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From [Heartwire](#)

ACCORD: New Wave of Results Tantalizes, Bolstering Cautions About "Intensive" Glycemic Control

Steve Stiles

June 30, 2010 (Orlando, Florida)— The **Action to Control Cardiovascular Risk in Diabetes** (ACCORD) trial produced three separate new analyses that made their appearance this week both at the **American Diabetes Association (ADA) 2010 Scientific Sessions** and in the literature [1,2]. There was cause for both optimism and discouragement in the new data from the trial, which tested three "intensive" medical strategies against standard drug therapy for treatment of high glycated hemoglobin (A_{1c}), dyslipidemia, and high systolic blood pressure in separate randomizations.

The new analyses go a long way toward fulfilling most of the 10 251-patient trial's prospectively planned analyses and then some, including primary outcomes for the three randomization arms at the prespecified "end" of the trial after five years of follow-up.

In one of the new analyses, **ACCORD Eye**, the pairing of **fenofibrate** with **simvastatin** for intensive dyslipidemia therapy (compared with simvastatin alone) as well as glycemia therapy to achieve A_{1c} levels of <6.0% (vs a target of 7.0% to 7.9%) significantly slowed the progression of diabetic retinopathy over four years [1]. The corresponding intensive strategy for hypertension, in which treatment aimed for a blood pressure target of <120 mm Hg (compared with <140 mm Hg), had no apparent effect on retinopathy progression.

The ACCORD Eye study was published online June 29, 2010 in the *New England Journal of Medicine* to coincide with its presentation at the ADA meeting.

Also published online in the *Lancet* and presented the same day was a secondary analysis of the intensive-glycemic-control strategy's effects on an array of microvascular complications [2].

No consistent picture emerged. Treatment effects were not seen for either of two primary composite end points that combined renal, eye, and neuropathy events. But benefits of intensive therapy were observed for some end points associated with microvascular disease (such as development of micro- and macroalbuminuria and a test of visual acuity), but not others (like elevated serum creatinine and loss of vibratory sensations).

A third presentation at the ADA followed patients in the trial's glycemia randomization for the full five years but also reported outcomes from the time of what may be one of ACCORD's defining events: in February 2008, the intensive-glycemic-therapy arm was terminated because its patients were showing increased mortality, as extensively covered

by **heartwire**. Those patients crossed over to the standard-therapy arm, and the entire cohort was followed out to five years, breaking the follow-up intervals of ACCORD's glycemic-therapy component into two phases, 3.7 years before the patients' transition from intensive to standard therapy and 1.3 years after the transition.

Intensive Glycemic Control and CV Outcomes

As reported by **Dr Hertzell C Gerstein** (McMaster University, Hamilton, ON) at the ADA sessions, cardiovascular and other clinical outcomes for the entire five-year follow-up were largely consistent with outcomes before the transition: no effect of intensive-glycemic-control therapy compared with standard therapy on the primary composite outcome of nonfatal MI, nonfatal stroke, or CV death but an increase in all-cause mortality.

Patients in ACCORD, conducted at 77 centers in North America, entered with an A_{1c} level ≥ 7.5 and additional CV risk factors: they could be at least 40 years old with a history of CV events or at least 55 with subclinical CV disease, albuminuria, LV hypertrophy, or at least two additional CV risk factors such as dyslipidemia, hypertension, smoking, or obesity.

A_{1c} Levels at Baseline, at the Intensive-Therapy Group's Transition to Standard Therapy, and After the Transition in the ACCORD Trial

Time of A _{1c} assessment	Intensive therapy, n=5128 (%)	Standard therapy, n=5123 (%)
Baseline	8.3	8.3
At transition	6.6	7.7
After transition	7.4	7.8

Levels of A_{1c} at baseline and at and after the transition followed their expected tracks in the two treatment groups, falling sharply during the first 3.7 years of intensive therapy and climbing again after the transition.

An average 3.7 years of intensive glycemic-control therapy, both in the interim and at five years, compared with standard therapy yielded no significant effects on the composite primary end point or on nonfatal stroke, a reduction in risk of nonfatal MI, and increased risk of cardiovascular and all-cause mortality.

Hazard Ratio (95% CI) for Effects of Intensive vs Standard Therapy for Glycemia on Clinical End Points in ACCORD, Pretransition and Over Five Years

End point	Pretransition, HR (95% CI)	Total follow-up, HR (95% CI)
Primary end point*	0.90 (0.78–1.03)	0.91 (0.81–1.03)
Nonfatal stroke	0.99 (0.72–1.38)	0.87 (0.65–1.17)
Nonfatal MI	0.79 (0.66–0.95); p=0.01	0.82 (0.70–0.96); p=0.01
CV mortality	1.27 (0.99–1.63); p=0.07	1.29 (1.04–1.60); p=0.02
All-cause mortality	1.21 (1.02–1.44); p=0.03	1.19 (1.03–1.38); p=0.02

*Nonfatal MI, nonfatal stroke, or CV death

"In some respects, ACCORD raises more questions than it answers," Gerstein told **heartwire** . "It clearly shows that the intervention does seem to be having a beneficial effect on cardiovascular disease--there were fewer MIs, for instance. But there is a mortality signal that remains unexplained today."

Other ACCORD analyses have suggested it can't be explained by hypoglycemia, he observed. And it's probably not explained by the degree of glucose lowering. "Indeed, the people who died seemed to be the ones whose glucose didn't go down despite being in the intensive-therapy group. Many hypotheses are possible, many have been explored, but so far none of those that have been looked at within ACCORD have given a satisfying explanation," Gerstein said.

"I would not at this point aggressively target [an A_{1c}] less than 6% in anybody. If they easily achieve it, that's great. But I wouldn't set out to add four different drugs to get there. Certainly <7% is going to have eye-disease benefits and other benefits, may or may not have a cardiovascular effect, and is probably less likely to cause the mortality--but that's an inference."

New Directions in the Treatment of Diabetic Microvascular Disease?

Dr Emily Y Chew (National Eye Institute, Bethesda, MD), who presented the ACCORD Eye study at the ADA sessions, said progression of diabetic retinopathy was the trial's "primary microvascular end point." She and her colleagues defined it as the "combined outcome of progression of diabetic retinopathy of at least three levels on the [**Early Treatment Diabetic Retinopathy Study Severity**] ETDRS scale assessed on fundus photographs at four years," compared with baseline retinal photography; or it could be the occurrence of photocoagulation therapy or vitrectomy during the follow-up.

By that definition, 8.9% of the substudy's 2856 patients had retinopathy progression after four years of follow-up. But its prevalence varied depending on which of the three ACCORD comparisons of intensive vs standard therapy the patients also belonged to. And intensive therapy significantly improved the prevalence of retinopathy progression in both the dyslipidemia and glycemia components of the trial.

Hazard Ratio (95% CI) for Progression of Retinopathy in the Three ACCORD Treatment Comparisons, Intensive vs Standard Therapy

ACCORD randomization	Intensive therapy (%)	Standard therapy (%)	HR (95% CI)	p
Glycemia arm	7.5	10.4	0.67 (0.51-0.87)	0.0025
Dyslipidemia arm	6.5	10.2	0.60 (0.42-0.86)	0.0056
High-systolic-BP arm	10.4	8.8	1.23 (0.84-1.79)	0.29

"To me," Gerstein said, "an effect on the eyes tells us that it is favorably affecting the vascular tree, at least at the endothelial-cell and small-vessel level. And the lower MI rate tells us there's a favorable effect at the macrovascular level. The higher mortality tells us there is something we don't understand. And we need to work harder to try to understand it."

Dr Darren McGuire (University of Texas Southwestern School of Medicine, Dallas) pointed out for *heartwire* that the retinal photographs that were central to the ACCORD Eye study's primary end point aren't as trustworthy as true clinical end points. "With retinal photography, you try to identify meaningful disease in the hope that it predicts clinical outcomes, and it may well do that, but we've been misled by so many intermediate markers of disease in the past."

As for the fibrate-statin combination's apparent effects on retinopathy, McGuire says, "It's an interesting observation. The reality is that it was observed in the [**Fenofibrate Intervention and Event Lowering in Diabetes**] FIELD trial and [now] in the lipid substudy of ACCORD, so there may be something to it."

Gerstein said, "It's a bit of a surprise, the magnitude of the effect, but after the FIELD trial there was a lot of interest in maybe seeing that. I think the reasons for it are unclear, but they certainly suggest that there may very well be a place for fibrates in the management of diabetes, with respect to at least the eyes."

In an editorial accompanying the published report [3], **Dr Barbara EK Klein** (University of Wisconsin, Madison) observes that "some may find the lack of an apparent beneficial effect of intensive blood-pressure control on progression of retinopathy in the ACCORD Eye study surprising." Blood pressure hasn't been related to retinopathy progression in observational studies, but nonetheless, "it may be that a longer follow-up period would be needed to show either a protective effect of blood-pressure lowering at the levels achieved in the ACCORD study or an increase to significance of the nonsignificant deleterious effect of intensive blood-pressure control that was found in the study."

Other effects of intensive glycemic control on microvascular-disease-related end points came to light in a presentation at the ADA sessions from **Dr Faramarz Ismail-Beigi** (Case Western Reserve University, Cleveland, OH), who is also lead author of the accompanying *Lancet* report. Some effects were favorable; others were neutral.

In their published report, Ismail-Beigi write, "The observed benefits associated with intensive glycemia management should be weighed against higher total and cardiovascular-related mortality, weight gain, and severe hypoglycemia in patients at high risk of cardiovascular disease."

Hazard Ratio (95% CI) for Effects of Intensive vs Standard Therapy for Glycemia on Microvascular End Points in ACCORD, Pretransition and Over Five Years (Selected Outcomes)

End point	Pretransition, HR (95% CI)	Total follow-up, HR (95% CI)
1st composite end point^a	1.00 (0.88–1.14)	0.95 (0.85–1.07)
2nd composite end point^b	0.96 (0.89–1.02)	0.95 (0.89–1.01)
Microalbuminuria	0.79 (0.69–0.90); p=0.0005	0.85 (0.77–0.94); p=0.0012
Cataract surgery	0.90 (0.79–1.02); p=0.105	0.89 (0.80–0.99); p=0.0265
3-line change in visual acuity	0.84 (0.73–0.97);	0.94 (0.89–1.00);

	p=0.0163	p=0.0467
Loss of ankle jerk during Jendrassik maneuver	0.94 (0.87–1.01); p=0.10	0.90 (0.84–0.97); p=0.005
Loss of pressure sensation	0.88 (0.77–1.00); p=0.0451	0.85 (0.75–0.95); p=0.0043

a. Renal failure (dialysis or end-stage renal disease, renal transplantation, or irreversible rise in serum creatinine >3.3 mg/dL) or diabetic eye complications (retinal photocoagulation or vitrectomy to treat diabetic retinopathy)

b. Renal failure, diabetic eye complications, or development of neuropathy

"Hence, caution should be exercised in pursuit of a strategy of intensive glycemic control for prevention of microvascular complications in patients with established type 2 diabetes and characteristics similar to those in the ACCORD trial," they write. "An HbA_{1c} target of 6.0% or less with present strategies seems imprudent."

McGuire was cautious as well. "At the end of the day, you can look through all of these data, and there's no positive imperative to be more intensive than our standard therapy today. Most of the societies have endorsed [an A_{1c}] target of 7%, but there still remains a smoldering enthusiasm for being even more aggressive. It's been based on the hypothesis that microvascular-disease benefits will justify that." But the current ACCORD analyses, he said, "don't have any strong signal that that's the case."

Gerstein discloses being a consultant to Sanofi-Aventis, GlaxoSmithKline, Novo Nordisk, Eli Lilly, Bristol-Myers Squibb, AstraZeneca, Roche, Boehringer Ingelheim, and Bayer; delivering "scientific talks" for Sanofi-Aventis, GlaxoSmithKline, Eli Lilly, Boehringer Ingelheim, and Bayer; receiving research grants from Sanofi-Aventis, GlaxoSmithKline, and Novo Nordisk; and receiving education and CME grants from Sanofi-Aventis, GlaxoSmithKline, Novo Nordisk, Eli Lilly, Bristol-Myers Squibb, and AstraZeneca. Disclosures for the other ACCORD investigators and Klein are listed in the papers or available at www.nejm.org. McGuire reports being a consultant to AstraZeneca, Biosite, Daiichi-Sankyo, Hoffman-La Roche, Novo Nordisk, and Tethys.

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