
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. Lin summarizes studies showing the benefits of aggressive lipid lowering in patients with diabetes and discusses the relevance of these studies to FPs.

by Peter Lin, MD, CCFP

Case Scenario: Mr. S.K.

- 55-year-old male; nonsmoker, diabetic
- Height: 173 cm; weight: 91 kg
- BP: 145/88 mmHg
- BMI: 30
- Waist circumference: 110 cm
- Fasting blood sugar: 10.0 mmol/L
- HbA1C: 0.078
- HDL-C: 1.4 mmol/L
- LDL-C: 3.0 mmol/L
- Total cholesterol: 5.4 mmol/L
- Triglycerides: 1.7 mmol/L
- Microalbumin: 156 mg/day
- Family history: Grandfather had two heart attacks, treated with morphine; father had one heart attack at age 60, treated with ASA and nitroglycerin; older brother had a heart attack, treated with cholesterol pills, a beta-blocker, ASA and an ACE inhibitor. Father and brother are nonsmokers with type II diabetes.

What kind of treatment should be prescribed for Mr. S.K.? Why?

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Introduction

His blood pressure (BP) is not horrible. His lab tests do not scream out at you, either. Often this kind of patient is glossed over.

This is an interesting case if you look at the family history first. His family history represents the last 50 years of cardiovascular medicine and highlights all the trials that have changed how we have practiced medicine. His grandfather lived in an era where clinical trials were not done and when the key opinion leaders basically said “please don’t measure the BP because you might want to treat it.” Hence, he only received symptomatic treatment. Then with his father, there was at least some attempt at secondary prevention. After his heart attack, he was prescribed ASA to try to prevent another event.

His brother shows the state-of-the-art treatment as we know it today. With the statin trials, the ACE inhibitor trials and the beta-blocker trials, the standard of care has changed. He is receiving quadruple therapy. What about our patient, Mr. S.K.?

He has not had any events yet, but he is at high risk, so we are trying to practice primary prevention in a high-risk individual. What studies can give us guidance regarding what to do with him?

Treating Mr. S.K.’s Blood Pressure

Let’s start off with his BP. Most would agree that he should be on an ACE inhibitor, thanks mainly to trials like the Heart Outcomes Prevention Evaluation (HOPE) trial, where there were reductions in CV risk in all of the groups studied. More impressive was MICRO-HOPE which focused on the diabetic HOPE patients and showed reductions in the primary outcome by 25%, and in which the individual endpoints of myocardial infarction, stroke and nephropathy were all reduced by a similar degree. Also, because there was not a large change in BP in the HOPE trial, the concept of “beyond BP” protection emerged. Through the HOPE trial, ramipril demonstrated vascular protection in multiple vascular beds that was not completely BP-dependent. So, Mr. S.K. should be placed on an ACE inhibitor. As a second add-on medication, a low-dose diuretic would be appropriate.

Treating Mr. S.K.’s Cholesterol

What about his lipids? Traditionally, it has been said that diabetics don’t have high LDL-C but have lots of triglycerides and low HDL-C. So statins may not be of any benefit to them. Some recent studies have shed at least some light on this issue. For example, the Heart Protection Study (HPS) had almost 6,000 high-risk diabetics within its trial population and half received simvastatin 40 mg regardless of their lipid profile. There was a consistent 22% reduction in the risk of primary events.

The lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA) examined 2,500 hypertensive diabetics within the larger study population. Amazingly, ASCOT-LLA had to be stopped early because of the overwhelming benefits of treatment with atorvastatin 10 mg. Diabetic patients showed a 23% reduction in total CV events with atorvastatin 10 mg. The hypertension arm of the trial is continuing.

The most recent trial that can help us with Mr. S.K. is the Collaborative Atorvastatin Diabetes Study (CARDS), which looked at the question: should diabetics be treated with statins? Remember, patients with diabetes don’t traditionally have high LDL, so there was always concern if this class of medications would be of any benefit. This trial included 2,800 diabetics who did not have coronary disease, cerebral vascular disease or peripheral artery disease. That is significant because, until this trial, diabetics were always just a subset of larger studies and most had existing vascular disease. So the CARDS trial looked at a group of Mr. S.K.-type patients: diabetics who did not yet have organ damage. The question being asked was: does treating these patients with atorvastatin 10 mg help? Like ASCOT-LLA, this trial was stopped early due to the overwhelming protection atorvastatin provided.

The atorvastatin group had a 37% reduction in major cardiovascular endpoints. There was also a 48% reduction in strokes. Interestingly, when the patients were grouped based on their lipid profiles, it didn’t really matter. Patients with low LDL-C did just as well as patients with high LDL-C. This has led us to the concept of perhaps protection “beyond cholesterol” just like the concept of “beyond BP” protection

with ACE inhibitors. There may be other effects of statins that may be at work that might explain why all patients, with high or low lipids, had benefits.

The REVERSAL trial might have shed some light on this concept. Pravastatin was one of the first statins to be cited as having effects outside of lipid lowering. It was stated as being anti-inflammatory, with anti-platelet effects. REVERSAL examined about 600 patients with coronary artery disease and used intravascular ultrasound (IVUS) to calculate the atheroma volume in the coronary arteries. Half the subjects were treated with pravastatin 40 mg (maximum dose) and half with atorvastatin 80 mg (maximum dose) for 18 months. Interestingly, the atorvastatin group had much lower atheroma progression than the

pravastatin group. To examine this further, in light of the fact that LDL-C was lower with atorvastatin, the investigators plotted the atheroma volume against the LDL-C levels. The regression graph showed that atorvastatin reached the zero atheroma progression mark at about 45% LDL-C reduction whereas, for pravastatin, reaching the zero mark required a 60% LDL-C reduction. In essence, you needed less LDL reduction to stop the atheroma progression with atorvastatin. Atorvastatin also produced a 36.4% reduction in C-reactive protein whereas pravastatin produced a 5.2% reduction. This may be an early sign that there are effects of statins beyond LDL-C reduction and that there may be differences between the different statins.

Case Discussion

A statin would be of great use for Mr. S.K. ASA would also be an important part of his care, as would dietary and physical activity changes to treat his diabetes.

One final thought: What would have happened if we saw him 10 years ago at 45 years of age? Perhaps he would have been in the metabolic syndrome stage. His waist circumference might have been 104 cm. His BP might have been slightly up and his sugars just edging over nor-

mal. All of those parameters that Dr. Lau explained in his article (page 4) might have been there 10 years ago.

So our challenge is not only to treat Mr. S.K. aggressively using ACE inhibitors and statins but to find young patients like Mr. S.K. that are in the early stages of the disease processes and perhaps, by treating them aggressively, we can help lift some of the future burden off our healthcare system. 