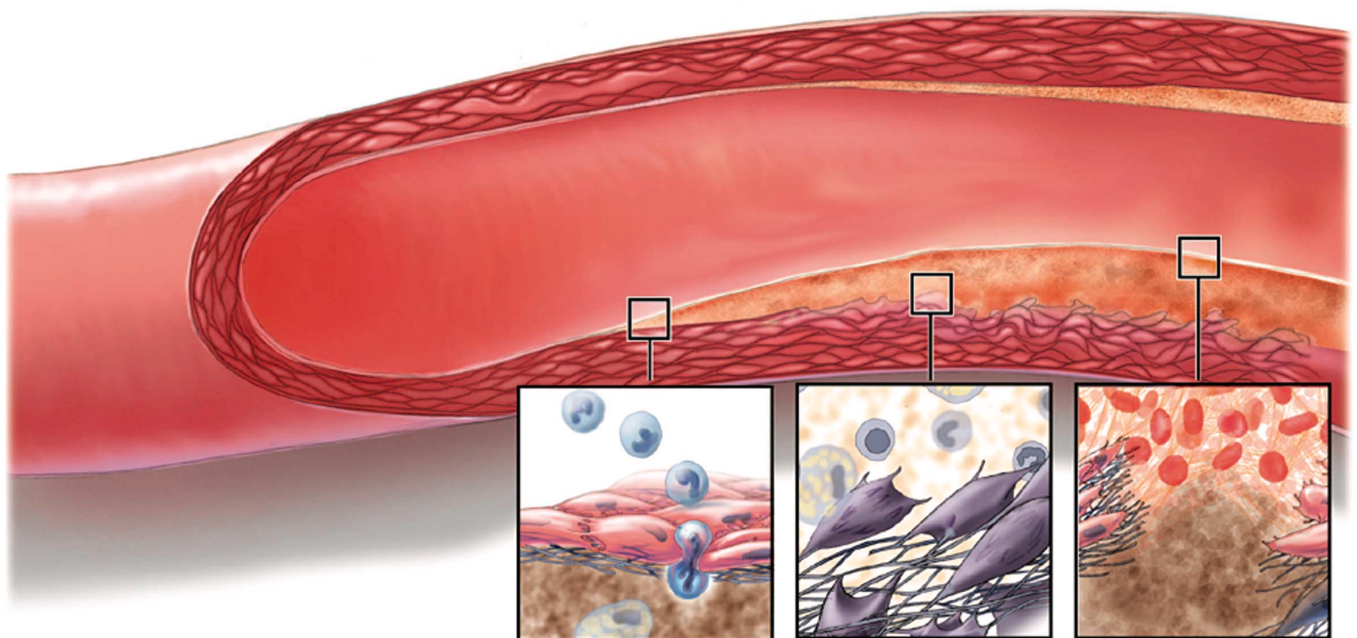


Atherosclerosis

April 2004

in Primary Care

Inflammation and Atherosclerosis



Neutrophil Adhesion

Endothelial Activation
and Cytokine Production

Atherosclerosis
Progression

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The Final Common Pathway Leading to Atherosclerosis



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Every day, we see in our offices patients who have hypertension, diabetes, obesity and dyslipidemia. We watch as these conditions, alone or in combination, alter the lives of our patients, reducing their quality of life, longevity and earning potential. Hospitalized for the sequelae of atherosclerosis (e.g., stroke, MI, etc.) we deal with the psychosocial impact this inflammatory condition has on the families we see. In an attempt to prevent these complications, we utilize biomarkers such as total cholesterol and LDL-C not only to define our high-risk population to initiate treatment, but as a therapeutic target for future risk reduction and as a goal for ongoing treatment titration. However, our biomarkers have been crude, occasionally missing patients. Framingham's 26-year follow-up defined that 50% of coronary heart disease occurred in people with below-average total cholesterol. As outlined in this issue's first article, research has defined additional biomarkers to prevent these patients from slipping through the cracks.

In a recent needs analysis, family physicians have ranked biomarkers, such as hs-CRP and the concept of endothelial dysfunction, as one of the top areas of interest.

C-reactive protein structurally looks like a five-sided martial arts throwing star. As this analogy has a sinister nature, so does this protein. Being not only a biomarker, CRP is a now thought to be a modifiable risk factor. Where LDL-C is able to define the calcified old lesions, hs-CRP is able to identify the new acutely high-risk plaques. Originally thought to be made by the liver, CRP has recently been shown to be made by adipose tissue. In the average patient, 30% of CRP is thought to be made by fat cells, but this amount increases as the patient becomes more obese. This finding can be seen early in the pediatric age group, where obese 10.5-year-old children were found to have increased CRP.

Dr. Roussin has stated that patients with inflammatory arthritis, such as rheumatoid arthritis, who are known to have very high CRPs have a 3.5-fold increase in risk of cardiovascular events.

Diabetics have elevated CRP. Poor glycemic control increases CRP and, in conjunction with elevated CRP, increases the rate of apoptosis (programmed cell death) in endothelial cells.

CRP has been shown to mediate its effect like angiotensin by working through the AT1 receptor. By mediating the negative effects on the smooth muscle

cells of the vessel wall and on macrophages, CRP is able to drive the atherosclerotic process. Hyperlipidemia has been shown by Nickenig to increase the number of AT1 receptors, potentially allowing CRP to have more sites to act. This upregulation of the AT1 receptor, he showed in his 1999 *Circulation* article, could be down-regulated with the use of a statin.

As outlined in the first article in this issue, several therapeutic agents are able to modulate vascular inflammation. Nitric-oxide production is increased (improved) with ACE inhibitors, CCBs, statins and several other medications. HMG CoA-reductase inhibitors have effects that go beyond LDL-C lowering. These pleiotropic effects are thought to result in acute and long-term benefits on vascular function through the reduction of vascular inflammation. Numerous studies with statins have shown CRP reduction (e.g., with atorvastatin by 14% to 47%, simvastatin by 11.8% to 28.7%, simvastatin and ezetimibe by 27% to 40%, pravastatin by 13% to 20%, lovastatin by 15%, fluvastatin by 0%, rosuvastatin by 34% to 39.8%). Though primary mortality endpoints for hs-CRP are not yet available, surrogate markers, such as the halting of atherogenic progression, have been shown in the REVERSAL study.

Currently, with the results of the Physicians and Women's Health Studies, the best biomarker as a predictor of risk is thought to be a sum of hs-CRP and non-HDL cholesterol. Though this may become the new guideline in the future, it is not yet ready for prime-time, as outlined in the article by Dr. Greenberg.

For years, we have focused on small areas of occlusion as being the main culprit lesion, losing sight of the fact that, in a relative value system, this represents a small area of 0.0002 square meters of a total human body vascular bed equal to 1,000 square metres. This diffuse vascular inflammation that we call atherosclerosis requires systemic medical management that we employ every day in our office. By using ASA, ACE inhibitors, CCBs, statins, lifestyle modification, etc., we alter not only surrogate markers, but primary endpoints such as death. This issue attempts to give understanding to the process and is not intended as a promotion for using new and evolving biomarkers on a regular basis. By putting the pathophysiologic and pharmacologic pieces together, we hope to give you an understanding of how the interventions we use on a daily basis evoke their benefit through modulation of the final common pathway referred to as vascular inflammation. ♡

Yours,

A handwritten signature in black ink, appearing to read 'Peter Wozniak', written over a horizontal line.

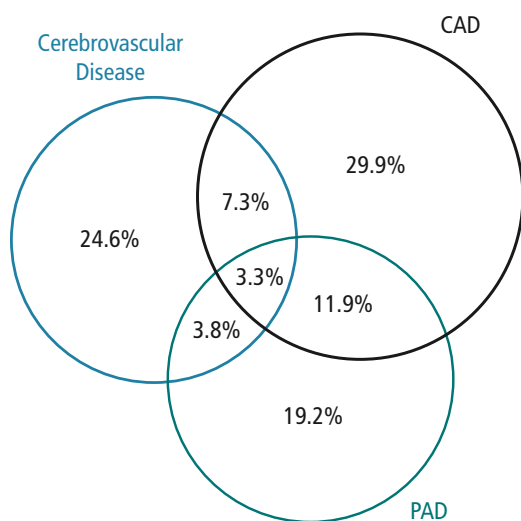
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Atherosclerosis, Inflammation and Clinical Events

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.

Subodh Verma, MD, PhD, FAHA

Dr. Verma is a scientist in the Division of Cardiac Surgery, University of Toronto and a clinical lecturer in the Department of Pharmacology and Therapeutics, University of Calgary. Dr. Verma is an international expert in the areas of inflammation, CRP and atherosclerosis, with active research programs in Toronto and Calgary.

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

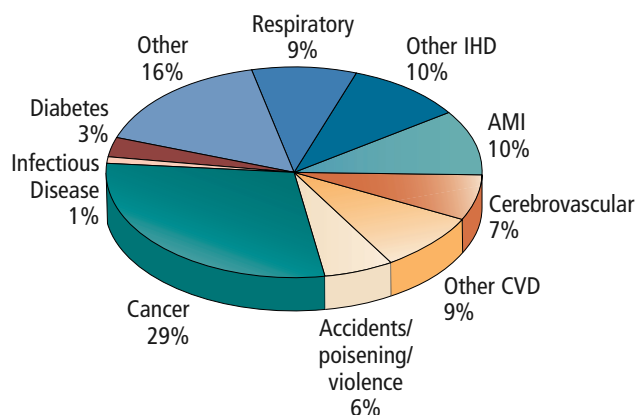
Population statistics also show the impact of atherosclerotic disease on mortality in Canada. These data show that 36% of all deaths in Canada are due to CV diseases, the majority of which are atherosclerotic in nature (Figure 2).⁵

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

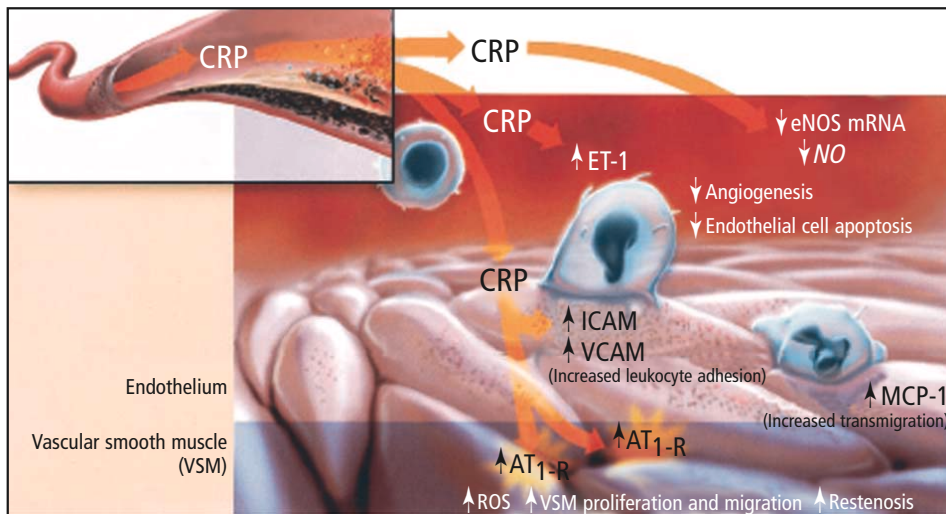


Adapted from: Heart and Stroke Foundation, 2003.

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
 AT_{1-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

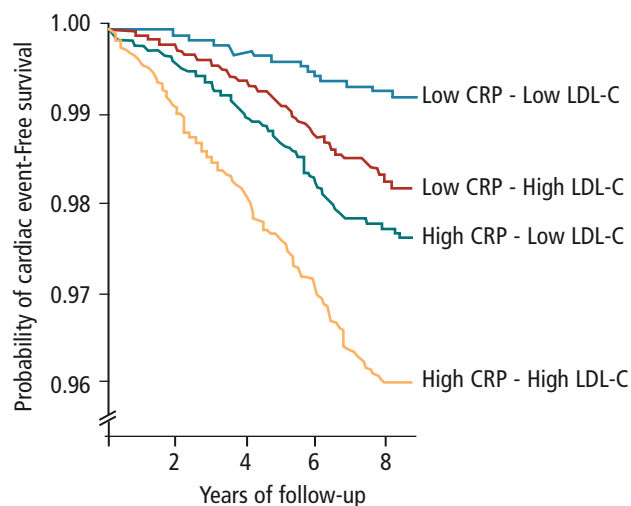
Once it is established that a patient is at risk due to vascular inflammation, whether it be through measurement of such novel markers as hs-CRP or through more traditional lipid analysis, ample data exists to guide evidence-based interventions. Angiotensin-converting enzyme (ACE) inhibitors,²³ ASA²⁴ 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

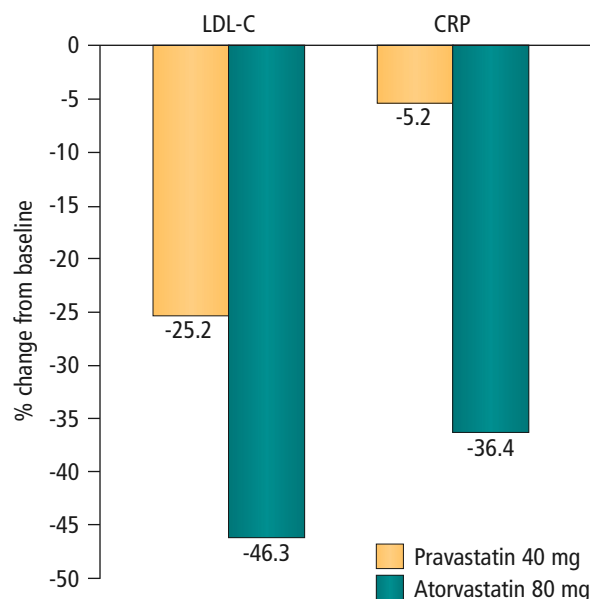
LDL-C levels between 3.2 mmol/L and 5.3 mmol/L to either pravastatin 40 mg or atorvastatin 80 mg.³⁰ The investigators found that atorvastatin was significantly more effective in the primary endpoint of change in atheroma volume (with a reduction of 0.4%, compared to an increase of 2.7% in the pravastatin 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. 

References:

1. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; 348(9038):1329-39.
2. Aronow WS, Ahn C. Prevalence of coexistence of coronary artery disease, peripheral arterial disease, and atherothrombotic brain infarction in men and women >62 years of age. *Am J Cardiol* 1994; 74:64-5.
3. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992; 326(6):381-6.
4. Manuel DG, Leung M, Nguyen K, et al. Burden of cardiovascular disease in Canada. *Can J Cardiol* 2003; 9(9):997-1004.
5. Heart and Stroke Foundation of Canada. The Growing Burden of Heart Disease and Stroke in Canada 2003. Ottawa, Canada, 2003.
6. Heart and Stroke Foundation of Canada. Statistics & Background Information—Incidence of Cardiovascular Disease. Available at: www.heartandstroke.ca. Accessed December 2003.
7. Libby P, Ridker PM, Maseri A. Inflammation and Atherosclerosis. *Circulation* 2002; 105:1135-43.
8. Szmítko PE, Wang CH, Weisel RD, et al. Biomarkers of vascular disease linking inflammation to endothelial activation: Part II. *Circulation* 2003; 108(17):2041-8.
9. Szmítko PE, Wang CH, Weisel RD, et al. New markers of inflammation and endothelial cell activation: Part 1. *Circulation* 2003; 108(16):1917-23.
10. 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: 913-9.
11. Verma S, Yeh, ET. C-reactive protein and atherothrombosis. Beyond a biomarker: an actual partaker of lesion formation. *Am J Physiol Regul Integr Comp Physiol* 2003; 285:R1253-6.
12. Verma S, Li SH, Badiwala MV, et al. Endothelin antagonism and interleukin-6 inhibition attenuate the proatherogenic effects of C-reactive protein. *Circulation* 2002; 105:1890-6.
13. Rosenson RS, Koenig W. High-sensitivity C-reactive protein and cardiovascular risk in patients with coronary heart disease. *Curr Opin Cardiol* 2002; 17(4):325.
14. Wang CH, Li SH, Weisel RD, et al. C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle. *Circulation* 2003; 107:1783-90.
15. Verma S, Buchanan MR, Anderson TJ. Endothelial function testing as a biomarker of vascular disease. *Circulation* 2003; 108(17):2054-9.
16. Bickel C, Rupprecht HJ, Blankenberg S, et al. Relation of markers of inflammation (C-reactive protein, fibrinogen, von Willebrand factor, and leukocyte count) and statin therapy to long-term mortality in patients with angiographically proven coronary artery disease. *Am J Cardiol* 2002; 89(8):901-8.
17. Ridker PM, Rifai N, Rose L, et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002; 347(20):1557-65.
18. Grewal J, Chan S, Frohlich J, et al. Assessment of novel risk factors in patients at low risk for cardiovascular events based on Framingham risk stratification. *Clin Invest Med* 2003; 26(4):158-65.
19. Cesari M, Penninx BW, Newman AB, et al. Inflammatory markers and onset of cardiovascular events: results from the Health ABC study. *Circulation* 2003; 108(19):2317-22.
20. Chin BS, Blann AD, Gibbs CR, et al. Prognostic value of interleukin-6, plasma viscosity, fibrinogen, von Willebrand factor, tissue factor and vascular endothelial growth factor levels in congestive heart failure. *Eur J Clin Invest* 2003; 33(11):941-8.
21. 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; 107:499-511.
22. Genest J, Frohlich J, Fodor G, et al. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: 2003 update. On-line appendix to *CMAJ* 2003; 168(9):921-4.
23. McFarlane SI, Kumar A, Sowers JR. Mechanisms by which angiotensin-converting enzyme inhibitors prevent diabetes and cardiovascular disease. *Am J Cardiol* 2003; 91(12A):30H-37H.
24. Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; 336(14):973-9.
25. Haffner SM, Greenberg AS, Weston WM, et al. Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. *Circulation*. 2002; 106(6):679-84.
26. Ridker PM, Rifai N, Pfeffer MA, et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. *Circulation* 1998; 98(9):839-44.
27. Ridker PM, Rifai N, Pfeffer MA, et al. Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators. *Circulation* 1999; 100(3):230-5.
28. Albert MA, Danielson E, Rifai N, et al. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 2001; 286(1):64-70.
29. Ridker PM, Rifai N, Clearfield M, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001; 344(26):1959-65.
30. 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.
31. Kinlay S, Schwartz GG, Olsson AG, et al. High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL study. *Circulation* 2003; 108(13):1560-6.

■ THE IMPORTANT ROLE OF INFLAMMATION IN ATHEROSCLEROSIS

Overview. Recent developments in basic and experimental sciences have forced the evolution of the definition of atherosclerosis. Once regarded as a bland lipid storage disease, atherosclerosis is now appreciated as being a dynamic disease involving an ongoing inflammatory response. It is now understood that inflammation plays a fundamental role in mediating all stages of atherosclerosis, from initiation to progression and the associated thrombotic complications.

It is becoming clear that an understanding of the important link between inflammation and atherosclerosis can yield clinically useful predictive and prognostic information. This information may include knowledge about the role of inflammation in atherosclerosis, about the markers indicative of inflammatory processes, and about the known trig-

gers for inflammation. Furthermore, insights into atherosclerosis-associated inflammation may help identify novel therapeutic strategies targeting better outcomes in patients with—or at risk for—this important disease.

Following an overview of inflammation in atherogenesis, this review goes on to identify triggers of inflammation including dyslipidemia, hypertension, diabetes, obesity and infection. A detailed look at inflammation in acute coronary syndromes is then presented, followed by discussions of the correlation between markers for inflammation and adverse prognoses, the prevalence of inflammation, and the implications of these data for preventive strategies.

Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002; 105:1135-43.

■ EFFECT OF HIGH-DOSE ATORVASTATIN ON HS-CRP IN THE DALI STUDY

Results. High-dose (80 mg/day) atorvastatin was associated with significant reductions in high-sensitivity C-reactive protein (hs-CRP), a nonspecific marker of inflammation and a strong predictor of cardiovascular risk, compared to low-dose (10 mg/day) atorvastatin and to placebo. Median CRP increased by 6.6% in the placebo group and decreased by 15% and 47% with atorvastatin 10 mg and 80 mg, respectively. The differences between atorvastatin 80 mg and placebo, and between atorvastatin 80 mg and 10 mg, were statistically significant ($p < 0.001$). Furthermore, of subjects with baseline CRP levels > 3.0 mg/L, 56% treated with atorvastatin 80 mg reached a level < 3.0 mg/L compared to 23% of atorvastatin 10 mg subjects ($p < 0.01$) and 17% of placebo subjects ($p < 0.005$).

The overall effect of atorvastatin on CRP was observed to be independent of gender, body mass

index (BMI), leukocytes, fasting glucose levels and interleukin-6 levels, and only 8% of the overall change in CRP was associated with changes in plasma lipids.

Methods. The prospective, double-blind Diabetes Atorvastatin Lipid Intervention (DALI) study randomized 197 subjects with type 2 diabetes mellitus, plasma triglycerides between 1.5 mmol/L and 6.0 mmol/L and total cholesterol between 4.0 mmol/L and 8.0 mmol/L to receive either placebo, atorvastatin 10 mg or atorvastatin 80 mg. Of these subjects, 186 were eligible for this analysis of the effect of treatment on CRP.

Patients did not have manifest coronary artery disease nor history of MI or angina, and were followed for 30 weeks of treatment. Fasting blood samples were collected for analysis at the end of the study period.

van de Ree MA, Huisman MV, Princen HMG, et al, for the DALI Study Group. Strong decrease of high sensitivity C-reactive protein with high-dose atorvastatin in patients with type 2 diabetes mellitus. *Atherosclerosis* 2003; 166:129-35.

■ THE ATHEROGENE STUDY: IMPACT OF INFLAMMATION MARKERS AND STATIN THERAPY ON MORTALITY

Results. Among patients with angiographically diagnosed coronary artery disease (CAD), four determined inflammatory markers (high-sensitivity C-reactive protein [hs-CRP], fibrinogen, von

Willebrand factor [vWF] and leukocyte count) were significantly higher among patients who died during follow-up than among survivors. Of these markers, only hs-CRP was assessed to be a significant predictor of CAD death in a multivariate, backward stepwise Cox regression model. Even among patients not treated with a statin

whose hs-CRP levels were not elevated, cardiac death was not increased compared to statin-treated patients (illustrating the strength of this inflammation marker as a prognostic indicator).

The predictive value of hs-CRP (and of the other three markers) was lost in statin-treated patients, in whom the levels of all four inflammatory markers were lower. Among subjects in the top quartile of hs-CRP, those not treated with a statin were at 2.3 times greater risk for fatal coronary events. Overall, compared to the absence of statin therapy, statin treatment was associated with a 51% reduction in relative risk of fatal coronary events ($p = 0.004$).

Methods. A total of 1,246 subjects who had undergone coronary angiography and been

■ CARDIOVASCULAR RISK IN PATIENTS WITH CHD: THE ROLE OF HS-CRP

Overview. High levels of high-sensitivity C-reactive protein (hs-CRP) have been correlated in many prospective studies with increased cardiovascular risk. Compared to other known markers of inflammation, hs-CRP yields results from standardized measurement methods that are reproducible and reliable. In clinical practice, these characteristics make hs-CRP valuable in identifying high-risk patients and monitoring the activity of inflammatory disease, and as a possible therapeutic target in altering the component of the disease process pertaining to inflammation.

This review briefly discusses atherosclerosis as a chronic inflammatory disorder and hs-CRP as an inflammatory marker before outlining the impor-

■ CRP AND LDL-C AS PREDICTORS OF CARDIOVASCULAR EVENTS

Results. C-reactive protein (CRP) level was a stronger predictor of cardiovascular events than low-density lipoprotein cholesterol (LDL-C) level. The adjusted relative risks of first cardiovascular events (myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes) among subjects, by increasing CRP quintile compared with the lowest quintile, were 1.4, 1.6, 2.0 and 2.3 ($p < 0.001$). For LDL-C, the adjusted relative risks (also by increasing quintile compared to lowest quintile) were 0.9, 1.1, 1.3 and 1.5 ($p < 0.001$). Similar results were seen for each component of this composite endpoint.

The two inflammatory markers were minimally

enrolled in the AtheroGene Study's cardiovascular registry were eligible for this analysis. Of these, 1,240 were followed for a median of 2.9 years; information about causes of death or cardiac events was obtained from hospital or general-practitioner charts. Blood samples were collected before coronary angiography was performed; 417 subjects had been treated with a statin for a minimum of four weeks at the time of sample collection.

Bickel C, Rupprecht HJ, Blankenberg S, et al, for the AtheroGene Investigators. Relation of markers of inflammation (C-reactive protein, fibrinogen, von Willebrand Factor, and leukocyte count) and statin therapy to long-term mortality in patients with angiographically proven coronary artery disease. *Am J Cardiol* 2002; 89:901-908.

tant role of hs-CRP in stratifying the risk of patients with coronary heart disease and examining some preventive measures that may attenuate cardiovascular risk in these patients by reducing hs-CRP. A review of evidence in stable and unstable angina, acute myocardial infarction, coronary revascularization is provided. Furthermore, the association between other cardiovascular risk factors (such as smoking, hyperlipidemia, diabetes and obesity) and hs-CRP is discussed. Finally, measures aimed at modulating inflammatory response, including antiplatelet therapies and lipid-altering therapies, are reviewed in terms of their ability to reduce cardiovascular risk and, specifically, affect hs-CRP levels.

Rosenson RS, Koenig W. High-sensitivity C-reactive protein and cardiovascular risk in patients with coronary heart disease. *Curr Opin Cardiol* 2002; 17:325-31.

correlated ($r = 0.08$), leading to the conclusion that each identifies a separate high-risk group and the finding that screening for both provided better prognostic information than screening for either marker alone.

Methods. CRP and LDL-C measurements were made at baseline in 27,939 apparently healthy women aged 45 years or older, who were subsequently followed for a mean of eight years for the occurrence of any of the components of the composite endpoint. The value of CRP and LDL-C measurements in predicting the risk of these cardiovascular events was assessed.

Ridker PM, Rifai N, Rose L, et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002; 347(20):1557-65.

Clinical Trials: What Do They Mean to Me?

Keeping abreast of current clinical trials and their results is challenging, if not impossible, for many family physicians (FPs). Recognizing the significance of clinical trial results and being able to apply the results into everyday family practice is even more of a challenge. In this article, Dr. Greenberg summarizes the highlights of three studies that point towards the importance of C-reactive protein in the diagnosis and management of CAD and discusses the relevance of these studies to FPs.

by David Greenberg, MD

Case Scenario

Mr. Promises comes to see you at your office for his annual physical. At 55 years of age, he's spent the last few years swearing that he's going to get his act together, get in shape, start eating properly, stop smoking and generally start looking after himself. In other words, he's a fairly typical patient. You've already sent him for fasting blood work and have the opportunity to review the results as well as the findings on your exam. Among other things, this is the information you present to him:

- Blood Pressure: 140/88 mmHg
- Total Cholesterol: 5.25 mmol/L
- HDL-cholesterol: 1.19 mmol/L

"So Doc," he asks, "how bad is it?"

"Well actually," you respond, "it doesn't look too bad, you just need to follow through on your 'threats' and things should be ok."

"But Doc, one of my buddies told me his GP gave him a number, and told him exactly how likely he was to have a heart attack in the next 10 years. Can you give me a number like that?"

"Sure" you reply, and dust off your 10-year CAD risk calculator.¹ To your mutual surprise, you find that even though his abnormalities are quite marginal, Peter's risk for CAD in the next 10 years is 25%, putting him in the high-risk category.

Is there any value in giving Peter a statin at this point?

If so, which one and why?

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Introduction

This article is being written from my own perspective, which is that of a reasonably busy community based GP. Probably much like you, on any given day, I may see patients with problems that fall into as many as 10 or 15 specialty areas. In addition, I'm bombarded with a huge amount of educationally oriented information. I obviously need to stay current in as many areas as possible but, time constraints being what they are, I need to prioritize. What I choose to focus on varies by my perception of need, but when a topic makes the cover of *Time* magazine, I know I'd better get on it because my patients will bring it up and likely know more than I will! So it is for the role of inflammation in CAD.

As we will see, atherosclerosis is not just a lipid-storage disease. I often tell patients that "not everything that makes good common sense makes good medical sense, but everything that makes good medical sense should make good common sense." So it is for the role of lipids in CAD. We've all seen patients with normal lipid profiles who develop CAD at a young age, so clearly it can't be the whole story. In addition, ASA has been seen to play a major role in preventing CAD. We've been told this relates to its platelet effects but, as it is by definition an anti-inflammatory drug, it stands to reason that inflammation may play a role. How significant a role, and what the mechanism is, is now being elucidated.

Inflammation in CAD

As Dr. Verma describes in his excellent article (page 4), even in the earliest stages of the atherosclerotic process, the endothelium, which we now know is not just a passive liner of the vessels, can attract leukocytes, which are mediators of the inflammatory process. This process also involves a variety of substances, all of which may play a role in atheroma development. The one that we'll focus on here is the pro-inflammatory C-reactive protein (CRP).

CRP contributes to the atherosclerotic process in a number of ways. These include inhibiting nitric oxide (an anti-inflammatory substance that helps prevent atheroma development through vasodilatation and suppression of adhesion molecules) and promoting both vasoconstrictive and adhesion-causing substances. It may also promote angiotensin-induced reactive oxygen species that contribute to restenosis and neointimal formation. More directly related to its pro-inflammatory role, CRP promotes factors which bind to lipoproteins, help them form plaques within the intimal wall and further stimulate the inflammatory process. This attracts macrophages which further contribute to lesion progression, can

degrade and ultimately destabilize the collagen in the outer layer of the plaque and stimulate tissue factor, a major procoagulant.

So, the bottom line on CRP is that it not only is involved in the development of plaques, but also helps destabilize them, which can lead to thrombosis.

There are several relatively current studies that point towards the importance of CRP in the diagnosis and management of CAD. For our purposes, I'll look at three. The first focuses more on diagnostics while the other two evaluate therapies.

The Women's Health Study

In this study, 27,939 healthy women aged 45 years and older were followed for eight years, monitoring for a first CV event (MI, ischemic CVA, coronary revascularization, CV death).² They all had baseline measures of LDL-C and CRP. Interestingly, there was only minimal correlation between these two risk factors, which is to say that you couldn't make any judgment of whether someone's high-sensitivity C-reactive protein (hs-CRP) was elevated based on their LDL-C or vice-versa. In the end, it was found that CRP was in fact a stronger predictor of a first ischemic event than LDL-C. The implication seems to be that there is a high-risk group that we're not identifying with the standard testing commonly performed by most GPs. Moreover, we probably can't even tell who the members of this group are without testing!

Diabetes Atorvastatin Lipid Intervention (DALI)

DALI was a prospective double-blind placebo-controlled trial that randomized 197 subjects (186 actually completed) with type 2 diabetes to placebo, low-dose (10 mg) or high-dose (80 mg) atorvastatin for 30 weeks.³ The trial was intended to measure the effect of treatment on hs-CRP. The results were quite striking. In the placebo group, median hs-CRP actually increased, while there was a significant decrease in hs-CRP in both treated groups. For those with hs-CRP > 3.0 mg/L, 56% of the high-dose group got below this threshold as opposed to 23% of the low-dose group and 17% of the placebo group. Moreover, only 8% of the hs-CRP change was accounted for by lipid changes. So we're lowering the risk of CAD in a high-risk group that we weren't really aware of by modifying a risk factor other than the one we thought we were modifying!

The AtheroGene Study: Impact of Inflammation Markers and Statin Therapy on Mortality

This study evaluated the connection between four different markers of inflammation in patients with CAD and death

from coronary causes.⁴ A total of 1,246 patients were followed, of which 417 received statins for at least four weeks. The only marker that was shown to be a valuable predictor of death from cardiac causes was hs-CRP. Even the patients with high LDL-C didn't have increased mortality when their hs-CRP levels were normal. The group that didn't receive statins (and whose hs-CRP therefore went untreated)

and had elevated hs-CRP had a 2.3-fold increase in fatal coronary events, irrespective of their LDL-C levels.

To summarize, people with elevated hs-CRP are at high risk for CAD. We can only find them if we test. If we give them statins, we lower their risk by lowering hs-CRP, again irrespective of their lipid levels.

So now what?

Case Discussion

This case was written to reflect some of the frustrations that one feels these days in general practice. One source of frustration is guidelines. In his article, Dr. Verma notes that it is a Class IIA recommendation of the AHA/CDC to routinely assess CRP and ostensibly treat patients deemed to be a 10% to 20% 10-year risk as per the Framingham risk assessment. In our case—and granted this is contrived—if Mr. Promises were a non-smoker, 54 years of age instead of 55, and his results changed to the following:

- BP: 139/88 mmHg (from 140/88 mmHg)
- Total Cholesterol: 5.17 mmol/L (from 5.25 mmol/L)
- HDL-C: 1.19 mmol/L (from 1.19 mmol/L)

...his total score would be 13 points instead of 16, giving him a 10% 10-year risk, which would place him at moderate risk and therefore make him eligible for CRP screening according to AHA/CDC guidelines. Given that these differences are small enough to be attributed to non-significant changes, it makes one wonder about basing decisions like expensive tests and potentially lifelong treatment on these obviously well validated guidelines.

Our frustrations with patients are clearly seen here. If we could just help this man to finally quit smoking and optimize his diet and exercise to lose the few pounds that would likely lower his BP and improve his lipid profile even marginally, we wouldn't have to worry about instituting the same lifelong therapies.

Our frustration with the government is clear. There is now, as we've seen, compelling evidence that there's a marker for CAD risk that may actually be better than LDL-C. The test through my local lab costs \$30.00 and is not covered by the MOH. In addition, since we can't really be sure who has a high hs-CRP, this brings up screening, a widespread implementation of which would wreak havoc on the system and therefore is strongly discouraged.

Our frustration with regulatory bodies is clear. While we see the evidence, even if we order a test for hs-CRP, and knowing that this is a risk factor even in patients with normal lipids, prescribing a statin to treat this would be off-license use of the drugs and, if there were problems, we would not be able to defend their use.

Having said all that, what do we do? In this case, obviously we'll do whatever we can to help Mr. Promises stop smoking, lose some weight and optimize his diet.

The corollary of my negative comments about the Framingham Risk Calculator is that it shows that relatively small (and inexpensive!) changes can have a big impact on 10-year risk, so it is certainly worth it to be persistent in trying to help. If there is mutual agreement that initiating a statin to lower risk is important, particularly in light of our new understanding of the role of inflammation, there is an additional consideration here.

In his article, Dr. Verma alludes to several earlier studies. In PRINCE and AFCAPS/TexCAPS, pravastatin and lovastatin had similar effects in lowering CRP. However, in REVERSAL, patients receiving 40 mg of pravastatin—even patients whose lipid profiles were below the mean—had progression of atheromatous plaques. In the group treated with 80 mg of atorvastatin, the growth of plaques was stopped. This was felt to be due to atorvastatin's more powerful anti-inflammatory effects as measured by CRP. Based on this, it would make sense that even with only marginal lipid elevation, there is potentially significant benefit to using a more potent statin.

Historically, it has been accepted that it takes as many as 12 years for an intervention for which there is good evidence to become the "gold standard." One hopes that, with the advent of enhanced information dissemination and the emphasis on "evidenced-based medicine," this number can be dramatically reduced.

In the meantime, clinicians should be aware that the use of more potent statins may be of added benefit in their at-risk patients. ☺

References

1. Genest J, Frohlich J, Fodor G, et al. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: 2003 update. *CMAJ* 2003; 169(9):921-4.
2. Ridker PM, Rifai N, Rose L, et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002; 347(20):1557-65.
3. van de Ree MA, Huisman MV, Princen HMG, et al, for the DALI Study Group. Strong decrease of high sensitivity C-reactive protein with high-dose atorvastatin in patients with type 2 diabetes mellitus. *Atherosclerosis* 2003; 166:129-35.
4. Bickel C, Rupprecht HJ, Blankenberg S, et al, for the AtheroGene Investigators. Relation of markers of inflammation (C-reactive protein, fibrinogen, von Willebrand Factor, and leukocyte count) and statin therapy to long-term mortality in patients with angiographically proven coronary artery disease. *Am J Cardiol* 2002; 89:901-908.

