FIELD Substudy: Fenofibrate in Patients with Diabetes, by Gender [1]

Fenofibrate Intervention and Event Lowering in Diabetes

BOTTOM LINE

At face value the article suggests that fenofibrate *LIPIDIL* should be prescribed for females with diabetes, high TGs, and low HDL. However, there are a number of factors that would warrant not adopting this as routine practice.

1) Note that the original FIELD study (2005) did not find significant benefit on CV events overall (primary end point), and as a sub-study of a subgroup, the results for women discussed here, would generally be considered hypothesis generating - worthy of further evaluation. The result is somewhat marginal, and not without limitations.

2) The results from this sub-study in women rely heavily on "adjusted analysis", which takes into account the lack of randomization and unequal treatment that may confound such sub-study analysis. Of particular note here is the difference in statin use between men and women, and the attempt to adjust for the impact of this and other factors.

3) When looking at the whole of the lipid lowering literature around fibrates in general, the cardiovascular and all cause mortality results have been disappointing, especially when indirectly compared to the results seen in statin RCTs.

4) Statins are the gold standard for lipid lowering therapy when it comes to reducing CV events +/- all-cause mortality in those at high CV risk, including those with diabetes. Statins have consistently demonstrated more benefit than harm. On a somewhat related note, the ACCORD-Lipid trial found that fenofibrate failed to show additional benefit in someone with T2DM already on statin therapy.

If one wants to lower CV risk in a female with diabetes, a statin would still have evidence supporting a first line role. Fenofibrate would be reasonable in a female with T2DM who was unable to take a statin, or in whom achieving specific TC and HDL targets was specifically desired.

BACKGROUND

The original FIELD study was published in 2005.[2] FIELD asked whether fibrates could reasonably be used over statins in prevention of cardiovascular disease in diabetics. The results were a non-significant reduction in CHD, a significant reduction in non-fatal MI, and a non-significant increase in cardiovascular mortality. The evidence did not support changing the guidelines to reflect greater fenofibrate use.

ACCORD was published in 2010.[3] It showed the combination of fenofibrate and a statin did not lead to improved outcomes compared to using a statin alone in diabetics; in fact, there was a trend towards women doing worse.

In light of the ACCORD findings, the FIELD investigators re-published their 2005 data as a sub-analysis according to gender in an effort to show fenofibrate is safe in women.[1]

TRIAL BACKGROUND

DESIGN: Randomized, double-blinded, multi-centre (Australia, New Zealand, Finland), placebo-controlled trial. Funded by Abbott Pharmaceuticals and the National Health and Medical Research Council of Australia.

INTERVENTION: Fenofibrate (micronized) 200mg daily versus placebo for 5 years.

INCLUSION: Patients were required to have all of the following: a) 50-75 years of age; b) type 2 diabetes; c) initial plasma total cholesterol of 3.0-6.5 mmol/L; d) initial plasma total cholesterol/HDL-cholesterol ratio of 4.0 or more OR plasma triglyceride concentration of 1.0-5.0 mmol/L.

EXCLUSION: Patients were excluded if they met any of the following: a) were taking a lipid-modifying agent; b) had significant renal impairment; c) had chronic liver disease; d) had symptomatic gallbladder disease; e) had experienced a cardiovascular event in the previous 3 months.

♀ **POPULATION** mean at baseline (*n*=3657 over 5 years): age 62 years; diabetes duration 5 years; weight 82 kg; LDL-cholesterol 3.12 mmol/L; HDL cholesterol 1.21 mmol/L; triglycerides 1.79 mmol/L; anti-thrombotic agents 27%; ACE-I/ARB 41%; metformin 52%

♂ **POPULATION** mean at baseline (*n*=6138 over 5 years): age 63 years; diabetes duration 5 years; weight 89 kg; LDL-cholesterol 3.03 mmol/L; HDL cholesterol 1.03 mmol/L; triglycerides 1.70 mmol/L; anti-thrombotic agents 34%; ACE-I/ARB 37%; metformin 47%

ACCORD=Action to Control Cardiovascular Risk in Diabetes **ACEI**=angiotensin converting enzyme inhibitor **ARB**=angiotensin receptor blocker **ARR**=absolute risk reduction **CHD**=coronary heart disease **CV**=cardiovascular risk **FIELD**= Fenofibrate Intervention and Event Lowering in Diabetes **HDL**=high density lipoprotein **LDL**=low density lipoprotein **MI**=myocardial infarction **NNH**=number needed to harm **NNT**=number needed to treat **NS**=non-significant **NR**=not reported **RCT**=randomized controlled trial **RR**=relative risk **S**=significant **TG**=triglycerides **T2DM**=type-2 diabetes

RESULTS

	Placebo	Fenofibrate	RR	ARR	NNT / NNH (5 years)	Significance*
Men (62.7%)	n = 3067	n = 3071				
Coronary events	6.7%	6.3%	0.94	0.4%	-	p=0.49
Total cardiovascular events (1°)	16.6%	15.4%	0.93	1.2%	-	p=0.20
Cardiovascular mortality	2.8%	3.5%	1.25	-0.7%	-	p=0.09
Non-fatal myocardial infarction	4.9%	3.8%	0.78	1.1%	-	p=0.05
Stroke	4.2%	3.8%	0.90	0.4%	-	p=0.41
All revascularization	12.0%	9.9%	0.82	2.1%	48	p=0.01
Overall mortality	8.0%	8.7%	1.09	-0.7%	-	NR
Cancer death	3.9%	3.8%	0.97	0.1%	-	NS
New invasive cancers	8.3%	8.7%	1.05	-0.4%	-	NS
Rhabdomyolysis	0.0%	0.1%	-	-0.1%	-	NS
Women (37.3%)	n = 1833	n = 1824				
Coronary events	4.5%	3.5%	0.78	1%	-	0.12
Total cardiovascular events (1°)	9.5%	7.7%	0.81	1.8%	56	p=0.02
Cardiovascular mortality	2.3%	1.8%	0.78	0.5%	-	0.26
Non-fatal myocardial infarction	3.1%	2.2%	0.71	0.9%	-	0.09
Stroke	2.5%	2.3%	0.92	0.2%	-	0.68
All revascularization	5.6%	4.2%	0.75	1.4%	-	0.06
Mortality	5.0%	5.7%	1.14	-0.7%	-	NR
Cancer death	1.7%	2.7%	1.59	-1.0%	-	NS
New invasive cancers	6.6%	7.0%	1.06	-0.4%	-	NS
Rhabdomyolysis	0.0%	0.0%	-	0.0%	-	NS

*p values provided for unadjusted analysis

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

• Large, well-designed study with a high number $^{n=3657}$ of female diabetics.

LIMITATIONS:

• 16.3% of women on fenofibrate began a statin during the study, while 37% of women on placebo began a statin during the study. In men the initiation rates were 21% and 36%, respectively. An attempt was made to adjust analysis based on the presence of statin therapy. Nonetheless, statin therapy was a large confounder and creates uncertainty in the results.

UNCERTAINTIES:

• ACCORD showed a trend towards harm in women taking fenofibrate with a statin; FIELD showed a trend towards benefit in women taking fenofibrate (mostly) without a statin. Neither study reached statistical significance.
• Fenofibrate raises HDL cholesterol and reduces triglycerides. Approximately 25% of the studied population had HDL cholesterol ≤ 0.88 mmol/L and triglycerides >2.3 mmol/L at baseline. However, cardiovascular event reductions in this population were non-significant.
• FIELD does not provide convincing evidence that fenofibrate should be used first-line over a statin in diabetic patients. Any potential benefits are small compared to the well-documented benefits of statins. Meanwhile, ACCORD may indicate that statins and fibrates are unsafe in women as combination therapy. **Thus the only good female candidates for fenofibrate therapy may be those who have been unable to tolerate multiple trials of statins.**

1. d'Emden, Michael C., et al. "Favourable effects of fenofibrate on lipids and cardiovascular disease in women with type 2 diabetes: results from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study." *Diabetologia* 57.11 (2014): 2296-2303.
2. Keech, A., et al. "Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial." *Lancet* 366.9500 (2005): 1849-1861.
3. The ACCORD Study Group. "Effects of combination lipid therapy in type 2 diabetes mellitus." *The New England journal of medicine* 362.17 (2010): 1563.