
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. Saunders summarizes studies showing the benefits of aggressive lipid lowering vs. usual care, and discusses the relevance of these studies to FPs.

by Kevin Saunders, MD

Case Scenario: Mr. A.T.

- 55-year-old male
- Uncomplicated angioplasty in two vessels four months ago after presentation to ER with new-onset unstable angina
- Very overweight and inactive prior to his event
- Now walks for one half hour three times per week, but has not lost any weight
- Medications: ASA 81 mg, clopidogrel 75 mg, ramipril 10 mg, atorvastatin 10 mg
- Total cholesterol: 4.9 mmol/L
- Triglycerides: 2.7 mmol/L
- HDL-C: 1.1 mmol/L
- LDL-C: 2.9 mmol/L
- Mr. A.T. questions you on the need to continue "all these medications"

Is there any value in altering Mr. A.T.'s treatment at this point? If so, why?

Introduction

Mr. A.T. presents a fairly typical treatment dilemma. His uncomplicated angioplasty procedure has caused him to underestimate the significance of the atherosclerotic disease process. Like many patients, he views this as an unfortunate "single episode" from which he has recovered and, now that he has made some mild lifestyle

modifications, he doubts the need for ongoing medical therapy. It is often very difficult for practitioners to get these patients to fully comprehend that the underlying atherosclerotic process is a lifelong problem that will certainly progress if aggressive management is not continued.

Recommendations for the Management of Dyslipidemia and the Prevention of Cardiovascular Disease: 2003 Update

The 2003 recommendations for lipid management include three levels of coronary risk: high, moderate and low. There are two treatment targets for each risk

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level: LDL-C and the ratio of total cholesterol to HDL-C. The ratio was chosen as the secondary treatment target because it was felt to be a more sensitive and specific index for CV risk than total cholesterol alone.

Patients in the high-risk category include all patients with known coronary artery disease, history of diabetes mellitus, or any atherosclerotic disease. These patients carry a 10-year risk of CV death or non-fatal cardiac event of greater than or equal to 20%. The target lipid levels for these individuals include an LDL-C level of less than 2.5 mmol/L and a total cholesterol to HDL-C ratio of less than 4.0.

Recommended treatment modalities to achieve both treatment targets include lifestyle modification through diet and exercise and, for patients in the high-risk category, concomitant use of medication. The upgraded guidelines suggest that individuals at high risk be treated with the equivalent of 40 mg/day simvastatin and that an LDL-C level of less than 2.5 mmol/L be achieved.

The treatment advice in the 2003 recommendations goes on to state that, if treatment targets are not achieved with monotherapy, potential further approaches could include more intensive lifestyle modification, increasing the statin dose, or proceeding with combination therapy.

Newer Trials

The Heart Protection Study (HPS) involved over 20,000 men and women at risk of coronary artery disease. The study subjects included those with coronary artery disease,

peripheral vascular disease, cerebral vascular disease, diabetes and/or hypertension. The study findings revealed a 13% decrease in the death rate and a 24% decrease in all CV endpoints for all subjects treated with simvastatin 40 mg, including those who had a baseline LDL-C level of less than 2.6 mmol/L at study start. This is the rationale for treating all individuals at high risk of coronary artery disease with the equivalent of 40 mg/day simvastatin and for setting minimum targets for LDL-C at 2.5 mmol/L or less and total cholesterol to HDL-C ratio at less than 4.0 mmol/L. Since the publication of the 2003 recommendations, there have been newer trials demonstrating further benefit in reducing the LDL-C below the 2.5 mmol/L level.

The PROVE-IT study demonstrated that aggressive lipid-lowering treatment with high-dose atorvastatin vs. standard-dose pravastatin reduced the progression of coronary atherosclerosis more significantly. The primary endpoint, a composite of death from any cause, MI, documented unstable angina requiring hospitalization, revascularization and stroke, was reduced by 16% with 80 mg atorvastatin. This despite the fact that the median LDL-C level achieved by the pravastatin group was 2.46 mmol/L, compared to a median LDL-C level of 1.6 mmol/L for patients receiving atorvastatin.

Several ongoing trials, such as the TNT trial comparing atorvastatin 80 mg to atorvastatin 10 mg, will hopefully help us determine the optimum LDL-C level that we should be attempting to achieve with our patients.

Case Discussion

Mr. A.T. not only needs to continue with statin therapy, he is actually under-treated at present.

At first glance, his lipid profile does not look too unreasonable, and a busy family physician may be tempted to shrug it off as being acceptable. The difficulty lies in the fact that Mr. A.T. is clearly not at target for either of his lipid measurements. His LDL-C needs to be 2.5 or less and recent data from trials such as the HPS and PROVE-IT would clearly indicate that more intensive treatment would provide additional benefit. The total cholesterol to HDL ratio is not at target either. This is a sensitive and specific index for CV risk and, as one of the two treatment targets, should not be overlooked.

In Mr. A.T.'s case, it would be very reasonable to attempt an intensification of his lifestyle therapy but, concomitantly, he should have an increase in his statin dose, as the current recommendation from the 2003 guidelines suggests that patients at high risk

should be treated with the equivalent of 40 mg/day simvastatin in order to achieve target levels. To get to target, his dose of atorvastatin could be increased to 20 mg/day. However, based on recent data such as that from PROVE-IT and REVERSAL trials, a more intensive statin therapy with an even higher dose could potentially provide incremental benefits over and above simply achieving the LDL-C and TC/HDL-C targets. There is a significant body of evidence that now exists, verifying that statin therapy is well tolerated and that "somewhat lower than target" is clearly more beneficial to our patients than "almost there." As Dr. Jean-Claude Tardif has noted in his article, these patients need intensive and ongoing medical therapy to reduce their overall CV risk.

Mr. "Almost There" not only requires an increase in his statin dose, but must also continue on with his other medications and lifestyle modifications in an attempt to minimize his long-term CV risk. As family physicians, this certainly remains our ongoing challenge. ♡