Therapeutic Class Overview
Cholesterol Absorption Inhibitors

Therapeutic Class

- **Overview/Summary:** Currently ezetimibe (Zetia®) is the only cholesterol absorption inhibitor available and it is Food and Drug Administration-approved for the treatment of primary hyperlipidemia, homozygous familial hypercholesterolemia and homozygous sitosterolemia.[1] Ezetimibe has a unique mechanism of action in that it works to reduce blood cholesterol by inhibiting the absorption of both dietary and biliary cholesterol by the small intestine, resulting in a decrease in hepatic cholesterol stores, an increase in hepatic cholesterol sequestering from the circulation and ultimately, lower systemic cholesterol levels.[1,2] In general, the role of ezetimibe in the management of hypercholesterolemia has not been well established. It is primarily used in combination with a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin); however, given the results of clinical trials evaluating the safety of and efficacy of ezetimibe added on to treatment with a statin, the use of more established lipid lowering therapies as add on therapy is likely to be preferred. Ezetimibe may be helpful in avoiding high doses of statins in patients who are unable to achieve their lipid goals on low dose statin therapy. In general, additional clinical trials are necessary as there is no evidence to demonstrate a reduction in cardiovascular outcomes with ezetimibe monotherapy or in combination with a statin.[2] When low density lipoprotein cholesterol lowering is required, initial treatment with a statin, a bile acid sequestrant or nicotinic acid (niacin) is recommended.[1] In general, the statins are considered first-line therapy for decreasing low density lipoprotein cholesterol levels.[3-6] 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.[3] Treatment guidelines recognize ezetimibe as a potential option to be added to statin therapy if lipid goals have not been met, or as a potential treatment option in patients who are not able to take statins.[4,5] Ezetimibe is available as a once daily, 10 mg tablet.[1]

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

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/ Strength	Generic Availability
Ezetimibe (Zetia®)	Adjunctive therapy to diet for the reduction of elevated total cholesterol, low density lipoprotein cholesterol and apolipoprotein B in patients with primary (heterozygous familial and non-familial) hyperlipidemia, adjunctive therapy in combination with a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) to diet for the reduction of elevated total cholesterol, low density lipoprotein cholesterol and apolipoprotein A with primary (heterozygous familial and non-familial) hyperlipidemia, adjunctive therapy in combination with fenofibrate to diet for the reduction of elevated total cholesterol, low density lipoprotein cholesterol, apolipoprotein B and non-high density lipoprotein cholesterol in adult patients with mixed hyperlipidemia, in combination with atorvastatin or simvastatin to reduce elevated total cholesterol and low density lipoprotein cholesterol levels in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid lowering treatments (e.g., low density lipoprotein apheresis) or if such treatments are unavailable, adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial	Tablet: 10 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/ Strength	Generic Availability
	sitosterolemia		

Evidence-based Medicine

- In general, the cholesterol absorption inhibitors consistently demonstrated "superiority" over placebo in the treatment of homozygous familial hypercholesterolemia, homozygous sitosterolemia and primary hyperlipidemia.[8-51]
- In line with treatment guidelines, results also demonstrated that the addition of a cholesterol absorption inhibitor to a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) has the potential to produce further reductions in low density lipoprotein cholesterol levels compared to monotherapy with either of the agents alone.[8-51]

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.[3-5]
  - In general, hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are considered first line therapy for decreasing low density lipoprotein cholesterol 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.[3-6]
  - In general, treatment guidelines recognize ezetimibe as a potential option to be added to statin therapy if lipid goals have not been met, or as a potential treatment option in patients who are unable to take statins.[4,5]
- Other Key Facts:
  - The branded agent Zetia® is the only cholesterol absorption inhibitor currently available in the United States.
  - To date, ezetimibe has not demonstrated a reduction in cardiovascular outcomes in clinical trials.

References

1. Zetia® [package insert]. Whitehouse Station (NJ): Merck & Co. Inc.; 2012 Jun.
2. Rosenson RS. Lipid lowering with drugs other than statins and fibrates. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Aug 14]. Available from: http://www.utdol.com/utd/index.do.
3. National Cholesterol Education Program (NCEP). Detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report, 2002 [guideline on the internet]. NCEP. 2002 [cited 2012 Aug 14]. Available from: http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm.
4. 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.
5. Institute for Clinical Systems Improvement (ISCI). Healthcare guideline: lipid management in adults 12th ed., 2011 [guideline on the Internet]. ICSI. 2011 [cited 2012 Aug 14]. Available from: http://www.icsi.org/lipid_management_3/lipid_management_in_adults_4.html.
6. 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.
7. Mikhailidis DP, Sibbring GC, Ballantyne CM, Davies GM, Catapano AL. Meta-analysis of the cholesterol-lowering effect of ezetimibe added to ongoing statin therapy (abstract). Curr Med Res Opin. 2007 Aug;23(8):2009-26.
8. Salen G, von Bergmann K, Lutjohann D, Kwiterovich P, Kane J, Patel SB, et al. Ezetimibe effectively reduces plasma plant sterols in patients with sitosterolemia. Circulation. 2004;109:966-71.
9. Musliner T, Cselovszky D, Sirah W, Sisk M, Sapre A, Salen G. Efficacy and safety of ezetimibe 40 mg vs ezetimibe 10 mg in the treatment of patients with homozygous sitosterolemia. Int J Clin Pract. 2008 Jul;62(7):995-1000.
10. Pearson GJ, Francis GA, Romney JS, Gilchrist DM, Opgenorth A, Gyenes GT. The clinical effect and tolerability of ezetimibe in high-risk patients managed in a specialty cardiovascular risk reduction clinic. Can J Cardiol. 2006;22(11):939-45.
11. Dujovne CA, Ettinger MP, McNeer JF, Lipka LJ, LeBeaut AP, Suresh R, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. Am J Cardiol. 2002 Nov 15;90(10):1092-7.

12. Gonzalez-Ortiz M, Martinez-Abundis E, Kam-Ramos AM,Hernandez-Salazar E, Ramos-Zavala MG. Effect of ezetimibe on insulin sensitivity and lipid profile in obese and dyslipidaemic patients. Cardiovasc Drugs Ther. 2006:20(2):143-6.
13. Knopp RH, Gitter H, Truitt T, Bays H, Manion CV, Lipka LJ, et al. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. Eur Heart J. 2003 Apr;24(8):729-41.
14. Knopp RH, Dujovne CA, Le Beaut A, Lipka LJ, Sresh R, Veltri EP, et al. Evaluation of the efficacy, safety, and tolerability of ezetimibe in primary hypercholesterolemia: a pooled analysis from two controlled phase III clinical studies. Int J Clin Pract. 2003 Jun;57(5):363-8.
15. Wierzbicki AS, Doherty E, Lumb PJ, Chik G, Crook MA. Efficacy of ezetimibe in patients with statin-resistant and statin-intolerant familial hyperlipaemias (abstract). Curr Med Res Opin. 2005;21(3):333-8.
16. Kalogirou M, Tsimihodimos V, Gazi I, Filippatos T, Saougos V, Tselepis AD, et al. Effect of ezetimibe monotherapy on the concentration of lipoprotein subfractions in patients with primary dyslipidaemia (abstract). Curr Med Res Opin. 2007 May; 23(5):1169-76.
17. Jelesoff NE, Ballantyne CM, Xydakis AM, Chiou P, Jones PH, Guyton JR. Effectiveness and tolerability of adding ezetimibe to niacin-based regimens for treatment of primary hyperlipidemia (abstract). Endocrine Practice. 2006;12(2):159-64.
18. Gagné C, Bays HE, Weiss SR, Mata P, Quinto K, Melino M, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol. 2002 Nov 15;90(10):1084-91.
19. Denke M, Pearson T, McBride P, Gazzara RA, Brady WE, Tershakovec AM. Ezetimibe added to ongoing statin therapy improves LDL-C goal attainment and lipid profile in patients with diabetes or metabolic syndrome. Diab Vasc Dis Res. 2006 Sep;3(2):93-102.
20. Pearson TA, Denke MA, McBride PE, Battisti WP, Brady WE, Palmisano J. A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. Mayo Clin Proc. 2005; May 80(5):587-95.
21. Pearson T, Denke M, McBride P, Battisti WP, Brady WE, Palmisano J. Effectiveness of the addition of ezetimibe to ongoing statin therapy in modifying lipid profiles and attaining low-density lipoprotein cholesterol goals in older and elderly patients: subanalyses of data from a randomized, double-blind, placebo-controlled trial. Am J Geriatr Pharmacother. 2005 Dec;3(4):218-28.
22. Pearson T, Denke M, McBride PE, Batisti WP, Gazzara RA, Brady WE, et al. Effectiveness of ezetimibe added to ongoing statin therapy in modifying lipid profiles and low-density lipoprotein cholesterol goal attainment in patients of different races and ethnicities: a substudy of the ezetimibe add-on to statin for effectiveness trial. Mayo Clin Prac. 2006 Sept;81(9):1177-85.
23. Simons L, Symons J. Ezetimibe added to statin therapy (EASY study). An evaluation by Australian general practitioners. Aust Fam Physician. 2007 Jan-Feb;36(1-2):90-2,96.
24. Blagden M, Chipperfield R. Efficacy and safety of ezetimibe co-administered with atorvastatin in untreated patients with primary hypercholesterolaemia and coronary heart disease (abstract). Curr Med Res Opin. 2007 Apr;23(4):767-75.
25. Ballantyne CM, Weiss R, Moccetti T, Vogt A, Eber B, Sosef F, et al. Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). Am J Cardiol. 2007 Mar 1;99(5):673-80.
26. Landry M, Baigent C, Leaper C, Adu D, Altmann P, Armitage J, et al. The second United Kingdom Heart and Renal Protection (UK-HARP-II) study: a randomized controlled study of the biochemical safety and efficacy of adding ezetimibe to simvastatin as initial therapy among patients with CKD. Am J Kidney Dis. 2006;47(3):385-95.
27. Patel JV, Hughes EA. Efficacy, safety and LDL-C goal attainment of ezetimibe 10 mg-simvastatin 20 mg vs placebo-simvastatin 20 mg in UK-based adults with coronary heart disease and hypercholesterolaemia. Int J Clin Pract. 2006 Aug;60(8):914-21.
28. Rodney RA, Sugimoto D, Wagman B, Zieve F, Kerzner B, Strony J, et al. Efficacy and safety of coadministration of ezetimibe and simvastatin in African-American patients with primary hypercholesterolemia. J Natl Med Assoc. 2006 May;98(5):772-8.
29. Masana L, Mata P, Gagné C, Sirah W, Cho M, Johnson-Levonas AO, et al. Long-term safety and, tolerability profiles and lipid-modifying efficacy of ezetimibe coadministered with ongoing simvastatin treatment: a multicenter, randomized, double-blind, placebo-controlled, 48-week extension study. Clin Ther. 2005 Feb;27(2):174-84.
30. Farnier M, Freeman MW, Macdonell G, Perevozskaya I, Davies MJ, Mitchel YB, et al. Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia. Eur Heart J. 2005; 26:897-905.
31. McKenney JM, Farnier M, Lo KW, Bays HE, Perevozkaya I, Carlson G, et al. Safety and efficacy of long-term co-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. J Am Coll Cardiol. 2006 Apr 18;47(8):1584-7.
32. Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation. 2003 May 20;107(19):2409-15.
33. Kerzner B, Corbelli J, Sharp S, Lipka LJ, Melani L, LeBeaut A, et al. Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. Am J Cardiol. 2003 Feb 15;91(4):418-24.
34. Melani L, Mills R, Hassman D, Lipetz R, Lipka L, LeBeaut A, et al. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Eur Heart J. 2003 Apr;24(8):717-28.
35. Davidson MH, McGarry T, Bettis R, Melani L, Lipka LJ, LeBeaut AP, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol. 2002 Dec 18;40(12):2125-34.
36. Goldberg AC, Sapre A, Liu J, Capece R, Mitchel YB. Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc. 2004 May;79(5):620-9.
37. Bays HE, Ose L, Fraser N, Tribble DL, Quinto K, Reyes R, et al. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared to ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. Clin Ther. 2004 Nov;26(11):1758-73.

38. Ose L, Johnson-Levonas A, Reyes R, Lin J, Shah A, Tribble D, et al. A multi-centre, randomized, double-blind 14-week extension study examining the long-term safety and efficacy profile of the ezetimibe/simvastatin combination tablet. Int J Clin Pract. 2007 Sep;61(9):1469-80.
39. Feldman T, Davidson M, Shah A, Maccubbin D, Meehan A, Zakson M, et al. Comparison of the lipid-modifying efficacy and safety profiles of ezetimibe coadministered with simvastatin in older versus younger patients with primary hypercholesterolemia: a post hoc analysis of subpopulations from three pooled clinical trials. Clin Ther. 2006 Jun;28(6):849-59.
40. Pearson T, Ballantyne C, Sisk C, Shah A, Veltri E, Maccubbin D. Comparison of effects of ezetimibe/simvastatin versus simvastatin versus atorvastatin in reducing C-reactive protein and low-density lipoprotein cholesterol levels. Am J Cardiol. 2007 Jun 15;99(12):1706-13.
41. Conrad S, Bays H, Leiter LA, Bird S, Lin J, Hanson ME, et al. Ezetimibe added to atorvastatin compared to doubling the atorvastatin dose in patients at high risk for coronary heart disease with diabetes mellitus, metabolic syndrome or neither. Diabetes Obes Metab. 2010;12:210-8.
42. Uemura Y, Watarai M, Ishii H, Koyasu M, Takemoto K, Yoshikawa D, et al. Atorvastatin 10 mg plus ezetimibe 10mg compared with atorvastatin 20 mg: impact on the lipid profile in Japanese patients with abnormal glucose tolerance and coronary artery disease. J Cardiol. 2012 Jan;59(1):50-6.
43. Piorkowski M, Fischer S, Stellbaum C, Jaster M, Martus P, Morguet AJ, et al. Treatment with ezetimibe plus low-dose atorvastatin compared to higher-dose atorvastatin alone: is sufficient cholesterol-lowering enough to inhibit platelets? J Am Coll Cardiol. 2007 Mar 13;49(10):1035-42.
44. Stein E, Stender S, Mata P, Sager P, Ponsonnet D, Melani L, et al. Achieving lipoprotein goals in patients at high risk with sever hypercholesterolemia: Efficacy and safety of ezetimibe co-administered with atorvastatin. Am Heart J. 2004 Sep;447-55.
45. Constance C, Westphal S, Chung N, Lund M, McCrary Sisk C, Johnson-Levonas AO, et al. Efficacy of ezetimibe/simvastatin 10/20 and 10/40 mg compared to atorvastatin 20 mg in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2007 Jul;9(4):575-84.
46. Goldberg RB, Guyton JR, Mazzone T, Weinstock RS, Polis A, Edwards P, et al. Ezetimibe/simvastatin vs atorvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia: the VYTAL study. Mayo Clin Proc. 2006 Dec;81(12):1579-88.
47. Hing Ling PK, Civeira F, Dan AG, Hanson ME, Massaad R, De Tilleghem Cle B, et al. Ezetimibe/simvastatin 10/40 mg versus atorvastatin 40 mg in high cardiovascular risk patients with primary hypercholesterolemia: a randomized, double-blind, active-controlled, multicenter study. Lipids Health Dis. 2012 Jan 31;11:18.
48. Stojakovic T, de Campo A, Scharnagl H, Sourij H, Schmolzer I, Wascher TC, et al. Differential effects of fluvastatin alone or in combination with ezetimibe on lipoprotein subfractions in patients at high risk of coronary events. Eur J Clin Invest. 2010;40(3):187-94.
49. Gaudiani LM, Lewin A, Meneghini L, Perevozskaya I, Plotkin D, Mitchel Y, et al. Efficacy and safety of ezetimibe co-administered with simvastatin in thiazolidinedione-treated type 2 diabetic patients. Diabetes Obes Metab. 2005 Jan;7(1):88-97.
50. Feldman T, Koren M, Insull W Jr, McKenney J, Schrott H, Lewin A, et al. Treatment of high-risk patients with ezetimibe plus simvastatin co-administration versus simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals. Am J Cardiol. 2004 Jun 15;93(12):1481-6.
51. Bays H, Sapre A, Taggart W, Liu J, Capece R, Tershakovec A. Long-term (48-week) safety of ezetimibe 10 mg/day coadministered with simvastatin compared to simvastatin alone in patients with primary hypercholesterolemia. Curr Med Res Opin. 2008;24(10):2953-66.

Therapeutic Class Review
Cholesterol Absorption Inhibitors

Overview/Summary

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

In addition to the medication classes mentioned above, the cholesterol absorption inhibitors are also effective in the management of hypercholesterolemia and have a unique mechanism of action compared to the other available treatments. Specifically, these agents work to reduce blood cholesterol by inhibiting the absorption of both dietary and biliary cholesterol by the small intestine, which results in a decrease in hepatic cholesterol stores, an increase in hepatic cholesterol sequestering from the circulation and ultimately, lower systemic cholesterol levels.[1,2] Zetia® (ezetimibe) is the only cholesterol absorption inhibitor available and is FDA-approved for the treatment of primary hyperlipidemia, homozygous familial hypercholesterolemia and homozygous sitosterolemia.[1] Ezetimibe is not currently available generically.

In general, the role of ezetimibe in the management of hypercholesterolemia is not well established. It is primarily used as monotherapy or in combination with a statin. In patients already receiving a statin, maximizing the dose of the statin can achieve similar reductions in low density lipoprotein cholesterol as adding ezetimibe to treatment. The addition of ezetimibe may be helpful in avoiding high doses of statins. Given the results of clinical trials evaluating the safety of and efficacy of ezetimibe added on to treatment with a statin, use of more established lipid lowering therapies as add on therapy is likely to be a more preferred treatment.[2]

In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia.[3-5] When low density lipoprotein cholesterol lowering is required, initial treatment with a statin, a bile acid sequestrant or niacin is recommended.[3] However, in general, the statins are considered first line therapy for decreasing low density lipoprotein cholesterol levels.[3-6] 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.[3] As mentioned previously, the role of ezetimibe in the management of lipid disorders is not well established. Treatment guidelines recognize ezetimibe as a potential option to be added to statin therapy if lipid goals have not been met, or as a potential treatment option in patients who are unable to take statins.[4,5]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Ezetimibe (Zetia®)	Cholesterol absorption inhibitors	-

Indications

Table 2. Food and Drug Administration Approved Indications[1]

Indication(s)	Ezetimibe
Homozygous Familial Hypercholesterolemia	
In combination with atorvastatin or simvastatin to reduce elevated total cholesterol and low density lipoprotein cholesterol levels in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid lowering treatments (e.g., low density	a

Indication(s)	Ezetimibe
lipoprotein apheresis) or if such treatments are unavailable	
Homozygous Sitosterolemia	
Adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia	a
Primary Hyperlipidemia	
Adjunctive therapy to diet for the reduction of elevated total cholesterol, low density lipoprotein cholesterol and apolipoprotein B in patients with primary (heterozygous familial and non-familial) hyperlipidemia	a
Adjunctive therapy in combination with a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) to diet for the reduction of elevated total cholesterol, low density lipoprotein cholesterol and apolipoprotein A with primary (heterozygous familial and non-familial) hyperlipidemia	a
Adjunctive therapy in combination with fenofibrate to diet for the reduction of elevated total cholesterol, low density lipoprotein cholesterol, apolipoprotein B and non-high density lipoprotein cholesterol in adult patients with mixed hyperlipidemia	a

Pharmacokinetics

Table 3. Pharmacokinetics[7]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Ezetimibe	Not reported	11	Ezetimibe glucuronide	19 to 30

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the cholesterol absorption inhibitors for the treatment of homozygous familial hypercholesterolemia, homozygous sitosterolemia and primary hyperlipidemia are outlined in Table 4.[8-63] In general, the cholesterol absorption inhibitors consistently demonstrated "superiority" over placebo in the management of these disease states.[8,10,12,13,15-38,40-45] In line with treatment guidelines, results also demonstrated that the addition of a cholesterol absorption inhibitor to a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) has the potential to produce further reductions in low density lipoprotein cholesterol levels compared to monotherapy with either of the agents alone.[8,9,13,14,22-33,36-45,50-60]

The exact role of the cholesterol absorption inhibitors in the management of lipid disorders is not well established and additional trials evaluating the efficacy of these agents on clinical outcomes is required to determine if true clinical benefits can be achieved with the use of these agents.[2]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Mikhailidis et al[8] (abstract) Ezetimibe 10 mg/day vs placebo All patients received a statin.	MA (2 ESs, 19 RCTs) Patients ≥18 years of age with diagnoses of nonfamilial or FH, hyperlipidemia and homozygous familial sitosterolemia and LDL-C above NCEP ATP II/III guideline criteria	N=5,039 6 to 24 weeks	Primary: Total number of patients attaining LDL-C goal; changes from baseline in TC, LDL-C and HDL-C Secondary: Not reported	Primary: The analysis of five RCTs indicated that when compared to placebo, the RR of obtaining the LDL-C treatment goal was higher with the addition of ezetimibe (*P*<0.0001). A WMD between treatments significantly favored the addition of ezetimibe over placebo for TC (-16.1%; 95% CI, -17.3 to -14.8), LDL-C (-23.6%; 95% CI, -25.6 to -21.7) and for HDL-C (1.7%; 95% CI, 0.9 to 2.5) (*P*<0.0001 for all). In an analysis of patients with or without CHD (in addition to hypercholesterolemia), the addition of ezetimibe was favored over placebo for the following (WMD): LDL-C, -23.6% (*P*<0.0001); TC, -16.1% (*P*<0.0001); HDL-C, 1.7% (*P*<0.0001); TG, -10.7%; Apo B, -17.3% (RR LDL-C treatment goal, 3.4; *P*<0.0001). The difference between treatments in all trials favored the addition of ezetimibe for all outcomes except TG and HDL-C. An analysis of data from a 48 week ES correlated with the pooled estimates of the short term trials in the MA revealed that ezetimibe plus simvastatin resulted in significantly lower levels of LDL-C, TC and TG when compared to placebo plus simvastatin (reductions of 20.4, 13.4 and 13.6%, respectively; *P*<0.001 for the difference between treatments). Secondary: Not reported
Homozygous Familial Hypercholesterolemia				
Gagné et al[9] Statin 40 mg/day for 14 weeks, followed by statin 40 mg/day plus ezetimibe 10 mg/day	DB, MC, RCT Patients ≥12 years of age with homozygous FH, LDL-C ≥100 mg/dL and TG ≤350 mg/dL (if on	N=50 26 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent change	Primary: LDL-C was reduced more by the addition of ezetimibe to the statin than by doubling the dose of statin (20.7 vs 6.7%; *P*=0.007). Secondary: TC was reduced more by the addition of ezetimibe to the statin than by doubling the dose of statin (18.7 vs 5.3%; *P*<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs statin 40 mg/day for 14 weeks, followed by statin 80 mg/day plus ezetimibe 10 mg/day vs statin 40 mg/day for 14 weeks, followed by statin 80 mg/day Statins evaluated included atorvastatin and simvastatin.	atorvastatin or simvastatin 40 mg/day)		from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B, apo AI and CRP	There was no significant difference in any of the other secondary outcome measures between the two treatments (*P*>0.05).
Homozygous Sitosterolemia				
Salen et al[10] Ezetimibe 10 mg/day vs placebo	DB, MC, PC, RCT Patients ≥10 years of age with a diagnosis of sitosterolemia who had plasma sitosterol levels >0.12 mmol/L despite current treatment	N=37 8 weeks	Primary: Percent change from baseline in sitosterol concentration Secondary: Not reported	Primary: Ezetimibe resulted in a mean percent reduction in sitosterol of 21% (*P*<0.001) compared to a nonsignificant increase of 4% with placebo (*P* value not reported). The between-group difference in mean percent change in sitosterol was -25% (95% CI, -36.7 to -13.2; *P*<0.001). The reduction in plasma sitosterol during the DB period was progressive beginning at week two, with greater reduction from baseline observed at each subsequent visit. Secondary: Not reported
Lutjohann et al[11] Ezetimibe 10 mg/day	ES of Salen et al[10] Patients ≥10 years of age with a diagnosis of sitosterolemia who	N=21 2 years	Primary: Percent change from baseline in sitosterol concentration	Primary: Ezetimibe resulted in significant mean percent reductions in sitosterol (-43.9%; 95% CI, -52.2 to -35.6; *P*<0.001). Progressively larger reductions in sitosterol were observed during the first 40 weeks of the OL extension phase, with maximal reductions achieved by 52 weeks of treatment (-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	had plasma sitosterol levels >0.12 mmol/L despite current treatment		Secondary: Percent change from baseline in campesterol concentration and LDL-C	47.6%; 95% CI, -50.9 to -44.4; *P* value not reported). Secondary: Ezetimibe resulted in significant mean reductions in campesterol (-50.8%; 95% CI, -58.8 to -42.7; *P*<0.001). Plasma concentrations progressively declined over the first 40 weeks of the trial reaching a maximum reduction of -53.6% (95% CI, -56.9 to -50.3) at week 52. After week 52, plasma concentrations remained generally stable for the remainder of the 104 week treatment period. Ezetimibe resulted in significant mean reductions from baseline in LDL-C (-13.1%; 95% CI, -25.0 to -1.2; *P*=0.032) at week 104.
Musliner et al[12] Ezetimibe 30 mg/day vs placebo All patients continued on OL ezetimibe 10 mg/day for the duration of the trial	DB, MC, PC, PG, RCT Patients ≥18 years of age with homozygous sitosterolemia who were taking ezetimibe 10 mg/day for ≥6 months prior to enrollment	N=27 26 weeks	Primary: Percent between-group change from baseline in sitosterol Secondary: Between-group changes in campesterol, lathosterol and achilles tendon thickness size; safety	Primary: Ezetimibe 40 mg/day resulted in a median percent change in sitosterol of 3.3 vs -10.0% with ezetimibe 10 mg/day, resulting in a between-group difference of 9.6% (*P*=0.180). Secondary: Median percent changes in campesterol were -9.7 vs -0.5% with ezetimibe 10 and 40 mg/day, resulting in a between-group difference of 7.6% (*P*=0.359). Median percent changes in lathosterol were 0.8 vs 1.1% with ezetimibe 40 and 10 mg/day, resulting in a between-group difference of 5.2% (*P*=0.701). Achilles tendon thickness increased slightly with ezetimibe 10 mg/day (2.2%) and remained unchanged with 40 mg/day, resulting in a nonsignificant between-group difference of -2.2% (*P*=0.404). Ezetimibe 40 mg/day was generally well tolerated. Laboratory safety parameters remained stable during the treatment period. No patients receiving ezetimibe in the trial experienced elevations in AST or AST greater than threefold or in creatinine kinase greater than tenfold the ULN.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hypercholesterolemia				
Pearson et al[13] Ezetimibe 10 mg/day Patients either received ezetimibe as monotherapy or in combination with a low or high dose statin.	RETRO Cohort Patients ≥18 years of age who took ezetimibe for ≥2 weeks	N=84 2 to 6 weeks	Primary: Change from baseline in fasting lipid profile, clinical effectiveness results stratified by primary vs secondary prevention Secondary: Percentage of patients able to achieve their LDL-C target levels, safety and tolerability	Primary: The mean reductions from baseline with ezetimibe were: TC, 1.11mmol/L (16.5%); LDL-C, 1.01 mmol/L (22.3%); TC:HDL, 0.68 mmol/L (12.8%) (*P*<0.001 for all). The HDL-C level increased by 0.06 mmol/L (4.6%) (*P*<0.001). Results were similar when stratified by primary (n=28) vs secondary (n=56) prevention. Among the primary prevention group, reductions in TC, LDL-C and TC:HDL were significant (*P*<0.001). In the secondary prevention group, the modifications in TC, LDL-C, HDL-C and TC:HDL-C were significant (*P*<0.001). LDL-C level reductions from baseline, stratified by drug regimen, were: -1.03 mmol/L (-20.5%; *P*<0.001) with ezetimibe, -1.19 mmol/L (-30.1%; *P*=0.0017) with ezetimibe plus a low dose statin, -0.95 mmol/L (-22.5%; *P*<0.001) with ezetimibe plus a high dose statin. Secondary: There were seven out of 34 (20.6%) patients receiving ezetimibe, five out of 12 (41.6%) patients receiving ezetimibe plus a low dose statin and 18 out of 38 (47.4%) patients receiving ezetimibe plus a high dose statin who achieved previously unattainable target LDL-C levels. There were four patients who discontinued therapy due to a treatment-related adverse event.
Bissonnette et al[14] Ezetimibe 10 mg/day plus a statin	MC, OL, PRO Patients ≥18 years of age with a confirmed diagnoses of hypercholesterolemia and elevated plasma LDL-C levels ≥2.5 mmol/L for patients at	N=953 6 weeks	Primary: Percentage of change from baseline in LDL-C Secondary: Percentage of patients who had achieved the	Primary: After six weeks, the addition of ezetimibe produced a significant mean reduction in LDL-C (30.5%; *P*<0.001). Secondary: After six weeks, 674 patients (80.5%) achieved the recommended target LDL-C levels. After six weeks, the addition of ezetimibe produced significant mean

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	high 10 year CAD risk, ≥3.5 mmol/L for patients at moderate 10 year CAD risk and ≥4.5 mmol/L for patients at low 10 year CAD risk and on a stable diet and statin regimen for ≥4 weeks before trial entry		recommended target LDL-C levels; percent change from baseline in TC, TG, HDL-C , apo B and TC:HDL-C; safety and tolerability	reductions in TC (20.8%), TG (10.1%), apo B (19.8%) and TC:HDL-C (19.9%) (*P*<0.001 for all). There were 50 mild, nonserious adverse events related to ezetimibe reported by 32 patients (3.4%). Frequently reported adverse events included constipation (0.7%), diarrhea (0.4%) and dizziness (0.4%).
Dujovne et al[15] Ezetimibe 10 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of primary hypercholesterolemia (LDL-C 130 to 250 mg/dL and plasma TG ≤350 mg/dL after adequate lipid lowering drug washout)	N=892 12 weeks	Primary: Percent change from baseline in LDL-C Secondary: Changes and percent changes from baseline in calculated LDL-C, TC, TG and HDL-C, HDL_2-C, HDL_3-C, apo AI, apo B and Lp(a); adverse events	Primary: Ezetimibe achieved a mean percent reduction from baseline in LDL-C of 16.9% compared to 0.4% with placebo (*P*<0.01). Secondary: There was a -17.68 vs 1.11% change in the calculated LDL-C from baseline with ezetimibe and placebo, respectively (*P*<0.01). Ezetimibe also significantly decreased apo B, TC and TG, as well as significantly increased HDL-C and HDL_3-C from baseline (*P*<0.01). However, there was no significant change in HDL_2-C and apo AI with ezetimibe compared to placebo (*P*=0.76 and *P*=0.50, respectively). Treatment-emergent adverse events occurred in 66% of patients receiving ezetimibe and 63% of patients receiving placebo. The most commonly reported adverse events with both treatments were upper respiratory tract infections and headache. The adverse events were considered to be mild to moderate and were similar between treatment groups (*P* value not reported).
Gonzalez-Ortiz et al[16] Ezetimibe 10 mg/day vs	DB, PC, RCT Obese patients 18 to 45 years of age with dyslipidemia	N=12 90 days	Primary: TC, LDL-C Secondary: HDL-C, TG, VLDL-C	Primary: Ezetimibe, compared to placebo, decreased TC (6.0 vs 4.2 mmol/L; *P*=0.011) and LDL-C (4.0 vs 2.2 mmol/L; *P*=0.003) without affecting insulin sensitivity. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				There were no significant differences in the changes in HDL-C, TG and VLDL-C between the two treatments (*P* values not significant).
Knopp et al[17] Ezetimibe 10 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of primary hypercholesterolemia (calculated LDL-C 130 to 250 mg/dL and TG ≤350 mg/dL)	N=827 12 weeks	Primary: Percentage change from baseline in LDL-C Secondary: Changes and percent changes from baseline in calculated LDL-C, TC, TG, HDL-C, HDL_2-C, HDL_3-C, apo AI, apo B and Lp(a); adverse events	Primary: The mean percent reduction from baseline in LDL-C was 17.7 vs 0.8% with ezetimibe and placebo (*P*<0.01). Secondary: Ezetimibe significantly decreased calculated LDL-C, apo B, TC and Lp(a), and significantly increased HDL-C and HDL_2-C (*P*≤0.01 for all). However, there was no significant change in HDL_3-C, apo AI and TG with ezetimibe compared to placebo (*P*=0.49, *P*=0.27 and *P*=0.09). The percentage of patients reporting treatment-emergent adverse events was 61 and 65% with ezetimibe and placebo. No individual adverse event was prevalent with either treatment and all were considered mild to moderate in severity. Overall, the adverse event profiles were similar between the two treatments (*P* value not reported).
Knopp et al[18] Ezetimibe 10 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of primary hypercholesterolemia (calculated LDL-C 130 to 250 mg/dL and plasma TG ≤350 mg/dL after adequate lipid lowering drug washout)	N=1,719 (Includes 827 patients from Knopp et al[17] plus 892 patients from a second trial) 12 weeks	Primary: Percentage change from baseline in LDL-C Secondary: Percentage change from baseline in TC, TG, HDL-C, HDL_2-C, HDL_3-C, apo AI, apo B and Lp(a); adverse events	Primary: In the pooled analysis, LDL-C was reduced by a mean 18.2% from baseline with ezetimibe compared to an increase of 0.9% with placebo (*P*<0.01). Secondary: Ezetimibe significantly decreased TC, apo B, Lp(a) and TG, and increased HDL-C compared to placebo (*P*<0.01). However, there were no significant differences in the change of HDL_2-C, HDL_3-C and apo AI between ezetimibe and placebo (*P*=0.08, *P*=0.06 and *P*=0.26). The overall adverse event profiles were similar between ezetimibe and placebo. Approximately 62% of patients receiving ezetimibe and 62% of patients receiving placebo reported adverse events. Also, there were no significant between group differences in the laboratory or clinical safety parameters or gastrointestinal, liver or muscle side effects.
Wierzbicki et al[19] (abstract)	PRO Patients with	N=200 Duration not	Primary: LDL-C, TG, HDL-C, CRP, ALT	Primary: Ezetimibe was associated with a seven and 11% reduction in LDL-C and apo B (*P* values not reported). The proportion of patients achieving LDL-C

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ezetimibe 10 mg/day vs placebo	refractory familial hyperlipidemia or intolerance to statin therapy	reported	Secondary: Not reported	<3 mmol/L increased from six to 18% (*P* value not reported). There were no significant differences in TG, HDL-C, CRP or ALT between the two treatments (*P* values not reported). Secondary: Not reported
Kalogirou et al[20] (abstract) Ezetimibe 10 mg/day vs placebo	PRO Patients with primary dyslipidemia and no evidence of CHD	N=50 16 weeks	Primary: Change in lipoprotein subfractions Secondary: Not reported	Primary: Ezetimibe significantly reduced baseline HDL-C from 1.5 to 1.4 mmol/L. The median change in HDL-C was -6.6% (*P*<0.001 vs placebo). A significant median reduction in TC from 7.1 to 5.8 mmol/L was also achieved with ezetimibe. The median change in TC was -15.5% with ezetimibe (*P*<0.001 vs placebo). Mean serum TG decreased from 1.5 to 1.4 mmol/L with ezetimibe. The median percent change was 9.3% (*P*<0.05 vs placebo). Mean serum LDL-C levels significantly decreased from 3.8 to 3.2 mmol/L with ezetimibe. The median percent change was -20.1% (*P*<0.001 vs placebo). Secondary: Not reported
Jelesoff et al[21] (abstract) Ezetimibe 10 mg/day vs placebo All patients received niacin.	RETRO Patients who received ezetimibe as add on therapy to stable doses of niacin and other lipid medications	N=53 Duration not reported	Primary: TC, LDL-C, TG, HDL-C Secondary: Percent change in patients meeting NCEP ATP III treatment guidelines	Primary: The addition of ezetimibe resulted in reductions of 18, 25 and 17% for TC, LDL-C and TG, respectively (*P*<0.001 for all). There were no significant differences in HDL-C (*P* value not significant). Secondary: Thirteen percent of patients met goals prior to the addition of ezetimibe, while 45% of patients met goals following the addition of ezetimibe (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Gagné et al[22] Ezetimibe 10 mg/day vs placebo All patients received a statin.	DB, MC, PC, RCT Patients ≥18 years of age currently on a stable daily dose of a statin for ≥6 weeks, must have been previously instructed on a cholesterol lowering diet, LDL-C at or above recommended target level for patient's risk category (<160 mg/dL for patients without CHD and ≤1 risk factor, <130 mg/dL for patients without CHD and ≥2 risk factors, ≤100 mg/dL for patients with established but stable CHD or CHD-equivalent disease)	N=769 8 weeks	Primary: Mean percentage change from baseline in LDL-C Secondary: Percentage of patients who achieved NCEP ATP III target levels for LDL-C, HDL-C, TC and TG; adverse events	Primary: The addition of ezetimibe produced an additional LDL-C reduction of 25.1% compared to 3.7% with placebo (*P*<0.001). Secondary: Including patients who were technically at LDL-C goal at baseline, 75.5% of those receiving ezetimibe achieved the prespecified NCEP ATP III target LDL-C levels compared to 27.3% of those receiving placebo (OR, 19.6; *P*<0.001). For those patients who were not at target LDL-C levels at baseline, 71.5 vs 18.9%, respectively, achieved target LDL-C goals (*P* values not reported). HDL-C was increased by 2.7% with the addition of ezetimibe compared to an increase of 1.0% with the addition of placebo, respectively (*P*<0.05). TG decreased by 14.0 and 2.9%, respectively (*P*<0.001). TC also improved significantly with the addition of ezetimibe (*P*<0.001). The overall incidence of treatment-related adverse events was similar between the two treatments (21 vs 17%; *P* value not reported).
Denke et al[23] Ezetimibe 10 mg/day vs placebo All patients received a statin.	DB, MC, PC, PG, RCT Patients ≥18 years of age with diabetes, metabolic syndrome without diabetes, or neither disorder who had LDL-C levels exceeding the NCEP ATP III goals who were taking a stable,	N=3,030 6 weeks	Primary: LDL-C reduction and additional lipid parameters, safety and tolerability Secondary: Not reported	Primary: After six weeks, the addition of ezetimibe reduced LDL-C in patients with diabetes and metabolic syndrome by 28 and 24% and increased LDL-C in patients with neither disease by 26% compared to a 3% reduction with the addition of placebo (*P*<0.001 for all). TG and HDL-C levels were significantly reduced in patients with diabetes and metabolic syndrome with the addition of ezetimibe compared to the addition of placebo (*P*<0.002). Non-HDL-C, TC, apo B:apo AI and CRP levels improved significantly in patients with diabetes and patients with elevated LDL-C levels without diabetes or metabolic syndrome with the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	approved dose of any statin, had been following a cholesterol lowering diet for ≥6 weeks prior to trial entry with TG levels ≤350 mg/dL			addition of ezetimibe compared to the addition of placebo (*P* values not reported). Drug-related adverse events occurred in 5.2% of patients receiving placebo and 5.1% receiving ezetimibe (*P* value not reported). Drug-related adverse events that led to drug discontinuation occurred in 1.6 vs 0.9% of patients. There were no significant differences between the two treatments in elevation of ALT, AST or in muscle CK beyond predefined limits. Secondary: Not reported
Pearson et al[24] EASE Ezetimibe 10 mg/day vs placebo All patients received a statin.	DB, MC, PC, PG Patients ≥18 years of age with hypercholesterolemia with LDL-C levels exceeding NCEP ATP III goals while taking a stable, approved dose of any statin, following a cholesterol lowering diet for ≥6 weeks	N=3,030 6 weeks	Primary: Percent reduction from baseline in LDL-C Secondary: Percentage of patients who achieved NCEP ATP III target LDL-C levels in the total population and by NCEP ATP III risk categories (<100 mg/dL for patients with CHD or CHD risk equivalent, <130 mg/dL for patients with multiple CHD risk factors conferring a 10 year risk of CHD ≤20% and <160	Primary: The addition of ezetimibe significantly reduced mean LDL-C levels by an additional 25.8% compared to a reduction of 2.7% with the addition of placebo (95% CI, -24.4 to -21.7; *P*<0.001). Secondary: Combination therapy resulted in an additional 23.8 to 25.7% reduction in LDL-C in all NCEP ATP III risk categories. Treatment differences were -24.0, -19.7 and -19.9% in the CHD or CHD risk equivalent, multiple risk factors and <2 risk factors groups, respectively (*P*<0.001 ezetimibe vs placebo for all). No significant differences were found according to age, sex or race category (*P*>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			mg/dL for patients with <2 CHD risk factors)	
Pearson et al[25] Ezetimibe 10 mg/day vs placebo All patients received a statin.	Subanalysis of Pearson et al[24] Patients >65 years old with hypercholesterolemia with LDL-C levels exceeding NCEP ATP III goals while taking a stable, approved dose of any statin, following a cholesterol lowering diet for ≥6 weeks	N=3,030 6 weeks	Primary: Mean change from baseline in LDL-C level; proportion of patients who reached LDL-C target across different races and ethnicities; change in serum cholesterol, TG and HDL-C Secondary: Not reported	Primary: Compared to placebo, the addition of ezetimibe achieved an LDL-C reduction of 23 (white patients), 23 (African American patients) and 21% (Hispanic patients) from baseline (*P*<0.001 for all). The difference in LDL-C lowering among the three races evaluated was not significant (*P*>0.5). A significantly greater proportion of patients receiving ezetimibe achieved their NCEP ATP III LDL-C goal (*P*<0.001). The addition of ezetimibe resulted in a significant reduction of 15.3 mg/dL in TC compared to the addition of placebo (*P*<0.001). The addition of ezetimibe resulted in a significant reduction of 11.5 mg/dL in TG compared to the addition of placebo (*P*<0.001). The addition of ezetimibe resulted in a significant increase of 2.1 mg/dL in HDL-C compared to the addition of placebo (*P*<0.001). Side effects were similar across treatments and races (*P* values not reported). Secondary: Not reported
Pearson et al[26] Ezetimibe 10 mg/day vs placebo All patients received	DB, MC, PG, PC, RCT Patients ≥18 years of age who followed a cholesterol lowering diet, were taking a stable approved dose of any United States marketed statin for ≥6	N=3,030 6 weeks	Primary: LDL-C and additional parameters, percentage of patients reaching LDL-C goal for the NCEP ATP III in racial and ethnic	Primary: The addition of ezetimibe significantly reduced LDL-C, TC, non-HDL-C and HDL-C compared to the addition of placebo (*P*<0.001). This effect was consistent across race and ethnicity (*P*>0.50 for treatment-by-race interactions). CRP level reduction was significant with the addition of ezetimibe compared to the addition of placebo (*P*<0.001). The treatment-by-race interaction was not significant (*P*=0.83), indicating a consistent treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
a statin.	weeks before trial entry, with LDL levels greater than the NCEP ATP III goal		subgroups Secondary: Safety and tolerability	effect of lowering CRP levels across race and ethnicity groups. The addition of ezetimibe significantly increased the percentage of patients attaining their LDL-C goal for the NCEP ATP III in African Americans by 63.0%, Hispanics by 64.8% and whites by 72.3% (*P*<0.001 vs placebo for all). Secondary: Ezetimibe was well tolerated and had an overall safety profile similar to that of placebo.
Simons et al[27] EASY Ezetimibe 10 mg/day vs placebo All patients received a statin.	OL Patients with CHD or diabetes mellitus who had already used ≥40 mg/day of a statin for ≥3 months with current TC >4 mmol/L for existing CHD or >6.5 mmol/L for diabetes or >5.5 mmol/L for diabetes if HDL-C <1.0 mmol/L	N=130 6 weeks	Primary: Percent change from baseline in LDL-C, percentage of patients who reached LDL-C goal <2.5 or <2.0 mmol/L, other lipid parameters Secondary: Not reported	Primary: LDL-C was reduced by 29% (95% CI, 25 to 34) with the addition of ezetimibe. A goal LDL-C <2.5 and <2.0 mmol/L was reached in 70 (95% CI, 59 to 79) and 50% (95% CI, 39 to 60) of patients receiving ezetimibe and placebo. TC and TG levels were reduced by 19 (95% CI, -21 to 16) and 11% (95% CI, -16 to -5) respectively, with the addition of ezetimibe and placebo. There were no significant changes in HDL-C with the two treatments (95% CI, 0 to 6). Secondary: Not reported
Blagden et al[28] (abstract) Ezetimibe 10 mg/day vs placebo All patients received	DB, MC, PC, RCT Patients with primary hypercholesterolemia and CHD	N=148 6 weeks	Primary: Mean percentage change from baseline in LDL-C Secondary: Percentage of patients achieving the new Joint British Society 2	Primary: The addition of ezetimibe provided significantly greater reductions in adjusted mean LDL-C level compared to the addition of placebo (-50.5 vs -36.5%; *P*<0.0001), equating to an additional 14.1% reduction (95% CI, -17.90 to -10.19). Secondary: A significantly higher proportion of patients receiving ezetimibe achieved the new Joint British Society 2 recommended LDL-C goal <2 mmol/L (62 vs 12%; *P*<0.0001) and the Joint British Society 2 minimum treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
atorvastatin 10 mg QD.			recommended LDL-C goal <2 mmol/L and the Joint British Society 2 minimum treatment standard <3 mmol/L, percentage of patients reaching LDL-C targets, safety and tolerability	standard <3 mmol/L (93 vs 79%; *P* value not reported) compared to placebo. Patients receiving ezetimibe were 12 times more likely to reach LDL-C targets (OR, 12.1; 95% CI, 5.8 to 25.1; *P*<0.0001) compared to patients receiving placebo. Clinical chemistry profiles and the incidence of adverse events were similar with both treatments (*P* value not reported).
Ballantyne et al[29] EXPLORER Ezetimibe 10 mg/day vs placebo All patients received rosuvastatin 40 mg/day	MC, OL, PG, RCT Patients ≥18 years of age with primary hypercholesterolemia and CHD or clinical evidence of atherosclerosis or a CHD risk equivalent (10 year CHD risk score >20%), and mean LDL-C between 160 to 250 mg/dL with the 2 last measurements within 15% of each other and TG <400 mg/dL	N=469 6 weeks	Primary: Percentage of patients achieving the NCEP ATP III LDL-C goal (<100 mg/dL) Secondary: Change from baseline in LDL-C, TC, non-HDL-C, TG, LDL-C:HDL-C, TC:HDL-C, non-HDL-C:HDL-C, apo B, CRP, HDL-C and apo AI; adverse effects	Primary: Significantly greater proportion of patients who added ezetimibe achieved their ATP III LDL-C goal compared to patients who added placebo (94.0 vs 79.1%; *P*<0.001). Secondary: The addition of ezetimibe was associated with a significantly greater reduction in LDL-C (70 vs 57%; *P*<0.001), TC (51 vs 42%; *P*<0.001), non-HDL-C (65 vs 52%; *P*<0.001), TG (35 vs 25%; *P*<0.001), LDL-C:HDL-C (72 vs 60%; *P*<0.001), TC:HDL-C (56 vs 45%; *P*<0.001), non-HDL-C:HDL-C (67 vs 55%; *P*<0.001), apo B (56 vs 45%; *P*<0.001) and CRP (46 vs 29%; *P*<0.001) compared to the addition of placebo. There was no significant difference in HDL-C increase (*P*=0.151) or apo AI reduction (*P*=0.202) between the two treatments. The frequency and types of adverse events were similar across the two treatments (31.5 vs 33.5%, respectively; *P* value not reported).
Landry et al[30] UK-HARP-II Ezetimibe 10 mg/day	MC, RCT Patients ≥18 years of age on predialysis with a creatinine level	N=203 6 months	Primary: LDL-C, TC, non-HDL-C, HDL-C, TG, apo B, apo AI	Primary: Both treatments produced significant reductions in LDL-C at one, three and six months compared to baseline (*P*<0.0001). The addition of ezetimibe was associated with reductions of 27, 26 and 21%, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo All patients received simvastatin 20 mg/day.	≥1.7 mg/dL, hemodialysis or peritoneal dialysis		Secondary: Safety and tolerability	The addition of ezetimibe was associated with reductions in TC of 16, 16 and 14% at one, three and six months, respectively. The addition of ezetimibe was associated with reductions in non-HDL-C of 24, 25 and 19% at one, three and six months, respectively. The addition of ezetimibe was associated with reductions in apo B of 15, 14 and 12% at one, three and six months, respectively. There were no significant effects on HDL-C, TG or apo AI (*P* values not significant), except for an increase of 7% in HDL-C at three months with the addition of ezetimibe (*P*=0.02). Secondary: There were no significant differences in muscle pain, muscle weakness, abdominal discomfort, nausea, constipation or appetite loss between the two treatments (*P* values not significant). More patients receiving ezetimibe reported diarrhea (27 vs 12%; *P*=0.009). There were no significant differences in CK levels or abnormal hepatic transaminase levels (*P* values not reported).
Patel et al[31] Ezetimibe 10 mg/day vs placebo All patients received simvastatin 20 mg/day.	DB, MC, PG, RCT Patients 18 to 75 years of age with primary hypercholesterolemia and CHD (≥3 months prior to baseline), not on lipid management therapy	N=153 6 weeks	Primary: Mean change from baseline in LDL-C level, proportion of patients who reached LDL-C target (<3 mmol/L) Secondary: Changes from baseline in serum cholesterol, TG and HDL-C	Primary: The addition of ezetimibe produced an additional LDL-C reduction of 14.6% compared to the addition of placebo (95% CI, 10.1 to 19.1; *P*<0.0001). A significantly greater proportion of patients receiving ezetimibe achieved their LDL-C goal compared to placebo (93 vs 75%, respectively; *P*<0.001). Patients receiving ezetimibe were 5.1 times more likely to reach target LDL-C levels compared to patients receiving placebo (95% CI, 1.8 to 15.0; *P*=0.003). Secondary: The addition of ezetimibe produced an additional TC reduction of 0.69 mmol/L compared to the addition of placebo (95% CI, 0.48 to 0.90;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P<0.0001). A significantly greater proportion of patients receiving ezetimibe reached TC target (<4 mmol/L) compared to patients receiving placebo (*P*<0.001). A greater reduction in TG was observed with the addition of ezetimibe compared to the addition of placebo (20.4 vs 12.4%; *P*=0.06). There was no significant difference in the change of HDL-C between the two treatments (~6% increase in each group; *P* value not reported). There was no significant difference in the incidence of treatment-emergent adverse events between the two treatments (40 vs 25%; *P*=0.07).
Rodney et al[32] Ezetimibe 10 mg/day vs placebo All patients received simvastatin 20 mg/day.	DB, MC, PG, RCT African-American patients with LDL-C ≥145 and ≤250 mg/dL and TG ≤350 mg/dL	N=247 12 weeks	Primary: Mean change from baseline in LDL-C level, TC, TG, HDL-C, non-HDL-C and apo B Secondary: Not reported	Primary: The addition of ezetimibe produced significant reductions in LDL-C (45.6 vs 28.3%; *P*≤0.01), TC (33 vs 21%; *P*≤0.01), TG (22 vs 15; *P*≤0.01), non-HDL-C (42 vs 26; *P*≤0.01) and apo B (38 vs 25; *P*≤0.01) compared to the addition of placebo. There was no significant difference in the change of HDL-C between the two treatments (~1 to 2% increase in each group; *P* value not reported). There was no significant difference in side effects between the two treatments (*P* value not reported). Secondary: Not reported
Masana et al[33] Ezetimibe 10 mg/day vs placebo	DB, ES, MC, RCT Patients ≥18 years of age with primary hypercholesterolemia, currently taking a stable daily dose of a statin for ≥6 weeks,	N=355 48 weeks	Primary: Percent change from baseline to week 12 in LDL-C Secondary: Percent change from baseline to	Primary: At week 12, the addition of ezetimibe produced a significant 27% reduction in LDL-C compared to the addition of placebo (*P*<0.001). The benefit was maintained up to 48 weeks (*P* value not reported). Secondary: At week 12, the addition of ezetimibe produced significant reductions in TC, TG, non-HDL-C, LDL-C:HDL-C and TC:HDL-C compared to the addition of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients received simvastatin 10 mg/day, titrated up to 80 mg/day	with LDL-C above the NCEP ATP II guideline target level, TG <350 mg/dL		week 12 in TC, TG, HDL-C, non-HDL-C, LDL-C:HDL-C and TC:HDL-C	placebo (*P*<0.001). At week 12, the addition of ezetimibe produced an increase in HDL-C of 2.6% compared to the addition of placebo (*P*=0.07). Treatment-related adverse effects were similar between the two treatments (19 and 17%, respectively; *P* value not reported). There were no cases of rhabdomyolysis or myopathy during the trial.
Farnier et al[34] Ezetimibe 10 mg/day vs fenofibrate (micronized) 160 mg/day vs ezetimibe 10 mg/day plus fenofibrate (micronized) 160 mg/day vs placebo	DB, MC, PC, RCT Patients 18 to 75 years of age with mixed hyperlipidemia and no CHD, CHD equivalent disease (except for type 2 diabetes) or a 10 year CHD risk >20%	N=619 12 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent change from baseline in other lipid, non-lipid and lipoprotein parameters	Primary: The mean percent reduction in LDL-C was significantly greater with combination therapy compared to monotherapy with either agent (*P*<0.001 for both). The corresponding reductions were -13.4, -5.5 and -20.4% with ezetimibe, fenofibrate and combination therapy. Secondary: When compared to fenofibrate or ezetimibe, significant reductions in apo B, non-HDL-C and LDL-C were observed with combination therapy (*P*<0.001 for both). When compared to placebo, significant decreases in TG and significant increases in HDL-C levels were observed with combination therapy and fenofibrate (*P*<0.001). The percent changes were as follows: -11.8% in TC, 3.9% in HDL-C, -11.1% in TG and -6.1% in hsCRP with ezetimibe; -10.8, 18.8, -43.2 and -28.0% with fenofibrate and -22.4, 19.0, -44.0 and -27.3% with combination therapy (*P*<0.05 for all).
McKenney et al[35] Ezetimibe 10 mg/day vs	ES of Farnier et al[34] Patients with mixed hyperlipidemia (LDL-C 130 to 220 mg/dL and TG 200 to 500 mg/dL)	N=576 48 weeks	Primary: Percent change from baseline in LDL-C Secondary:	Primary: Combination therapy significantly reduced LDL-C compared to placebo (-22.0 vs -8.6; *P*<0.001). Secondary: Combination therapy significantly reduced TC (-23.2 vs -13.6; *P*<0.001), TG

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
fenofibrate (micronized) 160 mg/day vs ezetimibe 10 mg/day plus fenofibrate (micronized) 160 mg/day vs placebo			Percent change from baseline in TC, HDL-C, TG, non-HDL-C, apo B, apo AI and hsCRP	(-46.0 vs -41.8; *P*=0.002), non-HDL-C (-31.6 vs -19.4; *P*<0.001) and apo B (-25.2 vs -16.2; *P*<0.001) compared to placebo. Combination therapy significantly increased HDL-C compared to placebo (20.9 vs 17.8; *P*=0.02). There were no significant differences in apo AI or hsCRP (*P* value not significant).
Ballantyne et al[36] Ezetimibe 10 mg/day vs atorvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day plus atorvastatin 10, 20, 40 or 80 mg/day vs placebo	DB, PC, RCT Patients ≥18 years of age with primary hypercholesterolemia (LDL-C 145 to 250 mg/dL and TG ≤350 mg/dL)	N=628 12 weeks	Primary: Percentage reduction from baseline in LDL-C Secondary: Changes from baseline in calculated LDL-C, TC, TG, HDL-C, TC:HDL-C, apo B, non-HDL-C, HDL_2-C, HDL_3-C, apo AI, Lp(a) and direct LDL-C:HDL-C; adverse events	Primary: There was a significantly greater mean reduction in LDL-C with combination therapy compared to either atorvastatin (*P*<0.01) or ezetimibe (*P*<0.01). Mean changes in LDL-C ranged from -50 to -60% with combination therapy compared to -35 to -51% with atorvastatin (*P*<0.01). Secondary: Calculated LDL-C was also significantly reduced more commonly with combination therapy compared to all doses of atorvastatin (*P*<0.01 for all). Greater reductions in LDL-C, TC and TG were observed with increasing doses of atorvastatin; however, there was not a favorable dose response with HDL-C. There were similar reductions in LDL-C (50 vs 51%), TC:HDL-C (43 vs 41%) and TG (31 vs 31%) with combination therapy (atorvastatin 10 mg) and atorvastatin 80 mg, respectively. However, there was a significantly greater increase in HDL-C (9 vs 3%) with combination therapy (*P* value not reported). Reductions in apo B, non-HDL-C and LDL-C:HDL-C were significantly greater with combination therapy compared to atorvastatin (*P*<0.01 for all)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				and ezetimibe (*P*<0.01 for all). Increases in HDL_2-C (*P*=0.53), HDL_3-C (*P*=0.06), apo AI (*P*=0.31) and Lp(a) (*P*=0.50) did not differ significantly between combination therapy and atorvastatin. There also was no significant difference between combination therapy and ezetimibe for increases in these same parameters (HDL_2-C; *P*=0.08, HDL_3-C; *P*=0.67, apo AI; *P*=0.80 and Lp(a); *P*=0.92). Combination therapy was well tolerated. Treatment-emergent adverse events were reported in 17% of patients receiving atorvastatin and 23% of patients receiving combination therapy. The majority of adverse events were mild to moderate in severity (*P* value not reported).
Kerzner et al[37] Ezetimibe 10 mg/day vs lovastatin 10, 20 or 40 mg/day vs ezetimibe 10 mg/day plus lovastatin 10, 20 or 40 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with mean plasma LDL-C 145 to 250 mg/dL as calculated by Friedewald equation and mean TG ≤350 mg/dL	N=548 12 weeks	Primary: Percentage decrease from baseline in LDL-C Secondary: Changes from baseline in calculated LDL-C, TC, TG, HDL-C, apo B, non-HDL-C, HDL_2-C, HDL_3-C, apo AI and LDL-C:HDL-C; adverse events	Primary: The reduction in LDL-C was significantly greater with combination therapy compared to either lovastatin or ezetimibe (*P*<0.01 for both). The mean percentage decrease in LDL-C with combination therapy was significantly greater than the decrease obtained from the corresponding lovastatin dose or next higher dose of lovastatin (*P*<0.01). The mean percentage change in LDL-C achieved with combination therapy (lovastatin 10 mg) was similar to lovastatin 40 mg (*P*=0.10). Secondary: In comparison to lovastatin, combination therapy significantly improved calculated LDL-C, TC, TG, HDL-C, apo B, non-HDL-C, HDL_2-C, HDL_3-C, LDL-C:HDL-C (*P*<0.01 for all) and apo AI (*P*=0.04). Combination therapy significantly increased HDL-C with lovastatin doses of 20 and 40 mg compared to the same lovastatin dose administered as monotherapy (*P*<0.01 and *P*<0.02, respectively), and significantly decreased TG levels (*P*<0.01 for both). Treatment-related adverse events were reported by 16% of patients receiving lovastatin and 17% of patients receiving combination therapy. The safety profile for combination therapy was similar to that for lovastatin and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				placebo (*P* values not reported).
Melani et al[38] Ezetimibe 10 mg/day vs pravastatin 10, 20 or 40 mg/day vs ezetimibe 10 mg/day plus pravastatin 10, 20 or 40 mg/day vs placebo	DB, MC, PC, RCT Patients 20 to 86 years of age with primary hypercholesterolemia (LDL-C 3.8 to 6.5 mmol/L as calculated by the Friedewald equation and TG ≤4.0 mmol/L)	N=538 12 weeks	Primary: Percent change from baseline LDL-C Secondary: Mean and percent changes from baseline in calculated LDL-C, TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo AI, apo B, HDL_2-C, HDL_3-C and Lp(a)	Primary: A mean percent change of -38 and -24% in LDL-C with combination therapy and pravastatin were observed (*P*<0.01). Combination therapy achieved a mean percentage change in LDL-C ranging from -34 to -41% compared to -20 to -29% with pravastatin (all doses). When combination therapy was compared to its corresponding pravastatin dose, the incremental mean percentage reductions in LDL-C were significant in favor of combination therapy (*P*≤0.01). In addition, combination therapy (pravastatin 10 mg) produced a larger mean percentage reduction in LDL-C compared to pravastatin 40 mg (*P*≤0.05). Secondary: In comparison to pravastatin, combination therapy improved calculated LDL-C, TG, TC, apo B, non-HDL-C, LDL-C:HDL-C and TC:HDL-C (*P*<0.01 for all). Both direct and calculated LDL-C levels at all pravastatin doses were significantly reduced with combination therapy (*P*<0.01). TG was also significantly reduced with combination therapy (pravastatin 10 and 20 mg) compared to pravastatin (*P*<0.05). Although combination therapy (pravastatin 10 and 40 mg) produced greater increases in HDL-C, it was not significant (*P* values not reported). The differences in change in HDL_2-C, HDL_3-C, apo AI and Lp(a) between combination therapy and pravastatin were not significant (*P* values not significant). Combination therapy was well tolerated and the overall safety profile was similar to pravastatin and placebo. There was no evidence to suggest that combination therapy would increase the risk of developing any nonlaboratory adverse event (*P* value not reported).
Chenot et al[39] Simvastatin 40 mg/day	RCT Patients admitted for an acute MI (with or	N=60 7 days	Primary: Change from baseline to days two, four and seven	Primary: Combination therapy produced a significant LDL-C reduction from baseline on days two, four and seven (27, 41 and 51%, respectively; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs simvastatin 40 mg/day plus ezetimibe 10 mg/day vs no lipid lowering therapy	without ST-segment elevation) to the coronary unit, with pain that started within 24 hours of admission		in LDL-C; proportion of patients achieving an LDL-C <70 mg/dL Secondary: Not reported	Simvastatin produced a significant LDL-C reduction from baseline on days two, four and seven (15, 27 and 25%, respectively; *P*<0.001). There was no significant reduction in LDL-C with no lipid lowering therapy (*P*≥0.09). Combination therapy achieved significant LDL-C reductions compared to simvastatin at days four (*P*=0.03) and seven (*P*=0.002). A greater proportion of patients receiving combination therapy achieved an LDL-C <70 mg/dL, compared to those receiving simvastatin at days four (45 vs 5%) and seven (55 vs 10%, respectively) (*P* values not reported). Secondary: Not reported
Davidson et al[40] Ezetimibe 10 mg/day plus simvastatin 10, 20, 40 or 80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day vs placebo	DB, MC, RCT Patients >18 years of age with primary hypercholesterolemia	N=668 20 week	Primary: Mean percent change from baseline in LDL-C Secondary: Mean and percent change from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B, apo AI and CRP	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to simvastatin (49.9 vs 36.1%; *P*<0.001). Similar results were observed with combination therapy compared to ezetimibe (49.9 vs 18.1%; *P*<0.001). Combination therapy (simvastatin 10 mg) and simvastatin 80 mg produced a 44% reduction in LDL-C at 12 weeks (*P* value not reported). Secondary: At each corresponding dose of simvastatin, combination therapy was associated with a significant reduction in LDL-C at 12 weeks (*P*<0.001). Combination therapy was associated with a significant reduction in LDL-C at 12 weeks, compared to the next highest dose of simvastatin (*P*<0.01). Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non-HDL-C and apo B at 12 weeks compared to simvastatin (*P*<0.01 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Averaged across all doses, combination therapy was associated with a significant increase in HDL-C compared to simvastatin (*P*=0.03). Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non–HDL-C and apo B at 12 weeks compared to ezetimibe (*P*<0.01 for all). Averaged across all doses, combination therapy was associated with a significant increase in HDL-C compared to ezetimibe (*P*=0.02). A significantly greater proportion of patients receiving combination therapy experienced a reduction in LDL-C >50% from baseline compared to simvastatin (*P* value not reported). Treatment-related adverse effects were similar in the pooled simvastatin and combination therapy groups (72 vs 69%, respectively; *P* value not reported).
Goldberg et al[41] Ezetimibe 10 mg/day plus simvastatin 10, 20, 40 or 80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day vs placebo	DB, MC, RCT Patients ≥18 years of age with primary hypercholesterolemia, ALT and AST ≤2 times the ULN, no active liver disease, CK ≤1.5 times the ULN	N=887 20 weeks	Primary: Mean percent change from baseline in LDL-C Secondary: Mean and percent changes from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B, apo AI and CRP; proportion of patients reaching their NCEP ATP III LDL-C goal <130 or <100 mg/dL at	Primary: Averaged across all doses, combination therapy was associated with a significant 14.8% reduction in LDL-C at 12 weeks compared to simvastatin (53.2 vs 38.5%; *P*<0.001). Secondary: At each corresponding dose of simvastatin, combination therapy was associated with a significant reduction in LDL-C at 12 weeks (*P*<0.001). Combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to the next highest dose of simvastatin (*P*<0.001). Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B and CRP at 12 weeks compared to simvastatin (*P*<0.001 for all). Averaged across all doses, combination therapy resulted in a greater proportion of patients reaching their NCEP ATP III LDL-C goal <130 or

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			12 weeks	<100 mg/dL at 12 weeks compared to simvastatin (92 and 82% vs 82 and 43%, respectively; *P*<0.001). Averaged across all doses, combination therapy was not associated with a significant change in HDL-C compared to simvastatin (*P*=0.53). Treatment-related adverse effects were similar in the pooled simvastatin and combination therapy groups, but were more frequent than with ezetimibe and placebo (13, 14, 9 and 9%, respectively; *P* values not reported).
Bays et al[42] Ezetimibe/ simvastatin 10/10, 10/20, 10/40 or 10/80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day vs placebo	DB, MC, RCT Patients 18 to 80 years of age with primary hypercholesterolemia with LDL-C >145 but ≤150 mg/dL and TG ≤350 mg/dL	N=1,528 24 weeks	Primary: Percent change from baseline in LDL-C Secondary: Mean and percent changes from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B, apo AI and CRP; proportion of patients reaching their NCEP ATP III LDL-C goal of <130, <100 or <70 mg/dL at 12 weeks	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to simvastatin (53 vs 39%; *P*<0.001) and ezetimibe (53 vs 18.9%; *P*<0.001). Secondary: At each corresponding dose of simvastatin, combination therapy was associated with a significant reduction in LDL-C at 12 weeks (*P*<0.001). Combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to the next highest dose of simvastatin (*P*<0.001). Averaged across all doses, combination therapy resulted in a greater proportion of patients reaching their NCEP ATP III LDL-C goal <130, <100 or <70 mg/dL at 12 weeks compared to simvastatin (92.2, 78.6 and 38.7 vs 79.2, 45.9 and 7.0%, respectively; *P*<0.001 for al). Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B and CRP at 12 weeks compared to simvastatin (*P*<0.001 for all). Averaged across all doses, combination therapy was not associated with a significant change in HDL-C compared to simvastatin (*P*=0.607). Treatment-related adverse effects were similar in the pooled simvastatin,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				combination and ezetimibe groups, but were more frequent than placebo (14.8, 15.1, 12.8 and 8.1%, respectively; *P* values not reported).
Ose et al[43] Simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe/simvastatin 10/10, 10/20, 10/40 or 10/80 mg/day vs ezetimibe 10 mg/day vs placebo	DB, MC, RCT Patients 22 to 83 years of age with primary hypercholesterolemia (LDL-C 145 to 250 mg/dL and TG <350 mg/dL)	N=1,037 14 weeks	Primary: Change from baseline in LDL-C level, TG, TC, non-HDL, CRP, LDL-C:HDL-C and TC:HDL-C; proportion of patients reaching LDL-C target (<100 or <70 mg/dL) Secondary: Not reported	Primary: Across all doses, combination therapy was associated with a significant reduction in LDL-C compared to simvastatin (53.7 vs 38.8%; *P*<0.001). Across all doses, combination therapy was associated with a significant reduction in TG, TC, non-HDL, CRP, LDL-C:HDL-C and TC:HDL-C compared to simvastatin (*P*<0.001 for all). A significantly greater proportion of patients receiving combination therapy achieved LDL-C <100 mg/dL compared to simvastatin (79.2 vs 47.9%; *P*<0.001). Similar results were observed with a LDL-C goal <70 mg/dL (30.4 vs 7.0%; *P*<0.001). The incidence of drug-related adverse effects was similar with combination therapy and simvastatin (7.4 vs 5.5%, respectively; *P* value not reported). Secondary: Not reported
Feldman et al[44] Ezetimibe/ simvastatin 10/10, 10/20, 10/40 or 10/80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day	MA (3 DB, PC, RCTs) Patients with primary hypercholesterolemia	N=3,083 28 weeks	Primary: Percent change from baseline in LDL-C, TG, non-HDL-C, apo B and CRP; achievement of LDL-C <100 mg/dL at week-12 among patients <65 and ≥65 years of age Secondary: Not reported	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C, TG, non-HDL-C, apo B and CRP at 12 weeks compared to simvastatin (*P*<0.001 for all). These affects did not differ between the older and younger patients (*P* value not reported). Combination therapy and simvastatin produced comparable increases in HDL-C (8 vs 7%, respectively; *P* value not reported). Significantly more patients, in all age groups, receiving combination therapy, regardless of the dose, achieved an LDL-C level <100 mg/dL at week 12 compared to patients receiving simvastatin (79 vs 42%; *P*<0.001). Similar results were observed with a LDL-C goal <70 mg/dL (37 vs 6%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				Treatment-related adverse effects were similar with simvastatin and combination therapy, regardless of dose used and age group (*P* values not reported). Secondary: Not reported
Pearson et al[45] Atorvastatin 10, 20, 40 or 80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day vs ezetimibe 10 mg/day plus simvastatin 10, 20, 40 or 80 mg/day vs placebo	MA (1 AC, DB, 3 PRO) Patients with primary hypercholesterolemia	N=4,373 12 weeks	Primary: Change from baseline in LDL-C level and CRP, proportion of patients reaching LDL-C target (<100 or <70 mg/dL) Secondary: Not reported	Primary: Across all doses, combination therapy was associated with significant reductions in LDL-C compared to simvastatin (52.5 vs 38.0%; *P*<0.001) and atorvastatin (53.4 vs 45.3%; *P*<0.001). Across all doses, combination therapy was associated with significant reductions in CRP compared to simvastatin (31.0 vs 14.3%; *P*<0.001). No significant difference was observed between combination therapy and atorvastatin (25.1 vs 24.8%; *P* value not reported). The reduction in CRP was not significantly different between simvastatin 10 mg and placebo (*P*>0.10). A significantly greater proportion of patients receiving combination therapy achieved LDL-C <100 mg/dL compared to simvastatin (78.9 vs 43.1%; *P*<0.001) and atorvastatin (79.8 vs 61.9%; *P*<0.001). Similar results were observed with an LDL-C goal <70 mg/dL (37.0 vs 5.7%; *P*<0.001 and 36.2 vs 16.8%; *P*<0.001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Okada et al[46] Ezetimibe 10 mg/day plus atorvastatin 10 mg/day vs ezetimibe 10 mg/day plus rosuvastatin 2.5 mg/day vs atorvastatin 20 mg/day vs rosuvastatin 5 mg/day	MC, OL, PG, PRO, RCT Patients ≥20 years of age with coronary artery disease whose LDL-C levels were ≥100 mg/dl after at least four weeks of treatment with atorvastatin 10 mg/day or rosuvastatin 2.5 mg/day	N=171 12 weeks	Primary: Change from baseline in LDL-C, HDL, TG, TC, proportion of patients achieving an LDL-C <100 mg/dL Secondary: Not reported	Primary: In both the ezetimibe plus statin group and the double-dose statin group, LDL-C levels decreased from baseline to 12 weeks; however, the decrease was significantly greater in the ezetimibe plus statin group (24.7±12.1 vs -16.4±11.7%; *P*<0.01). The proportion of patients achieving the LDL-C goal of <100 mg/dL was significantly higher in the ezetimibe plus statin group compared to doubling the statin dose (76.1 vs 58.9%; *P*<0.05). The HDL-C level increased in the ezetimibe plus statin group and decreased in the double-dose statin group (2.7±16.6 vs -1.0±17.2%; *P*<0.05). The triglyceride level decreased for patients receiving ezetimibe plus a statin compared to an increase in triglycerides for patients who received an increased dose of statin (-9.4±30.2 vs 3.1± 40.7%, *P*<0.05).
Ansquer et al[47] Fenofibrate 145 mg/day vs ezetimibe 10 mg/day vs fenofibrate 145 mg/day plus ezetimibe 10 mg/day	DB, MC, PG, PRO, RCT Patients 18 to 70 years of age with type IIb dyslipidemia and features of the metabolic syndrome according to the NCEP ATP III	N=180 12 weeks	Primary: Percent change from baseline in TG and HDL-C Secondary: Percent change from baseline in LDL-C, non-HDL-C, remnant-like particle cholesterol, TC:HDL-C, LDL size, apo AI, apo AII, and apo B:AI	Primary: Combination therapy reduced TG (-38.8%) to a similar extent as fenofibrate (-38.8%); however, combination therapy produced a slightly more pronounced increase in HDL-C (11.5 vs 7.9%; *P*=0.282). Secondary: Combination therapy reduced LDL-C (-36.2%) significantly more than either fenofibrate (-22.4%) or ezetimibe (-22.8%) (*P*<0.001 for both). The proportion of patients who achieved the NCEP ATP III target for intermediate cardiovascular risk (<130 mg/dL) was higher with combination therapy (56%) than with either of the monotherapies (fenofibrate, 23% and ezetimibe, 29%). Combination therapy was more effective in reducing non-HDL-C (-36.2%)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				than either fenofibrate (-24.8%) or ezetimibe (-20.9%). However, the proportion of patients who reached the NCEP ATP III target for intermediate cardiovascular risk (<160 mg/dL) with combination therapy (58%) was more than the sum of the percentages obtained with the monotherapies (46%). The difference between combination therapy (-36.2%) and fenofibrate (-30.7%) in remnant-like particle cholesterol was not significant; ezetimibe was less effective (-17.3%; *P*<0.001). The effect of combination therapy on LDL particle size (2.1%) was similar to that of fenofibrate (1.9%) (*P* value not reported). Combination therapy significantly increased apo AI (7.9 vs 5.1%) and AIII (24.2 vs 21.2%) compared to fenofibrate (*P* values not reported). Combination therapy was more effective in reducing apo B (-33.3%) than either fenofibrate or ezetimibe. The changes in apo B-containing lipoproteins with combination therapy resulted in clear improvements in risk ratios, with mean and median end-of-treatment values <4.0 for TC:HDL-C and <0.7 for apo B:apo AI.
Kumar et al[48] 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).
Coll et al[49] Ezetimibe 10 mg/day	RCT Patients ≥18 years of	N=20 6 weeks	Primary: LDL-C, TC, endothelial function	Primary: Ezetimibe produced a 20% (*P*=0.002) LDL-C reduction and a 10% TC reduction (*P*=0.003).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs fluvastatin ER 80 mg/day	age with HIV receiving stable HAART for ≥6 months and fasting LDL-C ≥3.30 mmol/L		Secondary: Not reported	Fluvastatin ER produced a 24% (*P*=0.02) LDL-C reduction and a 17% TC reduction (*P*=0.06). There were no significant differences in lipid lowering ability between the two treatments (*P* values not reported). Ezetimibe did not produce significant changes in endothelial function, while fluvastatin ER produced an increase in the rate of endothelial function by 11% (*P*=0.5). Secondary: Not reported
Conrad et al[50] Atorvastatin 40 mg/day plus ezetimibe 10 mg/day vs atorvastatin 80 mg/day	DB, MC, PG, RCT Patients 18 to 80 years of age at NCEP ATP III high risk with CHD or CHD risk equivalent, LDL-C ≥70 and ≤160 mg/dL and taking a stable dose of a statin of equal or lesser potency than atorvastatin 40 mg/day or were taking atorvastatin 40 mg/day with good adherence or were stain, ezetimibe or ezetimibe/simvastatin naïve	N=568 6 weeks	Primary: Proportion of patients reaching LDL-C <70 mg/dL; percent changes from baseline in LDL-C, HDL-C, non-HDL-C, TC, TG, apo B, apo AI, TC:HDL-C, LDL-C/HDL-C, apo B/AI, non-HDL-C/HDL-C and hsCRP Secondary: Adverse events	Primary: The proportion of patients reaching LDL-C <70 mg/dL was greater with combination therapy, with a larger between-treatment difference in proportions in patients with metabolic syndrome (without type 2 diabetes) compared to patients with type 2 diabetes or neither condition, which had similar between-treatment differences in proportions. In patients with type 2 diabetes, metabolic syndrome and those with neither condition, the reduction in LDL-C was greater in patients treated with combination therapy compared to doubling the dose of atorvastatin. The mean between-treatment difference (95% CI) was -17.4 (-21.7 to -13.1), -16.0 (-22.3 to -9.6) and -14.3% (-20.9 to -7.8). Reductions in TC, non-HDL-C and apo B were greater with combination therapy in all three patient populations. The magnitude of the differences between treatments in TG was numerically greater in patients with type 2 diabetes compared to the other two patient populations, but overall the differences were relatively small. There were no appreciable changes or between-treatment differences in HDL-C and apo AI in any patient population. The percent reduction in lipid ratios was greater with combination therapy in all three patient populations and between-treatment differences were consistent. Combination therapy resulted in numerically greater reductions from baseline in hsCRP in all three patient populations. The between-treatment differences in patients with metabolic syndrome (-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				11.8) and type 2 diabetes (-10.3) were larger than in patients with neither condition (-3.2). Secondary: There were comparable proportions of patients with one or more adverse event in the type 2 diabetes and metabolic syndrome populations regardless of treatment. The most commonly reported adverse events were gastrointestinal related.
Uemura et al[51] Ezetimibe 10 mg/day plus atorvastatin 10 mg/day vs atorvastatin 20 mg	AC, DB, OL, PRO, XO Patients with impaired glucose tolerance or type 2 diabetes who were receiving atorvastatin (10 mg/day) for dyslipidemia, and had coronary artery disease with angiographic stenosis (≥50% diameter stenosis on quantitative coronary angiography) or a history of coronary revascularization for stable angina	N=39 24 weeks	Primary: Change from baseline in MDA-LDL, HDL, triglycerides, Apo AI, Apo B and RLP Secondary: Not reported	Primary: Ezetimibe plus atorvastatin significantly reduced the serum concentration of MDA-LDL from 109.0 ± 31.9 IU/L at baseline to 87.7 ± 29.4 IU/L after 12 weeks (*P*=0.0009). The MDA-LDL was not significantly decreased in patients receiving atorvastatin monotherapy (from 109.0 ± 31.9 IU/L to 106.0 ± 34.9 IU/L (*P*=NS). The MDA-LDL level was significantly lower after treatment with ezetimibe plus atorvastatin compared to monotherapy with a higher dose of atorvastatin (*P*=0.0006). Both treatments significantly improved HDL from baseline (*P*<0.05 for both); however, there was no difference between the treatment groups (P>0.05). There were no statistically significant differences between combination therapy and atorvastatin monotherapy with regard to a reduction in serum triglycerides (*P*>0.05). Both treatment regimens significantly reduced total cholesterol from baseline (*P*<0.05 for both comparisons); however, combination therapy reduced total cholesterol significantly further than atorvastatin monotherapy (147.8 ± 21.3 vs 164.3 ± 25.8 mg/dL; *P*<0.05). Combination treatment with ezetimibe and atorvastatin increased Apo AI compared to baseline (*P*<0.05). Both treatment groups reduced Apo B compared to their respective baseline values (*P*<0.05 for both).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Combination therapy was associated with a statistically significant reduction in Apo B compared to atorvastatin monotherapy (73.9 ± 18.0 mg/dL vs 83.7 ± 17.2 mg/dL, respectively; *P*<0.05). A significantly lower Apo B/Apo AI ratio was achieved with combination therapy compared to atorvastatin monotherapy (*P*<0.05). No statistically significant difference occurred between combination therapy and atorvastatin monotherapy with regard to RLP-cholesterol (*P*>0.05).
Piorkowski et al[52] Ezetimibe 10 mg/day plus atorvastatin 10 mg/day vs atorvastatin 40 mg	RCT Patients 18 to 80 years of age with clinically stable angiographically documented CHD, receiving aspirin and clopidogrel and LDL-C >2.5 mmol/L despite therapy with atorvastatin 10 to 20 mg/day	N=56 4 weeks	Primary: Change from baseline in LDL-C, TG, liver transaminases, CK and HDL-C; percentage of patients achieving the NCEP ATP III LDL-C goal (≤2.5 mmol/L) Secondary: Not reported	Primary: Both treatments were associated with a significant reduction in LDL-C (*P*<0.005), with no significant differences between the two treatments in the degree of reduction (*P* value not reported). Both treatments were associated with a significant reduction in TG (atorvastatin; *P*<0.005 and combination therapy; *P*<0.05, respectively). Neither treatment produced significant changes in liver transaminases, CK or HDL-C (*P* values not reported). There was no significant difference between the two treatments in the percentage of patients achieving the NCEP ATP III LDL-C goal (≤2.5 mmol/L) (*P* value not reported). Secondary: Not reported
Stein et al[53] Ezetimibe 10 mg/day plus atorvastatin 10 mg/day, titrated up to 40 mg/day	DB, DD, MC Patients ≥18 years of age with primary hypercholesterolemia and documented CHD, ≥2	N=621 14 weeks	Primary: Percentage of patients achieving LDL-C ≤100 mg/dL Secondary: Effects on other	Primary: A significantly greater percentage of patients receiving combination therapy achieved LDL-C ≤100 mg/dL compared to atorvastatin (22 vs 7%; *P*<0.01). Secondary: Combination therapy was associated with significant reductions in LDL-C, TC and TG compared to atorvastatin (*P*<0.01 for all). Respectively, mean

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs atorvastatin 20 mg/day, titrated up to 80 mg/day	cardiovascular risk factors, or heterozygous FH with LDL-C ≥130 mg/dL despite treatment with diet and atorvastatin 10 mg/day		lipid parameters at four weeks	percent changes with combination therapy compared to atorvastatin were: -22.8 vs -8.6%, -17.3 vs -6.1% and -9.3 vs -3.9% (median change). In general, nonsignificant changes were observed for HDL-C levels (*P* values not reported).
Constance et al[54] Atorvastatin 20 mg/day vs ezetimibe 10 mg/day plus simvastatin 20 or 40 mg/day All patients received atorvastatin 10 mg/day during a 4 week run in period.	DB, MC, PG, RCT Patients ≥18 years of age, with type 2 diabetes, HbA_{1C} ≤10%, ALT/AST levels <1.5 times the ULN and CK <1.5 times the ULN	N=661 6 weeks	Primary: Change from baseline in LDL-C Secondary: Changes from baseline in TC, HDL-C, TG, non-HDL-C, apo B, LDL-C:HDL-C and TC:HDL-C	Primary: Across all doses, combination therapy was associated with a significant reduction in LDL-C compared to atorvastatin (*P*≤0.001). Secondary: Across all doses, combination therapy was associated with significant reductions in TC, non-HDL, apo B, LDL-C:HDL-C and TC:HDL-C compared to atorvastatin (*P*≤0.001 for all). Combination therapy (simvastatin 40 mg) was associated with a significant reduction in CRP compared to atorvastatin (*P*=0.006). A significantly greater proportion of patients receiving combination therapy achieved LDL-C <2.5 mmol/L compared to atorvastatin (90.5 [10/20 mg], 87.0 [10/40 mg] and 70.4%, respectively; *P*≤0.001). The incidence of drug-related adverse effects was similar with combination therapy and atorvastatin (0.5 [10/20 mg], 0.5 [10/40 mg] and 2.3%, respectively; *P* value not reported).
Goldberg et al[55] VYTAL Atorvastatin 10, 20 or 40 mg/day vs ezetimibe 10 mg/day	DB, MC, PG, RCT Patients 18 to 80 years of age with type 2 diabetes, HbA_{1c} ≤8.5%, LDL-C >100 mg/dL and TG <400 mg/dL	N=1,229 6 weeks	Primary: Percent reduction from baseline in LDL-C Secondary: Proportion of patients who achieved the NCEP	Primary: Combination therapy (10/20 mg) was associated with a significant reduction in LDL-C compared to atorvastatin (10 and 20 mg) (53.6 vs 38.3 and 44.6%, respectively; *P*<0.001). Combination therapy (10/40 mg) was associated with a significant reduction in LDL-C compared to atorvastatin (40 mg) (57.6 vs 50.9%, respectively; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
plus simvastatin 20 or 40 mg/day			ATP III LDL-C goal (<70 mg/dL); proportion of patients who achieved LDL-C level of <100 mg/dL; percent change from baseline in HDL-C, non–HDL-C, TC, TG and CRP	Secondary: A significantly greater proportion of patients receiving combination therapy (10/20 mg) achieved LDL-C<70 mg/dL compared to patients receiving atorvastatin (10 and 20 mg) (59.7 vs 21.5 and 35.0%, respectively; *P*<0.001). Similar results were observed with an LDL-C goal <100 mg/dL (90.3 vs 70.0 and 82.1%, respectively; *P*=0.007). A significantly greater proportion of patients receiving combination therapy (10/40 mg) achieved LDL-C<70 mg/dL compared to patients receiving atorvastatin (40 mg) (74.4 vs 55.2%, respectively; *P*<0.001). Patients receiving combination therapy and atorvastatin who achieved LDL-C <100 mg/dL was comparable (93.4 vs 88.8%, respectively; *P*=0.07). For all doses, combination therapy was associated with a significant increase in HDL-C (*P*≤0.001), and significant reductions in TC and non-HDL-C (*P*<0.001 for both) compared to atorvastatin. Combination therapy (10/20 mg) was associated with significant reductions in CRP and TG compared to atorvastatin (*P*=0.02). The incidence of side effects was similar between combination therapy and atorvastatin (19.8 vs 22.7%; *P* value not reported).
Hing Ling et al[56] Atorvastatin 40 mg/day vs ezetimibe 10 mg/day plus simvastatin 40 mg/day All patients received atorvastatin 20	AC, DB, MC, RCT Patients 18 to 79 years of age at high risk for CHD with primary hypercholesterolemia, LDL >100 mg/dL and <160 mg/dL, triglycerides <350 mg/dL, liver function tests within normal limits without active	N=250 6 weeks	Primary: Change from baseline in LDL-C, Secondary: Total cholesterol, HDL, CRP, Apo AI, Apo B, TG, non-HDL, LDL-C/HDL ratio, total cholesterol/HDL ratio, non-HDL/HDL ratio,	Primary: After six weeks, treatment with ezetimibe/simvastatin resulted in significantly greater reductions from baseline in LDL-C levels compared to atorvastatin 40 mg (-26.8 vs -11.8%; *P*<0.001). Secondary: Treatment with ezetimibe/simvastatin resulted in significantly greater reductions in total cholesterol (*P*<0.001), non-HDL cholesterol (*P*<0.001), Apo B (*P*=0.002), Apo AI (*P*<0.001), and all lipid ratios (*P*<0.001 for all). There were no significant differences between treatments with regard to the change from baseline in triglycerides (*P*=0.593), HDL cholesterol (*P*=0.211), or CRP (*P*=0.785).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/day for six weeks at baseline.	liver disease		Apo AI/Apo B ratio	
Stojakovic et al[57] Ezetimibe 10 mg/day plus fluvastatin 80 mg/day vs fluvastatin 80 mg/day	PRO, RCT, SB Patients with CHD or CHD risk equivalent with LDL-C 100 to 160 mg/dL	N=90 12 weeks	Primary: Changes from baseline in lipids, apolipoproteins and lipoprotein subfractions Secondary: Not reported	Primary: After 12 weeks, TC, LDL-C and apo B were significantly lowered with both treatments, but the reductions were significantly greater with combination therapy (P<0.001 for all). Combination therapy significantly reduced TG, apo CII, apo CIII and apo E compared to baseline (P<0.001 for all) and fluvastatin (P=0.008, P=0.002 and P=0.007). Apo AI and AII increased with fluvastatin and decreased with combination therapy. Accordingly, HDL-C increased with fluvastatin and decreased with combination therapy, but the difference was not significant (P=0.080). Similar results were observed when only patients with type 2 diabetes were analyzed. Secondary: Not reported
Gaudiani et al[58] Ezetimibe 10 mg/day plus simvastatin 20 mg/day vs simvastatin 40 mg/day All patients received simvastatin 20 mg/day for a 6 week run in period.	DB, MC, PG, RCT Patients 30 to 75 years of age with type 2 diabetes (HbA_{1C} ≤9%), treated with a stable dose of pioglitazone (15 to 45 mg/day) or rosiglitazone (2 to 8 mg/day) for ≥3 months, LDL-C >100 mg/dL and TG <600 mg/dL (if already on a statin therapy)	N=214 30 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent change from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B and apo AI	Primary: LDL-C was reduced more by the addition of ezetimibe to simvastatin than by doubling the dose of simvastatin (20.8 vs 0.3%; P<0.001). Secondary: TC (14.5 vs 1.5%; P<0.001), non-HDL-C (20.0 vs 1.7%; P<0.001), apo B (14.1 vs 1.8%; P<0.001), LDL-C:HDL-C (P<0.001), TC:HDL-C (P<0.001) and apo AI (P<0.001) were reduced more by the addition of ezetimibe to simvastatin than by doubling the dose of simvastatin. The increase in HDL-C was similar between the two treatments (P value not reported). The incidence of treatment-related adverse effects was lower with simvastatin compared to combination therapy (10.0 vs 18.3%, respectively; P value not reported).
Feldman et al[59]	DB, MC, RCT	N=710	Primary: Proportion of	Primary: A significantly greater proportion of patients receiving combination therapy

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ezetimibe 10 mg/day plus simvastatin 10, 20 or 40 mg/day vs simvastatin 20 mg/day	Patients 18 to 80 years of age with CHD or CHD risk equivalent disease and LDL-C ≥130 mg/dL and TG ≤350 mg/dL	23 weeks	patients with LDL-C <100 mg/dL at week five Secondary: Proportion of patients with LDL-C <100 mg/dL at 23 weeks	achieved LDL-C <100 mg/dL at week five compared to patients receiving simvastatin (*P*<0.001). Secondary: A significantly greater proportion of patients receiving combination therapy achieved LDL-C <100 mg/dL at week 23 compared to patients receiving simvastatin (*P*<0.001). At five weeks, there was a significant reduction in TC, non-HDL-C, apo B, TC:HDL-C and LDL-C:HDL-C with combination therapy compared to simvastatin (*P*<0.001 for all). HDL-C was significantly increased with combination therapy (10/20 mg) compared to simvastatin (*P*<0.05). At five weeks, combination therapy was associated with a significant reduction in TG compared to simvastatin (*P*<0.05). Treatment-related adverse effects were similar with simvastatin and combination therapy (10/10, 10/20 and 10/40 mg) (7.5, 9.6, 14.0 and 10.0%, respectively; *P* values not reported).
Bays et al[60] Ezetimibe 10 mg/day plus simvastatin 10, 20, 40 or 80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day	ES of Goldberg et al[41] Patients ≥18 years of age with primary hypercholesterolemia	N=768 48 weeks	Primary: Safety and tolerability Secondary: Not reported	Primary: In general, combination therapy did not substantively differ from simvastatin with respect to total adverse events (73 vs 69%), treatment related adverse events (13.5 vs 11.4%), treatment related serious adverse events (1 vs 0%), discontinuations due to treatment related adverse events (2.8 vs 2.6%) or discontinuations due to treatment-related serious adverse events (1 vs 0%). Combination therapy had a slightly higher rate of serious adverse events (5.2 vs 2.6%) and discontinuations due to adverse events (4.5 vs 2.6%) compared to simvastatin (*P*>0.20). But based on investigator assessment of causality, rates were similar between the treatments. There are no remarkable observations of between-treatment group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				differences whether or not they are related to a specific tissue or body system. In general, combination therapy did not differ from simvastatin with respect to total laboratory adverse events (12 vs 12%), treatment related laboratory adverse events (6.2 vs 5.3%), total laboratory serious adverse events (0 vs 0%), treatment related laboratory serious adverse events (0 vs 0%) or discontinuations due to laboratory serious adverse events (0 vs 0%). Secondary: Not reported
Winkler et al[61] Fluvastatin 80 mg/day plus fenofibrate 200 mg/day vs ezetimibe 10 mg/day plus simvastatin 20 mg/day	MC, OL, RCT, XO Patients 18 to 75 years of age with metabolic syndrome, low HDL-C, waist circumference ≥94 (men) or ≥80 cm (females) plus 1 of the following: TG ≥150 mg/dL, blood pressure (≥85/≥130 mm Hg), fasting glucose ≥100 mg/dL or prevalent type 2 diabetes	N=75 6 weeks	Primary: Changes from baseline in lipids, lipoproteins and apolipoproteins; LDL subfractions Secondary: Not reported	Primary: Reductions in TC, LDL-C and apo B were greater with ezetimibe plus simvastatin compared to fluvastatin plus fenofibrate, but differences only reached significance in patients without small, dense LDL (*P*=0.043, *P*=0.006 and *P*=0.20). Reductions in TG were only significant with fluvastatin plus fenofibrate compared to ezetimibe plus simvastatin in patients with small, dense LDL (*P*=0.029). Increases in HDL-C and apo AI were only significant with ezetimibe plus simvastatin compared to fluvastatin plus fenofibrate in patients without small, dense LDL (*P*=0.020 and *P*=0.015). In patients with small, dense LDL, apo AII was markedly increased by fluvastatin plus fenofibrate, whereas ezetimibe plus simvastatin had no or little effect. Although only significant in small, dense LDL patients, apo CIII was more effectively reduce by fluvastatin plus fenofibrate, while the reduction of apo CII was more pronounced with ezetimibe plus simvastatin in all patients. Secondary: Not reported
McKenney et al[62] COMPELL Rosuvastatin 10 mg/day for 4 weeks, followed by 20	MC, OL, PG, RCT Patients ≥21 years of age with hyper-cholesterolemia, eligible for treatment	N=292 12 weeks	Primary: Change from baseline in LDL-C Secondary: Change from	Primary: Atorvastatin plus niacin SR, rosuvastatin plus niacin SR, simvastatin plus ezetimibe and rosuvastatin were associated with similar reductions in LDL-C (56, 51, 57 and 53%, respectively; *P*=0.093). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/day for 4 weeks, followed by 40 mg/day vs atorvastatin 20 mg/day plus niacin SR 500 mg/day for 4 weeks, followed by atorvastatin 20 mg/day plus niacin SR 1,000 mg/day for 4 weeks, followed by atorvastatin 40 mg/day plus niacin SR 2,000 mg/day vs simvastatin 20 mg/day plus ezetimibe 10 mg/day for 8 weeks, followed by simvastatin 40 mg/day plus ezetimibe 10 mg/day vs rosuvastatin 10 mg/day plus niacin SR 500 mg/day for 4 weeks, followed by rosuvastatin 10	based on the NCEP ATP III guidelines, with 2 consecutive LDL-C levels within 15% of each other and mean TG ≤300 mg/dL		baseline in HDL-C non-HDL-C, TG, Lp(a) and apo B; side effects	Atorvastatin plus niacin SR was associated with a significant increase in HDL-C compared to simvastatin plus ezetimibe and rosuvastatin-containing therapy (22, 10 and 7%, respectively; *P*≤0.05). There was no significant differences in the reduction of non-HDL-C from baseline with any treatment (*P*=0.053). Atorvastatin plus niacin SR was associated with a significant reduction in TG compared to simvastatin plus ezetimibe and rosuvastatin-containing therapy (47, 33 and 25%, respectively; *P*≤0.05). Atorvastatin plus niacin SR was associated with a significant reduction in Lp(a) compared to simvastatin plus ezetimibe and rosuvastatin (20 mg)-containing therapy (-14, 7 and 18%, respectively; *P*≤0.05). Atorvastatin plus niacin SR was associated with a significant reduction in apo B compared to rosuvastatin (43 vs 39%, respectively; *P*≤0.05). Side effects were similar across treatments (*P* values not reported). There were no cases of myopathy or hepatotoxicity reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/day plus niacin SR 1,000 mg/day for 4 weeks, followed by rosuvastatin 20 mg/day plus niacin SR 1,000 mg/day				
Hypercholesterolemia Clinical Outcomes Trials				
Sampalis et al[63] Ezetimibe 10 mg/day vs placebo All patients received a statin.	Subanalysis Patients with hypercholesterolemia, LDL-C levels exceeding the NCEP ATP III goals and on statin therapy	N=825 6 weeks	Primary: Reduction in the 10 year risk of CAD Secondary: Not reported	Primary: Ezetimibe, added to a statin, was associated with a 25.3% reduction in the 10 year risk of CAD (*P*<0.001). Secondary: Not reported

Drug regimen abbreviations: ER=extended-release, SR=sustained-release
Study abbreviations: AC=active comparator, CI=confidence interval, DB=double=blind, DD=double dummy, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized control trial, RETRO=retrospective, RR=relative risk, WMD=weighted mean difference, XO=cross-over
Miscellaneous abbreviations: apo=apolipoprotein, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CAD=coronary artery disease, CHD=coronary heart disease, CK=creatine kinase, CRP=C-reactive protein, FH=familial hypercholesterolemia, HAART=highly active antiretroviral therapy, HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, HDL_2-C=HDL subfraction 2, HDL_3-C=HDL subfraction 3, HIV=human immunodeficiency virus, hsCRP=high-sensitivity C-reactive protein, LDL-C=low-density lipoprotein cholesterol, Lp(a)=lipoprotein(a), MDA-LDL= malondialdehydemodified LDL, MI=myocardial infarction, NCEP ATP=National Cholesterol Education Program Adult Treatment Panel, RLP-remnant-like particle, TC=total cholesterol, TG=triglyceride, ULN=upper limit of normal, VLDL-C=very low-density lipoprotein cholesterol

Special Populations

Table 5. Special Populations[1,64]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Ezetimibe	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Food and Drug Administration approved for use in children ages 10 to 17 for the treatment of heterozygous familial hypercholesterolemia.	No dosage adjustment required.	No dosage adjustment required in mild hepatic dysfunction. Use is not recommended in moderate to severe hepatic dysfunction.	C	Unknown; use with caution.

Adverse Drug Events

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

Adverse Event	Ezetimibe
Cardiovascular	
Chest pain	1.8 to 3.4
Central Nervous System	
Depression	a
Dizziness	1.8 to 2.7
Fatigue	1.9 to 2.8
Headache	6.3 to 8.0
Dermatologic	
Rash	a
Urticaria	a
Endocrine and Metabolic	
Cholecystitis	a
Cholelithiasis	a
Elevated creatine phosphokinase	a
Elevations in liver transaminase	2.7
Hepatitis	a
Pancreatitis	a
Gastrointestinal	
Abdominal pain	2.7 to 3.5
Diarrhea	2.8 to 3.7
Nausea	a
Hematologic	
Thrombocytopenia	a
Musculoskeletal	
Arthralgia	3.4 to 3.8
Back pain	3.4 to 4.3
Myalgia	4.5 to 5.0
Myopathy	a (rare)
Rhabdomyolysis	a (rare)

Adverse Event	Ezetimibe
Respiratory	
Angioedema	a
Coughing	2.3
Pharyngitis	2.3 to 3.1
Sinusitis	3.5 to 4.6
Upper respiratory tract infection	11.8 to 13
Other	
Anaphylaxis	a
Cholecystectomy	1.7
Hypersensitivity reactions	a
Infection viral	2.2

a Percent not specified.

Contraindications

Table 7. Contraindications[1,65]

Contraindication	Ezetimibe
Nursing mothers; when combination treatment with a statin is required	a
Patients with a known hypersensitivity to the any components of the product	a
Use in combination with a statin in patients with active liver disease or unexplained persistent elevations in liver enzymes	a
Women who are pregnant or who may become pregnant; when used in combination with a statin	a

Warnings/Precautions

Table 8. Warnings and Precautions[1,65]

Warning/Precaution	Ezetimibe
Ezetimibe and any statin/fibrate should be immediately discontinued if myopathy is diagnosed or suspected.	a
The effects of increased exposure of ezetimibe due to moderate to severe hepatic impairment are unknown	a
The use of ezetimibe with a specific statin or fenofibrate should be in accordance with the prescribing information of that product	a
When administered with a statin, assessment of liver function should be performed at baseline and according to the statin prescribing information	a

Drug Interactions

Table 9. Drug Interactions[1,65]

Drug	Interaction	Mechanism
Ezetimibe	Cyclosporine	Increased concentrations of ezetimibe and cyclosporine, resulting in an increase in pharmacologic effects and adverse events.

Dosage and Administration

Table 10. Dosing and Administration[1]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Ezetimibe	Adjunctive therapy to diet for the reduction of elevated TC, LDL-C and apo B in patients with	Adjunctive therapy to diet for the reduction of elevated TC, LDL-C and apo B in patients with primary	Tablet: 10 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	primary (heterozygous familial and non-familial) hyperlipidemia; Tablet: 10 mg QD Adjunctive therapy in combination with a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) to diet for the reduction of elevated TC, LDL-C and apo B with primary (heterozygous familial and non-familial) hyperlipidemia; Tablet: 10 mg QD Adjunctive therapy in combination with fenofibrate to diet for the reduction of elevated TC, LDL-C, apo B and non-HDL-C in adult patients with mixed hyperlipidemia; Tablet: 10 mg QD In combination with atorvastatin or simvastatin to reduce elevated TC and LDL-C levels in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid lowering treatments (e.g., low density lipoprotein apheresis) or if such treatments are unavailable; Tablet: 10 mg QD Adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia: Tablet: 10 mg QD	(heterozygous familial and non-familial) hyperlipidemia in children 10 to 17 years of age; Tablet: 10 mg QD Adjunctive therapy in combination with a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) to diet for the reduction of elevated TC, LDL-C and apo B with primary (heterozygous familial and non-familial) hyperlipidemia in children 10 to 17 years of age: Tablet: 10 mg QD	

Apo B=apolipoprotein B, HDL-C=high density lipoprotein cholesterol, LDL-C=low density lipoprotein cholesterol, QD=once a day, TC=total cholesterol

Clinical Guidelines

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

Table 11. Clinical Guidelines

Clinical Guideline	Recommendation
National Cholesterol Education Program:	· Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management.

Clinical Guideline	Recommendation
Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)[4]	· When low density lipoprotein cholesterol (LDL-C) lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. · Standard hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statin) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols). · When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. · Fibrates may have an adjunctive role in the treatment of patients with high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins. · In high risk patients with high TG or low HDL-C levels, consideration 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 coronary heart disease (CHD) risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. <u>Treatment of heterozygous familial hypercholesterolemia</u> · 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). <u>Treatment of homozygous familial hypercholesterolemia</u> · Statins may be moderately effective in some persons. · LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). <u>Treatment of familial defective apolipoprotein B-100</u> · TLC indicated. · All LDL-C lowering drugs are effective. · Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. <u>Treatment of polygenic hypercholesterolemia</u> · TLC indicated for all persons. · All LDL-C lowering drugs are effective. · If necessary to reach LDL-C goals, consider combined drug therapy.
National Cholesterol	<u>General recommendations</u>

Clinical Guideline	Recommendation
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)**[3]	· 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. <u>Statins</u> · Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals. <u>Bile acid sequestrants</u> · 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. <u>Nicotinic acid</u> · 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. <u>Fibric acid derivatives (fibrates)</u> · Fibrates can be recommended for patients with very high TG to reduce risk for acute pancreatitis. · They also can be recommended for patients with dysbetalipoproteinemia (elevated beta-very LDL). · Fibrate therapy should be considered an option for treatment of patients with established CHD who have low levels of LDL-C and atherogenic dyslipidemia.

Clinical Guideline	Recommendation
	· 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 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)**[66]	Lipid management · A lipid profile should be established for all patients, and for hospitalized patients, lipid-lowering therapy initiated before discharge. · Lifestyle modifications including daily physical activity and weight management are strongly recommended for all patients · Dietary therapy for all patients should include reduced intake of saturated fats (to <7% of total calories), trans fatty acids (to <1% of total calories), and cholesterol (to <200 mg/d). · Statin therapy should be prescribed in the absence of contraindications or documented adverse effects. · An adequate dose of statin should be used to reduce LDL-C to <100 mg/dL and at least a 30% lowering of LDL-C. · Patients with triglycerides >200 mg/dL should be treated with statins to lower non–HDL-C to 130 mg/dL. · Patients with triglycerides >500 mg/dL should receive fibrate therapy plus statin therapy to prevent acute pancreatitis. · If treatment with a statin (including trials of higher-dose statins and higher-potency statins) does not achieve the goal selected for a patient, intensification of LDL-C–lowering drug therapy with a bile acid sequestrant or niacin can be considered. · 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 triglycerides ≥200 mg/dL, a non–HDL-C goal of <100 mg/dL is reasonable. · The use of ezetimibe may be considered for patients unable to 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 may be considered. · For all patients, it may be reasonable to recommend omega-3 fatty acids from fish or fish oil capsules (1 g/d) for cardiovascular disease risk

Clinical Guideline	Recommendation
	reduction.
Institute for Clinical Systems Improvement: **Lipid Management in Adults (2011)**[5]	Ongoing drug therapy · The use of statin therapy is recommended in patients with established CHD or CHD risk equivalent (which 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 persons at low risk for CHD. The incidence of CHD in men <40 years and premenopausal women is very low, and drug treatment in these groups is discouraged. · Primary prevention trials of pharmacologic lipid lowering have not shown a decrease in mortality, although most trials have shown a 30% reduction in CHD events. Trial populations have consisted mostly of middle-aged men, some with other risk factors. Similar benefit in higher-risk women can be assumed but has not been demonstrated. · Patients with risk factors for CHD but no history of disease who receive lipid lowering therapy are likely to experience a decreased risk of CHD. · Patients with a history of CHD often benefit from statin therapy and trials have consistently shown a decrease in risk of death from CHD. · Specific statin and dose should be selected based on cost and amount of lipid lowering required. · Based on the information above, for patients with established CHD or CHD risk equivalents, the use of a statin is recommended. Statins are the drugs of choice for lowering LDL-C, and aggressive treatment should be pursued. The available statins include: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin and pitavastatin. · Statins also have a modest effect on reducing TGs and increasing HDL-C. Several trials with clinical endpoints support the use of statins in primary and secondary prevention. · In patients receiving a statin who experience myalgias, it is recommended that a lower dose or another statin be tried. A 10 to 14 day vacation from a statin can also be considered as a diagnostic maneuver to see if myalgia symptoms abate. The evidence is inconclusive at this time for treating myalgia with Vitamin D and coenzyme Q. · If patients are intolerant to a statin, they should try the other statins in reduced doses before the medication class is deemed inappropriate. · If patients are unable to take statins, bile acid sequestrants, niacin, fibric acid derivatives and ezetimibe are available. · The bile acid sequestrants reduce LDL-C by 15 to 30%, but they can increase TGs. Should only be used as monotherapy in patients with a baseline TG ≤200 mg/dL and should not be used at all if TG≥400 mg/dL. The effects of these agents are apparent within two to three weeks. · Niacin has a greater effect on HDL-C than other currently available lipid medications and exerts favorable effects on all lipids and lipoproteins. To improve tolerability and compliance, doses of niacin need to be titrated. Aspirin may be used to reduce flushing. · Niacin plus lovastatin has substantial effects on all lipid parameters. · Fibric acid derivatives have a variable effect on LDL-C and profound effect on TG. Prior to initiating a fibric acid, lifestyle therapies should be intensified for moderately elevated triglycerides. Fenofibrate may be more effective at lowering LDL-C than gemfibrozil. They are usually reserved for hypertriglyceridemia or for an isolated low HDL-C.

Clinical Guideline	Recommendation
	· Ezetimibe mainly reduces LDL-C, with minimal effect on TGs or HDL-C. No clinical outcome trials are currently available, but ezetimibe appears useful for reducing LDL-C in patients who cannot take a statin and in combination with other LDL reducing medications. Combination therapy · The limited evidence available suggests that combinations of lipid-lowering agents do not improve clinical outcomes more than statin monotherapy. Common combinations include statin-fibrate, statin-niacin and statin-ezetimibe. · Combination therapy can be considered on an individual basis; however, due to the additional cost, complexity and risk for side effects, routine use in not recommended. · A fibrate is commonly added to a statin in order to increase LDL-C lowering but also causes a higher incidence of myopathy. · The addition of ezetimibe to a statin improved LDL-C reduction more than either agent alone as monotherapy. Clinical outcomes with this combination have not been evaluated. Aspirin · Dosage appears unimportant, usually ranging from 60 mg every other day up to 325 mg/day. · Secondary prevention trials have demonstrated reduced cardiovascular and cerebrovascular endpoints. · Primary prevention trials in patients not selected for cardiovascular risk factors have shown minimal benefit. · Patients with hyperlipidemia are at intermediate risk and may derive greater benefit from aspirin than the lower risk populations evaluated in primary prevention trials. The recommendation of aspirin in hyperlipidemic patients is supported by this reasoning, and by the low cost and risk of this therapy. Lifestyle Modifications · 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-cholesterol level is lowered to the target range. · A diet low in saturated and trans fats, and high in soluble fiber, with consideration given to adding 2 grams of plant sterol/stanol is recommended. · Vitamin E supplements should not be used. · Light to moderate consumption of alcohol (no more than one drink per day for women or two drinks per day for men) may lower coronary heart disease rates. · Omega-3 fatty acids should be recommended in patients with dyslipidemia (1 gram of EPA/DHA by capsule supplement, or by eating at least two servings per week of fatty fish.
American Heart Association: **Drug Therapy of High Risk Lipid Abnormalities in**	· 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

Clinical Guideline	Recommendation
Children and Adolescents: A Scientific Statement From the American Heart Association (2007)[67]	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)**[6]	<u>Drugs</u> · Statins should be used as first-line treatment for patients with hypercholesterolemia or combined hyperlipidemia. · Statins decrease LDL cholesterol, reduce cardiovascular morbidity and mortality as well as the need for coronary artery interventions. Statins at doses that effectively reduce LDL cholesterol by 50% also seem to halt progression or even contribute to regression of coronary atherosclerosis. · Increased liver enzymes in plasma occur occasionally but are reversible in most cases. · Five to ten percent of patients receiving statins develop myopathy, but rhabdomyolysis is extremely rare. The risk of myopathy can be minimized by identifying vulnerable patients and/or by avoiding statin interactions with specific drugs · Selective cholesterol absorption inhibitors are not used as monotherapy to decrease LDL cholesterol concentrations. · Bile acid sequestrants also decrease total and LDL cholesterol but tend to increase triglyceride concentrations. · Fibrates and niacin are used primarily for triglyceride lowering and increasing HDL cholesterol. · Fish oils (omega-3 fatty acids) in doses of 2 to 4 g/day can lower triglycerides. When triglycerides are >900 mg/dL, restriction of alcohol, treatment of diabetes with insulin, withdrawal of estrogen therapy must be used in order to reduce the risk of acute pancreatitis. · In the rare patients with severe primary hypertriglyceridemia, it is necessary to restrict absolutely the intake of alcohol and severely restrict long-chain fat of both animal and vegetable origin. Fibrates are the drugs of choice for these patients, and prescription omega-3 fatty acids might be added if elevated triglycerides are not decreased adequately. <u>Drug Combinations</u> · Combinations of a statin and a bile acid sequestrant or a combination of a statin and ezetimibe can be used for greater reduction of LDL cholesterol than can be achieved with either drug alone. · Combination therapy allows for a lower statin dose to be used, thereby reducing adverse events. Statins should be used in the highest tolerable doses to reach the LDL cholesterol target level before combination therapy. · Combinations of niacin and a statin increase HDL cholesterol and decrease triglycerides better than either of these drugs alone, but flushing

Clinical Guideline	Recommendation
	may occur with niacin use. · Fibrates, particularly fenofibrate, may be useful, not only for decreasing high triglyceride concentrations and increasing low HDL cholesterol, but can further lower LDL cholesterol when used with a statin. · Fibrates should preferably be taken in the morning and statins in the evening to minimize peak dose concentrations and decrease the risk of myopathy. · If target lipid levels cannot be reached even on maximal doses of lipid-lowering therapy or drug combinations, 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.

Conclusions

Zetia® (ezetimibe) is the only cholesterol absorption inhibitor available and is Food and Drug Administration-approved for the treatment of primary hyperlipidemia, homozygous familial hypercholesterolemia and homozygous sitosterolemia.[1] Ezetimibe has a unique mechanism of action compared to the other well-established lipid lowering medication classes. Ezetimibe works to reduce blood cholesterol by inhibiting the absorption of cholesterol by the small intestine.[1] The results from clinical trials consistently demonstrate that ezetimibe is safe and effective for the management of lipid disorders, whether as monotherapy or in combination with a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin), is its primary role.[2,8-63] Ezetimibe is available as a branded 10 mg tablet that is administered once daily.[1] The role of ezetimibe in the management of hypercholesterolemia has not been well established. The primary role of ezetimibe has been as add on therapy with a statin.[2] The statins are considered first-line therapy in the management of hypercholesterolemia as a result of their ability to reduce low density lipoprotein cholesterol.[3-6] Ezetimibe may be helpful for avoiding high doses of statins in patients who are unable to achieve their lipid goals on low dose statin therapy. Additional clinical trials are warranted to further establish the place of ezetimibe in therapy, as there is no evidence to demonstrate a reduction in cardiovascular outcomes with ezetimibe monotherapy or in combination with a statin.[2]

References

1. Zetia® [package insert]. Whitehouse Station (NJ): Merck & Co. Inc.; 2012 Jun.
2. Rosenson RS. Lipid lowering with drugs other than statins and fibrates. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Aug 14]. Available from: http://www.utdol.com/utd/index.do.
3. National Cholesterol Education Program (NCEP). Detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report, 2002 [guideline on the internet]. NCEP. 2002 [cited 2012 Aug 14]. Available from: http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm.
4. 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.
5. Institute for Clinical Systems Improvement (ISCI). Healthcare guideline: lipid management in adults 12th ed., 2011 [guideline on the Internet]. ICSI. 2011 [cited 2012 Aug 14]. Available from: http://www.icsi.org/lipid_management_3/lipid_management_in_adults_4.html.
6. 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.
7. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2012 Aug 14]. Available from: http://www.thomsonhc.com/.
8. Mikhailidis DP, Sibbring GC, Ballantyne CM, Davies GM, Catapano AL. Meta-analysis of the cholesterol-lowering effect of ezetimibe added to ongoing statin therapy (abstract). Curr Med Res Opin. 2007 Aug;23(8):2009-26.
9. Gagné C, Gaudet D, Bruckert E. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation. 2002 May 28;105(21):2469-75.
10. Salen G, von Bergmann K, Lutjohann D, Kwiterovich P, Kane J, Patel SB, et al. Ezetimibe effectively reduces plasma plant sterols in patients with sitosterolemia. Circulation. 2004;109:966-71.
11. Lutjohann D, von Bergmann K, Sirah W, Macdonell G, Johnson-Levonas AO, Shah A, et al. Long-term efficacy and safety of ezetimibe 10 mg in patients with homozygous sitosterolemia: a 2-year, open-label extension study. Int J Clin Pract. 62(10):1499-510.
12. Musliner T, Cselovszky D, Sirah W, Sisk M, Sapre A, Salen G. Efficacy and safety of ezetimibe 40 mg vs ezetimibe 10 mg in the treatment of patients with homozygous sitosterolemia. Int J Clin Pract. 2008 Jul;62(7):995-1000.
13. Pearson GJ, Francis GA, Romney JS, Gilchrist DM, Opgenorth A, Gyenes GT. The clinical effect and tolerability of ezetimibe in high-risk patients managed in a specialty cardiovascular risk reduction clinic. Can J Cardiol. 2006;22(11):939-45.
14. Bissonnette S, Habib R, Sampalis F, Boukas S, Sampalis JS. Efficacy and tolerability of ezetimibe 10 mg/day coadministered with statins in patients with primary hypercholesterolemia who do not achieve target LDL-C while on statin monotherapy: A Canadian, multicentre, prospective study–the Ezetrol add-on study. Can J Cardiol. 2006;22(12):1035-44.
15. Dujovne CA, Ettinger MP, McNeer JF, Lipka LJ, LeBeaut AP, Suresh R, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. Am J Cardiol. 2002 Nov 15;90(10):1092-7.
16. Gonzalez-Ortiz M, Martinez-Abundis E, Kam-Ramos AM,Hernandez-Salazar E, Ramos-Zavala MG. Effect of ezetimibe on insulin sensitivity and lipid profile in obese and dyslipidaemic patients. Cardiovasc Drugs Ther. 2006:20(2):143-6.
17. Knopp RH, Gitter H, Truitt T, Bays H, Manion CV, Lipka LJ, et al. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. Eur Heart J. 2003 Apr;24(8):729-41.

18. Knopp RH, Dujovne CA, Le Beaut A, Lipka LJ, Sresh R, Veltri EP, et al. Evaluation of the efficacy, safety, and tolerability of ezetimibe in primary hypercholesterolemia: a pooled analysis from two controlled phase III clinical studies. Int J Clin Pract. 2003 Jun;57(5):363-8.
19. Wierzbicki AS, Doherty E, Lumb PJ, Chik G, Crook MA. Efficacy of ezetimibe in patients with statin-resistant and statin-intolerant familial hyperlipaemias (abstract). Curr Med Res Opin. 2005;21(3):333-8.
20. Kalogirou M, Tsimihodimos V, Gazi I, Filippatos T, Saougos V, Tselepis AD, et al. Effect of ezetimibe monotherapy on the concentration of lipoprotein subfractions in patients with primary dyslipidaemia (abstract). Curr Med Res Opin. 2007 May; 23(5):1169-76.
21. Jelesoff NE, Ballantyne CM, Xydakis AM, Chiou P, Jones PH, Guyton JR. Effectiveness and tolerability of adding ezetimibe to niacin-based regimens for treatment of primary hyperlipidemia (abstract). Endocrine Practice. 2006;12(2):159-64.
22. Gagné C, Bays HE, Weiss SR, Mata P, Quinto K, Melino M, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol. 2002 Nov 15;90(10):1084-91.
23. Denke M, Pearson T, McBride P, Gazzara RA, Brady WE, Tershakovec AM. Ezetimibe added to ongoing statin therapy improves LDL-C goal attainment and lipid profile in patients with diabetes or metabolic syndrome. Diab Vasc Dis Res. 2006 Sep;3(2):93-102.
24. Pearson TA, Denke MA, McBride PE, Battisti WP, Brady WE, Palmisano J. A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. Mayo Clin Proc. 2005; May 80(5):587-95.
25. Pearson T, Denke M, McBride P, Battisti WP, Brady WE, Palmisano J. Effectiveness of the addition of ezetimibe to ongoing statin therapy in modifying lipid profiles and attaining low-density lipoprotein cholesterol goals in older and elderly patients: subanalyses of data from a randomized, double-blind, placebo-controlled trial. Am J Geriatr Pharmacother. 2005 Dec;3(4):218-28.
26. Pearson T, Denke M, McBride PE, Batisti WP, Gazzara RA, Brady WE, et al. Effectiveness of ezetimibe added to ongoing statin therapy in modifying lipid profiles and low-density lipoprotein cholesterol goal attainment in patients of different races and ethnicities: a substudy of the ezetimibe add-on to statin for effectiveness trial. Mayo Clin Prac. 2006 Sept;81(9):1177-85.
27. Simons L, Symons J. Ezetimibe added to statin therapy (EASY study). An evaluation by Australian general practitioners. Aust Fam Physician. 2007 Jan-Feb;36(1-2):90-2,96.
28. Blagden M, Chipperfield R. Efficacy and safety of ezetimibe co-administered with atorvastatin in untreated patients with primary hypercholesterolaemia and coronary heart disease (abstract). Curr Med Res Opin. 2007 Apr;23(4):767-75.
29. Ballantyne CM, Weiss R, Moccetti T, Vogt A, Eber B, Sosef F, et al. Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). Am J Cardiol. 2007 Mar 1;99(5):673-80.
30. Landry M, Baigent C, Leaper C, Adu D, Altmann P, Armitage J, et al. The second United Kingdom Heart and Renal Protection (UK-HARP-II) study: a randomized controlled study of the biochemical safety and efficacy of adding ezetimibe to simvastatin as initial therapy among patients with CKD. Am J Kidney Dis. 2006;47(3):385-95.
31. Patel JV, Hughes EA. Efficacy, safety and LDL-C goal attainment of ezetimibe 10 mg-simvastatin 20 mg vs placebo-simvastatin 20 mg in UK-based adults with coronary heart disease and hypercholesterolaemia. Int J Clin Pract. 2006 Aug;60(8):914-21.
32. Rodney RA, Sugimoto D, Wagman B, Zieve F, Kerzner B, Strony J, et al. Efficacy and safety of coadministration of ezetimibe and simvastatin in African-American patients with primary hypercholesterolemia. J Natl Med Assoc. 2006 May;98(5):772-8.
33. Masana L, Mata P, Gagné C, Sirah W, Cho M, Johnson-Levonas AO, et al. Long-term safety and, tolerability profiles and lipid-modifying efficacy of ezetimibe coadministered with ongoing simvastatin treatment: a multicenter, randomized, double-blind, placebo-controlled, 48-week extension study. Clin Ther. 2005 Feb;27(2):174-84.

34. Farnier M, Freeman MW, Macdonell G, Perevozskaya I, Davies MJ, Mitchel YB, et al. Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia. Eur Heart J. 2005; 26:897-905.
35. McKenney JM, Farnier M, Lo KW, Bays HE, Perevozkaya I, Carlson G, et al. Safety and efficacy of long-term co-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. J Am Coll Cardiol. 2006 Apr 18;47(8):1584-7.
36. Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation. 2003 May 20;107(19):2409-15.
37. Kerzner B, Corbelli J, Sharp S, Lipka LJ, Melani L, LeBeaut A, et al. Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. Am J Cardiol. 2003 Feb 15;91(4):418-24.
38. Melani L, Mills R, Hassman D, Lipetz R, Lipka L, LeBeaut A, et al. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Eur Heart J. 2003 Apr;24(8):717-28.
39. Chenot F, Montant PF, Marcovitch O, Blaimont M, de Meester A, Descamps OS. Co-administration of ezetimibe and simvastatin in acute myocardial infarction. Eur J Clin Invest. 2007 May;37(5):357-63.
40. Davidson MH, McGarry T, Bettis R, Melani L, Lipka LJ, LeBeaut AP, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol. 2002 Dec 18;40(12):2125-34.
41. Goldberg AC, Sapre A, Liu J, Capece R, Mitchel YB. Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc. 2004 May;79(5):620-9.
42. Bays HE, Ose L, Fraser N, Tribble DL, Quinto K, Reyes R, et al. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared to ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. Clin Ther. 2004 Nov;26(11):1758-73.
43. Ose L, Johnson-Levonas A, Reyes R, Lin J, Shah A, Tribble D, et al. A multi-centre, randomized, double-blind 14-week extension study examining the long-term safety and efficacy profile of the ezetimibe/simvastatin combination tablet. Int J Clin Pract. 2007 Sep;61(9):1469-80.
44. Feldman T, Davidson M, Shah A, Maccubbin D, Meehan A, Zakson M, et al. Comparison of the lipid-modifying efficacy and safety profiles of ezetimibe coadministered with simvastatin in older versus younger patients with primary hypercholesterolemia: a post hoc analysis of subpopulations from three pooled clinical trials. Clin Ther. 2006 Jun;28(6):849-59.
45. Pearson T, Ballantyne C, Sisk C, Shah A, Veltri E, Maccubbin D. Comparison of effects of ezetimibe/simvastatin versus simvastatin versus atorvastatin in reducing C-reactive protein and low-density lipoprotein cholesterol levels. Am J Cardiol. 2007 Jun 15;99(12):1706-13.
46. Okada K, Kimura K, Iwahashi N, Endo T, Himeno H, Fukui K, et al. Clinical usefulness of additional treatment with ezetimibe in patients with coronary artery disease on statin therapy. - From the viewpoint of cholesterol metabolism. Circ J. 2011 Sep 22;75(10):2496-504.
47. Ansquer JC, Bekaert I, Guy M, Hanefeld M, Simon A. 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. Am J Cardiovasc Drugs. 2009;9(2):91-101.
48. Kumar SS, Lahey KA, Day A, LaHaye SA. Comparison of the efficacy of administering a combination of ezetimibe plus fenofibrate versus atorvastatin monotherapy in the treatment of dyslipidemia. Lipids Health Dis. 2009;8(56):1-8.
49. Coll B, Aragones G, Parra S, Alonso-Villaverde C, Masana L. Ezetimibe effectively decreases LDL-cholesterol in HIV-infection patients. AIDS. 2006 Aug;20(12):1675-7.
50. Conrad S, Bays H, Leiter LA, Bird S, Lin J, Hanson ME, et al. Ezetimibe added to atorvastatin compared to doubling the atorvastatin dose in patients at high risk for coronary heart disease with diabetes mellitus, metabolic syndrome or neither. Diabetes Obes Metab. 2010;12:210-8.
51. Uemura Y, Watarai M, Ishii H, Koyasu M, Takemoto K, Yoshikawa D, et al. Atorvastatin 10 mg plus ezetimibe 10mg compared with atorvastatin 20 mg: impact on the lipid profile in Japanese patients with abnormal glucose tolerance and coronary artery disease. J Cardiol. 2012 Jan;59(1):50-6.

52. Piorkowski M, Fischer S, Stellbaum C, Jaster M, Martus P, Morguet AJ, et al. Treatment with ezetimibe plus low-dose atorvastatin compared to higher-dose atorvastatin alone: is sufficient cholesterol-lowering enough to inhibit platelets? J Am Coll Cardiol. 2007 Mar 13;49(10):1035-42.
53. Stein E, Stender S, Mata P, Sager P, Ponsonnet D, Melani L, et al. Achieving lipoprotein goals in patients at high risk with sever hypercholesterolemia: Efficacy and safety of ezetimibe co-administered with atorvastatin. Am Heart J. 2004 Sep;447-55.
54. Constance C, Westphal S, Chung N, Lund M, McCrary Sisk C, Johnson-Levonas AO, et al. Efficacy of ezetimibe/simvastatin 10/20 and 10/40 mg compared to atorvastatin 20 mg in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2007 Jul;9(4):575-84.
55. Goldberg RB, Guyton JR, Mazzone T, Weinstock RS, Polis A, Edwards P, et al. Ezetimibe/simvastatin vs atorvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia: the VYTAL study. Mayo Clin Proc. 2006 Dec;81(12):1579-88.
56. Hing Ling PK, Civeira F, Dan AG, Hanson ME, Massaad R, De Tilleghem Cle B, et al. Ezetimibe/simvastatin 10/40 mg versus atorvastatin 40 mg in high cardiovascular risk patients with primary hypercholesterolemia: a randomized, double-blind, active-controlled, multicenter study. Lipids Health Dis. 2012 Jan 31;11:18.
57. Stojakovic T, de Campo A, Scharnagl H, Sourij H, Schmolzer I, Wascher TC, et al. Differential effects of fluvastatin alone or in combination with ezetimibe on lipoprotein subfractions in patients at high risk of coronary events. Eur J Clin Invest. 2010;40(3):187-94.
58. Gaudiani LM, Lewin A, Meneghini L, Perevozskaya I, Plotkin D, Mitchel Y, et al. Efficacy and safety of ezetimibe co-administered with simvastatin in thiazolidinedione-treated type 2 diabetic patients. Diabetes Obes Metab. 2005 Jan;7(1):88-97.
59. Feldman T, Koren M, Insull W Jr, McKenney J, Schrott H, Lewin A, et al. Treatment of high-risk patients with ezetimibe plus simvastatin co-administration versus simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals. Am J Cardiol. 2004 Jun 15;93(12):1481-6.
60. Bays H, Sapre A, Taggart W, Liu J, Capece R, Tershakovec A. Long-term (48-week) safety of ezetimibe 10 mg/day coadministered with simvastatin compared to simvastatin alone in patients with primary hypercholesterolemia. Curr Med Res Opin. 2008;24(10):2953-66.
61. 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.
62. McKenney JM, Jones PH, Bays HE, Knopp RH, Kashyap ML, Ruoff GE, et al. Comparative effects on lipid levels of combination therapy with a statin and extended-release niacin or ezetimibe versus a statin alone (the COMPELL study). Atherosclerosis. 2007 Jun;192(2):432-7.
63. Sampalis JS, Bissonnette S, Habib R, Boukas S. Reduction in estimated risk for coronary artery disease after use of ezetimibe with a statin. Ann Pharmacother. 2007 Sep;41(9):1345-51.
64. Ezetimibe: drug information. In: Basow DS (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Aug 14Available from: http://www.utdol.com/utd/index.do.
65. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2012 [cited 2012 Aug 14]. Available from: http://online.factsandcomparisons.com.
66. 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.
67. 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.