


Department of Vermont Health Access

***Therapeutic Class Review
Fibric Acid Derivatives***

Overview/Summary

There are several classes of medications used to alter lipids including the hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), fibric acid derivatives, bile acid sequestrants and nicotinic acid (niacin). Each medication class differs with respect to the mechanism by which they alter lipids, as well as to what degree; therefore, Food and Drug Administration (FDA) approved indications for a particular medication class are influenced by the underlying lipid abnormality.

The fibric acid derivatives encompass fenofibrate (Antara[®], Fenoglide[®], Lipofen[®], Lofibra[®], Tricor[®], Triglide[®]), fenofibric acid (Fibricor[®], Trilipix[®]) and gemfibrozil (Lopid[®]). Clofibrate was once available for use in the United States but has since been discontinued due to risks associated with the development of cholangiocarcinoma and other gastrointestinal cancers.¹ Fenofibrate and fenofibric acid are FDA approved for the treatment of hypercholesterolemia and mixed dyslipidemias, as well as hypertriglyceridemia.²⁻¹⁰ Gemfibrozil is FDA approved for the treatment of hypertriglyceridemia and to reduce the risk of developing coronary heart disease (CHD) in select patients.¹¹ Currently, all fibric acid derivatives are available generically in at least one dosage form and/or strength.

The major action of this class of medications is to reduce triglycerides (TG). The individual fibric acid derivatives may differ in their mechanisms of action; however, in general, these agents are agonists for the nuclear transcription factor peroxisome proliferator-activated receptor- α . Through this mechanism, the fibric acid derivatives downregulate the apolipoprotein (apo) CIII gene and upregulate genes for apo AI, fatty acid transport protein, fatty acid oxidation and lipoprotein lipase. The effects on lipoprotein lipase and apo CIII enhance the catabolism of TG-rich lipoproteins, and increased fatty acid oxidation reduces the formation of very low density lipoprotein TG. All of these effects result in the overall lowering of TG. In addition, serum TG lowering in combination with increased synthesis of apo AI and AII leads to increases in high density lipoprotein cholesterol (HDL-C) levels. Finally, TG lowering transforms small, dense low density lipoprotein cholesterol (LDL-C) into normal sized LDL.¹²

As mentioned previously, and in line with their FDA approved indications, the fibric acid derivatives are used primarily to reduce TG levels. Reductions in TG are typically 20 to 50%, with the greatest reductions observed in patients with severely high TG levels. In addition, these agents typically increase HDL-C by 10 to 35%, with even greater increases in patients with very high TG levels and very low HDL-C levels possible. Fibric acid derivatives have variable effects on LDL-C and typically result in a 10% or less reduction in patients with primary hypercholesterolemia, while only minimal changes are observed in patients with combined hyperlipidemia. Of note, LDL-C levels can increase with the use of fibric acid derivatives in patients with hypertriglyceridemia.

Gemfibrozil has demonstrated a reduction in the risk of fatal and nonfatal myocardial infarction for primary prevention, as well as a reduction in CHD death and nonfatal myocardial infarction and stroke for secondary prevention. Clinical trial results demonstrating that the fibric acid derivatives, as a class, reduce CHD incidence is less robust than that with statin therapy.¹² In addition, a reduction in all-cause mortality with fibric acid derivatives has not been demonstrated.¹²

In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia.¹²⁻¹⁴ When LDL lowering is

required, initial treatment with a statin, a bile acid sequestrant or niacin is recommended.¹² However, in general, the statins are considered first line therapy for decreasing LDL-C levels.¹²⁻¹⁵ If after six weeks of therapy lipid goals are not achieved on a statin alone, a dosage increase or the addition of a bile acid sequestrant or niacin should be considered.¹² The fibric acid derivatives are considered an option in patients who are unable to take a statin, but are typically reserved for the treatment of hypertriglyceridemia, to reduce the risk of pancreatitis, or for an isolated low HDL-C.^{12,14} They can also be considered an option for the treatment of patients with CHD who have low levels of LDL-C and atherogenic dyslipidemia, or in combination with a statin in patients who have elevated LDL-C and atherogenic dyslipidemia.¹²

Medications

Table 1. Medications Included Within Class Review

| Generic Name (Trade name) | Medication Class | Generic Availability |
|--|-------------------------|----------------------|
| Fenofibrate (Antara [®] , Fenoglide [®] , Lipofen [®] , Lofibra ^{®*} , Tricor [®] , Triglide [®]) | Fibric acid derivatives | ✓ |
| Fenofibric acid (Fibricor ^{®*} , Trilipix ^{®†}) | Fibric acid derivatives | ✓ |
| Gemfibrozil (Lopid ^{®*}) | Fibric acid derivatives | ✓ |

*Generic is available in at least one dosage form and/or strength.

†Choline fenofibrate.

Indications

Table 2. Food and Drug Administration (FDA) Approved Indications²⁻¹¹

| Indication | Fenofibrate | Fenofibric acid | Gemfibrozil |
|---|-------------|-------------------------------|-------------|
| Reducing the risk of developing coronary heart disease only in Type IIb patients without history of or symptoms of existing coronary heart disease who have had an adequate response to weight loss, dietary therapy, exercise and other pharmacologic agents and who have the following triad of lipid abnormalities: low high density lipoprotein cholesterol levels in addition to elevated low density lipoprotein cholesterol and elevated triglycerides | | | ✓ |
| Hypercholesterolemia and Mixed Dyslipidemia | | | |
| Adjunctive therapy to diet to reduce elevated low density lipoprotein cholesterol, total cholesterol, triglycerides and apolipoprotein B, and to increase high density lipoprotein cholesterol in patients with primary hypercholesterolemia or mixed dyslipidemia | ✓ | ✓ | |
| Adjunct to diet in combination with a statin to reduce triglycerides and increase high density lipoprotein cholesterol in patients with mixed dyslipidemia and coronary heart disease or a coronary heart disease risk equivalent who are on optimal statin therapy to achieve their low density lipoprotein cholesterol goal | | ✓ (Trilipix [®]) | |
| Hypertriglyceridemia | | | |
| Adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia | ✓ | ✓ * | |
| Treatment of adult patients with very high elevations of serum triglyceride levels who | | | ✓ |

| Indication | Fenofibrate | Fenofibric acid | Gemfibrozil |
|---|-------------|-----------------|-------------|
| present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them | | | |

*Fibricor[®] and Trilipix[®] are indicated in severe hypertriglyceridemia (≥ 500 mg/dL).

In addition to their Food and Drug Administration approved indications, the fibric acid derivatives may be used for several off-label conditions. Specifically, fenofibrate has the potential to be used off-label in the management of coronary arteriosclerosis, gout, secondary hyperlipidemia, hyperlipidemia due to an antiretroviral drug adverse reaction and type 3 hyperlipoproteinemia. In addition, gemfibrozil has the potential to be used off-label for the management of hyperlipidemia (including hyperlipidemia due to an antiretroviral drug adverse reaction and as prophylaxis following a cerebrovascular accident or for recurrent disorder of the cardiovascular system.¹⁶

Pharmacokinetics

Table 3. Pharmacokinetics¹⁶

| Generic Name | Bioavailability (%) | Metabolism | Active Metabolites | Elimination (%) | Half-Life (hours) |
|-----------------|--------------------------------|-----------------|--|------------------------|-------------------|
| Fenofibrate | 60 to 90 | Glucuronidation | Fenofibric acid, benzhydrol metabolite | Renal (60 to 93) | 20 to 22 |
| Fenofibric acid | 81 | Conjugation | Not reported | Renal (% not reported) | 20 |
| Gemfibrozil | Well absorbed (% not reported) | Oxidation | Not reported | Renal (70) | 1.5 |

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the fibric acid derivatives in their Food and Drug Administration (FDA) approved indications are outlined in Table 4.¹⁷⁻⁴⁸ In general, the fibric acid derivatives consistently demonstrated "superiority" over placebo in the management of hypercholesterolemia and hypertriglyceridemia.^{18-21,32-34} Results also demonstrate that fibric acid derivatives are safe and effective when used in combination with other well established lipid lowering agents.^{17-21,24,26-31,38} In a small, cross over, head-to-head trial, both fenofibrate and gemfibrozil were effective in significantly improving baseline lipid levels; however, fenofibrate resulted in significantly greater reductions in total and low density lipoprotein cholesterol levels compared to gemfibrozil ($P < 0.02$ for each). Of note, the dose of gemfibrozil evaluated in this trial was lower than its FDA approved dosing.²³

Several clinical trials have evaluated the efficacy of the fibric acid derivatives on clinical outcomes.³⁹⁻⁴⁸ The five year, placebo-controlled FIELD trial (N=9,975) demonstrated that fenofibrate did not significantly reduce the risk of the combined primary outcome of coronary events (coronary heart disease [CHD] death or nonfatal myocardial infarction [MI]) in patients with type 2 diabetes. However, when the individual endpoints were analyzed, fenofibrate was associated with a significant 24% reduction in nonfatal MI (hazard ratio [HR], 0.76; $P=0.010$), but a nonsignificant increase in CHD mortality (HR, 1.19; $P=0.22$) was noted. In this trial, fenofibrate demonstrated no effect on all-cause mortality.³⁹ The five year ACCORD trial (N=5,518) also evaluated the efficacy of fenofibrate on reducing the risk of major cardiovascular events in high risk type 2 diabetics and demonstrated similar results. In this trial, fenofibrate, in combination with simvastatin, again did not reduce the rate of the combined endpoint of nonfatal MI, nonfatal stroke or cardiovascular death compared to simvastatin. Fenofibrate did not demonstrate any effect on all-cause mortality, and when the individual endpoints were analyzed, no significant benefit was achieved.⁴⁰ The five year, placebo-controlled Helsinki Heart Study (N=4,081), a primary prevention trial, was one of the first clinical trials to evaluate the efficacy of gemfibrozil on clinical outcomes. In this trial, gemfibrozil demonstrated a significant 34% ($P < 0.02$) reduction in the incidence of cardiac events but demonstrated no effect on all-cause mortality.⁴¹ After 8.5 years of follow up, all-cause mortality were numerically higher

with gemfibrozil, but the increase did not meet significance.⁴⁴ The five year, placebo-controlled VA-HIT (N=2,531) evaluated gemfibrozil for secondary prevention. Results demonstrated that gemfibrozil was associated with a significant 22% reduction in the incidence of the combined primary outcome of nonfatal MI or CHD death ($P=0.006$). Gemfibrozil also demonstrated a significant 24% reduction in the incidence of the combined endpoint of nonfatal MI, CHD death or confirmed stroke ($P<0.001$). In this trial, gemfibrozil again did not demonstrate an effect on all-cause mortality.⁴⁵ Similar results were observed in Rubin et al (2,531).⁴⁶

Saha et al, a meta analysis that consisted of 10 randomized controlled trials (N=36,489), evaluated fibric acid derivatives for the primary and secondary prevention of cardiovascular events and demonstrated that treatment tended toward increased all-cause mortality (odds ratio [OR], 1.07; $P=0.08$) and was associated with a significant increase in noncardiovascular mortality (OR, 1.16; $P=0.004$). No effect of fibric acid derivatives was observed for cardiovascular mortality (OR, 0.98; $P=0.68$). However, when the individual fibric acid derivatives were analyzed, the odds of cardiovascular mortality was observed to be significantly lower with gemfibrozil (OR, 0.77; $P=0.05$).⁴⁷ Jun et al was a second meta analysis, published three years after Saha et al, that consisted of 18 randomized controlled trials (N=45,058) in which treatment with fibric acid derivatives demonstrated no effect on all-cause mortality (relative risk [RR], 1.00; $P=0.918$), cardiovascular mortality (RR, 0.97; $P=0.582$) or sudden death (RR, 0.89; $P=0.190$). An increased risk of noncardiovascular mortality was noted; however, this finding did not reach significance (RR, 1.10; $P=0.063$). This trial did not report results for individual fibric acid derivatives.⁴⁸

Table 4. Clinical Trials

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|--|---|--|---|---|
| Hypercholesterolemia | | | | |
| Kipnes et al ¹⁷ Fenofibric acid 135 mg/day plus a moderate dose statin (rosuvastatin 20 mg/day, simvastatin 40 mg/day or atorvastatin 40 mg/day) | ES, OL Patients with mixed dyslipidemia at the start of a 1 year, ES, OL | N=310 1 year (2 years of total therapy) | Primary: Safety and efficacy Secondary: Not reported | Primary: No deaths occurred during the two year trial. The incidence of serious adverse events was numerically highest with fenofibric acid plus rosuvastatin (14.9%) compared to fenofibric acid plus simvastatin (8.0%) or atorvastatin (5.8%). The incidences of adverse events were similar among all treatments as well (94.8, 90.0 and 97.7%). Adverse events tended to occur early in treatment, without the development of new types of adverse events over time. The most common treatment-related adverse events were muscle spasms (3.9%), increased blood creatine phosphokinase (3.5%), headache (2.9%), myalgia (2.9%), dyspepsia (2.3%) and nausea (2.3%). Rhabdomyolysis was not reported with any treatment. Nine patients discontinued therapy due to adverse events, with similar incidences among all treatments. Myalgia was the most common reason for discontinuation. No significant difference in the incidence of laboratory elevations was observed among the treatment groups. Incremental improvements in mean percentage changes in all efficacy variables were observed after the first visit in the year one ES (week 16). This effect was sustained for greater than two years and sizable mean percentage changes in all efficacy variables were observed at week 116. In the overall population, the mean percentage changes from baseline to week 116 in efficacy variables were: 17.4 (HDL-C), -46.4 (TG), -40.4 (LDL-C), -47.3 (non-HDL-C), -37.8 (TC) and -52.8% (VLDL-C). Significant differences among treatments were observed for non-HDL-C (-48.60±13.58 vs -41.70±13.10 vs -47.30±12.50%; <i>P</i> =0.011), TC (-38.70±12.16 vs -32.50±10.86 vs -38.60±10.85%; <i>P</i> =0.007) and VLDL-C (-56.80±25.17 vs -40.30±51.25 vs -51.20±35.42%; <i>P</i> =0.019). Secondary: Not reported |
| Jones et al ¹⁸ Fenofibric acid 135 mg/day | DB, MC, RCT Patients ≥18 years of age with mixed | N=543 12 weeks | Primary: Percentage changes from baseline in HDL-C and TG | Primary: The addition of fenofibric acid resulted in a significantly greater mean percentage improvement in HDL-C (13.0 vs 4.2%; <i>P</i> <0.001) and TG (-57.3 vs -39.7%; <i>P</i> <0.001) compared to placebo. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|--|--|--------------------------------|--|--|
| vs placebo All patients received atorvastatin 40 mg/day and ezetimibe 10 mg/day | dyslipidemia (fasting TG \geq 150 and $<$ 400 mg/dL, HDL-C $<$ 40 mg/dL in men and $<$ 50 mg/dL in women and LDL-C \geq 130 mg/dL) | | Secondary: Changes from baseline in apo AI, VLDL-C, apo CIII, non-HDL-C, apo B, hsCRP, LDL-C; proportion of patients achieving lipoprotein and apoprotein goals after 12 weeks of treatment; safety | Secondary: The addition of fenofibric acid resulted in significantly greater effect on all secondary variables on non-HDL-C ($P<0.001$), apo B ($P<0.001$), apo AI ($P=0.004$), VLDL-C ($P<0.001$), apo CIII ($P<0.001$) and hsCRP ($P<0.001$) compared to placebo. The addition of fenofibric acid and placebo resulted in a $>$ 50% reduction in LDL-C (52.9 vs 52.0%; P value not reported), for final mean levels of 70.3 and 72.2 mg/dL. A numerically higher proportion of patients who added fenofibric acid achieved the LDL-C goal $<$ 100 mg/dL (92.7 vs 86.3%), the combined target of LDL-C $<$ 100 mg/dL and non-HDL-C $<$ 130 mg/dL (91.2 vs 84.0%) and the combined target of LDL-C $<$ 100 mg/dL, non-HDL-C $<$ 130 mg/dL and apo B $<$ 90 mg/dL (88.4 vs 80.8%) (P values not reported). Similar proportions of patients receiving both treatments achieved the LDL-C goal $<$ 70 mg/dL (55.0 vs 56.5%) and the combined target of LDL-C $<$ 70 mg/dL, non-HDL-C $<$ 100 mg/dL and apo B $<$ 80 mg/dL specified for high risk patients (53.4 vs 51.3%) (P values not reported). Both treatments were generally well tolerated. The percentages of patients discontinuing treatment were similar (9.6 vs 11.0%; P value not reported). The most common adverse events leading to discontinuations were myalgia and increases in ALT and/or AST. The treatments were similar in the incidence of adverse events experienced, treatment-related adverse events, serious adverse events and adverse events leading to withdrawal. The most commonly reported adverse events (\geq 3%) were muscle spasms, myalgia, arthralgia, fatigue, diarrhea, nausea and headache. |
| Farnier et al ¹⁹ Ezetimibe 10 mg/day vs fenofibrate (micronized) 160 | DB, MC, PC, RCT Patients 18 to 75 years of age with mixed hyperlipidemia and no CHD, | N=619 12 weeks | Primary: Percent change from baseline in LDL-C Secondary: Percent change from baseline in | Primary: The mean percent reduction in LDL-C was significantly greater with combination therapy compared to monotherapy with either agent ($P<0.001$ for both). The corresponding reductions were -13.4, -5.5 and -20.4% with ezetimibe, fenofibrate and combination therapy. Secondary: When compared to fenofibrate or ezetimibe, significant reductions in apo B, non- |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|--|--------------------------------|--|--|
| mg/day vs ezetimibe 10 mg/day plus fenofibrate (micronized) 160 mg/day vs placebo | CHD equivalent disease (except for type 2 diabetes) or a 10 year CHD risk >20% | | other lipid, non-lipid and lipoprotein parameters | HDL-C and LDL-C were observed with combination therapy ($P<0.001$ for both). When compared to placebo, significant decreases in TG and significant increases in HDL-C levels were observed with combination therapy and fenofibrate ($P<0.001$). The percent changes were as follows: -11.8% in TC, 3.9% in HDL-C, -11.1% in TG and -6.1% in hsCRP with ezetimibe; -10.8, 18.8, -43.2 and -28.0% with fenofibrate and -22.4, 19.0, -44.0 and -27.3% with combination therapy ($P<0.05$ for all). |
| McKenney et al ²⁰ Ezetimibe 10 mg/day vs fenofibrate (micronized) 160 mg/day vs ezetimibe 10 mg/day plus fenofibrate (micronized) 160 mg/day vs placebo | ES of Farnier et al ¹⁹ Patients with mixed hyperlipidemia (LDL-C 130 to 220 mg/dL and TG 200 to 500 mg/dL) | N=576 48 weeks | Primary: Percent change from baseline in LDL-C Secondary: Percent change from baseline in TC, HDL-C, TG, non-HDL-C, apo B, apo AI and hsCRP | Primary: Combination therapy significantly reduced LDL-C compared to placebo (-22.0 vs -8.6; $P<0.001$). Secondary: Combination therapy significantly reduced TC (-23.2 vs -13.6; $P<0.001$), TG (-46.0 vs -41.8; $P=0.002$), non-HDL-C (-31.6 vs -19.4; $P<0.001$) and apo B (-25.2 vs -16.2; $P<0.001$) compared to placebo. Combination therapy significantly increased HDL-C compared to placebo (20.9 vs 17.8; $P=0.02$). There were no significant differences in apo AI or hsCRP (P value not significant). |
| Farnier et al ²¹ Fenofibrate 160 | DB, MC, PA, PC, R | N=611 12 weeks | Primary: Percent change from baseline in | Primary: LDL-C was significantly reduced with triple therapy (-45.8%) compared to fenofibrate (-15.7%; $P<0.01$) or placebo (-3.5%; $P<0.01$), but not when compared |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|--------------------------------|--|--|
| mg/day vs ezetimibe/ simvastatin 10/20 mg/day plus fenofibrate 160 mg/day vs ezetimibe/simvastatin 10/20 mg/day vs placebo | Patients 18 to 79 years of age with mixed hyperlipidemia and no CHD or CHD risk equivalent disease, or a 10 year CHD risk >20% according to NCEP ATP III criteria | | LDL-C Secondary: Changes from baseline in TC, TG, non-HDL-C, HDL-C, apo AI and apo B | to combination therapy (-47.1%; $P>0.2$). Secondary: HDL-C and apo AI were significantly increased with triple therapy (18.7 and 11.1%) compared to combination therapy (9.3 and 6.6%; $P<0.01$) or placebo (1.1 and 1.6%; $P<0.01$), but not when compared to fenofibrate (18.2 and 10.8%; $P>0.2$). TG, non-HDL-C and apo B were significantly reduced with triple therapy compared to all other active treatments (-50.0, -50.5 and -44.7%; $P<0.01$, respectively). |
| Corbelli et al ²² Gemfibrozil 1,200 mg/day to fenofibrate 201 mg/day | RETRO Patients who were switched from gemfibrozil to fenofibrate, due to inadequate lipid response or adverse effects | N=92 23 months | Primary: Mean TC, TG, HDL and non-HDL Secondary: Not reported | Primary: Compared to gemfibrozil, fenofibrate was associated with significant improvements in mean TC, TG, HDL-C and non-HDL-C ($P<0.005$ for all). Specifically, a significantly greater proportion of patients receiving fenofibrate achieved a TG goal <200 mg/dL compared to patients receiving gemfibrozil (64 vs 39%; $P<0.0005$). The trial demonstrates that patients switched from gemfibrozil to fenofibrate due to an inadequate lipid response experienced significant improvements in lipid parameters for up to 18 months. Secondary: Not reported |
| Insua et al ²³ Gemfibrozil 900 mg/day | DB, DD, RCT, XO Patients 45 to 70 | N=21 6 weeks | Primary: Cholesterol-lowering effectiveness | Primary: Gemfibrozil and fenofibrate significantly reduced TC, LDL-C, TG, apo B and fibrinogen ($P<0.01$ for all, except $P<0.05$ for fibrinogen with gemfibrozil), and significantly increased HDL-C ($P<0.01$). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|--|--------------------------------|--|--|
| vs fenofibrate 200 mg Daily | years of age with primary hyperlipoproteinemia (Fredrickson phenotypes IIa and IIb) | | Secondary: Not reported | <p>Neither gemfibrozil nor fenofibrate affected Lp(a), whereas only fenofibrate reduced uric acid ($P<0.01$).</p> <p>The percent reduction in TC and LDL-C was significantly greater with fenofibrate compared to gemfibrozil (22 vs 15%; $P<0.02$ and 27 vs 16%; $P<0.02$, respectively). In contrast, reductions in TG (54.0 vs 46.5%), apo B and fibrinogen, as well as the increase in HDL-C (9 vs 9%), revealed no significant difference between the two treatments (P values not reported).</p> <p>Separate analysis of patients with Type IIb hyperlipoproteinemia revealed essentially the same changes in lipid parameters as for the overall population, but with greater modifications in TG and HDL-C.</p> <p>Secondary: Not reported</p> |
| Ansquer et al ²⁴ Fenofibrate 145 mg/day vs ezetimibe 10 mg/day vs fenofibrate 145 mg/day plus ezetimibe 10 mg/day | DB, MC, PG, PRO, RCT Patients 18 to 70 years of age with type IIb dyslipidemia and features of the metabolic syndrome according to the NCEP ATP III | N=180 12 weeks | Primary: Percent change from baseline in TG and HDL-C Secondary: Percent change from baseline in LDL-C, non-HDL-C, remnant-like particle cholesterol, TC:HDL-C, LDL size, apo AI, apo AII, and apo B:AI | <p>Primary: Combination therapy reduced TG (-38.8%) to a similar extent as fenofibrate (-38.8%); however, combination therapy produced a slightly more pronounced increase in HDL-C (11.5 vs 7.9%; $P=0.282$).</p> <p>Secondary: Combination therapy reduced LDL-C (-36.2%) significantly more than either fenofibrate (-22.4%) or ezetimibe (-22.8%) ($P<0.001$ for both). The proportion of patients who achieved the NCEP ATP III target for intermediate cardiovascular risk (<130 mg/dL) was higher with combination therapy (56%) than with either of the monotherapies (fenofibrate, 23% and ezetimibe, 29%).</p> <p>Combination therapy was more effective in reducing non-HDL-C (-36.2%) than either fenofibrate (-24.8%) or ezetimibe (-20.9%). However, the proportion of patients who reached the NCEP ATP III target for intermediate cardiovascular risk (<160 mg/dL) with combination therapy (58%) was more than the sum of the percentages obtained with the monotherapies (46%).</p> <p>The difference between combination therapy (-36.2%) and fenofibrate (-30.7%) in</p> |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|--|--|--------------------------------|---|--|
| | | | | <p>remnant-like particle cholesterol was not significant; ezetimibe was less effective (-17.3%; $P<0.001$).</p> <p>The effect of combination therapy on LDL particle size (2.1%) was similar to that of fenofibrate (1.9%) (P value not reported).</p> <p>Combination therapy significantly increased apo AI (7.9 vs 5.1%) and AIII (24.2 vs 21.2%) compared to fenofibrate (P values not reported).</p> <p>Combination therapy was more effective in reducing apo B (-33.3%) than either fenofibrate or ezetimibe. The changes in apo B-containing lipoproteins with combination therapy resulted in clear improvements in risk ratios, with mean and median end-of-treatment values <4.0 for TC:HDL-C and <0.7 for apo B:apo AI.</p> |
| <p>Arca et al²⁵</p> <p>Atorvastatin 10 mg/day, titrated up to 80 mg/day</p> <p>vs</p> <p>fenofibrate 200 mg/day</p> | <p>OL, RCT</p> <p>Patients 30 to 75 years of age with diagnosis of familial combined hyperlipidemia with TC and/or TG levels $\geq 90^{\text{th}}$ Italian population percentiles, and/or hyper-apobeta-lipoproteinemia</p> | <p>N=56</p> <p>24 weeks</p> | <p>Primary: Change in TC, LDL-C, HDL-C, TG, apo A and endothelin-1</p> <p>Secondary: Not reported</p> | <p>Primary: Atorvastatin was associated with a significant 9% reduction in TC compared to fenofibrate (95% CI, 3.0 to 15.1; $P=0.004$).</p> <p>Atorvastatin was associated with a significant 17% reduction in LDL-C compared to fenofibrate (95% CI, 8.0 to 26.1; $P<0.001$).</p> <p>Fenofibrate was associated with a significant 15.5% reduction in TG compared to atorvastatin (95% CI, 3.35 to 27.70; $P=0.013$).</p> <p>Fenofibrate was associated with a significant 14.2% increase in HDL-C compared to atorvastatin (95% CI, 3.8 to 24.6%; $P=0.008$).</p> <p>Fenofibrate was associated with a significant 5.2 and 22.0% increase in apo AI and apo AII compared to atorvastatin ($P=0.044$ and $P<0.001$, respectively).</p> <p>Fenofibrate was associated with a significant 16.7% reduction in endothelin-1 from baseline ($P<0.05$). Atorvastatin was not associated with a significant change in endothelin-1 (P value not reported).</p> <p>Secondary: Not reported</p> |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|--|---|--|--|--|
| <p>Goldberg et al²⁶</p> <p>Fenofibric acid 135 mg/day</p> <p>vs</p> <p>atorvastatin 20, 40 or 80 mg/day</p> <p>vs</p> <p>fenofibric acid 135 mg/day plus atorvastatin 20 or 40 mg/day</p> | <p>AC, DB, MC, RCT</p> <p>Patients ≥18 years of age with mixed dyslipidemia (fasting TG ≥150 mg/dL, HDL-C <40 mg/dL for men and <50 mg/dL for women and LDL-C ≥130 mg/dL after lipid therapy washout)</p> | <p>N=613</p> <p>12 weeks</p> | <p>Primary: Percent changes from baseline in TG, HDL-C and LDL-C</p> <p>Secondary: Percent changes from baseline in VLDL-C, TC, apo B and hsCRP; safety</p> | <p>Primary: Combination therapy (atorvastatin 20 mg) resulted in significantly greater improvements in TG (-45.6 vs -16.5%; <i>P</i><0.001) and HDL-C (14.0 vs 6.3%; <i>P</i>=0.005) compared to atorvastatin 20 mg and LDL-C (-33.7 vs -3.4%; <i>P</i><0.001) compared to fenofibric acid.</p> <p>Similarly, significantly greater improvements were observed with combination therapy (40 mg) in TG (-42.1 vs -23.2%; <i>P</i><0.001) and HDL-C (12.6 vs 5.3%; <i>P</i>=0.010) compared to atorvastatin 40 mg and LDL-C (-35.4 vs -3.4%; <i>P</i><0.001) compared to fenofibric acid.</p> <p>Secondary: Combination therapy (20 mg) resulted in significantly higher mean percentages of decrease in non-HDL-C compared to fenofibric acid (<i>P</i>=0.026) and in VLDL-C compared to atorvastatin 20 mg (<i>P</i>=0.046). Combination therapy (40 mg) also resulted in significantly higher mean percentage of decrease in non-HDL-C compared to fenofibric acid (<i>P</i><0.001) and in VLDL-C compared to atorvastatin 40 mg (<i>P</i><0.001). Improvements in other secondary variables were similar between combination therapy and atorvastatin (TC; <i>P</i>=0.688, apo B; <i>P</i>=0.688 and hsCRP; <i>P</i>=0.074).</p> |
| <p>Jones et al²⁷</p> <p>Fenofibric acid DR 135 mg/day</p> <p>vs</p> <p>rosuvastatin 10, 20 or 40 mg/day</p> <p>vs</p> <p>fenofibric acid DR 135 mg/day plus rosuvastatin 10 or 20</p> | <p>AC, DB, MC, RCT</p> <p>Patients ≥18 years of age with mixed dyslipidemia (TG ≥150 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for women and LDL-C ≥130 mg/dL)</p> | <p>N=1,445</p> <p>16 weeks (includes 30 day safety evaluation)</p> | <p>Primary: Composite of mean percent changes from baseline in HDL-C, TG and LDL-C</p> <p>Secondary: Composite of mean percent changes from baseline in non-HDL-C, VLDL-C, TC, apo B and hsCRP</p> | <p>Primary: Combination therapy (rosuvastatin 10 and 20 mg) was associated with a significantly greater increase in HDL-C (10 mg: 20.3 vs 8.5%; <i>P</i><0.001 and 20 mg: 19.0 vs 10.3%; <i>P</i><0.001) and a significantly greater decrease in TG (10 mg: 47.1 vs 24.4%; <i>P</i><0.001 and 20 mg: 42.9 vs 25.6%; <i>P</i><0.001) compared to rosuvastatin (10 and 20 mg).</p> <p>Combination therapy was associated with a significantly greater decrease in LDL-C (10 mg: 37.2 vs 6.5%; <i>P</i><0.001 and 20 mg: 38.8 vs 6.5%; <i>P</i><0.001) compared to fenofibric acid.</p> <p>Secondary: Combination therapy (rosuvastatin 10 mg) was associated with a significantly greater reduction in non-HDL-C compared to fenofibric acid or rosuvastatin (10 mg) (<i>P</i><0.001). Combination therapy was also associated with significantly greater</p> |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| mg/day | | | | <p>improvements in VLDL-C ($P<0.001$), apo B ($P<0.001$) and hsCRP ($P=0.013$) compared to rosuvastatin.</p> <p>Combination therapy (rosuvastatin 20 mg) significantly improved non-HDL-C compared to fenofibric acid ($P<0.001$) and was associated with a significantly greater improvement in VLDL-C ($P=0.038$) and hsCRP ($P=0.010$) compared to rosuvastatin (20 mg), with similar reductions in non-HDL-C, apoB and TC (P values not reported).</p> |
| <p>Roth et al²⁸</p> <p>Rosuvastatin 5 mg/day</p> <p>vs</p> <p>fenofibric acid 135 mg/day</p> <p>vs</p> <p>rosuvastatin 5 mg/day plus fenofibric acid 135 mg/day</p> | <p>DB, MC, RCT</p> <p>Patients with fasting LDL-C ≥ 130 mg/dL, TG ≥ 150 mg/dL and HDL-C 40 mg/dL</p> | <p>N=760</p> <p>12 weeks (plus a 30 day safety follow up period)</p> | <p>Primary: Composite of mean percent changes from baseline in HDL-C, TG and LDL-C</p> <p>Secondary: Changes from baseline in non-HDL-C, VLDL-C, apo B, hsCRP and TC; safety; proportion of patients achieving LDL-C (<100 mg/dL) and non-HDL-C (<130 mg/dL) goals</p> | <p>Primary: Combination therapy resulted in a significantly greater mean percent change in HDL-C (23.0 vs 12.4%; $P<0.001$) and TG (-43.0 vs -17.5%; $P<0.001$) compared to rosuvastatin, and resulted in significantly higher mean percent decrease in LDL-C compared to fenofibric acid (28.7 vs 4.1%; $P<0.001$).</p> <p>Secondary: Combination therapy resulted in significantly greater improvements in non-HDL-C compared to either monotherapy, and significantly greater improvements in apo B, hsCRP, VLDL-C and TC compared to rosuvastatin.</p> <p>All treatments were generally well tolerated, with discontinuations due to adverse events being higher with combination therapy (8.3%) and fenofibric acid (7.5%) compared to rosuvastatin (4.4%). The most common adverse events leading to discontinuation were myalgia and muscle spasms and nausea, fatigue and ALT and AST increases. The overall incidence of treatment-emergent adverse events was similar across treatments (58.5 to 63.0%). No significant differences were observed between the combination therapy and either monotherapy in the incidence of any category of adverse events (muscle, hepatic and renal related).</p> <p>In patients with a 10 year CHD risk $>20\%$, the LDL-C goal <100 mg/dL was achieved by 50.5% of patients receiving combination therapy and rosuvastatin; the non-HDL-C goal <130 mg/dL was achieved by 49.5% of patients receiving combination therapy compared to 33.3% of patients receiving rosuvastatin ($P=0.03$). Both LDL-C and non-HDL-C goals were achieved by 44.3 vs 32.3% ($P=0.10$).</p> |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| <p>Mohiuddin et al²⁹</p> <p>Fenofibric acid 135 mg/day plus simvastatin 20 or 40 mg/day</p> <p>vs</p> <p>fenofibric acid 135 mg/day</p> <p>vs</p> <p>simvastatin 20, 40 or 80 mg/day</p> | <p>AC, DB, MC</p> <p>Patients >18 years of age with mixed dyslipidemia (TG ≥150 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for women, and LDL-C ≥130 mg/dL)</p> | <p>N=657</p> <p>16 weeks (includes 30 day safety evaluation)</p> | <p>Primary: Composite of mean percent changes from baseline in HDL-C, TG and LDL-C</p> <p>Secondary: Composite of mean percent changes from baseline in non-HDL-C, VLDL-C, TC, apo B and hsCRP</p> | <p>Primary: Combination therapy was associated with a significantly greater increase in HDL-C (20 mg: 17.8 vs 7.2%; <i>P</i><0.001 and 40 mg: 18.9 vs 8.5%; <i>P</i><0.001) and a significantly greater decrease in TG (20 mg: 37.4 vs 14.2%; <i>P</i><0.001 and 40 mg: 42.7 vs 22.4%; <i>P</i><0.001) compared to simvastatin (20 and 40 mg).</p> <p>Combination therapy was associated with a significantly greater decrease in LDL-C (20 mg: 24.0 vs 4.0%; <i>P</i><0.001 and 40 mg: 25.3 vs 4.0%; <i>P</i><0.001) compared to fenofibric acid.</p> <p>Secondary: Combination therapy (simvastatin 20 mg) was associated with a significantly greater decrease in non-HDL-C (<i>P</i><0.001) compared to fenofibric acid and simvastatin (20 mg).</p> <p>Combination therapy (simvastatin 20 mg) was associated with significant improvements in VLDL-C (<i>P</i><0.001), apo B (<i>P</i><0.001) and hsCRP (<i>P</i>=0.013) compared to simvastatin (20 mg).</p> <p>Combination therapy (simvastatin 40 mg) significantly (<i>P</i><0.001) improved non-HDL-C compared to fenofibric acid, and resulted in a significantly greater improvement in VLDL-C (<i>P</i>=0.005) compared to simvastatin (40 mg), with similar reductions in non-HDL-C, apo B and TC (<i>P</i> values not reported).</p> |
| <p>Kumar et al³⁰</p> <p>Ezetimibe 10 mg/day plus fenofibrate 160 mg/day</p> <p>vs</p> <p>atorvastatin 10 mg/day</p> | <p>RCT, XO</p> <p>Patients with hypercholesterolemia requiring pharmacotherapy</p> | <p>N=43</p> <p>12 weeks</p> | <p>Primary: Percentage reduction of LDL-C</p> <p>Secondary: Percent changes from baseline in TC, HDL-C and TG</p> | <p>Primary: LDL-C decreased by 34.6 vs 36.7% with combination therapy and atorvastatin (<i>P</i>=0.46).</p> <p>Secondary: Both treatments provided similar improvements in TC (-25.1 vs -24.6%; <i>P</i>=0.806) and HDL-C (10.1 vs 8.9%; <i>P</i>=0.778). Combination therapy showed a trend towards a greater reduction in TGs (25.4 vs 14.5%; <i>P</i>=0.079), although there were no significant difference between the two treatments in terms of the improvement in TC:HDL-C (-29.0 vs -28.7%; <i>P</i>=0.904).</p> |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| <p>Winkler et al³¹</p> <p>Fluvastatin 80 mg/day plus fenofibrate 200 mg/day</p> <p>vs</p> <p>ezetimibe 10 mg/day plus simvastatin 20 mg/day</p> | <p>MC, OL, RCT, XO</p> <p>Patients 18 to 75 years of age with metabolic syndrome, low HDL-C, waist circumference ≥ 94 (men) or ≥ 80 cm (females) plus 1 of the following: TG ≥ 150 mg/dL, blood pressure ($\geq 85/\geq 130$ mm Hg), fasting glucose ≥ 100 mg/dL or prevalent type 2 diabetes</p> | <p>N=75</p> <p>6 weeks</p> | <p>Primary: Changes from baseline in lipids, lipoproteins and apolipoproteins; LDL subfractions</p> <p>Secondary: Not reported</p> | <p>Primary: Reductions in TC, LDL-C and apo B were greater with ezetimibe plus simvastatin compared to fluvastatin plus fenofibrate, but differences only reached significance in patients without small, dense LDL ($P=0.043$, $P=0.006$ and $P=0.20$). Reductions in TG were only significant with fluvastatin plus fenofibrate compared to ezetimibe plus simvastatin in patients with small, dense LDL ($P=0.029$). Increases in HDL-C and apo AI were only significant with ezetimibe plus simvastatin compared to fluvastatin plus fenofibrate in patients without small, dense LDL ($P=0.020$ and $P=0.015$). In patients with small, dense LDL, apo AII was markedly increased by fluvastatin plus fenofibrate, whereas ezetimibe plus simvastatin had no or little effect. Although only significant in small, dense LDL patients, apo CIII was more effectively reduce by fluvastatin plus fenofibrate, while the reduction of apo CII was more pronounced with ezetimibe plus simvastatin in all patients.</p> <p>Secondary: Not reported</p> |
| Hypertriglyceridemia | | | | |
| <p>Davidson et al³²</p> <p>TRIMS</p> <p>Fenofibrate 130 mg Daily</p> <p>vs</p> <p>placebo</p> | <p>DB, MC, PC, RCT</p> <p>Patients 21 to 79 years of age with fasting TG levels ≥ 300 and $< 1,000$ mg/dL and ≥ 2 of 4 additional components of the metabolic syndrome as defined by the NCEP ATP III</p> | <p>N=146</p> <p>8 weeks</p> | <p>Primary: Percent change from baseline in fasting TG</p> <p>Secondary: Percent changes from baseline in TC, LDL-C, HDL-C, TC:HDL-C, VLDL-C, non-HDL-C, apo AI, apo B and apo CIII; remnant</p> | <p>Primary: Fenofibrate was associated with a significant percent reduction in TG (36.6%) compared to no change with placebo ($P<0.001$).</p> <p>Secondary: Changes in TC with fenofibrate and placebo were not significantly different ($P=0.085$).</p> <p>Fenofibrate significantly reduced LDL-C (15.0 vs 3.2%; $P=0.006$), TC:HDL-C (14.2 vs 0.8%; $P<0.001$), VLDL-C (33.0 vs 1.6%; $P<0.001$), non-HDL-C (7.5 vs 1.1%; $P=0.009$), apo B ($P<0.001$) and apo C-III ($P<0.001$).</p> <p>Fenofibrate significantly increased HDL-C compared to placebo (14.0 vs 0.8; $P<0.001$).</p> |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | lipoprotein cholesterol | <p>The increase in apo AI was not significantly different between fenofibrate and placebo (5.3 vs 2.0%; $P=0.212$).</p> <p>A significant reduction in remnant lipoprotein cholesterol was observed with fenofibrate (-35.1 vs 12.3%; $P<0.001$).</p> |
| <p>Rosenson et al³³</p> <p>Fenofibrate 160 mg Daily</p> <p>vs</p> <p>placebo</p> | <p>DB, PC, RCT</p> <p>Patients with fasting hypertriglyceridemia (≥ 1.7 and < 6.9 mmol/L) and ≥ 2 of the NCEP ATP III criteria for the metabolic syndrome</p> | <p>N=59</p> <p>19 weeks</p> | <p>Primary: Fasting TG, postprandial TG, oxidative stress, inflammatory response</p> <p>Secondary: Not reported</p> | <p>Primary: Fenofibrate reduced fasting TG (46.1%; $P<0.0001$) and postprandial TG (45.4%; $P<0.0001$) due to significant reductions in postprandial levels of large (40.8%; $P<0.0001$) and medium (49.5%; $P<0.0001$) VLDL particles.</p> <p>The number of fasting total LDL particles was reduced with fenofibrate (19.0%; $P=0.0033$) primarily due to reductions in small LDL particles (40.3%; $P<0.0001$); these treatment differences persisted postprandially.</p> <p>Fasting (15.3%; $P=0.0013$) and postprandial (31.0%; $P<0.0001$) oxidized fatty acids were reduced significantly with fenofibrate compared to placebo.</p> <p>Fenofibrate significantly lowered the following inflammatory markers: VCAM-1 ($P=0.0005$) and ICAM-1 ($P<0.0001$). Reductions in VCAM-1 and ICAM-1 were correlated with reductions in fasting and postprandial large VLDL particles ($P<0.0001$) as well as postprandial oxidized fatty acids ($P<0.0005$).</p> <p>Secondary: Not reported</p> |
| <p>No authors listed³⁴</p> <p>Fenofibrate 200 mg Daily</p> <p>vs</p> <p>placebo</p> <p>The trial was not</p> | <p>PC, R</p> <p>Patients with type 2 diabetes with good glycemic control, who had mild lipoprotein abnormalities typical of type 2 diabetes and ≥ 1</p> | <p>N=418</p> <p>3 years</p> | <p>Primary: Mean percentage stenosis, minimum coronary artery lumen diameter, mean segment diameter</p> <p>Secondary: Not reported</p> | <p>Primary: Fenofibrate was associated with a significantly smaller increase in percentage diameter stenosis compared to placebo (2.11 vs 3.65; $P=0.02$), a significantly smaller decrease in minimum lumen diameter (-0.06 vs -0.10 mm; $P=0.029$) and a nonsignificantly smaller decrease in mean segment diameter (-0.06 vs -0.08 mm; $P=0.171$).</p> <p>Secondary: Not reported</p> |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| <p>powered to examine clinical end points.</p> <p>Stalenhoef et al³⁵</p> <p>Omega-3-acid ethyl esters (Omacor*) 4 g/day</p> <p>vs</p> <p>gemfibrozil 1,200 mg/day</p> | <p>visible coronary lesion</p> <p>DB, DD, RCT</p> <p>Patients with primary hypertriglyceridemia</p> | <p>N=28</p> <p>12 weeks</p> | <p>Primary: Change in lipid profile, LDL-C subfraction profile</p> <p>Secondary: Not reported</p> | <p>Primary: Both omega-3-acid ethyl esters and gemfibrozil resulted in similar and significant decreases in serum TG, VLDL-TG and VLDL-C concentrations and increases in HDL-C and LDL-C ($P=0.05$ to $P<0.001$ from baseline and $P=0.29$ to $P=1.00$ between groups).</p> <p>Both therapies resulted in a more buoyant LDL-C subfraction profile ($P=0.05$ for omega-3-acid ethyl esters, $P<0.01$ for gemfibrozil and $P=0.09$ between groups in favor of gemfibrozil).</p> <p>Secondary: Not reported</p> |
| <p>Wi et al³⁶</p> <p>Niacin ER 500 mg/day for 5 weeks, followed by 1,000 mg/day for 4 weeks, followed by 1,500 mg/day</p> <p>vs</p> <p>fenofibrate 160 mg/day</p> <p>After discontinuation of any lipid modifying drug, patients entered an 8 week dietary run in period.</p> | <p>OL, RCT</p> <p>Patients 20 to 79 years of age with TG 150 to 499 mg/dL and HDL-C <45 mg/dL</p> | <p>N=201</p> <p>24 weeks (includes 8 week dietary run in period)</p> | <p>Primary: Percent change from randomization to week 16 in apo B/apo A-I</p> <p>Secondary: Percent changes in other lipid parameters, levels of glucose metabolism-related parameters, hsCRP</p> | <p>Primary: Apo B/apo A-I was reduced with both treatments with no difference between the two ($P=0.47$). The percent reduction in apo B was greater with niacin, whereas the percent elevation in apo A-I was higher with fenofibrate.</p> <p>Secondary: TC significantly decreased with both treatments, and TG decreased and HDL-C increased. LDL-C increased with fenofibrate but decreased with niacin. The percent reduction in TC was greater with niacin ($P=0.01$). TG decreased significantly more with fenofibrate ($P=0.045$), whereas the percent elevation in HDL-C was not different between the two treatments ($P=0.22$). The percent change in LDL-C was significantly different with the two treatments ($P<0.001$). Lp(a) levels were reduced with niacin only, and the change was significantly different compared to fenofibrate ($P<0.001$).</p> <p>FPG levels decreased with fenofibrate and increased significantly with niacin. HbA_{1c} levels increased with both treatments; the increase was borderline with fenofibrate and significant with niacin. The percent changes in FPG ($P<0.001$) and HbA_{1c} ($P<0.001$) levels were significantly different between the two treatments. Fasting insulin levels showed a borderline reduction with fenofibrate and a significant increase with niacin. HOMA-IR was decreased with fenofibrate and was</p> |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | <p>increased with niacin. Percent changes of insulin ($P<0.001$) and HOMA-IR ($P<0.001$) were significantly different between the two treatments.</p> <p>hsCRP levels were significantly lowered with both treatments, but the percent change was greater with niacin ($P=0.03$).</p> |
| <p>Guyton et al³⁷</p> <p>Niacin ER (Niaspan[®]) titrated up to 1,000 mg at bedtime for 4 weeks, followed by 1,500 mg at bedtime for 4 weeks, followed by 2,000 mg at bedtime for 8 weeks</p> <p>vs</p> <p>gemfibrozil 600 mg BID</p> | <p>DB, MC, PC, RCT</p> <p>Patients 21 to 75 years of age with HDL-C ≤ 40 mg/dL, LDL-C ≤ 160 mg/dL or < 130 mg/dL with atherosclerotic disease and TG ≤ 400 mg/dL</p> | <p>N=173</p> <p>8 weeks</p> | <p>Primary: Effect on HDL-C</p> <p>Secondary: Change in other Lps, adverse effects</p> | <p>Primary: Niacin 1,500 and 2,000 mg/day significantly increased HDL-C by 21 and 26%, respectively, compared to 13% with gemfibrozil ($P<0.02$).</p> <p>Secondary: Compared to gemfibrozil, niacin 1,500 and 2,000 mg/day significantly increased apo A-I (9 and 11 vs 4%), reduced TC:HDL-C ratio (-17 and -22 vs -12%), reduced Lp(a) (-7 and -20 vs no change) and had no adverse effect on LDL-C (2 and 0 vs 9%; $P<0.001$ to $P<0.02$).</p> <p>TG decreased by 40% with gemfibrozil compared to 16 and 29% with niacin 1,000 ($P<0.001$) and 2,000 mg/day ($P<0.06$).</p> <p>Effects on plasma fibrinogen levels were significantly favorable for niacin compared to gemfibrozil (-1 to -6% vs 5 to 9%, respectively; $P<0.02$).</p> <p>Flushing was significantly more frequent with niacin compared to gemfibrozil at every point (78 vs 10%; P values not reported). Flu syndrome occurred more frequently with niacin ($P=0.006$). Dyspepsia was more frequent with gemfibrozil ($P=0.009$).</p> |
| <p>Koh et al³⁸</p> <p>Fenofibrate 200 mg Daily</p> <p>vs</p> <p>fenofibrate 200 mg Daily plus candesartan 16 mg Daily</p> | <p>DB, PC, RCT, XO</p> <p>Patients with hypertriglyceridemia (≥ 150 mg/dL) and hypertension ($\geq 140/90$ mm Hg)</p> | <p>N=46</p> <p>6 months</p> | <p>Primary: Blood pressure, lipid profile, inflammatory markers, vasomotor function, plasma malondialdehyde, adioponectin, insulin resistance</p> | <p>Primary: All treatments significantly reduced blood pressure; however, combination therapy significantly reduced blood pressure more than fenofibrate or candesartan ($P<0.001$ for both).</p> <p>Fenofibrate and combination therapy significantly lowered TC, TG, apo B and non-HDL-C ($P<0.001$ for all), and significantly increased HDL-C ($P<0.001$). Compared to candesartan, these treatments were associated with significant improvements in lipid profiles ($P<0.001$). No significant differences between fenofibrate and combination therapy were observed (P value not significant).</p> |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| vs candesartan 16 mg Daily | | | Secondary: Not reported | All treatments significantly improved flow mediated dilator response to hyperemia. Combined therapy significantly decreased baseline plasma malondialdehyde, hsCRP and soluble CD40L levels. All of these improvements with combination therapy were significant compared to fenofibrate and candesartan ($P<0.001$, $P=0.002$, $P=0.050$ and $P=0.032$, respectively). All treatments significantly increased baseline plasma adiponectin levels and insulin sensitivity; however, the magnitudes of these increases were not significantly different among the three treatments ($P=0.246$ and $P=0.153$). Secondary: Not reported |
| Hypercholesterolemia Clinical Outcomes Trials | | | | |
| Keech et al ³⁹ FIELD Fenofibrate 200 mg Daily vs placebo | DB, PC, RCT Patients 50 to 75 years of age with type 2 diabetes | N=9,975 5 years | Primary: Coronary events (CHD death or nonfatal MI) Secondary: Total cardiovascular events (composite of cardiovascular death, MI, stroke, coronary and carotid revascularization), all-cause mortality | Primary: Coronary events occurred in 5.9 and 5.2% of patients receiving placebo and fenofibrate, respectively (RR, 11%; HR, 0.89; 95% CI, 0.75 to 1.05; $P=0.16$). This finding corresponds to a significant 24% reduction in nonfatal MI (HR, 0.76; 95% CI, 0.62 to 0.94; $P=0.010$) and a nonsignificant increase in CHD mortality (HR, 1.19; 95% CI, 0.90 to 1.57; $P=0.22$). Secondary: Total cardiovascular disease events were significantly reduced from 13.9 to 12.5% with fenofibrate (HR, 0.89; 95% CI, 0.80 to 0.99; $P=0.035$). This finding included a 21% reduction in coronary revascularization (HR, 0.79; 95% CI, 0.68 to 0.93; $P=0.003$). The incidence of all-cause mortality was 6.6 and 7.3% with placebo and fenofibrate ($P=0.18$). |
| No authors listed ⁴⁰ ACCORD Fenofibrate 160 mg/day | DB, MC, PC, RCT Patients 40 to 79 years of age with type 2 diabetes | N=5,518 5 years | Primary: First occurrence of a major cardiovascular event (nonfatal MI, nonfatal stroke or | Primary: The annual rate of the primary outcome was 2.2% with fenofibrate and 2.4% with placebo (HR, 0.92; 95% CI, 0.79 to 1.08; $P=0.32$). Secondary: The annual rate of the primary outcome plus revascularization or hospitalization |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| vs placebo All patients were receiving simvastatin. | and HbA _{1c} ≥7.5%, LDL-C 60 to 180 mg/dL, HDL-C <55 mg/dL for women or <50 mg/dL for men and TG <750 mg/dL if they were not receiving lipid therapy or <400 mg/dL if they were | | death from cardiovascular causes) Secondary: Combination of the primary outcome plus revascularization or hospitalization for CHF; a combination of a fatal coronary event, nonfatal MI or unstable angina; nonfatal MI; fatal or nonfatal stroke; nonfatal stroke; death from any cause; death from cardiovascular causes; hospitalization or death due to heart failure | for CHF was 5.35% with fenofibrate and 5.64% with placebo (HR, 0.94; 95% CI, 0.85 to 1.05; <i>P</i> =0.30). The annual rate of major coronary disease events was 2.58% with fenofibrate and 2.79% with placebo (HR, 0.92; 95% CI, 0.79 to 1.07; <i>P</i> =0.26). The annual rate of nonfatal MI was 1.32% with fenofibrate and 1.44% with placebo (HR, 0.91; 95% CI, 0.74 to 1.12; <i>P</i> =0.39). The annual rate of stroke was 0.38% with fenofibrate and 0.36% with placebo (HR, 1.05; 95% CI, 0.71 to 1.56; <i>P</i> =0.80). The annual rate of death from any cause was 1.47% with fenofibrate and 1.61% with placebo (HR, 0.91; 95% CI, 0.75 to 1.10; <i>P</i> =0.33). Rates for death from a cardiovascular cause were 0.72 and 0.83% (HR, 0.86; 95% CI, 0.66 to 1.12; <i>P</i> =0.26). The annual rate of fatal or nonfatal CHF was 0.90% with fenofibrate and 1.09% with placebo (HR, 0.82; 95% CI, 0.62 to 1.05; <i>P</i> =0.10). |
| Frick et al ⁴¹ Helsinki Heart Study Gemfibrozil 600 mg BID vs placebo | DB, RCT Asymptomatic adult patients with primary dyslipidemia (non-HDL-C ≥200 mg/dL in 2 consecutive | N=4,081 5 years | Primary: Risk of CHD (measured by incidence of cardiac events) Secondary: All-cause mortality | Primary: The cumulative rate of cardiac end points at five years was 27.3 per 1,000 with gemfibrozil and 41.4 per 1,000 with placebo, a reduction of 34% in the incidence of CHD (95% CI, 8.2 to 52.6; <i>P</i> <0.02). The decline in incidence with gemfibrozil became evident in the second year of treatment and continued throughout the trial. Secondary: There was no difference between the two treatments in all-cause mortality. Treatment did not influence cancer rates. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|--------------------------------------|--|--|
| | pretreatment measurements) | | | |
| Frick et al ⁴² Helsinki Heart Study Gemfibrozil 600 mg BID vs placebo | Post hoc analysis of Frick et al ⁴¹ Individuals who exhibited symptoms and signs of possible CHD during screening in the Helsinki Heart Study | N=311 5 years | Primary: Risk of CHD (measured by incidence of cardiac events) Secondary: All-cause mortality | Primary: The end point rate, consisting of fatal and nonfatal MI and cardiac death, did not differ significantly between placebo and gemfibrozil. Since there were key prognostic factors missing (e.g., true prevalence of CHD, extent of coronary artery obstructions, degree of left ventricular dysfunction), the data cannot be used to refute the thesis that treatment of dyslipidemia in apparent CHD is successful. Secondary: All-cause mortality did not differ significantly between placebo and gemfibrozil. |
| Heinonen et al ⁴³ Helsinki Heart Study Gemfibrozil 600 mg BID vs placebo | ES of Frick et al ⁴¹ Asymptomatic adult patients with primary dyslipidemia (non-HDL-C ≥200 mg/dL in 2 consecutive pretreatment measurements) | N=2,046 3.5 years (follow-up) | Primary: Definite fatal and nonfatal CHD events Secondary: Not reported | Primary: During the follow up period the numbers of definite CHD events in all patients were smaller than expected without treatment (54 vs 47; <i>P</i> value not significant), namely a reduction of around 40% for the original treatment groups. The mean incidence rates were in fact similar to that with placebo five years earlier. Cardiovascular mortality over the entire trial period was similar but all-cause mortality was slightly higher among men originally randomized to gemfibrozil compared to men originally randomized to placebo (<i>P</i> =0.19). Secondary: Not reported |
| Huttunen et al ⁴⁴ Gemfibrozil 600 mg BID vs placebo | ES of Frick et al ⁴¹ Asymptomatic adult patients with primary dyslipidemia (non-HDL-C ≥200 mg/dL in 2 consecutive pretreatment | N=4,081 8.5 years (follow-up) | Primary: Gastrointestinal symptoms, surgery, strokes, cancer incidence, morality by cause Secondary: Not reported | Primary: A first occurrence of a moderate to severe gastrointestinal side effect, mainly dyspepsia and abdominal pain, was reported by 20.1 and 15.1% of patients receiving gemfibrozil and placebo during the original five year trial (<i>P</i> <0.001). Side effects were reported at a consistently lower rate during the post-trial follow up than during the DB trial period. After switching from placebo to gemfibrozil, 4.6% of patients interrupted treatment as a result of adverse events (3.7% due to gastrointestinal symptoms). There was a nonsignificant excess of some illnesses and surgical procedures with |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|--------------------------------|--|---|
| | measurements) | | | <p>gemfibrozil during the five year trial period. During the 3.5 year post trial follow-up, cholecystectomies and appendectomies continued to be more common with gemfibrozil.</p> <p>Strokes due to any cause were slightly less common with gemfibrozil. Ischemic strokes continued to occur less frequently in the original gemfibrozil groups, whereas hemorrhagic strokes were about equal post-trial.</p> <p>The cumulative incidences of malignancies and cancer cases by type during the 8.5 years of follow-up were similar, except basal cell skin carcinoma (16 vs 9; $P=0.18$).</p> <p>Over the 8.5 year follow up there were 101 deaths with gemfibrozil and 83 deaths with placebo. The distributions by causes of death did not differ significantly ($P=0.12$). The difference in cancer-specific deaths (30 vs 18) was mainly because of cancer deaths during the post-trial follow up (20 vs 7), while post-trial cardio- and cerebrovascular mortality was equal (25 vs 23, respectively). Deaths caused by cerebrovascular accidents were similar during the entire 8.5 year follow up (8 vs 6). There were fewer fatal cerebral infarctions (1 vs 5) and more fatal intracranial hemorrhages (7 vs 1) with gemfibrozil. The excess mortality due to accidents or violence was reversed during the post-trial follow up, resulting in approximately equal numbers by the end of the trial. Total mortality with the two treatments remained almost equal during the trial period and the first year of the post-trial follow up; the excess mortality emerged towards the end ($P=0.19$).</p> <p>Secondary: Not reported</p> |
| <p>Robins et al⁴⁵ VA-HIT</p> <p>Gemfibrozil 1,200 mg/day</p> <p>vs</p> | <p>DB, MC, PC, RCT</p> <p>Men with a history of CHD who had low HDL-C and LDL-C</p> | <p>N=2,531</p> <p>5 years</p> | <p>Primary: Combined incidence of nonfatal MI or death from CHD</p> <p>Secondary: Not reported</p> | <p>Primary: Compared to placebo, gemfibrozil was associated with a 22% decrease in the incidence of nonfatal MI or death due to CHD (17.3 vs 21.7%; $P=0.006$).</p> <p>Compared to placebo, gemfibrozil was associated with a 24% decrease in the incidence for nonfatal MI, death due to CHD or confirmed stroke (20 vs 26%; $P<0.001$).</p> |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|--|---|
| placebo | | | | <p>A nonsignificant difference between gemfibrozil and placebo was observed for all-cause mortality (15.7 vs 17.4%; $P=0.23$).</p> <p>Concentrations of HDL-C were inversely related to CHD events.</p> <p>Multivariable cox proportional hazards analysis revealed that CHD events were reduced by 11% with gemfibrozil for every 5 mg/dL (0.13 mmol/L) increase in HDL-C ($P=0.02$). Events were reduced even further with gemfibrozil beyond that which is explained by increases in HDL-C values, particularly in the second through fourth quintiles of HDL-C values during treatment.</p> <p>During gemfibrozil treatment, only the increase in HDL-C significantly predicted a lower risk of CHD events; according to multivariable analyses, neither TG nor LDL-C levels at baseline or during the trial predicted CHD events.</p> <p>Secondary: Not reported</p> |
| Rubins et al ⁴⁶ Gemfibrozil 1,200 mg/day vs placebo | DB, MC, PC, RCT Men <74 years of age with CHD, HDL-C ≤40 mg/dL, LDL-C ≤140 mg/dL, TG ≤300 mg/dL and no serious coexisting conditions | N=2,531 5.1 years (mean follow up) | Primary: Combined incidence of nonfatal MI or death from CHD Secondary: Incidence of stroke, death from any cause, TIA, revascularization procedures, carotid endarterectomy and hospitalization for unstable angina or CHF | Primary: The combined primary endpoint occurred in 21.7 vs 17.3% of patients receiving placebo and gemfibrozil, which led to gemfibrozil being associated with a reduction of 22% (95% CI, 7 to 35; $P=0.006$). The effect was consistent for both components of the endpoint, but was only significant for a reduction in nonfatal MI (death from CHD, 22%; 95% CI, -2 to 41; $P=0.07$ and nonfatal MI, 23%; 95% CI, 4 to 38; $P=0.02$). The beneficial effect of gemfibrozil did not become apparent until about two years after randomization. Secondary: Gemfibrozil was not associated with a reduction in the incidence of stroke (6.0 vs 4.6%; RRR, 25%; 95% CI, -6 to 47; $P=0.10$). Gemfibrozil resulted in a RRR of 24% for the combined outcome of death from CHD, nonfatal MI or confirmed stroke (95% CI, 11 to 36; $P<0.001$). Gemfibrozil was associated with a significant reduction in the risk of TIA (RRR, 59%; 95% CI, 33 to 75; $P<0.001$). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|--|--|---|---|
| | | | | <p>Gemfibrozil was associated with a significant reduction in the risk of carotid endarterectomy (RRR, 65%; 95% CI, 37 to 80; $P<0.001$).</p> <p>The rates of death from any cause, coronary revascularization, hospitalization for unstable angina and cancer did not differ significantly between treatments.</p> |
| <p>Saha et al⁴⁷</p> <p>Fibrate therapy (bezafibrate*, clofibrate*, fenofibrate, gemfibrozil)</p> | <p>MA, SR (10 RCTs)</p> <p>Patients receiving fibrate therapy for the prevention of cardiovascular events (primary and secondary prevention)</p> | <p>N=36,489</p> <p>Mean duration of follow up ≥ 1 year (32 months to 18 years)</p> | <p>Primary: All-cause mortality, cardiovascular and non-cardiovascular mortality, fatal and nonfatal MI and stroke</p> <p>Secondary: Incidence of cancer and cancer related mortality</p> | <p>Primary: On pooled MA, the use of fibrate therapy tended to increase all-cause mortality (pooled OR, 1.07; $P=0.08$) and significantly increased the odds of noncardiovascular mortality by about 16% (pooled OR, 1.16; $P=0.004$). Fibrate therapy had no significant effect on cardiovascular mortality, with a pooled OR of 0.98 ($P=0.68$). The use of fibrate therapy did not affect the occurrence of fatal MI (pooled OR, 0.96; $P=0.76$), but significantly reduced the odds of nonfatal MI by about 22% (pooled OR, 0.78; $P<0.00001$). Fibrate therapy also had no significant effect on stroke, with a pooled OR of 0.96 ($P=0.56$).</p> <p>Secondary: The use of fibrates was not associated with an increase in the odds of developing cancer (pooled OR, 1.00; $P=0.98$) or cancer related mortality (pooled odds ratio, 1.11; $P=0.17$).</p> <p>Subgroup analyses revealed that the risk of all-cause mortality did not significantly differ among the various fibrates used. Noncardiovascular mortality was significantly higher with the use of clofibrate on pooled analysis of data from two primary prevention trials (pooled OR, 1.35; 95% CI, 1.13 to 1.62; $P=0.001$). The odds of cardiovascular mortality tended to be lower with gemfibrozil with a pooled OR of 0.77 ($P=0.05$), whereas neither bezafibrate nor fenofibrate had any significant effect on mortality. The odds of nonfatal MI were lower with gemfibrozil (pooled OR, 0.72; $P=0.001$) than with bezafibrate (pooled OR, 0.78; $P=0.02$) or fenofibrate (pooled OR, 0.77; $P=0.01$). No significant differences were observed among the different fibrates with regard to their effects on fatal MI, stroke, cancer or cancer related mortality.</p> |
| <p>Jun et al⁴⁸</p> <p>Fibrate therapy (bezafibrate*,</p> | <p>MA, SR (18 PRO, RCTs)</p> <p>Demographics</p> | <p>N=45,058</p> <p>Duration varied</p> | <p>Primary: Major cardiovascular events, coronary</p> | <p>Primary: Data for coronary events were available from 16 trials, including 44,667 patients in whom 4,552 coronary events were recorded.</p> |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|--|-------------------------------|--------------------------------|---|---|
| <p>clofibrate*, etofibrate*, fenofibrate and gemfibrozil)</p> <p>vs</p> <p>placebo</p> | <p>not reported</p> | | <p>events, stroke, heart failure, coronary revascularization, all-cause mortality, cardiovascular death, nonvascular death, sudden death, new onset albuminuria, drug related adverse events</p> <p>Secondary: Not reported</p> | <p>Overall, fibrate therapy reduced the risk of coronary events by 13% (RR, 0.87; 95% CI, 0.81 to 0.93; $P<0.0001$).</p> <p>Ten trials, including 42,131 patients, reported 2,485 nonfatal coronary outcomes with fibrate therapy, reducing the risk by 19% (RR, 0.81; 95% CI, 0.75 to 0.89); $P<0.0001$).</p> <p>For the 1,740 coronary deaths recorded in 13 trials no effect was noted (RR, 0.93; 95% CI, 0.85 to 1.02; $P=0.116$).</p> <p>Effects on coronary revascularization were reported in four trials, including 15,834 patients whom 1,737 events were reported, with fibrate therapy significantly reducing the risk by 12% (RR, 0.88; 95% CI, 0.78 to 0.98; $P=0.025$).</p> <p>A cumulative MA of all trials reporting coronary outcomes demonstrated consistent benefit from fibrate therapy on the risk of coronary events.</p> <p>Eight trials, including 27,021 patients, reported 1,391 stroke events, with no evidence that fibrate therapy protected against stroke risk (RR, 1.03; 95% CI, 0.91 to 1.16; $P=0.687$).</p> <p>Three trials, including 8,581 patients, reported 584 heart failure events, with no evidence that fibrate therapy protected against heart failure risk (RR, 0.94; 95% CI, 0.65 to 1.37; $P=0.759$).</p> <p>Sixteen trials, including 44,813 patients, reported 3,880 deaths, with six trials reporting separate data for vascular death (22,066 patients with 1,545 reported vascular deaths) and five trials providing separate data for sudden death (12,277 patients reported 596 sudden deaths). No effect of fibrate therapy on the risk of all-cause mortality (RR, 1.00; 95% CI, 0.93 to 1.08; $P=0.918$), vascular mortality (RR, 0.97; 95% CI, 0.88 to 1.07; $P=0.587$) or sudden death (RR, 0.89; 95% CI, 0.74 to 1.06; $P=0.190$) was noted. An increased risk of nonvascular mortality was noted; however, this finding did not reach significance (RR, 1.10; 95% CI, 0.995 to 1.21; $P=0.063$).</p> |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|------------------------|-------------------------------|--------------------------------|------------|---|
| | | | | <p>Three trials reported on the progression of albuminuria, including 15,731 patients and 3,859 events, with fibrate therapy reducing the risk by 14% (RR, 0.86; 95% CI, 0.75 to 0.98; $P=0.028$).</p> <p>Four trials reported data for total adverse events (17,413 patients reporting 225 events), demonstrating no significant increase in the risk of serious drug-related adverse events (RR, 22%; 95% CI, -9 to 61; $P=0.19$). Fibrate therapy did not significantly increase the risk of rhabdomyolysis (RR, 35%; 95% CI, -59 to 439; $P=0.42$), muscle abnormalities (RR, 0%; 95% CI, -1 to 2; $P=0.69$), gastrointestinal disorders (RR, 8%; 95% CI, -1 to 18; $P=0.08$) and gallbladder disease (RR, 19%; 95% CI, -11 to 60; $P=0.24$). Fibrate therapy was associated with an increase in creatinine (RR increase, 99%; 95% CI, 46 to 270; $P<0.0001$).</p> <p>Secondary: Not reported</p> |

*Not available in the United States.

Drug regimen abbreviations: BID=twice daily, DR=delayed-release, ER=extended-release

Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DD=double dummy, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open label, OR=odds ratio, PA=parallel arm, PC=placebo controlled, PG=parallel group, PRO=prospective, R=randomized, RCT=randomized controlled trial, RETRO=retrospective study, RR=relative risk, RRR=relative risk reduction, SR=systematic review, XO=crossover

Miscellaneous abbreviations: ALT=alanine transaminase, apo=apolipoprotein, AST=aspartate transaminase, CD40L=CD40 ligand, CHD=coronary heart disease, CHF=congestive heart failure, HbA_{1c}=glycosylated hemoglobin, HDL-C= high density lipoprotein cholesterol, hsCRP=high sensitivity C-reactive protein, ICAM-1=intercellular adhesion molecule-1, LDL-C=low density lipoprotein cholesterol, Lp(a)=lipoprotein(a), MI=myocardial infarction, NCEP ATP=National Cholesterol Education Program Adult Treatment Panel, TC=total cholesterol, TG=triglycerides, TIA=transient ischemic attack, VCAM-1=vascular cell adhesion molecule-1, VLDL-C=very low density lipoprotein cholesterol

Special Populations**Table 5. Special Populations**^{12,49,50}

| Generic Name | Population and Precaution | | | | |
|-----------------|--|--|--------------------------------|-----------------------|------------------------------|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| Fenofibrate | Dose adjustment may be required in the elderly; a decreased initial dose based on creatinine clearance may be recommended. Safety and efficacy in children have not been established. | Dose adjustment may be required; consult individual package labeling. | No dosage adjustment required. | C | Not reported or recommended. |
| Fenofibric acid | Dose adjustment may be required in the elderly; a decreased initial dose based on creatinine clearance may be recommended. Safety and efficacy in children have not been established. | Dose adjustment is required; for creatinine clearances 30 to 80 mL/minute, an initial dose of 35 mg (Fibricor [®]) or 45 mg once daily (Trilipix [®]) are recommended. Contraindicated in severe renal dysfunction. | No dosage adjustment required. | C | Unknown; contraindicated. |
| Gemfibrozil | No dosage adjustment required in the elderly. Safety and efficacy in children have not been established. | Use with caution in mild to moderate renal dysfunction. Use is contraindicated in severe renal dysfunction. | Use is contra- indicated. | C | Unknown; use with caution. |

Adverse Drug Events**Table 6. Adverse Drug Events (%)**⁶⁻¹⁵

| Adverse Event(s) | Fenofibrate | Fenofibric acid | Gemfibrozil |
|--------------------------|-------------|-----------------|-------------|
| Cardiovascular | | | |
| Angina pectoris | ✓ | - | - |
| Arrhythmia | ✓ | - | - |
| Atrial fibrillation | ✓ | - | 1 |
| Cardiovascular disorder | ✓ | - | - |
| Coronary artery disorder | ✓ | - | - |

| Adverse Event(s) | Fenofibrate | Fenofibric acid | Gemfibrozil |
|-------------------------------|-------------|------------------------------|-------------|
| Edema | ✓ | - | - |
| Electrocardiogram abnormal | ✓ | - | - |
| Hypertension | ✓ | - | - |
| Hypesthesia | - | - | ✓ |
| Hypotension | ✓ | - | - |
| Migraine | ✓ | - | - |
| Myocardial infarction | ✓ | - | - |
| Palpitation | ✓ | - | - |
| Peripheral edema | ✓ | - | - |
| Peripheral vascular disorder | ✓ | - | ✓ |
| Phlebitis | ✓ | - | - |
| Syncope | - | - | ✓ |
| Tachycardia | ✓ | - | - |
| Varicose vein | ✓ | - | - |
| Vascular disorder | ✓ | - | - |
| Vasodilatation | ✓ | - | - |
| Ventricular extrasystoles | ✓ | - | - |
| Central Nervous System | | | |
| Anxiety | ✓ | - | - |
| Confusion | - | - | ✓ |
| Convulsion | - | - | ✓ |
| Depression | ✓ | - | ✓ |
| Dizziness | ✓ | 4.1 (Trilipix [®]) | ✓ |
| Fatigue | - | 2 (Trilipix [®]) | 4 |
| Fever | ✓ | - | - |
| Headache | 3 | 3.2 to 12.7 | 1 |
| Hypertonia | ✓ | - | - |
| Insomnia | ✓ | - | - |
| Libido decreased | ✓ | - | ✓ |
| Nervousness | ✓ | - | - |
| Neuralgia | ✓ | - | - |
| Paresthesia | ✓ | - | ✓ |
| Pain | ✓ | 3.5 (Trilipix [®]) | - |
| Peripheral neuritis | - | - | ✓ |
| Somnolence | ✓ | - | ✓ |
| Vertigo | ✓ | - | 2 |
| Dermatological | | | |
| Acne | ✓ | - | - |
| Alopecia | ✓ | - | - |
| Angioedema | - | - | ✓ |
| Contact dermatitis | ✓ | - | - |
| Eczema | ✓ | - | 2 |
| Exfoliative dermatitis | - | - | ✓ |
| Fungal dermatitis | ✓ | - | - |
| Herpes simplex | ✓ | - | - |
| Herpes zoster | ✓ | - | - |
| Nail disorder | ✓ | - | - |
| Maculopapular rash | ✓ | - | - |
| Photosensitivity reaction | ✓ | - | ✓ |
| Pruritus | ✓ | - | - |
| Rash | - | - | 2 |

| Adverse Event(s) | Fenofibrate | Fenofibric acid | Gemfibrozil |
|--------------------------------|-------------|------------------------------|-------------|
| Skin disorder | ✓ | - | - |
| Skin ulcer | ✓ | - | - |
| Stevens-Johnson syndrome | ✓ | - | - |
| Sweating | ✓ | - | - |
| Toxic epidermal necrolysis | ✓ | - | - |
| Urticaria | ✓ | - | ✓ |
| Vasculitis | - | - | ✓ |
| Endocrine and Metabolic | | | |
| Diabetes mellitus | ✓ | - | - |
| Gout | ✓ | - | - |
| Gynecomastia | ✓ | - | - |
| Hypoglycemia | ✓ | - | - |
| Gastrointestinal | | | |
| Abdominal pain | 5 | 4.6 (Fibricor [®]) | 10 |
| Anorexia | ✓ | - | - |
| Cholestatic jaundice | - | - | ✓ |
| Colitis | ✓ | - | - |
| Constipation | 2 | 2.1 to 3.3 | 1 |
| Diarrhea | 2 | 3.9 (Trilipix [®]) | 7 |
| Duodenal ulcer | ✓ | - | - |
| Dyspepsia | ✓ | 3.7 (Trilipix [®]) | 20 |
| Eructation | ✓ | - | - |
| Esophagitis | ✓ | - | - |
| Flatulence | ✓ | - | - |
| Gastritis | - | - | - |
| Gastroenteritis | - | - | - |
| Gastrointestinal disorder | - | - | - |
| Increased appetite | - | - | - |
| Nausea | 2 | 2.3 to 4.3 | - |
| Nausea and vomiting | - | - | 2 |
| Peptic ulcer | ✓ | - | - |
| Rectal disorder | - | - | - |
| Rectal hemorrhage | - | - | - |
| Vomiting | ✓ | - | - |
| Weight gain/loss | ✓ | - | - |
| Genitourinary | | | |
| Creatinine increased | ✓ | - | - |
| Cystitis | ✓ | - | - |
| Decreased male fertility | - | - | ✓ |
| Dysuria | ✓ | - | - |
| Impotence | - | - | ✓ |
| Kidney function abnormal | ✓ | - | ✓ |
| Nephrotoxicity | - | - | ✓ |
| Prostatic disorder | ✓ | - | - |
| Unintended pregnancy | ✓ | - | - |
| Urinary frequency | ✓ | - | - |
| Vaginal moniliasis | ✓ | - | - |
| Hematologic | | | |
| Agranulocytosis | ✓ | - | - |
| Anemia | ✓ | - | ✓ |
| Ecchymosis | ✓ | - | - |

| Adverse Event(s) | Fenofibrate | Fenofibric acid | Gemfibrozil |
|--------------------------------------|-------------|------------------------------|-------------|
| Eosinophilia | ✓ | - | - |
| Leukopenia | ✓ | - | ✓ |
| Lymphadenopathy | ✓ | - | - |
| Thrombocytopenia | ✓ | - | ✓ |
| Hepatic | | | |
| Alanine aminotransferase increased | 3 | 1.2 to 3.0 | ✓ |
| Alkaline phosphokinase increased | - | - | ✓ |
| Aspartate aminotransferase increased | 3 | 3.4 (Fibricor [®]) | ✓ |
| Bilirubin increased | - | - | ✓ |
| Cholecystitis | ✓ | - | ✓ |
| Cholelithiasis | ✓ | - | ✓ |
| Creatinine phosphokinase increased | 3 | 3 (Fibricor [®]) | ✓ |
| Jaundice | - | - | ✓ |
| Liver fatty deposit | ✓ | - | - |
| Musculoskeletal | | | |
| Arthralgia | ✓ | 3.9 (Trilipix [®]) | ✓ |
| Arthritis | ✓ | - | - |
| Arthrosis | ✓ | - | - |
| Bursitis | ✓ | - | - |
| Back pain | 3 | 3.4 to 6.3 | - |
| Joint disorder | ✓ | - | - |
| Leg cramps | ✓ | - | - |
| Muscle pain | ✓ | - | - |
| Muscle spasm | - | 1.6 (Trilipix [®]) | - |
| Myalgia | ✓ | - | - |
| Myasthenia | ✓ | - | ✓ |
| Myopathy | ✓ | - | ✓ |
| Myositis | ✓ | - | - |
| Painful extremities | - | 4.5 (Trilipix [®]) | ✓ |
| Paresthesia | ✓ | - | ✓ |
| Rhabdomyolysis | ✓ | - | ✓ |
| Synovitis | - | - | ✓ |
| Weakness | ✓ | - | - |
| Respiratory | | | |
| Asthma | ✓ | - | - |
| Bronchitis | ✓ | - | - |
| Cough increased | ✓ | - | - |
| Dyspnea | ✓ | - | - |
| Laryngeal edema | - | - | ✓ |
| Laryngitis | ✓ | - | - |
| Nasopharyngitis | - | 3.5 (Trilipix [®]) | - |
| Pharyngitis | ✓ | - | - |
| Pneumonia | ✓ | - | - |
| Respiratory disorder | 6 | 5.3 to 6.2 | - |
| Rhinitis | 2 | 2.3 | - |
| Sinusitis | ✓ | 3.3 (Trilipix [®]) | - |
| Miscellaneous | | | |
| Allergic reaction | ✓ | - | - |
| Amblyopia | ✓ | - | - |
| Anaphylaxis | - | - | ✓ |
| Appendicitis, acute | - | - | 1 |

| Adverse Event(s) | Fenofibrate | Fenofibric acid | Gemfibrozil |
|-----------------------------|-------------|-----------------|-------------|
| Asthenia | 2 | - | - |
| Blurred vision | - | - | ✓ |
| Cataracts | ✓ | - | ✓ |
| Chest pain | ✓ | - | - |
| Conjunctivitis | ✓ | - | - |
| Cyst | ✓ | - | - |
| Drug-induced lupus syndrome | - | - | ✓ |
| Dry mouth | ✓ | - | - |
| Ear pain | ✓ | - | - |
| Eye disorder | ✓ | - | - |
| Flu syndrome | 2 | - | - |
| Hernia | ✓ | - | - |
| Infection | ✓ | - | - |
| Intracerebral hemorrhage | - | - | ✓ |
| Hypersensitivity reaction | ✓ | - | - |
| Malaise | ✓ | - | - |
| Otitis media | ✓ | - | - |
| Pancreatitis | - | - | ✓ |
| Raynaud's phenomenon | - | - | ✓ |
| Refraction disorder | ✓ | - | - |
| Retinal edema | - | - | ✓ |
| Seizure | - | - | ✓ |
| Syncope | - | - | ✓ |
| Taste perversion | - | - | ✓ |
| Vision abnormalities | ✓ | - | - |

✓ Percent not specified.

- Event not reported or incidence <1%.

Contraindications/Precautions

All of the fibric acid derivatives are contraindicated in patients with hypersensitivity to any of the individual agents or any component of their formulations. Fenofibrate and fenofibric acid are also contraindicated with hepatic dysfunction, including primary biliary cirrhosis and unexplained persistent liver function abnormalities, severe renal dysfunction, pre-existing gallbladder disease and breast feeding (Fenoglide[®] and fenofibric acid only). In addition, gemfibrozil is contraindicated with hepatic or severe renal dysfunction, primary biliary cirrhosis, pre-existing gallbladder disease and concurrent use with repaglinide.⁴⁹⁻⁵¹

Fibric acid derivatives may increase the risk of cholelithiasis and therapy should be discontinued if gallstones are found upon gallbladder studies.⁴⁹⁻⁵¹

Fibric acid derivatives may cause mild decreases in hemoglobin, hematocrit and white blood counts upon initiation which usually stabilizes with long term therapy. Anemia, leukopenia, thrombocytopenia and bone marrow hypoplasia have been rarely reported in patients receiving these agents. Because of this, periodic monitoring is recommended during the first year of therapy with fibric acid derivatives.⁴⁹⁻⁵¹

Myopathy and rhabdomyolysis have been associated with fibric acid derivatives; therefore, patients should be monitored closely. Patients should be instructed to report unexplained muscle pain, tenderness, weakness or brown urine.⁴⁹⁻⁵¹

Fenofibrate and fenofibric acid may cause severe elevations in hepatic transaminases. In addition, hepatocellular, chronic active and cholestatic hepatitis have been reported in patients receiving these

agents. Regular monitoring of liver function tests is required.^{49,50} Periodic monitoring of hepatic transaminases is required in patients receiving gemfibrozil.⁵¹

Rarely hypersensitivity reactions (e.g., severe skin rash, Stevens-Johnson syndrome, toxic epidermal necrolysis) may occur with the use of fenofibrate and fenofibric acid.^{49,50}

Use of fenofibrate and fenofibric acid have been associated with pulmonary embolism and deep vein thrombosis. Patients at risk for venous thromboembolism should use these agents with caution.^{49,50}

Gemfibrozil may increase the risk of cancer.⁵¹

Secondary causes of hyperlipidemia should be ruled out prior to therapy with gemfibrozil. If not lipid response is observed, therapy should be discontinued.⁵¹

Drug Interactions

Table 7. Drug-Drug Interactions⁵²

| Drug(s) | Interaction | Mechanism |
|--|--|--|
| Fibric acid derivatives (fenofibrate, gemfibrozil) | HMG-CoA reductase inhibitors (statins) | Severe myopathy or rhabdomyolysis may occur. |
| Fibric acid derivatives (fenofibrate, gemfibrozil) | Warfarin | Fibric acid derivatives may increase the hypoprothrombinemic effects of oral anticoagulants. Bleeding and death have occurred. |
| Fibric acid derivatives (gemfibrozil) | Repaglinide | Plasma concentrations of repaglinide may be elevated and prolonged, increasing the risk of severe and protracted hypoglycemia. |
| Fibric acid derivatives (gemfibrozil) | Thiazolidinediones | Plasma concentrations of thiazolidinediones may be elevated, increasing hypoglycemic and other adverse effects. |

HMG-CoA= hydroxymethylglutaryl coenzyme A.

Dosage and Administration

Table 8. Dosing and Administration⁶⁻¹⁵

| Generic Name | Usual Adult Dose | Usual Pediatric Dose | Availability |
|--------------|---|--|--|
| Fenofibrate | <p><u>Adjunctive therapy to diet to reduce elevated LDL-C, TC, TG and apo B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia:</u> Capsule (Antara[®]): 130 mg/day without regard to food</p> <p>Capsule (Lofibra[®]): initial, 200 mg/day with food</p> <p>Tablet (Fenoglide[®]): initial, 120 mg/day with food</p> <p>Tablet (Lipofen[®]): initial, 150 mg/day with food</p> <p>Tablet (Lofibra[®]): initial, 160 mg/day with food</p> <p>Tablet (Tricor[®]): initial, 145 mg/day without</p> | Safety and efficacy in children have not been established. | <p>Capsule: 43 mg (Antara[®]) 50 mg (Lipofen[®]) 67 mg (Lofibra[®]) 130 mg (Antara[®]) 134 mg (Lofibra[®]) 150 mg (Lipofen[®]) 200 mg (Lofibra[®])</p> <p>Tablet: 40 mg (Fenoglide[®]) 48 mg (Tricor[®]) 50 mg (Triglide[®]) 54 mg (Lofibra[®]) 120 mg (Fenoglide[®]) 145 mg (Tricor[®]) 160 mg (Lofibra[®], Triglide[®])</p> |

| Generic Name | Usual Adult Dose | Usual Pediatric Dose | Availability |
|-----------------|---|--|--|
| | <p>regard to food</p> <p>Tablet (Triglide[®]): initial, 160 mg/day without regard to food</p> <p><u>Adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia:</u></p> <p>Capsule (Antara[®]): initial, 43 to 130 mg/day without regard to food; maximum, 130 mg/day</p> <p>Capsule (Lofibra[®]): initial, 67 to 200 mg/day with food; maximum, 200 mg/day</p> <p>Tablet (Fenoglide[®]): initial, 40 to 120 mg/day with food; maximum, 120 mg/day</p> <p>Tablet (Lipofen[®]): initial, 50 to 150 mg/day with food; maximum, 150 mg/day</p> <p>Tablet (Lofibra[®]): initial, 54 to 160 mg/day with food; maximum, 160 mg/day</p> <p>Tablet (Tricor[®]): initial, 48 to 145 mg/day without regard to food; maximum, 145 mg/day</p> <p>Tablet (Triglide[®]): initial, 50 to 160 mg/day without regard to food; maximum, 160 mg/day</p> | | |
| Fenofibric acid | <p><u>Adjunctive therapy to diet to reduce elevated LDL-C, TC, TG and apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia:</u></p> <p>Delayed-release capsule: 135 mg/day without regard to meals</p> <p>Tablet: 105 mg/day without regard to meals; maximum, 105 mg/day</p> <p><u>Adjunct to diet in combination with a statin to reduce triglycerides and increase high density lipoprotein cholesterol in patients with mixed dyslipidemia and coronary heart disease or a coronary heart disease risk equivalent who are on optimal statin therapy to achieve their low density lipoprotein cholesterol goal:</u></p> <p>Delayed-release capsule: 135 mg/day without regard to meals</p> <p><u>Adjunctive therapy to diet for treatment of adult patients with severe hypertriglyceridemia:</u></p> <p>Delayed-release capsule: initial, 45 to 135 mg Daily without regard to meals; maximum, 135 mg/day</p> | Safety and efficacy in children have not been established. | <p>Delayed-release capsule (Trilipix[®]): 45 mg 135 mg</p> <p>Tablet (Fibracor[®]): 35 mg 105 mg</p> |

| Generic Name | Usual Adult Dose | Usual Pediatric Dose | Availability |
|--------------|--|--|----------------|
| | Tablet: initial, 35 to 105 mg/day without regard to meals | | |
| Gemfibrozil | <p><u>Reducing the risk of developing coronary heart disease only in Type IIb patients without history of or symptoms of existing coronary heart disease who have had an adequate response to weight loss, dietary therapy, exercise and other pharmacologic agents and who have the following triad of lipid abnormalities: low HDL-C in addition to elevated LDL-C and elevated TGs; treatment of adult patients with very high elevations of serum TG levels who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them:</u></p> <p>Tablet: 1,200 mg/day in two divided doses before the morning and evening meals</p> | Safety and efficacy in children have not been established. | Tablet: 600 mg |

Apo B=apolipoprotein B, HDL-C=high density lipoprotein cholesterol, LDL-C=low density lipoprotein cholesterol, TC=total cholesterol, TG=triglyceride

Clinical Guidelines

Current guidelines are summarized in Table 9. The guidelines addressing the management of hypercholesterolemia are presented globally, addressing the role of various medication classes in the management of this disease.

Table 9. Clinical Guidelines

| Clinical Guideline | Recommendation |
|--|--|
| <p>National Cholesterol Education Program: Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)¹³</p> | <ul style="list-style-type: none"> • Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low density lipoprotein cholesterol (LDL-C) lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. • Standard hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statin) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • Fibrates may have an adjunctive role in the treatment of patients with high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins. • In high risk patients with high TG or low HDL-C levels, consideration |

| Clinical Guideline | Recommendation |
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| | <p>can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent.</p> <ul style="list-style-type: none"> • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of coronary heart disease (CHD) risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. <p><u>Treatment of heterozygous familial hypercholesterolemia</u></p> <ul style="list-style-type: none"> • Begin LDL-C lowering drugs in young adulthood. • TLC indicated for all persons. • Statins, first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid). <p><u>Treatment of homozygous familial hypercholesterolemia</u></p> <ul style="list-style-type: none"> • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). <p><u>Treatment of familial defective apolipoprotein B-100</u></p> <ul style="list-style-type: none"> • TLC indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. <p><u>Treatment of polygenic hypercholesterolemia</u></p> <ul style="list-style-type: none"> • TLC indicated for all persons. • All LDL-C lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy. |
| <p>National Cholesterol Education Program: Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report (2002)¹²</p> | <p><u>General recommendations</u></p> <ul style="list-style-type: none"> • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of evidence is only moderate at present. National Cholesterol Education Program supports the American Heart Association’s recommendation that fish be included as part of a CHD risk reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate LDL lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first line drugs when LDL lowering drugs are indicated to achieve LDL-C treatment goals. • After six weeks if LDL-C goal is not achieved, intensify LDL lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. <p><u>Statins</u></p> <ul style="list-style-type: none"> • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals. |

| Clinical Guideline | Recommendation |
|--------------------|---|
| | <p><u>Bile acid sequestrants</u></p> <ul style="list-style-type: none"> Bile acid sequestrants should be considered as LDL lowering therapy for patients with moderate elevations in LDL-C, for younger patients with elevated LDL-C, for women with elevated LDL-C who are considering pregnancy and for patients needing only modest reductions in LDL-C to achieve target goals. Bile acid sequestrants should be considered in combination therapy with statins in patients with very high LDL-C levels. <p><u>Nicotinic acid</u></p> <ul style="list-style-type: none"> Nicotinic acid should be considered as a therapeutic option for higher risk patients with atherogenic dyslipidemia. Nicotinic acid should be considered as a single agent in higher risk patients with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol lowering drugs in higher risk patients with atherogenic dyslipidemia combined with elevated LDL-C levels. Nicotinic acid should be used with caution in patients with active liver disease, recent peptic ulcer, hyperuricemia, gout and type 2 diabetes. High doses of nicotinic acid (>3 g/day) generally should be avoided in patients with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia. <p><u>Fibric acid derivatives (fibrates)</u></p> <ul style="list-style-type: none"> Fibrates can be recommended for patients with very high TG to reduce risk for acute pancreatitis. They also can be recommended for patients with dysbetalipoproteinemia (elevated beta-very LDL). Fibrate therapy should be considered an option for treatment of patients with established CHD who have low levels of LDL-C and atherogenic dyslipidemia. They also should be considered in combination with statin therapy in patients who have elevated LDL-C and atherogenic dyslipidemia. <p><u>Omega-3 fatty acids</u></p> <ul style="list-style-type: none"> Omega-3 fatty acids (e.g., linolenic acid, docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA]) have two potential uses. In higher doses, DHA and EPA lower serum TGs by reducing hepatic secretion of TG-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3 to 12 g/day have been used depending on tolerance and severity of hypertriglyceridemia. Recent trials also suggest that relatively high intakes of omega-3 fatty acids (1 to 2 g/day) in the form of fish, fish oils or high-linolenic acid oils will reduce the risk for major coronary events in persons with established CHD. Omega-3 fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive trials are required before strongly recommending relatively high intakes of |

| Clinical Guideline | Recommendation |
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| <p>American Heart Association/American College of Cardiology/National Heart, Lung, and Blood Institute: American Heart Association/ American College of Cardiology Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update (2006)⁵³</p> | <p>omega-3 fatty acids (1 to 2 g/day) for either primary or secondary prevention.</p> <p><u>Lipid management</u></p> <ul style="list-style-type: none"> For patients without atherosclerotic disease, including those with other risk factors, recommendations of the National Cholesterol Education Program guidelines and their 2004 update should still be considered current. Therapeutic options to reduce non-HDL-C include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy). If TGs are ≥ 500 mg/dL, therapeutic options to prevent pancreatitis are fibrate or niacin before LDL lowering therapy. Treat LDL-C to goal after TG lowering therapy. Dietary supplement niacin must not be used as a substitute for prescription niacin. <p><u>All patients with coronary and other atherosclerotic vascular disease</u></p> <ul style="list-style-type: none"> In addition to other lifestyle modifications, increased consumption of omega-3 fatty acids in the form of fish or in capsule form (1 g/day) for risk reduction is encouraged. For treatment of elevated TGs, higher doses are usually necessary for risk reduction. |
| <p>Institute for Clinical Systems Improvement: Lipid Management in Adults (2009)¹⁴</p> | <ul style="list-style-type: none"> Diet and exercise are the cornerstones of treatment for asymptomatic patients with dyslipidemia. TLC may include diet, aerobic exercise, weight management, smoking cessation, evaluation of alcohol consumption, sterol and stanol ester nutritional supplement and fish oil (EPA-DHA). Omega-3 fats do not affect LDL levels but may help protect the heart in other ways. Trials have suggested that omega-3 fats reduce the risk of heart attack and death from heart disease for those who already have heart disease. No primary prevention trials have addressed pharmacologic lipid treatment in persons at low risk for CHD. The incidence of CHD in men <40 years and premenopausal women is very low, and drug treatment in these groups is discouraged. Primary prevention trials of pharmacologic lipid lowering have not shown a decrease in mortality, although most trials have shown a 30% reduction in CHD events. Trial populations have consisted mostly of middle-aged men, some with other risk factors. Similar benefit in higher-risk women can be assumed but has not been demonstrated. <p><u>Monotherapy</u></p> <ul style="list-style-type: none"> Patients with risk factors for CHD but no history of disease who receive lipid lowering therapy are likely to experience a decreased risk of CHD. Patients with a history of CHD often benefit from statin therapy and trials have consistently shown a decrease in risk of death from CHD. Specific statin and dose should be selected based on cost and amount of lipid lowering required. Based on the information above, for patients with established CHD or CHD risk equivalents, the use of a statin is recommended. Statin are the drugs of choice for lowering LDL-C, and aggressive treatment should be pursued. Statins also have a modest effect on reducing TGs and increasing HDL-C. Several trials with clinical |

| Clinical Guideline | Recommendation |
|--------------------|---|
| | <p>endpoints support the use of statins in primary and secondary prevention.</p> <ul style="list-style-type: none"> • In patients receiving a statin who experience myalgias, it is recommended that a lower dose or another statin be tried. A 10 to 14 day vacation from a statin can also be considered as a diagnostic maneuver to see if myalgia symptoms abate. The evidence is inconclusive at this time for treating myalgia with Vitamin D and coenzyme Q. • If patients are intolerant to a statin, they should try the other statins in reduced doses before the medication class is deemed inappropriate. • If patients are unable to take a statin, bile acid sequestrants, niacin, fibric acid derivatives and ezetimibe are available. • The bile acid sequestrants reduce LDL-C, but they can increase TGs so should only be used as monotherapy in patients with a baseline TG ≤ 200 mg/dL. • Niacin has a greater effect on HDL-C than other currently available lipid medications. To improve tolerability and compliance, doses of niacin need to be titrated. • Fibric acid derivatives have a variable effect on LDL-C. Fenofibrate may be more effective at lowering LDL-C than gemfibrozil. They are usually reserved for hypertriglyceridemia or for an isolated low HDL-C. • Ezetimibe mainly reduces LDL-C, with minimal effect on TGs or HDL-C. No clinical outcome trials are currently available, but ezetimibe appears useful for reducing LDL-C in patients who cannot take a statin and in combination with other LDL reducing medications. <p><u>Combination therapy</u></p> <ul style="list-style-type: none"> • Although combination therapy is not supported by outcome-based trials, some high risk patients will require combination therapy. These patients will most likely have CHD. • Using low doses of two complementary agents can often reduce LDL-C to a greater extent than a higher dose of either agent, with fewer side effects and possibly less cost. • In very resistant cases, triple therapy may be required. • Combination of a cholesterol lowering drug with a TG lowering drug to achieve the non-HDL-C goal may be most warranted in patients with established coronary artery disease who are a very high risk of recurrent coronary events. • Combining nicotinic acid with a statin is favorable for improving LDL-C, HDL-C and TGs. • Use of fibric acid derivatives leads to effective decreases in TGs and increased HDL-C, but the effect on LDL-C is varied. • An increased incidence of severe myopathy has been reported when a statin was combined with nicotinic acid or fibric acid derivatives. • In general, the combination of a statin and a fibric acid derivative raises the risk of myopathy and rhabdomyolysis. <p><u>Aspirin</u></p> <ul style="list-style-type: none"> • Dosage appears unimportant, usually ranging from 60 mg every other day up to 325 mg/day. • Secondary prevention trials have demonstrated reduced cardiovascular and cerebrovascular endpoints. |

| Clinical Guideline | Recommendation |
|---|---|
| | <ul style="list-style-type: none"> • Primary prevention trials in patients not selected for cardiovascular risk factors have shown minimal benefit. • Patients with hyperlipidemia are at intermediate risk and may derive greater benefit from aspirin than the lower risk populations evaluated in primary prevention trials. The recommendation of aspirin in hyperlipidemic patients is supported by this reasoning, and by the low cost and risk of this therapy. |
| <p>American Heart Association: Drug Therapy of High Risk Lipid Abnormalities in Children and Adolescents: A Scientific Statement From the American Heart Association (2007)⁵⁴</p> | <ul style="list-style-type: none"> • For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high risk lipid abnormalities, the presence of additional risk factors or high risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high risk lipid abnormalities in children is needed to evaluate the long term efficacy and safety and impact on the atherosclerotic disease process. • Niacin is rarely used to treat the pediatric population. • Given the reported poor tolerance, the potential for very serious adverse effects, and the limited available data, niacin cannot be routinely recommended but may be considered for selected patients. • This guideline does not contain recommendations regarding the use of omega-3 acid ethyl esters. |
| <p>European Society of Cardiology and Other Societies: Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2007)¹⁵</p> | <ul style="list-style-type: none"> • Statins are first line drugs for lowering LDL-C. • Bile acid sequestrants can serve as effective lipid lowering alternatives. • Bile acid sequestrants tend to increase TG; therefore, should only be used when TG are <180 mg/dL or given in conjunction with TG lowering agents. • Niacin is considered an effective lipid lowering agent but flushing may limit use. • Niacin is more effective in increasing HDL-C than fibrates. • When TGs are 450 to 900 mg/dL, either fibrates or statins may be used as first line drugs, and niacin is considered a good drug for selected patients. • Fish oils are also TG lowering agents and might be useful as a third line therapy for patients with hypertriglyceridemia resistant to or intolerant of fibrates or niacin or in combination with other TG lowering drugs. • Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels. |

Conclusions

The fibric acid derivatives encompass fenofibrate (Antara[®], Fenoglide[®], Lipofen[®], Lofibra[®], Tricor[®], Triglide[®]), fenofibric acid (Fibracor[®], Trilipix[®]) and gemfibrozil (Lopid[®]). The major action of this class of medications is to reduce triglycerides (TG), which is supported by their Food and Drug Administration (FDA) approved indications, as well as clinical guidelines.^{2-15,53,54} Fenofibrate and fenofibric acid are FDA approved for the treatment of hypercholesterolemia and mixed dyslipidemias, as well as hypertriglyceridemia.²⁻¹⁰ Gemfibrozil is FDA approved for the treatment of hypertriglyceridemia and to reduce the risk of developing coronary heart disease (CHD) in select patients.¹¹ Currently, all fibric acid derivatives are available generically in at least one dosage form and/or strength.

Several clinical trials demonstrate the “superiority” of the fenofibric acid derivatives over placebo for the treatment of hypercholesterolemia and hypertriglyceridemia, and the safety and efficacy of combination therapy with other well established lipid lowering agents.^{17-21,24,26-34,38} There have been several trials evaluating the efficacy of the fibric acid derivatives on clinical outcomes.³⁹⁻⁴⁸ In general, it appears that gemfibrozil has more evidence to support its use in both primary and secondary prevention. Specifically, gemfibrozil has demonstrated a reduction in the risk of fatal and nonfatal myocardial infarction for primary prevention, as well as a reduction in CHD death and nonfatal myocardial infarction and stroke for secondary prevention.² As mentioned previously, gemfibrozil is the only agent in the class to be FDA approved for reducing the risk of CHD.¹¹

Therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia.¹²⁻¹⁴ When low density lipoprotein cholesterol (LDL-C) lowering is required, initial treatment with a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin), a bile acid sequestrant or niacin is recommended.¹² However, in general, the statins are considered first line therapy for decreasing LDL-C levels.¹²⁻¹⁵ If after six weeks of therapy lipid goals are not achieved on a statin alone, a dosage increase or the addition of a bile acid sequestrant or niacin should be considered.¹² Treatment guidelines note that the fibric acid derivatives are considered an option for patients who are unable to take a statin, but that these agents are typically reserved for treatment of hypertriglyceridemia, to reduce the risk of pancreatitis, or for an isolated low high density lipoprotein cholesterol.^{12,14} These agents are also considered a treatment options in patients with CHD and/or atherogenic dyslipidemia.¹² Treatment guidelines do not consistently recommend one agent within the class over another.^{12-14,53,54} The 2009 Institute for Clinical Systems Improvement guideline on lipid management in adults note that fenofibrate may be more effective than gemfibrozil in lowering LDL-C, but that these agents are typically used to lower TG.¹⁴

Appendix I: Utilization Within This Drug Class for DVHA: January 1, 2011 to June 30, 2011

| Medication | Unique utilizers | # of Rx's | Market Share (%) | Plan Cost \$ | Avg \$/Rx |
|------------------------|------------------|--------------|------------------|---------------------|-----------------|
| Gemfibrozil | 395 | 744 | 56.79% | \$14,252.88 | \$19.16 |
| Tricor | 269 | 493 | 37.63% | \$143,264.08 | \$290.60 |
| Trilipix | 29 | 49 | 3.74% | \$15,298.84 | \$312.22 |
| Fenofibrate micronized | 6 | 14 | 1.07% | \$1,614.57 | \$115.33 |
| Fenofibrate | 6 | 10 | 0.76% | \$1,328.61 | \$132.86 |
| Class Total: | 705 | 1,310 | 100% | \$175,758.98 | \$134.17 |

Recommendations

Currently, gemfibrozil, Tricor[®] and TriLipix[®] are listed as preferred on the Department of Vermont Health Access (DVHA) preferred drug list (PDL). However, only gemfibrozil is available without a prior authorization. No changes to the Department of Vermont Health Access (DVHA) approval criteria for fibric acid derivatives (see below) are proposed.

Lopid[®]

- The patient has had a documented intolerance to generic gemfibrozil.

Tricor[®], TriLipix[®]

- The patient has been started and stabilized on either Tricor[®] or TriLipix[®] (Note: samples are not considered adequate justification for stabilization.)
OR
- The patient is taking a statin concurrently.
OR
- The patient has had a documented side effect, allergy, or treatment failure to gemfibrozil.

Antara[®], fenofibrate, fenofibrate micronized, Fenoglide[®], Fibracor[®], Lipofen[®], Lofibra[®] and Triglide[®]

- The patient is taking a statin concurrently and has had a documented side effect, allergy, or treatment failure with Tricor[®] or TriLipix[®]. (If a product has an AB rated generic, there must have been a trial with the generic formulation.)

OR

- The patient has had a documented side effect, allergy, or treatment failure to gemfibrozil and Tricor[®] or TriLipix[®]. (If a product has an AB rated generic, there must have been a trial with the generic formulation.)

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