

### Evidence Tables

**FIB 1: Are fibrates effective in improving lipid profiles and other outcomes compared to other treatments or placebo in people with type 2 diabetes?**

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding
Anon. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): Randomised controlled trial. <i>Lancet</i> . 2005; 366(9500):1849-1861. Ref ID: 658	RCT, double-blind, multi-centre  1++	N=9795 (N=2131 with previous cardiovascular disease, N=7664 without)  63 centres in Australia (N=6051), New Zealand (N=2351) and Finland (N=1393), recruited from hospital clinics and community-based sources	Inclusion criteria: type 2 diabetes, aged 50-75yrs, initial plasma total-cholesterol of between 3.0-6.5 mmol/L, either a total cholesterol/HDL-cholesterol ratio of 4.0 or more or a plasma triglyceride concentration of between 1.0 and 5.0mmol/L, with no clear indication for or treatment with, lipid-modifying therapy at study entry. Exclusion criteria: renal impairment (blood creatinine >130µmol/L), chronic liver disease or symptomatic gallbladder disease, and a cardiovascular event within 3 months before recruitment	N=4895 fenofibrate 200mg single daily dose with breakfast	N=4900 placebo single daily dose with breakfast	5 years (4-6 monthly study visits) <sup>1</sup>  Initially participants had a 16 week run-in period comprising 4 weeks of dietary modification, 6 weeks single-blind placebo and 6 weeks of single-blind fenofibrate therapy. There was no formal restriction on subsequent randomisation related to compliance	Weight, blood pressure, fasting plasma lipids, all major cardiovascular events (MI, strokes, death)  Adverse events	*Plasma lipids – full cohort Absolute (mmol/L) and relative (%) differences between treatment groups, fenofibrate compared with placebo p<0.05 for all time points.  <i>Total cholesterol</i> 4 mths: -0.58 (-11.4%) 1yr: -0.58 (-11.6%) 2 yrs: -0.56 (-11.1%) Study close: -0.33 (-6.9%)  <i>LDL cholesterol</i> 4 mths: -0.39 (-12.0%) 1yr: -0.38 (-11.9%) 2 yrs: -0.36 (-11.7%) Study close: -0.17 (-5.8%)  <i>HDL cholesterol</i> 4 mths: 0.05 (5.1%) 1yr: 0.05 (4.5%) 2 yrs: 0.04 (3.5%) Study close: 0.01 (1.2%)  <i>Triglycerides</i> 4 mths: -0.56 (-28.6%) 1yr: -0.58 (-30.2%)	Laboratoires Fournier

<sup>1</sup> Usual care from health professionals was on-going throughout the study, decisions about changes in therapy for diabetes or co-morbid conditions, including lipid lowering therapy were at the discretion of the primary care physician or specialist physician.

			The two treatment groups were well matched for baseline characteristics			during the run-in period.	<p>2 yrs: -0.52 (-27.4%) Study close: -0.41 (-21.9%)</p> <p>For those participants who started other lipid-lowering therapy(fenofibrate N=944, placebo N=1776, by study end), results for the first 2 years of the study showed the decreases in total cholesterol, LDL cholesterol and triglycerides and the increases in HDL cholesterol were smaller, significance between the treatment groups remained (p&lt;0.05). At study close the significant difference remained for total cholesterol (-0.08, -1.6%) and for triglycerides (-0.24, -10.9%), however, for LDL cholesterol there was a small NS increase and for HDL cholesterol a small NS decrease.</p> <p>*Apolipoprotein levels Compared with placebo fenofibrate increased concentrations of apolipoprotein A1 and A2 by 3.9% and 28% and decreased B by -13.6% at 4 months, at study close the differences were 1.8%, 23.37% and -7.5% respectively.</p> <p>*Clinical outcomes Primary - there was a significant 24% relative reduction in non-fatal MI with fenofibrate compared with placebo Secondary – for total cardiovascular disease events there was a significant 11% reduction with fenofibrate.</p> <p>*Adverse events N=38 (0.8%) in the fenofibrate and</p>
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								<p>N=24 (0.5%) in the placebo group had possible serious adverse drug reactions.</p> <p>N=1, placebo and N=3 fenofibrate had rhabdomyolysis, all resolved fully.</p> <p>Those in the fenofibrate group had significantly higher rates of pancreatitis and pulmonary embolism, but this was 1% or less in both groups.</p> <p>There were similar numbers of patients with newly diagnosed cancer in both groups.</p> <p>GI adverse events were the highest reported in both groups with 20% (N=975) reporting GI events in the fenofibrate group and 19% (N=927) in the placebo group</p> <p>*Discontinuation At 5 yrs; 950 (19%) of the placebo group and 954 (20%) of the fenofibrate group had discontinued study medication</p>	
<p>Anon. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study.[erratum appears in Lancet 2001 Jun</p>	<p>RCT, placebo controlled</p> <p>1++</p>	<p>N=418, 11 centres in Canada, Finland, France and Sweden</p>	<p>Inclusion criteria: T2D, aged 40-65 yrs, with or without previous coronary intervention, on treatment with glucose-lowering drugs, diagnosis after age 35, no history of ketoacidosis, adequate glycaemic control (HbA1c &lt;170% of the laboratory's upper limit), total cholesterol to HDL cholesterol ratio of 4 or more, plus either an</p>	<p>N=207 fenofibrate 200mg/day</p>	<p>N=211 placebo</p>	<p>At least 3 years, maximum treatment period was 57 months</p>	<p>Angiographic changes, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides</p>	<p>*Angiographic changes The fenofibrate group showed a 40% less progression in minimum lumen diameter compared with placebo (-0.06 vs. -0.10, p=0.029), 42% less progression in percentage diameter stenosis (2.11 vs. 3.65, p=0.02) and 25% (NS) less progression in mean segment diameter.</p> <p>*Lipids There were significant decreases in total cholesterol, LDL cholesterol and triglycerides and increases in HDL cholesterol in the fenofibrate group</p>	<p>Laboratoires Fournier</p>

<p>9;357(9271):1890].  <i>Lancet</i>. 2001;  357(9260):905-910.  Ref ID: 3388</p>			<p>LDL cholesterol concentration of 3.5-4.5mmol/L and triglyceride concentration of 5.2mmol/L or less , or an LDL cholesterol concentration of 4.5mmol/L or less and triglyceride concentration of 1.7-5.2mmol/L</p> <p>Groups were similar; the placebo group had slightly higher HDL cholesterol and fasting glucose concentrations than the fenofibrate group. Half of the participants had a clinical history of coronary disease.</p> <p>The American Heart Association/National Cholesterol Education programme step 1 diet was maintained throughout the treatment period. Glucose-lowering drug adjustment was allowed to optimise control in the individual patient.</p>					<p>compared with placebo (p&lt;0.001)</p> <p>*Discontinuation N=9 (fenofibrate) and N=15 (placebo) did not undergo their final angiogram</p> <p>*Adverse events  There were few serious AEs with no significant differences between the groups</p>	
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<p>Derosa G, Cicero AE, Bertone G et al. Comparison of fluvastatin + fenofibrate combination therapy and fluvastatin monotherapy in the treatment of combined hyperlipidaemia, type 2 diabetes mellitus, and coronary heart disease: a 12-month, randomized, double-blind, controlled trial. <i>Clinical Therapeutics</i>. 2004; 26(10):1599-1607. Ref ID: 3380</p>	<p>RCT, double-blind  1++</p>	<p>N=48, Italy</p>	<p>Inclusion criteria: aged 18-80 years, T2D, combined hyperlipidaemia (TC <math>\geq</math>200mg/dL, LDL-C <math>\geq</math>100mg/dL and TG <math>\geq</math>150mg/dL), CHD (defined as a history of MI, last episode of acute CHD &gt; 2 years prior to study entry)</p> <p>Exclusion criteria: uncontrolled hypertension (SBP &gt;140mmHG and/or DBP &gt;90mmHg), uncontrolled hypothyroidism, obstructive hepatic or biliary disease, alcoholism, autoimmune disease, chronic pancreatitis, active liver disease or hepatic dysfunction, muscle toxicity, known hypersensitivity to fibrates or statins, treatment with any lipid lowering drugs, use of heparin/oral anticoagulants/drugs associated with rhabdomyolysis in</p>	<p>N=25 fluvastatin 80mg (extended release) + fenofibrate 200mg</p>	<p>N=23 fluvastatin 80mg (extended release) + matched placebo</p>	<p>12 months</p>	<p>LDL-C, HDL-C, TC, TG levels HbA1c, fasting plasma glucose, postprandial glucose, Tolerability assessment</p>	<p>*Lipid levels 6 months - there were significant decreases in LDL-C and TC and increases IN HDL-C for the combination group compared with baseline. 12 months - there were significant decreases in LDL-C, TC and Tg levels and increases IN HDL-C for the combination group compared with baseline. Changes NS for monotherapy at 6 and 12 months.</p> <p>6 months – the decrease in LDL-C was significantly greater for the combination group than for the monotherapy (-25% vs. -13%, p&lt;0.05)</p> <p>12-months – the changes in LDL-C, HDL-C and Tg levels were significantly greater in the combination group compared with the monotherapy (LDL-C -35% vs. -25%; HDL-C 34% vs. 14%; Tg -34% vs. -17%, p&lt;0.05 for all).</p> <p>*HbA1c, FPG, PPG Changes in all (except HbA1c at 12 months which was significantly lower than the baseline for the combination group) at 12 months were NS compared to baseline and NS between the groups.</p> <p>*Adverse events There were serious AEs. 8.6% (monotherapy) and 12.0% (combination) reported AEs.</p>	<p>Not stated</p>
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<sup>2</sup> At enrolment all participants were following a dietary regimen, were receiving insulin therapy and were instructed to undertake physical therapy.

<sup>3</sup> Participants were allowed to use prescribed medications for comorbidities

			<p>combination with a statin/fibrate, treated with drugs with known effects on plasma lipid levels, history of MI, angioplasty or major surgery in the last 6 months.<sup>2 3</sup></p> <p>Demographic characteristics, lipid profile, utilisation of cardiac drugs and glycaemic status were comparable at baseline.</p>					<p>*Discontinuation N=5 did not complete the study (N=3 from the combination group and N=2 from the monotherapy group). N=2 (combination group) and N=1 monotherapy discontinued due to myalgia, N=1 monotherapy withdrew due to gastritis.</p>
<p>Muhlestein JB, May HT, Jensen JR et al. The reduction of inflammatory biomarkers by statin, fibrate, and combination therapy among diabetic patients with mixed dyslipidemia: the DIACOR (Diabetes and Combined Lipid Therapy Regimen) study. <i>Journal of the American College of Cardiology</i>. 2006; 48(2):396-401. Ref ID: 3376</p>	<p>RCT, double-blind 1++</p>	<p>N=300, single-centre, USA, ITT analysis</p>	<p>Inclusion criteria: T2D, HbA1c <math>\leq</math>9%, if taking hypoglycaemics must be on a stable dose for the previous 3 mths, if taking anti coagulants will have standard adjustment of anti coagulant dose, documented post wash-out dyslipidaemia defined as at least two of; LDL <math>\geq</math>100mg/dl, triglycerides <math>\geq</math>200mg/dl, HDL &lt;40mg/dl</p> <p>Exclusion criteria: T1D, creatinine kinase &gt;50% above upper limit of normal, history of coronary disease, myopathy or rhabdomyolysis, active</p>	<p>N=100 Simvastatin 20mg and fenofibrate placebo</p> <p>N=100 Fenofibrate 160mg and simvastatin placebo</p>	<p>N=100 Simvastatin 20mg and fenofibrate 160mg</p>	<p>12 weeks</p>	<p>High-sensitivity C-reactive protein (hsCRP), lipoprotein-associated phospholipase A2 (Lp-PLA2), lipids levels</p>	<p>*comparison with baseline Significant decreases in Lp-PLA2, total cholesterol, LDL-C, triglycerides and nonHDL-C, and increases in HDL-C were identified with all treatment groups; simvastatin, fenofibrate and the combination of simvastatin and fenofibrate. With hsCRP decreases with the fenofibrate and combined groups were NS, significant decreases were identified only with the simvastatin group</p> <p>*hsCRP NS were identified between the treatment groups</p> <p>*Lp-PLA2 NS changes were identified between the treatment groups</p> <p>*Total cholesterol</p>

			<p>liver disease, use of lipid lowering agents within the 6 (statins, fish oils, nicotinic acid, bile acid sequestrants) or 8 (fibrates) weeks prior to randomisation, uncontrolled hypertension, proteinuria, hypothyroidism, prohibited concomitant medications, hypersensitivity to statins or fibrates, partial ileal bypass</p> <p>Groups were broadly similar at baseline</p>					<p>Reductions with fenofibrate (226.2 to 196.1, -1.2%) were significantly lower than those found for simvastatin (229.3 to 169.1, -26.2%), <math>p &lt; 0.0001</math> and the combined group (230.7 to 165.2, -27.1%), <math>p &lt; 0.0001</math>. The reductions were NS between the simvastatin and combination groups.</p> <p><b>*LDL-C</b> Reductions with fenofibrate (135.4 to 121.7, -5.6%) were significantly lower than those found for simvastatin (141.3 to 92.0, -34.1%), <math>p &lt; 0.0001</math> and the combined group (136.9 to 92.0, -29.1%), <math>p &lt; 0.0001</math>. The reductions were NS between the simvastatin and combination groups.</p> <p><b>*non HDL-C</b> Reductions with fenofibrate (188.1 to 153.6, -16.1%) were significantly lower than those found for simvastatin (193.4 to 129.8, -32.5%), <math>p &lt; 0.0001</math> and the combined group (195.0 to 124.7, -34.3%), <math>p &lt; 0.0001</math>. The reductions were NS between the simvastatin and combination groups.</p> <p><b>*HDL-C</b> There was NS in the increases in HDL-C between the treatment groups</p> <p><b>*Triglycerides</b> Reductions with fenofibrate (270.5 to 154.5, -38.2%) were significantly higher than those found for simvastatin (230.0 to 182.5, -24.8%), <math>p = 0.001</math>. Reductions with simvastatin (230.0 to</p>	
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								182.5, -24.8%) were significantly lower than those found for the combination (284.0 to 138.0, -49.4%), p<0.0001. The changes were NS between the fenofibrate and combination groups.  *Adverse events No serious drug-related clinical AEs occurred, clinical AEs were similar among treatment groups  *Discontinuation N=19 dropped out of the study, none due to clinically drug related AEs	
Schweitzer M, Tessier D, Vlahos WD et al. A comparison of pravastatin and gemfibrozil in the treatment of dyslipoproteinemia in patients with non-insulin-dependent diabetes mellitus. <i>Atherosclerosis</i> . 2002; 162(1):201-210. Ref ID: 237	RCT, double-blind  1++	N=268 pre randomisation phase, 136 (50.7%) eligible for the study  ITT on N=136, per protocol on N=112  10 centres, Canada	Inclusion criteria: T2D, hypercholesterolaemia, those taking lipid lowering drugs could be include following a 4 week withdrawal (bile-acid binding agents, niacin, statins) prior to first lipid specimen and at least 8 weeks prior to randomisation, or a 8 week withdrawal (fibrates, probucol) prior to first lipid specimen and at least 12 weeks prior to randomisation, HbA1c ≤10% after pre-randomisation phase  Groups were similar with regard to clinical and demographic characteristics at baseline.	N=66 gemfibrozil 1200mg and pravastatin matched placebo  for 16 weeks following a single-blind 4 week placebo lead-in	N=70 pravastatin 40mg and gemfibrozil matched placebo  for 16 weeks following a single-blind 4 week placebo lead-in	28 weeks  8-12 weeks pre randomisation phase (dietary stabilisation/ drug washout 4-8 weeks; placebo lead-in period of 4 weeks)  16 weeks post randomisation phase	Total cholesterol, triglycerides, VLDL-C, LDL-C, HDL-C, changes in apolipoproteins and lipoprotein families	*Total cholesterol There was a significantly greater reduction in total cholesterol with pravastatin (-1.35) than with gemfibrozil (-0.42), p<0.001.  *LDL-C There was a significantly greater reduction in LDL-C with pravastatin (-1.3) than with gemfibrozil (-0.22), p<0.001  *TG There was a significantly greater reduction in TG levels with gemfibrozil (-0.77) than with pravastatin (-0.27), p<0.001.  *VLDL-C There was NS difference between the groups  *HDL-C There was NS difference between the groups	Bristol-Myers Squibb

								<p>*Apolipoproteins Pravastatin reduced concentrations of apoB (-24.9 compared with -6.5) and cholesterol rich Lp-B (-20.9 compared with -3.2) significantly more than gemfibrozil, p&lt;0.001. Other changes were NS</p> <p>*Adverse events There were N=121 AEs in the gemfibrozil group and N=153 in the pravastatin group, most were not severe, the most frequent were GI related (N=28 gemfibrozil, N=24 pravastatin)</p> <p>*Discontinuation N=6 (9.1%) gemfibrozil group and N=2 (2.8% in the pravastatin group discontinued the study treatment</p>	
Ashraf R, Amir K, Shaikh AR. Comparison between duration dependent effects of Simvastatin and Gemfibrozil on dyslipidemia in patients with type 2 diabetes. <i>JPMA - Journal of the Pakistan Medical</i>	RCT 1+	N=70, in Pakistani population	Inclusion criteria: type 2 diabetes, newly diagnosed dyslipidaemia (serum LDL-cholesterol above 130mg/dl, serum triglyceride above 150mg/dl, serum total cholesterol above 200mg/dl and serum HDL-cholesterol below 40mg/dl, >25 years	N=35, gemfibrozil 600mgs, BD with meals <sup>4</sup>	N=35, simvastatin 20mgs, once daily in the evening	12 weeks	Lipid profile, serum glucose	<p>*Lipid profile There were progressive, significant decreases with simvastatin and gemfibrozil for total cholesterol and triglycerides (p&lt;0.001) and progressive increases in HDL-cholesterol (p&lt;0.001). There were progressive and significant decrease in LDL-cholesterol with simvastatin (p&lt;0.001), but not with gemfibrozil.</p>	Not stated

<sup>4</sup> Both groups were advised and given a written diet and exercise plan.

Association. 2005; 55(8):324-327. Ref ID: 74			Exclusion criteria: allergy to simvastatin or gemfibrozil, type 1 diabetes, history of MI, CABG, CAD, unstable angina, clinically manifest heart failure, patients with acute liver conditions, impaired renal function, those taking systemic steroids, androgens, cyclosporine, immunosuppressant drugs or any other drug which may interact with anti lipidemic drugs.					*Discontinuation N=11 (N=6 in the gemfibrozil group, N=5 in the simvastatin group) Adverse events reported and causing drop-outs; N=4 gastric upset and diarrhoea (all gemfibrozil group), N=3 generalised weakness and muscle pain (all simvastatin group).	
Athyros VG, Papageorgiou AA, Athyrou VV et al. Atorvastatin and micronized fenofibrate alone and in combination in type 2 diabetes with combined hyperlipidemia.[see comment]. <i>Diabetes Care</i> . 2002; 25(7):1198-1202. Ref ID: 227	RCT 1+	N=120	Inclusion criteria: type 2 diabetes with combined hyperlipidaemia (CHL, total cholesterol >220mg/dl (5.7mmol/l), LDL cholesterol >130mg/dl (3.4mmol/l) triglycerides from 200 to 399mg/dl (2.3 to 4.5mmol/l) and apolipoprotein B >150mg/dl), HbA1c<8.5% <sup>5, 6</sup>  At baseline there were	N=40 fenofibrate 200mg/day  N=40 atorvastatin 20mg/day	N=40 combination of fenofibrate 200mg/day and atorvastatin 20mg/day	24 weeks	Glycaemic control, lipids, treatment goals, estimated MI risk, adverse events	*HbA1c HbA1c remained unchanged throughout the study in all groups.  *Lipids Combination treatment reduced total cholesterol (-37), triglycerides (-50) and LDL cholesterol (-46) significantly more than atorvastatin (-31, -30 and -40 respectively, p<0.05) and significantly more than fenofibrate (-16, -41 and -40 respectively, p<0.05).  Apolipoprotein A-1 increased significantly with combination treatment	Not stated

<sup>5</sup> Participants were on the National Cholesterol Expert Panel step 2 hypolipidaemic diet for 6 weeks, during which they received a placebo daily, following this if they still met the inclusion criteria they continued with the study.

<sup>6</sup> Hypoglycaemic or other concurrent treatments remained unchanged throughout the study

			no significant differences between the 3 groups					<p>(12) compared with monotherapy (atorvastatin, 3 and fenofibrate, 6, <math>p &lt; 0.05</math>). apolipoprotein B-100 decreased significantly with combination treatment (-41) compared with monotherapy (atorvastatin, -31 and fenofibrate, -14, <math>p &lt; 0.05</math>)</p> <p>Combination treatment significantly increased HDL cholesterol (22) compared with atorvastatin (16, <math>p &lt; 0.05</math>), but NS compared with fenofibrate.</p> <p>*Treatment goals The goal for LDL cholesterol of <math>&lt; 100 \text{ mg/dl}</math> (<math>2.4 \text{ mmol/l}</math>) was reached by 97.5% of those taking combination therapy which was significantly higher than for the monotherapy treatments. 80% of those in the atorvastatin group reached the LDL treatment goal which was significantly higher than the 5% for fenofibrate (<math>p &lt; 0.05</math>).</p> <p>The goal for triglycerides of <math>&lt; 200 \text{ mg/dl}</math> (<math>2.6 \text{ mmol/l}</math>) was reached by 100% of those taking combination therapy which was significantly higher than for the monotherapy treatments. 92.5% of those in the fenofibrate group reached the Tg treatment goal which was significantly higher than the 75% for atorvastatin (<math>p &lt; 0.05</math>).</p> <p>The goal for HDL cholesterol of <math>&gt; 45 \text{ mg/dl}</math> (<math>1.2 \text{ mmol/l}</math>) was reached by 60% of those taking combination therapy which was significantly higher</p>
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								<p>than for the monotherapy treatments. 30% of those in the fenofibrate group reached the HDL treatment goal which was significantly higher than the 17.5% for atorvastatin (p&lt;0.05).</p> <p>*Estimated risk of MI At baseline this was calculated to be 21.6%. This reduced to 4.2% with combination treatment significantly more than the monotherapy treatments (p&lt;0.05). With atorvastatin it reduced to 7.5%, significantly more than the 10.9% with fenofibrate (p&lt;0.05).</p> <p>*Adverse events No significant adverse events were recorded and no participants withdrew due to adverse events.</p>	
<p>Durrington PN, Tuomilehto J, Hamann A et al. Rosuvastatin and fenofibrate alone and in combination in type 2 diabetes patients with combined hyperlipidaemia. <i>Diabetes Research &amp; Clinical Practice</i>. 2004; 64(2):137-151. Ref ID: 3382</p>	<p>RCT, both double-blind and open-label phases, multi-centre</p> <p>1+</p>	<p>N=216, 47 centres in Northern Europe</p>	<p>Inclusion criteria: &gt;18 years, type 2 diabetes, hypertriglyceridaemia, HbA1c &lt;10%. Following completion of 6 week dietary lead-in period to be included further they had a fasting triglyceride between ≥200 and &lt;800mg/dl (≥2.26 to &lt;9.03mmol/l) and total cholesterol ≥200mg/dl (≥5.17mmol/l) and demonstrated compliance with the</p>	<p>N=51, placebo during double blind stage, rosuvastatin 10/20/40mg during dose titration phase<sup>7,8</sup></p> <p>N=49 placebo during double blind</p>	<p>N=60 rosuvastatin 5 mg during double blind stage, fenofibrate 67 mg once daily/BD/TID during dose titration phase</p> <p>N=53 rosuvastatin 5mg during double blind</p>	<p>32 weeks</p> <p>6 week lead-in, 6 week double blind fixed dose, 18 week open-label dose titration study divided into differing treatment blocks of 6 weeks</p>	<p>Fasting triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, apolipoprotein (apo) A-I, apo B, lipoprotein ratios (LDL:HDL,</p>	<p>Fixed dose phase</p> <p>*Triglycerides Decreased by -24.5% with rosuvastatin 5mg and -29.5% with rosuvastatin 10mg, both p&lt;0.001 vs. placebo which increased by 4.7%.</p> <p>*LDL-cholesterol Decreased by -40.7% with rosuvastatin 5mg and -45.8 with rosuvastatin 10mg, both p&lt;0.001 vs. placebo which decreased by -0.6%.</p> <p>*Total cholesterol Decreased by -36.6% with rosuvastatin</p>	<p>AstraZenica</p>

<sup>7</sup> Dosing was sequentially increased at 6-week intervals in the dose-titration phase for as long as the LDL cholesterol remained >50mg/dl (>1.3mmol/l)

<sup>8</sup> Minor dose adjustments of oral hypoglycaemic agents were made to ensure that fasting blood glucose remained <200mg/dl (11.0mmol/l) throughout the trial

			<p>NCEP step 1 diet (Eating Pattern Assessment Tool score of <math>\leq 28</math>).</p> <p>Exclusion criteria: type 1 diabetes, history of DKA, use of lipid lowering agents, acute ischaemic event in the previous 3 months, uncontrolled hypertension, active liver disease or hepatic dysfunction</p> <p>Treatment groups were generally well balanced</p>	<p>stage, fenofibrate 67 mg once daily/BD/TID during dose titration phase</p>	<p>stage, fenofibrate 67 mg once daily/BD/TID during dose titration phase</p>		<p>total cholesterol: HDL, non-HDL:HDL cholesterol, apo B: apo A-I</p>	<p>5mg and -31.4% with rosuvastatin 10mg, both <math>p &lt; 0.001</math> vs. placebo which increased by 1.1%.</p> <p>*Apo B Decreased by -34.2% with rosuvastatin 5mg and -38.9% with rosuvastatin 10mg, both <math>p &lt; 0.001</math> vs. placebo which decreased by -0.4%.</p> <p>*VLDL cholesterol Decreased by 33.9% with rosuvastatin 5mg and 34.9% with rosuvastatin 10mg, both <math>p &lt; 0.001</math> vs. placebo which increased by 4.7%.</p> <p>*HDL cholesterol Increased by 9.9% with rosuvastatin 5mg and 10.1% with rosuvastatin 10mg, both <math>p &lt; 0.001</math> vs. placebo which increased by 1.2%.</p> <p>*Apo A-I Increased by 3.0% with rosuvastatin 5mg and 0.7% with rosuvastatin 10mg, both <math>p &lt; 0.0253</math> vs. placebo which decreased by -1.4%.</p> <p>*LDL-C:HDL-C ratio Decreased by -45.6% with rosuvastatin 5mg and -50.6% with rosuvastatin 10mg, both <math>p &lt; 0.001</math> vs. placebo which decreased by -2.0%.</p> <p>*LDL-C goal At week 6 77.4% of those receiving rosuvastatin 10mg had reached the American Diabetes Association (ADA) LDL-C goal of <math>&lt; 100</math>mg/dl, compared</p>	
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								<p>with 8.3% in the combined placebo group.</p> <p><i>Dose titration phase</i> By the final stage of the dose-titration a smaller proportion of those in the groups which received rosuvastatin 10mg initially required titration upwards than in the other two groups.</p> <p>*Triglycerides Reductions in triglyceride levels between placebo/rosuvastatin and placebo/fenofibrate were NS. The decrease with rosuvastatin 10mg/fenofibrate group (-47.1%) was significant compared with the placebo/rosuvastatin (-30.3%), p=0.001</p> <p>*LDL-C There was a significant decrease in LDL cholesterol with placebo/rosuvastatin compared with an increase with placebo/fenofibrate (-46.7% vs. 0.7%, p&lt;0.001. There was a significant decrease with placebo/rosuvastatin compared with rosuvastatin 5mg/fenofibrate (-46.7% vs. -34.1%, p&lt;0.001), this was NS compared with rosuvastatin 10mgfenofibrate (-42.4%)</p> <p>*Apo B There was a significantly lower reduction in the placebo/fenofibrate (-7.6%) compared with placebo/rosuvastatin (-41.4%) group. The decreases in the rosuvastatin 5mg + fenofibrate (-35.0) and in the</p>
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								<p>rosuvastatin 10mg + fenofibrate group (-36.3%) were NS compared with the placebo/rosuvastatin</p> <p><b>*VLDL-C</b> Decreased NS in the placebo/fenofibrate (-30.1%), the rosuvastatin 5mg + fenofibrate (-46.8%) and in the rosuvastatin 10mg + fenofibrate (-44.2%) groups compared with the placebo/rosuvastatin (-43.6%) group</p> <p><b>*HDL-C</b> Increased NS in the placebo/fenofibrate (9.2%), the rosuvastatin 5mg + fenofibrate (10.8%) and in the rosuvastatin 10mg + fenofibrate (11.7%) groups compared with the placebo/rosuvastatin (6.4) group</p> <p><b>*Apo A-I</b> Increased NS in the placebo/fenofibrate (5.0%), the rosuvastatin 5mg + fenofibrate (4.7%) and in the rosuvastatin 10mg + fenofibrate (5.4%) groups compared with the placebo/rosuvastatin (2.7%) group</p> <p><b>*LDL-C:HDL-C ratio</b> There were significant decreases in the placebo/fenofibrate (-6.3%, p&lt;0.001) and in the rosuvastatin 5mg +fenofibrate (-38.8%, p=0.001) groups compared with the larger decrease with placebo/rosuvastatin (-48.9%) group. The decrease in the rosuvastatin 10mg + fenofibrate group (-46.8%) was NS compared with the placebo/rosuvastatin</p>	
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								<p>*Total cholesterol:HDL-C ratio There was a significantly lower reduction in the placebo/fenofibrate (-13.9%) compared with placebo/rosuvastatin (-39.2%) group. The decreases in the rosuvastatin 5mg + fenofibrate (-36.2%) and in the rosuvastatin 10mg + fenofibrate group (-41.9%) were NS compared with the placebo/rosuvastatin</p> <p>*Non-HDL-C:HDL-C ratio There was a significantly lower reduction in the placebo/fenofibrate (-16.6%) compared with placebo/rosuvastatin (-47.3%) group. The decreases in the rosuvastatin 5mg + fenofibrate (-43.5%) and in the rosuvastatin 10mg + fenofibrate group (-50.4%) were NS compared with the placebo/rosuvastatin</p> <p>*Apo B:Apo A-I ratio: There was a significantly lower reduction in the placebo/fenofibrate (-11.3%) compared with placebo/rosuvastatin (-41.9%) group. The decreases in the rosuvastatin 5mg + fenofibrate (-37.2%) and in the rosuvastatin 10mg + fenofibrate group (-42.7%) were NS compared with the placebo/rosuvastatin</p> <p>For each group those who attained the ADA goal of LDL-C of &lt;100mg/dl at week 24 were; rosuvastatin 40mg (86.0%, N=50); rosuvastatin 10mg + fenofibrate 67mg TID (75.5%, N=53);</p>	
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								<p>rosuvastatin 5mg + fenofibrate 67 TID (75.0%, N=60); fenofibrate (4.1%, N=49).</p> <p>*Adverse events  Placebo/rosuvastatin: flatulence (N=2), nausea (N=2), myalgia (N=1)  Placebo/fenofibrate: constipation (N=2), diarrhoea (N=1), flatulence (N=3), nausea (N=1), CK increase (N=1), headache (N=4), myalgia (N=1)  Rosuvastatin 5mg + fenofibrate: constipation (N=1), diarrhoea (N=2), flatulence (N=1), GGPT (N=1), nausea (N=4), vomiting (N=2), CK increase (N=2), AST increase (N=5), ALT increase (N=4), headache (N=1), myalgia (N=2)  Rosuvastatin 10mg + fenofibrate: constipation (N=1), flatulence (N=1), GGPT (N=2), CK increase (N=2), AST increase (N=1), ALT increase (N=2), myalgia (N=1)  N=2 participants died during the study with non study related reasons</p> <p>*Discontinuation  N=10 withdrew due to AEs, N=6 considered study related (N=3 from the placebo/rosuvastatin group with peripheral oedema, nausea, myositis; N=1 from the placebo/fenofibrate group with pruritus; N=2 from the rosuvastatin 5mg + fenofibrate group with diarrhoea/vomiting, myalgia</p>	
Rubins HB, Robins	RCT	N=627	Inclusion criteria: <74	N=not	N=not	Average 5.1	CHD death,	All CI 95%	Cooper

<p>SJ, Collins D et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). <i>Archives of Internal Medicine</i>. 2002; 162(22):2597-2604. Ref ID: 3386</p>	<p>1+</p>	<p>diabetic from an overall sample of N=2,531 in the Veterans Affairs High-Density Lipoprotein Intervention Trial<sup>9</sup> ITT analysis, USA</p>	<p>years, established diagnosis of CHD, HDL-C 40mg/dl or less (<math>\leq 1.04</math>mmol/L), an LDL-C of 140mg/dL or less (<math>\leq 3.63</math>mmol/L), triglyceride level of 300mg/dL or less (<math>\leq 3.39</math>mmol/L). Exclusion criteria: taking warfarin, clinical chronic heart failure, left ventricular ejection fraction less than 35%</p> <p>Within each group baseline characteristics were well matched between the gemfibrozil and placebo arms. Though the diabetes group did have increased prevalence of prior stroke, hypertension, CHF, a higher mean BMI and were more likely to be taking ACE inhibitors, digoxin and calcium channel blockers but less likely to be taking aspirin or beta blockers. They also had significantly lower HDL-C, LDL-C and total</p>	<p>reported for diabetic subgroup Gemfibrozil 1200mg/day</p>	<p>reported for diabetic subgroup matched placebo</p>	<p>years</p>	<p>nonfatal MI, confirmed stroke, changes in lipid levels</p>	<p>*Major cardiovascular events Cumulative incidences of major cardiovascular events (combined end points) was significantly higher in the diagnosed (36.5%) and undiagnosed (34.3%) groups than the impaired fasting glucose (23.8%) and normal fasting glucose (21%) groups, <math>p &lt; 0.001</math>. Gemfibrozil compared with placebo showed a significant risk reduction of 32% (HR, 0.68, 0.53 to 0.88, <math>p = 0.004</math>) in the diabetes groups which was higher than in the non-diabetic groups, 18% risk reduction (HR, 0.82, 0.67 to 1.02, <math>p = 0.07</math>). The risk reductions of 32% and 18% were non significant between the groups.</p> <p>Nonfatal MI – risk reductions in both diabetic and non-diabetic participants were NS</p> <p>CHD death – those in the diabetes groups showed a significant reduction with gemfibrozil compared with placebo, 41% risk reduction (HR 0.59, 0.39 to 0.91, <math>p = 0.02</math>). Those in the non-diabetes groups showed NS changes</p> <p>Stroke – those in the diabetes groups showed a significant reduction with gemfibrozil compared with placebo, 40% risk reduction (HR 0.60, 0.37 to 0.99, <math>p = 0.02</math>). Those in the non-</p>	<p>ative studies program of the department of veterans affairs, Washington DC Parke-Davis</p>
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<sup>9</sup> Participants were placed in mutually exclusive categories of diagnosed diabetes (N=627, 25%), undiagnosed diabetes (N=142, 6%), impaired fasting glucose (N=323, 13%) and normal (N=1425, 57%).

			cholesterol levels and higher triglyceride levels than those with a normal FBG.					diabetes groups showed NS changes  *Lipid levels All groups showed significant increases in HDL-C level and significant decreases in triglyceride and total cholesterol levels compared with placebo. LDL- levels were not affected. The increases in HDL-C (5% vs 8%, p=0.02) and decreases in triglyceride levels (-20% vs. -29%, p<0.001) were significantly lower in the diagnosed diabetes group than in the normal FPG group.	
Vakkilainen J, Steiner G, Ansquer JC et al. Relationships between low-density lipoprotein particle size, plasma lipoproteins, and progression of coronary artery disease: the Diabetes Atherosclerosis Intervention Study (DAIS). <i>Circulation</i> . 2003; 107(13):1733-1737. Ref ID: 3385	RCT  1+	N=418	Inclusion criteria: type 2 diabetes, 40-65yrs, with or without previous coronary intervention, total cholesterol/HDL-C ratio of $\geq 4$ , plus either LDL-C 3.5 to 4.5mmol/L and Tg of $\leq 5.2$ mmol/L, or a Tg of 1.7 to 5.2mmol/L and LDL-C $\leq 4.5$ mmol/L.  There were no significant differences between groups at baseline	N=198 fenofibrate 200mg/day	N=207 placebo	Average time from baseline to final angiogram was 39.6 months	Triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol, apolipoprotein (apo) B, LDL-C/apo B ratio, LDL particle size	*Lipids and lipoproteins Fenofibrate treatment significantly increased LDL particle size ( $0.98 \pm 1.04$ ) and HDL-cholesterol ( $0.07 \pm 0.14$ ), compared with placebo, p<0.001.  Fenofibrate treatment significantly decreased plasma triglycerides ( $-0.89 \pm 1.05$ ), total cholesterol ( $0.54 \pm 0.64$ ), LDL-cholesterol ( $-0.21 \pm 0.62$ ) and apolipoprotein B ( $-0.13 \pm 0.21$ ), compared with placebo (p<0.001).	Laboritès Fournier, the Helsinki University Central Hospital Research Foundation, the Biomedicum Research Foundation, the Aarne and Aili Turunen Foundation

<p>Wagner AM, Jorba O, Bonet R et al. Efficacy of atorvastatin and gemfibrozil, alone and in low dose combination, in the treatment of diabetic dyslipidemia. <i>Journal of Clinical Endocrinology &amp; Metabolism</i>. 2003; 88(7):3212-3217. Ref ID: 3384</p>	<p>RCT, 1+</p>	<p>N=46, Spain</p>	<p>Inclusion criteria: T2D, aged 35-75 yrs, taking no treatment known to interfere with lipid metabolism in the month preceding inclusion in the study, LDL greater than 100mg/dl (2.6mmol/L), triglycerides less than 400mg/dl (4.51mmol/L).</p> <p>Exclusion criteria: serum creatinine more than 1.7mg/dl (150µmol/L), hepatic dysfunction (transaminases &gt;1.5 times upper normal limit), creatinine kinase more than 3 times the upper limit, acute or chronic disorders that might interfere with compliance</p>	<p>N=22 gemfibrozil 900-1200 mg/day then crossover</p> <p>N=22 atorvastatin 10-20 mg/day then crossover<sup>10</sup></p>	<p>N=41 combination, gemfibrozil 900 mg/day and atorvastatin 10 mg/day</p>	<p>48 weeks</p> <p>12 weeks atorvastatin/gemfibrozil, 4 weeks wash out, 12 weeks atorvastatin/gemfibrozil, 4 week washout, 12 weeks combined treatment</p>		<p>Drug dose was increased from 10 to 20 mg/day at 6 wks in 45% of participants treated with atorvastatin (mean final dose 14.5 mg/day) and from 900 to 1200 mg/day in 88% of those treated with gemfibrozil (mean final dose 1161 mg/day)</p> <p>*LDL Atorvastatin showed significantly greater reductions in LDL cholesterol compared with gemfibrozil (152±2.7 to 99±2.7 vs. 147±2.7 to 142±2.7), p&lt;0.0001</p> <p>*Adverse events GI related (abdominal discomfort, constipation, loose stools, nausea), N=6 (atorvastatin), N=11 (gemfibrozil), N=8 (combination)</p> <p>*Discontinuation N=2 discontinued following randomisation and prior being dosed N=1 dropped out due to gemfibrozil side effects (unspecified), N=2 discontinued prior to combination phase</p>	<p>Pfizer</p>
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<sup>10</sup> For the first 6 weeks participants were given the lower dose of the drugs, if any of the following were not achieved; LDL less than 100mg/dl (2.6mmol/L), triglycerides less than 150mg/dl (1.7mmol/L) and apoB less than 1.0g/L and in the absence of side effect; then the doses were increased to gemfibrozil 1200 mg/day and atorvastatin 20 mg/day