Therapeutic Class Overview
Fibric Acid Derivatives

Therapeutic Class

- **Overview/Summary:** The fibric acid derivatives are agonists of the peroxisome proliferator activated receptor α (PPARα). Activation of PPARα increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII. The resulting decrease in triglycerides (TG) produces an alteration in the size and composition of low-density lipoprotein cholesterol (LDL-C) from small, dense particles to large buoyant particles. There is also an increase in the synthesis of high-density lipoprotein cholesterol (HDL-C), as well as apoprotein AI and AII.[1-10] The major action of this class of medications is to reduce TG. The fibric acid derivatives can decrease TG by 20 to 50% and increase HDL-C by 10 to 35%. They also lower LDL-C by 5 to 20%; however, in patients with hypertriglyceridemia, LDL-C may increase with the use of fibric acid derivatives.[11]

  Several fenofibrate products are currently available, including micronized and non-micronized formulations. The different fenofibrate formulations are not equivalent on a milligram-to-milligram basis. Micronized fenofibrate is more readily absorbed than non-micronized formulations, which allows for a lower daily dose. Fenofibrate (micronized and non-micronized formulations), fenofibric acid, and gemfibrozil are available generically in at least one dosage form and/or strength.[12] Fenofibrate and fenofibric acid are Food and Drug Administration (FDA)-approved for the adjunctive treatment of primary hypercholesterolemia or mixed dyslipidemias, as well as an adjunctive treatment for hypertriglyceridemia. Trilipix® has the additional indication of adjunct therapy to diet in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.[9] Gemfibrozil is FDA-approved for the treatment of hypertriglyceridemia and to reduce the risk of developing coronary heart disease (CHD) in select patients.[13] Gemfibrozil has demonstrated a reduction in the risk of fatal and nonfatal myocardial infarction (MI) for primary prevention, as well as a reduction in CHD death and nonfatal MI 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.[11]

Table 1. Current Medications Available in the Therapeutic Class[1-10]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/ Strength	Generic Availability
Fenofibrate (Antara®*, Fenoglide®, Lipofen®, Lofibra®*, Tricor®*, Triglide®)	Adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia. Adjunctive therapy to diet to reduce elevated LDL-C, total cholesterol, TG and apolipoprotein B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia.	Capsule: 50 mg (Lipofen®) 150 mg (Lipofen®) Capsule, Micronized: 30 mg (Antara®) 43 mg (Antara®) 67 mg (Lofibra®) 90 mg (Antara®) 130 mg (Antara®) 134 mg (Lofibra®) 200 mg (Lofibra®) Tablet: 40 mg (Fenoglide®) 48 mg (Tricor®) 50 mg (Triglide®) 54 (Lofibra®) 120 mg (Fenoglide®) 145 mg (Tricor®)	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/ Strength	Generic Availability
		160 mg (Lofibra®, Triglide®)	
Fenofibric acid (Fibricor®*, Trilipix®†)	Adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fibricor®).‡ Adjunctive therapy to diet to reduce elevated LDL-C, total cholesterol, TG and apolipoprotein B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia.	Delayed-release capsule: 45 mg (Trilipix®) 135 mg (Trilipix®) Tablet: 35 mg (Fibricor®) 105 mg (Fibricor®)	✔
Gemfibrozil (Lopid®*)	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. Reducing the risk of developing CHD only in Type IIb patients without history of or symptoms of existing CHD 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 levels in addition to elevated LDL-C and elevated TG.	Tablet: 600 mg	✔

CHD=coronary heart disease, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, TG=triglycerides
*Generic is available in at least one dosage form and/or strength.
†Choline fenofibrate.
‡Indicated for therapy in patients with triglycerides ≥500 mg/dL.

Evidence-based Medicine

- In general, the fibric acid derivatives consistently demonstrate greater efficacy compared to placebo in the management of hypercholesterolemia and hypertriglyceridemia.[14-18]
- The addition of fibric acid derivatives to other well established lipid lowering agents has been shown to be safe and resulted in additional improvements in lipid profile compared to each drug given as monotherapy.[16-28]
- 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 (CHD), death or nonfatal myocardial infarction (MI) in patients with type 2 diabetes. When individual endpoints were analyzed, fenofibrate significantly reduced nonfatal MI by 24% (hazard ratio [HR], 0.76; *P*=0.010), but a nonsignificant increase in CHD mortality (HR, 1.19; *P*=0.22) was observed.[29] Similar results were observed in the ACCORD trial (N=5,518) which evaluated the efficacy of fenofibrate on reducing the risk of major cardiovascular events in high risk type 2 diabetics.[30]
- In the five year, Helsiniki Heart Study (N=4,081), a primary prevention trial, gemfibrozil demonstrated a significant 34% (*P*<0.02) reduction in the incidence of cardiac events but demonstrated no effect on all-cause mortality.[31] After 8.5 years of follow up, all-cause mortality was numerically higher with gemfibrozil, but the increase did not meet significance.[32] In a secondary prevention component of the Helsinki Heart Study, there was no difference between gemfibrozil and placebo in the incidence of fatal and nonfatal MI and cardiac death.[33]
- A meta-analysis 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 to increase 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). When the individual fibric acid derivatives

were analyzed, the odds of cardiovascular mortality were significantly lower with gemfibrozil (OR, 0.77; *P*=0.05).[34]

- A second meta-analysis of 18 randomized controlled trials (N=45,058) 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).[35]
- Fenofibric acid was added to rosuvastatin in patients with chronic kidney disease and it was shown that there was a significantly greater decrease in median percent TGs compared to rosuvastatin alone after eight weeks (P<0.001) and 16 weeks (P<0.001) along with an increase in HDL-C over the same time periods (P<0.001).[36]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Therapeutic lifestyle changes remain an essential modality in the management of patients with hypercholesterolemia.[37-44]
  - In general, hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are considered first line therapy for decreasing low density lipoprotein cholesterol (LDL-C) levels. If after six weeks, lipid goals are not achieved with statin monotherapy, a dosage increase or the addition of a bile acid sequestrant or nicotinic acid (niacin) should be considered.[37-44]
  - Due to increased muscle side effects including rhabdomyolysis, gemfibrozil is not recommended to be used in a combination with statins.[43]
  - Fibric acid derivatives are typically reserved for the treatment of hypertriglyceridemia, to reduce the risk of pancreatitis, or for an isolated low high density lipoprotein cholesterol.[37,40]
  - Fibric acid derivatives can be considered in patients with coronary heart disease 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.[37]
  - The National Institute for Health and Clinical Excellence (NICE) guidelines recommend non-routine use of fibrates if intolerant to statins as monotherapy and recommend against the use of niacin, bile acid sequestrants, and omega-3 fatty acids or any combination of a stains plus either a fibrate, niacin, bile acid sequestrants, or omega-3 fatty acids for primary or secondary prevention of coronary vascular disease due to lack of evidence.[44]

- Other Key Facts:
  - Gemfibrozil (Lopid®) is the only fibric acid derivative approved for reducing the risk of developing coronary heart disease in select patients.[10]
  - Currently, all fibric acid derivatives are available generically in at least one dosage form and/or strength.[12]

References

1. Antara® [package insert]. Baltimore (MD): Lupin Pharma; 2013 Oct.
2. Fenoglide® [Prescribing information]. San Diego (CA): Santarus, Inc.; 2012 Oct.
3. Lofibra® capsule [package insert]. Horsham (PA): Teva Select Brands; 2012 Aug.
4. Lofibra® tablet [package insert]. Horsham (PA): Teva Select Brands; 2014 Feb.
5. Lipofen® [package insert]. Montgomery, AL: Kowa Pharmaceuticals America, Inc.; 2013 Jan.
6. Tricor® [package insert]. Florham Park (NJ): AbbVie, Inc.; 2013 Jul.
7. Triglide® [package insert]. Florham Park (NJ): Shionogi Inc.; 2013 Aug.
8. Fibricor® [package insert]. Detriot (MI): URL Pharma, Inc.; 2013 Oct.
9. Trilipix® [package insert]. Florham Park (NJ): AbbVie, Inc.; 2014 Mar.
10. Lopid® [package insert]. New York (NY); Pfizer Inc; 2013 Oct.
11. National Institutes of Health: National Cholesterol Education Program. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
12. DRUGS@FDA.com [database on the internet]. Rockville (MD): U.S. Food and Drug Administration [cited 2014 Aug 25]. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.
13. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2014 Aug 25]. Available from: http://www.thomsonhc.com/.
14. Rosenson RS, Wolff DA, Huskin AL, Helenowski IB, Rademaker AW. Fenofibrate therapy ameliorates fasting and postprandial lipoproteinemia, oxidative stress, and the inflammatory response in patients with hypertriglyceridemia and the metabolic syndrome. Diabetes Care. 2007 Aug;30(8):1945-51.

15. Davidson MH, Bays HE, Stein E, Maki KC, Shalwitz RA, Doyle R; TRIMS Investigators. Effects of fenofibrate on atherogenic dyslipidemia in hypertriglyceridemic patients. Clin Cardiol. 2006 Jun;29(6):268-73.
16. Jones PH, Goldberg AC, Knapp HR, Kelly MT, Setze CM, Stolzenbach J, et al. Efficacy and safety of fenofibric acid in combination with atorvastatin and ezetimibe in patients with mixed dyslipidemia. Am Heart J. 2010;160:759-66.
17. Farnier M, Roth E, Gil-Extremera B, Mendez G, Macdonell G, Hamlin C, et al. Efficacy and safety of the coadministration of ezetimibe/simvastatin with fenofibrate in patients with mixed hyperlipidemia. Am Heart J. 2007 Feb;153(2):335.e1-8.
18. Farnier M, Freeman M, Macdonell G, Perevozskaya I, Davies MJ, Mitchel YB, et al. Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidemia. Eur Heart J. 2005 May;26(9):897-905.
19. Goldberg A, Bays H, Ballantyne C, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with atorvastatin in patients with mixed dyslipidemia. Am J Cardiol 2009;103:515-22.
20. Roth EM, Rosenson RS, Carlson DM, Fukumoto SM, Setze CM, Blasetto JW, et al. Efficacy and safety of rosuvastatin 5 mg in combination with fenofibric acid 135 mg in patients with mixed dyslipidemia-a phase 3 study. Cardiovasc Drugs Ther. 2010;24:421-8.
21. Jones P, Davidson M, Kashyap M, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with rosuvastatin in patients with mixed dyslipidemia: A phase 3 study. Atherosclerosis 2009;204:208-215.
22. Ferdinand KC, Davidson MH, Kelly MT, Setze CM. One-year efficacy and safety of rosuvastatin + fenofibric acid combination therapy in patients with mixed dyslipidemia. Evaluation of dose response. Am J Cardiovasc Drugs. 2012;12(2):117-25.
23. Mohiuddin S, Pepine C, Kelly M, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with simvastatin in patients with mixed dyslipidemia: a phase 3, randomized, controlled study. Am Heart J 2009;157:195-203.
24. Derosa G, Maffioli P, Salvadeo SA, et al. Fenofibrate, simvastatin and their combination in the management of dyslipidaemia in type 2 diabetic patients. Curr Med Res Opin 2009;25:1973-83.
25. May HT, Anderson JL, Pearson RR, et al. Comparison of effects of simvastatin alone vs fenofibrate alone vs simvastatin plus fenofibrate on lipoprotein subparticle profiles in diabetic patients with mixed dyslipidemia (from the Diabetes and Combined Lipid Therapy Regimen study). Am J Cardiol 2008;101:486-9.
26. Jones P, Davidson M, Goldberg A, et al. Efficacy and safety of fenofibric acid in combination with a statin in patients with mixed dyslipidemia: pooled analysis of three phase 3, 12-week randomized, controlled studies. J Clin Lipidology 2009;3:125-37.
27. Bays H, Jones P, Mohiuddin S, et al. Long-term safety and efficacy of fenofibric acid in combination with statin therapy for the treatment of patients with mixed dyslipidemia. J Clin Lipidology 2008;2:426-35.
28. Kipnes MS, Roth EM, Rhyne JM, et al. Year two assessment of fenofibric acid and moderate-dose statin combination: a phase 3, open-label, extension study. Clin Drug Investig 2010;30:51-61.
29. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, et al. FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD Study): randomized controlled trial. Lancet. 2005 Nov 26;366(9500):1849-61.
30. The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362:1563-74.
31. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, et al. Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med. 1987 Nov 12;317(20):1237-45.
32. Huttunen JK, Heinonen OP, Manninen V, Koskinen P, Hakulinen T, Teppo L, et al. The Helsinki Heart Study: an 8.5-year safety and mortality follow-up. J Intern Med. 1994;235:31-9.
33. Frick MH, Heinonen OP, Huttunen JK, Koskinen P, Mänttäri M, Manninen V. Efficacy of gemfibrozil in dyslipidemic patients with suspected heart disease. An ancillary study in the Helsinki Heart Study frame population. Ann Med. 1993 Feb;25(1):41-5.
34. Saha SA, Kizhakepunnur LG, Bahekar A, Arora RR. The role of fibrates in the prevention of cardiovascular disease-a pooled meta-analysis of long-term randomized placebo-controlled clinical trials. Am Heart J. 2007;154:943-53.
35. Jun M, Foote C, Lv Jicheng , Neal B, Patel A, Nicholls SJ, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. Lancet. 2010;375:1875-84.
36. Weinstein DL, Williams LA, Carlson DM, Kelly MT, Burns KM, et al. A randomized, double-blind study of fenofibric acid plus rosuvastatin compared with rosuvastatin alone in stage 3 chronic kidney disease. Clin Ther. 2013 Aug;35(8):1186-98. doi: 10.1016/j.clinthera.2013.06.013. Epub 2013 Jul 26.
37. National Institutes of Health: National Cholesterol Education Program. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
38. Jellinger PS, Smith DA, Mehta AE, Ganda O, Handelsman Y, Rodbard HW et al. American Association of Clinical Endocrinologists' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis. Endocr Pract. 2012 Mar-Apr;18 Suppl 1:1-78.
39. Smith SC Jr, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. J Am Coll Cardiol. 2011 Nov 29;58(23):2432-46.
40. Institute for Clinical Systems Improvement (ISCI). Healthcare guideline: lipid management in adults 12th ed., 2011 [guideline on the Internet]. ICSI. 2011 [cited 2014 Aug 25]. Available from: http://www.icsi.org/lipid_management_3/lipid_management_in_adults_4.html.
41. Grundy SM, Cleeman JI, Merz NB, Brewer Jr B, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation. 2004;110:227-39.
42. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WM, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur J Prev Cardiol. 2012 Aug;19(4):585-667.

43. Kernan WN, Ovbiagele B, Black HR, Bravata DW, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014 May;45:2160-2236.
44. National Institute for Health and Clinical Excellence. Lipid modification: cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. National Institute for Health and Clinical Excellence; London (UK): 2014 [cited 2014 Aug 15]. Available from: https://www.nice.org.uk/Guidance

Therapeutic Class Review
Fibric Acid Derivatives

Overview/Summary

The fibric acid derivatives are agonists of the peroxisome proliferator activated receptor α (PPARα). Activation of PPARα increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII. The resulting decrease in triglycerides (TG) produces an alteration in the size and composition of low-density lipoprotein cholesterol (LDL-C) from small, dense particles to large buoyant particles. There is also an increase in the synthesis of high-density lipoprotein cholesterol (HDL-C), as well as apoprotein AI and AII.[1-10] The major action of this class of medications is to reduce TG. The fibric acid derivatives can decrease TG by 20 to 50% and increase HDL-C by 10 to 35%. They also lower LDL-C by 5 to 20%; however, in patients with hypertriglyceridemia, LDL-C may increase with the use of fibric acid derivatives.[11]

Several fenofibrate products are currently available, including micronized and non-micronized formulations. The different fenofibrate formulations are not equivalent on a milligram-to-milligram basis. Micronized fenofibrate is more readily absorbed than non-micronized formulations, which allows for a lower daily dose. Fenofibric acid is the active metabolite of fenofibrate. Fenofibrate (micronized and non-micronized formulations), fenofibric acid, and gemfibrozil are available generically in at least one dosage form and/or strength.[12] Fenofibrate and fenofibric acid are Food and Drug Administration (FDA)-approved for adjunctive therapy to diet to reduce elevated LDL-C, total cholesterol, TG and apolipoprotein B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia, as well as for the adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia.[1-9] Trilipix® has the additional indication of adjunct therapy to diet in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and coronary heart disease (CHD) or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.[9] Gemfibrozil is FDA-approved for the 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 and to reduce the risk of developing CHD in Type IIb patients without history of or symptoms of existing CHD 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 levels in addition to elevated LDL-C and elevated TG.[10,13] Gemfibrozil has demonstrated a reduction in the risk of fatal and nonfatal myocardial infarction (MI) for primary prevention, as well as a reduction in CHD death and nonfatal MI 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.[11]

In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When LDL lowering is required, statins are considered first line therapy for decreasing LDL-C levels.[11,14-18] 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.[11] The fibric acid derivatives are typically reserved for the treatment of severe hypertriglyceridemia (TG >500 mg/dL), to reduce the risk of pancreatitis, or for an isolated low HDL-C. 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.[11,14-16] Due to increased muscle side effects including rhabdomyolysis, gemfibrozil is not recommended to be used in a combination with statins.[17] The National Institute for Health and Clinical Excellence (NICE) guidelines recommend non-routine use of fibrates if intolerant to statins as monotherapy and recommend against the use of niacin, bile acid sequestrants, and omega-3 fatty acids or any combination of a stains plus either a fibrate, niacin, bile acid sequestrants, or omega-3 fatty acids for primary or secondary prevention of CVD due to lack of evidence.[18]

Medications

Table 1. Medications Included Within Class Review[1-10]

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 Indications[1-10]

Indication	Fenofibrate	Fenofibric acid	Gemfibrozil
Hypertriglyceridemia			
Adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia	✔	✔ *	
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			✔
Primary Hypercholesterolemia and Mixed Dyslipidemia			
Adjunctive therapy to diet to reduce elevated LDL-C, total cholesterol, TG and apolipoprotein B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia	✔	✔	
Reducing the risk of developing CHD only in Type IIb patients without history of or symptoms of existing CHD 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 levels in addition to elevated LDL-C and elevated TG			✔
Adjunct to diet in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal		✔ (Trilipix®)	

CHD=coronary heart disease, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, TG=triglycerides
*Fibricor®: Triglycerides (TG) ≥500 mg/dL.
†Patients who present such risk typically have serum TG over 2,000 mg/dl and have elevations of very low-density lipoprotein cholesterol (VLDL)-cholesterol as well as fasting chylomicrons (Type V hyperlipidemia). Patients who consistently have total serum or plasma TG below 1,000 mg/dL are unlikely to present a risk of pancreatitis. Gemfibrozil may be considered for those patients with TG elevations between 1,000 and 2,000 mg/dl who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis.

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.[13]

Pharmacokinetics

Table 3. Pharmacokinetics[1-10,13]

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 (Percent not reported)	20
Gemfibrozil	Well absorbed (Percent not reported)	Oxidation	Not reported	Renal (70)	1.5

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the fibric acid derivatives in their respective Food and Drug Administration (FDA)-approved indications are outlined in Table 4.[19-68] In general, the fibric acid derivatives consistently demonstrated greater efficacy compared to placebo in the management of hypercholesterolemia and hypertriglyceridemia.[19-21,34,37,53] The addition of fibric acid derivatives to other well established lipid lowering agents has been shown to be safe and resulted in additional improvements in lipid profile compared to each drug given as monotherapy.[21,24-40,44-46,54] 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 (LDL-C) 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.[48] Fenofibric acid was added to rosuvastatin in patients with chronic kidney disease and it was shown that there was a significantly greater decrease in median percent TGs compared to rosuvastatin alone after eight weeks (P<0.001) and 16 weeks (P<0.001) along with an increase in HDL-C over the same time periods (P<0.001).[54]

Several clinical trials have evaluated the efficacy of the fibric acid derivatives for primary and secondary prevention of coronary heart disease (CHD) events.[55-68] 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 (CHD), death or nonfatal 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 observed. In this trial, fenofibrate demonstrated no effect on all-cause mortality.[55] Similar results were observed in the five year ACCORD trial (N=5,518) which evaluated the efficacy of fenofibrate on reducing the risk of major cardiovascular events in high risk type 2 diabetics. 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.[59]

The five year, placebo-controlled Helsiniki 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.[61] After 8.5 years of follow up, all-cause mortality were numerically higher with gemfibrozil, but the increase did not meet significance.[64] Furthermore, in a secondary prevention component of the Helsinki Heart Study, there was no difference observed between gemfibrozil and placebo in the incidence of fatal and nonfatal MI and cardiac death.[62] 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.[61] A study by Rubins et al (N=2,531) has produced similar results.[66]

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 to increase 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 were observed to be significantly lower with gemfibrozil (OR, 0.77; *P*=0.05).[67] A second meta-analysis, published three years after Saha et al, 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).[68]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypercholesterolemia				
Rosenson et al[19] Fenofibrate 160 mg QD vs placebo	DB, PC, RCT Patients with fasting hypertriglyceridemia (≥1.7 and <6.9 mmol/L) and 2 or more of the NCEP ATP III criteria for the metabolic syndrome	N=59 19 weeks	Primary: Fasting TG, postprandial TG, oxidative stress, inflammatory response Secondary: Not reported	Primary: Fenofibrate treatment lowered fasting TG (-46.1%; *P*<0.0001) and postprandial (area under the curve) TG (-45.4%; *P*<0.0001) due to significant reductions in postprandial levels of large (-40.8%; *P*<0.0001), medium (-49.5%; *P*<0.0001) and VLDL particles. The number of fasting total LDL particles was reduced in fenofibrate-treated patients (-19.0%; *P*=0.0033) primarily due to reductions in small LDL particles (-40.3%; *P*<0.0001); these treatment differences persisted postprandially. Fasting and postprandial oxidized fatty acids were reduced in fenofibrate-treated patients compared to placebo-administered patients (-15.3%; *P*=0.0013, and 31.0%; *P*<0.0001, respectively). Fenofibrate therapy lowered inflammatory markers as follows: fasting and postprandial soluble VCAM-1 decreased by -10.9% for fasting VCAM-1 (*P*=0.0005), and by -12.0% for postprandial VCAM-1 (*P*=0.0001); and fasting and postprandial soluble ICAM-1 decreased by -14.8% for fasting ICAM-1 (*P*<0.0001) and by -15.3% for postprandial 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). Secondary: Not reported
Davidson et al[20] TRIMS Fenofibrate 130 mg QD vs placebo	DB, MC, PC, RCT Patients between the ages of 21 and 79 years, with fasting TG levels ≥300 and <1,000 mg/dL,	N=146 8 weeks	Primary: Changes or percent changes from baseline to the end-of-treatment in fasting TG Secondary: Changes or	Primary: There was a significant change from baseline in the mean percent decrease of TG in the fenofibrate group (36.6%) compared to essentially no change in the placebo group (*P*<0.001). Secondary: There was no significant difference in TC change between the fenofibrate treatment and the placebo groups (*P*=0.085). LDL-C increased by a mean of 15.0% in the fenofibrate group compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	and ≥2 of 4 additional components of the metabolic syndrome as defined by the NCEP ATP III		percent changes from baseline in TC, LDL-C, HDL-C, the TC:HDL-C ratio, VLDL-C, non-HDL-C; apo AI, B, and C-III; and remnant lipoprotein cholesterol	3.2% in the placebo group (*P*=0.006). HDL-C increased by a mean of 14.0% in the fenofibrate group compared to 0.8% for placebo (*P*<0.001). The ratio of TC to HDL-C decreased with fenofibrate compared to placebo (-14.2 vs 0.8%; *P*<0.001). VLDL-C declined by 33% with fenofibrate compared to a 1.6% decline with placebo treatment (*P*<0.001). Non-HDL-C decreased significantly more in the fenofibrate group (-7.5 vs -1.1%; *P*=0.009). There was no significant difference in the rise in apo AI among the fenofibrate group vs the placebo response (5.3 vs 2.0%; *P*=0.212). Apo B declined significantly with fenofibrate compared to placebo (*P*<0.001, respectively). Apo CIII was markedly reduced in the fenofibrate group (*P*<0.001 compared to placebo). A significant reduction in remnant lipoprotein cholesterol was observed with fenofibrate treatment (-35.1 vs 12.3%; *P*<0.001).
Jones et al[21] Fenofibric acid 135 mg/day vs placebo All patients received atorvastatin 40 mg/day and ezetimibe 10 mg/day	DB, MC, RCT Patients ≥18 years of age with mixed dyslipidemia (fasting TG ≥150 and <400 mg/dL, HDL-C <40 mg/dL in men and <50 mg/dL in women	N=543 12 weeks	Primary: Percentage changes from baseline in HDL-C and TG Secondary: Changes from baseline in apo AI, VLDL-C, apo CIII, non-HDL-C, apo B, hsCRP,	Primary: The addition of fenofibric acid resulted in a significantly greater mean percentage improvement in HDL-C (13.0 vs 4.2%; *P*<0.001) and TG (-57.3 vs -39.7%; *P*<0.001) compared to placebo. 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	and LDL-C ≥130 mg/dL)		LDL-C; proportion of patients achieving lipoprotein and apoprotein goals after 12 weeks of treatment; safety	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 (≥3%) were muscle spasms, myalgia, arthralgia, fatigue, diarrhea, nausea, and headache.
Hogue et al[22] Fenofibrate 200 mg QD vs atorvastatin 20 mg QD	RCT Patients with type 2 diabetes and hypertriglyceridemia	N=40 6 weeks	Primary: Lipids and TRL, inflammation and adhesion molecules Secondary: Not reported	Primary: Treatment with atorvastatin led to a significant decrease in plasma TC (-37.7%; *P*<0.0001), plasma TG (-37.6%, *P*<0.0001), plasma apo B (-43.2%, *P*<.0001), TRL-C (-44.1%, *P*<0.0001), TRL-TG (-36.9%, *P*<0.0001), TRL apo B (-13.8%, *P*=0.04), LDL-C (-43.0%, *P*<0.0001), LDL apo B (-42.7%, *P*<0.0001), and a significant increase in HDL-C (17.9%, *P*=0.001), and HDL apo A-I levels (10.3%, *P*=0.004). Treatment with fenofibrate led to a significant decrease in plasma C (-10.9%, *P*=0.0001), plasma TG (-41.4%, *P*=0.0002), plasma apo B (-9.9%, *P*=0.01), TRL-C (-52.8%, *P*<0.0001), TRL-TG (-46.3%, *P*=0.0002), and TRL apo B (-14.8%, *P*=0.02) and a significant increase in LDL-C (15.9%, *P*=0.04) and HDL-C (8.9%, *P*=0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were significant differences in the percentage changes of plasma cholesterol, plasma apo B, LDL-C, and LDL apo B between the two treatment groups. There was no significant difference in the percentage in changes of plasma TG between the treatment groups. Treatment with atorvastatin significantly decreased plasma levels of CRP (-26.9%, *P*=0.004), soluble ICAM-1 (-5.4%, *P*=0.03), soluble VCAM-1 (-4.4%, *P*=0.008), soluble E-selectin (-5.7%, *P*=0.02), MMP-9 (-39.6%, *P*=0.04), soluble phospholipase A2 (-14.8%, *P*=0.04), and oxidized LDL (-38.4%, *P*<0.0001). Fenofibrate significantly decreased soluble E-selectin levels only (-6.0, *P*=0.04) and increased soluble phospholipase A2 levels (22.5%, *P*=0.004). Secondary: Not reported
Arca et al[23] Fenofibrate 200 mg/day vs atorvastatin 10 mg/day, titrated up to 80 mg/day	OL, RCT Patients 30 to 75 years of age with diagnosis of familial combined hyperlipidemia with TC and/or TG levels ≥90th Italian population percentiles, and/or hyper-apobeta-lipoproteinemia	N=56 24 weeks	Primary: Change in TC, LDL-C, HDL-C, TG, apo A and endothelin-1 Secondary: Not reported	Primary: Atorvastatin was associated with a significant 9% reduction in TC compared to fenofibrate (95% CI, 3.0 to 15.1; *P*=0.004). Atorvastatin was associated with a significant 17% reduction in LDL-C compared to fenofibrate (95% CI, 8.0 to 26.1; *P*<0.001). Fenofibrate was associated with a significant 15.5% reduction in TG compared to atorvastatin (95% CI, 3.35 to 27.70; *P*=0.013). 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). 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). 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Goldberg et al[24] Fenofibric acid 135 mg QD plus atorvastatin 20 to 40 mg QD vs fenofibric acid 135 mg QD vs atorvastatin 20 to 40 mg QD	AC, DB, MC, RCT 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)	N=613 12 weeks	Primary: Percent changes from baseline in TG, HDL-C and LDL-C Secondary: Percent changes from baseline in VLDL-C, TC, apo B and hsCRP; safety	Primary: Combination therapy (atorvastatin 20 mg) resulted in significantly greater improvements in TG (-45.6 vs -16.5%; *P*<0.001) and HDL-C (14.0 vs 6.3%; *P*=0.005) compared to atorvastatin 20 mg and LDL-C (-33.7 vs -3.4%; *P*<0.001) compared to fenofibric acid. Similarly, significantly greater improvements were observed with combination therapy (40 mg) in TG (-42.1 vs -23.2%; *P*<0.001) and HDL-C (12.6 vs 5.3%; *P*=0.010) compared to atorvastatin 40 mg and LDL-C (-35.4 vs -3.4%; *P*<0.001) compared to fenofibric acid. Secondary: Combination therapy (20 mg) resulted in significantly higher mean percentages of decrease in non-HDL-C compared to fenofibric acid (*P*=0.026) and in VLDL-C compared to atorvastatin 20 mg (*P*=0.046). Combination therapy (40 mg) also resulted in significantly higher mean percentage of decrease in non-HDL-C compared to fenofibric acid (*P*<0.001) and in VLDL-C compared to atorvastatin 40 mg (*P*<0.001). Improvements in other secondary variables were similar between combination therapy and atorvastatin (TC; *P*=0.688, apo B; *P*=0.688 and hsCRP; *P*=0.074).
Roth et al[25] Rosuvastatin 5 mg/day vs fenofibric acid 135 mg/day vs rosuvastatin 5 mg/day plus fenofibric acid 135 mg/day	DB, MC, RCT Patients with fasting LDL-C ≥130 mg/dL, TG ≥150 mg/dL and HDL-C 40 mg/dL	N=760 12 weeks (plus a 30 day safety follow up period)	Primary: Composite of mean percent changes from baseline in HDL-C, TG and LDL-C Secondary: Changes from baseline in non-HDL-C, VLDL-C,	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). 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. All treatments were generally well tolerated, with discontinuations due to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			apo B, hsCRP and TC; safety; proportion of patients achieving LDL-C (<100 mg/dL) and non-HDL-C (<130 mg/dL) goals	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). 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).
Jones et al[26] Fenofibric acid 135 mg QD and rosuvastatin (10 or 20 mg) QD vs fenofibric acid 135 mg QD vs rosuvastatin 10, 20, or 40 mg QD	AC, DB, MC, RCT 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)	N=1,445 16 weeks (includes 30 day safety evaluation)	Primary: Composite of mean percent changes from baseline in HDL-C, TG and LDL-C Secondary: Composite of mean percent changes from baseline in non-HDL-C, VLDL-C, TC, apo B and hsCRP	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%; *P*<0.001 and 20 mg: 19.0 vs 10.3%; *P*<0.001) and a significantly greater decrease in TG (10 mg: 47.1 vs 24.4%; *P*<0.001 and 20 mg: 42.9 vs 25.6%; *P*<0.001) compared to rosuvastatin (10 and 20 mg). Combination therapy was associated with a significantly greater decrease in LDL-C (10 mg: 37.2 vs 6.5%; *P*<0.001 and 20 mg: 38.8 vs 6.5%; *P*<0.001) compared to fenofibric acid. 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) (*P*<0.001). Combination therapy was also associated with significantly greater improvements in VLDL-C (*P*<0.001), apo B (*P*<0.001) and hsCRP (*P*=0.013) compared to rosuvastatin. Combination therapy (rosuvastatin 20 mg) significantly improved non-HDL-C compared to fenofibric acid (*P*<0.001) and was associated with a significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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, apo B and TC (P values not reported).
Ferdinand et al[27] Fenofibric acid 135 mg QD and rosuvastatin 10 mg QD for 12 weeks, followed by fenofibric acid 135 mg QD and rosuvastatin 20 mg QD for up to 52 weeks Outcomes were evaluated from the end of the initial 12 week period (baseline) up to 52 weeks of treatment.	Post-hoc analysis 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)	N=187 1 year	Primary: Change in baseline LDL-C, HDL-C, non-HDL-C, apo B, TG, hsCRP; proportion of patients achieving individual and combined goals for LDL-C and non-HDL-C; safety Secondary: Not reported	Primary: Increasing rosuvastatin from 10 to 20 mg, in combination with fenofibric acid for up to 52 weeks, resulted in significant changes from baseline in LDL-C (-9.5%), non-HDL-C (-0.6%), apoB (-8.5%), and HDL-C (3.6%) (*P*≤0.005 for all). TG levels remained unchanged (0.8%; *P*=0.055) at week 52. A greater proportion of patients achieved risk-stratified lipid goals at week 52 compared to baseline for LDL-C (89 vs 84%; *P*=0.26), non-HDL-C (50 vs 25%; P value not reported), and both LDL-C and non-HDL-C (50 vs 19%; P value not reported). The incidences of muscle-, hepatic-, and renal-related adverse events and laboratory values were within the expected range for combination therapy. The most commonly reported treatment-emergent adverse events (>10%) were upper respiratory tract infection (14.4%), headache (13.9%), and back pain (10.7%)/ Treatment-emergent serious adverse events occurred in seven percent of patients, and one death (MI) occurred, none of which were deemed to be treatment-related. Secondary: Not reported
Mohiuddin et al[28] Fenofibric acid 135 mg QD plus simvastatin 20 to 40 mg QD vs fenofibric acid 135 mg QD vs	AC, DB, MC Patients >18 years of age with mixed dyslipidemia (TG ≥150 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for	N=657 16 weeks (includes 30 day safety evaluation)	Primary: Composite of mean percent changes from baseline in HDL-C, TG and LDL-C Secondary: Composite of mean percent	Primary: Combination therapy was associated with a significantly greater increase in HDL-C (20 mg: 17.8 vs 7.2%; *P*<0.001 and 40 mg: 18.9 vs 8.5%; *P*<0.001) and a significantly greater decrease in TG (20 mg: 37.4 vs 14.2%; *P*<0.001 and 40 mg: 42.7 vs 22.4%; *P*<0.001) compared to simvastatin (20 and 40 mg). Combination therapy was associated with a significantly greater decrease in LDL-C (20 mg: 24.0 vs 4.0%; *P*<0.001 and 40 mg: 25.3 vs 4.0%; *P*<0.001) compared to fenofibric acid. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
simvastatin 20 to 80 mg QD	women, and LDL-C ≥130 mg/dL)		changes from baseline in non-HDL-C, VLDL-C, TC, apo B and hsCRP	Combination therapy (simvastatin 20 mg) was associated with a significantly greater decrease in non-HDL-C (*P*<0.001) compared to fenofibric acid and simvastatin (20 mg). Combination therapy (simvastatin 20 mg) was associated with significant improvements in VLDL-C (*P*<0.001), apo B (*P*<0.001) and hsCRP (*P*=0.013) compared to simvastatin (20 mg). Combination therapy (simvastatin 40 mg) significantly (*P*<0.001) improved non-HDL-C compared to fenofibric acid, and resulted in a significantly greater improvement in VLDL-C (*P*=0.005) compared to simvastatin (40 mg), with similar reductions in non-HDL-C, apo B and TC (P values not reported).
Derosa et al[29] Fenofibrate 145 mg/day and simvastatin 40 mg/day vs fenofibrate 145 mg/day vs simvastatin 40 mg/day	DB, MC, RCT Caucasian patients ≥18 years of age with type 2 diabetes mellitus and combined dyslipidemia who had never been treated with lipid-lowering medications	N=241 12 months	Primary: Lipid and lipoprotein profiles at six and 12 months Secondary: Not reported	Primary: After six months of therapy, there was a significant reduction in TC and LDL-C with simvastatin and fenofibrate plus simvastatin (*P*<0.05 and *P*<0.01, respectively). There was no significant change in the fenofibrate group. After 12 months of therapy, there was a significant decrease in TC and LDL-C in all treatment groups (*P*<0.05 for fenofibrate, *P*<0.01 for the simvastatin and *P*<0.001 for fenofibrate plus simvastatin). TC was significantly lower with fenofibrate plus simvastatin compared to simvastatin monotherapy and fenofibrate monotherapy (*P*<0.05). LDL-C was significantly lower with fenofibrate plus simvastatin compared to simvastatin monotherapy and fenofibrate monotherapy (*P*<0.01). After six months of therapy, there was a significant reduction in TG with fenofibrate and fenofibrate plus simvastatin (*P*<0.05, respectively). There was no significant change in the simvastatin group. After 12 months of therapy, there was a significant decrease in TG in all treatment groups (*P*<0.01 for fenofibrate, *P*<0.05 for simvastatin and *P*<0.001 for fenofibrate plus simvastatin). TG was significantly lower with fenofibrate + simvastatin compared to fenofibrate (*P*<0.05) or simvastatin (*P*<0.01). After six months of therapy, there was a significant increase in HDL-C with fenofibrate and fenofibrate plus simvastatin (*P*<0.05 and *P*<0.01, respectively). There was no change in the simvastatin group. After 12 months of therapy,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				there was a significant increase in HDL-C in all treatment groups (*P*<0.01 for fenofibrate, *P*<0.05 for simvastatin and *P*<0.001 for fenofibrate plus simvastatin). HDL-C was significantly higher with fenofibrate plus simvastatin compared to simvastatin monotherapy and fenofibrate monotherapy (*P*<0.05). After six months of therapy, there was no significant change in apo A1 or apo B in any treatment group. After 12 months of therapy, there was a significant increase of apo A1 with fenofibrate plus simvastatin. There was no significant difference between the treatment groups. After 12 months of therapy, there was a significant decrease of apo B in all groups (*P*<0.05 for fenofibrate, *P*<0.05 for simvastatin and *P*<0.01 for fenofibrate plus simvastatin). There was no significant difference between the treatment groups. There were no significant differences in Lp(a) after six or 12 months of therapy in any of the treatment groups. After six months of therapy, there was a significant decrease in hsCRP with fenofibrate plus simvastatin (*P*<0.05), but not in the other groups. After 12 months of therapy, there was a significant decrease in hsCRP with simvastatin and with fenofibrate plus simvastatin (*P*<0.05 and *P*<0.01, respectively), but not with fenofibrate. The hsCRP value was significantly lower with fenofibrate plus simvastatin compared to fenofibrate or simvastatin (*P*<0.05). Secondary: Not reported
May et al[30] DIACOR Fenofibrate 160 mg and simvastatin 20 mg QD vs fenofibrate 160 mg QD vs	DB, PC, RCT Patients with type 2 diabetes, no CHD, and biochemical evidence of mixed dyslipidemia (having 2 of the following	N=300 12 weeks	Primary: Lipid and lipoprotein profiles Secondary: Not reported	Primary: Fenofibrate plus simvastatin significantly reduced dense VLDL-C compared to fenofibrate (*P*<0.001) and simvastatin (*P*<0.0001). Simvastatin significantly reduced IDL-C compared to fenofibrate (*P*<0.003). The percentage of LDL-C pattern B constituting total LDL-C was significantly reduced by fenofibrate (-13.7%; *P*<0.0001) and fenofibrate plus simvastatin (-11.1%, *P*<0.0001). There was no significant change with simvastatin (-2.4%; *P*=0.27).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
simvastatin 20 mg QD	3 lipid parameters: LDL-C >100 mg/dL, TG >200 mg/dL, and HDL-C <40 mg/dL)			Fenofibrate and fenofibrate plus simvastatin significantly increased the percentage of buoyant LDL-C constituting total LDL-C (-19.6%; *P*<0.0001 and -16.9%; *P*<0.0001, respectively). There was no significant change with simvastatin (-3.1%; *P*=0.06). Secondary: Not reported
Jones et al[31] Fenofibric acid 135 mg QD vs low-dose statin (rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg) QD vs fenofibric acid 135 mg plus low-dose statin (rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg) QD vs moderate-dose statin (rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg) QD vs	Pooled analysis of 3 AC, DB, MC, RCT Patients >18 years of age, with HDL-C <40 mg/dL (men) or <50 mg/dL (women), TGs ≥150 mg/dL, and LDL-C ≥130 mg/dL ≥130 mg/dL	N=2,715 12 weeks	Primary: Mean percent change in HDL-C, TGs (fenofibric acid plus atorvastatin vs atorvastatin), and LDL-C (fenofibric acid plus atorvastatin vs fenofibric acid) Secondary: Mean percent change in non-HDL-C, VLDL-C, TC, apo B, and hsCRP; safety	Primary: Fenofibric acid plus low-dose statin combination therapy resulted in a greater mean percent increase in HDL-C (18.1 vs 7.4%; *P*<0.001) and a greater mean percent decrease in TG (-43.9 vs -16.8%; *P*<0.001) compared to low-dose statin monotherapy, and a greater mean percent decrease in LDL-C (-33.1 vs -5.1%; *P*<0.001) compared to fenofibric acid monotherapy. Fenofibric acid plus moderate-dose statin combination therapy resulted in a greater mean percent increase in HDL-C (17.5 vs 8.7%; *P*<0.001) and a greater mean percent decrease in TG (-42.0 vs -23.7%; *P*<0.001) compared to moderate-dose statin monotherapy, and a greater mean percent decrease in LDL-C (-34.6 vs -5.1%; *P*<0.001) compared to fenofibric acid monotherapy. No formal comparisons were made between the high-dose statin monotherapy group and the other treatment groups. Secondary: Greater improvements in non-HDL-C, VLDL-C, TC, and apo B were observed for fenofibric acid plus low-dose statin combination therapy compared to corresponding monotherapies (*P*≤0.001). Combination therapy was generally well tolerated, and safety profiles were similar to monotherapies. No rhabdomyolysis was reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fenofibric acid 135 mg QD plus moderate-dose statin QD vs high-dose statin (rosuvastatin 40 mg, simvastatin 80 mg, or atorvastatin 80 mg) QD				
Bays et al[32] Fenofibric acid 135 mg plus moderate dose statin (rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg) Extension study patients received the same type of statin that was used in the statin-containing arms of the controlled study in which they participated	MC, OL Patients with mixed dyslipidemia completing 1 of 3 MC, PRO, DB, RCT 12-week studies were eligible	N=2,201 1 year	Primary: Safety, percent changes from baseline in TG, HDL-C, and LDL-C Secondary: Percent changes in non-HDL-C, VLDL-C, TC, apoB, and hs-CRP	Primary: Of the 2,201 patients who received at least one dose of fenofibric acid plus statin combination therapy, six patients (0.3%) died during the conduct of the ES; no death was considered by the investigator to be treatment related. Overall, 148 (6.7%) patients had treatment-emergent serious adverse events (fenofibric acid plus rosuvastatin, 7.2%; fenofibric acid plus simvastatin, 7.8%; fenofibric acid + atorvastatin 4.6%). The most common treatment-emergent serious adverse events were osteoarthritis, deep vein thrombosis, CAD, MI, and chest pain, diverticulitis, syncope, and intervertebral disc protrusion. A total of 1,856 patients (84.3%) had one or more treatment-emergent adverse events (fenofibric acid plus rosuvastatin, 83.1%; fenofibric acid plus simvastatin, 86.2%; fenofibric acid plus atorvastatin, 85.2%). The most frequently reported adverse events were headache, upper respiratory tract infection, nasopharyngitis, and back pain. Among patients who received fenofibric acid monotherapy in a controlled study, treatment with fenofibric acid plus moderate-dose statin combination therapy for 52 weeks resulted in an additional median percent decrease in TG (-22.0%), mean percent decrease in LDL-C (-38.1%), and mean percent increase in HDL-C (6.2%). Among patients who received moderate-dose statin monotherapy in a controlled study, treatment with fenofibric acid plus moderate-dose statin combination therapy for 52 weeks resulted in an additional median percent

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				decrease in TG (-30.5%) and mean percent increases in HDL-C (13.1%) and LDL-C (3.1%). Among patients who received fenofibric acid plus low-dose statin combination therapy in a controlled study, there was an additional median percent decrease in TG (-4.2%), mean percent increase in HDL-C (4.8%), and mean percent decrease in LDL-C (-9.7%) after the statin dose was increased for 52 weeks. The group of patients who were treated with fenofibric acid plus moderate-dose statin in a controlled study and continued the same therapy in the extension study exhibited sustained improvements in lipid parameters throughout the course of therapy. For this group of patients, treatment with fenofibric acid plus moderate-dose statin combination therapy for a total of 64 weeks decreased TG from a mean baseline of 297.8 mg/dL to a mean final level of 138.0 mg/dL, decreased LDL-C from a mean baseline of 153.1 mg/dL to a mean final level of 94.2 mg/dL, and increased HDL-C from a mean baseline of 38.2 mg/dL to a mean final level of 47.7 mg/dL. Secondary: Among patients who received fenofibric acid monotherapy or moderate-dose statin monotherapy in the controlled studies, treatment with fenofibric acid plus moderate-dose statin combination therapy in the extension study resulted in additional mean percent decreases in non-HDL-C, VLDL-C, TC, and apo B, and median percent decrease in hsCRP that were sustained throughout 52 weeks of combination therapy. For patients initially treated with fenofibric acid plus low-dose statin combination therapy, increasing the statin dose resulted in additional mean percent decreases in non-HDL-C, TC, and apo B and median percent decrease in hsCRP, which were sustained throughout the study.
Kipnes et al[33] Fenofibric acid 135 mg plus moderate dose	ES, OL Patients with mixed	N=310 1 year (2 years of	Primary: Safety and efficacy	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
statin (rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg) ES patients received the same type of statin that was used in the statin-containing arms of the controlled study in which they participated.	dyslipidemia at the start of a 1 year, ES, OL	total therapy)	Secondary: Not reported	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%; *P*=0.011), TC (-38.70±12.16 vs -32.50±10.86 vs -38.60±10.85%; *P*=0.007) and VLDL-C (-56.80±25.17 vs -40.30±51.25 vs -51.20±35.42%; *P*=0.019). Secondary: Not reported
Farnier et al[34] Fenofibrate 160 mg QD and ezetimibe 10 mg QD vs fenofibrate 160 mg QD vs	DB, MC, PC, RCT Men and women 18 to 75 years of age with mixed hyperlipidemia and no CHD, CHD-equivalent	N=619 12 weeks	Primary: Percent change in LDL-C from baseline to study end point Secondary: Percent change in other lipid, non-lipid, and	Primary: The mean percent change in LDL-C reduction was significantly greater in the micronized fenofibrate and ezetimibe group when compared to the other treatment groups (*P*<0.001 compared to micronized fenofibrate and ezetimibe). These reductions were 13.4% in the ezetimibe group, 5.5% in the micronized fenofibrate group, and 20.4% in the micronized fenofibrate and ezetimibe group. Secondary: When compared to micronized fenofibrate or ezetimibe monotherapy,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ezetimibe 10 mg QD vs placebo	disease (except for type 2 diabetes), or 10-year CHD risk >20%		lipoprotein parameters from baseline to study end point	significant reductions in apo B, non-HDL-C and LDL-C were observed in the micronized fenofibrate and ezetimibe group; *P*<0.001. When compared to placebo, significant decreases in TG levels and significant increases in HDL-C level were observed in both the micronized fenofibrate plus ezetimibe and micronized fenofibrate treatment groups; *P*<0.001. The percent changes from baseline to study end point were as follows: -11.8% in TC, 3.9% in HDL-C, -11.1% in TG, and -6.1% in hsCRP in the ezetimibe group; -10.8% in TC, 18.8% in HDL-C, -43.2% in TG, and -28.0% in hsCRP in the micronized fenofibrate group; -22.4% in TC, 19.0% in HDL-C, -44.0% in TG, and -27.3% in hsCRP in the micronized fenofibrate and ezetimibe group (*P*<0.05 for all).
Tribble et al[35] Ezetimibe 10 mg and fenofibrate 160 mg QD (FENO + EZE) vs ezetimibe 10 mg QD (EZE) vs fenofibrate 160 mg QD (FENO) vs placebo	DB, MC, PC, RCT Patients 18 to 75 years of age with mixed hyperlipidemia (LDL-C 130 to 220 mg/dL and TG 200 to 500 mg/dL) and no CHD or CHD-risk equivalent disease, or 10-year CHD risk >20% according to NCEP ATP III criteria	N=625 12 weeks	Primary: Changes in cholesterol mass within the major lipoprotein fractions and subfractions and LDL particle distribution profiles and particle size Secondary: Not reported	Primary: The effects of EZE, FENO, and FENO + EZE on VLDL subfractions were similar to those for VLDL overall. All active treatments reduced IDL-C. Treatment with FENO significantly reduced LDL-C1, LDL-C3, and LDL-C4 and significantly increased LDL-C2 compared to placebo. FENO + EZE produced a pattern of changes similar to those of FENO alone. The reductions in LDL-C1 and LDL-C3 were greater with the combination due to the added effects of EZE. There were no significant changes in cholesterol associated with Lp(a). Fenofibrate and FENO + EZE increased median HDL-C2 and HDL-C3 compared to EZE and placebo. In patients treated with EZE, there were reductions in VLDL-C, IDL-C, and LDL-C density ranges without a shift in LDL density distributions or changes in the HDL-C range. In patients treated with FENO, there were reductions in VLDL-C and IDL-C. HDL-C was increased and there was a shift in the distribution of LDL toward larger, more buoyant LDL particles with a small effect on LDL-C values overall.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In patients treated with FENO + EZE, there were reductions in VLDL-C, IDL-C, and LDL-C. HDL-C was increased and there was a shift from smaller, more dense to larger, more buoyant LDL subfractions. EZE did not significantly affect LDL peak particle size. FENO and FENO + EZE increased LDL peak particle size. Secondary: Not reported
McKenney et al[36] Fenofibrate 160 mg QD and ezetimibe 10 mg QD vs fenofibrate 160 mg QD vs ezetimibe 10 mg QD for 12 weeks, then fenofibrate 160 mg and ezetimibe 10 mg QD for 48 weeks vs placebo for 12 weeks, then fenofibrate 160 mg for 48 weeks	DB Patient who completed base study with mixed hyperlipidemia	N=576 48 weeks	Primary: Percent change in LDL-C from baseline of the base study to study end point in the extension Secondary: Percent change from baseline to study end point in TC, HDL-C, TG, non-HDL-C, apo B, apo AI, and hsCRP	Primary: Fenofibrate plus ezetimibe showed significantly greater percent reductions in LDL-C compared to fenofibrate alone (-22.0 vs -8.6; *P*<0.001). Secondary: Fenofibrate plus ezetimibe showed significantly greater percent reductions from baseline to extension study end point in TC (-23.2 vs -13.6; *P*<0.001), TG (-46.0 vs -41.0; *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 fenofibrate. There was a significantly greater percent increase in HDL-C (20.9 vs 17.8; *P*=0.02) with fenofibrate plus ezetimibe vs fenofibrate alone. There was not a significantly greater percent increase in apo AI (10.1 vs 7.8; *P*=0.12) with fenofibrate plus ezetimibe vs fenofibrate alone. Reductions in median hsCRP levels were not different between treatments (-25.3 vs -21.1; *P*=0.46) for fenofibrate plus ezetimibe vs fenofibrate alone, respectively.
Ansquer et al[37] Fenofibrate (Tricor®) 145 mg and ezetimibe 10 mg QD	DB, MC, RCT Patients 18 to 70 years of age with type IIb	N=60 12 weeks	Primary: Percentage change from baseline in TG and HDL-C	Primary: Fenofibrate plus ezetimibe and fenofibrate reduced TG by -38.3% (P value not significant) and increased HDL-C to a similar extent (11.5 and 7.9%, respectively; *P*=0.282).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fenofibrate (Tricor®) 145 mg QD vs ezetimibe 10 mg QD	dyslipidemia (LDL-C ≥160 mg/dL, TG 150 to 405 mg/dL) and ≥2 features of the metabolic syndrome according to the NCEP ATP III definition		Secondary: Percentage change in LDL-C, non-HDL-C, remnant-like particle cholesterol (RLP-C) and related parameters, change in glucose metabolism parameters, hsCRP, safety	Secondary: Fenofibrate plus ezetimibe reduced LDL-C by -36.2% compared to -22.4% with fenofibrate and -22.8% with ezetimibe (*P*<0.001 for both). Fenofibrate plus ezetimibe lowered non-HDL-C by -36.2% compared to fenofibrate (-24.8%) and ezetimibe (-20.9%) (P value not reported). There was no significant difference between fenofibrate plus ezetimibe and fenofibrate with regards to RLP-C (-36.2 vs -30.7%; P value not significant). Ezetimibe was less effective than fenofibrate plus ezetimibe (-17.3%; *P*<0.001). The effect of fenofibrate plus ezetimibe on LDL particle size (+2.1%) was similar to that of fenofibrate (+1.9%). Fenofibrate plus ezetimibe was more effective than monotherapy with fenofibrate or ezetimibe in reducing apo B (-33.3%). Fenofibrate plus ezetimibe had the same effect as fenofibrate on apo AI (+7.9 vs +5.1%, respectively) and apo AII (+24.2 vs +21.2%, respectively; P value not reported). Fenofibrate plus ezetimibe and fenofibrate reduced hsCRP to a similar degree. There was a higher incidence of treatment-related adverse events with fenofibrate/ezetimibe, which was primarily due to abnormal laboratory changes, including moderate increases in CK, liver enzymes, and blood creatinine.
Farnier et al[38] Fenofibrate 160 mg QD and simvastatin-ezetimibe 20-10 mg QD	DB, MC, PA, PC, RCT Patients 18 to 79 years old with mixed	N=611 12 weeks	Primary: Percent change from baseline in LDL-C Secondary:	Primary: Simvastatin-ezetimibe plus fenofibrate group exhibited significant reduction in LDL-C from baseline compared to the fenofibrate monotherapy group (45.8 vs 15.7%; *P*<0.05). There was no significant difference between LDL-C reduction seen with the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fenofibrate 160 mg QD vs simvastatin-ezetimibe 20-10 mg QD vs placebo	hyperlipidemia and no CHD or CHD-risk equivalent disease, or 10-year CHD risk >20% according to NCEP ATP III criteria		Percent change from baseline in TC, TG, HDL-C, non-HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C/HDL-C, apo B	simvastatin-ezetimibe plus fenofibrate therapy and simvastatin-ezetimibe therapy (45.8 vs 47.1%; *P*>0.2). Secondary: Simvastatin-ezetimibe plus fenofibrate group exhibited significant reduction from baseline in non-HDL-C, TG, and apo B compared to the other treatment groups (*P*<0.01). There was no significant difference between TC reduction seen with the simvastatin-ezetimibe plus fenofibrate therapy and simvastatin-ezetimibe therapy (38.7 vs 35.4%; *P*>0.05). Simvastatin-ezetimibe plus fenofibrate group exhibited significant increase from baseline in HDL-C compared to the simvastatin-ezetimibe group (18.7 vs 9.3%; *P*<0.01). Simvastatin-ezetimibe plus fenofibrate group exhibited significant reduction from baseline in LDL-C:HDL-C, TC:HDL-C compared to the simvastatin-ezetimibe group (*P*=0.03). There was no significant difference between the percentage of patients able to reach their LDL-C goal with the simvastatin-ezetimibe plus fenofibrate therapy and simvastatin-ezetimibe therapy (88.5 vs 92.9%).
Farnier et al[39] Fenofibrate 160 mg and ezetimibe-simvastatin 10-20 mg QD vs fenofibrate 160 mg QD vs	RCT, DB, MC, PC Patients 18 to 79 years of age with mixed hyperlipidemia and no CHD, CHD-equivalent disease (except for type 2 diabetes), or	N=611 12 weeks	Primary: Percent change in cholesterol associated with lipoprotein subfractions (VLDL-C 1+2 and VLDL-C 3, IDL-C, LDL-C 1 to 4, Lp[a], HDL-C_2 and HDL-C_3,	Primary: The effects of ezetimibe-simvastatin, fenofibrate, and ezetimibe/simvastatin plus fenofibrate on VLDL subclasses were similar to those for VLDL-C overall. The maximal changes in IDL-C are achieved by ezetimibe-simvastatin with little additional effect of fenofibrate. Significant reductions were observed for all LDL-C subfractions with ezetimibe-simvastatin treatment. When coadministered with fenofibrate, the effects of both treatments were evident. Ezetimibe-simvastatin plus fenofibrate resulted in a pattern of changes that were similar to fenofibrate monotherapy indicating that the change in LDL-C pattern was primarily a function of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ezetimibe-simvastatin 10-20 mg QD vs placebo	CHD risk score >20% (as defined by NCEP ATP III), LDL-C 130 to 220 mg/dL and TG 150 to 500 mg/dL		and changes in LDL particle size) Secondary: Not reported	fenofibrate. There was no significant difference in cholesterol associated with Lp(a) among the treatment groups. Fenofibrate and ezetimibe-simvastatin plus fenofibrate led to similar increases in median HDL-C_2 and HDL-C_3 compared to ezetimibe-simvastatin and placebo. Ezetimibe-simvastatin did not significantly affect LDL particle size. Fenofibrate and ezetimibe-simvastatin plus fenofibrate increased LDL particle size. At the end of the study, the percentages of patients exhibiting LDL size pattern B was 64, 49, 14, and 17% in the placebo, ezetimibe-simvastatin, fenofibrate, and ezetimibe-simvastatin plus fenofibrate groups, respectively. Secondary: Not reported
Kumar et al[40] Ezetimibe 10 mg/day plus fenofibrate 160 mg/day vs atorvastatin 10 mg/day	RCT, XO Patients with hypercholesterolemia requiring pharmacotherapy	N=43 12 weeks	Primary: Percentage reduction of LDL-C Secondary: Percent changes from baseline in TC, HDL-C and TG	Primary: LDL-C decreased by 34.6 vs 36.7% with combination therapy and atorvastatin (*P*=0.46). Secondary: Both treatments provided similar improvements in TC (-25.1 vs -24.6%; *P*=0.806) and HDL-C (10.1 vs 8.9%; *P*=0.778). Combination therapy showed a trend towards a greater reduction in TGs (25.4 vs 14.5%; *P*=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%; *P*=0.904).
Winkler et al[41] Fluvastatin 80 mg/day plus fenofibrate 200 mg/day vs ezetimibe 10 mg/day plus	MC, OL, RCT, XO Patients 18 to 75 years of age with metabolic syndrome, low HDL-C, waist	N=75 6 weeks	Primary: Changes from baseline in lipids, lipoproteins and apolipoproteins; LDL subfractions	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
simvastatin 20 mg/day	circumference ≥94 (men) or ≥80 cm (females) plus 1 of the following: TG ≥150 mg/dL, BP (≥85/≥130 mm Hg), FPG ≥100 mg/dL or prevalent type 2 diabetes		Secondary: Not reported	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. Secondary: Not reported
Wi et al[42] Niacin ER 500 mg/day for 5 weeks, followed by 1,000 mg/day for 4 weeks, followed by 1,500 mg/day vs fenofibrate 160 mg/day After discontinuation of any lipid modifying drug, patients entered an 8 week dietary run in period.	OL, RCT Patients 20 to 79 years of age with TG 150 to 499 mg/dL and HDL-C <45 mg/dL	N=201 24 weeks (includes 8 week dietary run in period)	Primary: Percent change from randomization to week 16 in apo B/apo AI Secondary: Percent changes in other lipid parameters, levels of glucose metabolism-related parameters, hsCRP	Primary: Apo B/apo AI 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 AI was higher with fenofibrate. 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). 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 increased with niacin. Percent changes of insulin (*P*<0.001) and HOMA-IR (*P*<0.001) were significantly different between the two treatments.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				hsCRP levels were significantly lowered with both treatments, but the percent change was greater with niacin (*P*=0.03).
Alrasadi et al[42] Protocol 1 Fenofibrate 200 mg/day for 8 weeks vs atorvastatin 20 mg/day for 8 weeks vs niacin SR 1 g BID for 8 weeks Protocol 2 Fenofibrate 200 mg/day and atorvastatin 20 mg/day for 8 weeks vs niacin SR 1 g BID and atorvastatin 20 mg/day for 8 weeks Patients in whom a statin was required were switched or maintained on atorvastatin 20 mg throughout the study in Protocol 2.	XO Men with HDL-C <5th percentile for age- and gender-matched patients and an identified genetic cause of HDL deficiency or ≥1 first degree relative affected with HDL deficiency	N=19 32 weeks	Primary: Percent changes in HDL-C and TC/HDL-C ratio Secondary: Not reported	Primary: Protocol 1 The mean percent change in HDL-C was +6, -6, and +22% in patients receiving fenofibrate, atorvastatin, and niacin, respectively. Only niacin significantly raised HDL-C (*P*<0.05). The mean percent change in TC/HDL-C ratio was +19, -26, and -22% in patients receiving fenofibrate, atorvastatin, and niacin, respectively. Both niacin and atorvastatin significantly lowered TC/HDL-C (*P*<0.05 and *P*<0.01, respectively). Protocol 2 The mean percent change in HDL-C was -2 and +18% in patients receiving fenofibrate plus atorvastatin and niacin plus atorvastatin, respectively. Only the group receiving niacin experienced a significant increase in HDL-C (*P*<0.05). The mean percent change in TC/HDL-C ratio was +32 and -32% in patients receiving fenofibrate plus atorvastatin and niacin plus atorvastatin, respectively. Only the group receiving niacin experienced a significant decrease in TC/HDL-C (*P*<0.01). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Balasubramanyam et al[44] Usual care vs low saturated fat diet and exercise (D/E) vs D/E and fenofibrate 145 mg/day (Tricor®) vs D/E and niacin SR 2,000 mg/day (Niaspan®) vs D/E and fenofibrate 145 mg/day and niacin SR 2,000 mg/day	DB, PC, RCT Patients 21 to 65 years of age with hypertriglyceridemia (fasting TG >150 mg/dL) and receiving stable ART therapy for 6 months	N=191 24 weeks	Primary: Baseline changes in lipid parameters Secondary: Baseline changes in insulin sensitivity, glycemia, adiponectin, CRP, energy expenditure, and body composition	Primary: Patients receiving fenofibrate achieved significant improvements in TG (*P*=0.002), TC (*P*=0.02), and non-HDL-C (*P*=0.003), compared to patients receiving niacin who achieved significant improvements in HDL-C (*P*=0.03), and both groups of patients achieved significant improvements in TC:HDL-C (*P*=0.005 and *P*=0.01). The combination of D/E plus fenofibrate plus niacin provided maximal benefit, reducing TG (-52% vs usual care; *P*=0.003), increasing HDL-C (12% vs usual care; *P*<0.001), and decreasing non-HDL-C (-18.5% vs usual care; *P*=0.003) and TC:HDL-C (-24.5% vs usual care; *P*<0.001). Secondary: Of the secondary endpoints evaluated, there was an effect of niacin on FPG (*P*=0.0002), oral glucose tolerance test area under the curve for glucose (*P*=0.02), fasting insulin (*P*=0.03), HOMA-IR (*P*=0.008), insulin sensitivity index (*P*=0.007), and adiponectin (*P*<0.0001), and an effect of fenofibrate on creatinine (*P*=0.002).
Roth et al[45] Phase I Fenofibrate 130 mg (FENO) QD and omega-3 acid ethyl esters 4 g (P-OM3) QD for 8 weeks vs fenofibrate 130 mg (FENO)	DB, MC, PC, RCT Patients 18 to 79 years of age with Fredrickson type IV dyslipidemia, BMI 25 to 43 kg/m^2, and TG 500 to 1,300	N=167 16 weeks	Primary: Median percent change in TG Secondary: Additional lipid and cardiovascular risk factors	Primary: After eight weeks of therapy, median TG values were reduced from 649.5 to 267.5 mg/dL (-60.8%) with P-OM3 + FENO and from 669.3 to 310 mg/dL (-53.8%) with FENO monotherapy (*P*=0.059). There was no significant difference between the treatment groups (*P*=0.059). Secondary: LDL-C was significantly increased with P-OM3 + FENO compared to FENO monotherapy (48.2 vs 39.0%, respectively; *P*=0.030). There was no significant difference in non-HDL-C among the treatment groups

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD and placebo for 8 weeks Phase II Fenofibrate 130 mg (FENO) QD and omega-3 acid ethyl esters 4 g (P-OM3) QD for 8 weeks	mg/dL			(-8.2% for P-OM3 + FENO vs -7.1% for FENO; *P*=0.767). There was a greater reduction in VLDL-C with P-OM3 + FENO than with FENO monotherapy (-57.6 vs -47.6%, respectively; *P*=0.016). There was a greater reduction in RLP-C with P-OM3 + FENO than with FENO monotherapy (-72.0 vs -62.1%; *P*=0.029). In the first eight week ES, the addition of P-OM3 to FENO monotherapy significantly reduced TGs compared to the end of the DB treatment period (-17.5%, *P*=0.003). In the first eight week ES, the addition of P-OM3 to FENO monotherapy significantly increased LDL-C (+8.1%; *P*=0.001) compared to the group previously receiving P-OM3 + FENO (+0.4%). There was no significant change in non-HDL-C following the addition of P-OM3 to FENO. VLDL-C and RLP-C were significantly reduced by the addition of P-OM3 (-15.4%, *P*=0.030 and -25.8%, *P*=0.035, respectively). There was no significant difference in final lipid results for those who received P-OM3 + FENO for 16 weeks and those in which P-OM3 was added to FENO monotherapy during the OL phase of the study. In the pooled analysis of all patients enrolled in the eight week OL extension phase, the overall reductions of TGs and VLDL-C were -60.0 and -56.5%, respectively (*P*<0.001 for both). Non-HDLC and TC were also significantly reduced (*P*<0.001) over the 16 week treatment period in the pooled analysis. LDL-C increased 52.2% (*P*<0.001). There was no significant change in apo B at the end of the 16 week treatment study (*P*=0.544). The treatments were generally well tolerated and there was no significant difference in the safety profiles. The most adverse events were upper respiratory infection, nausea, diarrhea, constipation, gastroenteritis, dyspepsia, and headache.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Koh et al[46] Fenofibrate 160 mg/day vs omega-3 fatty acids 2 g/day vs placebo	PC, PG, RCT, SB Patients with primary hypertriglyceridemia (>150 mg/dL)	N=50 2 months	Primary: Change in baseline lipid profile; change in baseline vasomotor function, hsCRP, and fibrinogen; change in baseline adiponectin, HbA_{1c}, and insulin resistance Secondary: Not reported	Primary: Placebo treatment significant reduced TG and TG:HDL-C, but increased LDL-C from baseline. Omega-3 fatty acids significantly reduced TG and TG:HDL-C from baseline. Fenofibrate significantly reduced T C, TG, apo B, TG:HDL-C, and non-HDL-C, and increased HDL-C and apo AI from baseline. Effects of fenofibrate on TC and T G were both significant compared to placebo (P<0.05). The magnitude of change in HDL-C, apo AI, TG:HDL-C, and non-HDL-C were significantly different when omega-3 fatty acids and fenofibrate therapy were compared, but both treatments resulted in comparable improvements in TG (P<0.05). Placebo did not significantly improve flow-mediated dilator response to hyperemia, but omega-3 fatty acids and fenofibrate significantly improved flow-mediated dilator response to hyperemia after two months when compared to baseline (P<0.001), and when compared to placebo (P<0.001). Brachial artery dilator responses to nitroglycerin were not significantly different between any of the therapies. Placebo and omega-3 fatty acids did not significantly change hsCRP and fibrinogen levels relative to baseline measurements. Fenofibrate significantly reduced hsCRP and fibrinogen levels after two months compared to baseline (P<0.001) or when compared to placebo (P<0.05). Omega-3 fatty acids did not significantly change insulin, plasma adiponectin levels, or insulin sensitivity compared to placebo. Compared omega-3 fatty acids, fenofibrate significantly decreased fasting insulin (P=0.023) and increased plasma adiponectin (P=0.002) and insulin sensitivity (P=0.015). Secondary: Not reported
Koh et al[47] Fenofibrate 200 mg QD and candesartan 16 mg QD vs	DB, PC, RCT, XO Patients with hypertriglyceridemia (≥150	N=46 6 months	Primary: BP, lipid profile, inflammatory markers, vasomotor function, plasma	Primary: Fenofibrate, combined therapy, or candesartan therapy significantly reduced BP. However, combined therapy significantly reduced BP more than fenofibrate or candesartan alone (P<0.001). When compared to candesartan, fenofibrate or combined therapy significantly improved the lipoprotein profile.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fenofibrate 200 mg QD vs candesartan 16 mg QD	mg/dL) and hypertension (≥140/90 mm Hg)		malondialdehyde, adiponectin, and insulin resistance Secondary: Not reported	Fenofibrate alone or combined therapy significantly lowered TC, TG, apo B, and non-HDL-C levels (*P*<0.001 for all) and increased HDL-C levels (*P*<0.001) when compared to baseline. These reductions were significantly greater than those observed with candesartan alone (*P*<0.001). However, there were no significant differences between fenofibrate alone and fenofibrate plus candesartan for these parameters (P value not significant). All three treatment arms significantly improved flow-mediated dilator response to hyperemia. Combined therapy significantly decreased plasma malondialdehyde (a biomarker for oxidative stress), hsCRP, and soluble CD40L levels relative to baseline measurements. Importantly, these parameters were changed to a greater extent with combined therapy when compared to monotherapy (*P*<0.001, *P*=0.002, *P*=0.050, and *P*=0.032, respectively). Fenofibrate, combined therapy, and candesartan significantly increased plasma adiponectin levels and insulin sensitivity relative to baseline measurements. However, the magnitudes of these increases were not significantly different among the three therapies (*P*=0.246 for adiponectin levels and *P*=0.153 for insulin sensitivity). Secondary: Not reported
Insua et al[48] Gemfibrozil 900 mg daily vs fenofibrate 200 mg QD	DB, DD, RCT, XO Patients between the ages of 45 and 70 years with primary hyperlipo-proteinemia, Fredrickson phenotypes IIa	N=21 6 weeks	Primary: Cholesterol-lowering effectiveness Secondary: Not reported	Primary: Both drugs significantly reduced TC, calculated LDL-C, TG, apo B, and fibrinogen (*P*<0.01 for all calculations, except *P*<0.05 for fibrinogen with gemfibrozil therapy) and increased HDL-C (*P*<0.01). Neither drug affected Lp(a), whereas uric acid was reduced only by fenofibrate (*P*<0.01). The percentage decrease in TC and LDL-C was greater with fenofibrate compared to gemfibrozil (-22 vs -15%; *P*<0.02; and -27 vs -16%; *P*<0.02, respectively). In contrast, reductions in levels of TG (-54 vs -46.5%), apo B, and fibrinogen, as well as the increase in HDL-C (9% for both drugs), showed

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	and IIb			no significant difference between treatments. Separate analysis of patients with type IIb hyperlipoproteinemia showed essentially the same plasma lipid changes as for the overall group, but with greater modifications in TG and HDL-C concentrations. Secondary: Not reported
Corbelli et al[49] Gemfibrozil (mean daily dose 1,200 mg) vs fenofibrate (mean daily dose of 201 mg)	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-C, and non-HDL-C Secondary: Not reported	Primary: Compared to gemfibrozil, patients showed statistically significant improvements in mean TC, TG, HDL-C, and non-HDL (*P*<0.005). Specifically, more patients achieved a TG goal <200 mg/dL with fenofibrate (64%) compared to gemfibrozil (39%; *P*<0.0005). The study demonstrated 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
Guyton et al[50] 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 vs gemfibrozil 600 mg BID	DB, MC, PC, RCT 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	N=173 8 weeks	Primary: Effect on HDL-C Secondary: Change in other lipoproteins, adverse effects	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). Secondary: Compared to gemfibrozil, niacin 1,500 and 2,000 mg/day significantly increased apo AI (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.). 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). Effects on plasma fibrinogen levels were significantly favorable for niacin compared to gemfibrozil (-1 to -6% vs 5 to 9%, respectively; *P*<0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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).
Stalenhoef et al[51] Omega-3-acid ethyl esters (Omacor*) 4 g/day vs gemfibrozil 1,200 mg/day	DB, DD, RCT Patients with primary hyper-triglyceridemia	N=28 12 weeks	Primary: Change in lipid profile, LDL-C subfraction profile Secondary: Not reported	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). 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). Secondary: Not reported
van Dam et al[52] Omega-3 acid ethyl esters (Omacor*) 4 g/day vs gemfibrozil 1,200 mg/day	RCT, DB Patients with hypertriglyceride mia (TG >400 mg/dL)	N=89 12 weeks	Primary: Percent change in TG Secondary: Percent change in TC, HDL-C, VLDL-C	Primary: The mean percent change in TG was -28.9% with omega-3 acid ethyl esters and -51.2% with gemfibrozil (*P*=0.007). Secondary: The mean percent change in HDL-C and TC were +1.2 and -10.2%, respectively, with omega-3 acid ethyl esters and +27.9 and -13.0%, respectively, with gemfibrozil (*P*=0.012 and *P*=0.513, respectively). The mean percent change in VLDL-C was -11.8% with omega-3 acid ethyl esters and -19.4% with gemfibrozil (*P*=0.494).
Munoz et al[53] Fish Oil vs fenofibrate	Cohort, MC, OS, PRO Patients ≥18 years of age diagnosed with HIV-infection	N=493 6 weeks	Primary: Absolute change in TG levels Secondary: Not reported	Primary: The mean decrease in TG values for patients who initiated fish oil was 40 mg/dL in unadjusted analyses (IQR, -73 to -7; P=0.02). A total of 9% (7/76) of patients on fish oil received a target TG value, <150 mg/dL compared with 18% (14/80) on fenofibrate, 22% (10/46) on gemfibrozil, and 28% (80/291) on atorvastatin. After adjusting for age, sex, baseline CD4+ cell count, protease inhibitor use, and duration of time between pre- and post-TGs, the change in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs gemfibrozil vs atorvastatin	and who initiated fish oil, fenofibrate, gemfibrozil, or atorvastatin between 1/1/00 and 12/31/09			TG values was 71 mg/dL (IQR, -126 to -15; P=0.01). The comparative effectiveness analyses, significantly greater reductions were seen in gemfibrozil (-80; 95% CI, -150 to -10; P=0.02) compared with fish oil. Gemfibrozil and fenofibrate demonstrated similar reductions in TG values with overlapping Cis; although, fenofibrate did not demonstrate a statistically significant greater reduction compared with fish oil (-49; 95% CI, -108 to 11; P=0.1). Atorvastatin was not associated with a statistically significant greater reduction in TG values compared with fish oil (-33; 95% CI, -81 to 15; P = 0.2). This may be due to the lower baseline TG values of patients on fish oil and atorvastatin. Secondary: Not reported
Weinstein et al[54] Fenofibric acid 45 mg and rosuvastatin 5 mg QD vs rosuvastatin 5 mg QD Rosuvastatin dose was increased from 5 mg to 10 mg in both groups after eight weeks.	AC, DB, MC, RCT Patients ≥18 years of age diagnosed CKD and mixed dyslipidemia.	N=275 16 weeks	Primary: Median percent change in TGs at week eight Secondary: Percent changes in HDL-C at week eight, median percent change in TG and HDL-C at week 16, and mean percent changes in LDL-C, TC, non–HDL-C, VLDL-C, and apoB from baseline to weeks eight and	Primary: Combination therapy with fenofibric acid and rosuvastatin resulted in significantly greater median percent decreases in TG, compared with rosuvastatin monotherapy, from baseline to week eight (−38.0% compared to −22.4%, P<0.001). Secondary: Combination therapy with fenofibric acid and rosuvastatin also resulted in significantly greater median percent decreases in TG, compared with rosuvastatin monotherapy at week 16 (−42.6% compared to −29.7%, P<0.001). Combination therapy resulted in a significantly greater mean percent increase in HDL-C compared with rosuvastatin alone, from baseline to week eight (16.9% compared to 7.8%, P<0.001) and week 16 (17.3% compared to 8.9%, P<0.001). Combination therapy also resulted in significant improvements in mean percent changes in non−HDL-C (–41.5% compared to –37.9%, P=0.01) and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			16	apoB (–35.0% compared to –31.6%, P=0.021) versus the rosuvastatin monotherapy group at week eight. No other significant differences between combination therapy and rosuvastatin monotherapy were observed at week eight or week 16.
Primary Prevention of Coronary Heart Disease Events				
Keech et al[55] FIELD Fenofibrate 200 mg QD vs placebo	DB, PC, RCT Patients aged 50 to 75 years with type 2 diabetes mellitus	N=9,975 5 years	Primary: Coronary events (CHD, death or nonfatal MI) Secondary: Total cardiovascular events which included the composite of cardiovascular death, MI, stroke, and coronary and carotid revascularizatio n; total mortality	Primary: Coronary events occurred in 5.9% of patients on placebo and 5.2% of patients on fenofibrate (HR, 0.89; 95% CI, 0.75 to 1.05; *P*=0.16). There was a 24% reduction in nonfatal MI with fenofibrate (HR, 0.76; 95% CI, 0.62 to 0.94; *P*=0.010). There was a nonsignificant increase in coronary heart disease 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). There was a 21% reduction in coronary revascularization with fenofibrate (HR, 0.79; 95% CI, 0.68 to 0.93; *P*=0.003). Total mortality was 6.6% in the placebo group and 7.3% in the fenofibrate group (*P*=0.18).
Tonkin et al[56] FIELD Fenofibrate 200 mg QD vs placebo	Subgroup analysis of FIELD comparing the effect of fenofibrate on cardiovascular disease between patients with	N=9,975 (n=2,131 with prior cardio-vascular disease and n=7,664 without prior cardio-vascular	Primary: Lipids and the effect of fenofibrate treatment, compliance with trial medication and use of other drugs, unadjusted	Primary: There were small but significant differences between patients with and without prior cardiovascular disease in their pattern of lipid response to treatment. At 12 months after randomization, the effect of fenofibrate on increasing HDL-C and decreasing LDL-C and TG was greater in patients with no prior cardiovascular disease compared to those with prior cardiovascular disease (*P*<0.05 for all). At 24 months after randomization, difference in treatment effect between prior cardiovascular subgroups were observed for HDL-C (*P*=0.046) and TG (*P*=0.002). At trial end, differences were observed for LDL-C (*P*=0.01) and TG (*P*=0.006).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	prior cardiovascular disease and those without Patients aged 50 to 75 years with type 2 diabetes mellitus	disease) 5 years	effect of treatment on outcomes, components of total cardiovascular disease, adjusted analyses of treatment effect Secondary: Not reported	Over the course of the trial, patients receiving placebo had a higher uptake of lipid-lowering therapy (mainly statins) compared to those receiving fenofibrate (17 vs 8%). There was a higher uptake of statins among patients with prior cardiovascular disease compared those without and a slightly higher uptake of other cardiovascular medications. Patients with prior cardiovascular disease discontinued fenofibrate more often than those without prior cardiovascular disease (14 vs 9%). The unadjusted effect of fenofibrate on future total cardiovascular disease events differed by prior cardiovascular disease status (interaction *P*=0.05). There was an independently significant reduction in the risk of a cardiovascular disease event (HR, 0.81; 95% CI, 0.70 to 0.94; *P*=0.004) in the group without prior cardiovascular disease, whereas in the prior cardiovascular disease group, there was no significant effect of treatment (HR, 1.02; 95% CI, 0.86 to 1.20; *P*=0.9). There was a significant difference in treatment effect between those with and those without prior cardiovascular disease for coronary events (interaction *P*=0.03) but not stroke (*P*=0.56) or revascularization (*P*=0.053). For coronary events, there was an independently significant reduction in the risk of an event (HR, 0.75; 95% CI, 0.59 to 0.94; *P*=0.01) in the group without prior cardiovascular disease, whereas in the prior cardiovascular disease group, there was no significant effect of treatment (HR, 1.08; 95% CI, 0.84 to 1.38; *P*=0.55). After the adjustment for uneven uptake of statins and other cardiovascular disease medications across treatment arms, the treatment-by-prior-cardiovascular disease interaction term remained significant (statins only; *P*=0.05 and statins plus other cardiovascular disease medications; *P*=0.04). However, after adjustment for baseline covariates, differences in treatment effects were no longer significant (*P*=0.06). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ting et al (abstract)[57] FIELD Fenofibrate 200 mg QD vs placebo	Subgroup analysis of FIELD evaluating the effects of fenofibrate on cardiovascular and ESRD events, according to eGFR Patients aged 50 to 75 years with type 2 diabetes mellitus	N=9,975 5 years	Primary: Coronary events (CHD, death or nonfatal MI), safety Secondary: Not reported	Primary: The benefit of fenofibrate observed within the FIELD trial (HR, 0.89; 95% CI, 0.80 to 0.99; *P*=0.035), was not statistically different across eGFR groupings analyzed within this subgroup analysis (interaction *P*=0.2) (eGFR 30 to 50 mL/min/1.73m^2: HR, 0.68; 95% CI, 0.47 to 0.97; *P*=0.035; eGFR ≥90 mL/min/1.73m^2: HR, 0.85; 95% CI, 0.70 to 1.02; *P*=0.08). ESRD rates were similar between treatment arms, without adverse safety signals of fenofibrate use in renal impairment. Secondary: Not reported
DAIS[58] Fenofibrate, micronized 200 mg QD vs placebo	PC, RCT Men and women with type 2 diabetes with good glycemic control, who had mild lipoprotein abnormalities typical of type 2 diabetes and at least one visible coronary lesion	N=418 3 years	Primary: Mean percentage stenosis, minimum coronary artery lumen diameter, mean segment diameter Secondary: Not reported	Primary: Plasma TC, HDL-C, LDL-C, and TG concentrations all changed significantly more from baseline in the fenofibrate group (N=207) compared to the placebo group (N=211). The fenofibrate group showed a significantly smaller increase in percentage diameter stenosis than the placebo group (mean 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 an insignificant smaller decrease in mean segment diameter (-0.06 vs -0.08 mm; *P*=0.171). The trial was not powered to examine clinical end points. Secondary: Not reported
No authors listed[59] ACCORD	DB, MC, PC, RCT	N=5,518 5 years	Primary: First occurrence of a major	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fenofibrate 160 mg/day vs placebo All patients were receiving simvastatin.	Patients 40 to 79 years of age with type 2 diabetes 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		cardiovascular event (nonfatal MI, nonfatal stroke or 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	Secondary: The annual rate of the primary outcome plus revascularization or hospitalization for CHF was 5.35% with fenofibrate and 5.64% with placebo (HR, 0.94; 95% CI, 0.85 to 1.05; *P*=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; *P*=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; *P*=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; *P*=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; *P*=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; *P*=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; *P*=0.10).
Bonds et al[60] ACCORD	Subgroup analysis of ACCORD,	N=1,212 (patients who	Primary: Characteristics predicting	Primary: Patients who were older, male, used an angiotensin converting enzyme-inhibitor at baseline, used a thiazolidinedione at four months post-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fenofibrate 160 mg/day vs placebo All patients were receiving simvastatin.	evaluating outcomes in patients with a fenofibrate-associated creatinine increase (increase in serum creatinine of ≥20% from baseline to month 4 in patients receiving fenofibrate) Patients 40 to 79 years of age with type 2 diabetes 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	experienced a fenofibrate-associated creatinine increase) 5 years	creatinine elevation Secondary: Long-term renal and cardiovascular outcomes	randomization, had baseline cardiovascular disease, and had lower baseline serum creatinine and LDL-C were all more likely to meet the criteria for fenofibrate-associated creatinine increase). Secondary: No differences in study outcomes were seen by fenofibrate-associated creatinine increase; there was no increase in renal disease or cardiovascular outcome observed in patients demonstrating fenofibrate-associated creatinine increases.
Frick et al[61] Helsinki Heart Study	DB, RCT	N=4,081	Primary: Risk of CHD	Primary: There were minimal changes in serum lipid levels in the placebo group. The

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gemfibrozil 600 mg BID vs placebo	Asymptomatic middle-aged men (40 to 55 years of age) with primary dyslipidemia (non-HDL-C ≥200 mg/dL in 2 consecutive pretreatment measurements)	5 years	measured by incidence of cardiac events Secondary: Total mortality	cumulative rate of cardiac end points at five years was 27.3 per 1,000 in the gemfibrozil group and 41.4 per 1,000 in the placebo group, a reduction of 34% in the incidence of CAD (95% CI, 8.2 to 52.6; *P*<0.02; two-tailed test). The decline in incidence in the gemfibrozil group became evident in the second year and continued throughout the study. Secondary: There was no difference between the groups in the total death rate, nor did the treatment influence the cancer rates.
Frick et al[62] Helsinki Heart Study Gemfibrozil 600 mg BID vs placebo	DB, RCT Individuals who exhibited symptoms and signs of possible CHD during screening in the Helsinki Heart Study	N=311 5 years	Primary: Risk of CAD measured by incidence of cardiac events Secondary: Total mortality	Primary: The end point rate, consisting of fatal and nonfatal MI and cardiac death, did not differ significantly between the placebo and gemfibrozil groups. Since there were key prognostic factors missing (e.g., true prevalence of CHD, extent of coronary artery obstructions, degree of left ventricular dysfunction, and their distribution in the groups render the results less reliable), the data cannot be used to refute the thesis that treatment of dyslipidemia in manifest CHD is successful. Secondary: Total mortality did not differ significantly between the placebo and gemfibrozil groups.
Heinonen et al[63] Helsinki Heart Study Gemfibrozil 600 mg BID vs placebo	DB, MC Asymptomatic middle-aged men (40 to 55 years of age) with non-HDL-C greater than or equal to 200 mg/dL in 2 consecutive	N=2,046 3.5 years	Primary: Definite fatal and nonfatal CHD events Secondary: Not reported	Primary: During the post-trial period the numbers of definite CHD events in both groups (54 vs 47; P value not significant) were smaller than expected without treatment, namely a reduction of around 40% for the original treatment groups. The mean incidence rates were in fact similar to that in the placebo group five years earlier. Cardiovascular mortality over the entire study period was similar but all-cause mortality was slightly higher among men of the original gemfibrozil group compared to the placebo group men (*P*=0.19).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	pretreatment measurements)			Secondary: Not reported
Huttunen et al[64] Gemfibrozil 600 mg BID vs placebo	ES Asymptomatic adult patients with primary dyslipidemia (non-HDL-C ≥200 mg/dL in 2 consecutive pretreatment measurements)	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 (*P*<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 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. 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. 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). 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				during the trial period and the first year of the post-trial follow up; the excess mortality emerged towards the end (*P*=0.19). Secondary: Not reported
Robins et al.[65] VA-HIT Gemfibrozil 1,200 mg daily vs placebo	DB, MC, PC, RCT Men with a history of CHD who had low HDL-C levels and low LDL-C levels	N=2,531 7 years	Primary: Nonfatal MI or death from coronary causes Secondary: Not reported	Primary: Compared to placebo, gemfibrozil showed a 22% decreased risk of nonfatal MI or death due to CHD (17.3 vs 21.7%; *P*=0.006). Compared to placebo, gemfibrozil showed a 24% decreased risk for nonfatal MI, death due to CHD or confirmed stroke (20 vs 26%; *P*<0.001). A nonsignificant difference was seen in all-cause mortality with gemfibrozil compared to placebo (15.7 vs 17.4%; *P*=0.23). Concentrations of HDL-C were inversely related to CHD events. Multivariable Cox proportional hazards analysis showed 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 explained by increases in HDL-C values, particularly in the second through fourth quintiles of HDL-C values during treatment. 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. Secondary: Not reported
Rubins et al[66] Gemfibrozil 1,200 mg/day vs	DB, MC, PC, RCT Men <74 years of age with	N=2,531 5.1 years (mean follow up)	Primary: Combined incidence of nonfatal MI or death from CHD	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	CHD, HDL-C ≤40 mg/dL, LDL-C ≤140 mg/dL, TG ≤300 mg/dL and no serious coexisting conditions		Secondary: Incidence of stroke, death from any cause, TIA, revascularization procedures, carotid endarterectomy and hospitalization for unstable angina or CHF	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%; RR reduction, 25%; 95% CI, -6 to 47; *P*=0.10). Gemfibrozil resulted in a RR reduction 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). Gemfibrozil was associated with a significant reduction in the risk of carotid endarterectomy (RR reduction, 65%; 95% CI, 37 to 80; *P*<0.001). The rates of death from any case, coronary revascularization, hospitalization for unstable angina and cancer did not differ significantly between treatments.
Saha et al[67] Fibrate therapy (bezafibrate*, clofibrate*, fenofibrate, gemfibrozil)	MA, SR (10 RCTs) Patients receiving fibrate therapy for the prevention of cardiovascular events (primary and secondary prevention)	N=36,489 Mean duration of follow up ≥1 year (32 months to 18 years)	Primary: All-cause mortality, cardiovascular and non-cardiovascular mortality, fatal and nonfatal MI and stroke Secondary: Incidence of cancer and cancer related mortality	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). 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). Subgroup analyses revealed that the risk of all-cause mortality did not significantly differ among the various fibrates used. Noncardiovascular

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.
Jun et al[68] Fibrate therapy (bezafibrate*, clofibrate*, etofibrate*, fenofibrate and gemfibrozil) vs placebo	MA, SR (18 PRO, RCTs) Demographics not reported	N=45,058 Duration varied	Primary: Major cardiovascular events, coronary events, stroke, heart failure, coronary revascularization, all-cause mortality, cardiovascular death, nonvascular death, sudden death, new onset albuminuria, drug related adverse events Secondary: Not reported	Primary: Data for coronary events were available from 16 trials, including 44,667 patients in whom 4,552 coronary events were recorded. Overall, fibrate therapy reduced the risk of coronary events by 13% (RR, 0.87; 95% CI, 0.81 to 0.93; *P*<0.0001). 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). 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). 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). A cumulative MA of all trials reporting coronary outcomes demonstrated consistent benefit from fibrate therapy on the risk of coronary events. 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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). 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). 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). 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). Secondary: Not reported

*Not available in the United States.
†Agent not available within the United States.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, QD=once daily, SR=sustained-release
Study abbreviations: AC=active comparator, DB=double-blind, DD=double dummy, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open-label, PA=parallel arm, PC=placebo controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective study, SB=single-blind, SR=systematic review, XO=crossover

Other abbreviations: apo=apolipoprotein, ALT=alanine aminotransferase, AST=aspartate aminotransferase, B*P*=blood pressure, BMI=body mass index, CAD=coronary artery disease, CHD=coronary heart disease, CHF=congestive heart failure, CI=confidence interval, CR*P*=C-reactive protein, CVK=chronic kidney disease, eGFR=estimated glomerular filtration rate, ESRD=end stage renal disease, EZE=ezetimibe, FENO=fenofibrate, FPG=fasting plasma glucose, HbA1c=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, HIV=human immunodeficiency virus, HOMA-IR=Homeostasis Model of Assessment-Insulin Resistance, HR=hazard ratio, hsCR*P*=high sensitivity C-reactive protein, ICAM-1=intercellular adhesion molecule-1, IDL-C=intermediate-density lipoprotein-cholesterol , IQR=Interquartile range, LDL-C=low-density lipoprotein cholesterol, Lp(a)=Lipoprotein(a), MI=myocardial infarction, MMP-9=matrix metallopeptidase-9, NCEP AT*P*=National Cholesterol Education Program Adult Treatment Panel, OR=odds ratio, P-MO3=prescription omega-3 fatty acid, RL*P*=remnant like particle cholesterol, RR=relative risk, TC=total cholesterol, TG=triglycerides, TIA=transient ischemic attack, TRL=triglyceride rich lipoproteins, VCAM-1=vascular cell adhesion molecule-1, VLDL-C=very low-density lipoprotein cholesterol

Special Populations

Table 5. Special Populations[1-10]

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.	Renal dose adjustment is recommended in patients with mild to moderate renal impairment. Not recommended for use in patients with severe renal impairment.	Safety and efficacy in patients with hepatic insufficiency have not been established. Contraindicated in patients with active liver disease.	C	Unknown; contraindicated in nursing mothers.
Fenofibric acid	Dose adjustment may be required in the elderly; a lower initial dose based on creatinine clearance is recommended. Safety and efficacy in children have not been established.	Renal dose adjustment is recommended in patients with mild to moderate renal impairment. Not recommended for use in patients with severe renal impairment.	Safety and efficacy in patients with hepatic insufficiency have not been established. Contraindicated in patients with active liver disease.	C	Unknown; contraindicated in nursing mothers.
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. Worsening of renal function has been reported in patients with baseline serum creatinine >2 mg/dL. Use is contraindicated in severe renal dysfunction.	Contraindicated in patients with hepatic impairment.	C	Unknown

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-10]

Adverse Event	Fenofibrate	Fenofibric Acid	Gemfibrozil
Cardiovascular			
Angina pectoris	✔	-	-
Arrhythmia	✔	-	-
Atrial fibrillation	✔	-	1
Cardiovascular disorder	✔	-	-
Coronary artery disorder	✔	-	-
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	✔	3 to 4	✔
Fatigue	-	2 to 3	4
Fever	✔	-	-
Headache	3	12 to 13	1
Hypertonia	✔	-	-
Insomnia	✔	✔	-
Libido decreased	✔	-	✔
Nervousness	✔	-	-
Neuralgia	✔	-	-
Paresthesia	✔	-	✔
Pain	✔	-	-
Peripheral neuritis	-	-	✔
Somnolence	✔	-	✔
Vertigo	✔	-	2
Dermatological			
Acne	✔	-	-
Alopecia	✔	-	-
Angioedema	-	-	✔
Contact dermatitis	✔	-	-
Eczema	✔	-	2

Adverse Event	Fenofibrate	Fenofibric Acid	Gemfibrozil
Exfoliative dermatitis	-	-	✔
Fungal dermatitis	✔	-	-
Herpes simplex	✔	-	-
Herpes zoster	✔	-	-
Nail disorder	✔	-	-
Maculopapular rash	✔	-	-
Photosensitivity reaction	✔	-	✔
Pruritus	✔	-	-
Rash	-	-	2
Skin disorder	✔	-	-
Skin ulcer	✔	-	-
Stevens-Johnson syndrome	✔	✔	-
Sweating	✔	-	-
Toxic epidermal necrolysis	✔	✔	-
Urticaria	✔	-	✔
Vasculitis	-	-	✔
Endocrine and Metabolic			
Diabetes mellitus	✔	-	-
Gout	✔	-	-
Gynecomastia	✔	-	-
Hypoglycemia	✔	-	-
Hyperuricemia	✔	-	-
Gastrointestinal			
Abdominal pain	5	✔	10
Anorexia	✔	-	-
Cholestatic jaundice	-	-	✔
Colitis	✔	-	-
Constipation	2	3	1
Diarrhea	2	3 to 4	7
Duodenal ulcer	✔	3 to 5	-
Dyspepsia	✔	-	20
Eructation	✔	-	-
Esophagitis	✔	-	-
Flatulence	✔	-	-
Nausea	2	4 to 6	2
Peptic ulcer	✔	-	-
Vomiting	✔	-	2
Weight gain/loss	✔	-	-
Genitourinary			
Creatinine increased	✔	-	-
Cystitis	✔	-	-
Decreased male fertility	-	-	✔
Dysuria	✔	-	-
Impotence	-	-	✔
Kidney function abnormal	✔	-	✔
Nephrotoxicity	✔	✔	✔
Prostatic disorder	✔	-	-
Unintended pregnancy	✔	-	-
Urinary frequency	✔	-	-
Urinary tract infection	-	✔	-
Vaginal moniliasis	✔	-	-

Adverse Event	Fenofibrate	Fenofibric Acid	Gemfibrozil
Hematologic			
Agranulocytosis	✔	✔	-
Anemia	✔	✔	✔
Ecchymosis	✔	-	-
Eosinophilia	✔	-	-
Hematocrit decreased	-	✔	-
Hemoglobin decreased	-	✔	-
Leukopenia	✔	✔	✔
Lymphadenopathy	✔	-	-
Thrombocytopenia	✔	✔	✔
Hepatic			
Alanine aminotransferase increased	3	1 to 3	✔
Aspartate aminotransferase increased	3	✔	✔
Bilirubin increased	-	-	✔
Cirrhosis	✔	✔	-
Creatinine kinase increased	3	✔	✔
Hepatic enzymes increased	✔	✔	-
Hepatitis	✔	✔	-
Jaundice	-	-	✔
Liver fatty deposit	✔	-	-
Laboratory Test Abnormalities			
Serum creatinine increased	✔	✔	-
Musculoskeletal			
Arthralgia	✔	4	✔
Arthritis	✔	-	-
Arthrosis	✔	-	-
Bursitis	✔	-	-
Back pain	3	4 to 6	-
Joint disorder	✔	-	-
Leg cramps	✔	-	-
Muscle pain/spasm	✔	3 to 4	-
Myalgia	✔	3 to 4	-
Myasthenia	✔	-	✔
Myopathy	✔	-	✔
Myositis	✔	✔	-
Painful extremities	-	3 to 5	✔
Paresthesia	✔	-	✔
Rhabdomyolysis	✔	✔	✔
Synovitis	-	-	✔
Tenosynovitis	✔	-	-
Weakness	✔	✔	-
Respiratory			
Asthma	✔	-	-
Bronchitis	✔	✔	-
Cough	✔	✔	-
Dyspnea	✔	-	-
Laryngeal edema	-	-	✔
Laryngitis	✔	-	-
Nasopharyngitis	-	4 to 5	-
Pharyngitis	✔	-	-
Pneumonia	✔	-	-

Adverse Event	Fenofibrate	Fenofibric Acid	Gemfibrozil
Pulmonary embolism	✔	✔	-
Respiratory disorder	6	-	-
Rhinitis	2	-	-
Sinusitis	✔	3 to 4	-
Upper respiratory infection	-	4 to 5	-
Other			
Allergic reaction	✔	-	-
Amblyopia	✔	-	-
Anaphylaxis	-	-	✔
Appendicitis, acute	-	-	1
Asthenia	2	-	-
Blurred vision	-	-	✔
Cataracts	✔	-	✔
Chest pain	✔	-	-
Cholecystitis	✔	-	✔
Cholelithiasis	✔	✔	✔
Conjunctivitis	✔	-	-
Cyst	✔	-	-
Deep vein thrombosis	✔	✔	-
Drug-induced lupus syndrome	-	-	✔
Dry mouth	✔	-	-
Ear pain	✔	-	-
Eye disorder	✔	-	-
Flu syndrome	2	-	-
Hernia	✔	-	-
Hypersensitivity reaction	✔	✔	-
Infection	✔	-	-
Influenza	-	✔	-
Intracerebral hemorrhage	-	-	✔
Malaise	✔	-	-
Otitis media	✔	-	-
Pancreatitis	✔	✔	✔
Pharyngolaryngeal pain	-	✔	-
Raynaud's phenomenon	-	-	✔
Refraction disorder	✔	-	-
Retinal edema	-	-	✔
Seizure	-	-	✔
Syncope	-	-	✔
Taste perversion	-	-	✔
Vision abnormalities	✔	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Contraindications

Table 7. Contraindications[1-10]

Contraindications	Fenofibrate	Fenofibric Acid	Gemfibrozil
Active liver disease, including primary biliary cirrhosis	✔ *	✔ *	✔
Known hypersensitivity to fenofibric acid or fenofibrate	✔	✔	-
Known hypersensitivity to gemfibrozil	-	-	✔
Nursing mothers	✔	✔	-
Pre-existing gallbladder disease	✔	✔	✔
Severe renal impairment, including dialysis	✔	✔	✔
Use in combination with repaglinide	-	-	✔
Use in combination with simvastatin	-	-	✔

* Including unexplained persistent liver function abnormalities.

Warnings and Precautions

Table 8. Warnings and Precautions[1-10]

Warnings/Precautions	Fenofibrate	Fenofibric Acid	Gemfibrozil
Coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established	✔	✔	✔
Coumarin anticoagulants; use caution with concomitant treatment and reduce coumarin dosage to prevent bleeding complications	✔	✔	✔
Hematologic changes, including mild to moderate decreases in hemoglobin, hematocrit, white blood cells and platelets; monitoring of blood counts is recommended	✔	✔	✔
Hypersensitivity reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis; have been reported	✔	✔	-
Increased serum transaminases	✔	✔	✔
Myopathies, including rhabdomyolysis; the risk may be increased when fenofibrate is co-administered with a statin (with a significantly higher rate observed with gemfibrozil), particularly in elderly patients and in patients with diabetes, renal failure, or hypothyroidism	✔	✔	✔
Pancreatitis; has been reported	✔	✔	-
Renal impairment, serum creatinine greater than 2 mg/dL; consider alternative therapy	-	-	✔
Reversible increases in serum creatinine; monitor renal function in patients with renal impairment	✔	✔	-
Risk of cholelithiasis; discontinue therapy if gallstones are found	✔	✔	✔
Severe high-density lipoprotein decreases; monitoring is recommended and discontinuation of therapy may be required	✔	✔	-
Venothromboembolic events; have been reported	✔	✔	-

Drug Interactions

Table 9. Drug-Drug Interactions[1-10]

Drug(s)	Interaction	Mechanism
Fibric acid derivatives (fenofibrate, fenofibric acid, gemfibrozil)	Colchicine	Myopathy, including rhabdomyolysis have been reported.
Fibric acid derivatives (fenofibrate, fenofibric acid, gemfibrozil)	Bile-acid Binding Resins	May cause decrease in absorption if given concurrently. Separate administration by at least one hour.
Fibric acid derivatives (fenofibrate, fenofibric acid, gemfibrozil)	HMG-CoA reductase inhibitors (statins)	Severe myopathy or rhabdomyolysis may occur.
Fibric acid derivatives (fenofibrate, fenofibric acid)	Immunosuppressants	Certain immunosuppressants can produce nephrotoxicity leading to deterioration of renal function.
Fibric acid derivatives (fenofibrate, fenofibric acid, 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 10. Dosing and Administration[1-10]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Fenofibrate	Adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia: Capsule (Antara®): 43 to 130 mg once daily; maximum, 130 mg/day Capsule (Lofibra®): initial, 67 to 200 mg once daily; maximum, 200 mg/day Capsule (Lipofen®): 50 to 150 mg once daily; maximum, 150 mg/day Tablet (Fenoglide®): initial, 40 to 120 mg/day Tablet (Lofibra®): initial, 54 to 160 mg once daily; maximum, 160 mg/day Tablet (Tricor®): initial, 48 to 145 mg once daily; maximum, 145 mg/day Tablet (Triglide®): 50 to 160 mg once daily; maximum, 160 mg/day Adjunctive therapy to diet to reduce elevated LDL-C, total cholesterol, TG and apolipoprotein B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia: Capsule (Antara®): 90 mg once daily; Maximum, 90 mg/day Capsule (Lofibra®): 67 to 200 mg once daily; maximum, 200 mg/day Capsule (Lipofen®): 150 mg once daily; maximum, 150 mg/day Tablet (Fenoglide®): 120 mg once daily; maximum, 120 mg/day Tablet (Lofibra®): 54 to 160 mg once daily; maximum, 160 mg/day Tablet (Tricor®): 145 mg once daily; maximum, 145 mg/day Tablet (Triglide®): 160 mg once daily; maximum, 160 mg/day	Safety and efficacy in children have not been established.	Capsule: 50 mg (Lipofen®) 150 mg (Lipofen®) Capsule, Micronized: 30 mg (Antara®) 43 mg (Antara®) 67 mg (Lofibra®) 90 mg (Antara®) 130 mg (Antara®) 134 mg (Lofibra®) 200 mg (Lofibra®) Tablet: 40 mg (Fenoglide®) 48 mg (Tricor®) 50 mg (Triglide®) 54 (Lofibra®) 120 mg (Fenoglide®) 145 mg (Tricor®) 160 mg (Lofibra®, Triglide®)

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Fenofibric acid	Adjunctive therapy to diet to reduce elevated LDL-C, total cholesterol, TG and apolipoprotein B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia: Delayed-release capsule: 135 mg once daily Tablet: 135 mg/day Tablet: 105 mg once daily; maximum, 105 mg/day Adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia: Delayed-release capsule: 45 to 135 mg once daily; maximum, 135 mg/day Tablet: 35 to 105 mg once daily; maximum, 105 mg/day Adjunct to diet in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal: Delayed-release capsule: 135 mg once daily; maximum, 135 mg/day	Safety and efficacy in children have not been established.	Delayed-release capsule: 45 mg (Trilipix®) 135 mg (Trilipix®) Tablet: 35 mg (Fibricor®) 105 mg (Fibricor®)
Gemfibrozil	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: Tablet: 600 mg twice daily; maximum, 1,200 mg/day Reducing the risk of developing CHD only in Type IIb patients without history of or symptoms of existing CHD 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 levels in addition to elevated LDL-C and elevated TG: Tablet: 600 mg twice daily; maximum, 1,200 mg/day	Safety and efficacy in children have not been established.	Tablet: 600 mg

Apo B=apolipoprotein B, CHD=coronary heart disease, 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 11. The guidelines addressing the management of hypercholesterolemia are presented globally, addressing the role of various medication classes in the management of this disease.

Table 11. Clinical Guidelines

Clinical Guideline	Recommendation(s)
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)**[11]	General recommendations • 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. Statins • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals. Bile acid sequestrants • 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. Nicotinic acid • 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. Fibric acid derivatives (fibrates) • 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

Clinical Guideline	Recommendation(s)
	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. Omega-3 fatty acids • 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 omega-3 fatty acids (1 to 2 g/day) for either primary or secondary prevention.
American Association of Clinical Endocrinologists: **Guidelines for the management of dyslipidemia and prevention of atherosclerosis (2012)**[14]	• Aggressive lipid-modifying therapy is recommended to lower LDL-C to <100 mg/dL in patients with average or elevated LDL-C. This has been shown to reduce vascular mortality in patients at high risk. • An LDL-C goal <70 mg/dL is recommended as an appropriate goal for *all* patients with established CAD. Current evidence indicates that LDL-C can be aggressively lowered with statin therapy regardless of baseline levels and suggests that there is no threshold below which LDL-C lowering ceases to be effective. • Patients for whom aggressive therapy is recommended: o Patients undergoing coronary artery bypass graft. o Patients with acute coronary syndrome. o Certain healthy and functional older patients at high risk. • Statins are the drug of choice for LDL-C reduction on the basis of findings from morbidity and mortality outcome trials. Agents currently available are atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and pitavastatin. • Fibrates are recommended for treatment of severe hypertriglyceridemia (triglycerides >500 mg/dL). Adjunct use of 2 to 4 g of omega 3 acids can be used, if necessary, to achieve satisfactory triglyceride lowering. • Niacin is recommended for reducing triglycerides, increasing HDL-C, and reducing LDL-C. Adjunct use of 2 to 4 g of omega-3 fish oil can be used, if necessary, to achieve satisfactory triglyceride lowering. • Bile acid sequestrants are recommended for reducing LDL-C and apo B and modestly increasing HDL-C, but they may increase triglycerides. Bile acid sequestrants have a glucose-lowering effect; colesevelam is now also approved for treatment of type 2 diabetes. Available agents in this drug class are cholestyramine, colestipol, and colesevelam. • Cholesterol absorption inhibitors are effective as monotherapy in reducing LDL-C and apo B. Combination therapy with statins is recommended because current research indicates that this enhances these benefits and further improves the beneficial effects of statins on triglycerides and HDL-

Clinical Guideline	Recommendation(s)
	C. It is uncertain whether cholesterol absorption inhibitor therapy has a direct benefit on reducing cardiovascular events. • Combination therapy be considered in the following circumstances: o When the cholesterol level is markedly increased and monotherapy does not achieve the therapeutic goal. o When mixed dyslipidemia is present. o Niacin or fibrates in combination with statins may be appropriate options for many patients with hypertriglyceridemia and associated low HDL-C. o To reduce the risk of dosage-related adverse effects. • Recommendations for lipid management in children include: o Colesevelam has been approved for patients older than 8 years. o Atorvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin have been approved for the treatment of familial hypercholesterolemia in patients 10 years or older. Cholestyramine may also be used in children.
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: 2011 Update (2011)**[15]	<u>Lipid management</u> • Goal: treatment with statin therapy; use statin therapy to achieve LDL-C of <100 mg/dL; for very high risk patients an LDL-C <70 mg/dL is reasonable; if TG are ≥200 mg/dL, non-HDL-C should be <130 mg/dL, whereas non-HDL-C <100 mg/dL for very high risk patients is reasonable. • Lifestyle modifications (daily physical activity and weight management) are strongly recommended for all patients. • In addition to lifestyle modifications, statin therapy should be prescribed in the absence of contraindications or documented adverse events. • An adequate dose of statin should be used that reduces LDL-C to <100 mg/dL and achieves ≥30% lowering of LDL-C. • Patients who have TG ≥200 mg/dL should be treated with statins to lower non-HDL-C to <130 mg/dL. • Patients who have TG >500 mg/dL should be started on fibrate therapy in addition to statin therapy to prevent acute pancreatitis. • If treatment with a statin does not achieve the goal selected for an individual patient, intensification of LDL-C-lowering drug therapy with a bile acid sequestrant or niacin is reasonable. • For patients who do not tolerate statins, LDL-C-lowering therapy with bile acid sequestrants and/or niacin is reasonable. • It is reasonable to treat very high risk patients with statin therapy to lower LDL-C to <70 mg/dL. • In patients who are at very high risk and who have TG ≥200 mg/dL, a non-HDL-C goal of <100 mg/dL is reasonable. • The use of ezetimibe may be considered for patients who do not tolerate or achieve target LDL-C with statins, bile acid sequestrants, and/or niacin. • For patients who continue to have an elevated non-HDL-C while on adequate statin therapy, niacin or fibrate therapy or fish oil may be reasonable. For all patients, it may be reasonable to recommend omega-3 fatty acids from fist or fish oil capsules (1 g/day) for cardiovascular disease risk reduction.
Institute for Clinical Systems Improvement: **Lipid Management in Adults (2011)**[16]	<u>Clinical highlights</u> • Initiate a statin with patients who have a history of CHD or CHD risk equivalents. • Establish lipid goals based on risk level. • Instruct patients on healthy lifestyle and adjunctive measures.

Clinical Guideline	Recommendation(s)
	• Patient adherence with recommended therapy should be reinforced during scheduled follow-up. • An LDL goal <70 mg/dL can be considered for patients with established CAD, non-cardiac atherosclerosis, or CAD equivalent. <u>Ongoing drug therapy</u> • The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). • Combination therapy can be considered on an individual basis. • No primary prevention trials have addressed pharmacologic lipid treatment in patients at low risk for CHD, and there is no evidence to support drug treatment in this population. • Primary prevention trials of pharmacologic lipid-lowering have not shown a decrease in mortality, although most have shown about a 30% reduction in CHD events. <u>Monotherapy</u> • 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. • The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). • Statins are the drugs of choice for lowering LDL-C, and aggressive treatment with statins should be pursued. Statins also have a modest effect on reducing TG and increasing HDL-C. • Several trials with clinical endpoints support the use of statins in primary and secondary prevention. • If a patient is intolerant to a statin, patients should try another statin before ruling all of them out. • Incidence of muscle symptoms or signs is the most prevalent and important adverse effect of statin therapy. • Specific statin and dose should be selected based on cost and amount of lipid-lowering required. • If patients are unable to take a statin, then bile acid sequestrants, niacin, fibric acid derivatives or fibrates, and ezetimibe are available. • Many crystalline (immediate-release) and sustained-release preparations of niacin are available over-the-counter. The extended-release preparation of niacin is a prescription drug. Niacin exerts favorable effects on all lipids and lipoproteins, and is good for mixed hyperlipidemia. • Long-term use of niacin is usually limited for many patients due to side effects (e.g., flushing and pruritus, liver toxicity, gastrointestinal complaints, etc). • Combination therapy with niacin and a statin may increase the risk of myopathy based on early experience with lovastatin. • Prior to initiating a fibric acid (gemfibrozil, fenofibrate, and fenofibrate micronized), lifestyle therapies should be intensified for moderately elevated TG. With fibric acids, TG are reduced 30 to 50%, HDL-C is increased 10 to 20%, TC is reduced 5 to 20% in patients without elevated TG, and the effect on LDL-C is variable. Fibric acids are good for severe

Clinical Guideline	Recommendation(s)
	hypertriglyceridemia (>500 mg/dL) in patients at risk for pancreatitis and for prevention of CHD (not proven for fenofibrate). • Myositis, cholelithiasis, and cholecystitis can occur with fibric acid, and caution should be exercised with a history of liver disease. • The long-term effects of ezetimibe on cardiovascular morbidity and mortality are unknown. Ezetimibe is associated with a LDL-C lowering of about 18%, and additive LDL-C lowering occurs when used in combination with a statin. • The short-term tolerability of ezetimibe is similar to placebo, and the long-term safety is unknown. • Bile acid sequestrants reduce LDL-C by 15 to 30% and TG may increase 15%; therefore, are these agents are useful for patients with moderately elevated LDL-C. The effects of the bile acid sequestrants are apparent within one week and maximum at two to three weeks. Bile acid sequestrants are good for combination therapy and are most potent with a statin. • Bile acid sequestrants are not systemically absorbed; therefore, side effects are limited to the gastrointestinal tract. In addition, drug interactions are minimized by taking other medications one hour before the sequestrant or four hours after. <u>Combination therapy</u> • It has become common practice to adjust medication therapy, including using combinations of medications, to achieve LDL-C goals. Common combinations include statin/fibrate, statin/niacin, and statin/ezetimibe. o A fibrate is commonly added to a statin, which results in enhanced lowering of LDL-C, as well as a higher incidence of myopathy. o No published clinical trial to date has evaluated the clinical benefit of combination therapy with a statin and niacin on vascular events. o The addition of ezetimibe to a statin significantly improves LDL-C over either agent alone. To date no large clinical trials have been completed evaluating this combination therapy compared to statin monotherapy on clinical vascular endpoints. • Combinations of lipid-lowering agents do not improve clinical outcomes more than statin monotherapy. • Combination therapy can be considered on an individual basis, but the additional cost, complexity, and risk for side effects argue against routine use until further trials indicate what groups of patients might benefit. • There are negative trials of cholesterylester transfer protein inhibitors when used in combination with statins. • No randomized-controlled trials looking at clinical vascular endpoints are available for other agents such as fish oils or bile-acid sequestrants used in combination therapy. <u>Lifestyle modifications</u> • Patients who are overweight should be advised to reduce their caloric intake to achieve weight loss. • Patients should follow a diet and exercise program for a reasonable amount of time to determine whether their LDL-C level is lowered to the target range. • A diet low saturated and trans fats, and high in soluble fiber, with consideration given to adding two grams of plant sterol/stanol is

Clinical Guideline	Recommendation(s)
	recommended. • Vitamin E supplementation should not be used. • Light to moderate consumption of alcohol may lower CHD rates. Omega-3 fatty acids should be recommended in patients with dyslipidemia (one gram of EPA/DHA by capsule supplement, or by eating at least two servings per week of fatty fish).
American College of Cardiology/American Heart Association Task Force on Practice Guidelines: **Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2013)**[17]	Statin treatment • The panel makes no recommendations for or against specific low density lipoprotein cholesterol (LDL-C) or non-high density lipoprotein cholesterol (HDL-C) targets for the primary or secondary prevention of arteriosclerotic cardiovascular disease (ASCVD). • High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age that have clinical ASCVD, unless contraindicated. • In individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated. • In individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it. • Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required): use high-intensity statin therapy unless contraindicated. For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity. • For individual's ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction. • For individuals ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a nonstatin drug may be considered to further lower LDL-C. Evaluate the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and consider patient preferences. • Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus. • High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated 10-year ASCVD risk unless contraindicated. • In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy. • Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes and an estimated 10-year ASCVD risk ≥7.5% should be treated with moderate- to high-intensity statin therapy. • It is reasonable to offer treatment with a moderate intensity statin to adults 40 to 75 years of age, with LDL-C 70 to 189 mg/dL, without clinica ASCVD or diabetes and an estimated 10-year ASCVD risk of 5.0 to <7.5%.

Clinical Guideline	Recommendation(s)
	• Before initiating statin therapy for the primary prevention of ASCVD in adults with LDL-C 70 to 189 mg/dL without clinical ASCVD or diabetes it is reasonable for clinicians and patients to engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions, and patient preferences for treatment. • In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk based treatment decision is uncertain, additional factors may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluating the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and discussion of patient preference. <u>Statin safety</u> • To maximize the safety of statins, selection of the appropriate statin and dose in men and nonpregnant/nonnursing women should be based on patient characteristics, level of ASCVD risk, and potential for adverse effects. • Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin associated adverse effects are present. • Characteristics predisposing individuals to statin adverse effects include, but are not limited to: o Multiple or serious comorbidities, including impaired renal or hepatic function. o History of previous statin intolerance or muscle disorders. o Unexplained alanine transaminase elevations >3 times upper limit of normal. o Patient characteristics or concomitant use of drugs affecting statin metabolism. o >75 years of age. • Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to: o History of hemorrhagic stroke. o Asian ancestry. • Creatine kinase should not be routinely measured in individuals receiving statin therapy. • Baseline measurement of creatinine kinase is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk for myopathy. • During statin therapy, it is reasonable to measure creatinine kinase in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue. • Baseline measurement of hepatic transaminase levels should be performed before initiating statin therapy. • During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark colored urine or yellowing of the skin or sclera).

Clinical Guideline	Recommendation(s)
	• Decreasing the statin dose may be considered when two consecutive values of LDL-C levels are <40 mg/dL. • It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily. • Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes screening guidelines. Those who develop diabetes mellitus during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events. • For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals that are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (e.g., those who have undergone solid organ transplantation or are receiving treatment for human immunodeficiency virus (HIV). A review of the manufacturer's prescribing information may be useful before initiating any cholesterol-lowering drug. • It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm: o To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy. o If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating creatinine kinase, creatinine, and a urinalysis for myoglobinuria. • If mild to moderate muscle symptoms develop during statin therapy: o Discontinue the statin until the symptoms can be evaluated. o Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases). o If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy. o If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin. o Once a low dose of a statin is tolerated, gradually increase the dose as tolerated. o If, after two months without statin treatment, muscle symptoms or elevated creatinine kinase levels do not resolve completely, consider other causes of muscle symptoms listed above. o If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose. • For individuals presenting with a confusional state or memory impairment

Clinical Guideline	Recommendation(s)
	while on statin therapy, it may be reasonable to evaluate the patient for nonstatin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy. <u>Monitoring and optimizing statin therapy</u> • Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within four to 12 weeks after initiation or dose adjustment, and every three to 12 months thereafter. Other safety measurements should be measured as clinically indicated. • The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended, but not tolerated. • Individuals who have a less-than anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed: o Reinforce medication adherence. o Reinforce adherence to intensive lifestyle changes. o Exclude secondary causes of hyperlipidemia. • It is reasonable to use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring: o High-intensity statin therapy generally results in an average LDL-C reduction of ≥50% from the untreated baseline; o Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30 to <50% from the untreated baseline; o LDL-C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards. • Individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less than-anticipated therapeutic response, addition of a nonstatin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. • Higher-risk individuals include: o Individuals with clinical ASCVD <75 years of age. o Individuals with baseline LDL-C ≥190 mg/dL. o Individuals 40 to 75 years of age with diabetes mellitus. o Preference should be given to non-statin cholesterol-lowering drugs shown to reduce ASCVD events in controlled trials. • In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use non-statin cholesterol lowering drugs that have been shown to reduce ASCVD events in controlled trials if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. <u>Non statin safety</u> • Baseline hepatic transaminases, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained before initiating niacin, and again during up-titration to a maintenance dose and every six months thereafter. • Niacin should not be used if:

Clinical Guideline	Recommendation(s)
	○ Hepatic transaminase elevations are higher than two to three times upper limit of normal. ○ Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout or unexplained abdominal pain or gastrointestinal symptoms occur. ○ New-onset atrial fibrillation or weight loss occurs. • In individuals with adverse effects from niacin, the potential for ASCVD benefits and the potential for adverse effects should be reconsidered before reinitiating niacin therapy. • To reduce the frequency and severity of adverse cutaneous symptoms, it is reasonable to: ○ Start niacin at a low dose and titrate to a higher dose over a period of weeks as tolerated. ○ Take niacin with food or premedicating with aspirin 325 mg 30 minutes before niacin dosing to alleviate flushing symptoms. ○ If an extended-release preparation is used, increase the dose of extended-release niacin from 500 mg to a maximum of 2,000 mg/day over four to eight weeks, with the dose of extended release niacin increasing not more than weekly. ○ If immediate-release niacin is chosen, start at a dose of 100 mg three times daily and up-titrate to 3 g/day, divided into two or three doses. • Bile acid sequestrants should not be used in individuals with baseline fasting triglyceride levels ≥300 mg/dL or type III hyperlipoproteinemia, because severe triglyceride elevations might occur. • A fasting lipid panel should be obtained before bile acid sequestrants are initiated, three months after initiation, and every six to 12 months thereafter. • It is reasonable to use bile acid sequestrants with caution if baseline triglyceride levels are 250 to 299 mg/dL, and evaluate a fasting lipid panel in four to six weeks after initiation. Discontinue the bile acid sequestrants if triglycerides exceed 400 mg/dL. • It is reasonable to obtain baseline hepatic transaminases before initiating ezetimibe. When ezetimibe is coadministered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe if persistent alanine transaminase elevations >3 times upper limit of normal occur. • Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis. • Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are >500 mg/dL, are judged to outweigh the potential risk for adverse effect. • Renal status should be evaluated before fenofibrate initiation, within three months after initiation, and every six months thereafter. Assess renal safety with both a serum creatinine level and an estimated glomerular filtration rate based on creatinine. • Fenofibrate should not be used if moderate or severe renal impairment, defined as estimated glomerular filtration rate <30 mL/min per 1.73 m^2, is present. • If estimated glomerular filtration rate is between 30 and 59 mL/min per 1.73 m^2, the dose of fenofibrate should not exceed 54 mg/day.

Clinical Guideline	Recommendation(s)
	• If, during follow-up, the estimated glomerular filtration rate decreases persistently to ≤30 mL/min per 1.73 m^2, fenofibrate should be discontinued. o If eicosapentaenoic acid and/or docosahexanoic acid are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.
National Institute for Health and Clinical Excellence: **Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease (2014)**[18]	• Be aware that when deciding on lipid modification therapy for the prevention of cardiovascular disease (CVD), drugs are preferred for which there is evidence in clinical trials of a beneficial effect on CVD morbidity and mortality • When a decision is made to prescribe a statin use a statin of high intensity and low acquisition cost. Lipid Measurement and Referral: • Measure both total and high-density lipoprotein (HDL) cholesterol to achieve the best estimate of CVD risk. • Before starting lipid modification therapy for the primary prevention of CVD, take at least one lipid sample to measure a full lipid profile. This should include measurement of total cholesterol, HDL cholesterol, non-HDL cholesterol and triglyceride concentrations. A fasting sample is not needed. • Use the clinical findings, lipid profile and family history to judge the likelihood of a familial lipid disorder rather than the use of strict lipid cut-off values alone. • Exclude possible common secondary causes of dyslipidemia (such as excess alcohol, uncontrolled diabetes, hypothyroidism, liver disease and nephrotic syndrome) before referring for specialist review. • Consider the possibility of familial hypercholesterolemia if they have a total cholesterol concentration >7.5 mmol/L and a family history of premature coronary heart disease. • Arrange for specialist assessment of people with a total cholesterol concentration of more than 9.0 mmol/L or a non-HDL cholesterol concentration of more than 7.5 mmol/L even in the absence of a first-degree family history of premature coronary heart disease. • Refer for urgent specialist review if a person has a triglyceride concentration of more than 20 mmol/L that is not a result of excess alcohol or poor glycemic control. • In people with a triglyceride concentration between 10 and 20 mmol/L: o Repeat the triglyceride measurement with a fasting test (after an interval of five days, but within two weeks) and o Review for potential secondary causes of hyperlipidemia and o See specialist advice if the triglyceride concentration remains above 10 mmol/L • In people with a triglyceride concentration between 4.5 and 9.9 mmol/L: o Be aware that the CVD risk may be underestimated by risk assessment tools and o Optimize the management of other CVD risk factors present and o Seek specialist advice if non-HDL cholesterol concentration is more than 7.5 mmol/litre. Statins for the prevention of CVD:

Clinical Guideline	Recommendation(s)
	• The decision whether to start statin therapy should be made after an informed discussion between the clinician and the person about the risks and benefits of statin treatment, taking into account additional factors such as potential benefits from lifestyle modifications, informed patient preference, comorbidities, polypharmacy, general frailty and life expectancy. • Before starting statin treatment perform baseline blood tests and clinical assessment, and treat comorbidities and secondary causes of dyslipidemia. Include smoking status, alcohol consumption, blood pressure, body mass index or other obesity measure, total cholesterol, non-HDL cholesterol, HDL cholesterol, triglyceride level, glycosylated hemoglobin (HbA_{1c}),renal function and estimated glomerular filtration rate (eGFR), transaminase levels, and thyroid stimulating hormone in the assessment. Statins for the Primary Prevention of CVD: • Before offering statin treatment for primary prevention, discuss the benefits of lifestyle modification and optimize the management of all other modifiable CVD risk factors if possible. • Recognize that people may need support to change their lifestyle. To help them do this, refer them to programs such as exercise referral schemes. • Offer people the opportunity to have their risk of CVD assessed again after they have tried to change their lifestyle. • If lifestyle modification is ineffective or inappropriate, offer statin treatment after risk assessment. • Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. • For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction. Be aware of factors that may make treatment inappropriate. Statins for the Secondary Prevention of CVD: • Start statin treatment in people with CVD with atorvastatin 80 mg. Use a lower dose of atorvastatin if there are potential drug interactions, high risk of adverse effects, or patient preference. • Do not delay statin treatment in secondary prevention to manage modifiable risk factors. • If a person has acute coronary syndrome, do not delay statin treatment. Take a lipid sample on admission and about three months after the start of treatment. Statins for the Primary Prevention of CVD for People with Type 1 Diabetes: • Consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes. • Offer statin treatment for the primary prevention of CVD to adults with type 1 diabetes who are older than 40 years, have had diabetes for more than 10 years, have established nephropathy, or have other CVD risk factors. • Start treatment for adults with type 1 diabetes with atorvastatin 20 mg. Statins for the Primary Prevention of CVD in People with Type 2 Diabetes: • Offer atorvastatin 20 mg for the primary prevention of CVD to people with

Clinical Guideline	Recommendation(s)

	type 2 diabetes who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool.
	
	Statins for People with CKD:
	• Offer atorvastatin 20 mg for the primary or secondary prevention of CVD to people with CKD
	  o Increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and eGFR is 30 mL/min/1.73 m^2 or more.
	  o Agree the use of higher doses with a renal specialist if eGFR is less than 30 mL/min/1.73 m^2.
	
	Follow-up of People Started on Statin Therapy:
	• Measure total cholesterol, HDL cholesterol and non-HDL cholesterol in all people who have been started on high-intensity statin treatment at three months of treatment and aim for a greater than 40% reduction in non-HDL cholesterol.
	• If a greater than 40% reduction in non-HDL cholesterol is not achieved, discuss adherence to lifestyle modifications and drug therapy, timing of dose.
	  o Consider increasing the dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk score or using clinical judgement.
	• Provide annual medication reviews for people taking statins.
	• Discuss with people who are stable on a low- or middle-intensity statin the likely benefits and potential risks of changing to a high-intensity statin when they have a medication review and agree with the person whether a change is needed.
	
	Monitoring Statin Therapy for Adverse Effects:
	• Advise people who are being treated with a statin that other drugs, some foods (e.g., grapefruit juice) and some supplements may interfere with statins and to always consult the patient information leaflet, a pharmacist or prescriber for advice when starting other drugs or thinking about taking supplements.
	• Remind the person to restart the statin if they stopped taking it because of drug interactions or to treat intercurrent illnesses.
	• Before offering a statin, ask the person if they have had persistent generalized unexplained muscle pain, whether associated or not with previous lipid-lowering therapy. If they have, measure creatine kinase levels.
	  o If creatine kinase levels are more than five times the upper limit of normal, re-measure creatine kinase after seven days. If creatine kinase levels are still five times the upper limit of normal, do not start statin treatment.
	  o If creatine kinase levels are raised but less than five times the upper limit of normal, start statin treatment at a lower dose.
	• Advise people who are being treated with a statin to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs, measure creatine kinase.
	• If people report muscle pain or weakness while taking a statin, explore other possible causes of muscle pain or weakness and raised creatine

Clinical Guideline	Recommendation(s)
	kinase if they have previously tolerated statin therapy for more than three months. • Do not measure creatine kinase levels in asymptomatic people who are being treated with a statin. • Measure baseline liver transaminase before starting a statin. Measure liver transaminase within three months of starting treatment and at 12 months, but not again unless clinically indicated. • Do not routinely exclude from statin therapy people who have liver transaminase levels that are raised but are less than three times the upper limit of normal. • Do not stop statins because of an increase in blood glucose level or HbA_{1c}. • Statins are contraindicated in pregnancy and women of childbearing potential should be advised of the potential teratogenic risk of statins and to stop taking them if pregnancy is a possibility. o Advise women planning pregnancy to stop taking statins three months before they attempt to conceive and to not restart them until breastfeeding is finished. Intolerance to Statin Therapy: • If a person is not able to tolerate a high-intensity statin aim to treat with the maximum tolerated dose. • Tell the person that any statin at any dose reduces CVD risk. If someone reports adverse effects when taking high-intensity statins discuss the following possible strategies with them: o stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin and o reducing the dose within the same intensity group and o changing the statin to a lower intensity group. • Seek specialist advice about options for treating people at high risk of CVD such as those with CKD, type 1 diabetes, type 2 diabetes or genetic dyslipidemias, and those with CVD, who are intolerant to three different statins. Fibrates for Preventing CVD: • Do not routinely offer fibrates for the prevention of CVD to people who are being treated for primary or secondary prevention, or people with CKD or diabetes type 1 or 2. Nicotinic Acid for Preventing CVD: • Do not offer nicotinic acid (niacin) for the prevention of CVD to people who are being treated for primary or secondary prevention, or people with CKD or diabetes type 1 or 2. Bile Acid Sequestrants (Anion Exchange Resins) for Preventing CVD: • Do not offer bile acid sequestrants for the prevention of CVD to people who are being treated for primary or secondary prevention, or people with CKD or diabetes type 1 or 2. Omega-3 Fatty Acid Compounds for Preventing CVD: • Do not offer omega-3 fatty acid compounds for the prevention of CVD to people who are being treated for primary or secondary prevention, or

Clinical Guideline	Recommendation(s)
	people with CKD or diabetes type 1 or 2. • Tell people that there is no evidence that omega-3 fatty acid compounds help to prevent CVD. Omega-3 Fatty Acid Compounds for Preventing CVD: • Do not offer the combination of a bile acid sequestrant (anion exchange resin), fibrate, nicotinic acid or omega-3 fatty acid compound with a statin for the primary or secondary prevention of CVD. Ezetimibe for Preventing CVD: • People with primary hypercholesterolemia should be considered for ezetimibe treatment.
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)**[69]	• 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 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 TG and low HDL-C, especially in combination with statins. • In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of 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. Treatment of heterozygous FH • 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). Treatment of homozygous familial hypercholesterolemia • Statins may be moderately effective in some persons. • LDL-apheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia).

Clinical Guideline	Recommendation(s)
	Treatment of familial defective apo B-100 • TLC indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous FH. Treatment of polygenic hypercholesterolemia • TLC indicated for all persons. • All LDL-C lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
American Heart Association: **Drug Therapy of High Risk Lipid Abnormalities in Children and Adolescents: A Scientific Statement From the American Heart Association (2007)**[70]	• 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.
European Society of Cardiology and Other Societies: **Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2012)**[71]	Drugs • Currently available lipid-lowering drugs include statins, fibrates, bile acid sequestrants, niacin, and selective cholesterol absorption inhibitors (e.g., ezetimibe). • Statins, by reducing LDL-C, reduce cardiovascular morbidity and mortality as well as the need for coronary artery interventions. • Statins should be used as the drugs of first choice in patients with hypercholesterolemia or combined hyperlipidemia. • Selective cholesterol absorption inhibitors are not used as monotherapy to decrease LDL-C. • Bile acid sequestrants also decrease TC and LDL-C, but tend to increase TG. • Fibrates and niacin are used primarily for TG lowering and increasing HDL-C, while fish oils (omega-3 fatty acids) in doses of 2 to 4 g/day are used for TG lowering. • Fibrates are the drugs of choice for patients with severely elevated TG, and prescription omega-3 fatty acids might be added if elevated TG is not decreased adequately. Drug combinations • Patients with dyslipidemia, particularly those with established CVD, diabetes, or asymptomatic high risk patients, may not always reach treatment targets; therefore, combination treatment may be needed. • Combinations of a statin and a bile acid sequestrants or a combination of a statin and ezetimibe can be used for greater reduction in LDL-C than can

Clinical Guideline	Recommendation(s)
	be achieved with either agent used as monotherapy. • Another advantage of combination therapy is that lower doses of statins can be utilized, thus reducing the risk of adverse events associated with high dose statin therapy. However, statins should be used in the highest tolerable dose to reach LDL-C target level before combination therapy is initiated. • Combinations of niacin and a statin increase HDL-C and decrease TG better than either drug used as monotherapy, but flushing is the main adverse event with niacin, which may affect compliance. • Fibrates, particularly fenofibrate, may be useful, not only for decreasing TG and increasing HDL-C, but can further lower LDL-C when administered in combination with a statin. • If target levels cannot be reached with maximal doses of lipid-lowering therapy or combination therapy, patients will still benefit from treatment to the extent to which dyslipidemia has been improved. In these patients, increased attention to other risk factors may help to reduce total risk.
American Heart Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (2014)**[72]	• Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or transient ischemic attack (TIA) presumed to be of atherosclerotic origin and an LDL-C level ≥100mg/Dl with or without evidence for other clinical ASCVD. • Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin, and LDL-C level <100 mg/dL, and no evidence for other clinical ASCVD. • Patients with ischemic stroke or TIA and other comorbid ASCVD should be otherwise managed according to the 2013 ACC/AHA cholesterol guidelines,[17] which include lifestyle modifications, dietary recommendations, and medication recommendations.

Conclusions

Several fibric acid derivatives are currently available, including fenofibrate, fenofibric acid and gemfibrozil. These agents are approved for the treatment of hypertriglyceridemia, primary hypercholesterolemia, and mixed dyslipidemia.[1-10] The fibric acid derivatives decrease TG by 20 to 50% and increase HDL-C by 10 to 35%. They can also lower LDL-C by 5 to 20%; however, LDL-C may increase in patients with hypertriglyceridemia.[11] Fenofibric acid is the active metabolite of fenofibrate.[13] Fenofibrate (micronized and non-micronized formulations), fenofibric acid, and gemfibrozil are available in a generic formulation.[12]

Clinical trials have demonstrated that the fibric acid derivatives can effectively lower TG and increase HDL-C, as well as positively impact other lipid/lipoprotein parameters. Complementary lipid effects were also observed in clinical trials when fibric acid derivatives were coadministered with ezetimibe and statins.[19-54] Treatment with fenofibrate was associated with a significant reduction in total cardiovascular disease events and revascularization compared to placebo in patients with type 2 diabetes; however, the reduction in CHD events was non-significant.[55] Similarly, in another study of high-risk type 2 diabetics, no significant difference was observed between combination therapy with fenofibrate and simvastatin and simvastatin monotherapy in the annual rate of first occurrence of major cardiovascular events.[59]

Gemfibrozil has demonstrated a reduction in the risk of fatal and nonfatal MI for primary prevention, as well as a reduction in CHD death and nonfatal MI and stroke for secondary prevention.[61,65,66] Overall, because of chemical, pharmacological, and clinical similarities between the fibric acid derivatives, the findings from these studies may apply to all of the agents in this class.[1-10] Muscle toxicity has been reported in patients treated with fibric acid derivatives, particularly when combined with a statin. This

interaction with the statin is more likely with gemfibrozil than with fenofibrate or fenofibric acid.[17] Fibric acid derivatives are also associated with hematologic changes and may potentiate effects of orally administered anticoagulants. In addition, fenofibrate and fenofibric acid may increase serum creatinine levels.[14]

In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When LDL lowering is required, initial treatment with a statin is recommended for decreasing LDL-C levels. 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, niacin, or ezetimibe should be considered. The fibric acid derivatives are recommended for the treatment of hypertriglyceridemia, to reduce the risk of pancreatitis, or for an isolated low HDL-C. 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. Guidelines do not give preference to one fibric acid derivative over another in most cases, but recommend not using gemfibrozil with a statin due to increased muscle adverse effects.[11,14-17]

References

1. Antara® [package insert]. Baltimore (MD): Lupin Pharma; 2013 Oct.
2. Fenoglide® [Prescribing information]. San Diego (CA): Santarus, Inc.; 2012 Oct.
3. Lofibra® capsule [package insert]. Horsham (PA): Teva Select Brands; 2012 Aug.
4. Lofibra® tablet [package insert]. Horsham (PA): Teva Select Brands; 2014 Feb.
5. Lipofen® [package insert]. Montgomery, AL: Kowa Pharmaceuticals America, Inc.; 2013 Jan.
6. Tricor® [package insert]. Florham Park (NJ): AbbVie, Inc.; 2013 Jul.
7. Triglide® [package insert]. Florham Park (NJ): Shionogi Inc.; 2013 Aug.
8. Fibricor® [package insert]. Detriot (MI): URL Pharma, Inc.; 2013 Oct.
9. Trilipix® [package insert]. Florham Park (NJ): AbbVie, Inc.; 2014 Mar.
10. Lopid® [package insert]. New York (NY); Pfizer Inc; 2013 Oct.
11. National Institutes of Health: National Cholesterol Education Program. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
12. DRUGS@FDA.com [database on the internet]. Rockville (MD): U.S. Food and Drug Administration [cited 2014 Aug 15]. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.
13. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2014 Aug 15]. Available from: http://www.thomsonhc.com/.
14. Jellinger PS, Smith DA, Mehta AE, Ganda O, Handelsman Y, Rodbard HW et al. American Association of Clinical Endocrinologists' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis. Endocr Pract. 2012 Mar-Apr;18 Suppl 1:1-78.
15. Smith SC Jr, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. J Am Coll Cardiol. 2011 Nov 29;58(23):2432-46.
16. Institute for Clinical Systems Improvement (ISCI). Healthcare guideline: lipid management in adults 12th ed., 2011 [guideline on the Internet]. ICSI. 2011 [cited 2013 Jul 3]. Available from: http://www.icsi.org/lipid_management_3/lipid_management_in_adults_4.html.
17. The American Heart Association requests that this document be cited as follows: Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PWF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;00:000–000. DOI: 10.1161/01.cir.0000437738.63853.7a.
18. National Institute for Health and Clinical Excellence. Lipid modification: cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. National Institute for Health and Clinical Excellence; London (UK): 2014 [cited 2014 Aug 15]. Available from: https://www.nice.org.uk/Guidance
19. Rosenson RS, Wolff DA, Huskin AL, Helenowski IB, Rademaker AW. Fenofibrate therapy ameliorates fasting and postprandial lipoproteinemia, oxidative stress, and the inflammatory response in patients with hypertriglyceridemia and the metabolic syndrome. Diabetes Care. 2007 Aug;30(8):1945-51.
20. Davidson MH, Bays HE, Stein E, Maki KC, Shalwitz RA, Doyle R; TRIMS Investigators. Effects of fenofibrate on atherogenic dyslipidemia in hypertriglyceridemic patients. Clin Cardiol. 2006 Jun;29(6):268-73.
21. Jones PH, Goldberg AC, Knapp HR, Kelly MT, Setze CM, Stolzenbach J, et al. Efficacy and safety of fenofibric acid in combination with atorvastatin and ezetimibe in patients with mixed dyslipidemia. Am Heart J. 2010;160:759-66.
22. Hogue JC, Lamarche B, Tremblay AJ, et al. Differential effect of atorvastatin and fenofibrate on plasma oxidized low-density lipoprotein, inflammation markers, and cell adhesion molecules in patients with type 2 diabetes mellitus. Metabolism 2008;57:380-6.

23. Arca M, Montali A, Pigna G, Antonini R, Antonini TM, Luigi P, et al. Comparison of atorvastatin vs fenofibrate in reaching lipid targets and influencing biomarkers of endothelial damage in patients with familial combined hyperlipidemia. Metabolism. 2007 Nov;56(11):1534-41.
24. Goldberg A, Bays H, Ballantyne C, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with atorvastatin in patients with mixed dyslipidemia. Am J Cardiol 2009;103:515-22.
25. Roth EM, Rosenson RS, Carlson DM, Fukumoto SM, Setze CM, Blasetto JW, et al. Efficacy and safety of rosuvastatin 5 mg in combination with fenofibric acid 135 mg in patients with mixed dyslipidemia-a phase 3 study. Cardiovasc Drugs Ther. 2010;24:421-8.
26. Jones P, Davidson M, Kashyap M, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with rosuvastatin in patients with mixed dyslipidemia: A phase 3 study. Atherosclerosis 2009;204:208-215.
27. Ferdinand KC, Davidson MH, Kelly MT, Setze CM. One-year efficacy and safety of rosuvastatin + fenofibric acid combination therapy in patients with mixed dyslipidemia. Evaluation of dose response. Am J Cardiovasc Drugs. 2012;12(2):117-25.
28. Mohiuddin S, Pepine C, Kelly M, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with simvastatin in patients with mixed dyslipidemia: a phase 3, randomized, controlled study. Am Heart J 2009;157:195-203.
29. Derosa G, Maffioli P, Salvadeo SA, et al. Fenofibrate, simvastatin and their combination in the management of dyslipidemia in type 2 diabetic patients. Curr Med Res Opin 2009;25:1973-83.
30. May HT, Anderson JL, Pearson RR, et al. Comparison of effects of simvastatin alone vs fenofibrate alone vs simvastatin plus fenofibrate on lipoprotein subparticle profiles in diabetic patients with mixed dyslipidemia (from the Diabetes and Combined Lipid Therapy Regimen study). Am J Cardiol 2008;101:486-9.
31. Jones P, Davidson M, Goldberg A, et al. Efficacy and safety of fenofibric acid in combination with a statin in patients with mixed dyslipidemia: pooled analysis of three phase 3, 12-week randomized, controlled studies. J Clin Lipidology 2009;3:125-37.
32. Bays H, Jones P, Mohiuddin S, et al. Long-term safety and efficacy of fenofibric acid in combination with statin therapy for the treatment of patients with mixed dyslipidemia. J Clin Lipidology 2008;2:426-35.
33. Kipnes MS, Roth EM, Rhyne JM, et al. Year two assessment of fenofibric acid and moderate-dose statin combination: a phase 3, open-label, extension study. Clin Drug Investig 2010;30:51-61.
34. Farnier M, Freeman M, Macdonell G, Perevozskaya I, Davies MJ, Mitchel YB, et al. Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidemia. Eur Heart J. 2005 May;26(9):897-905.
35. Tribble DL, Farnier M, Macdonell G, et al. Effects of fenofibrate and ezetimibe, both as monotherapy and in coadministration, on cholesterol mass within lipoprotein subfractions and low-density lipoprotein peak particle size in patients with mixed hyperlipidemia. Metabolism 2008;57:796-801.
36. McKenney JM, Farnier M, Lo KW, Bays HE, Perevozkaya I, Carlson G, et al. Safety and efficacy of long-term c-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. J Am Coll Cardiol. 2006 Apr 18;47(8):1584-7.
37. Ansquer JC, Bekaert I, Guy M, et al. Efficacy and safety of coadministration of fenofibrate and ezetimibe compared to each as monotherapy in patients with type IIb dyslipidemia and features of the metabolic syndrome: a prospective, randomized, double-blind, three-parallel arm, multicenter, comparative study. Am J Cardiovasc Drugs 2009;9:91-101.
38. Farnier M, Roth E, Gil-Extremera B, Mendez G, Macdonell G, Hamlin C, et al. Efficacy and safety of the coadministration of ezetimibe/simvastatin with fenofibrate in patients with mixed hyperlipidemia. Am Heart J. 2007 Feb;153(2):335.e1-8.
39. Farnier M, Perevozskaya I, Taggart WV, et al. VAP II analysis of lipoprotein subclasses in mixed hyperlipidemic patients on treatment with ezetimibe/simvastatin and fenofibrate. J Lipid Res 2008;49:2641-7.
40. Kumar SS, Lahey KA, Day A, LaHaye SA. Comparison of the efficacy of administering a combination of ezetimibe plus fenofibrate vs atorvastatin monotherapy in the treatment of dyslipidemia. Lipids Health Dis. 2009;8(56):1-8.

41. Winkler K, Schewe T, Putz G, Odunc N, Schafer G, Siegel E, et al. Fluvastatin/fenofibrate vs simvastatin/ezetimibe in patients with metabolic syndrome: different effects on LDL-profiles. Eur J Clin Invest. 2009;39(6):463-70.
42. Wi J, Kim JY, Park S, Kang SM, Jang Y, Chung N. Optimal pharmacologic approach to patients with hypertriglyceridemia and low high-density lipoprotein-cholesterol: randomized comparison of fenofibrate 160 mg and niacin 1,500 mg. Atherosclerosis. 2010;213:235-40.
43. Alrasadi K, Awan Z, Alwaili K, et al. Comparison of treatment of severe high-density lipoprotein cholesterol deficiency in men with daily atorvastatin (20 mg) vs fenofibrate (200 mg) vs extended-release niacin (2 g). Am J Cardiol 2008;102:1341-7.
44. Balasubramanyam A, Coraza I, O'Brian Smith E, Scott LW, Patel P, Iyer D, et al. Combination of niacin and fenofibrate with lifestyle changes improves dyslipidemia and hypoadiponectinemia in HIV patients on antiretroviral therapy: results of "Heart Positive," a randomized, controlled trial. J Clin Endocrinol Metab. 2011;96:2236-47.
45. Roth EM, Bays HE, Forker AD, et al. Prescription omega-3 fatty acid as an adjunct to fenofibrate therapy in hypertriglyceridemic patients. J Cardiovasc Pharmacol 2009;54:196-203.
46. Koh KK, Quon MJ, Shin KC, Lim S, Lee Y, Sakuma I, et al. Significant differential effects of omega-3 fatty acids and fenofibrate in patients with hypertriglyceridemia. Atherosclerosis. 2012;220:537-44.
47. Koh KK, Quon MJ, Han SH, Chung WJ, Ahn JY, Kim JA, et al. Additive beneficial effects of fenofibrate combined with candesartan in the treatment of hypertriglyceridemic hypertensive patients. Diabetes Care. 2006 Feb;29(2):195-201.
48. Insua A, Massari F, Rodrigues Moncalvo JJ, Rubén Zanchetta J, Insua AM. Fenofibrate or gemfibrozil for treatment of types IIa and IIb primary hyperlipoproteinemia: a randomized, double-blind, crossover study. Endocr Pract. 2002 Mar-Apr;8(2):96-101.
49. Corbelli JC, Bullano MF, Willey VJ, Cziraky MJ, Corbelli ME, Waugh W. Effects of gemfibrozil conversion to fenofibrate on lipids in patients on statin therapy. Am J Cardiol. 2002 Dec 15;90(12):1388-91.
50. Guyton JR, Blazing MA, Hagar J, Kashyap ML, Knopp RH, McKenney JM, et al. Extended-release niacin vs gemfibrozil for the treatment of low levels of high-density lipoprotein cholesterol. Arch Intern Med. 2000;160:1177-84.
51. Stalenhoef AFH, de Graaf J, Wittekoek ME, Bredie SJH, Demacker PNM, Kastelein JJP. The effect of concentrated n-3 fatty acids vs gemfibrozil on plasma lipoproteins, low density lipoprotein heterogeneity and oxidizability in patients with hypertriglyceridemia. Atherosclerosis. 2000;153:129-38.
52. Van Dam M, Stalenhoef AFH, Wittekoek J, et al. Efficacy of concentrated omega-3 fatty acids in hypertriglyceridemia: A comparison with gemfibrozil. Clin Drug Invest 2001;21:175–181.
53. Muñoz MA, Liu W, Delaney JA, Brown E, Mugavero MJ, et al. Comparative effectiveness of fish oil versus fenofibrate, gemfibrozil, and atorvastatin on lowering triglyceride levels among HIV-infected patients in routine clinical care. J Acquir Immune Defic Syndr. 2013 Nov 1;64(3):254-60. doi: 10.1097/QAI.0b013e3182a60e82.
54. Weinstein DL, Williams LA, Carlson DM, Kelly MT, Burns KM, et al. A randomized, double-blind study of fenofibric acid plus rosuvastatin compared with rosuvastatin alone in stage 3 chronic kidney disease. Clin Ther. 2013 Aug;35(8):1186-98. doi: 10.1016/j.clinthera.2013.06.013. Epub 2013 Jul 26.
55. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, et al. FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD Study): randomized controlled trial. Lancet. 2005 Nov 26;366(9500):1849-61.
56. Tonkin A, Hunt D, Voysey M, Kesaniemi A, Hamer A, Waites J, et al. Effects of fenofibrate on cardiovascular events in patients with diabetes: the Fenofibrate Intervention and Event Lowering In Diabetes (FIELD) study. A Heart J. 2012;163:508-14.
57. Ting RD, Keech AC, Drury PL, Donoghoe MW, Hedley J, Jenkins AJ, et al. Benefits and safety of long-term fenofibrate therapy in people with type 2 diabetes and renal impairment: the FIELD study (abstract). Diabetes Care. 2012 Feb;35(2):218-25.
58. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomized study. Lancet. 2001 Mar 24;357(9260):905-10.

59. The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362:1563-74.
60. Bonds DE, Craven TE, Buse J, Crouse JR, Cuddihy R, Elam M, et al. Fenofibrate-associated changes in renal function and relationship to clinical outcomes among individuals with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) experience. Diabetologia. 2012;55:1641-50.
61. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, et al. Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med. 1987 Nov 12;317(20):1237-45.
62. Frick MH, Heinonen OP, Huttunen JK, Koskinen P, Mänttäri M, Manninen V. Efficacy of gemfibrozil in dyslipidemic patients with suspected heart disease. An ancillary study in the Helsinki Heart Study frame population. Ann Med. 1993 Feb;25(1):41-5.
63. Heinonen OP, Huttunen JK, Manninen V, Mänttäri M, Koskinen P, Tenkanen L, et al. The Helsinki Heart Study: coronary heart disease incidence during an extended follow-up. J Intern Med. 1994 Jan;235(1):41-9.
64. Huttunen JK, Heinonen OP, Manninen V, Koskinen P, Hakulinen T, Teppo L, et al. The Helsinki Heart Study: an 8.5-year safety and mortality follow-up. J Intern Med. 1994;235:31-9.
65. Robins SJ, Collins D, Wittes JT, Papademetriou V, Deedwania PC, Schaefer EJ, et al; VA-HIT Study Group. Veterans Affairs High-Density Lipoprotein Intervention Trial. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. JAMA. 2001 Mar 28;285(12):1585-91.
66. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. N Engl J Med. 1999;341:410-8.
67. Saha SA, Kizhakepunnur LG, Bahekar A, Arora RR. The role of fibrates in the prevention of cardiovascular disease-a pooled meta-analysis of long-term randomized placebo-controlled clinical trials. Am Heart J. 2007;154:943-53.
68. Jun M, Foote C, Lv Jicheng , Neal B, Patel A, Nicholls SJ, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. Lancet. 2010;375:1875-84.
69. Grundy SM, Cleeman JI, Merz NB, Brewer Jr B, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation. 2004;110:227-39.
70. McCrindle BW, Urbina EM, Dennison BA, Jacobson MS, Steinberger J, Rocchini AP, et al. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. Circulation. 2007 Apr;115(14):1948-67.
71. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WM, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur J Prev Cardiol. 2012 Aug;19(4):585-667.
72. Kernan WN, Ovbiagele B, Black HR, Bravata DW, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014 May;45:2160-2236.