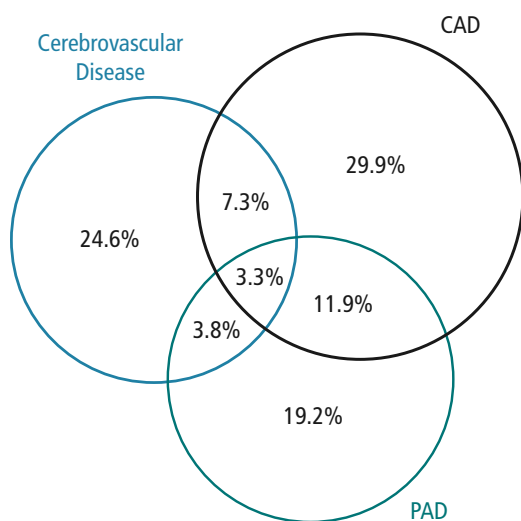


Atherosclerosis, Inflammation and Clinical Events

By Subodh Verma, MD, PhD, FAHA

Clinicians and medical scientists alike have long understood that atherosclerosis is a major contributor to negative clinical outcomes. That being said, however, our understanding of the process and its effects has evolved significantly over the past decade. Since our earlier assertion that atherosclerosis was simply a “lipid-storage disease,” research has shown us that there are a number of factors at play that influence the progression of atherosclerosis and increase risk for cardiovascular (CV) events. Among these processes, inflammation plays a central role.

Figure 1 Overlap of Atherosclerotic Disease (CAPRIE study)



Adapted from: CAPRIE Steering Committee. Lancet 1996; 348:1329-39.

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This review examines the prevalence of atherosclerotic disease in Canada, discusses the concept of atherosclerosis as a whole-body disease (regardless of the presenting vascular bed) and explores the processes involved in atherogenesis and atherosclerotic progression (with a focus on inflammation). It also discusses means by which clinicians can track atherosclerotic changes and details the treatment modalities that can intervene in these processes.

Atherosclerosis: A Systemic Problem

While the nomenclature of atherosclerotic conditions has always focused on the particular vascular bed in which symptoms are noted (*i.e.*, coronary artery disease [CAD], cerebrovascular disease, peripheral arterial disease [PAD]), atherosclerosis should be considered in the context of the entire patient. Those with atherosclerotic disease in one vascular bed are likely to have similar findings throughout the body.

Statistics from population studies and large, randomized clinical trials have supported the observation that atherosclerosis is a systemic condition. The Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study included patients with symptomatic atherosclerotic disease with a diagnosis of CAD, cerebrovascular disease or PAD.¹

While patients were placed into subgroups based on the diagnosis that made them eligible for entry into the study, the investigators found that there was significant overlap of atherosclerotic disease into the other categories (Figure 1). Other studies have reported even higher incidence of overlap; a 1994 study by Aronow et al² showed that 32% of patients with CAD also had cerebrovascular disease, while 33% had PAD. In patients with cerebrovascular disease, CAD was present in 53% and PAD was present in 33%. Finally, in patients with PAD, 58% also had CAD and 34% also had cerebrovascular disease.

In terms of risk, patients with one manifestation of atherosclerosis are known to be at increased risk not only for events in that vascular bed, but also for

events in other areas. A patient with PAD, for example, is 6.6 times more likely to die from CAD than are normal controls.³ These statistics clearly illustrate the concept of atherosclerosis as a whole-body disease. Interventions that target the atherosclerotic process therefore should be effective at reducing risk for major cardiovascular events in all vascular beds.

Impact of Atherosclerosis in Canada

While no statistics are available counting the total number of Canadians with “atherosclerosis” *per se*, recent data from the Canadian Community Health Survey show that 5.4% of men and 4.6% of women reported having “heart disease” as diagnosed by a medical professional.⁴ The burden of disease increases as people age. The Heart and Stroke Foundation of Canada reports that, by the age of 70 years, one in five women and one in four men will have been told by a physician that they have heart problems.⁵ Overall, it is estimated that one in four Canadians (almost eight million people) has some form of heart disease or disease of the blood vessels, or is at risk for stroke.⁶

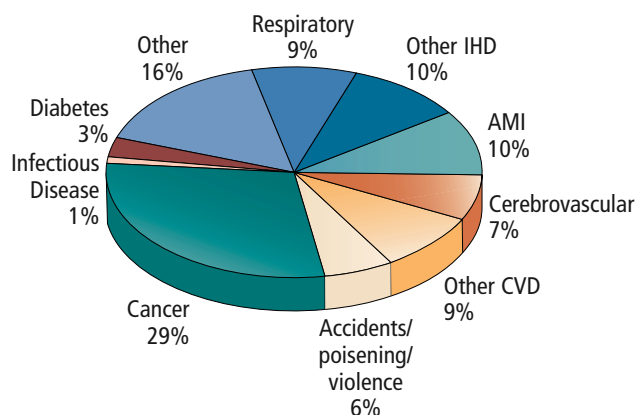
Population statistics also show the impact of atherosclerotic disease on mortality in Canada. These data show that 36% of all deaths in Canada are due to CV diseases, the majority of which are atherosclerotic in nature (Figure 2).⁵

Processes of Atherogenesis: The Role of Inflammation

The link between inflammation and atherosclerosis has been explored in detail in recent reviews.⁷⁻⁹ This review described how, even in the earliest stages of the atherosclerotic process, the endothelium becomes more likely to attract leukocytes, which are mediators of host defenses and inflammation.⁷⁻⁹ The mechanism by which the endothelium attracts leukocytes involves the expression of various adhesion molecules. One of the most important of these is vascular-cell adhesion molecule-1 (VCAM-1), which has been found to bind with the types of leukocytes found in early-stage atheromas.⁷⁻⁹

The multifactorial process that leads to expression of such factors as VCAM-1 is thought to include a decrease in the level of nitric oxide (NO), a potent vasodilator and anti-inflammatory compound (which can inhibit the expression of VCAM-1), released by the endothelium.⁷ This decrease in NO

Figure 2 Cardiovascular Diseases are the Leading Cause of Death in Canada

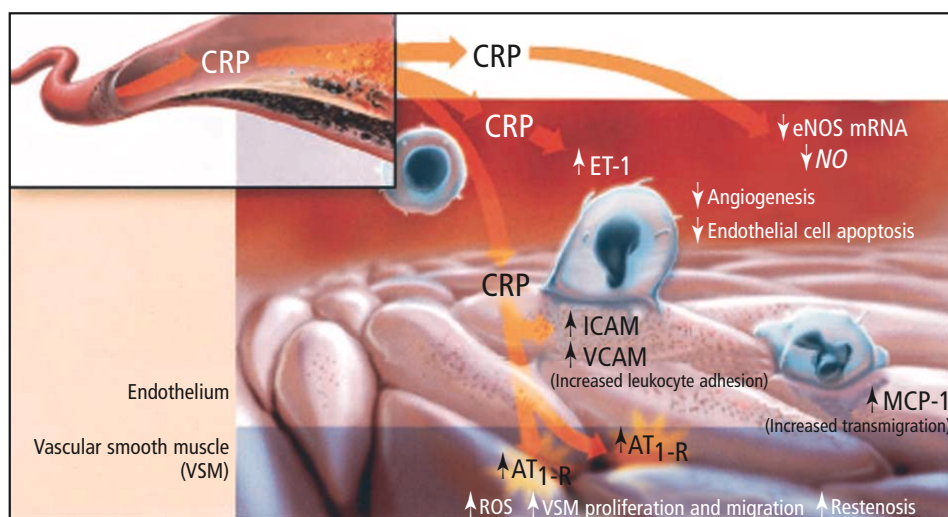


Adapted from: Heart and Stroke Foundation, 2003.

production can occur as a result of shear stress. Other proinflammatory and proatherogenic changes that may occur in this scenario include an upregulation of intercellular adhesion molecule-1 (ICAM-1) and an increase in the production of proteoglycans. C-reactive protein (CRP) is now considered to be an active partaker in the process of atherogenesis, with evidence suggesting that it directly quenches endothelial nitric oxide production,^{10,11} while promoting the production of the potent vasoconstrictor endothelin-1¹² and adhesion molecules like ICAM-1 and VCAM-1.^{12,13} Recent evidence also suggests that CRP may promote restenosis and neointimal formation, in part, by increasing angiotensin-induced reactive oxygen species production.¹⁴ The direct proatherogenic effects of CRP are depicted in Figure 3.¹⁵ These latter factors, produced by vascular smooth muscle cells (SMCs), bind with lipoprotein particles, facilitating their retention in the vessel wall and stimulating oxidation and inflammation. The inflammatory process within the vessel wall leads to the formation of macrophage foam cells and growth factors, which are key elements of lesion progression.

As well as playing a role in the formation and progression of atheromas, inflammation also can help precipitate events through the destabilization and rupture of plaques. The activated macrophages degrade collagen to weaken the outer cap of the plaque, and stimulate the production of tissue factor (the major procoagulant in thrombosis).

Figure 3 CRP: A Circulating Biomarker of Endothelial Dysfunction



ET-1 = endothelin-1
 AT₁-R = angiotensin type 1 receptor
 ROS = reactive oxygen species
 MCP = monocyte chemoattractant protein

Adapted from: Verma S, et al. *Circulation* 2003; 108(17):2054-9.

Table 1 Novel Markers of Inflammation in Cardiovascular Disease

- High-sensitivity C-reactive protein (hs-CRP)
- Interleukin-6 (IL-6)
- Intercellular adhesion molecule-1 (ICAM-1)
- Tumor necrosis factor alpha (TNF- α)
- IL-18
- PAI-1 (plasminogen-activator inhibitor-1)
- Lipoprotein(a)
- Lipoprotein-phospholipase A2 (Lp-PLA2)
- Endothelial progenitor cells

While the nomenclature of atherosclerotic conditions has always focused on the particular vascular bed in which symptoms are noted (i.e., coronary artery disease, cerebrovascular disease, peripheral arterial disease), atherosclerosis should be considered in the context of the entire patient. Those with atherosclerosis in one vascular bed are likely to have similar findings throughout the body.

Markers of Inflammation in Atherosclerosis

With our growing understanding of the important role of inflammation in the nascent stages of atherosclerosis, in disease progression and in precipitating events, finding and monitoring inflammatory changes has become an important part of comprehensive management strategies.

Recent research has identified several possible markers that clinicians can use to identify and track inflammation, including CRP, interleukin-6 (IL-6), tissue factor, ICAM, and tumor necrosis factor alpha (TNF- α) (Table 1).¹⁶⁻²⁰ High-sensitivity CRP (hs-CRP) has been found to be a significant, independent predictor of cardiovascular events¹⁷ and

death from coronary artery disease.¹⁶ In fact, one report found that hs-CRP was a better independent marker of deleterious CV complications than low-density lipoprotein cholesterol (LDL-C).¹⁷ Significantly, both hs-CRP and the adhesion molecule, s-ICAM-1, also have been shown to be independent predictors of CV risk, even in patients at low risk of CV events.¹⁸

TNF- α also has been correlated with CAD and heart failure.¹⁹ All of these findings give clinicians a series of powerful tools with which to gauge CV risk, and provide meaningful markers to target and monitor when plotting and maintaining an intervention strategy.

The proinflammatory cytokine IL-6 and tissue factor also have demonstrated prognostic value in CV medicine. A recent study showed that IL-6 and tissue factor levels are correlated with adverse outcomes in patients with heart failure.²⁰

The American Heart Association (AHA) and Centers for Disease Control (CDC) have recently issued a Class IIa recommendation for the routine assessment of CRP in the moderate risk patient.²¹ Indeed, the greatest value of a biomarker is in patients deemed to be at a 10% to 20% 10-year risk, as per the Framingham Risk Assessment. Indeed, in these patients, an elevated CRP (>3 mg/L) may suggest a doubling or the 10-year Framingham risk. Despite the mountain of evidence suggesting that CRP predicts diverse vascular insults, what remains to be determined is whether CRP-lowering therapies are associated with a reduction in hard endpoints. However, what remains fascinating is that CRP is an independent predictor of vascular events, with a predictive value exceeding that of LDL-C, and that there exists a poor correlation between CRP and LDL-C. Said differently, elevated LDL-C provides no index as to whether someone's CRP is elevated and vice versa. As shown in Figure 4, otherwise healthy individuals with high CRP levels, yet low LDL-C levels, are at greater risk than people with low CRP and high LDL-C levels.

Canadian recommendations also recognize the prognostic importance of hs-CRP beyond traditional risk-stratification techniques (*i.e.*, Framingham risk score).²² Use of hs-CRP screening will help identify patients at increased risk who might normally “slip through the cracks” with routine screening of lipids.²²

Management of Inflammation in Atherosclerotic Disease

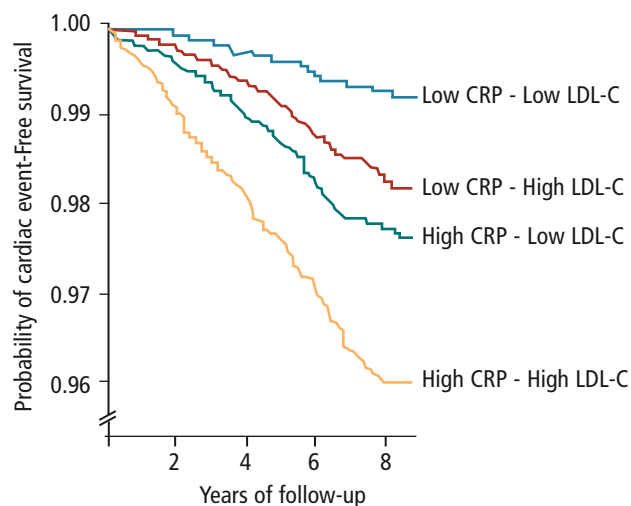
Once it is established that a patient is at risk due to vascular inflammation, whether it be through measurement of such novel markers as hs-CRP or through more traditional lipid analysis, ample data exists to guide evidence-based interventions. Angiotensin-converting enzyme (ACE) inhibitors,²³ ASA²⁴ and thiazolidinediones²⁵ all have shown an ability to reduce inflammatory markers in various populations. The reduction associated with the use of aspirin in the risk of a first myocardial infarction appears to be directly related to the level of CRP.²⁴

The most compelling body of evidence, however, shows the efficacy of the statin class of lipid-lowering

Figure 4 CRP and LDL-C Define Distinct Risk Groups

Event-free survival according to baseline CRP and LDL-C

n = 28,000



Adapted from: Ridker PM, et al. *N Engl J Med* 2002; 347(20):1557-65.

agents in reducing inflammatory mediators and markers independently of their lipid-lowering activity.

In the Cholesterol and Recurrent Events (CARE) study, for example, the effects of pravastatin were analyzed based on quartile of hs-CRP level.²⁶ The investigators found that the association between inflammation and CAD risk was attenuated in patients treated with the statin, and that this was independent of the drug's lipid-lowering effects.^{26,27} It is therefore postulated that the effect of these agents in improving survival and reducing major events is mediated, at least in part, by the reduction of inflammation.

The effects of pravastatin on CRP also were studied in a prospective, randomized trial involving 1,702 subjects with no known cardiovascular disease.²⁸ Over the trial's 24-week period, pravastatin was shown to lower CRP levels by 16.9%.²⁸ This finding is similar to the 14.8% lowering of CRP found with lovastatin in the AFCAPS/TexCAPS study.²⁹

Recent findings have shown that agents which have already been proven to have more profound impact on LDL-C-lowering also are associated with more significant reductions in CRP. The Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study randomized 654 patients with symptomatic CAD, a 20% or greater stenosis by angiography, and

Background Literature Review

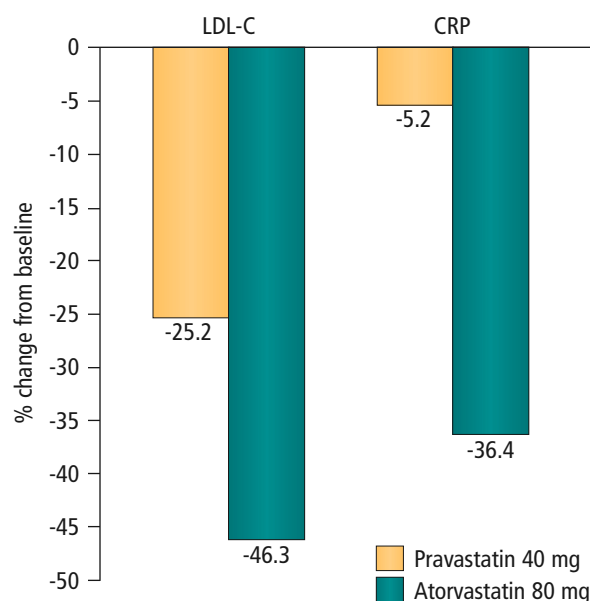
LDL-C levels between 3.2 mmol/L and 5.3 mmol/L to either pravastatin 40 mg or atorvastatin 80 mg.³⁰ The investigators found that atorvastatin was significantly more effective in the primary endpoint of change in atheroma volume (with a reduction of 0.4%, compared to an increase of 2.7% in the pravastatin group) as measured by intravascular ultrasound. In secondary analyses (Figure 5), the investigators also found that atorvastatin, compared to pravastatin, more significantly lowered LDL-C (46.3% compared to 25.2%) and CRP (36.4% vs. 5.2%).

The findings from the REVERSAL study are highly significant in terms of the effect of statin therapy on the course of atherosclerotic disease. While pravastatin 40 mg showed progression of atherosclerosis, atorvastatin 80 mg was able to halt the growth of atheromatous lesions with its more profound impact on LDL-C and CRP. The study investigators hypothesized that the highly significant differences in the primary endpoint were mediated in large part by the different effects of the two regimens on inflammation, as measured by CRP.³⁰ In REVERSAL, the subgroups of lipids and CRP levels above and below the mean showed highly consistent results, with no progression in the atorvastatin arm and significant progression in the pravastatin arm. Strikingly, even patients whose baseline LDL-C was below the mean showed progression in the pravastatin arm. Thus, although some patients reached low LDL-C levels with pravastatin treatment, progression was not avoided. When a restricted analysis was performed to evaluate pravastatin-treated patients who reached LDL-C levels below 100 mg/dL, it was apparent that, despite attaining a low LDL-C level on pravastatin, these patients showed highly significant progression in atheroma volume when compared to atorvastatin. These results suggest that it is not only important to reach target, but the statin you choose to reach target may influence atherosclerotic burden.³⁰

Atorvastatin also has been evaluated with respect to inflammatory markers in higher-risk populations of patients. In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, for example, the investigators compared the effects of atorvastatin 80 mg vs. placebo on CRP, serum amyloid A (SAA) and IL-6 in 2,402 patients with unstable angina or non-Q-wave myocardial infarction.³¹ The patients were treated for 16 weeks.

Because these patients were recovering from an acute coronary event, the baseline markers were highly elevated. Nonetheless, patients in the atorvastatin group had more significant reductions in CRP

Figure 5 Changes in LDL-C and CRP: Pravastatin 40 mg vs. Atorvastatin 80 mg



Adapted from: Nissen S, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA*. 2004;291(9):1071-80.

and SAA over the study period. At 16 weeks, CRP was 34% lower with atorvastatin than with placebo, which highlights the importance of early statin treatment in patients who experience acute coronary events.

While the findings with statins have been compelling in terms of reduction of inflammation, a great deal of research is ongoing or remains to be done. Database analyses are underway with the Heart Protection Study (HPS) and Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) cohorts to determine the effects of simvastatin and atorvastatin, respectively, on inflammation in those studies.


Conclusion

Atherosclerosis is a systemic disease, simultaneously affecting any number of vascular beds throughout the body. It can manifest in CAD, cerebrovascular disease or PAD, or in any combination of these conditions.

Atherosclerosis plays a key role in the development of CV disease and in the occurrence of CV events. While it has historically been characterized as essentially a lipid-storage disease, our evolving understanding now highlights the importance of inflammation

throughout the disease process. Inflammatory activities are involved in the genesis, progression and consequences (*i.e.*, events) of atherosclerosis.

Research has shown the importance of several inflammatory markers, including hs-CRP, which allow clinicians to identify patients at higher risk of events and direct treatment accordingly. A number of

interventions have demonstrated an ability to reduce these markers of inflammation; the most compelling evidence to date involves statin therapy. The accumulated evidence shows that, by aggressively using these risk-reduction therapies, clinicians can reduce the burden of inflammation and, potentially, halt the atherosclerotic process altogether. 

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