
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

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