, or bupropion or varenicline. Dietary therapy can be assisted by registered dietitians with a focus on weight reduction and improved glycemic control in those with diabetes.

Summary

REACH tells us that too many of our patients with diffuse vascular disease experience an acute event within a relatively short period of follow-up. These observations argue for more aggressive risk-reduction strategies in patients with CAD, CVD and PAD, as they are at risk for an event, not only in the index vascular bed but in others as well. More widespread use of proven pharmacologic and non-pharmacologic interventions would significantly reduce the rates of acute vascular events. As primary-care physicians, we have an obligation to implement these strategies in all patients with diffuse vascular disease, regardless of where the disease is manifest.

Adapted with permission from: Bell AD. "Optimal risk reduction in diffuse vascular disease: focus on peripheral arterial disease." Medical Education Network Inc. Based on presentations from the Primary Care Today Educational Conference and Medical Exposition, Toronto, Ontario, May 8-10, 2008.