LIPID CASE 254 Combination Therapy in T2DM The ACCORD Trial

I want to share a case that will get us into a discussion of the results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study at ACC last Sunday. First the case:

A 52 year old asymptomatic man with a history of venous thrombosis in 2003 had a CXR showing cardiac calcification but then had a "negative" coronary angiogram. He is normotensive and has a BMI of 29 (wt 215 lbs). At presentation he was using lifestyle and Coumadin. There is a family history of T2DM but no premature atherosclerosis.

He had the following initial profile 9 years ago

TC = 226 HDL-C = 40 LDL-C = 109 TG = 385 VLDL-C = 77 Non-HDL-C = 186 TG/HDL-C = 9.6
Large VLDL-P was significantly elevated
Total LDL-P was 1900 nmol/L (very high risk)
LDL size 20.1 (Pattern B) or small

His glucose values have run 98-104 with HgbA1c < 6). Liver enzymes have been normal with occasional minimal aminase elevations. Initial microalbumin level was slightly high.

In an attempt to get to lipoprotein goal (as now endorsed by the 2008 ACC/ADA consensus statement for patients with cardiometabolic risk) he was progressively over time treated with a statin (Crestor 20 mg), ezetimibe (Zetia) and fenofibrate (originally TriCor then Lipofen). He also uses 2000 mg daily of metformin

TC = 142 HDL-C = 54 LDL-C = 78 TG = 51 VLDL-C = 10 Non-HDL-C = 88 TG/HDL-C = .9
Large VLDL-P was borderline elevated
Total LDL-P was 966 nmol/L (perfect)
LDL size 20.4 (Pattern B) small but larger than previous

So I guess I get a star for lipoprotein management. However now we have the overall conclusion from the ACCORD study: The combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone. These results do not support the routine use of combination therapy with fenofibrate and simvastatin to reduce cardiovascular risk in the majority of high-risk patients with type 2 diabetes. (10.1056/NEJMoa1001282) was published on March 14, 2010, at NEJM.org). Should I stop the fenofibrate?

DAYSPRING DISCUSSION:

I used the statin/ezetimibe/fenofibrate regimen (in a stepwise fashion) in this patient because of the high TG and increased TG-rich lipoproteins which most of us believe significantly elevate this man's risk (evidenced by the increased large VLDL-P and LDL-P, most of which were small). I was aware of the DAIS (Diabetes Atherosclerosis Intervention Study Investigators) data (a very successful angiographic trial used fenofibrate monotherapy (with zero statin contamination) vs. placebo - Lancet 2001;357: 905–10). That was also the first trial to show that fenofibrate delayed the onset or caused a disappearance of microalbuminuria (a microvascular endpoint). Of course since then we have had The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study trial theoretically looking at fenofibrate vs. placebo in T2DM patients (of course lots of statin drop ins occurred in the higher risk folks with abnormal lipids) and despite the overall null outcome, we got evidence that in metabolic syndrome patients with TG/HDL axis disorders (like the patient at hand) there was very significant benefit in those using fenofibrate (Diabetes Care 32:493–498, 2009). Although very few still use gemfibrozil (because of medicolegal reasons in a polypharmacy world) and no one in the US uses bezafibrate we know from the Helsinki trial

(gemfib), and the BIP trial (beza) that the those fibrates were most successful in patients with elevated TG and low HDL-C. Glance at the following table (N Engl J Med 2010. DOI: 10.1056/NEJMoa1001282).

Trial (Drug)	Primary Endpoint: Entire Cohort (P-value)	Lipid Subgroup Criterion	Primary Endpoint: Subgroup (P-value)
HHS (Gemfibrozil)	-34% (0.02)	TG > 200 mg/dl LDL-C/HDL-C > 5.0	-71% (0.005)
BIP (Bezafibrate)	-7.3% (0.24)	TG $\geq$ 200 mg/dl	-39.5% (0.02)
FIELD (Fenofibrate)	-11% (0.16)	TG $\geq$ 204 mg/dl HDL-C < 42 mg/dl	-27% (0.005)
ACCORD (Fenofibrate)	-8% (0.32)	TG $\geq$ 204 mg/dl HDL-C $\leq$ 34 mg/dl	-31%

Looks like Fenofibrate duplicated the benefit all of the other fibrate trials in patients with elevated TG and low HDL-C. I do not know of any other drugs, other than statins that have such an impressive record of helping our patients with TG/HDL-C axis disorders reduce adverse outcomes. Niacin would come closest using angiographic but no outcome data.

So what do I now advise, after ACCORD Lipid about future use of fenofibrate? This trial actually reinforced a lot of what we previously knew and I believe supports continued aggressive care of high risk patients (with T2DM and/or metabolic syndromes) who have TG/HDL axis disorders (with a TG > 200 mg/dl) with statin/TG synthesis inhibitor use. TG synthesis inhibitor is a term I use to include fibrates/fibric acids, higher dose niacin (Niaspan) and very high dose N-3 fatty acid (Lovaza) therapy (all of those drugs do reduce TG beyond inhibiting FA and TG synthesis, but I find it a convenient description). In this case the microalbuminuria makes the feno the reasonable drug of choice to add on to the statin or statin/ezetimibe. As we all know in FIELD, in diabetics there was also significantly less need for laser photocoagulation therapy of the retina and a significant reduction in neuropathic-related amputations of feet and toes (an off label use of fenofibrate that must be considered in real world lipid management).

So let's look at the ACCORD Lipid trial in depth:

5518 patients with T2DM with TG< 700 or on-treatment TG < 400 and an abnormal HgbA1c (>7.5%)
LDL-C < 180 mg/dL HDL-C < 55 for blacks and women < 50 for all others
Mean Follow-Up: 4.7 years Mean Patient Age: 62 years % Female: 31%
Age: 40-79 years with clinical cardiovascular disease or age 55-79 years with subclinical cardiovascular disease or at least two additional cardiovascular risk factors

Endpoints:
Combination of the primary outcome plus revascularization or hospitalization for heart failure
Combination of a fatal coronary event, nonfatal myocardial infarction, or unstable angina
Nonfatal myocardial infarction
Nonfatal stroke
All cause death
Cardiovascular death
Hospitalization due to CHF
There were also prespecified subgroup endpoints including to look at those with the highest TB/HDL axis

Baseline data in both treatment and placebo arms:
BMI ~32 Normotensive
TG ~ 162 (interquartile range 113-229)
HDL-C ~ 38
LDL-C ~ 100
Females 1/3 of cohort Blacks 15% Hispanics 7%
No lipoprotein concentration or non-HDL-C data released (mindboggling)

2765 assigned to receive fenofibrate plus simvastatin and 2753 assigned to receive placebo plus simvastatin (20-40 mg as need to normalize HDL-C). In some patients other drugs were needed to achieve LDL-C goal (6%) likely with ezetimibe. The average simvastatin dose was only 22 mg. There was ~ 80% compliance rate with study drugs and placebo

Mean LDL-C fell from 100.0 to 81.1 in the fenofibrate group & from 101.1 to 80.0 in placebo group
Mean HDL-C increased from 38.0 to 41.2 mg per deciliter in the fenofibrate group & from 38.2 to 40.5 mg per deciliter in the placebo group.
Median TG decreased from 189.0 to 147.0 in the fenofibrate group & from 186.2 to 170.0 in placebo group.

Main Outcome: The annual rate of the primary outcome was 2.2% in the fenofibrate group, as compared with 2.4% in the placebo group (hazard ratio in the fenofibrate group, 0.92; 95% CI 0.79 to 1.08; P = 0.32)

Hazard ratios for the secondary outcomes, including the individual components of the primary outcome, ranged from 0.82 to 1.17 (P≥0.10 for all comparisons)

Annual rates of death from all causes were 1.5% in the fenofibrate group and 1.6% in the placebo group (hazard ratio, 0.91; 95% CI, 0.75 to 1.10; P = 0.33 Finally we have a fibrate trial where no one can conjecture about increasing overall or CV mortality (even though such data was always null in all previous trials)

In patients who had a TG level in the highest third (≥204) and an HDL-C level in the lowest third (≤34) were compared with all the other patients (P = 0.057 for interaction). In patients with high TG levels and low HDL-C levels, the primary outcome rate was 12.4% in the fenofibrate group, versus 17.3% in the placebo group, whereas such rates were 10.1% in both study groups for all other patients. The authors note: "*Our subgroup results and those of these previous trials support the view that the addition of fenofibrate to a statin may benefit patients with type 2 diabetes who have substantial dyslipidemia. The use of combination fibrate–statin therapy in such patients is consistent with current guidelines that recommend treatment for patients with hypertriglyceridemia and low HDL cholesterol levels that persist despite statin therapy."*

So why the heck did they even study folks with TG < 200 mg/dL? There was indeed no lower limit for TG which would make a person ineligible for trial entry. The authors point out (in the supplemental paper available on line) that in reality only 15-20% of diabetics have TG > 200

mg/dL and finding > 5000 such patients would have been impossible. They correctly mention if they would have excluded patients with TG < 200 mg, we would have had a trial that only enlightened us on 20% of the diabetic population (that have TG > 200 mg/dL). We really needed to know what statin/feno would offer all T2 diabetics. They thought that the first trial looking at combo therapy had to look at the entire T2DM population. No one can argue with that. As a result of ACCORD, we now are a lot smarter. We now pretty much know with as much certainty as we will ever have, that in T2DM patients without elevated TG there is no clear indication to add a fibrate to a statin to reduce events. We can still add colesevelam, ezetimibe or Niaspan to get to goal in those patients with TG < 200. However, we now have additional data (supporting the findings of Helsinki, BIP and FIELD) that fenofibrate works best in those with TG > 200 mg/dL (see table above). If you did lipoprotein evaluations of those patients you would find large VLDLs, VLDL remnants, CE-poor TG-rich large LDLs and lots of CE-poor small LDLs (all atherogenic particles contributing to apoB that usually do not respond well to statin monotherapy). Since the NCEP goal of therapy for patients with high TG is non-HDL-C, I wish they had analyzed that. There is no NMR analysis I am aware of from the study. It would be really interesting to see what happened to total HDL-P and HDL subspecies, which seemed to be so important in explaining the benefit of gemfibrozil in the VA-HIT trial.

World class experts (Frank Sachs, JC Fruchart, etc.) of the Residual Risk Reduction Initiative faculty (www.r3i.org web site) state the following (and if you are not regularly viewing this web site, please do so):
"The benefit of fenofibrate was only seen in the group of patients with atherogenic dyslipidemia, and none of the primary or secondary endpoints were statistically significant in the total study population which included many patients with LDL-C at goal and without combined atherogenic dyslipidemia. There is a risk that the positive and clinically important results seen in ACCORD Lipid will be lost in the context of ACCORD being seen as a 'negative' study. ----- ACCORD-Lipid shows that residual vascular risk can be safely and effectively addressed in patients with type 2 diabetes and atherogenic dyslipidemia. It is up to all of us to ensure that this message is communicated as effectively as possible to fellow physicians across the world as soon as possible."

I also believe we got lots of other great info from this trial. More data on how safe fenofibrate and statin are. Virtually no toxicity. No venous thromboses or PE whatsoever as was seen in FIELD. No myositis over statin/placebo. No pancreatitis. No gallbladder toxicity, no cancers, etc.

For whatever reason (and I offer no explanation) there seemed to be worse results in women (not adjusted for lipid quartiles). This is bizarre because In FIELD there was actually a trend towards more benefit in women than men. This is likely one of those unexplainable findings that occasionally show up when lots of data is analyzed.

So the Dayspring take home from ACCORD is:

In patients with cardiometabolic risk (high TG low HDL-C), especially those with T2DM the risk is high because of too many atherogenic lipoproteins (almost all explained by TG). Statin monotherapy helps, but residual risk remains unacceptable (the PROVE-IT trial showed if statins in ACS patients have the LDL-C < 70 but TG remains > 150, the residual risk is high). If on the statin or statin/ezetimibe (LDL receptor therapy) therapy the non-HDL-C remains high because the VLDL-C is high (remember VLDL-C is TG/5) then a fibrate add-on makes sense - so does high dose Niaspan or very high dose Lovaza (N-3 FA) but in diabetics the ACCORD results and the microalbumin benefit makes the fenofibrate an attractive as well as logical choice.