iDiS PEARL: Prompt Evidence Assessment and Review of the Literature

Did ACCORD show discord on how to manage BP and lipids in diabetic patients? Not totally.

The clinical issue:

Maintaining a normal blood pressure and lowering lipids have long been mainstays of managing the patient with diabetes, at least as important as tight glycemic control.[1] But to what targets? Is lowest always best? Last month, a surprising set of papers were published in the *New England Journal of Medicine* that seemed to raise questions about some basic beliefs about diabetes care, suggesting that aiming for rock-bottom BP and lipid levels may not benefit such patients more than attaining more modest goals.

The new studies:

The ACCORD (Action to Control Cardiovascular Risk in Diabetics) trial comprised two sub-studies. **ACCORD-BP**[2] compared intensive vs. standard BP control (<120 mm vs. <140mm systolic). **ACCORD-LIPID**[3] evaluated intensive vs. conventional lipid lowering regimens (simvastatin + fenofibrate vs. simvastatin alone). All study subjects were adult diabetics with existing cardiovascular disease or evidence of atherosclerosis.

More intensive BP control produced few benefits, but added risks:

The blood pressure trial included 4,733 patients. Patients in the intensive group had an average systolic blood pressure of 119 mmHg; in the standard group group, the average systolic blood pressure was 134 mmHg. After a mean follow up of 4.7 years, **patients assigned to intensive BP reduction did not have a significant advantage in risk of the study's primary outcome of CV death, MI, or stroke** (1.9% in the intensive group versus 2.1% in the usual care group; p=0.20; see **Figure 1**). All-cause mortality was also about the same (1.3% versus 1.2%). However, there were significantly fewer strokes in the intensive-BP control group (0.32% versus 0.53%, p=0.01).

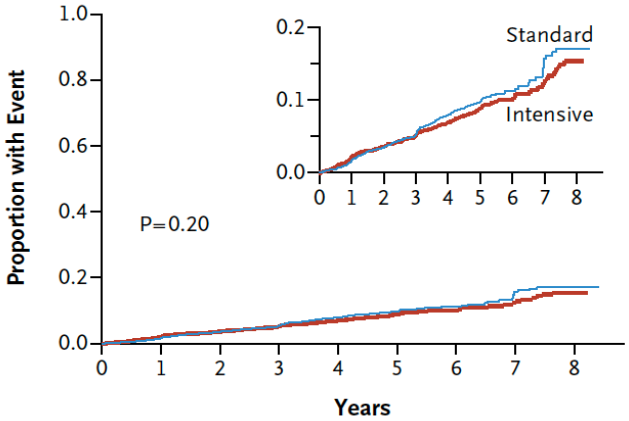

Figure 1: The proportions of patients treated with intensive and standard blood pressure control who had a primary outcome (nonfatal MI, nonfatal stroke, or death from CV causes). Reproduced with permission from The ACCORD Study Group. Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. NEJM 2010 Mar 14.

The rate of serious adverse effects of treatment were significantly higher in the intensive group (3.3% versus 1.3%, p<0.001). These included hypotension, hyperkalemia, and bradycardia.

Simvastatin alone was as good as simvastatin plus a fibrate:

In ACCORD-LIPID, the mean LDL at baseline was 100 mg/dL, and triglycerides were about 160 mg/dL. The daily dose of simvastatin in both study groups was about 20 mg, with fenofibrate added to the intensive-treatment group. By trial's end, mean LDL had fallen to about 80 mg/dL in both groups. Triglycerides fell to 144 in the simva-alone group, and to 122 in the group with added fibrate.

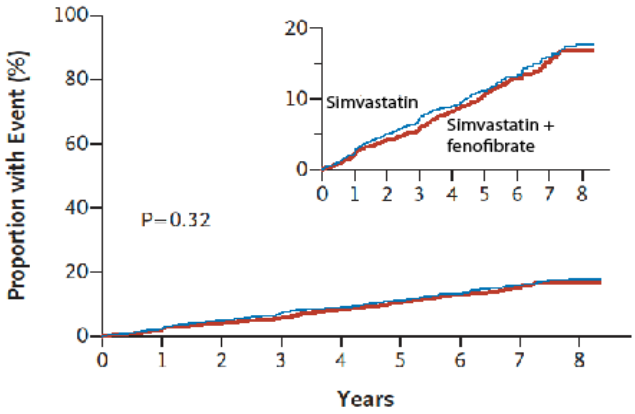

Figure 2: The incidence of the primary outcome (nonfatal MI, nonfatal stroke, or death from CV causes) for patients treated with simvastatin alone or simvastatin plus fenofibrate. Reproduced with permission from The ACCORD Study Group. Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. NEJM 2010 Mar 14. Copyright © 2010 Massachusetts Medical Society. All rights reserved.

Despite the greater triglyceride reduction, after a mean follow up of 4.7 years, **both groups had about the same rate of the study's primary outcome** of cardiovascular death, myocardial infarction, or stroke: 2.2% in the fenofibrate+simvastatin group vs. 2.4% in simvastatin alone group; p=0.32 (see **Figure 2**). Rates of other outcomes, including death, were also not significantly different (all p-values >0.1).

Patients randomized to statin-fibrate combination were much more likely to develop renal impairment (p<0.001); rates of other serious adverse events were equal.

Some limitations:

The ACCORD studies were non-blinded, which could have affected adverse event reporting, and patients generally had a lower-than-expected rate of cardiovascular events, which limited statistical power to detect differences in the regimens. ACCORD was started before publication of the current JNC7 recommendations for blood pressure control in diabetes,[3] which recommended a BP goal of ≤ 130/80, a level that was not formally tested in ACCORD-BP.

Bottom-line clinical take-home points:

ACCORD suggest that in patients with diabetes with coronary disease (or at high risk for it):

- ☑ a systolic blood pressure target of < 140 mmHg is overall as effective as and safer than more intensive blood pressure lowering to a goal of <120;
- ☑ fenofibrate should not routinely be added to statin therapy.

References: 1. NEJM 2008;358(6):580-591. 2. Published online at www.nejm.org March 14, 2010 (10.1056/NEJMoa1001282); 3. Published online at www.nejm.org March 14, 2010 (10.1056/NEJMoa1001286)

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