Asking about Atherosclerosis

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Atherosclerotic vascular disease remains the leading cause of death and disability in North America. At least 40% of Canadians will die from myocardial infarction, stroke or peripheral vascular disease. More worrisome is that, for as many as half of these individuals, a sudden cardiac death will be the first manifestation.

Atherosclerosis is a disease of the vessel wall characterized by endothelial dysfunction, lipid deposition and inflammation.[1] In susceptible individuals, the process begins in the teen years and progresses over a period of decades. Recent research has highlighted the important interaction of cholesterol and inflammation in this process.

How is vascular risk assessed?

While the diagnosis is self-evident in patients who present with angina pectoris, claudication or transient ischemic attacks, a vast majority of subjects are asymptomatic. Major cardiovascular risk factors are well known and have been incorporated into risk algorithms that are readily used at the bedside.

The Framingham Risk Score is the most widely used tool in North America and has been advocated by the Canadian Working Group on Hypercholesterolemia.[2] A score is generated from factors, including age, gender, total (or low-density lipoprotein) and high-density lipoprotein cholesterol, cigarette smoking and blood pressure. Target lipid values are then suggested based on the overall Framingham Risk Score.

Blood pressure targets are available from the Canadian Hypertension Society (**www.chs.md**). However, recent

Steve's Case

Steve, 45, has no history of vascular disease. He has had "borderline" hypertension for the past few years. He is now asking questions about his cardiovascular risk, as his neighbour has just suffered a myocardial infarction.

He is currently asymptomatic with a normal physical exam:

- Blood pressure: 145/88 mmHg
- Body mass index: 29
- Waist circumference: 95 cm
- Total cholesterol: 5.7 mmol/L
- High-density lipoprotein (HDL): 1.0 mmol/L
- Triglycerides (TG): 1.7 mmol/L
- Low-density lipoprotein (LDL): 3.9 mmol/L
- Fasting glucose: 5.6 mmol/L
- Non-smoker

Is Steve at risk?

Case discussion...

Steve's Framingham Risk Score gives him a 10-year risk of hard cardiovascular events of 8% (low risk < 10%). Based on this, his LDL goal is < 4.5 mmol/L and TG/HDL ratio is less than than six. He meets both of these criteria. His blood pressure should be repeated on several occasions and if exercise and weight loss fail to lower it to > 140/90 mmHg over the next few months, pharmacotherapy could be considered.

If his C-reactive protein was found to be 4.2 mg/L (high risk), then his risk might be estimated at about double his Framingham estimate. Steve would now be in the moderate risk category and the Canadian guidelines would recommend a goal LDL < 3.5 mmol/L.

Therapy with a statin might be undertaken if diet and exercise fail to achieve these goals.

insights into our understanding of the pathophysiology of the atherosclerotic process provide optimism that new markers might be helpful in risk stratification.

What new biomarkers are on the horizon?

Biomarkers are measurable biochemical, genetic, structural or physiologic parameters that represent some aspect of the atherosclerotic process. While hundreds of potential markers have been studied, only very few show promise for future clinical use.[3]

To be useful, the biomarker should add independent information to easily obtainable, clinical parameters, such as blood pressure, measures of obesity, lipids and glucose. Subclinical atherosclerosis can be detected by measuring the intima medial thickness in the carotid artery with high-resolution ultrasound.

Similarly, calcification in the coronary arteries is measured with electron-beam computed tomography. Both show some promise, but suffer from availability, expense and comprehensive data. Inflammatory markers, particularly high-sensitivity C-reactive protein (CRP), have gained recent prominence (Table 1).

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Should I be ordering CRP in my patients?

CRP is an inflammatory marker that actively participates in the atherosclerotic process and is an independent predictor of cardiovascular outcomes in a variety of patient populations.[4,5] Based on recent data, the Centres for Disease Control and Prevention and The American Heart Association have suggested that CRP could be measured in individuals deemed to be at moderate risk to help in risk stratification.[6]

CRP has most of the attributes of a potentially useful biomarker, including the fact that it is reasonably inexpensive. One major drawback is the day-to-day variability in CRP levels as it is very sensitive to inflammation of any kind, including infections, injury, medications and other factors.

While widespread use is not clearly advocated until results are available from ongoing trials, certain points should be kept in mind if one is going to order the test:

- Patient should be at medium risk for vascular events, in whom the test result may be used to decide about the need for more aggressive pharmacotherapy. In subjects at high risk, aggressive risk reduction is indicated regardless of the CRP value.
- Ensure that your lab is measuring the high-sensitivity assay.
- Low risk is < 1 mg/L, medium risk is 1 mg/L to 3 mg/L and higher risk is > 3 mg/L.
- If the value is > 10 mg/L, suspect an inflammatory process and repeat in two to four weeks.
- It should not be used to guide pharmacotherapy with statins.
- It should be used in conjunction with the Framingham Risk Score.
- Since a high-risk CRP is associated with an approximate doubling of risk, one approach is to double the Framingham Risk Score and to treat targets based on the new post-CRP risk estimate. This approach needs to be confirmed with studies.

Recently, it has been suggested that an important component of the beneficial effect of statins is related to their CRP-lowering effect and targets for future subjects with established coronary disease might include both cholesterol and CRP goals.[7]

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Table 1

New markers of atherosclerotic vascular disease

- High-sensitivity CRP: Carotid intima media thickness
- Apolipoproteins: Ankle-brachial index
- Lipoprotein: Electron beam computed tomography
- Adipokines (leptin, adiponectin): Endothelium-dependent vasodilation
- Markers of metabolic syndrome: Measures of arterial compliance
- Measures of oxidative stress inflammation: Intravascular ultrasound

CRP: C-reactive protein

References
1. Libby P, Ridker PM, Maseri A: Inflammation and Atherosclerosis. Circulation 2002; 105(9):1135-43.
2. Genest JJ Jr., Frohlich J, Fodor G, et al: Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: Summary of the 2003 update. CMAJ 2000; 162(10):1441-7.
3. Ridker PM, Brown NJ, Vaughan DE, et al: Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. Circulation 2004; 109(25 Suppl 1):IV6-19.
4. Verma S, Wang CH, Li SH, et al: A Self-Fulfilling Prophecy: C-Reactive Protein Attenuates Nitric Oxide Production and Inhibits Angiogenesis. Circulation 2002; 106(8):913-9.
5. Ridker PM: Clinical Application of C-Reactive Protein for Cardiovascular Disease Detection and Prevention. Circulation 2003; 107(3):363-9.
6. Pearson TA, Mensah GA, Alexander RW, et al: Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice: A Statement for Healthcare Professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003; 107(3):499-511.
7. Ridker PM, Cannon CP, Morrow D, et al: C-Reactive Protein Levels and Outcomes after Statin Therapy. New Engl J Med 2005; 352(1):20-8.