



Another Defeat for Conventional Wisdom

Well, it's happened again: Common sense and conventional wisdom have taken another beating. What seemed eminently reasonable didn't hold up under the demanding standards of a clinical research trial. What we thought was reasonable was objectively proven not to be so, and we should all be humbled in the process.

What I'm referring to are the most recent reports from the National Institutes of Health-sponsored Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which commenced more than a decade ago to find effective strategies to reduce cardiovascular risk in patients with type 2 diabetes. It's an irrefutable fact that diabetes predisposes to a fearsome panoply of macrovascular diseases, including coronary artery, cerebrovascular, and peripheral arterial diseases. These afflictions are in addition to the disastrous microvascular complications that diabetes predisposes to—namely, the neuropathy, nephropathy, and retinopathy that can be devastating for their victims.

As one of the principal investigators, I had the privilege of being in on the ground floor of the study design. After considerable debate, we decided to test 3 strategies for reducing cardiovascular risk in our planned cohort of over 10,000 older patients with type 2 diabetes. We used a 2 x 2 design, which meant that participants were double-randomized: First, either to intensive or conventional glycemic control, and second, either to the blood pressure or lipid study.

In the glycemia wing of the study, we decided to test the effects of an aggressive HbA_{1c} goal of less than 6%, compared with a conventional goal of 7% to 8%. In the blood pressure study,

we wanted to compare the cardiovascular risk in patients with a systolic blood pressure (SBP) goal of less than 120 mm Hg, as opposed to a goal of less than 140 mm Hg (which many thought was not low enough in light of the American Diabetes Association recommendation that patients with diabetes maintain an SBP less than 130 mm Hg). In the lipid study, we sought to determine the benefit of adding a standard dose of fenofibrate to baseline statin therapy. Statins are good at lowering low-density lipoprotein levels, but we thought there might be additional benefits by targeting the low high-density lipoprotein (HDL) and elevated triglyceride (TGL) levels that are so common in patients with diabetes.

We made history when we had to terminate the glycemic study in February 2008, when our Data Safety and Monitoring Board told us that participants with the aggressive HbA_{1c} goal were dying at a greater rate than those with the conventional goal; to the tune of a 22% increase. This finding flew in the face of the belief that an aggressive goal is better. We soon learned that 2 other trials, the VA Diabetes trial and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation trial, also failed to show any benefit of an aggressive HbA_{1c} goal.

In spite of these disconcerting findings, we soldiered on with the blood pressure and lipid studies, hoping that we still might identify strategies that would reduce cardiovascular risk. Alas, that was not to be. The truth can hurt sometimes, but the truth is the truth. The results of both studies were reported in March 2010 at the American College of Cardiology meet-

ing. Both trials were negative, indicating that the lower SBP goal afforded no reduction in cardiovascular events, and there was only a trend (no statistical significance) in favor of adding the fibrate to baseline statin therapy. In fact, the trend was driven entirely by a subset of participants who had both a significant elevation in TGL levels and a significant reduction in HDL levels.

So, the results of the ACCORD and similar trials are indeed humbling. Tighter glycemic control sounds good, but trying to achieve these goals may well kill your patients. Tighter blood pressure and lipid control also sound very appealing, but they don't work. With regard to cardiovascular risk factor reduction in type 2 diabetes, I have come up with what I call the "Brylcreem theory of risk reduction," with apologies to younger readers who may not recognize the once ubiquitous Brylcreem slogan, "A little dab'll do ya." So in the end, we're left with the old adage that moderation in all things is ultimately the best strategy. ●

Author disclosures

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