Therapeutic Class Overview
HMG CoA Reductase Inhibitors

Therapeutic Class

- **Overview/Summary:** The hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) work by inhibiting HMG CoA reductase, the rate-limiting step in cholesterol synthesis. Statins are the most effective class of medications available to lower low density lipoprotein cholesterol (LDL-C) with a potential decrease of 18 to 55% depending on the specific statin and dose administered. Statins also have positive effects on high density lipoprotein cholesterol (HDL-C) and triglycerides with increases of five to 10% and decreases of seven to 30% observed, respectively. In addition to being the most effective class of medications for reducing LDL-C, statins provide significant cardiovascular benefits in primary and secondary prevention of coronary heart disease (CHD).[1,2] The available statins include atorvastatin (Lipitor®), fluvastatin (Lescol®, Lescol XL®), lovastatin (Altoprev®, Mevacor®), pitavastatin (Livalo®), pravastatin (Pravachol®), rosuvastatin (Crestor®) and simvastatin (Zocor®). Of these, atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin are available generically. Certain statins are also available as fixed-dose combination products with other cardiovascular medications, including a calcium channel blocker (amlodipine/atorvastatin [Caduet®]), a cholesterol absorption inhibitor (ezetimibe/atorvastatin [Liptruzet®], ezetimibe/simvastatin [Vytorin®]) and a niacin derivative (niacin extended-release [ER]/lovastatin [Advicor®], niacin ER/simvastatin [Simcor®]). Amlodipine/atorvastatin is currently the only combination product available generically.[3-16]

  In general, statins are indicated to manage primary hyperlipidemia, as well as other specific lipid abnormalities. Certain statins have demonstrated cardiovascular benefits. Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin are all Food and Drug Administration (FDA)-approved for the prevention of cardiovascular disease in primary prevention, secondary prevention or both.[6,7,8,12,13,16] Specific FDA-approved indications are outlined in Table 1. When LDL-C 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 LDL-C levels.[1,17-19] 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.[1] Statins are also recommended in patients with established CHD or CHD risk equivalents, with the choice of a specific agent being based on cost and the amount of lipid lowering required for a specific patient.[18] In June 2011 the FDA issued a safety warning that simvastatin 80 mg be restricted due to an increased risk of muscle damage associated with the agent. Patients who have been receiving simvastatin 80 mg for more than 12 months with no evidence of myopathy may continue treatment; however, this strength should not be initiated in new patients.[20-22]

Table 1. Current Medications Available in the Therapeutic Class[3-16]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Atorvastatin (Lipitor®*)	**Hypertriglyceridemia:** treatment of patients with elevated triglyceride (TG) levels **Primary hypercholesterolemia and mixed dyslipidemia:** reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), and TG and to increase high-density lipoprotein cholesterol HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia, reduce TC, LDL-C, and apo B levels in children with heterozygous familial hypercholesterolemia (FH) if after an adequate trial of diet therapy the following findings are present: LDL-C remains ≥190 mg/dL OR LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease or two or more other cardiovascular risk factors are present in the pediatric patient†, reduce TC and LDL-C in patients with homozygous FH as an adjunct to other lipid-lowering treatments or if such treatments are unavailable, treatment of patients with primary dysbetalipoproteinemia who do not respond adequately to diet **Prevention of cardiovascular disease:** reduce the risk of myocardial infarction (MI) and stroke in patients with type 2 diabetes, and without clinically evidence coronary heart disease (CHD), but with multiple risk factors for CHD such as retinopathy, albuminuria, smoking, or hypertension (HTN), reduce the risk of MI, stroke, and for revascularization procedures and angina in adult patients without clinically evident CHD, but with multiple risk factors for CHD such as age, smoking, HTN, low HDL-C, or a family history of early CHD, reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in patients with clinically evidence CHD	Tablet: 10 mg 20 mg 40 mg 80 mg	✔
Fluvastatin (Lescol®*, Lescol XL®)	**Primary hypercholesterolemia and mixed dyslipidemia:** reduce elevated TC, LDL-C, apo B, and TG and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia, reduce TC, LDL-C, and apo B levels in children with heterozygous FH if after an adequate trial of diet therapy the following findings are present: LDL-C remains ≥ 190 mg/dL OR LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease or two or more other cardiovascular risk factors are present in the pediatric patient‡ **Prevention of cardiovascular disease:** reduce the risk of undergoing coronary revascularization procedures and slow the progression of coronary atherosclerosis in patients with clinically evidence CHD	Capsule (Lescol®): 20 mg 40 mg Extended-release tablet (Lescol XL®): 80 mg	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Lovastatin (Altoprev®, Mevacor®*)	**Primary hypercholesterolemia and mixed dyslipidemia**: reduce elevated TC, LDL-C, apo B, and TG and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (ER)§, reduce TC, LDL-C, and apo B levels in children with heterozygous FH if after an adequate trial of diet therapy the following findings are present: LDL-C remains ≥189 OR LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease or two or more other cardiovascular risk factors are present in the pediatric patient (IR)‖, reduction of elevated TC and LDL-C levels in patients with primary hypercholesterolemia§	Extended-release tablet (Altoprev®): 20 mg 40 mg 60 mg Tablet (Mevacor®): 10 mg 20 mg 40 mg	✔
	Prevention of cardiovascular disease: reduce the risk of MI, unstable angina, and coronary revascularization procedures in patients without symptomatic cardiovascular disease, average to moderately elevated TC and LDL-C, and below average HDL-C, slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower TC and LDL-C to target levels		
Pitavastatin (Livalo®)	**Primary hypercholesterolemia and mixed dyslipidemia:** reduce elevated TC, LDL-C, apo B, and TG and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia	Tablet: 1 mg 2 mg 4 mg	-
Pravastatin (Pravachol®*)	**Hypertriglyceridemia:** treatment of patients with elevated TG levels	Tablet: 10 mg 20 mg 40 mg 80 mg	✔
	Primary hypercholesterolemia and mixed dyslipidemia: reduce elevated TC, LDL-C, apo B, and TG and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia, reduce TC, LDL-C, and apo B levels in children with heterozygous FH if after an adequate trial of diet therapy the following findings are present: LDL-C remains ≥190 mg/dL OR LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease or two or more other cardiovascular risk factors are present in the pediatric patient¶, treatment of patients with primary dysbetalipoproteinemia who do not respond adequately to diet		
	Prevention of cardiovascular disease: reduce the risk of MI, undergoing myocardial revascularization procedures, and cardiovascular mortality with no increase in death from noncardiovascular causes in patients with hypercholesterolemia without clinically evident CHD, reduce the risk of total mortality by reducing coronary death, MI, undergoing myocardial revascularization procedures, stroke and stroke/transient ischemic attack, and to slow the progression of coronary atherosclerosis in patients with clinically evidence CHD		
Rosuvastatin (Crestor®)	**Hypertriglyceridemia:** treatment of adult patients with hypertriglyceridemia	Tablet: 5 mg 10 mg 20 mg	-
	Primary hypercholesterolemia and mixed dyslipidemia: reduce elevated TC, LDL-C, apo B, and TG and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia, reduce TC, LDL-C, and apo B levels in children with heterozygous FH if after an		

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	adequate trial of diet therapy the following findings are present: LDL-C remains ≥190 mg/dL OR LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease or two or more other cardiovascular risk factors are present in the pediatric patient‡, reduce TC, LDL-C, and apo B in adult patients with homozygous FH as adjunctive therapy to other lipid-lowering treatments or alone if such treatments are not available, treatment of patients with primary dysbetalipoproteinemia who do not respond adequately to diet	40 mg	
	Prevention of cardiovascular disease: adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower TC and LDL-C to target levels, reduce the risk of stroke, MI, and arterial revascularization procedures in patients without clinically evidence CHD but with an increased risk of cardiovascular disease based on age ≥50 years old in men and ≥60 years old in women, high sensitivity C-reactive protein ≥2 mg/L, and the presence of at least one additional cardiovascular disease risk factor such as HTN, low HDL-C, smoking, or a family history of premature CHD		
Simvastatin (Zocor®*)	**Hypertriglyceridemia:** reduce elevated TG in patients with hypertriglyceridemia	Tablet: 5 mg 10 mg 20 mg 40 mg 80 mg	✔
	Primary hypercholesterolemia and mixed dyslipidemia: reduce elevated TC, LDL-C, apo B, and TG and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia, reduce TC, LDL-C, and apo B levels in children with heterozygous FH if after an adequate trial of diet therapy the following findings are present: LDL-C remains ≥190 mg/dL OR LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease or two or more other cardiovascular risk factors are present in the pediatric patient‡, reduce elevated TG and very LDL-C in patients with primary dysbetalipoproteinemia, reduce TC and LDL-C in patients with homozygous FH as an adjunct to other lipid-lowering treatments or if such treatments are unavailable		
	Prevention of cardiovascular disease: reduce the risk of total mortality by reducing CHD deaths, non-fatal MI and stroke, and need for coronary and non-coronary revascularization procedures in patients at high risk of coronary events because of existing CHD, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease		
Amlodipine/ atorvastatin (Caduet®*)	**Hypertriglyceridemia:** Treatment of patients with elevated TG levels (atorvastatin)	Tablet: 2.5/10 mg 2.5/20 mg 2.5/40 mg 5/10 mg 5/20 mg 5/40 mg 5/80 mg	✔
	Primary hypercholesterolemia and mixed dyslipidemia: reduce elevated TC, LDL-C, apo B, and TG and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (atorvastatin), reduce TC, LDL-C, and apo B levels in children with heterozygous FH if after an adequate trial of diet therapy the following findings are present: LDL-C remains ≥190 mg/dL OR LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease or two or more other cardiovascular risk factors are present in the pediatric patient†, reduce TC and LDL-C in patients with homozygous FH as an adjunct to other		

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	lipid-lowering treatments or if such treatments are unavailable, treatment of patients with primary dysbetalipoproteinemia who do not respond adequately to diet	10/10 mg 10/20 mg 10/40 mg 10/80 mg	
	Prevention of cardiovascular disease: reduce the risk of MI and stroke in patients with type 2 diabetes, and without clinically evidence CHD, but with multiple risk factors for CHD such as retinopathy, albuminuria, smoking, or HTN, reduce the risk of MI, stroke, and for revascularization procedures and angina in adult patients without clinically evident CHD, but with multiple risk factors for CHD such as age, smoking, HTN, low HDL-C, or a family history of early CHD, reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in patients with clinically evidence CHD		
	Other: reduce the risk of hospitalization for angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented CAD by angiography and without heart failure or an ejection fraction <40%, symptomatic treatment of chronic stable angina, treatment of confirmed or suspected vasospastic angina, treatment of HTN		
Ezetimibe/ atorvastatin (Liptruzet®)	**Primary hypercholesterolemia and mixed dyslipidemia:** reduce elevated TC, LDL-C, apo B, and TG and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia, reduce TC and LDL-C in patients with homozygous FH as an adjunct to other lipid-lowering treatments or if such treatments are unavailable	Tablet: 10/10 mg 10/20 mg 10/40 mg 10/80 mg	-
Ezetimibe/ simvastatin (Vytorin®)	**Primary hypercholesterolemia and mixed dyslipidemia:** reduce elevated TC, LDL-C, apo B, and TG and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia, reduce TC and LDL-C in patients with homozygous FH as an adjunct to other lipid-lowering treatments or if such treatments are unavailable	Tablet: 10/10 mg 10/20 mg 10/40 mg 10/80 mg	-
Niacin ER/ lovastatin (Advicor®)	**Hypertriglyceridemia:** treatment of adult patients with very high serum TG levels who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them (niacin)	Tablet: 500/20 mg 750/20 mg 1,000/20 mg 1,000/40 mg	-
	Primary hypercholesterolemia and mixed dyslipidemia: treatment of adult patients with very high serum TG levels who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them (niacin)[#], reduction of elevated TC and LDL-C levels in patients with primary hypercholesterolemia (lovastatin)[§],		
	Prevention of cardiovascular disease: reduce the risk of MI, unstable angina, and coronary revascularization procedures in patients without symptomatic cardiovascular disease, average to moderately elevated TC and LDL-C, and below average HDL-C (lovastatin), reduce the risk of recurrent non-fatal MI in patients with a history of MI and hypercholesterolemia (niacin), slow		

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower TC and LDL-C to target levels (lovastatin)		
Niacin ER/ simvastatin (Simcor®)	**Hypertriglyceridemia:** reduce elevated TG in patients with hypertriglyceridemia **Primary hypercholesterolemia and mixed dyslipidemia:** reduce elevated TC, LDL-C, apo B, and TG and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia	Tablet: 500/20 mg 500/40 mg 750/20 mg 1,000/20 mg 1,000/40 mg	-

ER=extended-release, IR=immediate-release
*Generic available in at least one dosage form and/or strength.
† In boys and postmenarchal girls 10 to 17 years of age.
‡ In adolescent boys and adolescent girls who are at least one year postmenarche, 10 to 16 years of age.
§ When the response to diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate.
‖ In adolescent boys and girls, who are at least one year postmenarche, 10 to 17 years of age.
¶ In children and adolescent patients ages eight years of age and older.
# When the response to an appropriate diet has been inadequate.

Evidence-based Medicine

- A benefit in all-cause mortality, as well as other cardiovascular outcomes, with rosuvastatin in primary prevention of cardiovascular disease was demonstrated in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial (N=17,802).[23]
    - JUPITER sought to evaluate the efficacy of rosuvastatin in reducing cardiac events in patients with elevated high sensitivity C-reactive protein levels, which they note as being a predictor for cardiac events.
    - JUPITER was terminated early (median duration, 1.9 years) due to the significant benefits observed. Compared to placebo, rosuvastatin significantly reduced the risk of a first major cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, revascularization procedure or cardiovascular death) by 44% (P<0.0001).
    - When the endpoints were analyzed individually, rosuvastatin was associated with a significant benefit for all primary outcomes, as well as all-cause mortality (P=0.02).
- Other recently published clinical trials evaluating the hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) in the treatment of hyperlipidemia or in the prevention of cardiovascular disease did not produce clinically different results compared to trials included in the previous therapeutic class review.[24-46]
- For a full description of clinical trials evaluating the statins in the prevention of cardiovascular disease in primary prevention or secondary prevention, please see the full therapeutic class review.

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.[1,17,18]
    - In general, hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are considered first line therapy for decreasing low density lipoprotein cholesterol (LDL-C) levels. If after six weeks, lipid goals are not achieved with statin monotherapy, a dosage increase or the addition of a bile acid sequestrant or nicotinic acid (niacin) should be considered.[1,17-19]
    - Statins are recommended in patients with established coronary heart disease (CHD) or CHD risk equivalents. Choice of statin and dose should be based on cost and the amount of lipid lowering required for a specific patient.[18]
    - Patients with risk factors for CHD but with no history of disease are likely to decrease their risk of CHD with lipid lowering therapy.[18]
- Other Key Facts:
    - In June 2011, the Food and Drug Administration (FDA) recommended that the use of high dose (80 mg) simvastatin be restricted after an increased risk of muscle damage associated with the agent was observed after a review of the Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial, other clinical data and analyses of adverse events submitted to the FDA's Adverse Event Reporting System.[20-22]
        - Patients may remain on simvastatin 80 mg if they have been receiving therapy for more than 12 months with no evidence of myopathy, but the dosage should not be initiated in new patients.
        - The restriction also comes with new warnings regarding the use of simvastatin concurrently with certain medications known to increase simvastatin concentrations.
        - The approved labeling for simvastatin (Zocor®) and simvastatin-containing medications (Simcor® [niacin extended-release/simvastatin] and Vytorin® [ezetimibe/simvastatin]) have been updated to reflect these new recommendations.
    - Atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin are available generically.
    - The fixed combination of amlodipine/atorvastatin is available generically.

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Therapeutic Class Review
HMG CoA Reductase Inhibitors

Overview/Summary

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

The statins are the most effective class of medications for reducing low density lipoprotein cholesterol (LDL-C). These agents work by inhibiting HMG CoA reductase, the rate-limiting step in cholesterol synthesis, which results in a reduction of LDL-C. Specifically, inhibiting the synthesis of cholesterol reduces hepatic content which leads to an increase in the expression of LDL receptors, which in turn reduces serum LDL-C. Intermediate and very low density cholesterol are also removed via the LDL receptors. Depending on the specific statin and dose administered, reductions in LDL-C of 18 to 55% have been observed. Of note, reductions in LDL-C are dose dependent with statins.[1] Of the available statins, rosuvastatin is the most potent in terms of reducing LDL-C, with both rosuvastatin and atorvastatin being more potent compared to the rest of the statins at maximal prescribed doses.[2] Statins are also typically associated with a five to 10% increase in high density lipoprotein cholesterol (HDL-C), but greater increases in patients with low HDL-C and elevated triglycerides (TG) have also been observed. In addition, these agents generally lower TGs by seven to 30%.[1]

In addition to being the most effective class of medications for reducing LDL-C, the evidence demonstrating that statins are beneficial in both primary and secondary prevention of coronary heart disease (CHD) is well established. Overall, decreases in the risk for acute coronary syndromes, coronary procedures, strokes and other coronary outcomes has been demonstrated.[1]

Included in this review are the statin single-entity agents and combination products.[3-16] Specifically, the single-entity agents include atorvastatin (Lipitor®), fluvastatin (Lescol®), lovastatin (Mevacor®), pitavastatin (Livalo®), pravastatin (Pravachol®), rosuvastatin (Crestor®) and simvastatin (Zocor®). Of these, atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin are available generically. The combination products include amlodipine/atorvastatin (Caduet®), ezetimibe/atorvastatin (Liptruzet®), ezetimibe/simvastatin (Vytorin®), niacin extended-release/lovastatin (Advicor®) and niacin extended-release/simvastatin (Simcor®). The amlodipine/atorvastatin combination product is available generically.

The specific FDA-approved indications for each of the agents are outlined in Table 2. In general, statins are indicated to manage primary hyperlipidemia, as well as other specific lipid abnormalities. Certain statins have also demonstrated cardiovascular benefits. Atorvastatin, rosuvastatin and simvastatin are FDA-approved for the prevention of cardiovascular disease in primary prevention, secondary prevention or both.[3,10,11] In June 2011, the recommended that the use of simvastatin 80 mg be restricted due to an increased risk of muscle damage associated with the agent. Patients who have been receiving simvastatin 80 mg for more than 12 months without evidence of myopathy may continue treatment; however, this strength should not be initiated in new patients.[17-18]

In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia.[1,19,20] When LDL lowering is required, initial treatment with a statin, a bile acid sequestrant or niacin is recommended.[1] However, in general, the statins are considered first line therapy for decreasing LDL-C levels.[1,19,21] 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.[1] In addition, statins are recommended in patients with established CHD or CHD risk equivalents. Choice of statin and dose should be based on cost and the amount of lipid lowering required for a specific patient. Patients with risk factors for CHD but no history of disease are likely to decrease their risk of CHD with lipid lowering therapy.[21]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single-Entity Agents		
Atorvastatin (Lipitor®*)	HMG CoA reductase inhibitors	✔
Fluvastatin (Lescol®*, Lescol XL®)	HMG CoA reductase inhibitors	✔
Lovastatin (Altoprev®, Mevacor®*)	HMG CoA reductase inhibitors	✔
Pitavastatin (Livalo®)	HMG CoA reductase inhibitors	-
Pravastatin (Pravachol®*)	HMG CoA reductase inhibitors	✔
Rosuvastatin (Crestor®)	HMG CoA reductase inhibitors	-
Simvastatin (Zocor®*)	HMG CoA reductase inhibitors	✔
Combination Products		
Amlodipine/atorvastatin (Caduet®*)	Calcium channel blockers/ HMG CoA reductase inhibitors	✔
Ezetimibe/atorvastatin (Liptruzet®)	Cholesterol absorption inhibitors/ HMG CoA reductase inhibitors	-
Ezetimibe/simvastatin (Vytorin®)	Cholesterol absorption inhibitors/ HMG CoA reductase inhibitors	-
Niacin extended release/lovastatin (Advicor®)	Niacin derivatives/ HMG CoA reductase inhibitors	-
Niacin extended release/simvastatin (Simcor®)	Niacin derivatives/ HMG CoA reductase inhibitors	-

HMG CoA=hydroxymethylglutaryl coenzyme A
*Generic available in at least one dosage form and/or strength.

Indications

Table 2. Food and Drug Administration Approved Indications[3-16]

Indications	Single-Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin*	Atorvastatin/ ezetimibe	Ezetimibe/ simvastatin	Niacin/ lovastatin†	Niacin/ simvastatin‡
Hypertriglyceridemia												
Reduce elevated triglycerides (TG) in patients with hypertriglyceridemia							✔					✔
Treatment of adult patients with hypertriglyceridemia						✔						
Treatment of adult patients with very high serum TG levels who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them											✔ (niacin)	
Treatment of patients with elevated TG levels	✔				✔			✔ (atorvastatin)				
Primary Hypercholesterolemia and Mixed Dyslipidemia												
Reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), and TG and to increase high-density lipoprotein cholesterol HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia	✔	✔	✔ § (ER)	✔	✔	✔	✔	✔ (atorvastatin)	✔	✔	✔ ‖ (niacin)	✔
Reduce TC, LDL-C, and apo B levels in children with heterozygous familial hypercholesterolemia (FH) if after an adequate trial of diet therapy the following findings are present: LDL-C remains ≥189 (lovastatin only) or 190 mg/dL OR LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease or two or more other cardiovascular risk factors are present in the pediatric patient	✔ ¶	✔ #	✔ ** (IR)		✔ ††	✔ **	✔ **	✔ ¶ (atorvastatin)				
Reduce elevated TG and very LDL-C in patients with primary dysbetalipoproteinemia							✔					
Reduce TC and LDL-C in patients with homozygous FH as an adjunct to other lipid-lowering treatments or if such treatments are unavailable	✔						✔	✔ (atorvastatin)	✔	✔		

Indications	Single-Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin*	Atorvastatin/ ezetimibe	Ezetimibe/ simvastatin	Niacin/ lovastatin†	Niacin/ simvastatin‡
Reduce TC, LDL-C, and apo B in adult patients with homozygous FH as adjunctive therapy to other lipid-lowering treatments or alone if such treatments are not available						✔						
Reduction of elevated TC and LDL-C levels in patients with primary hypercholesterolemia			✔ §								✔ § (lovastatin)	
Treatment of patients with primary dysbetalipoproteinemia who do not respond adequately to diet	✔				✔	✔		✔ (atorvastatin)				
Prevention of Cardiovascular Disease												
Adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower TC and LDL-C to target levels						✔						
Reduce the risk of myocardial infarction (MI) and stroke in patients with type 2 diabetes, and without clinically evidence coronary heart disease (CHD), but with multiple risk factors for CHD such as retinopathy, albuminuria, smoking, or hypertension (HTN)	✔							✔ (atorvastatin)				
Reduce the risk of MI, stroke, and for revascularization procedures and angina in adult patients without clinically evident CHD, but with multiple risk factors for CHD such as age, smoking, HTN, low HDL-C, or a family history of early CHD	✔							✔ (atorvastatin)				
Reduce the risk of MI, undergoing myocardial revascularization procedures, and cardiovascular mortality with no increase in death from noncardiovascular causes in patients with hypercholesterolemia without clinically evident CHD					✔							
Reduce the risk of MI, unstable angina, and coronary revascularization procedures in patients without symptomatic cardiovascular disease, average to moderately elevated TC and LDL-C, and below average			✔								✔ (lovastatin)	

Indications	Single-Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin*	Atorvastatin/ ezetimibe	Ezetimibe/ simvastatin	Niacin/ lovastatin†	Niacin/ simvastatin‡
HDL-C												
Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in patients with clinically evidence CHD	✔							✔ (atorvastatin)				
Reduce the risk of recurrent non-fatal MI in patients with a history of MI and hypercholesterolemia											✔ (niacin)	
Reduce the risk of stroke, MI, and arterial revascularization procedures in patients without clinically evidence CHD but with an increased risk of cardiovascular disease based on age ≥50 years old in men and ≥60 years old in women, high sensitivity C-reactive protein ≥2 mg/L, and the presence of at least one additional cardiovascular disease risk factor such as HTN, low HDL-C, smoking, or a family history of premature CHD						✔						
Reduce the risk of total mortality by reducing coronary death, MI, undergoing myocardial revascularization procedures, stroke and stroke/transient ischemic attack, and to slow the progression of coronary atherosclerosis in patients with clinically evidence CHD					✔							
Reduce the risk of total mortality by reducing CHD deaths, non-fatal MI and stroke, and need for coronary and non-coronary revascularization procedures in patients at high risk of coronary events because of existing CHD, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease							✔					
Reduce the risk of undergoing coronary revascularization procedures and slow the progression of coronary atherosclerosis in patients with clinically evidence CHD		✔										
Slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment			✔								✔ (lovastatin)	

Indications	Single-Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin*	Atorvastatin/ ezetimibe	Ezetimibe/ simvastatin	Niacin/ lovastatin†	Niacin/ simvastatin‡
strategy to lower TC and LDL-C to target levels												
Other												
Reduce the risk of hospitalization for angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented CAD by angiography and without heart failure or an ejection fraction <40%								✔ (amlodipine)				
Symptomatic treatment of chronic stable angina								✔ (amlodipine)				
Treatment of confirmed or suspected vasospastic angina								✔ (amlodipine)				
Treatment of HTN								✔ (amlodipine)				

*Indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate.
†Indicated for use when treatment with both niacin and lovastatin is appropriate.
‡Indicated for use when treatment with simvastatin monotherapy or niacin monotherapy is considered inadequate.
§When the response to diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate.
‖When the response to an appropriate diet has been inadequate.
¶In boys and postmenarchal girls 10 to 17 years of age.
#In adolescent boys and adolescent girls who are at least one year postmenarche, 10 to 16 years of age.
**In adolescent boys and girls, who are at least one year postmenarche, 10 to 17 years of age.
††In children and adolescent patients ages eight years of age and older.
ER=extended-release, IR=immediate-release.

Pharmacokinetics

Table 3. Pharmacokinetics[3-16,22]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single-Entity Agents				
Atorvastatin	14	1 to 2	2-, 4-hydroxy-atorvastatin acid; ortho- and parahydroxylated derivatives	7 to 14 (9 to 32*)
Fluvastatin	20 to 30	5	None	<3
Lovastatin	5	10	β-hydroxyacid derivative	Not reported
Pitavastatin	51	15	None	11 to 12
Pravastatin	17	20	None	2.6 to 3.2
Rosuvastatin	20	10	N-desmethyl rosuvastatin†	19
Simvastatin	5	13	β-hydroxyacid form	Not reported
Combination Products				
Amlodipine/ atorvastatin	64 to 90/14	70/1 to 2	Not reported/2-, 4-hydroxy-atorvastatin acid; ortho- and parahydroxylated derivatives	30 to 60/7 to 14 (9 to 32*)
Ezetimibe/ atorvastatin	Not reported/14	11/1 to 2	Ezetimibe glucuronide/β-hydroxyacid form/ and 2-, 4-hydroxy-atorvastatin acid; ortho- and parahydroxylated derivatives	19 to 30/7 to 14
Ezetimibe/ simvastatin	Not reported/5	11/13	Ezetimibe glucuronide/β-hydroxyacid form	19 to 30/Not reported
Niacin extended release/ lovastatin	60 to 76/5	60 to 76/10	Nicotinamide adenine dinucleotide/β-hydroxyacid derivative	Not reported/Not reported
Niacin extended release/ simvastatin	60 to 76/5	60 to 76/13	Nicotinamide adenine dinucleotide/β-hydroxyacid form	Not reported/Not reported

*Metabolites.
†Somewhat active.

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the high dose hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) in their Food and Drug Administration (FDA)-approved indications are outlined in Table 4.[23-213]

Statins are the most effective drugs available for lowering low density lipoprotein cholesterol (LDL-C).[1] Several clinical trials have consistently demonstrated the benefits of high dose statins on serum lipid levels in patients with lipid disorders. Based on the amount of LDL-C lowering required for a particular patient, one statin may be preferred over another; however, all available statins produced significant improvements in baseline serum lipid levels.[28-98,180-205]

Statins have also demonstrated significant cardiovascular benefits when used in primary prevention of coronary heart disease (CHD).[1,110-131] Two early primary prevention trials (West of Scotland Coronary Prevention Study [WOSCOPS] and Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS) demonstrated that the use of statins significantly reduced the risk for major coronary events.[116,120] Specifically the WOSCOPS trial (N=6,959) demonstrated that compared to placebo, pravastatin (40 mg/day) was associated with a significant 31% reduction in the risk of the combined endpoint of CHD death and nonfatal myocardial infarction (MI) (P<0.001). A reduction in the secondary endpoint of cardiovascular death was also significant in favor of pravastatin (32%; P=0.033).[120] The

AFCAPS/TexCAPs trial (N=6,605) demonstrated similar benefits but with lovastatin (20 to 40 mg/day). In this trial, lovastatin was associated with a significant 37% reduction in the risk of the combined endpoint of fatal or nonfatal MI, unstable angina or sudden cardiac death (*P*<0.001). The AFCAPS/TexCAPs trial contained too few events to perform survival analysis on cardiovascular and CHD mortality.[116]
The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT, N=10,305) was terminated early (median duration, 3.3 years) due to the significant benefits observed with atorvastatin. In this trial, patients had average cholesterol concentrations but were at an increased risk for CHD due to the presence of hypertension and three additional CHD risk factors. Compared to placebo, atorvastatin significantly reduced the risk of the combined endpoint of CHD death and nonfatal MI by 35% (*P*=0.0005).[114] Despite not demonstrating any benefit on all-cause mortality within the ASCOT trial (*P*=0.1649), atorvastatin has been associated with significant reductions in all-cause mortality in other primary prevention trials.[111,114,115] A benefit in all-cause mortality, as well as other cardiovascular outcomes, with rosuvastatin in primary prevention was more recently demonstrated in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial (N=17,802). This trial sought to evaluate the efficacy of rosuvastatin in reducing cardiac events in patients with elevated high sensitivity C-reactive protein levels, which they note as being a predictor for cardiac events. This trial was also terminated early (median duration 1.9, years) due to the significant benefits observed with rosuvastatin. Compared to placebo, rosuvastatin significantly reduced the risk of a first major cardiovascular event (nonfatal MI, nonfatal stroke, hospitalization for unstable angina, revascularization procedure or cardiovascular death) by 44% (*P*<0.0001). When analyzed individually, rosuvastatin was associated with a significant benefit for all primary outcomes, as well as all-cause mortality (*P*=0.02).[121]

Meta-analyses support the findings observed in the individual primary prevention trials.[127-131] Because head-to-head primary prevention trials are rare it is difficult to determine if one particular statin is more effective than another. Treatment guidelines do not distinguish among the available statins for primary prevention. Specifically, guidelines state that patients with risk factors for CHD but no history of disease are likely to decrease their risk of CHD with lipid lowering therapy.[20] Again, the statins currently FDA-approved for primary prevention include atorvastatin, lovastatin, pravastatin and rosuvastatin.[3,6,7,9,10] Consideration of specific FDA-approved indications and potential percentage of LDL-C lowering for an individual statin may help determine which agent may be more appropriate for a particular patient based on their medical history and risk factors.

Similar to primary prevention, the evidence supporting the use of statins in secondary prevention of CHD is well established. Overall, the absolute benefits of statins are larger in secondary prevention than in primary prevention.[1,100-109,132-179] In terms of clinical outcomes in secondary prevention, unlike with primary prevention, head-to-head trials have been conducted. The Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) trial (N=8,888) compared intensive lipid lowering therapy with atorvastatin 80 mg/day to moderate therapy with simvastatin 20 mg/day (with the potential to increase to 40 mg/day based on improvements in lipid profile). In this trial, atorvastatin significantly reduced the risk of the primary composite endpoint of CHD death, nonfatal MI or cardiac arrest with resuscitation by 11% (*P*=0.07), but the treatments were no different in terms of all-cause (*P*=0.81), cardiovascular (*P*=0.78) or noncardiovascular (*P*=0.47) mortality. In addition, intensive therapy with atorvastatin 80 mg/day was associated with a significantly higher incidence of discontinuations due to adverse events (*P*<0.001).[173]

Several trials have demonstrated that statins are effective in delaying the progression of atherosclerotic disease in patients with CHD.[99-109] Included in these is the head-to-head REVERSAL trial that demonstrated that intensive lipid lowering with atorvastatin 80 mg/day was associated with a significantly lower median percentage change in atheroma volume compared to moderate lipid lowering with pravastatin 40 mg/day after 18 months (*P*=0.02).[106] Fluvastatin, lovastatin, pravastatin and rosuvastatin are the only statins FDA-approved to slow the progression of coronary atherosclerosis in patients with clinically evident CHD.[4-7,9,10]

The majority of secondary prevention trials have evaluated the use of statins initiated three to six months after an acute cardiac event; however, evidence supports the use of these agents initiated right after an acute event.[151,160,162,166] The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial (N=3,086), a placebo-controlled trial with atorvastatin, is noteworthy as it demonstrated

that when initiated in the hospital following an acute coronary syndrome, atorvastatin was safe and associated with a 16% reduction in the composite of death, nonfatal acute MI, resuscitated cardiac arrest or recurrent symptomatic myocardial ischemia after 16 weeks (*P*=0.048).[146] Of the head-to-head trials, the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial (N=4,162) again compared intensive lipid therapy with atorvastatin 80 mg/day to standard therapy with pravastatin 40 mg/day (with a potential to increase to 80 mg/day based on improvements in lipid profile). Patients who were hospitalized with an acute coronary syndrome within the preceding 10 days were enrolled. After two years, atorvastatin significantly reduced the combined endpoint of all-cause mortality, MI, unstable angina requiring hospitalization, coronary revascularization performed >30 days after randomization and stroke by 16% compared to pravastatin (*P*=0.005). Among the individual endpoints, atorvastatin was significant for reducing the risk of revascularization (*P*=0.04) and unstable angina (*P*=0.02). In this trial, discontinuations due to adverse events were similar between the two treatments (*P*=0.11).[166]

Similar to primary prevention, guidelines do not distinguish among the available statins for use in secondary prevention. Specifically, statins are recommended in patients with established CHD or CHD risk equivalents, and choice of agent should be based on cost and the amount of lipid lowering required for a specific patient.[20] Statins that are FDA-approved for use in secondary prevention include atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin (slow progression of coronary atherosclerosis only) and simvastatin.[3,7,9-11]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Familial Hypercholesterolemia (Single-Entity Agents)				
Avis et al[23] PLUTO Rosuvastatin 5, 10 or 20 mg/day for 12 weeks vs placebo All patients were randomized after a 6-week diet lead in period. After 12 weeks, patients entered a 40 week, OL, dose-titration phase. Patients originally randomized to placebo and those with LDL-C <100 mg/dL on their assigned rosuvastatin dose began the OL phase on rosuvastatin 5 mg/day. All others continued	DB, MC, PC, RCT Children 10 to 17 years of age with a heterozygous FH by documentation of a genetic defect or by predefined clinical criteria, Tanner stage ≥11, with female patients being ≥1 year post menarche and fasting LDL-C ≥190 or >160 mg/dL if there was a family history of premature cardiovascular disease or if the patient had ≥2 other risk factors for cardiovascular disease	N=177 12 weeks	Primary: Percent change from baseline in LDL-C Secondary: Changes from baseline in lipoproteins, proportion of patients achieving LDL-C goal (<110 mg/dL), safety	Primary: Rosuvastatin was associated with a significant reduction in LDL-C compared to placebo (38, 45 and 50 vs 1%; *P*<0.001 for all). Secondary: Compared to placebo, significant reductions with rosuvastatin were achieved for TC (*P*<0.001 for all) and apo B (*P*<0.001), but not for TG (*P*=0.8, *P*=0.1 and *P*=0.1). HDL-C (*P*=0.4, *P*=0.2 and *P*=0.5) and apo AI (*P*=0.7, *P*=0.3 and *P*=0.6) were not significantly different from placebo. No patient receiving placebo achieved the LDL-C goal compared to 12, 41 and 41% of patients receiving rosuvastatin 5, 10 and 20 mg during the DB phase. In the OL phase, the goal was achieved by 40% of patients. A LDL-C goal of <130 mg/dL was achieved by 68% of patients in the OL phase. At the end of the OL phase, 26 patients were receiving rosuvastatin 5 mg, 25 patients were receiving 10 mg and 122 patients were receiving 20 mg. During the DB phase, the overall frequencies of adverse events were 50, 64, 55 and 54% (*P* value not reported). The most commonly reported adverse events included nasopharyngitis, influenza, myalgia and nausea. One serious adverse event of blurred vision occurred with placebo and one patient receiving rosuvastatin 20 mg had a vesicular rash during the OL phase. There was no hepatic, skeletal muscle or renal adverse events reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
their rosuvastatin dose from the DB phase.				
Avis et al[24] Standard statin therapy (pravastatin, fluvastatin, lovastatin, rosuvastatin, simvastatin, atorvastatin) vs placebo	MA (6 RCTs) Patients <18 years of age with heterozygous FH	N=798 Up to 2 years	Primary: Percentage change in TC, LDL-C, TG, HDL-C, apo B and apo AI; difference in absolute changes in IMT; safety Secondary: Not reported	Primary: Statin therapy was associated with a 23% reduction in TC compared to placebo (95% CI, 19 to 27; *P* value not reported). Statin therapy was associated with a 30% reduction in LDL-C compared to placebo (95% CI, 24 to 36; *P* value not reported). Statin therapy was associated with a 3.6% increase in HDL-C compared to placebo (95% CI, 1.33 to 5.94; *P* value not reported). Statin therapy was associated with a 25% reduction in apo B compared to placebo (95% CI, 19 to 31; *P* value not reported). Statin therapy was associated with a 2.4% reduction in apo AI compared to placebo (95% CI, 0.41 to 4.45; *P* value not reported). Statin therapy was associated with a significant carotid IMT regression compared to placebo (*P*=0.02). Statin therapy was not associated with a significant risk of adverse events compared to placebo (RR, 0.99; 95% CI, 0.79 to 1.25). Statin therapy was not associated with a significant risk of AST (RR, 0.98; 95% CI, 0.23 to 4.26), ALT (RR, 2.03; 95% CI, 0.24 to 16.95) or CK elevation (RR, 1.38; 95% CI, 0.18 to 10.82) compared to placebo. Secondary: Not reported
Marais et al[25] Rosuvastatin 80 mg QD for 6 weeks	DB, RCT, XO Patients >10 years of age, weighing ≥32 kg	N=44 30 weeks (includes the 18	Primary Percent change in LDL-C from baseline to week	Primary Rosuvastatin 20 to 80 mg achieved a significant reduction in LDL-C from baseline after 18 weeks of therapy (21.4%; *P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs atorvastatin 80 mg QD for 6 weeks All patients were randomized following a 18 week OL titration phase during which patients received rosuvastatin 20 mg QD for 6 weeks, titrated up to 40 mg/day for 6 weeks, titrated up to 80 mg/day for another 6 weeks, all after a 4 week dietary lead in period.	with homozygous FH, fasting LDL-C >500 mg/dL, TG <600 mg/dL and either xanthomata before 10 years of age or both parents with FH	week OL titration phase)	18 Secondary Response rate; percent change in TC, apo B, TG and HDL-C	Patients without a portacaval shunt and those not receiving plasmapheresis who received rosuvastatin 20 to 80 mg experienced a 15% reduction in LDL-C from baseline after 18 weeks of therapy (*P* value not reported). Secondary: Rosuvastatin was associated with an overall 72% response rate (≥15% reduction in baseline LDL-C) (*P* value not reported). Rosuvastatin 20 to 80 mg was associated with a significant reduction in TC and apo B from baseline after 18 weeks of therapy (20%; *P*<0.0001). Rosuvastatin 20 to 80 mg was associated with a nonsignificant increase in TG and HDL-C from baseline after 18 weeks of therapy (3.3 and 3.1%, respectively; *P*>0.05). At week 24, rosuvastatin and atorvastatin did not differ in the magnitude of LDL-C reduction from baseline (19.1 vs 18.0%; *P*=0.67). At week 24, there was no significant difference between treatments in reductions from baseline TC (17.6 vs 17.9%; *P*=0.91), TG (6.3 vs 13.9%; *P*=0.21) or apo B (11.4 vs 11.7%; *P*=0.90). The only significant difference between the two treatments was in the change from baseline in apo AI. While patients receiving rosuvastatin experienced an increase, atorvastatin-treated patients exhibited a reduction in apo AI (*P*=0.001).
Arca et al[26] Atorvastatin 10 mg/day, titrated up to 80 mg/day vs	OL, RCT Patients 30 to 75 years of age with diagnosis of familial combined hyperlipidemia with TC and/or TG levels	N=56 24 weeks	Primary: Change in TC, LDL-C, HDL-C, TG, apo A and endothelin-1 Secondary: Not reported	Primary: Atorvastatin was associated with a significant 9% reduction in TC compared to fenofibrate (95% CI, 3.0 to 15.1; *P*=0.004). Atorvastatin was associated with a significant 17% reduction in LDL-C compared to fenofibrate (95% CI, 8.0 to 26.1; *P*<0.001). Fenofibrate was associated with a significant 15.5% reduction in TG

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
fenofibrate 200 mg/day	≥90th Italian population percentiles, and/or hyperapobeta-lipoproteinemia			compared to atorvastatin (95% CI, 3.35 to 27.70; *P*=0.013). Fenofibrate was associated with a significant 14.2% increase in HDL-C compared to atorvastatin (95% CI, 3.8 to 24.6%; *P*=0.008). Fenofibrate was associated with a significant 5.2 and 22.0% increase in apo AI and AII compared to atorvastatin (*P*=0.044 and *P*<0.001, respectively). Fenofibrate was associated with a significant 16.7% reduction in endothelin-1 from baseline (*P*<0.05). Atorvastatin was not associated with a significant change in endothelin-1 (*P* value not reported). Secondary: Not reported
Gagné et al[27] Statin 40 mg/day for 14 weeks, followed by statin 40 mg/day plus ezetimibe 10 mg/day 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	DB, MC, RCT Patients ≥12 years of age with homozygous FH, LDL-C ≥100 mg/dL and TG ≤350 mg/dL (if on atorvastatin or simvastatin 40 mg/day)	N=50 26 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, apo AI and hsCRP	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). There was no significant difference in any of the other secondary outcome measures between the two treatments (*P*>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
by statin 80 mg/day Statins evaluated included atorvastatin and simvastatin.				
Hypercholesterolemia (Single-Entity Agents)				
Koshiyama et al[28] KISHIMEN Pitavastatin 1 to 2 mg/day	MC, OL, PRO Patients with TC ≥220 mg/dL and TG <400 mg/dL	N=178 12 months	Primary: Changes from baseline in LDL-C, HDL-C, remnant-like particle cholesterol, TG and hsCRP Secondary: Not reported	Primary: LDL-C was significantly reduced by 32.6, 31.0 and 30.3% after three, six and 12 months, respectively (*P* value not reported). HDL-C was significantly increased by 3.1, 5.9 and 2.6% after three, six and 12 months, respectively. In patients with baseline HDL-C <40 mg/dL, HDL-C increased by 16.2, 22.4 and 19.0% after three, six and 12 months (*P* values not reported). Remnant-like particle cholesterol were significantly reduced by 14.0, 20.2 and 22.8% after three, six and 12 months, respectively (*P* value not reported). TG was significantly reduced by 17.7 and 15.9% after three and 12 months, respectively, in patients whose baseline TG >150 mg/dL, although TG was not significantly reduced in the overall population (*P* value not reported). hsCRP were significantly reduced in 31 patients after 12 months (*P*<0.01). hsCRP was significantly reduced in patients with diabetes (*P*<0.05). Secondary: Not reported
Motomura et al[29] Pitavastatin 2 mg/day	MC, OL, PRO Patients >20 years of age with type 2 diabetes, LDL-C ≥120 mg/dL, TG <400	N=65 6 months	Primary: Changes from baseline in lipid panel and hsCRP Secondary:	Primary: Significant reductions in TC, LDL-C and TG and significant increases in HDL-C were observed at one, three and six months after treatment with pitavastatin was initiated (*P*<0.05 for all). After six months, average reductions in TC, LDL-C and TG were: 27.1,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	mg/dL, HbA_{1c} <9.0% and not on hypolipidemic medication for the preceding 4 weeks		Not reported	41.1 and 6.2%. Average increase in HDL-C at six months was 4.5%. Changes in hsCRP were not significant after three months of treatment (0.49 to 0.43 mg/L; *P*=0.057), but was significantly reduced at six months (0.49 to 0.37 mg/L; *P*<0.05). Secondary: Not reported
Ose et al[30] Pitavastatin 4 mg QD	ES, OL Patients with primary hypercholesterolemia or combined dyslipidemia who had previously received pitavastatin, atorvastatin or simvastatin for 12 weeks during a DB, Phase III trial	N=1,353 52 weeks	Primary: Safety and tolerability Secondary: Proportion of patients achieving NCEP and European Atherosclerosis Society LDL-C goals (not specified), changes from baseline in lipid profiles	Primary: Overall, 54.8% of patients reported experiencing at least one treatment emergent adverse event, 12.0% of which were determined by the investigators to be related to pitavastatin. Furthermore, 4.1% (n=55) of patients discontinued due to treatment emergent adverse events and 3.6% (n=49) of patients experienced a serious treatment emergent adverse event, none of which were related to pitavastatin. Two patients died during the trial, neither of which were determined to be related to pitavastatin. The most commonly reported adverse events were increased CK levels (5.8%), nasopharyngitis (5.4%) and myalgia/myalgia intercostals (4.1%). Secondary: At the end of the original DB phases, 71.5 and 69.4% of patients had achieved the LDL-C goals. After 52 weeks, 74.0 and 73.5% of patients achieved the goals. The reductions in mean LDL-C observed at the end of the DB phases were sustained throughout the ES. HDL-C showed a gradual increase; mean HDL-C at week 52 was 57.0 mg/dL (equivalent to a mean change of 14.3% above baseline and 8.7% above end of the DB phases; *P* value not reported). Non-HDL-C was associated with a sustained decrease from baseline during the ES (38.9% at end of DB phases and 39.6% at week 52). Concentrations of TG, TC, apo AI, apo B, TC:HDL-C, non-HDL-C:HDL-C and apo B:AI were similar at the end of the ES to those observed at the end of the DB phases.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Stein et al[31] Rosuvastatin 40 mg/day for ≤96 weeks All patients entered a 6-week dietary lead in period.	MC, OL Patients ≥18 years of age with LDL-C ≥190 to ≤260 mg/dL and TG <400 mg/dL	N=1,380 ≤96 weeks	Primary: Percentage of patients who achieved NCEP ATP III LDL-C goals (<160, <130 or <100 mg/dL) at 12 weeks Secondary: Reduction in LDL-C, HDL-C, apo ratio, LDL-C:HDL-C, TC, TC:HDL-C, non-HDL-C, TG and apo B	Primary: At 12 weeks, 83% of patients achieved an LDL-C goal (95% CI, 81 to 85; *P* value not reported). Secondary: At 48 weeks, rosuvastatin was associated with a significant reduction from baseline in LDL-C, apo ratio, LDL-C:HDL-C, TC, TC:HDL-C, non-HDL-C, TG and apo B (*P*<0.0001). At 48 weeks, rosuvastatin was associated with a significant increase from baseline in HDL-C (11%; *P*<0.0001). During the 96-week trial period, 13.0% of patients experienced a serious adverse event, 0.4% of these patients died and 2.0% experienced myalgia (*P* value not reported).
Preston et al[32] RESPOND Amlodipine 5 or 10 mg QD plus atorvastatin 10, 20, 40 or 80 mg QD (all possible dosing combinations) vs amlodipine 5 or 10 mg QD vs atorvastatin 10, 20, 40 or 80 mg QD	DB, RCT Patients 18 to 75 years of age with hypertension and dyslipidemia	N=1,660 8 weeks	Primary: Mean change from baseline in SBP and LDL-C Secondary: Augmentation of BP lowering with the addition of atorvastatin and augmentation of LDL-C lowering with the addition of amlodipine, reduction in 10 year Framingham risk scores, adverse effects	Primary: Regardless of dose, combination therapy was associated with significantly greater reductions in SBP compared to atorvastatin (*P*<0.001 for all comparisons). Overall, combination therapy and atorvastatin achieved comparable decreases in LDL-C. Only the combination of amlodipine 5 mg plus atorvastatin 10 mg achieved significant reductions in LDL-C compared to atorvastatin 10 mg (*P*=0.007). Secondary: Regardless of dose, there was no difference in terms of SBP lowering between combination therapy and amlodipine (*P*>0.05 for all comparisons). Regardless of dose, combination therapy significantly reduced LDL-C compared to amlodipine (*P*<0.001 for all comparisons). A maximal reduction in 10 year Framingham risk scores was observed with combination therapy (5/80 and 10/80 mg; *P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs placebo				The proportion of patients who discontinued therapy due to adverse effects was similar with all treatments (5.6 vs 5.4 vs 4.1, respectively; *P* value not reported).
Messerli et al[33] AVALON Amlodipine 5 mg/day for 8 weeks, followed by the addition of atorvastatin 10 mg/day for another 8 weeks vs atorvastatin 10 mg/day for 8 weeks, followed by the addition of amlodipine 5 mg/day for an additional 8 weeks vs amlodipine/ atorvastatin 5/10 mg/day for 16 weeks vs placebo for 16 weeks	DD, MC, OL, RCT Patients with hypertension and dyslipidemia	N=847 28 weeks	Primary: Proportion of patients who reached the JNC 7 and NCEP ATP III goals, side effects Secondary: Not reported	Primary: A significantly greater proportion of patients receiving combination therapy achieved JNC 7 and NCEP ATP goals at eight weeks compared to patients receiving amlodipine or patients receiving atorvastatin monotherapy (45.0 vs 8.3 and 28.6%, respectively; *P*<0.001). The incidence of side effects was similar across all treatments (*P* value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
All patients received an additional 12 weeks of OL treatment following the first 16 weeks of therapy.				
Hunninghake et al[34] Colesevelam 3.8 g/day vs atorvastatin 10 mg/day vs colesevelam 3.8 g/day plus atorvastatin 10 mg/day vs atorvastatin 80 mg/day vs placebo	DB, MC, PC, RCT Patients with LDL-C ≥160 mg/dL and TG ≤300 mg/dL	N=91 4 weeks	Primary: Change from baseline in LDL-C Secondary: Change from baseline in TC, HDL-C, TG, apo B, apo AI and Lp(a)	Primary: All treatments resulted in significant LDL-C reductions as compared to baseline. LDL-C reductions from baseline were -12% with colesevelam (*P*<0.05), -38% with atorvastatin 10 mg (*P*<0.0001), -48% with colesevelam plus atorvastatin (*P*<0.0001) and -53% with atorvastatin 80 mg (*P*<0.0001), respectively. Secondary: Colesevelam reduced TC by six percent (*P*<0.05), increased HDL-C by three percent (*P*<0.05) and increased TG by 10% (*P* value not reported). Atorvastatin 10 mg reduced TC by 27% (*P*<0.0001), increased HDL-C by eight percent (*P*<0.05) and reduced TG by 24% (*P*<0.05). Colesevelam plus atorvastatin reduced TC by 31% (*P*<0.0001), increased HDL-C by 11% (*P*<0.05) and reduced TG by one percent (*P* value not reported). Atorvastatin 80 mg reduced TC by 39% (*P*<0.0001), increased HDL-C by five percent (*P*<0.05) and reduced TG by 33% (*P*<0.0001). Reductions in TC were significant between all treatment groups except atorvastatin 10 mg relative to colesevelam plus atorvastatin. No significant differences in HDL-C were found between the treatment groups (*P* values not reported). Apo B levels decreased significantly for with all treatments relative to baseline (*P*<0.01). No significant changes in apo AI and Lp(a) were reported (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Brown et al[35] Colestipol 5 to 10 g TID plus niacin 125 mg BID, titrated to 1 to 1.5 g TID vs Colestipol 5 to 10 g TID plus lovastatin 20 mg BID, titrated to 40 mg BID vs placebo (or colestipol if LDL-C was elevated)	DB, PC, RCT Men ≤62 years of age with elevated apo B and a family history of CAD	N=120 32 months	Primary: Average change in the percent stenosis for the worst lesion in each of the nine proximal segments Secondary: Average changes in all lesions measured in each patient and in proximal lesions causing ≥50% (severe) stenosis or <50% (mild) stenosis at baseline	Primary: On average, placebo (conventional therapy) increased the index of stenosis by 2.1 percentage points from a baseline of 34%. By contrast, it decreased by 0.7 percentage points with colestipol plus lovastatin and by 0.9 percentage points with colestipol and niacin (*P*<0.003 for trend). At trial end, on average, these nine lesions were almost three percentage points less severe among patients treated intensively compared to conventionally. This difference represents almost 1/10 of the amount of disease present at baseline (34% stenosis). Secondary: Placebo (conventional therapy) resulted in consistent worsening of disease when looking at the effect of treatment on certain subsets of lesions (all lesions measured in each patient, lesions causing severe or mild stenosis and those that did not cause total occlusion at baseline). The results with both treatment groups were significantly different from those receiving conventional therapy for each subset, demonstrating either a mean regression or no change in severity of disease.
Kerzner et al[36] 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	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
placebo				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 placebo (*P* values not reported).
Lewis et al[37] Pravastatin 80 mg QD vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with hypercholesterolemia, LDL-C ≥100 and TG <400 mg/dL, with ≥6 month history of compensated liver disease	N=326 36 weeks	Primary: Percent change from baseline at week 12 in LDL-C, TC and TG; ALT event rate (ALT at least two times the ULN for those with normal ALT at baseline or a doubling of the baseline ALT for those with elevated ALT at baseline) Secondary: Not reported	Primary: Pravastatin was associated with a significant reduction in LDL-C, TC and TG at week 12 compared to placebo (*P*<0.0001). There was no significant difference between the two treatments in the ALT event rate at any time during the trial (*P*>0.05). By week 36, 7.5 and 12.5% of patients receiving pravastatin and placebo had at least one ALT event (*P*=0.1379). Secondary: Not reported
Melani et al[38] Ezetimibe 10 mg/day vs pravastatin 10, 20 or 40 mg/day vs	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	N=538 12 weeks	Primary: Percent change from baseline LDL-C Secondary: Mean and percent changes from baseline in calculated LDL-C,	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
ezetimibe 10 mg/day plus pravastatin 10, 20 or 40 mg/day vs placebo	mmol/L)		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)	percentage reduction in LDL-C compared to pravastatin 40 mg ($P \leq 0.05$). 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).
Coll et al[39] Ezetimibe 10 mg/day vs fluvastatin ER 80 mg/day	RCT Patients ≥18 years of age with HIV receiving stable HAART for ≥6 months and fasting LDL-C ≥3.30 mmol/L	N=20 6 weeks	Primary: LDL-C, TC, endothelial function Secondary: Not reported	Primary: Ezetimibe produced a 20% ($P=0.002$) LDL-C reduction and a 10% TC reduction ($P=0.003$). 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Illingworth et al[40] Lovastatin 10 to 80 mg/day vs niacin IR 0.25 mg to 1.5 g TID	MC, OL, RCT Patients 21 to 75 years of age with primary hypercholesterolemia and either an LDL-C >160 mg/dL and CHD or ≥2 CHD risk factors without CHD or LDL-C >190 mg/dL without CHD or ≥2 risk factors after rigorous diet	N=136 26 weeks	Primary: Change from baseline in lipid parameters Secondary: Safety	Primary: Lovastatin reduced TC, LDL-C and apo B significantly more than niacin (*P*<0.01 for all). At weeks 10, 18 and 26, LDL-C was reduced by 26, 28 and 32% with lovastatin compared to five, 16 and 21% with niacin, respectively. The target treatment goal of LDL-C <130 mg/day for patients with CHD or less than two risk factors was achieved in 14, 19 and 35% of patients receiving lovastatin compared to zero, 18 and 26% of patients receiving placebo at weeks 10, 18 and 26, respectively (*P* values not significant). For the majority of those patients with CHD or two or more risk factors in whom the LDL-C goal was <110 mg/dL, neither drug was effective in achieving this goal. In these patients only 13 and 11% achieved this goal at week 26, respectively (*P* value not reported). Niacin was more effective in decreasing TG at week 26 (*P*<0.01 vs lovastatin). Both treatments were effective in reducing VLDL-C, with no significant difference observed between the two treatments (*P* value not reported). Niacin produced reductions in Lp(a) of 14, 30 and 35% at weeks 10, 18 and 26, whereas lovastatin had no effect (*P*<0.05 or *P*<0.01 between drugs at each time point). Niacin was significantly more effective at increasing HDL-C and apo A-I (*P*<0.01 vs lovastatin), except for the change in apo A1 at week 10 (*P* value not reported). Niacin increased HDL-C by 20, 29 and 33% and apo AI by 11, 19 and 22% at weeks 10, 18 and 26. Lovastatin resulted in a modest increase in HDL-C and apo AI of 7 and 6%, respectively, at week 26. Secondary: Four deaths occurred in the trial, one with niacin and three with lovastatin.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				All were related to atherosclerosis, and none were deemed to be drug-related. Five and nine patients receiving lovastatin and niacin discontinued treatment because of adverse experiences (excluding deaths). For those who discontinued treatment, the reason was considered drug-related in four and eight patients receiving lovastatin and niacin (*P* value not significant). The major reasons for discontinuation of niacin were cutaneous complaints, including flushing, pruritis and rash. One patient discontinued lovastatin because of myalgias. Overall, patient tolerance to the treatments was better with lovastatin. Adverse events (in decreasing frequency) that occurred more frequently with niacin include flushing, paresthesia, pruritis, dry skin, nausea/vomiting, asthenia and diarrhea.
Eriksson et al[41] Cholestyramine 16 g/day vs cholestyramine 8 g/day plus pravastatin 20 mg/day vs pravastatin 20 or 40 mg/day	MC, RCT Patients 30 to 65 years of age	N=2,036 12 months	Primary: Percent change from baseline in LDL-C Secondary: Compliance	Primary: Percent changes in LDL-C from baseline to endpoint with cholestyramine, cholestyramine plus pravastatin, pravastatin 20 mg and pravastatin 40 mg were -26 (95% CI, -23 to -29), -36 (95% CI, -33 to -39), -27 (95% CI, -25 to -29) and -32% (95% CI, -30 to -34). Secondary: Compliance rates with cholestyramine, cholestyramine plus pravastatin, pravastatin 20 mg and pravastatin 40 mg were 44, 53, 76 and 78% (*P* values not reported). Pravastatin adverse events were the most common reasons for withdrawal. Adverse events were most common with cholestyramine and cholestyramine plus pravastatin.
Ballantyne et al[42] Ezetimibe 10 mg/day	DB, PC, RCT Patients ≥18 years of age with primary	N=628 12 weeks	Primary: Percentage reduction from baseline in LDL-C	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
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	hypercholesterolemia (LDL-C 145 to 250 mg/dL and TG ≤350 mg/dL)		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	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) 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).
Hing Ling et al[43] Atorvastatin 40 mg/day vs	AC, DB, MC, RCT Patients 18 to 79 years of age at high risk for CHD with primary	N=250 6 weeks	Primary: Change from baseline in LDL-C, Secondary: TC, HDL, CRP,	Primary: After six weeks, treatment with ezetimibe/simvastatin resulted in significantly greater reductions from baseline in LDL-C levels compared to treatment with atorvastatin 40 mg (-26.8 vs -11.8%; *P*<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
ezetimibe 10 mg/day plus simvastatin 40 mg/day All patients received atorvastatin 20 mg/day for six weeks at baseline.	hypercholesterolemia, LDL >100 mg/dL and <160 mg/dL, triglycerides <350 mg/dL, liver function tests within normal limits without active liver disease		Apo AI, Apo B, TG, non-HDL, LDL-C/HDL ratio, TC/HDL ratio, non-HDL/HDL ratio, Apo AI/Apo B ratio	Treatment with ezetimibe/simvastatin resulted in significantly greater reductions in TC (*P*<0.001), non-HDL-C (*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 TG (*P*=0.593), HDL-C (*P*=0.211), or CRP (*P*=0.785).
Pearson et al[44] 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 hsCRP, 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 hsCRP 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 hsCRP 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
Winkler et al[45] Fluvastatin 80	MC, OL, RCT, XO Patients 18 to 75	N=75 6 weeks	Primary: Changes from baseline in lipids,	Primary: Reductions in TC, LDL-C and apo B were greater with ezetimibe plus simvastatin compared to fluvastatin plus fenofibrate, but differences only

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day plus fenofibrate 200 mg/day vs ezetimibe 10 mg/day plus simvastatin 20 mg/day	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, BP (≥85/≥130 mm Hg), fasting glucose ≥100 mg/dL or prevalent type 2 diabetes		lipoproteins and apolipoproteins; LDL subfractions Secondary: Not reported	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
Becker et al[46] Simvastatin 40 mg/day plus traditional counseling vs alternative treatment (therapeutic lifestyle changes and ingestion of red yeast rice and fish oil supplements)	RCT Patients 18 to 80 years of age with hypercholesterolemia who met NCEP ATP III criteria for primary prevention using statin therapy	N=74 3 months	Primary: Percent change from baseline in LDL-C Secondary: Percent change from baseline in HDL-C and TG, weight loss	Primary: There was a significant reduction in LDL-C with both simvastatin (39.6±20.0%) and alternative treatment (42.4±15.0%) (*P*<0.001), with no significant difference noted between the two treatments (*P* value not reported). Secondary: Alternative treatment was associated with a significant reduction in TG compared to simvastatin (29 vs 9%; 95% CI, 61.0 to 11.7; *P*=0.003). No differences between the two treatments were noted in improvements with HDL-C (*P*=0.21). Alternative treatment was associated with a significant reduction in weight loss compared to simvastatin (5.5 vs 0.4%; 95% CI, 5.5 to 3.4; *P*<0.001).
Meredith et al[47] Simvastatin 20 mg QD vs	DB, PG, RCT Patients who had undergone elective coronary angiography, had stable CAD and	N=107 16 weeks	Primary: Change from baseline in hsCRP Secondary: Change from	Primary: There was no difference between simvastatin 20 and 80 mg in terms of change from baseline in hsCRP (*P*=0.82). Secondary: Simvastatin, regardless of dose, was more effective than placebo in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
simvastatin 80 mg QD vs placebo	hsCRP >3 mg/L		baseline in LDL-C, TC and TG	baseline reductions of LDL-C (*P*<0.001). Simvastatin, regardless of dose, was more effective than placebo in baseline reductions in hsCRP (*P*=0.007). Simvastatin, regardless of dose, was more effective than placebo in baseline reductions in TC (*P*<0.001). Simvastatin, regardless of dose, was more effective than placebo in baseline reductions in TG (*P*=0.01).
Knapp et al[48] Colesevelam 3.8 g/day vs simvastatin 10 mg/day vs colesevelam 3.8 g/day plus simvastatin 10 mg/day vs colesevelam 2.3 g/day vs simvastatin 20	DB, MC, PC, RCT Patients ≥18 years of age with LDL-C ≥160 mg/dL and TG ≤300 mg/dL who are not taking cholesterol lowering medication	N=258 6 weeks	Primary: Change from baseline in LDL-C Secondary: Percent change in LDL-C; mean and percent change from baseline in TC, HDL-C, TG, apo B and apo AI	Primary: LDL-C changes from baseline were -7 mg/dL with placebo (*P*<0.05), -31 mg/dL with colesevelam 3.8 g (*P*<0.0001), -48 mg/dL with simvastatin 10 mg (*P*<0.0001), -80 mg/dL with colesevelam 3.8 g plus simvastatin 10 mg (*P*<0.0001), -17 mg/dL with colesevelam 2.3 g (*P*<0.0001), -61 mg/dL with simvastatin 20 mg (*P*<0.0001) and -80 mg/dL with colesevelam 2.3 g plus simvastatin 20 mg (*P*<0.0001), respectively. Secondary: LDL-C percent changes from baseline were -4% with placebo (*P*<0.05), -16% with colesevelam 3.8 g (*P*<0.0001), -26% with simvastatin 10 mg (*P*<0.0001), -42% with colesevelam 3.8 g plus simvastatin 10 mg (*P*<0.0001), -8% with colesevelam 2.3 g (*P*<0.0001), -34% with simvastatin 20 mg (*P*<0.0001) and -42% with colesevelam 2.3 g plus simvastatin 20 mg (*P*<0.0001), respectively. Significant changes from baseline were observed for all treatments in mean and percent change in TC (*P*<0.0001 for all, except colesevelam 2.3 g; *P*<0.05). Significant changes from baseline were observed for mean and percent change in HDL-C with simvastatin 10 mg (*P*<0.05), colesevelam 3.8 g plus simvastatin 10 mg (*P*<0.0001), colesevelam 2.3 g (*P*<0.05), simvastatin 20 mg (*P*<0.05) and colesevelam 2.3 g plus simvastatin 20 mg (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day vs colesevelam 2.3 g/day plus simvastatin 20 mg/day vs placebo				Significant changes from baseline were observed for mean and percent change in TG with colesevelam 3.8 g (P<0.05), simvastatin 10 mg (P<0.05), simvastatin 20 mg (P<0.05) and colesevelam 2.3 g plus simvastatin 20 mg (P<0.05). Significant reductions from baseline for apo B were observed with all treatments. Reductions were significant (P<0.05) compared to placebo for all treatments except colesevelam 2.3 g (P value not reported). Significant increases in apo AI were achieved with all treatments except simvastatin 10 mg (P<0.05).
Chenot et al[49] Simvastatin 40 mg/day vs simvastatin 40 mg/day plus ezetimibe 10 mg/day vs no lipid lowering therapy	RCT Patients admitted for an acute MI (with or without ST-segment elevation) to the coronary unit, with pain that started within 24 hours of admission	N=60 7 days	Primary: Change from baseline to days two, four and seven in LDL-C; proportion of patients achieving an LDL-C <70 mg/dL Secondary: Not reported	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). 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[50] Ezetimibe 10 mg/day	DB, MC, RCT Patients >18 years of	N=668 20 week	Primary: Mean percent change from	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to simvastatin (49.9

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
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	age with primary hypercholesterolemia		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 hsCRP	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). 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Goldberg et al[51] 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 hsCRP; proportion of patients reaching their NCEP ATP III LDL-C goal <130 or <100 mg/dL at 12 weeks	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 hsCRP 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 <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).
Brown et al[52] Niacin 2.4±2.0 g/day (mean dose) plus simvastatin 13±6 mg/day (mean dose)	DB, PC Patients with clinical CAD (previous MI, coronary interventions or confirmed angina) and with ≥3 stenosis	N=160 3 years	Primary: Changes in lipid profile, arteriographic evidence of change in coronary stenosis (percent of	Primary: The mean levels of LDL-C, HDL-C and TG were significantly altered by -42 (*P*<0.001), 26 (*P*<0.001) and -36% (*P*<0.001), respectively, with niacin plus simvastatin, but were unaltered with antioxidants or placebo. Similar changes were observed when antioxidants were added to niacin plus simvastatin.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs antioxidants (vitamin E 800 IU/day, vitamin C 1,000 mg/day, beta carotene 25 mg/day and selenium 100 µg/day) vs niacin plus simvastatin plus antioxidants vs placebo Niacin was initiated as ER niacin 250 mg BID and increased to 1,000 mg BID at 4 weeks. Patients whose HDL-C had not increased by 5 mg/dL at 3 months, 8 mg/dL at 8 months and 10 mg/dL at 12 months were switched to niacin IR (Niacor®) up to a maximum of 4 g/day.	≥30% of the luminal diameter or 1 stenosis ≥50%, low HDL-C and normal LDL-C		stenosis caused by most severe lesion in each of nine proximal coronary segments), occurrence of first cardiovascular event (death from coronary causes, MI, stroke or re-vascularization) Secondary: Mean change in percent stenosis in lesions of varying degrees of severity, mean change in luminal diameter in proximal lesions and all lesions	The protective increase in HDL2 (considered to be the most protective component of HDL-C) with niacin plus simvastatin (65%) was attenuated by concurrent therapy with antioxidants (28%; *P*=0.02). The average stenosis progressed by 3.9% with placebo, 1.8% with antioxidants (*P*=0.16 vs placebo) and 0.7% with niacin plus simvastatin plus antioxidants (*P*=0.004) and regressed by 0.4% with niacin plus simvastatin (*P*<0.001). The frequency of the composite primary endpoint (death from coronary causes, MI, stroke or revascularization) was 24% with placebo, 3% with niacin plus simvastatin, 21% with antioxidants and 14% with niacin plus simvastatin plus antioxidants. The risk of the composite primary endpoint was 90% lower with niacin plus simvastatin compared to placebo (*P*=0.03). The risk with the other treatments did not differ significantly from that with placebo (*P* values not reported). Secondary: In general, the treatment effects observed with respect to the primary angiographic endpoint were confirmed for the various subcategories of stenosis and were supported by the results for the mean minimal luminal diameter.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Placebo tablets contained niacin IR 50 mg.				
Zhao et al[53] Niacin 2.4±2.0 g/day (mean dose) plus simvastatin 13±6 mg/day (mean dose) vs antioxidants (vitamin E 800 IU/day, vitamin C 1,000 mg/day, beta carotene 25 mg/day and selenium 100 µg/day) vs niacin plus simvastatin plus antioxidants vs placebo	ES of Brown et al[37] Patients with clinical CAD (previous MI, coronary interventions or confirmed angina) including 25 with diabetes with mean LDL-C 128 mg/dL, HDL-C 31mg/dL and TG 217 mg/dL	N=160 38 months	Primary: Side effects, response to the question "Overall, how difficult is it to take the study medication?" Secondary: Not reported	Primary: Patients receiving niacin plus simvastatin experienced similar frequencies of clinical or laboratory side effects compared to placebo; any degree of flushing (30 vs 23%; *P* value not significant), symptoms of fatigue, nausea and/or muscle aches (9 vs 5%; *P* value not significant), AST at least three times the ULN (3 vs 1%; *P* value not significant), CPK at least two times the ULN (3 vs 4%; *P* value not significant), new onset of uric acid ≥7.5 mg/dL (18 vs 15%; *P* value not significant) and homocysteine ≥15 µmol/L (9 vs 4%; *P* value not significant). There were no side effects attributable to the antioxidant regimen. Glycemic control among diabetics declined mildly with niacin plus simvastatin, but returned to pre-treatment levels at month eight and remained stable for the rest of the trial. Niacin plus simvastatin was repeatedly described by 91% of treated patients vs 86% of placebo subjects as "very easy" or "fairly easy" to take. Secondary: Not reported
Stalenhoef et al[54] COMET Rosuvastatin 10 mg/day for 6 weeks, titrated up to	DB, DD, PG, RCT Patients ≥18 years of age with metabolic syndrome, LDL-C ≥3.36 mmol/L and 10	N=401 12 weeks	Primary: Percentage change from baseline in LDL-C at six weeks Secondary:	Primary: After six weeks, rosuvastatin 10 mg was associated with a significant reduction in LDL-C compared to atorvastatin 10 mg (41.7 vs 35.7%, respectively; *P*<0.001) and placebo (42.7 vs 0.3%, respectively; *P*<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
rosuvastatin 20 mg/day for 6 weeks vs atorvastatin 10 mg/day for 6 weeks, titrated up to atorvastatin 20 mg/day for 6 weeks vs placebo daily for 6 weeks, followed with rosuvastatin 20 mg/day for 6 weeks	year CHD risk score of >10%		Percentage changes from baseline in TC, LDL-C, HDL-C, non-HDL-C at 12 weeks	After 12 weeks, rosuvastatin 20 mg was associated with a significant reduction in LDL-C compared to atorvastatin 20 mg (48.9 vs 42.5%, respectively; *P*<0.001). After six and 12 weeks, rosuvastatin was associated with significantly greater improvements in TC (*P*<0.001), HDL-C (*P*<0.01) and non-HDL-C (*P*<0.001) compared to atorvastatin.
Constance et al[55] 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} ≤10.0%, 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 hsCRP 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%,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				respectively; *P* value not reported).
Goldberg et al[56] VYTAL Atorvastatin 10, 20 or 40 mg/day vs ezetimibe 10 mg/day plus simvastatin 20 or 40 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 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 hsCRP	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). 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 hsCRP 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).
Kumar et al[57] Ezetimibe 10 mg/day	RCT, XO Patients with	N=43 12 weeks	Primary: Percentage reduction of LDL-C	Primary: LDL-C decreased by 34.6 vs 36.7% with combination therapy and atorvastatin (*P*=0.46).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
plus fenofibrate 160 mg/day vs atorvastatin 10 mg/day	hypercholesterolemia requiring pharmacotherapy		Secondary: Percent changes from baseline in TC, HDL-C and TG	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).
Goldberg et al[58] Fenofibric acid 135 mg/day vs atorvastatin 20, 40 or 80 mg/day vs fenofibric acid 135 mg/day plus atorvastatin 20 or 40 mg/day	AC, DB, MC, RCT Patients ≥18 years of age with mixed dyslipidemia (fasting TG ≥150 mg/dL, HDL-C <40 mg/dL for men and <50 mg/dL for women and LDL-C ≥130 mg/dL after lipid therapy washout)	N=613 12 weeks	Primary: Percent changes from baseline in TG, HDL-C and LDL-C Secondary: Percent changes from baseline in VLDL-C, TC, apo B and hsCRP; safety	Primary: Combination therapy (atorvastatin 20 mg) resulted in significantly greater improvements in TG (-45.6 vs -16.5%; *P*<0.001) and HDL-C (14.0 vs 6.3%; *P*=0.005) compared to atorvastatin 20 mg and LDL-C (-33.7 vs -3.4%; *P*<0.001) compared to fenofibric acid. Similarly, significantly greater improvements were observed with combination therapy (40 mg) in TG (-42.1 vs -23.2%; *P*<0.001) and HDL-C (12.6 vs 5.3%; *P*=0.010) compared to atorvastatin 40 mg and LDL-C (-35.4 vs -3.4%; *P*<0.001) compared to fenofibric acid. Secondary: Combination therapy (20 mg) resulted in significantly higher mean percentages of decrease in non-HDL-C compared to fenofibric acid (*P*=0.026) and in VLDL-C compared to atorvastatin 20 mg (*P*=0.046). Combination therapy (40 mg) also resulted in significantly higher mean percentage of decrease in non-HDL-C compared to fenofibric acid (*P*<0.001) and in VLDL-C compared to atorvastatin 40 mg (*P*<0.001). Improvements in other secondary variables were similar between combination therapy and atorvastatin (TC; *P*=0.688, apo B; *P*=0.688 and hsCRP; *P*=0.074).
Bays et al[59] ADVOCATE Niacin ER/lovastatin 1,000/40 mg/day	MC, OL, RCT Patients 18 to 70 years of age with 2 consecutive LDL-C ≥160 (if no CAD) or	N=315 16 weeks	Primary: Percent change from baseline in LDL-C and HDL-C Secondary:	Primary: Atorvastatin was associated with a significant 49% reduction in LDL-C compared to a 39, 42 and 39% reduction observed with niacin ER/lovastatin 1,000/40 mg, niacin ER/lovastatin 2,000/40 mg and simvastatin, respectively (*P*≤0.05 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs niacin ER/lovastatin 2,000/40 mg/day vs simvastatin 40 mg/day vs atorvastatin 40 mg/day	≥130 mg/dL (with CAD), TG <300 mg/dL and HDL-C <45 (men) or <50 mg/dL (women)		Percent change from baseline in TC, apo B, apo AI, and HDL_2-C and HDL_3-C; median percent change in TG and Lp(a)	Combination therapy was associated with a significant increase in HDL-C compared to atorvastatin and simvastatin (17, 32, 6 and 7%, respectively; *P*≤0.05 for all). Secondary: Combination therapy and atorvastatin were associated with significant reductions in TG compared to simvastatin (29, 49, 31 and 19%, respectively; *P*≤0.05 for all). Combination therapy was associated with a significant reduction in Lp(a) compared to atorvastatin and simvastatin (19, 21, 0 and 2%, respectively; *P*≤0.05 for all). Combination therapy and simvastatin were associated with significant increases in apo AI compared to atorvastatin (7, 14, 6 and 2%, respectively; *P*<0.05 for all). Combination therapy (2,000/40 mg) and atorvastatin were associated with significant reductions in apo B compared to combination therapy (2,000/40 mg) and simvastatin (38, 40, 33 and 31%, respectively; *P*<0.05). Combination therapy was associated with a significant increase in HDL_2-C and HDL_3-C compared to atorvastatin and simvastatin (*P*<0.05).
Sansanayudh et al[60] Pitavastatin 1 mg QD vs atorvastatin 10 mg QD	OL, PG, RCT Patients ≥18 years of age with hypercholesterolemia who had an indication for statin therapy according to the NCEP ATP III guidelines	N=100 8 weeks	Primary: Change from baseline in serum lipid levels Secondary: Proportion of patients who achieved NCEP ATP III LDL-C goal, safety, monthly cost per percent of	Primary: Both treatments achieved significant reductions in TC and LDL-C (*P*<0.05). The percentages of reduction in TC and LDL-C with pitavastatin was significantly less compared to atorvastatin (27.55 vs 32.31%; *P*=0.005 and 37.37 vs 45.75%; *P*<0.001). Pitavastatin was associated with significant reductions in TG (*P*=0.001), while atorvastatin was not (*P*=0.062); however, the changes between the two treatments were not different (*P*=0.661). Changes in HDL-C were also not significantly different between the two treatments (*P*=0.294). Secondary: Overall, 79% of all patients achieved their LDL-C goal and there was no

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			LDL-C reduction	significant difference between the two treatments (74 vs 84%; *P*=0.220). In the high risk category (LDL-C goal <100 mg/dL), there was no difference in the proportion of patients who achieved their LDL-C goal (42.86 vs 71.43%; *P*=0.127). The possible adverse events of pitavastatin vs atorvastatin included muscle pain (five vs two patients), vertigo (two vs two patients), nausea (three vs one patients), vomiting (one vs one patient), headache (one vs one patient), muscle weakness (one vs zero patients) and stomach ache (zero vs one patients) (*P*>0.05). During the trial, two patients receiving pitavastatin withdrew from treatment due to an adverse event.
Gumprecht et al[61] Atorvastatin 20 mg/day vs pitavastatin 4 mg/day	AC, DB, DD, MC, NI Patients 18 to 75 with type 2 diabetes mellitus (hemoglobin HbA_{1c} ≤7.5% and combined dyslipidemia and TG despite diet modification and oral antidiabetic treatment or insulin	N=418 56 weeks (12 weeks DB, 44 weeks OL extension)	Primary: Change in LDL-C at 12 weeks, proportion of patients achieving LDL-C targets at weeks 16 and 44 and safety and tolerability at 56 weeks Secondary: TC, HDL-C, TG, TC/HDL-C ratio, non-HDL-C, non-HDL-C/HDL-C ratio, Apo B, Apo AI, Apo B/ Apo AI ratio, hs-CRP, adiponectin LDL, remnant-like particle cholesterol, oxidized LDL and safety	Primary: The mean percent change in LDL-C at week 12 was -40.8% for pitavastatin and -43.3% for atorvastatin. The NI analysis of changes in LDL-C at the week 12 did not fulfill the predefined NI criterion since the mean treatment difference for pitavastatin 4 mg compared to atorvastatin 20 mg was -2.33%, outside the lower bound of the 95% CI (-6.18%). A high proportion of patients in the pitavastatin and atorvastatin groups achieved lipid targets during long-term treatment (percentages not reported). Most adverse events were mild or moderate in severity with few discontinuations due to treatment-related adverse events (2.5 and 3.6% for pitavastatin and atorvastatin in the core study, and 2.1 and 1.4%, respectively, in the extension study). One patient in the pitavastatin group died of a MI during the study, which was not considered to be related to the study drug. The most common adverse events considered to be treatment related were nasopharyngitis and myalgia. The incidence of myalgia during the extension study was slightly lower in the pitavastatin group than in the atorvastatin group (4.2 vs 7.0%, respectively). The incidence of clinically significant elevation of liver enzymes was low in both groups in both the core and extension studies.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				During the core study, mean blood glucose levels in the pitavastatin group showed a non-significant increase of 2.1% from baseline to week 12. By contrast, mean blood glucose in the atorvastatin group increased significantly from baseline to week 12 by 7.2% (*P*<0.05). Secondary: Mean TC, TG and non-HDL-C levels decreased from baseline in both the core study and the end of the extension study to a similar degree in both groups. There were no notable between-treatment differences in the observed effects on other lipid parameters such as TC/HDL-C ratio, non-HDL-C/HDL-C ratio and Apo-B. Pitavastatin and atorvastatin were similar in their effect on increasing HDL-C. By the end of the extension study, more patients receiving pitavastatin had increased their HDL-C levels. Pitavastatin and atorvastatin treatment also reduced CRP, oxidized LDL and increased levels of adiponectin to similar extents.
Yoshitomi et al[62] Pitavastatin 1 mg QD vs atorvastatin 10 mg QD	MC, OL Patients ≥18 years of age with hypercholesterolemia (LDL >140 mg/dL and TG <400 mg/dL) treated with or without lipid lowering agents	N=137 12 weeks	Primary: Mean percent reductions from baseline in TC, LDL-C, HDL-C and TG Secondary: Safety	Primary: There were no significant differences between the two treatments in reducing baseline TC (28±8 vs 29%±10) and LDL-C (38±13 vs 41%±12) (*P* values not reported). There were no differences between the two treatments in increasing baseline HDL-C (3±12 vs 7%±12; *P* value not reported). Atorvastatin achieved a significantly greater mean percent reduction from baseline in TG compared to pitavastatin (21±25 vs 11%±30; *P*<0.05). Secondary: Treatment with both pitavastatin and atorvastatin was well tolerated. No serious adverse event was associated with the treatment. No adverse events of musculoskeletal, renal or hepatocellular toxicity occurred and no patient had an elevation of the CK level that was >3 times the ULN.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Lee et al[63] Pitavastatin 2 mg QD vs atorvastatin 10 mg QD Patients who did not achieve the LDL-C goal by week 4 received a double dose of the assigned medications for an additional 4 weeks.	MC, OL, RCT Patients 20 to 79 years of age with untreated hypercholesterolemia, fasting TG <400 mg/dL and a LDL-C >130 mg/dL after a 4 week dietary lead in period	N=268 8 weeks	Primary: Changes from baseline in lipid parameters and hsCRP Secondary: Tolerability	Nine (8.2%) patients receiving pitavastatin and 12 (10.7%) patients receiving atorvastatin did not achieve the LDL-C goal by week four and received a double dose of their assigned medication for the remaining four weeks. Primary: There was no significant difference between the two treatments in the proportion of patients achieving the LDL-C goal at eight weeks (92.7 vs 92.0%; *P* value not reported). There was no difference between the two treatments in terms of the mean percent changes in LDL-C (-42.9 vs -44.1%), TC (-28.0 vs -29.6%), TG (-9.9 vs -11.0%), HDL-C (7.1 vs 6.7%) and hsCRP (-23.9 vs -15.4%) (*P* values not reported). Secondary: Both treatments were well tolerated and 21 adverse reactions considered related to study medication occurred in 14 patients receiving pitavastatin and 23 occurred in 19 patients receiving atorvastatin. There were no clinically relevant changes in laboratory values.
Sasaki et al[64] Pitavastatin 2 mg QD vs atorvastatin 10 mg QD	MC, OL, PG, RCT Patients ≥20 years of age with LDL-C ≥140 mg/dL, HDL-C <80 mg/dL, TG <500 mg/dL and glucose intolerance	N=189 52 weeks	Primary: Percent change from baseline in serum HDL-C Secondary: Percent change from baseline in LDL-C, non-HDL-C, LDL-C:HDL-C, TG, apo AI, apo B, apo B:AI and apo E; tolerability	Primary: Pitavastatin was associated with an increase in HDL-C of 8.2%, which was significantly greater than atorvastatin (2.9%; *P*=0.031). Secondary: Atorvastatin was associated with significant reductions LDL-C (-40.1 vs -33.0%; *P*=0.002), non-HDL-C (-37.4 vs -31.1%; *P*=0.004), apo B (-35.1 vs -28.2%; *P*<0.001) and apo E (-28.1 vs -17.8%; *P*<0.001) compared to pitavastatin. There were no differences between the two treatments in terms of changes in LDL-C:HDL-C, apo B:AI and TG. Apo AI increased significantly more with pitavastatin compared to atorvastatin (5.1 vs 0.6%; *P*=0.019).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Effects on glucose metabolism were similar between the two treatments, measured by fasting plasma insulin, FPG and HbA_{1c}. Initiation of medication use for the treatment of diabetes occurred at a similar rate with both treatments (11%). Adverse events occurred at a similar rate between the two treatments.
Saito et al[65] Pitavastatin 2 mg/day vs pravastatin 10 mg/day	DB, MC, PG, RCT Patients 20 to 75 years of age with primary hyperlipidemia (TC ≥200 mg/dL and TG <400 mg/dL)	N=240 12 weeks	Primary: Mean percent changes from baseline in TC, LDL-C and TG Secondary: Mean percent changes from baseline in apo B, apo CII, apo CIII and apo E; safety	Primary: Pitavastatin achieved significantly greater mean percent reductions from baseline in TC and LDL-C (28.2 and 37.6%) compared to pravastatin (14.0 and 18.4%; both *P*<0.001). In cases of a baseline TG level ≥150 mg/dL, the mean percent reduction of TG with pitavastatin (23.3%) showed non-inferiority to that observed with pravastatin (20.2%; *P*=0.024). Secondary: Mean percent reductions in apo B, apo CII, apo CIII and apo E with pitavastatin (33.8, 15.7, 9.5 and 22.9%) were significantly greater compared to pravastatin (16.9, 6.1, 2.6 and 12.6%; *P* values not reported). The adverse event profile was similar for both treatments and neither treatment caused clinically relevant laboratory abnormalities. Three patients receiving pitavastatin and two patients receiving pravastatin withdrew from the study due to adverse events considered to be drug-related.
Park et al[66] Pitavastatin 2 mg QD vs simvastatin 20 mg QD	MC, OL, Phase III, PRO, RCT Patients 20 to 75 years of age with hypercholesterolemia, fasting TG <600 mg/dL and LDL-C >130 mg/dL after a 4 week dietary lead in period	N=104 8 weeks	Primary: Mean percent change from baseline in LDL-C Secondary: Mean percent change from baseline in TC, TG and HDL-C; safety	Primary: There was no significant difference between the two treatments in the reduction in LDL-C (11.6 vs 12.9%; *P*=0.648). Secondary: There were no significant differences between the two treatments in the changes in TC (-8.9 vs -8.7%; *P*=0.405), TG (-20.6 vs 36.9%; *P*=0.147), or HDL-C (13.4 vs 16.2%; *P*=0.127). No serious adverse events were observed in either treatment. One patient receiving pitavastatin and four patients receiving simvastatin had to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				discontinue the study medication due to adverse events. Elevations in CK greater than two times ULN were observed in 3.8 and 9.8% of pitavastatin- and atorvastatin-treated patients (*P*=0.269). Mild elevations in AST less than two fold times ULN was observed in one patient receiving simvastatin.
Ose L et al[67] Pitavastatin 2 or 4 mg/day vs simvastatin 20 or 40 mg/day	AC, DB, DD, PRO, RCT Patients diagnosed with either primary hypercholesterolemia or combined dyslipidemia	N=857 12 weeks	Primary: Changes in lipid panel Secondary: Safety profiles	Primary: Pitavastatin 2 mg was associated with a significant improvement in LDL-C, non-HDL-C and TC compared to simvastatin 20 mg (*P*=0.014, 0.021 and 0.041 respectively). LDL-C was reduced by 39% with pitavastatin 2 mg compared to 35% with simvastatin 20 mg. Pitavastatin 4 mg and simvastatin 40 mg had similar effects on the lipid panel. Reductions in LDL-C were 44% with pitavastatin 4 mg and 43% for simvastatin 40 mg. Secondary: Safety profiles were similar at all dose levels.
Eriksson et al[68] Pitavastatin 4 mg/day vs simvastatin 40 mg/day	AC, DB, DD, MC, NI, PG, RCT Patients 18 to 75 years of age with primary hypercholesterolemia or combined dyslipidemia that was uncontrolled (LDL-C ≥130 mg/dL and ≤5,220 mg/dL; TG ≤400 mg/dL) despite dietary measures, and at least two cardiovascular risk factors	N=355 12 weeks	Primary: Percentage change in LDL-C from baseline Secondary: Proportion of patients reaching LDL-C targets, percentage changes from baseline in concentrations of TG, TC, HDL-C, non-HDL-C, apo B and apo AI, and absolute changes from baseline in	Primary: The mean LDL-C concentrations decreased from baseline by -44.0% with pitavastatin compared to -43.8% with simvastatin. The adjusted mean treatment difference was 0.31%, which was within the predefined limits of NI (95% CI, -2.47 to 3.09; *P*=0.829). Secondary: There was no statistically significant difference in the proportion of patients achieving NCEP LDL-C targets (87.1 vs 85.6%; *P*=0.695) or EAS LDL-C targets (87.1 vs 81.4%; *P*=0.170) between patients treated with pitavastatin or simvastatin. Pitavastatin provided a significantly greater reduction in triglycerides compared to simvastatin (-19.8 vs -14.8%; *P*=0.044), as well as a greater increase in HDL-C with pitavastatin (6.8 vs. 4.5%), which was not statistically significant (*P*=0.083). There were no other significant differences in secondary lipid measures between the two groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			concentrations of oxidized LDL, CRP and ratios of TC/HDL-C, non-HDL/HDL-C, and apo B/apo A1 and safety	Treatment-emergent adverse events occurred in 51.1% of patients receiving pitavastatin and 50.4% of patients receiving simvastatin. The most commonly reported treatment-emergent adverse events were headache, nasopharyngitis, constipation, myalgia and back pain.
Park et al[69] Rosuvastatin 10 mg/day vs atorvastatin 10 mg/day	MC, OL, PG Patients ≥18 years of age with nondiabetic metabolic syndrome and hypercholesterolemia	N=351 6 weeks	Primary: Percent change from baseline in TC, LDL-C, HDL-C, TG, non-HDL-C, apo AI and apo B; proportion of patients achieving NCEP ATP III LDL-C goals (<100, <130 and <160 mg/dL); change from baseline in metabolic parameters; safety Secondary: Not reported	Primary: After six weeks, significantly greater reductions in TC (35.94±11.38 vs 30.07±10.46%; *P*<0.001), LDL-C (48.04±14.45 vs 39.52±14.42%; *P*<0.001), non-HDL-C (42.93±13.15 vs 35.52±11.76%; *P*<0.001) and apo B (38.7±18.85 vs 32.57±17.56%; *P*=0.002) were achieved with rosuvastatin compared to atorvastatin. No differences between treatments were observed in changes in HDL-C (*P*=0.448), TG (*P*=0.397) and apo AI (*P*=0.756). Overall, the proportion of patients achieving the LDL-C goals was significantly greater with rosuvastatin compared to atorvastatin (87.64 vs 69.88%; *P*<0.001). Corresponding proportions for the LDL-C goals <100, <130 and <160 mg/dL were: 82.7 vs 59.2 (*P*<0.001), 94.3 vs 84.2 (*P*=0.032) and 96.8 vs 97.3% (*P*=0.990). Changes in glucose (*P*=0.231), insulin (*P*=0.992), HbA_{1c} (*P*=0.456) and HOMA index (*P*=0.910) were not significantly different between the two treatments. The safety and tolerability of the two treatments were similar. Secondary: Not reported
Betteridge et al[70] ANDROMEDA Rosuvastatin 10	DB, MC, PG, RCT Patients ≥18 years of age with type 2	N=509 16 weeks	Primary: Percentage change from baseline in LDL-C	Primary: Rosuvastatin was associated with a significant reduction in LDL-C compared to atorvastatin (57.4 vs 46.0%; *P*=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day for 8 weeks, titrated up to 20 mg/day for 8 weeks vs atorvastatin 10 mg/day for 8 weeks, titrated up to 20 mg/day for 8 weeks All patients were randomized after a 4 week dietary lead in period.	diabetes, ≥2 FPG levels of ≥7 mmol/L and TG ≤6 mmol/L		Secondary: Percentage changes from baseline in LDL-C, TC, HDL-C, TG, non-HDL-C, cholesterol ratios, apo B, apo ratio and HbA_{1c}; proportion of patients achieving 2003 Joint European Societies LDL-C (<2.5 mmol/L) and TC (<4.5 mmol/L) goals	Secondary: Rosuvastatin was associated with a significant reduction in apo ratio, LDL-C:HDL-C, TC, TC:HDL-C, non-HDL-C and apo B compared to atorvastatin (*P*<0.001). Rosuvastatin was associated with a significant reduction in HbA_{1c} compared to atorvastatin (*P*=0.049). A significantly greater proportion of patients receiving rosuvastatin achieved LDL-C goals compared to patients receiving atorvastatin (95.6 vs 87.3%; *P*=0.002). A significantly greater proportion of patients receiving rosuvastatin achieved TC goals compared to patients receiving atorvastatin (93.4 vs 86.0%; *P*=0.01).
Betteridge et al[71] Rosuvastatin 10 mg/day for 8 weeks, titrated up to 20 mg/day for 8 weeks vs atorvastatin 10 mg/day for 8 weeks, titrated up to 20 mg/day for 8 weeks All patients were randomized after a 4 week dietary lead in	Subanalysis of ANDROMEDA trial[53] Patients ≥18 years of age with type 2 diabetes, ≥2 FPG levels of ≥7 mmol/L and TG of ≤6 mmol/L	N=509 16 weeks	Primary: Composite of changes from baseline in hsCRP <2 mg/L and LDL-C <70 mg/dL Secondary: Not reported	Primary: Rosuvastatin was associated with a significant reduction in the primary endpoint compared to atorvastatin (58 vs 37%; *P*<0.001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
period.				
Clearfield et al[72] PULSAR Rosuvastatin 10 mg QD vs atorvastatin 20 mg QD	MC, OL, PG, RCT Patients ≥18 years of age with hypercholesterolemia and either a history of CHD or a CHD risk equivalent, with the mean of the 2 most recent LDL-C (within 15% of each other) ≥130 to <220 mg/dL, as well as TG <400 mg/dL	N=996 6 weeks	Primary: Percentage change from baseline in LDL-C Secondary: Proportion of patients achieving the NCEP ATP III and the 2003 European LDL-C goals (<100 mg/dL), the 2003 European LDL-C goal for patients at greatest risk, the NCEP ATP III non-HDL-C goal (<130 mg/dL), combined LDL-C:TC goal <175 to 190 mg/dL; percentage changes from baseline in HDL-C, TC, TG, non-HDL-C, apo B, LDL-C:HDL-C, TC:HDL-C, non-HDL-C:HDL-C and Lp(a); safety	Primary: Rosuvastatin was associated with a significant reduction in LDL-C compared to atorvastatin (42.7 vs 44.6%; *P*<0.05). Secondary: A significantly greater proportion of patients receiving rosuvastatin achieved NCEP ATP III and the 2003 European LDL-C goals compared to patients receiving atorvastatin (68 vs 63%; *P*<0.05). In addition, a significantly greater proportion of high risk CHD patients receiving rosuvastatin achieved the 2003 European LDL-C goals compared to high risk CHD patients receiving atorvastatin (65.6 vs 60.3%; *P*>0.05). A nonsignificant greater proportion of patients receiving rosuvastatin achieved the NCEP ATP III non-HDL-C goal compared to patients receiving atorvastatin (69.7 vs 65.0%; *P*>0.05). A nonsignificant greater proportion of patients receiving rosuvastatin achieved the NCEP ATP III combined LDL-C:TC goal compared to atorvastatin (55.2 vs 53.3%; *P*>0.05). Rosuvastatin was associated with a significant increase in HDL-C compared to atorvastatin (6.4 vs 3.1%; *P*<0.001). There was no difference in the changes of TC, TG, non-HDL-C and apo B observed with rosuvastatin and atorvastatin (*P*>0.05). Rosuvastatin was associated with a significant reduction in LDL-C:HDL-C compared to atorvastatin (47.6 vs 44.0%; *P*<0.001). Rosuvastatin was associated with a significant reduction in TC:HDL-C compared to atorvastatin (34.6 vs 32.3%; *P*<0.01). Rosuvastatin was associated with a significant reduction in non-HDL-C:HDL-C compared to atorvastatin (43.3 vs 40.2%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Atorvastatin was associated with a significant increase in Lp(a) compared to rosuvastatin (13.3 vs 2.1%; *P*<0.001). The frequency and type of adverse events were similar with both treatments (27.5 vs 26.1%; *P* value not reported). The most commonly reported adverse effects were myalgia and urinary tract infections.
Deedwania et al[73] IRIS Rosuvastatin 10 or 20 mg/day vs atorvastatin 10 or 20 mg/day All patients were randomized after a 6 week dietary lead in period.	MC, OL, RCT South-Asian patients ≥18 years of age with CHD or CHD risk equivalent and LDL-C ≥100 mg/dL or ≥2 risk factors, 10 year CHD risk 10 to 20% and LDL-C ≥130 mg/dL or 0 to 1 risk factor and LDL-C ≥160 mg/dL, with TG <500 mg/dL	N=740 6 weeks	Primary: Percentage change from baseline in LDL-C Secondary: Proportion of patients achieving NCEP ATP III LDL-C goals; percentage change from baseline in non-HDL-C, HDL-C, TC and TG; safety	Primary: At six weeks, rosuvastatin 10 mg was associated with a significant reduction in LDL-C compared to atorvastatin 10 mg (*P*=0.0023). The difference in LDL-C reduction from baseline at six weeks between rosuvastatin 20 mg and atorvastatin 20 mg was not significant (*P* value not reported). Secondary: The proportion of patients achieving NCEP ATP III LDL-C goals was similar with rosuvastatin 10 and 20 mg and atorvastatin 10 and 20 mg (79, 89, 76 and 85%, respectively; *P* value not reported). At six weeks, rosuvastatin 10 mg was associated with a significant reduction in LDL-C:HDL-C compared to atorvastatin 10 mg (*P*<0.017). There were no clinically relevant differences between treatments in adverse events or incidence of CK >10 times the ULN, ALT >3 times the ULN, proteinuria or hematuria.
Ferdinand et al[74] ARIES Rosuvastatin 10 or 20 mg QD vs atorvastatin 10 or 20 mg QD	OL, RCT African American patients ≥18 years of age with LDL ≥160 to ≤300 mg/dL, TG <400 mg/dL	N=774 6 weeks	Primary: The change from baseline in LDL-C Secondary: Changes from baseline in other lipid parameters	Primary: Rosuvastatin was associated with a significant reduction in LDL-C compared to atorvastatin (*P*<0.017). Secondary: Rosuvastatin was associated with a significant reduction in TC, non-HDL-C, apo B and lipoprotein and apo ratios compared to atorvastatin (*P*<0.017). Rosuvastatin was associated with a significant increase in HDL-C

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
All patients were randomized after a 6 week dietary lead in period.				compared to atorvastatin (*P*<0.017). Adverse events were similar with rosuvastatin and atorvastatin (34.4 and 33.6%, respectively; *P* value not reported).
Lloret et al[75] STARSHIP Rosuvastatin 10 or 20 mg QD vs atorvastatin 10 or 20 mg QD All patients were randomized after a 6 week dietary lead in period.	MC, OL, RCT Hispanic American patients ≥18 years of age with a 10 year risk >10% for CHD, current CHD or its equivalent, LDL ≥130 to ≤300 mg/dL on 2 measurements within 15% of each other, TG <400 mg/dL	N=696 6 weeks	Primary: Percent change from baseline in LDL-C Secondary: Proportion of patients achieving NCEP ATP III lipid goals; percent change from baseline in TC, apo B, non-HDL-C, TG, HDL, apo AI, LDL-C:HDL-C, TC:HDL-C and apo B:apo AI; safety	Primary: Rosuvastatin 10 and 20 mg was associated with a significant reduction in LDL-C compared to atorvastatin 10 and 20 mg (45, 50, 36 and 42%, respectively; *P*<0.0001). Secondary: A greater proportion of patients receiving rosuvastatin 10 and 20 mg achieved LDL-C goals compared to atorvastatin 10 and 20 mg (78, 88, 60 and 73%, respectively; *P* value not reported). Rosuvastatin 10 and 20 mg was associated with a significant reduction in TC compared to atorvastatin 10 and 20 mg (10 mg; *P*<0.0001, 20 mg; *P*<0.01, respectively). Rosuvastatin 10 and 20 mg was associated with a significant reduction in apo B compared to atorvastatin 10 and 20 mg (10 mg; *P*<0.0001, and 20 mg; *P*<0.017, respectively). Rosuvastatin 10 and 20 mg was associated with a significant reduction in LDL-C:HDL-C compared to atorvastatin 10 and 20 mg, respectively, at six months (*P*<0.0001 for both, respectively). Rosuvastatin 10 and 20 mg was associated with a significant reduction in TC:HDL-C compared to atorvastatin 10 and 20 mg (10 mg; *P*<0.0001, 20 mg; *P*<0.01, respectively). Rosuvastatin 10 and 20 mg was associated with a significant reduction in non-HDL-C:HDL-C compared to atorvastatin 10 and 20 mg (10 mg; *P*<0.0001, 20 mg; *P*<0.01, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Rosuvastatin 10 and 20 mg was associated with a significant reduction in apo B:apo AI compared to atorvastatin 10 and 20 mg (*P*<0.01 for both, respectively). Adverse events were similar between treatments (*P* value not reported). There were no cases of myopathy, rhabdomyolysis or clinically significant increases in serum CK.
Milionis et al[76] ATOROS Rosuvastatin 10 mg QD for 6 weeks, titrated to 20 mg/day vs atorvastatin 20 mg QD for 6 weeks, titrated to 40 mg/day All patients were randomized after a 6 week dietary lead in period.	OL, PG, RCT Adult patients free of symptomatic ischemic heart disease or any other clinically evident heart disease, at moderate risk for CHD according to NCEP ATP classification, with baseline TC >240 mg/dL and TG <350 mg/dL	N=180 24 weeks	Primary: Proportion of patients achieving the NCEP ATP III LDL-C goal (<130 mg/dL) Secondary: Changes from baseline in LDL-C, HDL-C, TC, TG, non-HDL-C and apo B	Primary: After six weeks, 75.0 and 71.7% of patients achieved the NCEP ATP III LDL-C goal with rosuvastatin and atorvastatin, respectively (*P* value not reported). Secondary: Both rosuvastatin and atorvastatin were associated with significant reductions in LDL-C (48.7 vs 44.6%; *P*<0.001). Rosuvastatin was associated with a significant five percent increase in HDL-C (*P*<0.001). Atorvastatin was associated with a significant 2.1% reduction in HDL-C (*P*<0.001). Compared to atorvastatin, rosuvastatin was associated with a significantly greater increase in HDL-C (*P*=0.002). Both rosuvastatin and atorvastatin were associated with significant reductions in TC (36.1 vs 36.9%; *P*<0.001). Both rosuvastatin and atorvastatin were associated with significant reductions in TG (29.0 vs 27.8%; *P*<0.001). Both rosuvastatin and atorvastatin were associated with significant reductions in non-HDL-C (45 vs 46%; *P*<0.001). Both rosuvastatin and atorvastatin were associated with significant reductions in apo B (29 vs 26%; *P*<0.001). The incidence of myalgia was similar with both treatments (3%; *P* value not reported). There were no reports of significant ALT or CK elevations.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Ai et al[77] STELLAR Rosuvastatin 40 mg/day vs atorvastatin 80 mg/day	OL Patients ≥18 years of age with hypercholesterolemia, LDL-C ≥160 to <250 mg/dL and TG <400 mg/dL	N=271 6 weeks	Primary: Changes from baseline in direct LDL-C and small dense LDL-C Secondary: Percentage changes from baseline in HDL-C, TC, TG, non-HDL-C and TC:HDL-C	Primary: Rosuvastatin was associated with a significant reduction from baseline in direct LDL-C compared to atorvastatin (52 vs 50%; *P*=0.01). Rosuvastatin was associated with a significant reduction from baseline in small dense LDL-C compared to atorvastatin (53 vs 46%; *P*<0.001). Secondary: Rosuvastatin was associated with a significant increase from baseline in HDL-C compared to atorvastatin (10 vs 2%; *P*<0.001). There was no difference between treatments in TC (*P*=0.10) and TG (*P*=0.50) reductions. Rosuvastatin was associated with a significant reduction in non-HDL-C compared to atorvastatin (51 vs 48%; *P*<0.0078). Rosuvastatin was associated with a significant reduction in TC:HDL-C compared to atorvastatin (46 vs 39%; *P*<0.001).
Leiter et al[78] POLARIS Rosuvastatin 40 mg QD vs atorvastatin 80 mg QD	DB, PG, RCT Patients 45 to 80 years of age with hypercholesterolemia and a history of CHD, clinical evidence of atherosclerosis or a 10 year Framingham CHD risk score >20%, with LDL-C ≥160 to <250 mg/dL and TG <400 mg/dL	N=871 26 weeks	Primary: The percentage change from baseline in LDL-C levels at week eight Secondary: Percentage change from baseline in LDL-C levels at week 26, percentage change from baseline in other lipids and lipoproteins at weeks eight and	Primary: After eight weeks, rosuvastatin was associated with a significantly greater reduction in LDL-C compared to atorvastatin (56 vs 52%; *P*<0.001). Secondary: After 26 weeks, rosuvastatin was associated with a significantly greater reduction in LDL-C compared to atorvastatin (57 vs 53%; *P* value not reported). After eight weeks, rosuvastatin was associated with a significantly greater reduction in TG (27.0 vs 22.2%; *P*<0.05), non-HDL-C (50.8 vs 48.3%; *P*<0.01), LDL-C:HDL-C (58.5 vs 53.6%; *P*<0.001), TC:HDL-C (44.4 vs 41.1%; *P*<0.001), non-HDL-C:HDL-C (53.6 vs 49.6%; *P*<0.001), apo B (44.6 vs 42.3%; *P*<0.05) and apo AI (4.2 vs -0.5%; *P*<0.001) compared to atorvastatin.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			26, proportion of patients achieving NCEP ATP III and 2003 European lipid goals at eight and 26 weeks, safety	After eight weeks, rosuvastatin was associated with a significantly greater increase in HDL-C compared to atorvastatin (9.6 vs 4.4%; *P*<0.001). After six weeks, a significantly greater proportion of patients receiving rosuvastatin achieved the NCEP ATP III LDL-C goals of <100 (80 vs 72%; *P*<0.01) and <70 mg/dL (36 vs 18%; *P*<0.001) compared to patients receiving atorvastatin. After six weeks, a significantly greater proportion of patients receiving rosuvastatin achieved the 2003 European lipid goals compared to patients receiving atorvastatin (79 vs 69%; *P*<0.001). The incidence of drug-related adverse events was low with both treatments (0.5 vs 0.2%; *P* value not reported).
Wolffenbuttel et al[79] CORALL Rosuvastatin 10 mg QD for 6 weeks, titrated to 20 mg QD for 6 weeks, titrated to 40 mg QD for 6 weeks vs atorvastatin 20 mg QD for 6 weeks, titrated to 40 mg QD for 6 weeks, titrated to 80 mg QD for 6 weeks All patients were randomized after a 6	MC, OL, PG, RCT Patients ≥18 years of age with type 2 diabetes for ≥3 months, LDL ≥3.36 mmol/L in statin naïve patients or LDL 2.99 to 5 mmol/L in patients exposed to statin therapy within the previous 4 weeks, TG <4.52 mmol/L and HbA_{1c}<10.0%	N=265 24 weeks	Primary: Reduction in LDL-C, HDL-C, apo ratio, LDL-C:HDL-C, TC, TC:HDL-C, non-HDL-C, TG and apo B; percentage of patients who achieved LDL-C goals (<2.6 or <2.5 mmol/L) at 18 weeks Secondary: Not reported	Primary: Rosuvastatin and atorvastatin were associated with significant reductions from baseline in LDL-C, apo ratio, LDL-C:HDL-C, TC, TC:HDL-C, non-HDL-C, TG and apo B (*P*<0.001). Rosuvastatin was associated with significant reduction in LDL-C (*P*<0.01), apo ratio (*P*<0.05), LDL-C:HDL-C (*P*<0.01), TC (*P*<0.05), TC:HDL-C (*P*<0.05), non-HDL-C (*P*<0.05) and apo B (*P*<0.05) compared to atorvastatin. A significantly greater percentage of patients receiving rosuvastatin achieved LDL-C goals at 18 weeks compared to patients receiving atorvastatin (*P*<0.05). The incidence of treatment-related adverse events was similar between the two treatments (47 vs 50%, respectively; *P* value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
week dietary lead in period.				
Bullano et al[80] Rosuvastatin (mean daily dose, 11 mg) vs atorvastatin (mean daily dose, 15 mg)	RETRO Patients ≥18 years of age, initiated on rosuvastatin or atorvastatin between August 1, 2003 and September 30, 2004 with ≥1 lipid level (LDL-C, TG, HDL-C, TC) obtained prior to and after therapy initiation	N=453 Up to 79 days of therapy	Primary: Percentage change from baseline in LDL-C Secondary: Proportion of patients achieving the NCEP ATP III LDL-C goals (<100 mg/dL), percentage change from baseline in HDL-C, TC, TG and non-HDL-C	Primary: Rosuvastatin was associated with a significant reduction in LDL-C compared to atorvastatin (35 vs 26%; *P*<0.001). Secondary: A significantly greater proportion of patients receiving rosuvastatin achieved NCEP ATP III LDL-C goals compared to atorvastatin, when adjusted for age, sex, LDL-lowering required to reach goal, risk category and duration of therapy (74 vs 65%; *P*<0.05). Unadjusted attainment rates were similar with both treatments (*P*=0.088). Patients receiving rosuvastatin required greater LDL-C reduction to reach their LDL-C goal compared to patients receiving atorvastatin (26.3 vs 23.5%; *P*<0.05). In addition, significantly more patients receiving rosuvastatin reached the updated, optional NCEP ATP III LDL-C goals compared to patients receiving atorvastatin (61 vs 48%; *P*<0.05). There was no difference between the two treatments in the change in HDL-C (*P*=0.234). Rosuvastatin was associated with a greater reduction in TC compared to atorvastatin (26 vs 20%; *P*<0.001). There was no difference between the two treatments in the change in TG (*P*=0.192). Rosuvastatin was associated with a significant reduction in non-HDL-C compared to atorvastatin (33 vs 25%; *P*<0.001).
Wlodarczyk et al[81] Rosuvastatin 5, 10, 20 or 40 mg/day vs	MA (25 head-to-head RCTs) Patients with hypercholesterolemia	N=19,621 Mean 8.6 weeks (range, 4 to 12 weeks)	Primary: Change from baseline in LDL-C Secondary: Safety	Primary: At equivalent doses, rosuvastatin produced significantly larger reductions in LDL-C compared to atorvastatin (mean treatment difference, -8.52%; 95% CI, -9.23 to -7.81) or a two times higher atorvastatin dose (-3.24%; 95% CI, -4.10 to -2.38). No difference between the two treatments were observed when rosuvastatin was compared to a four times higher

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
atorvastatin 10, 20, 40 or 80 mg/day				atorvastatin dose (1.12%; 95% CI, -0.24 to 2.48). Results were similar for DB and OL trials. The percentage of LDL-C decrease associated with rosuvastatin ranged from 41.0 to 56.0% for the 5 and 40 mg dosing regimens, respectively. Atorvastatin ranged from 37.2 to 51.3% for the 10 and 80 mg dosing regimens. Secondary: Event rates for myalgia ranged from 3.5 to 4.2% for atorvastatin 80 mg and rosuvastatin 5 mg. No clear dose-response relation was evident for either treatment and no difference between the two treatments was noted. Rates of withdrawal were low, ranging from 4.1 to 6.4% for rosuvastatin 5 mg and atorvastatin 40 mg. Rates due to adverse events were similar between the two treatments. At the 1:1 dose ratio, the trend toward a higher rate with rosuvastatin did not reach significance (OR, 1.258; 99% CI, 0.972 to 1.627). This trend was no longer evident when only DB trials were included (OR, 0.89; 95% CI, 0.48 to 1.63). Serious adverse events tended to be lower with rosuvastatin at each dose ratio, but there was no strong evidence of a treatment effect. There were nine patients with CK >10 times the ULN and 23 deaths were reported. Rates of ALT greater than three times the ULN were highest with atorvastatin 80 mg (2.2/100 patients) and rosuvastatin 40 mg (0.8/100 patients). Within treatment MA showed that GFR tended to increase with atorvastatin and rosuvastatin by 3.8% (99% CI, 2.77 to 4.77) and 2.7% (99% CI, 1.79 to 3.58). No difference was noted between the two treatments.
Fox et al[82] Rosuvastatin	RETRO Adult patients ≥18	N=277 Patients	Primary: Percent reduction from baseline in	Primary: A switch to rosuvastatin was associated with a significant reduction in LDL-C compared to a switch to simvastatin (18.5 vs 5.8%; *P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs simvastatin	years of age switching to either rosuvastatin or simvastatin from another statin between August 2003 and March 2006, not receiving other antidyslipidemic medications in the 12 months before or after initiating statin therapy	received statin therapy between August 2003 and March 2006	LDL-C Secondary: Not reported	A significantly greater proportion of patients who switched to rosuvastatin achieved a LDL-C reduction >25% compared to those who switched to simvastatin (44 vs 29%; *P*<0.05). Patients who switched from atorvastatin to rosuvastatin experienced a significantly greater reduction in LDL-C compared to those who switched to simvastatin therapy (14.6 vs 4.6%; *P*<0.05). Secondary: Not reported
Bullano et al[83] Rosuvastatin 5 to 40 mg/day vs other statins (atorvastatin 10 to 80 mg/day, simvastatin 5 to 80 mg/day, pravastatin 10 to 80 mg/day, lovastatin 10 to 80 mg/day and fluvastatin 20 to160 mg/day)	RETRO Patients ≥18 years of age initiated on a statin between August 1, 2003 and September 30, 2004 with ≥1 LDL-C level obtained prior to and after therapy initiation	N=8,251 Up to 122 days of therapy	Primary: Percentage change from baseline in LDL-C Secondary: Proportion of patients achieving the NCEP ATP III LDL-C goals (<100 mg/dL), percentage change from baseline in HDL-C, TC and TG	Primary: Rosuvastatin was associated with a significant reduction in LDL-C compared to other statins (33 vs 24 [atorvastatin], 20 [simvastatin], 18 [pravastatin], 13 [fluvastatin] and 16% [lovastatin]; *P*<0.05). Rosuvastatin 10 mg/day was associated with a significantly greater reduction in LDL-C compared to atorvastatin 10 to 20 mg/day (*P*<0.05) or simvastatin 10 to 20 mg/day (*P*<0.05). Secondary: A significantly greater proportion of patients receiving rosuvastatin achieved the NCEP ATP III LDL-C goals compared to patients receiving other statins (*P*<0.05). Patients receiving rosuvastatin required greater LDL-C reduction to reach their LDL-C goal compared to patients treated with other statins (29 vs 23 to 27%; *P*<0.05). A significantly greater proportion of patients receiving rosuvastatin achieved the updated, optional NCEP ATP III LDL-C goals compared to patients receiving other statins (58 vs 29 to 48%; *P*<0.05). There was no difference between rosuvastatin and other statins in HDL-C reductions (*P*>0.05). Rosuvastatin was associated with a significant reduction in TC compared to other statins (24% vs 18 [atorvastatin], 14 [simvastatin], 13 [pravastatin], 10 [fluvastatin] and 13% [lovastatin]; *P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Rosuvastatin was associated with a significant reduction in TG compared to other statins (11% vs 6 [simvastatin], 4 [pravastatin], 4 [fluvastatin] and 5% [lovastatin]; *P*<0.05). There was no difference in TG reduction between rosuvastatin and atorvastatin (11 vs 10%; *P*>0.05).
Fox et al[84] Rosuvastatin (average dose, 11.7 mg/day) vs other statins (atorvastatin, pravastatin, lovastatin, simvastatin, fluvastatin; dosed 17 to 64 mg/day)	RETRO Adult patients with diabetes who were newly prescribed a statin between August 2003 and March 2006	N=4,754 Patients received statin therapy between August 2003 and March 2006	Primary: Percent reduction from baseline in LDL-C, proportion of patients achieving LDL-C goal <100 mg/dL Secondary: Not reported	Primary: Rosuvastatin was associated with a significant reduction in small dense LDL-C compared to atorvastatin (22.5%), simvastatin (20.1%), pravastatin (13.7%), lovastatin (17.3%) and fluvastatin (15.8%) (*P*<0.0001 for all). Compared to other statins, a significantly greater proportion of patients receiving rosuvastatin achieved the LDL-C goal (*P*<0.05). Secondary: Not reported
Jones et al[85] Fenofibric acid DR 135 mg/day vs rosuvastatin 10, 20 or 40 mg/day vs fenofibric acid DR 135 mg/day plus rosuvastatin 10 or 20	AC, DB, MC, RCT Patients ≥18 years of age with mixed dyslipidemia (TG ≥150 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for women and LDL-C ≥130 mg/dL)	N=1,445 16 weeks (includes 30 day safety evaluation)	Primary: Composite of mean percent changes from baseline in HDL-C, TG and LDL-C Secondary: Composite of mean percent changes from baseline in non-HDL-C, VLDL-C, TC, apo B and hsCRP	Primary: Combination therapy (rosuvastatin 10 and 20 mg) was associated with a significantly greater increase in HDL-C (10 mg: 20.3 vs 8.5%; *P*<0.001 and 20 mg: 19.0 vs 10.3%; *P*<0.001) and a significantly greater decrease in TG (10 mg: 47.1 vs 24.4%; *P*<0.001 and 20 mg: 42.9 vs 25.6%; *P*<0.001) compared to rosuvastatin (10 and 20 mg). Combination therapy was associated with a significantly greater decrease in LDL-C (10 mg: 37.2 vs 6.5%; *P*<0.001 and 20 mg: 38.8 vs 6.5%; *P*<0.001) compared to fenofibric acid. Secondary: Combination therapy (rosuvastatin 10 mg) was associated with a significantly greater reduction in non-HDL-C compared to fenofibric acid or rosuvastatin (10 mg) (*P*<0.001). Combination therapy was also associated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day				with significantly greater improvements in VLDL-C (*P*<0.001), apo B (*P*<0.001) and hsCRP (*P*=0.013) compared to rosuvastatin. Combination therapy (rosuvastatin 20 mg) significantly improved non-HDL-C compared to fenofibric acid (*P*<0.001) and was associated with a significantly greater improvement in VLDL-C (*P*=0.038) and hsCRP (*P*=0.010) compared to rosuvastatin (20 mg), with similar reductions in non-HDL-C, apo B and TC (*P* values not reported).
Roth et al[86] Rosuvastatin 5 mg/day vs fenofibric acid 135 mg/day vs rosuvastatin 5 mg/day plus fenofibric acid 135 mg/day	DB, MC, RCT Patients with fasting LDL-C ≥130 mg/dL, TG ≥150 mg/dL and HDL-C 40 mg/dL	N=760 12 weeks (plus a 30 day safety follow up period)	Primary: Composite of mean percent changes from baseline in HDL-C, TG and LDL-C Secondary: Changes from baseline in non-HDL-C, VLDL-C, apo B, hsCRP and TC; safety; proportion of patients achieving LDL-C (<100 mg/dL) and non-HDL-C (<130 mg/dL) goals	Primary: Combination therapy resulted in a significantly greater mean percent change in HDL-C (23.0 vs 12.4%; *P*<0.001) and TG (-43.0 vs -17.5%; *P*<0.001) compared to rosuvastatin, and resulted in significantly higher mean percent decrease in LDL-C compared to fenofibric acid (28.7 vs 4.1%; *P*<0.001). Secondary: Combination therapy resulted in significantly greater improvements in non-HDL-C compared to either monotherapy, and significantly greater improvements in apo B, hsCRP, VLDL-C and TC compared to rosuvastatin. All treatments were generally well tolerated, with discontinuations due to adverse events being higher with combination therapy (8.3%) and fenofibric acid (7.5%) compared to rosuvastatin (4.4%). The most common adverse events leading to discontinuation were myalgia and muscle spasms and nausea, fatigue and ALT and AST increases. The overall incidence of treatment-emergent adverse events was similar across treatments (58.5 to 63.0%). No significant differences were observed between the combination therapy and either monotherapy in the incidence of any category of adverse events (muscle, hepatic and renal related). In patients with a 10 year CHD risk >20%, the LDL-C goal <100 mg/dL was achieved by 50.5% of patients receiving combination therapy and rosuvastatin; the non-HDL-C goal <130 mg/dL was achieved by 49.5% of patients receiving combination therapy compared to 33.3% of patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				receiving rosuvastatin (*P*=0.03). Both LDL-C and non-HDL-C goals were achieved by 44.3 vs 32.3% (*P*=0.10).
Rogers et al[87] Simvastatin 10, 20, 40 or 80 mg/day vs atorvastatin 10, 20, 40 or 80 mg/day	MA (18 trials) Patients >18 years of age with elevated TC and LDL-C	N=8,320 Up to 12 weeks	Primary: Reductions in TC, LDL-C and TG; increases in HDL-C Secondary: Not reported	Primary: Simvastatin appeared to be comparable to atorvastatin in terms of TC reduction from baseline at four times the dose of atorvastatin (*P*>0.05). Simvastatin 20 and 40 mg were less effective at reducing LDL-C from baseline compared to atorvastatin 40 and 80 mg, respectively (*P*<0.001). Simvastatin 40 to 80 mg was comparable to atorvastatin 20 mg in terms of TG reduction from baseline (*P*=0.22 and *P*=0.53, respectively). Atorvastatin 40 to 80 mg was more effective in reducing TG from baseline compared to all simvastatin doses evaluated (*P*<0.001). Simvastatin 10, 20 and 80 mg were more effective than atorvastatin 80 mg in increasing HDL-C from baseline (*P*<0.05). Secondary: Not reported
Hall et al (abstract)[88] SPACE ROCKET Simvastatin 40 mg/day vs rosuvastatin 10 mg/day	MC, OL, RCT Patients with a history of acute MI	N=1,263 3 months	Primary: Proportion of patients achieving the European Society of Cardiology 2003 TC (<174 mg/dL) or LDL-C (<97 mg/dL) goals Secondary: Not reported	Primary: There was no difference between the two treatments in the proportions of patients who achieved lipid goals (77.6 vs 79.9%; OR, 1.16; 95% CI, 0.88 to 1.53; *P*=0.29). A post hoc analysis demonstrated a significantly higher achievement of the new European Society of Cardiology, American Heart Association and American College of Cardiology LDL-C goal (<70 mg/dL) with rosuvastatin (37.8 vs 45.0%; OR, 1.37; 95% CI, 1.09 to 1.72; *P*=0.007). The proportion of patients achieving the Fourth Joint Task Force European Guidelines TC (<155 mg/dL) and LDL-C (<77 mg/dL) goals were also significantly higher with rosuvastatin (38.7 vs 47.7%; OR, 1.48; 95% CI, 1.18 to 1.86; *P*=0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Not reported
Feldman et al[89] Ezetimibe 10 mg/day plus simvastatin 10, 20 or 40 mg/day vs simvastatin 20 mg/day	DB, MC, RCT 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	N=710 23 weeks	Primary: Proportion of patients with LDL-C <100 mg/dL at week five Secondary: Proportion of patients with LDL-C <100 mg/dL at 23 weeks	Primary: A significantly greater proportion of patients receiving combination therapy 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).
Gaudiani et al[90] Ezetimibe 10 mg/day plus simvastatin 20 mg/day vs simvastatin 40 mg/day	DB, MC, PG, RCT Patients 30 to 75 years of age with type 2 diabetes (HbA_{1c} ≤9.0%), treated with a stable dose of pioglitazone (15 to 45 mg/day) or rosiglitazone (2 to 8 mg/day) for ≥3	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-	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
All patients received simvastatin 20 mg/day for a 6 week run in period.	months, LDL-C >100 mg/dL and TG <600 mg/dL (if already on a statin therapy)		HDL-C, apo B and apo AI	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).
Bays et al[91] 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[36] 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). Based on investigator assessment of causality, rates were similar between the treatments. There are no remarkable observations of between-treatment group 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
Mohiuddin et al[92] Fenofibric acid 135 mg/day plus	AC, DB, MC Patients >18 years of age with mixed	N=657 16 weeks (includes 30 day	Primary: Composite of mean percent changes from baseline in	Primary: Combination therapy was associated with a significantly greater increase in HDL-C (20 mg: 17.8 vs 7.2%; *P*<0.001 and 40 mg: 18.9 vs 8.5%; *P*<0.001) and a significantly greater decrease in TG (20 mg: 37.4 vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
simvastatin 20 or 40 mg/day vs fenofibric acid 135 mg/day vs simvastatin 20, 40 or 80 mg/day	dyslipidemia (TG ≥150 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for women, and LDL-C ≥130 mg/dL)	safety evaluation)	HDL-C, TG and LDL-C Secondary: Composite of mean percent changes from baseline in non-HDL-C, VLDL-C, TC, apo B and hsCRP	14.2%; *P*<0.001 and 40 mg: 42.7 vs 22.4%; *P*<0.001) compared to simvastatin (20 and 40 mg). Combination therapy was associated with a significantly greater decrease in LDL-C (20 mg: 24.0 vs 4.0%; *P*<0.001 and 40 mg: 25.3 vs 4.0%; *P*<0.001) compared to fenofibric acid. Secondary: Combination therapy (simvastatin 20 mg) was associated with a significantly greater decrease in non-HDL-C (*P*<0.001) compared to fenofibric acid and simvastatin (20 mg). Combination therapy (simvastatin 20 mg) was associated with significant improvements in VLDL-C (*P*<0.001), apo B (*P*<0.001) and hsCRP (*P*=0.013) compared to simvastatin (20 mg). Combination therapy (simvastatin 40 mg) significantly (*P*<0.001) improved non-HDL-C compared to fenofibric acid, and resulted in a significantly greater improvement in VLDL-C (*P*=0.005) compared to simvastatin (40 mg), with similar reductions in non-HDL-C, apo B and TC (*P* values not reported).
Calza et al (abstract)[93] Rosuvastatin 10 mg QD vs pravastatin 20 mg QD vs atorvastatin 10 mg	OL, PRO, RCT Patients with HIV receiving protease inhibitor therapy ≥12 months with protease inhibitor-associated hypercholesterolemia ≥3 months and unresponsive to a hypolipidemic diet and physical exercise	N=94 12 months	Primary: Changes from baseline in TC and LDL-C Secondary: Not reported	Primary: Statins led to a mean reduction of 21.2 and 23.6% in TC and LDL-C (*P*=0.002). The mean decrease in TC was significantly greater with rosuvastatin (25.2%) compared to pravastatin (17.6%; *P*=0.01) and atorvastatin (19.8%; *P*=0.03). During the 12 months, all statins demonstrated a favorable tolerability profile, and patient's HIV viral load did not present any variation. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
QD				
Insull et al[94] SOLAR Rosuvastatin 10 mg/day daily for 6 weeks, followed by doubling of the dose and treatment for another 6 weeks if LDL-C target (<100 mg/dL) was not achieved vs atorvastatin 10 mg/day for 6 weeks, followed by doubling of the dose and treatment for another 6 weeks if LDL-C target (<100 mg/dL) was not achieved vs simvastatin 20 mg/day for 6 weeks, followed by doubling of the dose and treatment for another 6 weeks if LDL-C target (<100 mg/dL) was not achieved	MC, RCT Patients ≥18 years of age who were enrolled in a managed care health plan and classified as high risk by NCEP ATP III risk assessment	N=1,632 12 weeks	Primary: Proportion of patients achieving NCEP ATP III high risk LDL-C goal (<100 mg/dL) at week six Secondary: Proportion of patients achieving the high risk LDL-C goal at 12 weeks, proportion of hyper-triglyceridemic patients who achieved both the LDL-C goal (<100 mg/dL) and the non-HDL-C goal (<130 mg/dL) for high risk patients, changes from baseline in LDL-C and other lipid parameters at six and 12 weeks	Primary: After six weeks, a significantly greater proportion of patients receiving rosuvastatin 10 mg achieved the high risk LDL-C goal compared to patients receiving atorvastatin 10 mg and patients receiving simvastatin 20 mg (65 vs 41 vs 39%, respectively; *P*<0.001). Secondary: After 12 weeks, 76% of patients receiving rosuvastatin 20 mg achieved the high risk LDL-C goal compared to 58 and 53% of patients receiving atorvastatin 20 mg and simvastatin 40 mg, respectively (*P*<0.001). After six weeks, 44% of hypertriglyceridemic patients receiving rosuvastatin 10 mg achieved the combined LDL-C and non-HDL-C goals compared to 19% of patients receiving simvastatin 20 mg, respectively (*P*<0.001). There was no difference between rosuvastatin 10 mg and atorvastatin 10 mg (44 vs 22%; *P* value not reported). After 12 weeks, 57% of hypertriglyceridemic patients taking rosuvastatin 20 mg reached the combined LDL-C and non-HDL-C goal compared to 31% of patients taking simvastatin 40 mg, respectively (*P*<0.001). There was no difference between rosuvastatin 20 mg and atorvastatin 20 mg (57 vs 36%; *P* value not reported). Rosuvastatin was associated with a significant reduction in LDL-C compared to atorvastatin and simvastatin at six and 12 weeks (*P*<0.001 for both). Rosuvastatin was associated with a significant reduction in TC compared to atorvastatin and simvastatin at six and 12 weeks (*P*<0.001). Rosuvastatin was associated with a significant reduction in non-HDL-C compared to atorvastatin and simvastatin at six and 12 weeks (*P*<0.001). Rosuvastatin was associated with a significant reduction in non-HDL-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
All patients were randomized after a 6 week dietary lead in period.				C:HDL-C compared to atorvastatin and simvastatin at six and 12 weeks (*P*<0.001). Rosuvastatin was associated with a significant increase in HDL-C compared to atorvastatin and simvastatin at 12 weeks (*P*<0.001). Patients randomized to rosuvastatin experienced a statistically significant reduction in TG from baseline compared to simvastatin at six and 12 months (*P*<0.001). The frequency and types of adverse events were similar with all treatments (*P* value not reported).
Ballantyne et al[95] MERCURY II Rosuvastatin 20 mg/day for 8 weeks vs atorvastatin 10 or 20 mg/day for 8 weeks vs simvastatin 20 or 40 mg/day for 8 weeks All patients were randomized after a 6 week dietary lead in period. After 8 weeks of treatment, patients	MC, OL, RCT Patients ≥18 years of age, at high risk for CHD events, fasting LDL-C ≥130 to <250 mg/dL on 2 separate measurements within 15% of each other and a fasting TG <400 mg/dL	N=1,993 16 weeks	Primary: The proportion of patients achieving LDL-C <100 mg/dL at week 16 Secondary: The proportion of patients meeting the LDL-C target at week eight, change in lipid and lipoprotein measures at weeks eight and 16, adverse events	Primary: After 16 weeks, a larger proportion of patients receiving rosuvastatin achieved the LDL-C goal compared to patients receiving all other treatments (83, 42, 64, 32 and 56%, respectively; *P* value not reported). After 16 weeks, significantly more patients who switched to rosuvastatin therapy achieved LDL-C target level <100 mg/dL compared to patients who remained on their initial statin therapy (*P*<0.001). Secondary: After 16 weeks, patients who switched to rosuvastatin experienced a significant LDL-C reduction from baseline compared to patients remaining on their initial medication regimen (*P*<0.001). After eight weeks, a significantly greater proportion of patients receiving rosuvastatin achieved the LDL-C goal <100 mg/dL compared to patients receiving all other treatments (82, 43, 62, 33 and 55%, respectively; *P*<0.0001). After 16 weeks, a significantly greater proportion of patients randomized to rosuvastatin achieved the LDL-C goal <70 mg/dL compared to patients receiving all other treatments (37, 7, 13, 1 and 10%, respectively; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
received an additional 8 weeks of either initial statin or rosuvastatin therapy.				After 16 weeks, patients who switched to rosuvastatin experienced a significant atherogenic lipid measure and ratio reduction from baseline compared to patients remaining on their initial medication regimen (*P*<0.001). After 16 weeks, a significantly greater proportion of hypertriglyceridemic patients receiving rosuvastatin achieved the LDL-C goal <100 mg/dL and non-HDL-C goals compared to patients receiving all other treatments (80, 20, 42, 19 and 29%, respectively; *P* value not reported). The frequency and type of adverse events were similar with all treatments (*P* value not reported). In addition, there were no symptomatic adverse events associated with hepatic dysfunction.
Jones et al[96] STELLAR Rosuvastatin 10 to 40 mg/day vs pravastatin 10 to 40 mg/day vs atorvastatin 10 to 80 mg/day vs simvastatin 10 to 80 mg/day	OL, PG Patients ≥18 years of age with hypercholesterolemia and LDL-C ≥160 to <250 mg/dL at the 2 most recent consecutive visits	N=2,431 6 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent changes from baseline in HDL-C, TG and TC	Primary: Compared to all doses of atorvastatin and pravastatin, rosuvastatin was associated with a greater reduction in LDL-C (*P*<0.001 for both). When compared to baseline, the following reductions in LDL-C were observed: rosuvastatin; 45.8 to 55.0%, atorvastatin; 36.8 to 51.1%, simvastatin; 28.3 to 45.8% and pravastatin; 20.1 to 29.7%. The greatest reductions in LDL-C observed were a 55% reduction with rosuvastatin 40 mg and a 51% reduction with atorvastatin 80 mg (*P*=0.006). Secondary: Rosuvastatin 10 to 40 mg/day was associated with a 7.7 to 9.6% increase in HDL-C, a 19.8 to 26.1% reduction in TG and a 32.9 to 40.2% reduction in TC (*P* values not reported). Pravastatin 10 to 40 mg/day was associated with a 3.2 to 5.6% increase in HDL-C, a 7.7 to 13.2% reduction in TG and a 14.7 to 21.5% reduction in TC (*P* value not reported). Atorvastatin 10 to 80 mg/day was associated with a 2.1 to 5.7% increase in HDL-C, a 20.0 to 28.2% reduction in TG and a 27.1 to 38.9% reduction

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				in TC (*P* value not reported). Simvastatin 10 to 80 mg/day was associated with a 5.2 to 6.8% increase in HDL-C, an 11.9 to 18.2% reduction in TG and a 20.3 to 32.9% reduction in TC (*P* value not reported).
McKenney et al[97] COMPELL Rosuvastatin 10 mg/day for 4 weeks, followed by 20 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	MC, OL, PG, RCT Patients ≥21 years of age with hyper-cholesterolemia, eligible for treatment based on the NCEP ATP III guidelines, with 2 consecutive LDL-C levels within 15% of each other and mean TG ≤300 mg/dL	N=292 12 weeks	Primary: Change from baseline in LDL-C Secondary: Change from baseline in HDL-C non-HDL-C, TG, Lp(a) and apo B; side effects	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: 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	Endpoints	Results
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 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				
Kipnes et al[98] Fenofibric acid 135 mg/day plus a moderate dose statin (rosuvastatin 20 mg/day, simvastatin 40 mg/day or atorvastatin 40 mg/day)	ES, OL Patients with mixed dyslipidemia at the start of a 1 year, ES, OL	N=310 1 year (2 years of total therapy)	Primary: Safety and efficacy Secondary: Not reported	Primary: No deaths occurred during the two year trial. The incidence of serious adverse events was numerically highest with fenofibric acid plus rosuvastatin (14.9%) compared to fenofibric acid plus simvastatin (8.0%) or atorvastatin (5.8%). The incidences of adverse events were similar among all treatments as well (94.8, 90.0 and 97.7%). Adverse events tended to occur early in treatment, without the development of new types of adverse events over time. The most common treatment-related adverse events were muscle spasms (3.9%), increased blood creatine phosphokinase (3.5%), headache (2.9%), myalgia (2.9%), dyspepsia (2.3%) and nausea (2.3%). Rhabdomyolysis was not reported with any treatment. Nine patients discontinued therapy due to adverse events, with similar incidences among all treatments. Myalgia was the most common reason for discontinuation. No significant difference in the incidence of laboratory elevations was observed among the treatment groups. Incremental improvements in mean percentage changes in all efficacy variables were observed after the first visit in the year one ES (week 16).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				This effect was sustained for greater than two years and sizable mean percentage changes in all efficacy variables were observed at week 116. In the overall population, the mean percentage changes from baseline to week 116 in efficacy variables were: 17.4 (HDL-C), -46.4 (TG), -40.4 (LDL-C), -47.3 (non-HDL-C), -37.8 (TC) and -52.8% (VLDL-C). Significant differences among treatments were observed for non-HDL-C (-48.60±13.58 vs -41.70±13.10 vs -47.30±12.50%; *P*=0.011), TC (-38.70±12.16 vs -32.50±10.86 vs -38.60±10.85%; *P*=0.007) and VLDL-C (-56.80±25.17 vs -40.30±51.25 vs -51.20±35.42%; *P*=0.019). Secondary: Not reported
Hypercholesterolemia Clinical Outcomes Trials (Single-Entity Agents)				
Delaying the Progression of Atherosclerosis (Single-Entity Agents)				
Nissen et al[99] ASTEROID Rosuvastatin 40 mg QD	MC, OL, PRO Patients ≥18 years of age requiring coronary angiography for a stable or unstable ischemic chest pain syndrome or abnormal exercise test, with ≥1 obstruction ≥20% angiographic luminal diameter narrowing in a coronary vessel, not on statin therapy for >3 months within the last 12 months	N=507 24 months	Primary: PAV, absolute change in TAV in the 10 mm subsegment of the coronary artery with the largest plaque volume at baseline Secondary: Change in normalized TAV, lipid parameters	Primary: Rosuvastatin achieved a significant reduction in PAV from baseline (-0.79%; 95% CI, -1.21 to -0.53; *P*<0.001). Rosuvastatin achieved significant reduction from baseline in atheroma volume in the most diseased 10 mm subsegment (-5.6 mm^3; 95% CI, -6.82 to -3.96; *P*<0.001). Secondary: Rosuvastatin achieved a significant reduction from baseline in normalized TAV (-12.5 mm^3; 95% CI, -15.08 to -10.48; *P*<0.001). Rosuvastatin achieved a significant reduction from baseline in the total normalized TAV (-6.8%; 95% CI, -7.82 to -5.60; *P*<0.001). Rosuvastatin achieved a significant reduction from baseline in TC (33.0%), LDL-C (53.2%), TG (14.5%), LDL-C:HDL-C ratio (58.5%) and non-HDL-C (47.2%; *P*<0.001). Rosuvastatin achieved a significant increase from baseline in HDL-C (14.7%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Furberg et al[100] ACAPS Lovastatin 20 to 40 mg QD plus warfarin 1 mg QD vs lovastatin 20 to 40 mg QD plus warfarin placebo vs lovastatin placebo plus warfarin 1 mg QD vs lovastatin placebo plus warfarin placebo	DB, MC, PC, RCT Asymptomatic patients 40 to 79 years of age, with early carotid atherosclerosis as defined by B-mode ultrasonography and moderately elevated LDL-C (between the 60th and 90th percentiles)	N=919 3 years	Primary Three year change in the mean maximum IMT in 12 walls of the carotid arteries (near and far walls of the common carotid, the bifurcation and the internal carotid arteries on both sides of the neck) Secondary Change in single maximum IMT, incidence of major cardiovascular events and adverse events	Primary The progression rate of mean maximum IMT was less with lovastatin plus warfarin than with lovastatin (*P*=0.04). The overall annualized progression rates of mean maximum IMT with lovastatin and placebo were -0.009 and 0.006 mm/year, respectively (*P*=0.001). Secondary: The changes in single maximum IMT with lovastatin and placebo were -0.036±0.022 and 0.000±0.011 mm/year, respectively (*P*=0.12). Fourteen of the 459 patients receiving lovastatin-placebo had a major cardiovascular event (four CHD deaths, five strokes and five nonfatal MI) compared to five of the 460 patients receiving placebo (*P*=0.04). There was one death in patients receiving lovastatin and eight in patients receiving lovastatin plus placebo (*P*=0.02). All six cardiovascular deaths were with lovastatin plus placebo, the remaining three deaths were cancer deaths. Lovastatin and lovastatin-placebo demonstrated no difference in ALT elevations of ≥200% the ULN.
Byington et al[101] PLAC-II Pravastatin 20 mg QD in the evening, titrated up to 40 mg/day vs placebo	DB, PC, RCT Patients with a history of CHD and ≥1 extracranial carotid lesion with the maximum IMT ≥1.3 mm	N=151 3 years	Primary: Change in the mean of maximum IMT measurements in the common, internal and bifurcation carotid artery segments Secondary: Effects on individual carotid	Primary: Pravastatin did not result in a significant reduction in the progression of mean maximum IMT (*P*=0.44). Pravastatin was associated with a significant 35% reduction in IMT progression in the common carotid artery (*P*=0.03). There was no significant effect on bifurcation (*P*=0.49) or on the internal carotid artery (*P*=0.93) with pravastatin. Secondary: Pravastatin was associated with a 60% reduction in clinical coronary

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			artery segments and clinical events	events (*P*=0.09). When compared to placebo, a significant 61% reduction in the incidence of any coronary events and all-cause mortality was seen with pravastatin (*P*=0.04).
Yu et al[102] Atorvastatin 80 mg QD vs atorvastatin 10 mg QD	DB, RCT Patients with CHD (confirmed by angiographic evidence of coronary stenosis, previous MI, PCI or angina pectoris), hypercholesterolemia and LDL-C >100 mg/dL	N=112 26 weeks	Primary: Improvement in IMT Secondary: Reduction in hsCRP level, proinflammatory cytokines at week 26	Primary: Atorvastatin 10 mg was not associated with a significant improvement in either left or right carotid IMT (*P* value not reported). Atorvastatin 80 mg led to a significant improvement in left carotid IMT (*P*=0.02) as well as the right carotid IMT from baseline (*P*=0.01). Secondary: Atorvastatin 10 mg was not associated with a significant change in hsCRP (*P* value not reported). Atorvastatin 80 mg led to a significant reduction in hsCRP level from baseline (*P*=0.01). Atorvastatin 10 mg was associated with a significant reduction in interleukin-8 (*P*=0.01), interleukin-18 (*P*<0.001) and tumor necrosis factor (*P*<0.001). Atorvastatin 80 mg led to a significant reduction in all the proinflammatory cytokines from baseline (*P*<0.05).
Schmermund et al[103] Atorvastatin 10 mg QD vs atorvastatin 80 mg QD	DB, MC, RCT Patients 32 to 80 years of age without a history of MI, coronary revascularization or hemodynamically relevant stenoses, with moderate calcified coronary atherosclerosis (coronary artery calcification score ≥30), LDL-C 130 to	N=471 12 months	Primary: The percent change in total coronary artery calcification volume score Secondary: Change in LDL-C	Primary: There was no significant difference in the primary endpoint between the two treatments (*P*=0.6477). Secondary: Atorvastatin 80 mg was associated with a 20% reduction in LDL-C compared to atorvastatin 10 mg (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	250 mg/dL in the absence of statin therapy or between 100 to 130 mg/dL under statin therapy, TG <400 mg/dL, ≥2 cardiovascular risk factors			
Crouse et al[104] METEOR Rosuvastatin 40 mg QD vs placebo	DB, RCT Patients 45 to 70 years of age with LDL-C 120 to 190 mg/dL among patients whose only CHD risk factor was age, and an LDL-C 120 to 160 mg/dL for patients with ≥2 CHD risk factors and a 10 year risk of CHD events of <10%, HDL-C ≤60 mg/dL, TG <500 mg/dL and maximum CIMT 1.2 to 3.5 mm from 2 separate ultrasounds	N=984 2 years	Primary: Annualized rate of change in maximum CIMT of the 12 carotid artery sites (near and far walls of the right and left common carotid artery, carotid bulb and internal carotid artery) Secondary: Annualized rate of change in maximum CIMT of the common carotid artery, carotid bulb and internal carotid artery sites; annualized rate of change in mean CIMT	Primary: Rosuvastatin was associated with a significant reduction in the annualized rate of change in maximum CIMT from baseline compared to placebo (*P*<0.001). Secondary: Rosuvastatin was associated with a significant 49% reduction in LDL-C from baseline compared to placebo (*P*<0.001). Rosuvastatin was associated with a significant reduction in the annualized rate of change in the maximum CIMT for the common carotid artery sites (*P*<0.001), carotid bulb (*P*<0.001) and internal carotid artery sites (*P*=0.02) from baseline compared to placebo. Rosuvastatin was associated with a significant reduction in the annualized rate of change in the mean CIMT for the common carotid artery sites (*P*<0.001) from baseline compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Chan et al[105] ASTRONOMER Rosuvastatin 40 mg/day vs placebo	DB, PC, RCT Patients 18 to 82 years of age with asymptomatic mild to moderate aortic stenosis	N=269 3 to 5 years	Primary: Hemodynamic parameters of aortic stenosis severity Secondary: Composite of aortic valve replacement and cardiac death	Primary: Progression of aortic stenosis measured by the peak gradient and aortic valve area did not differ between the two treatments (*P* values not reported). The mean changes in the peak aortic stenosis gradient, mean gradient and aortic valve area were no significantly different between the two treatments (*P*=0.32, *P*=0.49 and *P*=0.79, respectively). The annual increase in peak aortic stenosis was 6.1±8.2 and 6.3±6.9 mm Hg with placebo and rosuvastatin (*P*=0.83). The annual increase in the mean gradient was 3.9±4.9 and 3.8±4.4 mm Hg with placebo and rosuvastatin (*P*=0.79). The annual decrease in aortic valve area was 0.08±0.21 and 0.07±0.15 cm^2 (*P*=0.87). The linear mixed models did not show any significant differences in the primary outcomes between the two treatments at any time point during the follow up. Secondary: There were a total of seven cardiac deaths, one of which was associated with aortic valve replacement, and a total of 55 patients with aortic valve replacement. The survival curves of the outcome events (cardiac death or aortic valve replacement) were not significantly different between the two treatments (*P*=0.45).
Nissen et al[106] REVERSAL Atorvastatin 40 mg BID	DB, MC, RCT Patients 30 to 75 years of age with >1 angiographic luminal	N=654 18 months	Primary: Percentage change in atheroma volume from baseline	Primary: Atorvastatin was associated with a significant delay in atheroma volume progression compared to pravastatin (*P*=0.02). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs pravastatin 40 mg QD	narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C 125 to 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long		Secondary: Nominal change in atheroma volume, nominal change in atheroma volume in the 10 contiguous cross-sections with the greatest and the least atheroma volume	Atorvastatin was associated with a significant nominal change in total atheroma volume compared to pravastatin (*P*=0.02). Atorvastatin was associated with a significant change in the percentage of atheroma volume compared to pravastatin (*P*<0.001). Atorvastatin was associated with a significant change in atheroma volume in the most severely diseased 10 mm vessel subsegment compared to pravastatin (*P*=0.01). Progression of coronary atherosclerosis from baseline occurred in 2.7% of pravastatin-treated patients (*P*=0.001) and none of the atorvastatin-treated patients (*P*=0.98). Atorvastatin 80 mg was associated with a significant reduction in TC, LDL-C, TG, apo B and hsCRP (*P*<0.001) compared to the pravastatin.
Schoenhagen et al[107] Atorvastatin 40 mg BID vs pravastatin 40 mg QD	Serial intravascular ultrasound observations from the REVERSAL trial[87] Patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C 125 to 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long	N=654 18 months	Primary: Percentage change from baseline in external elastic membrane area lesion, lumen area lesion, plaque area lesion and remodeling ratio Secondary: Not reported	Primary: Atorvastatin was associated with a significant 6.6% increase in the external elastic membrane area lesion from baseline (*P*<0.0001). Atorvastatin was associated with a significant 7.3% increase in the lumen area lesion from baseline (*P*=0.0002). Atorvastatin was associated with a significant 7.9% increase in the plaque area lesion from baseline (*P*=0.0002). Atorvastatin was associated with a significant 3.3% reduction in remodeling ratio from baseline (*P*=0.024). Pravastatin was associated with a significant 9% increase in the external elastic membrane area lesion from baseline (*P*=0.0002). Pravastatin was associated with a significant 9.5% increase in the lumen area lesion from baseline (*P*=0.0003).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Pravastatin was associated with a significant 9.9% increase in the plaque area lesion from baseline (*P*=0.0022). Pravastatin was associated with a significant 2.7% reduction in remodeling ratio from baseline (*P*=0.0013). There was no significant difference between atorvastatin and pravastatin in terms of increase in plaque area from baseline (7.9 vs 9.9%, respectively; *P*=0.57). There was no significant difference between atorvastatin and pravastatin in terms of reduction in remodeling ratio from baseline (3.3 vs 2.7%, respectively; *P*=0.68). Secondary: Not reported
Nicholls et al[108] Atorvastatin 40 mg BID vs pravastatin 40 mg QD	Subanalysis of REVERSAL trial[87] Obese patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C 125 to 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long, stratified based on BMI >29.6 kg/m^2 or BMI <29.6 kg/m^2	N=654 18 months	Primary: Percentage change from baseline in lipid parameters, atheroma volume Secondary: Not reported	Primary: Compared to the BMI <29.6 kg/m^2 group, obese patients receiving atorvastatin exhibited a significantly lower reduction in TC (40 vs 36%; *P*=0.007), LDL-C (55 vs 49%; *P*=0.008) and TG (35 vs 23%; *P*=0.04). Compared to the BMI <29.6 kg/m^2 group, obese patients receiving atorvastatin exhibited a significantly higher reduction in hsCRP (33 vs 40%; *P*=0.04). There was no significant difference in lipid parameters between the BMI groups among patients randomized to pravastatin (*P*>0.05). Compared to the BMI <29.6 kg/m^2 group, obese patients receiving atorvastatin exhibited a significantly greater benefit on the total atheroma volume (*P*=0.01) and percent atheroma volume (*P*=0.0005). In contrast, pravastatin was associated with a significant 6.5% increase in atheroma volume in the obese group (*P*=0.006). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Not reported
Nissen et al[109] Atorvastatin 40 mg BID vs pravastatin 40 mg QD	Subanalysis of REVERSAL trial[87] evaluating the effect of statin therapy on LDL-C, hsCRP and CAD Patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C 125 to 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long, stratified based on BMI >29.6 kg/m^2 or BMI <29.6 kg/m^2	N=654 18 months	Primary: Percent change in TC, TG, CRP, non-HDL-C, HDL-C and atheroma volume Secondary: Not reported	Primary: Both treatments achieved a significant reduction from baseline in TC (63%; *P*<0.001), LDL-C (56%; *P*<0.001), TG (40%; *P*=0.002), CRP (22.4%; *P*<0.001) and non-HDL-C (33%; *P*<0.001). HDL-C was not significantly increased from baseline with either treatment (4.2%; *P*=0.11). Atorvastatin exhibited a slower rate of disease progression (atheroma volume) compared to pravastatin (0.2 vs 1.6%; *P* value not reported). Patients whose LDL-C and hsCRP reductions were greater than the median experienced a significantly slower rate of disease progression compared to patients with lower LDL-C and hsCRP reductions (*P*=0.001). Secondary: Not reported
Primary Prevention of Coronary Heart Disease (Single-Entity Agents)				
Knopp et al[110] ASPEN Atorvastatin 10 mg QD vs placebo	DB, MC, PG, RCT Patients 40 to 75 years of age with type 2 diabetes for ≥3 years prior to screening, LDL-C ≤140 (if they had a history of an MI or an interventional	N=2,410 4 years	Primary: Time to occurrence of the composite clinical endpoint including cardiovascular death, nonfatal MI, nonfatal stroke, recanalization, CABG surgery,	Primary: There was no significant difference between the two treatments in the time to first primary event (HR, 90; 95% CI, 0.73 to 1.12; *P*=0.034). Less patients receiving atorvastatin experienced the primary endpoints compared to patients receiving placebo (13.7 vs 15.0%; *P*=0.034). Secondary: Atorvastatin was associated with a significant decrease in LDL-C compared to placebo (29.0 vs 1.6%; *P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	procedure >3 months before screening) or ≤160 mg/dL, TG ≤600 mg/dL		resuscitated cardiac arrest or worsening or unstable angina requiring hospitalization Secondary: Time to occurrence of cardiovascular death, noncardiovascular death, TIA, worsening or unstable angina not requiring hospitalization, worsening or unstable angina requiring hospitalization, surgery for newly diagnosed peripheral artery disease and acute ischemic heart failure requiring hospitalization; cholesterol level reduction; safety	Among patients without a prior history of an MI or interventional procedure, 10.4 and 10.8% of atorvastatin- and placebo-treated patients experienced a primary endpoint (HR, 97; 95% CI, 0.74 to 1.18). Among patients with a prior history of an MI or interventional procedure, 26.2 and 30.8% of atorvastatin- and placebo-treated patients experienced a primary endpoint (HR, 82; 95% CI, 0.59 to 1.15). RRRs in fatal and nonfatal MI were 27% overall (*P*=0.10), 19% for patients treated for primary protection (*P*=0.41) and 36% for patients treated for secondary protection (*P*=0.11). Adverse events were similar in both treatments for the total, primary and secondary prevention groups (*P* value not reported). Serious adverse events occurred in 37.7 and 35.4% of atorvastatin- and placebo-treated patients (*P* value not reported).
Colhoun et al[111] CARDS Atorvastatin 10 mg/day	DB, MC, RCT Patients 40 to 75 years of age with type 2 diabetes without a	N=2,838 3.9 years	Primary: Incidence of major cardiovascular events (CHD death, nonfatal MI,	Primary: Atorvastatin led to a significant 37% reduction in the RR of the primary endpoint compared to placebo (95% CI, 17 to 52; *P*=0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs placebo All patients were randomized after a 6 week placebo lead in period.	history of CHD, LDL-C ≤160 mg/dL, TG ≤600 mg/dL and ≥1 other CHD risk factor		including silent MI on annual ECG, fatal or nonfatal stroke, resuscitated cardiac arrest and coronary revascularization procedures) Secondary: All-cause mortality, acute hospital-verified cardiovascular endpoint (major cardiovascular disease events, angina, TIA, peripheral vascular disease requiring hospitalization or surgery), reduction in coronary revascularization, lipid reduction	Atorvastatin led to a significant 27% reduction in the RR of all-cause mortality compared to placebo (95% CI, 1 to 48; *P*=0.059). Atorvastatin led to a significant 32% reduction in the RR of any cardiovascular endpoint compared to placebo (95% CI, 15 to 45; *P*=0.001). Atorvastatin was associated with a significant reduction in stroke compared to placebo (1.5 vs 2.8%; HR, 0.52; 95% CI, 0.31 to 0.89). Atorvastatin was not associated with a significant reduction in coronary revascularization compared to placebo (HR, 0.69; 95% CI, 0.41 to 1.16). Atorvastatin was associated with a significant 40% reduction in baseline LDL-C compared to placebo (*P*<0.0001). Atorvastatin was associated with a significant 26% reduction in baseline TC levels compared to placebo (*P*<0.0001). Atorvastatin was associated with a significant one percent increase in baseline HDL-C compared to placebo (*P*=0.0002). Atorvastatin was associated with a significant 36% reduction in baseline non-HDL-C compared to placebo (*P*<0.0001). Atorvastatin was associated with a significant 19% reduction in baseline TG compared to placebo (*P*<0.0001). Atorvastatin was associated with a significant 23% reduction in baseline apo B compared to placebo (*P*<0.0001). The frequency of adverse events was similar between the two treatments (*P* value not reported).
Neil et al[112]	Post hoc analysis of CARDS[107]	N=2,838	Primary: Major	Primary: Atorvastatin led to a significant 38% reduction in the RR of the primary

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Atorvastatin 10 mg/day vs placebo All patients were randomized after a 6 week placebo lead in period.	Adult patients with type 2 diabetes without a history of CHD, LDL-C ≤160 mg/dL, TG ≤600 mg/dL and ≥1 other CHD risk factor; stratified by age (≥65 years of age)	3.9 years	cardiovascular events (acute CHD death, nonfatal MI, including silent MI on annual ECG, fatal or nonfatal stroke, resuscitated cardiac arrest and coronary revascularization procedures) among patients ≥65 and <65 years of age Secondary: All-cause mortality, acute hospital-verified cardiovascular endpoint (major cardiovascular disease events, angina, TIA, peripheral vascular disease requiring hospitalization or surgery) among patients ≥65 and <65 years of age	endpoint in patients ≥65 years of age (95% CI, 8 to 58; ARR, 3.9%, *P*=0.017). Consequently, 21 patients would need to be treated for four years to prevent one major cardiovascular event. Atorvastatin led to a significant 37% reduction in the RR of the primary endpoint in patients <65 years of age (95% CI, 7 to 57; ARR, 2.7%; *P*=0.019). Consequently, 33 patients would need to be treated for four years to prevent one major cardiovascular event. Secondary: There was no significant effect on all-cause mortality in either the <65 (*P*=0.98) or the ≥65 year old population (*P*=0.245). Atorvastatin led to a significant reduction in LDL-C among both the younger and the older patients compared to placebo (38 and 41%, respectively; *P*<0.001). Atorvastatin led to a significant reduction in TC among both the younger and the older patients compared to placebo (26 and 27%, respectively; *P*<0.001). Atorvastatin led to a significant reduction in TG among both the younger and the older patients compared to placebo (*P*<0.001). The frequency of adverse events was similar between the two treatments (*P* value not reported).
Hitman et al[113] Atorvastatin 10 mg/day vs	Subanalysis of CARDS[107] Patients 40 to 75 years of age with type 2 diabetes without a	N=2,838 3.9 years	Primary: Fatal or nonfatal stroke, type of stroke, risk factors for stroke	Primary: Atorvastatin was associated with a significant 48% reduction in stroke compared to placebo (1.5 vs 2.5%; HR, 0.52; 95% CI, 0.31 to 0.89; *P*=0.016). Atorvastatin was associated with a significant 50% reduction in non-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
placebo All patients were randomized after a 6 week placebo lead in period.	history of CHD, LDL-C ≤160 mg/dL, TG ≤600 mg/dL and ≥1 other CHD risk factor		Secondary: Not reported	hemorrhagic stroke compared to placebo (1.1 vs 2.2%; HR, 0.50; 95% CI, 0.27 to 0.91; *P*=0.024). Atorvastatin was associated with a significant 42% reduction in stroke or TIAs compared to placebo (2.1 vs 3.6%; HR, 0.58; 95% CI, 0.37 to 0.92; *P*=0.019). Independent risk factors predicting stroke were age (HR, 2.3; *P*<0.001), microalbuminuria (HR, 2.0; *P*=0.007) and glycemic control (HR, 2.7; *P*=0.007). Women were at a lower risk for stroke than men (HR, 0.3; *P*=0.004). Secondary: Not reported
Sever et al[114] ASCOT-LLA Atorvastatin 10 mg/day vs placebo All patients received antihypertensive treatment (amlodipine or atenolol with additional therapy as needed to reach SBP and DBP goals of <140 and 90 mm Hg, respectively).	DB, MC, RCT Patients 40 to 79 years of age with either untreated or treated hypertension, TC ≤6.5 mmol/L and not currently taking a statin or a fibrate; patients were also required to have >3 of the following cardiovascular disease risk factors: left-ventricular hypertrophy, ECG abnormality, diabetes type 2, peripheral artery disease, previous stroke or TIA, age >55 years,	N=10,305 3.3 years	Primary: Combined endpoint of nonfatal MI and fatal CHD Secondary: The primary outcome without silent events, all-cause mortality, total cardiovascular mortality, fatal and nonfatal heart failure, fatal and nonfatal stroke, total coronary endpoints, total cardiovascular events and procedures	Primary: Atorvastatin was associated with a significant 36% reduction in the primary endpoint compared to placebo (HR, 0.64; 95% CI, 0.50 to 0.83; *P*=0.0005). Secondary: Atorvastatin was associated with a significant 38% reduction in the primary endpoint, excluding silent MIs, compared to placebo (HR, 0.62; 95% CI, 0.47 to 0.81; *P*=0.0005). Atorvastatin was not associated with a significant reduction in all-cause mortality (*P*=0.1649), cardiovascular mortality (*P*=0.5066) or fatal and nonfatal heart failure (*P*=0.5794) compared to placebo. Atorvastatin was associated with a significant 27% reduction in the risk for fatal and nonfatal strokes compared to placebo (HR, 0.73; 95% CI, 0.56 to 0.96; *P*=0.0236). Atorvastatin was associated with a significant 29% reduction in the risk for total coronary events compared to placebo (HR, 0.71; 95% CI, 0.59 to 0.86; *P*=0.005).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	microalbuminuria or proteinuria, male sex, smoking, TC:HDL-C >6 or family history of CHD			Atorvastatin was associated with a significant 21% reduction in the risk for total cardiovascular events and procedures compared to placebo (HR, 0.79; 95% CI, 0.69 to 0.90; *P*=0.0005).
Sever et al[115] Atorvastatin 10 mg/day vs placebo All patients received antihypertensive treatment (amlodipine or atenolol with additional therapy as needed to reach SBP and DBP goals of <140 and 90 mm Hg, respectively).	2 year extension of ASCOT-LLA[95] Patients 40 to 79 years of age with either untreated or treated hypertension, TC ≤6.5 mmol/L and not currently taking a statin or a fibrate; patients were also required to have >3 of the following cardio-vascular disease risk factors: left-ventricular hypertrophy, ECG abnormality, diabetes type 2, peripheral artery disease, previous stroke or TIA, age >55 years, microalbuminuria or proteinuria, male sex, smoking, TC:HDL-C >6 or family history of CHD	N=10,305 5.5 years	Primary: Combined endpoint of nonfatal MI and fatal CHD Secondary: The primary outcome without silent events, all-cause mortality, total cardiovascular mortality, fatal and nonfatal stroke, fatal and nonfatal heart failure, total coronary endpoints, total cardiovascular events	Primary: Atorvastatin was associated with a significant 36% reduction in the primary endpoint compared to placebo (HR, 0.64; 95% CI, 0.53 to 0.78; *P*≤0.0001). Secondary: Atorvastatin was associated with a significant 37% reduction in the primary endpoint, excluding silent MIs, compared to placebo (HR, 0.63; 95% CI, 0.51 to 0.77; *P*≤0.0001). Atorvastatin was associated with a significant 15% reduction in the risk for all-cause mortality compared to placebo (HR, 0.85; 95% CI, 0.74 to 0.98; *P*=0.0219). Atorvastatin was not associated with a significant reduction in cardiovascular mortality (*P*=0.1281), or fatal and nonfatal heart failure (*P*=0.9809) compared to placebo. Atorvastatin was associated with a significant 23% reduction in the risk for fatal and nonfatal strokes compared to placebo (HR, 0.77; 95% CI, 0.63 to 0.95; *P*=0.0127). Atorvastatin was associated with a significant 27% reduction in the risk for total coronary events compared to placebo (HR, 0.73; 95% CI, 0.63 to 0.85; *P*≤0.0001). Atorvastatin was associated with a significant 19% reduction in the risk for total cardiovascular events and procedures compared to placebo (HR, 0.81; 95% CI, 0.73 to 0.89; *P*≤0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Downs et al[116] AFCAPS/TexCAPS Lovastatin 20 to 40 mg QD vs placebo	DB, MC, PC, RCT Men 45 to 73 years of age and postmenopausal women 55 to 73 years of age on a low-saturated fat, low-cholesterol diet with TC 180 to 264 mg/dL, LDL-C 130 to 190 mg/dL, HDL ≤45 mg/dL for men or ≤47 mg/dL for women and TG ≤400 mg/dL, without a prior history of MI, angina, claudication, cerebrovascular accident or TIA; patients with LDL-C 125 to 129 mg/dL were included when TC:HDL-C >6	N=6,605 5.2 years	Primary First acute major coronary event (fatal or nonfatal MI, unstable angina or sudden cardiac death) Secondary Fatal or nonfatal coronary revascularization procedure, unstable angina, fatal or nonfatal MI, fatal or nonfatal cardiovascular events, fatal or nonfatal coronary events, cardiovascular mortality and CHD mortality, total mortality, fatal and nonfatal cancer, safety, discontinuation rates	Primary After an average follow up of 5.2 years, lovastatin was associated with a significant 37% lower incidence of the first acute major coronary event compared to placebo (95% CI, 0.50 to 0.79; *P*<0.001). Secondary Lovastatin was associated with a significant 33% reduction in revascularization (95% CI, 0.52 to 0.85; *P*=0.001), 32% reduction in unstable angina (95% CI, 0.49 to 0.95; *P*=0.02), 40% reduction in the incidence of fatal or nonfatal MI (95% CI, 0.43 to 0.83; *P*=0.002), 25% reduction in fatal or nonfatal cardiovascular events (95% CI, 0.62 to 0.91; *P*=0.003) and 25% reduction in fatal or nonfatal coronary events (95% CI, 0.61 to 0.92; *P*=0.006) compared to placebo. There were too few events to perform survival analysis on cardiovascular (1.0 vs 1.4%) and CHD mortality (0.6 vs 0.8%) events based on prespecified criteria. The overall mortality rate and fatal and nonfatal cancer rates were similar between the two treatments (*P* value not reported). Discontinuation rates due to adverse events were 13.6 and 13.8% with lovastatin and placebo (*P* value not reported). Both treatments had similar rates of serious adverse events (34.2 vs 34.1%; *P* value not reported).
No authors listed[117] ALLHAT-LLT Pravastatin 40 mg/day vs	MC, OL, RCT Patients ≥55 years of age, with Stage 1 or 2 hypertension, ≥1 additional CHD risk factor, fasting LDL-C	N=10,355 Mean, 4.8 years (maximum 7.8 years)	Primary: All-cause mortality Secondary: Composite of fatal CHD or nonfatal MI, cause-specific	Primary: All-cause mortality did not differ significantly between the two treatments (RR, 0.99; 95% CI, 0.89 to 1.11; *P*=0.88). Secondary: Rates of CHD (fatal CHD plus nonfatal MI) and stroke were slightly lower with pravastatin compared to usual care (RR, 0.91; 95% CI, 0.79 to 1.04;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
usual care Vigorous cholesterol-lowering therapy in the usual care group was discouraged.	120 to 189 mg/dL for patients with no known CHD or 100 to 129 mg/dL for patients with known CHD and fasting TG <350 mg/dL		mortality, total and site-specific cancers	*P*=0.16). There were 209 total strokes with pravastatin and 231 total strokes with usual care (RR, 0.91; 95% CI, 0.75 to 1.09; *P*=0.31). Heart failure rates were similar between the two treatments (RR, 0.99; 95% CI, 0.83 to 1.18; *P*=0.89). The six year cancer rates were similar between the two treatments (RR, 1.03; 95% CI, 0.89 to 1.19; *P*=0.66).
Nakamura et al[118] MEGA Pravastatin 10 to 20 mg/day plus NCEP step I diet vs NCEP step I diet	OL, PRO, RCT Patients 40 to 70 years of age weighing ≥40 kg, with hypercholesterolemia, without a history of CHD or FH	N=8,214 Mean 5.2 years	Primary: CHD incidence, sudden cardiac deaths, MIs, coronary revascularization Secondary: CHD and cerebral infarction, all cardiovascular events, strokes, all-cause mortality	Primary: Pravastatin plus diet was associated with a significant reduction in the incidence of CHD compared to diet (3.3 vs 5.0%; HR, 0.67; 95% CI, 0.49 to 0.91; *P*=0.01). There was no significant difference between the two treatments in the incidence of sudden cardiac deaths or anginal episodes (*P*>0.05 for both). Secondary: Pravastatin plus diet was associated with a significant reduction in the incidence of MIs compared to diet (0.9 vs 1.6%; HR, 0.52; 95% CI, 0.29 to 0.94; *P*=0.03). Pravastatin plus diet was associated with a significant reduction in the incidence of coronary revascularizations compared to diet (2.0 vs 3.2%; HR, 0.60; 95% CI, 0.41 to 0.89; *P*=0.01). Secondary: Pravastatin plus diet was associated with a significant reduction in the incidence of CHD and cerebral infarctions compared to diet (5.0 vs 7.1%; HR, 0.70; 95% CI, 0.54 to 0.90; *P*=0.005). Pravastatin plus diet was associated with a significant reduction in the incidence of all cardiovascular events compared to diet (6.4 vs 8.5%; HR, 0.74; 95% CI, 0.59 to 0.94; *P*=0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				There was no significant difference between the two treatments in all-cause mortality or the incidence of strokes (*P*>0.05 for both).
No authors listed[119] PMS-CRP Pravastatin 20 to 40 mg/day vs placebo	DB, MC, PC, RCT Adult patients with hypercholesterolemia	N=1,062 26 weeks	Primary: Lipid levels at 13 and 26 weeks, occurrence of cardiovascular events Secondary: Not reported	Primary: After 13 weeks, pravastatin was associated with significant reductions in LDL-C (26%), TC (19%) and TG (12%) and significant elevations in HDL-C (7%) compared to placebo (*P*<0.001 for all). Throughout the 26 weeks, there were no differences in the total incidence of clinical adverse events between the two treatments. No MIs or cerebral infarctions occurred with pravastatin, and a total of six MIs and three cerebral infarctions occurred with placebo (*P* value not reported). Secondary: Not reported
Shepherd et al[120] WOSCOPS Pravastatin 40 mg/day vs placebo	DB, PC Men 45 to 64 years of age with hypercholesterolemia and no history of MI	N=6,595 4.9 years	Primary: Incidence of nonfatal MI or death from CHD as a first event Secondary: Incidence of death from CHD and nonfatal MI	Primary: Pravastatin was associated with a significant 31% reduction in the risk of the combined primary endpoint of definite nonfatal MI and death from CHD (95% CI, 17 to 43; *P*<0.001) compared to placebo. The absolute difference in the risk at five-years was 2.4%. Secondary: The reduction in the risk of nonfatal MI with pravastatin was significant whether the definite cases of MI were considered alone or in combination with suspected cases (*P*≤0.001). In the analysis of both definite and suspected cases of death from CHD, there was a significant risk reduction of 33% with pravastatin (95% CI, 1 to 55; *P*=0.042), but not in the analysis of definite cases alone (*P* value not reported). When the effect of pravastatin on death from all cardiovascular causes was analyzed, a 32% risk reduction was observed (95% CI, 3 to 53; *P*=0.033).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Additionally, pravastatin was associated with a significant 31% reduction in the frequency of coronary angiography (95% CI, 10 to 47; *P*=0.007) and a 37% reduction in the frequency of revascularization procedures (95% CI, 11 to 56; *P*=0.009) compared to placebo.
Ford et al[121] Pravastatin 40 mg/day vs placebo	ES of WOSCOPS[38] Men 45 to 64 years of age with hypercholesterolemia and no history of MI	N=6,595 15 years of total follow-up	Primary: Mortality from CHD or nonfatal MI, CHD, cardiovascular causes, all-cause mortality Secondary: Not reported	Primary: Pravastatin was associated with a significant reduction in the risk of death from CHD or nonfatal MI compared to placebo over a 15 year period (11.8 vs 15.5%; HR, 0.73; 95% CI, 0.63 to 0.83; *P*<0.001). Pravastatin was associated with a significant reduction in the risk of death from all causes compared to placebo over a 15 year period (18.7 vs 20.5%; HR, 0.88; 95% CI, 0.79 to 0.99; *P*=0.03). Pravastatin was associated with a significant reduction in the risk of death from cardiovascular causes compared to placebo over a 15 year period (7.6 vs 9.0%; HR, 0.81; 95% CI, 0.68 to 0.96; *P*=0.01). Pravastatin was associated with a significant reduction in the risk of death from CHD compared to placebo over a 15 year period (5.1 vs 6.3%; HR, 0.78; 95% CI, 0.64 to 0.96; *P*=0.02). Pravastatin was associated with a small increase in the risk of death from stroke compared to placebo over a 15 year period (1.6 vs 1.1%; HR, 1.37; 95% CI, 0.90 to 2.09; *P*=0.14). Secondary: Not reported
Ridker et al[122] JUPITER Rosuvastatin 20 mg/day vs	DB, MC, PC, RCT Men ≥50 years of age and women ≥60 years of age with no known history of cardiovascular disease, LDL-C <130	N=17,802 1.9 years	Primary: Incidence of a first major cardiovascular event (nonfatal MI, nonfatal stroke, hospitalization for unstable angina,	Primary: At the time of trial termination (median follow up, 1.9 years; maximal follow up, 5.0 years), 142 first major cardiovascular events had occurred with rosuvastatin compared to 251 first major cardiovascular events with placebo. The rates of the primary endpoint were 0.77 and 1.36 per 100 persons-years of follow up with rosuvastatin and placebo, respectively (HR for rosuvastatin, 0.56; 95% CI, 0.46 to 0.69; *P*<0.00001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
placebo	mg/dL, hsCRP ≥2 mg/L and TG <500 mg/dL		arterial revascularization procedure or confirmed death from cardiovascular causes) Secondary: Individual components of the primary endpoint, all-cause mortality	The number of patients who would need to be treated with rosuvastatin for two years to prevent the incidence of one primary endpoint is 95, and the NNT for four years is 31. Secondary: Rosuvastatin was associated with significant reductions in rates of the individual components of the primary endpoint. The corresponding rates per 100 persons-years of follow up for the individual endpoints with rosuvastatin and placebo were: 0.17 and 0.37 for fatal or nonfatal MI (HR, 0.46; 95% CI, 0.30 to 0.70; *P*=0.0002); 0.18 and 0.34 for fatal or nonfatal stroke (HR, 0.52; 95% CI, 0.34 to 0.79; *P*=0.002); 0.41 and 0.77 for revascularization or unstable angina (HR, 0.53; 95% CI, 0.40 to 0.70; *P*<0.00001) 0.45 and 0.85 for the combined endpoint of MI, stroke or death from cardiovascular causes (HR, 0.53; 95% CI, 0.40 to 0.69; *P*<0.00001) and 1.00 and 1.25 for death from any cause (HR, 0.80; 95% CI, 0.67 to 0.97; *P*=0.02). In analyses limited to deaths for which the date of death was known with certainty, there was a similar reduction in the HR associated with rosuvastatin (0.81; 95% CI, 0.67 to 0.98; *P*=0.03). For patients with elevated hsCRP levels but no other major risk factor other than increased age, the benefit of rosuvastatin was similar to that for higher risk patients (HR, 0.63; 95% CI, 0.44 to 0.92; *P*=0.01).
Everett et al[123] Rosuvastatin 20 mg/day vs placebo	Post hoc analysis of JUPITER[97] Men ≥50 years of age and women ≥60 years of age with no known history of cardiovascular disease, LDL-C <130 mg/dL, hsCRP ≥2 mg/L and TG <500 mg/dL	N=17,802 1.9 years (maximum, 5.0 years)	Primary: Incidence of stroke Secondary: Not reported	Primary: At the time of trial termination, 33 and 64 strokes occurred in patients receiving rosuvastatin and placebo. Rosuvastatin resulted in a 48% reduction in the HR of fatal and nonfatal stroke compared to placebo (incidence rate, 0.18 vs 0.34 per 100 person-years; HR, 0.52; 95% CI, 0.34 to 0.79; *P*=0.002), a finding that was consistent across all examined subgroups. This finding was due to a 51% reduction in the rate of ischemic stroke (HR, 0.49; 95% CI, 0.30 to 0.81; *P*=0.004), with no difference in the rates of hemorrhagic stroke (HR, 0.67; 95% CI, 0.24 to 1.88; *P*=0.44). TIAs were observed with similar frequency in the two treatments (HR, 0.93; 95% CI, 0.56 to 1.56; *P*=0.79). The projected NNT for five-years to prevent one stroke was 123.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Secondary: Not reported
Koenig et al[124] Rosuvastatin 20 mg/day vs placebo	Post hoc analysis of JUPITER[97] Men ≥50 years of age and women ≥60 years of age with no known history of cardiovascular disease, LDL-C <130 mg/dL, hsCRP ≥2 mg/L and TG <500 mg/dL; patients with high global cardiovascular risk (10 year Framingham risk score >20% and 10 year European systematic coronary risk evaluation ≥5%)	N=17,802 (9 and 52% were considered to be high risk based on 10 year Framingham risk score and 10 year European systematic coronary risk evaluation) 1.9 years (maximum, 5.0 years)	Primary: Incidence of first MI, stroke or cardiovascular death; first incidence of a first major cardiovascular event (nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial revascularization procedure or confirmed death from cardiovascular causes); all-cause mortality Secondary: Not reported	Primary: Patients with a 10 year Framingham risk score >20% the rate of the combined endpoint of MI, stroke or cardiovascular death was 9.4 and 18.2 per 1,000 person-years with rosuvastatin and placebo (HR, 0.50; 95% CI, 0.27 to 0.93; *P*=0.028). Rosuvastatin had no significant effect on the incidence of major cardiovascular events (*P*=0.155) and all-cause mortality (*P*=0.193). Among patients with a 10 year European systematic coronary risk evaluation ≥5%, the corresponding rates were 6.9 vs 12.0 using a model extrapolating risk for age ≥65 years (HR, 0.57; 95% CI, 0.43 to 0.78; *P*=0.0003) and rates were 5.9 vs 12.7 when risk for age was capped at 65 years of age (HR, 0.47; 95% CI, 0.32 to 0.68; *P*<0.0001). Rosuvastatin significantly reduced the incidence of major coronary events (*P*=0.0003) but not all-cause mortality (*P*=0.076) in patients with a 10 year European systematic coronary risk evaluation ≥5% extrapolating risk for age ≥65 years. When the risk for age was capped at 65 years of age, rosuvastatin had significant effect on the incidence of major cardiovascular events (*P*<0.0001) and all-cause mortality (*P*=0.022). Secondary: Not reported
Ridker et al[125] Rosuvastatin 20 mg/day vs placebo	Post hoc analysis of JUPITER[97] Men ≥50 years of age and women ≥60 years of age with no known history of cardiovascular disease, LDL-C <130 mg/dL, hsCRP ≥2	N=17,802 (n=3,267 with moderate CKD) 1.9 years (maximum, 5.0 years)	Primary: Incidence of a first major cardiovascular event (nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial revascularization	Primary: Among patients with eGFR <60 mL/min, the incidence rate of the primary endpoint was significantly lower with rosuvastatin compared to placebo (incidence rate, 1.08 vs 1.95 per 100 person-years; HR, 0.55; 95% CI, 0.38 to 0.82; *P*=0.002). Irrespective of treatment, at trial end 111 and 282 patients with eGFR <60 and ≥60 mL/min suffered a primary endpoint (incidence rate, 1.51 vs 0.95 per 100 person-years; HR, 1.54; 95% CI, 1.23 to 1.92; *P*=0.0002).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	mg/L and TG <500 mg/dL; stratified by kidney function (eGFR <60 mL/min and eGFR ≥60 mL/min)		procedure or confirmed death from cardiovascular causes), all-cause mortality Secondary: Individual components of the primary endpoint, all-cause mortality	Secondary: Among patients with eGFR <60 mL/min, rosuvastatin significantly reduced the rate of MI (incidence rate, 0.21 vs 0.54 per 100 person-years; HR, 0.40; 95% CI, 0.17 to 0.90; *P*=0.02), arterial revascularization (0.51 vs 1.07; HR, 0.48; 95% CI, 0.28 to 0.83; *P*=0.006), the combined MI, stoke or confirmed cardiovascular death (0.64 vs 1.09; HR, 0.59; 95% CI, 0.36 to 0.99; *P*=0.04), venous thromboembolism (0.16 vs 0.46; HR, 0.14 to 0.88; *P*=0.02), all-cause mortality (0.85 vs 1.53; HR, 0.56; 95% CI, 0.37 to 0.85; *P*=0.005), combined primary endpoint plus any death (1.72 vs 3.13; HR, 0.55; 95% CI, 0.41 to 0.75; *P*=0.0001) and the primary endpoint plus VTE plus any death (1.86 vs 3.51; HR, 0.53; 95% CI, 0.40 to 0.71; *P*<0.0001) compared to placebo. Among patients with eGFR <60 mL/min, rosuvastatin demonstrated no benefit compared to placebo in reducing the risk of stroke (incidence rate, 0.27 vs 0.38 per 100 person-years; HR, 0.71; 95% CI, 0.31 to 1.59; *P*=0.40).
Ridker et al[126] Rosuvastatin 20 mg/day vs placebo	Post hoc analysis of JUPITER[97] Men ≥50 years of age and women ≥60 years of age with no known history of cardiovascular disease, LDL-C <130 mg/dL, hsCRP ≥2 mg/L and TG <500 mg/dL	N=17,802 1.9 years (maximum, 5 years)	Primary: Incidence of a first major cardiovascular event Secondary: Not reported	Primary: For the endpoint of MI, stroke, revascularization or death, the five-year NNT was 20 (95% CI, 14 to 34). All subgroups had five-year NNTs for this combined endpoint below 50 (men, 17; women, 31; whites, 21; nonwhites, 19; BMI ≤25 kg/m^2, 18; BMI >25 kg/m^2, 21; with or without a family history of coronary disease, 9 and 6; with or without metabolic syndrome, 19 and 22; estimated 10 years Framingham risk >10% and <10%, 14 and 37). For the combined primary endpoint plus VTE, the five-year NNT was 18 (95%; 13 to 29). For the endpoint of MI, stroke or death, the five-year NNT was 29 (95% CI, 19 to 56). In sensitivity analyses addressing the theoretical utility of alternative agents, five-year NNT values of 38 and 57 were estimated for statin regimens that deliver 75 and 50% of the relative benefit observed in JUPITER, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Secondary: Not reported
Taylor et al[127] Statins vs placebo or usual care	SR (14 RCTs) Patients ≥18 years of age with no restrictions on TC, LDL-C or HDL-C levels, population had ≤10% of patients with a previous history of cardiovascular disease	N=34,272 ≥12 months	Primary: All-cause mortality; fatal and nonfatal CHD; cardiovascular disease and stroke events; combined endpoint of fatal and non fatal CHD, cardiovascular disease and stroke Secondary: Change from baseline in TC, revascularization, adverse events, quality of life	Primary: None of the individual trials (eight) showed strong evidence of a reduction in all-cause mortality, but pooled analysis demonstrated that statins were associated with a significant 16% decrease in all-cause mortality (RR, 0.84; 95% CI, 0.79 to 0.96). Four trials demonstrated a significant reduction in the combined endpoint of fatal and nonfatal CHD in favor of statins (RR, 0.72; 95% CI, 0.65 to 0.79). Six trials demonstrated a significant reduction in combined endpoint of fatal and nonfatal cardiovascular disease in favor of statins (RR, 0.74; 95% CI, 0.66 to 0.85). Seven trials demonstrated a significant reduction in stroke events in favor of statins (RR, 0.78; 95% CI, 0.65 to 0.94). Three trials demonstrated a significant reduction in the combined endpoint of fatal and nonfatal CHD, cardiovascular disease and stroke in favor or statins (RR, 0.70; 95% CI, 0.61 to 0.79). Secondary: Five trials demonstrated a significant reduction in revascularization in favor of statins (RR, 0.66; 95% CI, 0.53 to 0.83). Nine and 11 trials reported on TC and LDL-C, demonstrating significant reductions in both with a statin (0.89 mmol/L [95% CI, -1.20 to -0.57] and 0.92 [95% CI, -1.10 to -0.74]). In terms of adverse events, incidence rates indicated no difference between statins and control groups (RR, 0.99; 95% CI, 0.94 to 1.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				There was no reliable data on patient quality of life.
Mora et al[128] Statin therapy vs placebo	MA (5 primary prevention statin RCTs) Women receiving statin therapy	N=not reported Duration not reported	Primary: Cardiovascular disease, all-cause mortality Secondary: Not reported	Primary: Compared to placebo, statin therapy in women significantly reduced cardiovascular disease by about one third in exclusively primary prevention trials. The summary RR for the three trials was 0.63 (95% CI, 0.49 to 0.82; *P*<0.001). When trials that included predominately primary prevention were analyzed together with the exclusively primary prevention trials, the summary RR was similar but no significant (0.79; 95% CI, 0.59 to 1.05; *P*=0.11). When two additional trials were included that did not report sex specific outcomes for women, the summary RR was unchanged (0.82; 95% CI, 0.69 to 0.98; *P*=0.03). The summary RR for the three exclusively primary prevention trials (n=13,154 women; 216 deaths) that reported sex specific total mortality was 0.78 (95% CI, 0.53 to 1.15; *P*=0.21). When all trials that reported sex specific mortality outcomes in predominantly or exclusively primary prevention in women were included, the summary RR was similar. Secondary: Not reported
Baigent et al[129] Statins (pravastatin 40 mg/day, fluvastatin 40 to 80 mg/day, simvastatin 20 to 40 mg/day, atorvastatin 10 mg/day, lovastatin 20 to 80 mg/day) vs placebo	MA (14 RCTs) Demographics not reported	N=90,056 ≥2 years	Primary: All-cause mortality, CHD mortality, non-CHD mortality Secondary: Effect on CHD death and on major coronary events (nonfatal MI or CHD death) in prespecified subgroups; effect on stroke, cancer, and vascular	Primary: Statin therapy was associated with a significant 12% reduction in all-cause mortality per 1 mmol/L reduction in LDL-C compared to placebo (RR, 0.88; 95% CI, 0.84 to 0.91; *P*<0.0001). Statin therapy was associated with a significant 19% reduction in CHD mortality compared to placebo (3.4 vs 4.4%; RR, 0.81; 95% CI, 0.76 to 0.85; *P*<0.0001). Statin therapy was associated with a nonsignificant 17% reduction in non-CHD mortality compared to placebo (1.2 vs 1.3%; RR, 0.93; 95% CI, 0.83 to 1.03; *P* value not reported). Secondary: Statin therapy was associated with a significant 17% reduction in vascular

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			procedures, vascular events	mortality compared to placebo (4.7 vs 5.7%; RR, 0.83; 95% CI, 0.79 to 0.87; *P*<0.0001). Statin therapy was associated with a significant 21% reduction in major vascular events compared to placebo (RR, 0.79; 95% CI, 0.77 to 0.81; *P*<0.0001). Statin therapy was associated with a significant 26% reduction in nonfatal MI compared to placebo (RR, 0.74; 99% CI, 0.70 to 0.79; *P*<0.0001). Statin therapy was associated with a significant 23% reduction in any major coronary event compared to placebo (RR, 0.77; 95% CI, 0.74 to 0.80; *P*<0.0001). Statin therapy was associated with a significant 24% reduction in any coronary revascularization compared to placebo (RR, 0.76; 95% CI, 0.73 to 0.80; *P*<0.0001). Statin therapy was associated with a significant 21% reduction in any stroke compared to placebo (RR, 0.79; 95% CI, 0.77 to 0.81; *P*<0.0001). Statin therapy was associated with a nonsignificant increase in the incidence of rhabdomyolysis compared to placebo (*P*=0.4).
No authors listed[130] CTT Collaborators Statins (pravastatin 40 mg/day, fluvastatin 40 to 80 mg/day, simvastatin 20 to 40 mg/day, atorvastatin 10 mg/day, lovastatin 20 to 80 mg/day)	MA, subanalysis (14 trials) Demographics not reported	N=90,056 ≥2 years	Primary: All-cause mortality, CHD mortality, non-CHD mortality among diabetes and non-diabetes patients Secondary: Effect on CHD death and on major coronary events	Primary: Among patients with diabetes, statins were associated with a significant nine percent reduction in all-cause mortality per each additional mmol/L reduction in LDL-C compared to placebo (RR, 0.91; 99% CI, 0.82 to 1.01; *P*=0.02). Among patients without diabetes, statins were associated with a significant 13% reduction in all-cause mortality per each additional mmol/L reduction in LDL-C compared to placebo (RR, 0.87; 99% CI, 0.82 to 0.92; *P*<0.0001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs placebo			(nonfatal MI or CHD death), major vascular events among diabetic and non-diabetic patients	Among patients with diabetes, statins were associated with a significant 13% reduction in vascular mortality per each additional mmol/L reduction in LDL-C compared to placebo (RR, 0.87; 99% CI, 0.76 to 1.00; *P*=0.008) and no effect on nonvascular mortality (RR, 0.97; 99% CI, 0.82 to 1.16; *P*=0.7). Among patients with diabetes, statins were associated with a significant 21% reduction in major vascular events per each additional mmol/L reduction in LDL-C compared to placebo (RR, 0.79; 99% CI, 0.72 to 0.86; *P*<0.0001). Among patients without diabetes, statins were associated with a significant 21% reduction in major vascular events per each additional mmol/L reduction in LDL-C compared to placebo (RR, 0.79; 99% CI, 0.76 to 0.82; *P*<0.0001). Among patients with diabetes, statins were associated with a significant 22% reduction in MI or coronary death (RR, 0.78; 99%CI, 0.69 to 0.87; *P*<0.0001), 25% reduction in coronary revascularization (RR, 0.75; 99% CI, 0.64 to 0.88; *P*<0.0001) and 21% reduction in stroke (RR, 0.79; 99% CI, 0.67 to 0.93; *P*=0.0002) compared to placebo. After five-years of treating 1,000 diabetic patients with statin therapy, 42 patients may be prevented from having a major vascular event (95% CI, 30 to 55; *P* value not reported). The benefit was greater among patients with diabetes and known vascular disease at baseline.
O'Regan et al[131] Statins (atorvastatin 10 to 80 mg/day, simvastatin 20 to 40 mg/day, fluvastatin 40 to 80 mg/day, pravastatin 10 to 40 mg/day, lovastatin 20	MA (41 primary prevention trials, 1 secondary prevention trial) Demographics not reported	N=121,285 Up to 6 years	Primary: All-cause mortality, all-stroke incidence Secondary: Incidence of cardiovascular deaths, nonhemorrhagic	Primary: Compared to placebo, statin therapy was associated with a significant reduction in the risk of all-cause mortality (RR, 0.88; 95% CI, 0.83 to 0.93). Compared to placebo, statin therapy was associated with a significant reduction in the risk of strokes (RR, 0.84; 95% CI, 0.79 to 0.91). Secondary: Compared to placebo, statin therapy was associated with a significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
to 73 mg/day) vs placebo			cerebrovascular events, hemorrhagic strokes, fatal strokes	reduction in the risk of cardiovascular death (RR, 0.81; 95% CI, 0.74 to 0.90). Compared to placebo, statin therapy was associated with a significant reduction in the risk of nonhemorrhagic cerebrovascular events (RR, 0.81; 95% CI, 0.69 to 0.94). Compared to placebo, statin therapy was associated with a nonsignificant reduction in the risk hemorrhagic strokes (RR, 0.94; 95% CI, 0.68 to 1.30). Compared to placebo, statin therapy was associated with a nonsignificant reduction in the risk of fatal strokes (RR, 0.99; 95% CI, 0.80 to 1.21). A meta-regression analysis determined that every unit increase in LDL-C was associated with a 0.3% increased risk of mortality (RR, 1.003; 95% CI, 1.0005 to 1.006; *P*=0.02).
Secondary Prevention of Coronary Heart Disease (Single-Entity Agents)				
Bushnell et al[132] Statin therapy vs no statin therapy	MA Patients with CHD or vascular disease	N=22,943 90 days	Primary: Incidence of stroke at 90 days, stroke severity, mortality from strokes, differences between sexes Secondary: Not reported	Primary: Patients reporting statin therapy had lower rates of stroke at 90 days of follow up (HR, 0.72; 95% CI, 0.53 to 0.97; *P* value not reported). Statin therapy was not associated with a significant reduction in stroke mortality (*P*=0.8). Women had an increased risk of experiencing a severe stroke compared to men (*P*=0.035). Statin therapy was not associated with a significant reduction in stroke severity among women (*P*=0.096). Secondary: Not reported
LaRosa et al[133] TNT	DB, MC, PG, RCT Patients 35 to 75	N=10,001 5 years	Primary: First major cardiovascular	Primary: Compared to 10 mg, 80 mg was associated with a significant 22% reduction in the incidence of the primary endpoint (10.9 vs 8.7%; HR, 0.78;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease)		event (death from CHD, nonfatal MI, resuscitation after cardiac arrest or fatal or nonfatal stroke) Secondary: Individual components of a major coronary event, cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary event, side effects	95% CI, 0.69 to 0.89; *P*=0.0002). Secondary: Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of strokes (3.1 vs 2.3%; HR, 0.75; 95% CI, 0.59 to 0.96; *P*=0.021). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of cerebrovascular events (5.0 vs 3.9%; HR, 0.77; 95% CI, 0.64 to 0.93; *P*=0.007). Each 1 mg/dL reduction in LDL-C was associated with a 0.6% RRR in cerebrovascular events (*P*=0.002) and a 0.5% RRR in stroke (*P*=0.041). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of nonfatal MIs (6.2 vs 4.9%; HR, 0.78; 95% CI, 0.66 to 0.93; *P*=0.004). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of major coronary events (8.3 vs 6.7%; HR, 0.80; 95% CI, 0.69 to 0.92; *P*=0.0019). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any coronary events (26.5 vs 21.6%; HR, 0.79; 95% CI, 0.73 to 0.86; *P*<0.0001). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any cardiovascular events (33.5 vs 28.1%; HR, 0.81; 95% CI, 0.75 to 0.87; *P*<0.0001). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of hospitalization for heart failure (33.5 vs 28.1%; HR, 0.81; 95% CI, 0.75 to 0.87; *P*<0.0001). There was no significant difference between the two treatments in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				incidence of death from CHD (3.3 vs 2.4%; HR, 0.74; 95% CI, 0.59 to 0.94; *P*=0.01). There was no significant difference between the two treatments in the incidence of resuscitation after cardiac arrest (0.5%; HR, 0.96; 95% CI, 0.56 to 1.67; *P*=0.89). There was no significant difference between the two treatments in the incidence of peripheral artery disease (5.6 vs 5.5%; HR, 0.97; 95% CI, 0.83 to1.15; *P*=0.76). There was no significant difference between the two treatments in the incidence of death from any cause (5.6 vs 5.7%; HR, 1.01; 95% CI, 0.85 to 1.19; *P*=0.92). Compared to 10 mg, 80 mg was associated with a significantly higher incidence of treatment-related adverse events (5.8 vs 8.1%; *P*<0.001). Compared to 10 mg, 80 mg was associated with a significantly higher incidence of ALT and AST elevations greater than three times the ULN (0.2 vs 1.2%; *P*<0.001).
Shah et al[134] Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Subanalysis of TNT[108] Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) with a previous CABG	N=4,654 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest or fatal or nonfatal stroke) Secondary: Safety	Primary: A first major cardiovascular event occurred in 11.4% (n=529) of patients with prior CABG and 8.5% (n=453) of those without prior CABG (HR, 1.38; 95% CI, 1.22 to 1.56; *P*<0.0001). Among post-CABG patients, a primary endpoint event occurred in 9.7 (n=224) vs 13.0% (n=305) of patients receiving 80 and 10 mg/day, resulting in a 27% RRR and a 3.3% ARR (HR, 0.73; 95% CI, 0.62 to 0.87; *P*=0.0004). During follow up, 11.3 (n=262) vs 15.9% (n=371) of patients receiving 80 and 10 mg/day underwent repeat coronary revascularization, either with CABG or percutaneous coronary intervention, resulting in a 30% RRR and a 4.6% ARR (HR, 0.70; 95% CI, 0.60 to 0.82; *P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				The combined endpoint of a major cardiovascular event or coronary revascularization occurred in 18.0 (n=417) vs 24.2% (n=566) in patients receiving 80 and 10 mg/day, resulting in a 28% RRR and a 6.2% ARR (HR, 0.72; 95% CI, 0.64 to 0.82; *P*<0.0001). Secondary: In the CABG cohort, discontinuations from therapy due to treatment-related adverse events during the five-years of follow up occurred in 3.8 (n=87) vs 2.7% (n=62) of patients receiving 80 and 10 mg/day (*P*=0.004). Treatment-related myalgias were reported in 1.3% of patients receiving both treatments, and no post-CABG patient experienced an elevation of CK >10 times the ULN on two consecutive measurements. Elevated AST and ALT greater than three times the ULN on consecutive measurements occurred in 1.1 and 0.3% of patients receiving 80 and 10 mg/day (*P*=0.0003).
Waters et al[135] Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Subanalysis of TNT[108] Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease)	N=10,001 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest or fatal or nonfatal stroke) Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, peripheral artery	Primary: Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of the primary endpoint (10.9 vs 8.7%; HR, 0.78; 95% CI, 0.69 to 0.89; *P*=0.0002). Secondary: Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of strokes (3.1 vs 2.3%; HR, 0.75; 95% CI, 0.59 to 0.86; *P*=0.021). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of cerebrovascular events (5.0 vs 3.9%; HR, 0.77; 95% CI, 0.64 to 0.93; *P*=0.007). Each 1 mg/dL reduction in LDL-C was associated with a 0.6% RRR in cerebrovascular events (*P*=0.002) and a 0.5% RRR in stroke (*P*=0.041). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of nonfatal MIs (6.2 vs 4.9%; HR, 0.78; 95% CI, 0.66 to 0.93;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			disease, all-cause mortality, any cardiovascular event, any coronary event	*P*=0.004). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of major coronary events (8.3 vs 6.7%; HR, 0.80; 95% CI, 0.69 to 0.92; *P*=0.0019). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any coronary events (26.5 vs 21.6%; HR, 0.79; 95% CI, 0.73 to 0.86; *P*<0.0001). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any cardiovascular events (33.5 vs 28.1%; HR, 0.81; 95% CI, 0.75 to 0.87; *P*<0.0001). There was no significant difference between the two treatments in the incidence of TIAs (*P*=0.099). There was no significant difference between the two treatments in the incidence of death from CHD (*P*=0.087). Compared to 10 mg, 80 mg was associated with a significantly higher incidence of treatment-related adverse events (5.8 vs 8.1%; *P*<0.001). Compared to 10 mg, 80 mg was associated with a significantly higher incidence of ALT and AST elevations at least three times the ULN (0.2 vs 1.2%; *P*<0.001).
Deedwania et al[136] Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Post hoc analysis of TNT[108] Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization, angina with objective	N=5,584 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest or fatal or nonfatal stroke) among	Primary: Compared to 10 mg, 80 mg was associated with a significant 29% reduction in the incidence of the primary endpoint among patient with metabolic syndrome (13.0 vs 9.5%; HR, 0.71; 95% CI, 0.61 to 0.84; *P*<0.0001). Secondary: Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of cerebrovascular events among patients with metabolic

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	evidence of coronary disease), stratified by metabolic syndrome		patients with metabolic syndrome Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, any coronary event among patients with metabolic syndrome	syndrome (HR, 0.74; 95% CI, 0.59 to 0.93; *P*=0.011). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of major coronary events among patients with metabolic syndrome (HR, 0.72; 95% CI, 0.60 to 0.86; *P*=0.0004). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any coronary events among patients with metabolic syndrome (HR, 0.75; 95% CI, 0.67 to 0.83; *P*<0.0001). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any cardiovascular events among patients with metabolic syndrome (HR, 0.78; 95% CI, 0.71 to 0.85; *P*<0.0001). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of hospitalization for CHF among patients with metabolic syndrome (HR, 0.73; 95% CI, 0.55 to 0.96; *P*=0.027). There was no significant difference between the two treatments in the incidence of all-cause mortality among patients with metabolic syndrome (*P* value not reported).
Shepherd et al[137] Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Post hoc analysis of TNT[108] Patients 35 to 75 years of age with type 2 diabetes and CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease)	N=1,501 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest or fatal or nonfatal stroke) among patients with type 2 diabetes Secondary: Any occurrence of	Primary: Compared to 10 mg, 80 mg was associated with a significant 25% reduction in the incidence of the primary endpoint among patients with diabetes (17.9 vs 13.8%; HR, 0.75; 95% CI, 0.58 to 0.97; *P*=0.026). Secondary: Significant differences between the treatments in favor of 80 mg/day were observed for the secondary outcomes of time to cerebrovascular event (HR, 0.69; 95% CI, 0.48 to 0.98; *P*=0.037) and time to cardiovascular event (HR, 0.85; 95% CI, 0.73 to 1.00; *P*=0.044) There was no significant difference between the two treatments in the incidence of cerebrovascular events among patients with diabetes (*P*=0.437).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			a major coronary event, cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, any coronary event among patients with type 2 diabetes	Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of nonfatal MI among patients with diabetes (HR, 0.79; 95% CI, 0.55 to 1.14; *P*=0.202). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of fatal and nonfatal stroke among patients with diabetes (HR, 0.67; 95% CI, 0.43 to 1.04; *P*=0.075). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of death from CHD among patients with diabetes (HR, 0.74; 95% CI, 0.47 to 1.18; *P*=0.203). There was no significant difference between the two treatments in the incidence of major coronary events among patients with diabetes (*P*=0.922). There was no significant difference between the two treatments in the incidence of any coronary events among patients with diabetes (*P*=0.192). There was no significant difference between the two treatments in the incidence of any cardiovascular events among patients with diabetes (*P*=0.458). There was no significant difference between the two treatments in the incidence of major cardiovascular events among patients with diabetes (*P*=0.689). There was no significant difference between the two treatments in the incidence of hospitalization with heart failure among patients with diabetes (*P*=0.277). There was no significant difference between the two treatments in the incidence of all-cause mortality among patients with diabetes (*P*=0.521).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				There was no significant difference between the two treatments in the incidence of peripheral artery disease among patients with diabetes (*P*=0.789). There was no significant difference between the two treatments in the incidence of treatment-related adverse effects or persistent elevations in liver enzymes (*P* values not reported).
Wenger et al[138] Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Post hoc analysis of TNT[108] Patients ≥65 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease)	N=3,809 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest or fatal or nonfatal stroke) Secondary: Individual components of a major coronary event, cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary event, side effects	Primary: Compared to 10 mg, 80 mg was associated with a significant 19% reduction in the incidence of the primary endpoint among patients ≥65 years of age (12.6 vs 10.3%; HR, 0.81; 95% CI, 0.67 to 0.98; *P*=0.032). Consequently, in treating 35 patients with 80 mg vs 10 mg, one cardiovascular event could be prevented over a five-year period. Secondary: Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of cerebrovascular events among patients ≥65 years of age (*P*=0.010). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of nonfatal MI among patients ≥65 years of age (HR, 0.79; 95% CI, 0.60 to 1.03; *P*=0.084). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of fatal and nonfatal stroke among patients ≥65 years of age (HR, 0.79; 95% CI, 0.57 to 1.09; *P*=0.158). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of death from CHD among patients ≥65 years of age (HR, 0.91; 95% CI, 0.63 to 1.29; *P*=0.59). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of resuscitated cardiac arrests among patients ≥65 years of age (HR, 1.19; 95% CI, 0.49 to 2.87; *P*=0.70).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any cardiovascular events among patients ≥65 years of age (*P*<0.001). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any coronary events among patients ≥65 years of age (*P*<0.001). Compared to 10 mg, 80 mg was associated with a significant reduction in incidence of hospitalization for heart failure among patients ≥65 years of age (*P*=0.008). There was no significant difference between the two treatments in the incidence of major coronary events among patients ≥65 years of age (*P*=0.128). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of death from cardiovascular causes among patients ≥65 years of age (HR, 0.91; 95% CI, 0.67 to 1.24; *P*=0.55). Compared to patients receiving 10 mg, more patients receiving 80 mg died from noncardiovascular causes among patients ≥65 years of age (HR, 1.26; 95% CI, 0.93 to 1.70; *P*=0.129). More patients ≥65 years of age receiving 80 mg experienced treatment-related adverse events compared to patients ≥65 years of age receiving 10 mg (*P* value not reported).
Khush et al[139] Atorvastatin 10 mg/day vs atorvastatin 80	Post hoc analysis of TNT[108] Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization,	N=10,001 5 years	Primary: Hospitalization for heart failure among patients with and without a history of heart failure Secondary:	Primary: Prior history of heart failure is a significant risk factor for hospitalization from heart failure. While 14.1% of patients with heart failure at baseline were hospitalized for heart failure, only 1.9% of patients who did not have heart failure at baseline were hospitalized for heart failure during the trial period (*P*<0.001). Compared to 10 mg, 80 mg was associated with a significant reduction in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day	angina with objective evidence of coronary disease)		Not reported	the incidence of hospitalization from heart failure among patients with heart failure at baseline (17.3 vs 10.6%; HR, 0.59; 95% CI, 0.4 to 0.80; *P*=0.008). Mortality was significantly higher among patients with heart failure compared to patients without heart failure at baseline (15.0 vs 4.9%; *P*<0.001). Each reduction of 1 mg/dL in LDL-C was associated with a reduction in the risk of hospitalization for heart failure by 0.6% (*P*=0.007). Secondary: Not reported
LaRosa et al[140] Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Post hoc analysis of TNT[108] Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease), stratified by LDL-C level	N=9,769 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients with LDL-C <64 mg/dL (Quintile 1), 64 to ≤77 mg/dL (Quintile 2), 77 to ≤90 mg/dL (Quintile 3), 90 to ≤106 mg/dL (Quintile 4), and ≥106 mg/dL (Quintile 5) Secondary: Any occurrence of a major coronary	Primary: Patients in the lowest LDL-C Quintiles were associated with the most reduction in the primary endpoint (*P*<0.0001). Secondary: Patients in the lowest LDL-C Quintiles were associated with the most reduction in the risk of death from CHD (*P*<0.01). Patients in the lowest LDL-C Quintiles were associated with the most reduction in the risk of nonfatal MIs (*P*<0.0001). Patients in the lowest LDL-C Quintiles were associated with the most reduction in the risk of stroke (*P*<0.05). There were no differences in the incidence of all-cause mortality across LDL-C Quintiles (*P*=0.104). There were no differences in the incidence of cardiovascular mortality across quintiles (*P*=0.060). There were no differences in the incidence of all-cause mortality across LDL-C Quintiles (*P*=0.653).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			event, cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary event among patients classified as Quintile 1, 2, 3, 4 or 5 (from above)	There were no differences in the incidence of treatment-related adverse effects across LDL-C Quintiles (*P* value not reported).
Barter et al[141] Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Post hoc analysis of TNT[108] Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease), stratified by HDL-C level	N=9,770 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients with HDL-C <38 mg/dL (Quintile 1), 38 to 42 mg/dL (Quintile 2), 43 to 47 mg/dL (Quintile 3), 48 to 54 mg/dL (Quintile 4), and ≥55 mg/dL (Quintile 5)	Primary: Patients in the highest HDL-C Quintiles were associated with the greatest reduction in the primary endpoint (*P*=0.04). Compared to patients in HDL-C Quintile 1, patients classified as HDL-C Quintile 5 had a 25% reduction in risk of a major cardiovascular event (HR, 0.75; 95% CI, 0.60 to 0.95). An increase in 1 mg/dL in HDL-C reduces the risk of major cardiovascular events by 1.1% at three months (*P*=0.003). Patients with the lowest LDL-C:HDL-C were at a significantly lower risk for major cardiovascular events (*P*=0.006). Patients with the lowest TC:HDL-C were at a significantly lower risk for major cardiovascular events (*P* value not reported). Among patients whose LDL-C was <70 mg/dL, those in the highest HDL-C

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			Secondary: Not reported	Quintile were at the lowest risk for a major cardiovascular event (*P*=0.03). Secondary: Not reported
Shepherd et al[142] Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Post hoc analysis of TNT[108] Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease)	N=9,770 5 years	Primary: GFR Secondary: Not reported	Primary: Eighty mg was associated with a significant increase in GFR from baseline over the five-year trial period compared to 10 mg (*P*<0.0001). Secondary: Not reported
Pitt et al[143] AVERT Atorvastatin 80 mg/day vs percutaneous coronary transluminal angioplasty	MC, OL, RCT Adult patients with stable CAD, LDL-C ≥115 mg/dL, TG ≤500 mg/dL, stenosis ≥50% in ≥1 coronary artery and had been recommended for treatment with percutaneous revascularization, asymptomatic or with Canadian Cardiovascular Society Class I or II angina, able to complete ≥4 minutes of a treadmill test or a bicycle exercise test	N=341 18 months	Primary: Number of ischemic events and/or need for revascularization, angina symptoms, adverse events Secondary: Not reported	Primary: Atorvastatin was associated with a significantly lower incidence of ischemic events compared to revascularization procedure (21 vs 13%; *P*=0.048). Atorvastatin was associated with a significantly longer time to the first ischemic event compared to revascularization procedure (*P*=0.03). A significantly smaller proportion of patients receiving atorvastatin had an improvement in the Canadian Cardiovascular Society classification of angina symptoms compared to revascularization procedure (41 vs 54%; *P*=0.009). Adverse events were similar between the two treatments (*P* value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	without marked ECG changes indicative of ischemia			
Athyros et al[144] GREACE Atorvastatin 10 mg/day, titrated up to 80 mg/day vs usual medical care (lifestyle modification and pharmacotherapy, including lipid lowering agents)	RCT Adult patients with established CHD not at LDL-C goal (<100 mg/dL) according to the NCEP criteria	N=1,600 3 years	Primary: Death, nonfatal MI, unstable angina, CHF, revascularization (coronary morbidity), stroke Secondary: Safety	Primary: Compared to usual care, atorvastatin was associated with a significant 51% reduction in the risk for CHD recurrent events or death (24.5 vs 12.0%; *P*<0.0001). Compared to usual care, atorvastatin was associated with a significant 43% reduction in all-cause mortality (5.0 vs 2.9%; *P*=0.0021). Compared to usual care, atorvastatin was associated with a significant 47% reduction in the risk of stroke (2.1 vs 1.1%; *P*=0.034). Compared to usual care, atorvastatin was associated with a significant 47% reduction in the risk of coronary mortality (4.8 vs 2.5%; *P*=0.0017). Compared to usual care, atorvastatin was associated with a significant 54% reduction in the risk of coronary morbidity (*P*<0.0001). Atorvastatin was associated with a reduction in TC by 36%, LDL-C by 46%, TG by 31% and non-HDL-C by 44% and an increase in HDL-C by seven percent (*P* value not reported). Compared to usual care, a greater proportion of patients receiving atorvastatin achieved the NCEP LDL-C goals (3 vs 95%, respectively; *P* value not reported). Compared to usual care, a greater proportion of patients receiving atorvastatin achieved the NCEP non-HDL-C goals (14 vs 97%, respectively; *P* value not reported). Secondary: Withdrawals due to adverse effects were similar between the two treatments (0.75 vs 0.40%; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Athyros et al[145] Atorvastatin 10 mg/day, titrated up to 80 mg/day vs usual medical care (lifestyle modification and pharmacotherapy, including lipid lowering agents)	Post hoc analysis of GREACE[119] Adult patients with established CHD not at LDL-C goal (<100 mg/dL) according to the NCEP criteria, stratified by the presence of metabolic syndrome	N=1,600 3 years	Primary: Vascular events, estimated GFR, serum uric acid level Secondary: Not reported	Primary: Among patients with metabolic syndrome, atorvastatin was associated with a significant 57% reduction in the incidence of vascular events compared to usual medical care (12.1 vs 28.0%; RR, 0.43; 95% CI, 0.20 to 0.64; *P*<0.0001). Among patients without metabolic syndrome, atorvastatin was associated with a significant 41% reduction in the incidence of vascular events compared to usual medical care (RR, 0.59; 95% CI, 0.41 to 0.79; *P*<0.0001). Atorvastatin was associated with a significant increase in GFR and a reduction in serum uric acid level from baseline (*P*<0.05), regardless of metabolic syndrome status. Usual medical care was associated with a significant reduction in GFR and an increase in serum uric acid level from baseline (*P*<0.05), regardless of metabolic syndrome status. Compared to patients without metabolic syndrome, patients with metabolic syndrome experienced a greater increase in GFR with atorvastatin (*P*=0.02). Secondary: Not reported
Schwartz et al[146] MIRACL Atorvastatin 80 mg/day vs placebo Treatment was administered within 96 hours of hospital admission with an	DB, MC, RCT Patients >18 years of age with unstable angina or non-Q-wave acute MI, with chest pain or discomfort ≥15 minutes that occurred at rest or with minimal exertion within the 24 hour period preceding hospitalization and representing a change from their usual	N=3,086 16 weeks	Primary: A composite endpoint of death, nonfatal acute MI, resuscitated cardiac arrest or recurrent symptomatic myocardial ischemia with objective evidence requiring hospitalization	Primary: Compared to placebo, atorvastatin was associated with a 16% reduction in the risk of a composite endpoint of death, nonfatal acute MI, resuscitated cardiac arrest and recurrent symptomatic myocardial ischemia requiring hospitalization (17.4 vs 14.8%; *P*=0.048). Secondary: Compared to placebo, atorvastatin was associated with a significant 26% reduction in the risk of a recurrent ischemia requiring hospitalization (RR, 0.74; 95% CI, 0.57 to 0.95; *P*=0.02). Compared to placebo, atorvastatin was associated with a significant 50% reduction in the risk of a fatal and nonfatal stroke (RR, 0.50; 95% CI, 0.26 to 0.99; *P*=0.045).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
ACS.	anginal pattern		Secondary: Occurrence of the individual components of the primary endpoint, nonfatal stroke, new or worsening heart failure requiring hospitalization, worsening angina requiring hospitalization but without new objective evidence of ischemia and coronary revascularization; time to occurrence of any of the above; percent changes from baseline in lipid levels; safety	There were no significant differences between the two treatments in the incidence of coronary revascularization procedures, worsening heart failure, worsening angina, occurrence of at least one secondary endpoint or occurrence of at least one primary or secondary endpoint (*P* value not reported). Liver transaminase elevation was more common with atorvastatin (2.5 vs 0.6%; *P*<0.001).
Olsson et al[147] Atorvastatin 80 mg/day vs placebo Treatment was administered within	Post hoc analysis of MIRACL[121] Patients ≥65 years of age with unstable angina or non-Q-wave acute MI, with chest pain or discomfort ≥15 minutes duration that occurred at rest or with minimal exertion	N=3,086 16 weeks	Primary: A composite endpoint of death, nonfatal acute MI, resuscitated cardiac arrest or recurrent symptomatic myocardial ischemia with objective evidence	Primary: Compared to placebo, atorvastatin was associated with a nonsignificant 14% reduction in the RR of the primary endpoint in patients ≥65 years of age (HR, 0.86; 95% CI, 0.70 to 1.07; ARR, 2.9%; *P*=0.18). Compared to placebo, atorvastatin was associated with a nonsignificant 22% reduction in the RR of the primary endpoint in patients <65 years of age (HR, 0.78; 95% CI, 0.56 to 1.06; ARR, 2.5%; *P*=0.11). Secondary: There was no significant difference in any of the secondary endpoints

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
96 hours of hospital admission with an ACS.	within the 24 hour period preceding hospitalization and representing a change from their usual anginal pattern		requiring hospitalization among patients ≥65 and <65 years of age Secondary: Occurrence of the individual components of the primary endpoint, nonfatal stroke, new or worsening heart failure requiring hospitalization, worsening angina requiring hospitalization but without new objective evidence of ischemia, coronary revascularization, time to occurrence of any of the above; percent change from baseline in lipid levels among patients ≥65 and <65 years of age; safety	between patients ≥65 and <65 years of age (*P*>0.05). The frequency of adverse events was similar between the two treatments (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Amarenco et al[148] SPARCL Atorvastatin 80 mg/day vs placebo	DB, PC, RCT Patients ≥18 years of age who had an ischemic or hemorrhagic stroke or TIA 1 to 6 months before trial entry (patients with a prior hemorrhagic stroke could be included if they were deemed to be at risk for ischemic stroke or CHD) and LDL-C ≥100 to ≤190 mg/dL	N=4,731 4.9 years	Primary: Time to first occurrence of a nonfatal or fatal stroke Secondary: Occurrence of major cardiovascular events (stroke, cardiac death, nonfatal MI or resuscitated cardiac arrest)	Primary: Patients with a reduction in LDL-C >16% had a significant reduction in stroke compared to those with a reduction <16% (11.0 vs 13.4%; HR, 0.792; 95% CI, 0.671 to 0.935; *P*=0.0058). Secondary: Patients with a reduction in LDL-C >16% had a significant reduction in major cardiovascular events compared to those with a reduction <16% (13.9 vs 17.3; HR, 0.761; 95% CI, 0.657 to 0.881; *P*=0.0003).
Amerenco et al[149] Atorvastatin 80 mg/day vs placebo	Subanalysis of SPARCL[123] to evaluate stroke subtypes Patients ≥18 years of age who had an ischemic or hemorrhagic stroke or TIA 1 to 6 months before trial entry (patients with a prior hemorrhagic stroke could be included if they were deemed to be at risk for ischemic stroke or CHD) and LDL-C ≥100 to ≤190 mg/dL	N=4,731 4.9 years	Primary: Time to first occurrence of a nonfatal or fatal stroke Secondary: Occurrence of major cardiovascular events (stroke, cardiac death, nonfatal MI or resuscitated cardiac arrest), all-cause mortality	Primary: Atorvastatin was similarly effective in reducing the primary endpoint for all entry event stroke subtypes (large vessel, TIA, small vessel and unknown). Although there was no overall heterogeneity between subtypes, the patients with baseline hemorrhagic stroke receiving atorvastatin were qualitatively different and were more than three times more likely to have a recurrent stroke compared to placebo. Secondary: Atorvastatin was similarly effective in reducing the occurrence of major cardiovascular events for all entry event stroke subtypes (large vessel, TIA, small vessel and unknown). Mortality rates were similar across all entry event stroke subtypes. The analyses were also carried out with adjustment for BP, diabetes and ambulatory score at baseline and the results did not differ.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Serruys et al[150] LIPS Fluvastatin 40 mg BID vs placebo	DB, MC, PC, RCT Patients 18 to 80 years of age with angina or silent ischemia following successful completion of their first PCI, with baseline TC 135 to 270 mg/dL and fasting TG <400 mg/dL	N=1,677 3 to 4 years	Primary: Incidence of major adverse cardiac events (cardiac death, nonfatal MI or a reintervention procedure of CABG or repeat PCI) Secondary: Major adverse cardiac events excluding reintervention procedures (surgical or PCI) occurring in the first six months of follow up for lesions treated at the index procedure, cardiac mortality, combined cardiac mortality and MI, combined all-cause mortality and MI, treatment effects on measured lipid levels, discontinuation rates, tolerability, safety	Primary: Major adverse cardiac event-free survival time was significantly longer with fluvastatin compared to placebo (*P*=0.01). Major adverse cardiac events occurred significantly less frequently with fluvastatin compared to placebo (21.4 vs 26.7%; RR, 0.78; 95% CI, 0.64 to 0.95; *P*=0.01). During the follow up period, 13 patients (1.5%) receiving fluvastatin compared to 24 patients (2.9%) receiving placebo died from cardiac causes, 30 patients (3.6%) compared to 38 patients (4.6%) had a nonfatal MI and 167patients (19.8%) compared to193 patients (23.2%) underwent CABG or PCI (*P* values not reported). Secondary: The risk of major adverse cardiac events, excluding reintervention procedures (surgical or PCI), occurring in the first six months of follow up for lesions treated at the index procedure was 33% lower (RR, 0.67; 95% CI, 0.54 to 0.8; *P*<0.001) with fluvastatin. There was no difference in the reduction of cardiac mortality, combined cardiac mortality and MI and combined all-cause mortality and MI between the two treatments (*P*=0.07, *P*=0.07 and *P*=0.08, respectively). After six weeks, fluvastatin significantly reduced LDL-C by 27% (95% CI, 25 to 29% compared to an 11% reduction with placebo (95% CI, 9 to 13; *P*<0.001). TG reductions were greater with fluvastatin compared to placebo (22 vs 14%; *P* value not reported). HDL-C increased by a median of 22% with both treatments (*P* value not reported). Discontinuation rates due to adverse events were 21.2 and 24.0% with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				fluvastatin and placebo. Death rates due to noncardiac causes were 2.7 and 3.0% with fluvastatin and placebo. There were three reported cases of elevations in CK ≥10 times the ULN with placebo. There were 10 patients receiving fluvastatin and three patients receiving placebo who had elevations of at least three times the ULN level in AST or ALT on two consecutive occasions. Cancers were reported in 46 and 49 patients receiving fluvastatin and placebo (*P* values not reported).
Liem et al[151] FLORIDA Fluvastatin 80 mg/day vs placebo	DB, PC, PG, RCT Adult patients with an acute MI and TC <6.5 mmol/L, new or markedly increased chest pain lasting >30 minutes or a new pathological Q wave ≥0.04 seconds duration, or ≥25% of the corresponding R wave amplitude, both in ≥2 contiguous leads	N=540 1 year	Primary: Presence of either ischemia on ambulatory ECG monitoring at 12 months or the occurrence of a major clinical event Secondary: Six week and 12 month incidence of ischemia on the ambulatory ECG, six week and 12 month change in ischemic burden, 12 month change in lipid profile, safety and tolerability	Primary: After 12 months, fluvastatin did not significantly affect ischemia on ambulatory ECG (*P*=0.67), nor the occurrence of any major clinical event (*P*=0.24) when compared to placebo. Secondary: In patients with ischemia at baseline, 29 and 38% receiving fluvastatin and placebo were ischemic on the ambulatory ECG at six weeks and 27 and 21% were again positive for ischemia at 12 months (*P* value not reported). The six week and 12 month ischemic burden was lowered by 6.1 and 7.7%, respectively, with fluvastatin and by 10.5 and 13.0%, respectively, with placebo (*P*=0.81 and *P*=0.43, respectively between treatment groups). After 12 months, fluvastatin lowered LDL-C by 21% compared to an increase of nine percent with placebo (*P*<0.001). There were 62 and 68 patients receiving fluvastatin and placebo who had at least one major clinical event (*P*=0.764). All-cause mortality was 2.6 and 4.0% with fluvastatin and placebo (*P* value not reported).
Sacks et al[152] CARE Pravastatin 40 mg QD	DB, MC, RCT Adult post MI patients with TC <240 mg/dL, LDL-C 115 to 174	N=4,159 5 years	Primary: Death from CHD (including fatal MI, either definite or probable, sudden	Primary: When compared to placebo, there was a significant 24% lower incidence of the primary endpoint with pravastatin (13.2 vs 10.2%; 95% CI, 9 to 36; *P*=0.003).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs placebo	mg/dL, TG <350 mg/dL, glucose ≤220 mg/dL, left ventricular ejection fractions ≥25 percent and no symptomatic CHF		death, death during a coronary intervention and death from other coronary causes) or a symptomatic nonfatal MI confirmed by serum CK Secondary: Not reported	Pravastatin was associated with a significant 23% risk reduction in nonfatal MIs compared to placebo (*P*=0.02). Pravastatin was associated with a nonsignificant 37% reduction in the rate of fatal MIs (95% CI, -5 to 62; *P*=0.07) and a nonsignificant 25% reduction in the rate of total MIs (95% CI, 8 to 39; *P*=0.06) compared to placebo. Secondary: Not reported
No authors listed[153] LIPID Pravastatin 40 mg QD vs placebo	DB, MC, PC Patients 31 to 75 years of age who were post MI or who had a hospital discharge diagnosis of unstable angina between 3 and 36 months before trial entry	N=9,014 6.1 years	Primary: Death from CHD Secondary: Incidence of MI and stroke, rate of CABG surgery	Primary: Death from CHD occurred in 6.4 and 8.3% of patients receiving pravastatin and placebo (RRR, 24%; 95% CI, 12 to 35; *P*<0.001). Secondary: Pravastatin was associated with a significant 29% reduction in the incidence of MI compared to placebo (7.4 vs 10.3%; *P*<0.001). Pravastatin was associated with a significant 19% reduction in the incidence of stroke compared to placebo (3.7 vs 4.5%; *P*=0.048). Pravastatin was associated with a significant 22% reduction in the risk of CABG surgery compared to placebo (9.2 vs 11.6%; *P*<0.001). Pravastatin was associated with a significant 19% reduction in the risk of coronary angioplasty compared to placebo (4.7 vs 5.6%; *P*=0.024). Pravastatin was associated with a significant 12% reduction in the risk of unstable angina compared to placebo (22.3 vs 24.6%; *P*=0.005).
Shepherd et al[154] PROSPER Pravastatin 40 mg	DB, MC, PC, RCT Patients 70 to 82 years of age with pre-	N=5,804 Mean, 3.2 years (range, 2.8 to	Primary: Combined endpoint of definite or suspect death from	Primary: Pravastatin was associated with a significant 15% reduction in the risk of the primary endpoint compared to placebo (14.1 vs 16.2%; HR, 0.85; 95% CI, 0.74 to 0.97; *P*=0.014).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
QD vs placebo	existing vascular disease (coronary, cerebral or peripheral) or at an increased risk of such disease due to risk factors (smoking, hypertension or diabetes) with TC 4 to 9 mmol/L and TG <6 mmol/L	4.0 years)	CHD, nonfatal MI and fatal or nonfatal stroke Secondary: Examination of coronary and cerebrovascular components separately, assessment of cognitive function, adverse events, cancer	Secondary: When the primary endpoint was separated into coronary and cerebrovascular components, the authors noted a 19% reduction in coronary events with pravastatin, but no apparent effect on cerebrovascular events (*P* value not reported). Pravastatin was associated with a significant 19% reduction in the risk of CHD death or nonfatal MI compared to placebo (10.1 vs 12.2%; HR, 0.81; 95% CI, 0.69 to 0.94; *P*=0.006). When examining the rates of fatal or nonfatal stroke, there was no significant difference between the two treatments (HR, 1.03; 95% CI, 0.81 to 1.31; *P*=0.81). There was no significant difference in cognitive function between the two treatments (*P*>0.05). The rate of serious adverse events reported was similar between the two treatments (56 vs 55%, respectively; *P* value not reported). There were no patients with either treatment reported rhabdomyolysis or CK concentrations >10 times the ULN (*P* value not reported). There were no significant differences in the rates of cancer development between the two treatments (*P*>0.05).
Thompson et al[155] PACT Pravastatin 20 to 40 mg/day vs placebo	DB, MC, PC, RCT Patients 18 to 85 years of age with <24 hours onset of symptoms and diagnosis of acute MI or unstable angina pectoris	N=3,408 4 weeks	Primary: Composite of death from any cause, acute MI or readmission to hospital with unstable angina pectoris during the first month following	Primary: Pravastatin 40 mg was associated with a nonsignificant 6.4% reduction in the risk of the primary endpoint compared to placebo (*P*=0.48). Secondary: There were no significant differences in the frequency of individual components of the primary endpoint in the 30 days after randomization between the two treatments (*P*>0.05). The frequency of adverse events did not differ between the two treatments

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			randomization Secondary: Incidence of individual causes of death, acute MI other than the index event, readmission for angina in the first month, urgent revascularization procedure, other nonfatal cardiovascular events; adverse events	(*P* value not reported).
No authors listed[156] 4S Simvastatin 10 mg/day, titrated up to 40 mg/day vs placebo	DB, PC, RCT Patients 35 to 70 years of age with CHD, a history of angina pectoris or previous MI, TC 212 to 309 mg/dL and TG <221 mg/dL on a lipid-lowering diet	N=4,444 5.4 years	Primary: All-cause mortality Secondary: Major coronary events (coronary deaths, definite or probable hospital-verified nonfatal acute MI, resuscitated cardiac arrest and definite silent MI)	Primary: Simvastatin was associated with a 30% reduction in all-cause mortality compared to placebo (8 vs 12%; RR, 0.70; 95% CI, 0.58 to 0.85; *P*=0.0003). Secondary: Overall, patients receiving placebo experienced at least one secondary event compared to patients receiving simvastatin (28 vs 19%, respectively; *P* value not reported). There were 189 (8.5%) coronary deaths with placebo compared to 111 (5.0%) coronary deaths with simvastatin (RR, 0.58; 95% CI, 0.46 to 0.73; *P* value not reported). There were 270 (12.1%) definite acute MI with placebo compared to 164 (7.4%) definite acute MI with simvastatin. There were 418 (18.8%) definite or probable acute MI with placebo compared to 279 (12.6%) definite or probable acute MI with simvastatin. There were 110 (4.9%) silent MIs with placebo compared to 88 (4.0%) silent MIs with simvastatin. There was one patient receiving simvastatin who experienced

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				resuscitated cardiac arrest. (*P* values not reported). Additionally, a cerebrovascular event occurred in 95 (4.3%) patients with placebo compared to 61 (2.7%) patients with simvastatin (RR, 95% CI; *P* value not reported).
Chonchol et al[157] Simvastatin 10 mg/day, titrated up to 40 mg/day vs placebo	Subanalysis of 4S[125] Patients 35 to 70 years of age with CHD, a history of angina pectoris or previous MI, TC 212 to 309 mg/dL and TG <221 mg/dL on a lipid-lowering diet, stratified by estimated GFR of ≥75 or <75 mL/min/1.73 m^2	N=4,420 5.4 years	Primary: All-cause mortality Secondary: Major coronary events (coronary deaths, definite or probable hospital-verified nonfatal acute MI, resuscitated cardiac arrest and definite silent MI)	Primary: Simvastatin was associated with a significant reduction in all-cause mortality among patients with chronic renal insufficiency (HR, 0.70; 95% CI, 0.55 to 0.91; *P* value not reported). Secondary: Simvastatin was associated with a significant reduction in the incidence of major coronary events among patients with chronic renal insufficiency (HR, 0.68; 95% CI, 0.57 to 0.80; *P* value not reported). Simvastatin was associated with a significant reduction in the incidence of CHD deaths or nonfatal MIs among patients with chronic renal insufficiency (HR, 0.66; 95% CI, 0.55 to 0.79; *P* value not reported). Simvastatin was associated with a significant reduction in the incidence of coronary revascularization among patients with chronic renal insufficiency (HR, 0.63; 95% CI, 0.51 to 0.79; *P* value not reported). Simvastatin was not associated with a significant reduction in the incidence of stroke among patients with chronic renal insufficiency (HR, 0.86; 95% CI, 0.54 to 1.36; *P* value not reported).
No authors listed[158] MRC/BHF (HPS) Simvastatin 40 mg QD vs placebo	DB, MC, PC, RCT Patients 40 to 80 years of age with a history of CHD, peripheral artery disease, cerebrovascular disease, diabetes or treated hypertension	N=20,536 5 years	Primary: All-cause mortality and CHD death events Secondary: Noncoronary causes of death, major coronary events (nonfatal MI	Primary: During the trial, 12.9 (1,328/10,269) vs 14.7% (1,507/10,267) of patients receiving simvastatin and placebo died (*P*=0.0003). The effect of simvastatin on all-cause mortality was mainly due to the definite 17% (SE, 4; 95% CI, 9 to 25) proportional reduction in the death rate from vascular causes (7.6 vs 9.1%; *P*<0.0001), which consists of a highly significant 18% (SE, 5) reduction in the coronary death rate (5.7 vs 6.9%; *P*=0.0005) and a nonsignificant 16% (SE, 9) reduction in the death rate from other vascular causes (1.9 vs 2.2%; *P*=0.07). There were no differences in all nonvascular deaths (5.3 vs 5.6%; *P*=0.4) or in any of the prespecified

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	(if also male and ≥65 years of age) with TC ≥135 mg/dL		or CHD death), stroke, revascularization, major vascular events (nonfatal MI, CHD death, stroke or revascularization), cancer	categories of nonvascular deaths (renal, hepatic and trauma). Secondary: Simvastatin was associated with a significant 38% (SE, 5; 95% CI, 30 to 46) proportional reduction in the incidence rate of first nonfatal MI (3.5 vs 5.6%; *P*<0.0001). For the endpoint of major coronary events, there was a significant 27% (SE, 4; 95% CI, 21 to 33) proportion reduction in the incidence rate of combined first nonfatal MI or coronary death (8.7 vs 11.8%; *P*<0.0001). Overall, simvastatin was associated with a significant 25% (SE, 5; 95% CI, 15 to 34) proportional reduction in the incidence rate of fist stroke (4.3 vs 5.7%; *P*<0.0001). This was due to mainly to a significant 30% (SE, 6; 95% CI, 19 to 40) proportional reduction in the incidence rate of strokes attributed to ischemia (2.8 vs 4.0%; *P*<0.0001), with no apparent difference in strokes attributed to hemorrhage (0.5 vs 0.5%; *P*=0.8). Overall, simvastatin was associated with a significant 24% (SE, 4; 95% CI, 17 to 30) proportional reduction in the incidence rate of first revascularization procedure (9.1 vs 11.7%; *P*<0.0001). Specifically, simvastatin was associated with a significant 30% (SE, 5; 95% CI, 22 to 38) proportional reduction in the incidence rate of coronary revascularization (5.0 vs 7.1%; *P*<0.0001). Similar results were observed for noncoronary revascularization (4.4 vs 5.2%; *P*=0.006). When the data for major coronary events (first nonfatal MI or coronary death), stroke and revascularization are combined for the endpoint of major vascular events, simvastatin was associated with a significant 24% (SE, 3; 95% CI, 19 to 28) proportional reduction in the event rate (19.8 vs 25.2%; *P*<0.001). New primary cancers were diagnosed in 7.9 and 7.9% of patients receiving simvastatin and placebo (rate ratio, 1.00; 95% CI, 0.91 to 1.11). These cases were associated with death in 3.5 vs 3.4% of patients (rate ratio, 1.03; 95% CI, 0.89 to 1.19). There were also no differences in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				incidence of cancers in any particular body system.
Collins et al[159] MRC/BHF (HPS) Simvastatin 40 mg QD vs placebo	DB, MC, PC, RCT Patients 40 to 80 years of age with a history of CHD, peripheral artery disease, cerebrovascular disease, diabetes or treated hypertension (if also male and ≥65 years of age) with TC ≥135 mg/dL	N=20,536 (5,963 diabetics and 14,573 patients with occlusive arterial disease without diabetes) 5 years	Primary: Incidence of first nonfatal MI or coronary death; fatal or nonfatal stroke; revascularization procedures; first incidence of major coronary events, strokes and revascularizations Secondary: Not reported	Primary: Simvastatin was associated with a significant 27% reduction in the incidence of first nonfatal MI or coronary death compared to placebo (95% CI, 21 to 33; *P*<0.0001). Among diabetic patients, simvastatin was associated with a significant 27% reduction in the incidence of first nonfatal MI or coronary death compared to placebo (95% CI, 19 to 34; *P*<0.0001). Simvastatin was associated with a significant 25% reduction in the incidence of first nonfatal or fatal strokes compared to placebo (95% CI, 15 to 34; *P*<0.0001). Simvastatin was associated with a significant 26% reduction in the incidence of fatal strokes compared to placebo (95% CI, 14 to 36; *P*=0.0002). Among diabetic patients, simvastatin was associated with a significant 24% reduction in the incidence of fatal strokes compared to placebo (95% CI, 6 to 39; *P*=0.01). Simvastatin was associated with a significant 24% proportional reduction in the incidence of first revascularization compared to placebo (95% CI, 17 to 30; *P*<0.0001). Among diabetic patients, simvastatin was associated with a significant 17% reduction in the incidence of first revascularization procedure compared to placebo (95% CI, 3 to 30; *P*=0.02). Simvastatin was associated with a significant 24% reduction in the first incidence of major coronary events, strokes and revascularizations compared to placebo (95% CI, 19 to 28; *P*<0.0001). Among diabetic patients, simvastatin was associated with a significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				22% reduction in the incidence of first incidence of major coronary events, strokes and revascularizations compared to placebo (95% CI, 13 to 30; *P*<0.0001). Secondary: Not reported
de Lemos et al[160] A to Z trial Simvastatin 40 mg/day for 1 month, titrated up to 80 mg/day (intensive therapy) vs placebo for 4 months, followed by simvastatin 20 mg/day (delayed initiation of a less intensive therapy)	DB, MC, PC Adult patients with either non-ST-elevation ACS or STEMI	N=4,497 2 years	Primary: Composite of cardiovascular death, nonfatal MI, readmission for ACS (requiring new ECG changes or cardiac marker elevation) and stroke Secondary: Individual components of the primary endpoint, revascularization due to documented ischemia, all-cause mortality, new-onset CHF (requiring admission or initiation of heart failure medications), cardiovascular rehospitalization	Primary: Simvastatin 80 mg was associated with a nonsignificant reduction in the risk of the primary endpoint compared to simvastatin 20 mg (14.4 vs 16.7%; HR, 0.89; 95% CI, 0.76 to 1.04; *P*=0.14). Secondary: Simvastatin 80 mg was associated with a significant reduction in the risk of cardiovascular death compared to simvastatin 20 mg (HR, 0.75; 95% CI, 0.57 to 1.00; *P*=0.05). There was no significant difference between the two treatments in the secondary endpoints of MI, readmission for ACS, revascularization due to documented ischemia or stroke (*P*>0.05 for all). Simvastatin 80 mg was associated with a significant reduction in the risk of new onset CHF compared to simvastatin 20 mg (3.7 vs 5.0%; HR, 0.72; 95% CI, 0.53 to 0.98; *P*=0.04).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
No authors listed[161] Simvastatin 40 mg QD vs placebo	DB, MC, RCT Patients 40 to 80 years of age with a history of CHD, peripheral artery disease, cerebrovascular disease, diabetes or treated hypertension (if also male and ≥65 years of age) with TC ≥135 mg/dL	N=20,536 5 years	Primary: The first major coronary event (nonfatal MI or coronary death), first major vascular event (major coronary event, stroke or revascularization) Secondary: Not reported	Primary: In the overall population, simvastatin was associated with a significant 24% reduction in the first incidence of a major vascular event compared to placebo (19.8 vs 25.2%; *P*<0.0001). Among patients with baseline peripheral artery disease, simvastatin was associated with a significant 22% reduction in the first incidence of a major vascular event compared to placebo (26.4 vs 32.7%; *P*<0.0001). Among patients without baseline peripheral artery disease, simvastatin was associated with a significant 25% reduction in the first occurrence of a major vascular event compared to placebo (16.5 vs 21.5%; *P*<0.0001). The difference in the reduction of the risk of major vascular events with statin therapy between the peripheral artery disease and non-peripheral artery disease groups was not significant (*P*=0.05). In the overall population, simvastatin was associated with a significant 27% reduction in the first incidence of a major coronary event compared to placebo (8.7 vs 11.8%; *P*<0.0001). Among patients with baseline peripheral artery disease, simvastatin was associated with a significant reduction in the first incidence a major coronary event compared to placebo (10.9 vs 13.8%; *P*<0.0001). Among patients without baseline peripheral artery disease, simvastatin was associated with a significant reduction in the first incidence of a major coronary event compared to placebo (7.7 vs 10.8%; *P*<0.0001). The difference in the reduction of the risk of major coronary events with statin therapy between the peripheral artery disease and non-peripheral artery disease groups was not significant (*P*=0.03). In the overall population, simvastatin was associated with a significant 25% reduction in the first incidence of stroke compared to placebo (4.3 vs 5.7%; *P*<0.0001). Among patients with baseline peripheral artery disease, simvastatin was associated with a significant reduction in the first incidence of stroke compared to placebo (5.3 vs 7.2%; *P*<0.0001). Among patients without baseline peripheral artery disease, simvastatin was associated with a significant reduction in the first incidence of stroke

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				compared to placebo (3.8 vs 5.0%; *P*<0.0001). The difference in the reduction of the risk of stroke with statin therapy between the peripheral artery disease and non-peripheral artery disease groups was not significant (*P*=0.07). In the overall population, simvastatin was associated with a significant 24% reduction in the first incidence of revascularization compared to placebo (9.1 vs 11.7%; *P*<0.0001). Among patients with baseline peripheral artery disease, simvastatin was associated with a significant reduction in the first incidence of revascularization compared to placebo (13.8 vs 17.9%; *P*<0.0001). Among patients without baseline peripheral artery disease, simvastatin was associated with a significant reduction in the first incidence of revascularization compared to placebo (6.9 vs 8.7%; *P*<0.0001). The difference in the reduction of the risk of revascularization with statin therapy between the peripheral artery disease and non-peripheral artery disease groups was not significant (*P*=0.07). In the overall population, simvastatin was associated with a significant 16% reduction in the risk of first incidence of a peripheral vascular event compared to placebo (4.7 vs 5.5%; *P*=0.006). This risk reduction was independent of baseline LDL-C, age, diabetes or coronary disease (*P* values not reported). Secondary: Not reported
Briel et al[162] Statins (pravastatin 10 to 40 mg, fluvastatin 80 mg, atorvastatin 20 to 80 mg, simvastatin 40 to 80 mg) vs	MA (12 PC, RCTs) Patients with ACS (MI or unstable angina), started on statin therapy within 14 days of ACS and with a follow up ≥30 days	N=13,024 ≥30 days	Primary: Composite endpoint of nonfatal MI, nonfatal stroke and total death Secondary: Total death, total MI, total stroke,	Primary: At either month one or four follow up, there was no significant difference in the primary endpoint between statin therapy and placebo (*P*=0.39 and *P*=0.30, respectively). Secondary: At either month one or four of follow up, there was no significant difference in any of the secondary endpoints (except for unstable angina) between statin therapy and placebo (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
placebo			cardiovascular death, fatal and nonfatal MI, revascularization procedures (CABG surgery, angioplasty) and unstable angina (recurrent myocardial ischemia requiring emergency hospitalization)	After four months of therapy, statin therapy was associated with a significant moderate reduction in the incidence of unstable angina compared to placebo (*P*=0.05).
Mood et al[163] Statins (atorvastatin 20 to 40 mg/day, pravastatin 40 mg/day, fluvastatin 40 mg BID) vs placebo or usual care	MA (6 RCTs) Therapy was initiated around the time of a PCI	N=3,941 up to 45 months	Primary: Incidence of MI Secondary: All-cause mortality, cardiovascular mortality, surgical or percutaneous revascularization, stroke	Primary: Compared to placebo or usual care, statin therapy was associated with a significant 43% reduction in the risk for MI (5.2 vs 3.0%; OR, 0.57; 95% CI, 0.42 to 0.78; *P*<0.0001). Secondary: Compared to placebo or usual care, statin therapy was associated with a nonsignificant 26% reduction in all-cause mortality (3.0 vs 2.3%; OR, 0.74; 95% CI, 0.5 to 1.1; *P*=0.14). Compared to placebo or usual care, statin therapy was associated with a nonsignificant 42% reduction in cardiovascular mortality (1.20 vs 0.71%; OR, 0.58; 95% CI, 0.30 to 1.11; *P*=0.10). Compared to placebo or usual care, statin therapy was associated with a nonsignificant 11% reduction in the incidence of repeat surgical or percutaneous revascularization (21.9 vs 19.6%; OR, 0.89; 95% CI, 0.78 to 1.02; *P*=0.098). The incidence of stroke was nonsignificantly higher with statin therapy compared to placebo or usual care (0.40 vs 0.08%; OR, 3.00; 95% CI, 0.60 to 14.77; *P*=0.18).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Afilalo et al[164] Moderate statin therapy (pravastatin 40 mg/day, fluvastatin 80 mg/day, simvastatin 20 to 40 mg/day) vs placebo	MA (9 RCTs) Patients ≥50 years of age with CHD	N=19,569 (9 studies) ≥6 months	Primary: All-cause mortality, CHD mortality, stroke, revascularization, nonfatal MI Secondary: Not reported	Primary: Statin therapy was associated with a lower rate of all-cause mortality compared to placebo (15.6 vs 18.7%; RR, 0.78; 95% CI, 0.65 to 0.89; *P* value not reported). Statin therapy was associated with a significant reduction in the risk of CHD mortality by 30% (RR, 0.70; 95% CI, 0.53 to 0.83), nonfatal MI by 26% (RR, 0.74; 95% CI, 0.60 to 0.89), revascularization by 30% (RR, 0.70; 95% CI, 0.53 to 0.83) and stroke by 25% (RR, 0.75; 95% CI, 0.56 to 0.94). The calculated NNT with statin therapy to save one life was 28 (95% CI, 15 to 56). Secondary: Not reported
Hulten et al[165] Intensive statin therapy (pravastatin 40 mg/day, fluvastatin 80 mg/day, simvastatin 80 mg/day, atorvastatin 20 mg/day, atorvastatin 80 mg daily) vs placebo or lower dosed statin therapy	MA (13 RCTs) Adult patients initiated on intensive statin therapy or control within 14 days of hospitalization for ACS	N=17,963 (13 studies) Up to 2 years of follow up	Primary: Composite of death, recurrent ischemia and recurrent MI; death and cardiovascular events; cardiovascular death; ischemia; MI; LDL-C reduction; safety Secondary: Not reported	Primary: In patients with recent ACS, intensive statin therapy was associated with a significantly lower rate of mortality and cardiovascular events over 24 months of follow up (HR, 0.81; 95% CI, 0.77 to 0.87; *P*<0.001). In patients with recent ACS, intensive statin therapy was associated with a lower risk of overall cardiovascular events over 24 months of follow up (HR, 0.84; 95% CI, 0.76 to 0.94; *P* value not reported). In patients with recent ACS, intensive statin therapy was associated with lower cardiovascular mortality over 24 months of follow up (HR, 0.76; 95% CI, 0.66 to 0.87). In patients with recent ACS, intensive statin therapy was associated with lower ischemia over 24 months of follow up (HR, 0.68; 95% CI, 0.50 to 0.92). In patients with recent ACS, intensive statin therapy was not associated with a lower incidence of MIs over 24 months of follow up (HR, 0.89; 95%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				CI, 0.60 to 1.33). Intensive statin therapy was associated with a significantly greater reduction in LDL-C compared to controls (*P*<0.001). Adverse effects were similar between the two treatments (*P* value not reported). Secondary: Not reported
Cannon et al[166] PROVE IT-TIMI 22 Atorvastatin 80 mg/day (intensive regimen) vs pravastatin 40 mg/day (standard regimen)	DB, DD, MC, RCT Patients ≥18 years of age in stable condition after a hospitalization for an ACS with either an acute MI or high risk unstable angina in the preceding 10 days, with TC ≤240 mg/dL measured within the first 24 hours after the onset of the ACS or up to 6 months earlier if no sample had been obtained during the first 24 hours; patients who were receiving long-term lipid-lowering therapy at the time of the ACS had a TC ≤200 mg/dL	N=4,162 Up to 3 years (mean 2 years)	Primary: Rates of composite death from any cause, MI, documented unstable angina requiring hospitalization, revascularization and stroke Secondary: Risk of death due to CHD, nonfatal MI or revascularization; risk of the individual components of the primary endpoint; discontinuation rates; safety	Primary: The rates of composite death from any cause, MI, unstable angina requiring hospitalization, revascularization and stroke at two years were 26.3 and 22.4% with pravastatin and atorvastatin, representing a 16% reduction in the HR favoring atorvastatin (95% CI, 5 to 26; *P*=0.005). Secondary: The risk of death due to CHD, nonfatal MI or revascularization was reduced by 14% with atorvastatin (*P*=0.029) with a two year event rate of 19.7% compared to a two year event rate of 22.3% with pravastatin. The risk of death, MI or urgent revascularization was reduced by 25% with atorvastatin (*P*<0.001). Among the individual components of the primary endpoint, atorvastatin was associated with a significant reduction of 14% for revascularization (*P*=0.04) and a 29% reduction in the risk of recurrent unstable angina (*P*=0.02) compared to pravastatin. There were nonsignificant reductions in the rates of death or MI (18%, *P*=0.06) and the rates of stroke (*P* value not reported) between the two treatments. The discontinuation rates due to adverse events or for other reasons were 21.4 and 22.8% with pravastatin and atorvastatin at one year (*P*=0.30) and 33.0 and 30.4%, respectively at two years (*P*=0.11). Discontinuation rates due to myalgias or muscle aches or elevations in CK levels were 2.7 and 3.3% with pravastatin and atorvastatin (*P*=0.23). There were 1.1 and 3.3%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				of patients receiving pravastatin and atorvastatin who had elevations in ALT levels that were at least three times the ULN (*P*<0.001).
Ray et al[167] Atorvastatin 80 mg/day (intensive regimen) vs pravastatin 40 mg/day (standard regimen)	Subanalysis of PROVE IT-TIMI 22[135] Patients ≥18 years of age in stable condition after a hospitalization for an ACS with either an acute MI or high risk unstable angina in the preceding 10 days, with TC ≤240 mg/dL measured within the first 24 hours after the onset of the ACS or up to 6 months earlier if no sample had been obtained during the first 24 hours; patients who were receiving long-term lipid-lowering therapy at the time of the ACS had a TC ≤200 mg/dL	N=4,162 Up to 3 years (mean, 2 years)	Primary: A composite of all-cause mortality, MI, unstable angina requiring hospitalization, revascularization or stroke Secondary: A composite of death, MI or unstable angina requiring hospitalization	Primary: After 30 days, 3.0 and 4.2% of patients receiving atorvastatin and pravastatin experienced a primary endpoint (HR, 72; 95% CI, 0.52 to 0.99; *P*=0.046). From six months to the end of the trial, 15.1 and 17.7% of patients receiving atorvastatin and pravastatin experienced a primary endpoint (HR, 82; 95% CI, 0.69 to 0.99; *P*=0.037). Secondary: Atorvastatin was associated with a significant reduction in the risk of the triple composite endpoint compared to pravastatin (15.7 vs 20.0%; HR, 76; 95% CI, 0.66 to 0.88; *P*=0.0002). After 30 days, patients receiving atorvastatin experienced a significantly greater reduction in LDL-C and hsCRP level compared to patients receiving pravastatin (*P*<0.001 for both).
Ahmed et al[168] Atorvastatin 80 mg/day (intensive regimen) vs pravastatin 40	Subanalysis of PROVE IT-TIMI 22[135] Patients ≥18 years of age in stable condition after a hospitalization for an ACS with either an acute MI or high risk unstable angina in	N=4,162 Up to 3 years (mean, 2 years)	Primary: A composite of death, MI, unstable angina requiring hospitalization, revascularization with PCI or CABG surgery occurring within 30 days after	Primary: There was no significant difference between the two treatments in terms of the primary endpoint among patients with diabetes (31.8 vs 28.4%; HR, 88; *P*=0.28). Secondary: Atorvastatin was associated with a significantly lower rate for the secondary composite endpoint compared to pravastatin among patients with diabetes (21.1 vs 26.6%; HR, 0.75; *P*=0.03) and patients without

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day (standard regimen)	the preceding 10 days, with TC ≤240 mg/dL measured within the first 24 hours after the onset of the ACS or up to 6 months earlier if no sample had been obtained during the first 24 hours; patients who were receiving long-term lipid-lowering therapy at the time of the ACS had a TC ≤200 mg/dL, stratified by type 2 diabetes		randomization or stroke within two years after trial onset Secondary: A composite of death, MI or unstable angina requiring hospitalization; LDL-C <70 mg/dL goal; hsCRP <2 mg/L goal; MI; unstable angina requiring hospitalization	diabetes (14 vs 18%; HR, 0.76; *P*=0.002). Consequently, treating 1,000 diabetic and nondiabetic patients with atorvastatin would prevent 55 and 40 events, respectively (*P* value not reported). Compared to nondiabetic patients, fewer patients with diabetes receiving atorvastatin achieved the dual goal of LDL-C <70 mg/dL and hsCRP <2 mg/L (37.6 vs 45.4%; *P*=0.004). Out of diabetic patients receiving atorvastatin, 62% failed to reach the dual goal of LDL-C <70 mg/dL and hsCRP <2 mg/L. Diabetic patients who reached the dual LDL-C and CRP goals had significantly lower rates of the secondary endpoint compared to patients who failed to reach the goal (17.7 vs 24.7%; *P*=0.021). In the diabetic population, among the individual components of the primary and secondary composite endpoints, the only variable exhibiting a significant reduction with atorvastatin compared to pravastatin was unstable angina requiring hospitalization (3.1 vs 7.4%; *P*=0.003).
Scirica et al[169] Atorvastatin 80 mg/day (intensive regimen) vs pravastatin 40 mg/day (standard regimen)	Subanalysis of PROVE IT-TIMI 22[135] Patients ≥18 years of age in stable condition after a hospitalization for an ACS with either an acute MI or high risk unstable angina in the preceding 10 days, with TC ≤240 mg/dL measured within the first 24 hours after the onset	N=4,162 Up to 3 years (mean, 2 years)	Primary: Hospitalization for heart failure occurring ≥30 days after randomization Secondary: Not reported	Primary: Atorvastatin was associated with a significant reduction in the rate of hospitalization for heart failure compared to pravastatin (1.6 vs 3.1%; HR, 0.55; 95% CI, 0.35 to 0.85; *P*=0.008). The benefit observed with atorvastatin was independent on recurrent MI or prior history of heart failure. Higher BNP was associated with an increased risk for heart failure (HR, 2.6; 95% CI, 1.2 to 5.5; *P*=0.016). Among patients with a high BNP level (>80 pg/mL), atorvastatin was associated with a lower incidence of heart failure compared to pravastatin (HR, 0.32; 95% CI, 0.13 to 0.8; *P*=0.014).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	of the ACS or up to 6 months earlier if no sample had been obtained during the first 24 hours; patients who were receiving long-term lipid-lowering therapy at the time of the ACS had a TC ≤200 mg/dL			Secondary: Not reported
Ray et al[170] Atorvastatin 80 mg/day (intensive regimen) vs pravastatin 40 mg/day (standard regimen)	Subanalysis of PROVE IT-TIMI 22[135] Patients ≥18 years of age in stable condition after a hospitalization for an ACS with either an acute MI or high risk unstable angina in the preceding 10 days, with TC ≤240 mg/dL measured within the first 24 hours after the onset of the ACS or up to 6 months earlier if no sample had been obtained during the first 24 hours; patients who were receiving long-term lipid-lowering therapy at the time of the ACS had a TC ≤200 mg/dL, stratified by age (<75	N=4,162 Up to 3 years (mean, 2 years)	Primary: Cardiac mortality; MI; unstable angina requiring hospitalization; relationship between NCEP goal and a composite primary endpoint of all-cause mortality, MI, unstable angina requiring hospitalization, revascularization or stroke Secondary: A composite of death, MI or unstable angina requiring hospitalization	Primary: Aft 30 days, a greater proportion of patients in both age groups receiving atorvastatin achieved the NCEP goals compared to patients in both age groups receiving pravastatin (*P*<0.001). Among patients ≥75 years of age, the achievement of the NCEP LDL-C goal was associated with an eight percent reduction in the risk of primary endpoint from baseline (*P*=0.008). The younger age group achieving the NCEP LDL-C goal was associated with a 2.3% reduction in the risk of primary endpoint from baseline (*P*=0.013). Patients <75 years of age were associated with a lower risk of the primary composite endpoint compared to patients ≥75 years of age (23.0 vs 30.4%; *P*<0.0001). Patients <75 years of age were associated with a lower risk of all-cause mortality (*P*<0.0001), MIs (*P*<0.0001), unstable angina requiring hospitalization (*P*=0.01) or strokes (*P*=0.004) compared to patients ≥75 years of age. Secondary: The composite triple endpoint occurred more frequently in patients ≥75 years of age (20.1 vs 11.0%; HR, 1.93; 95% CI, 1.59 to 2.33; *P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	years of age and ≥75 years of age)			
Deedwania et al[171] SAGE Atorvastatin 80 mg/day (intensive regimen) vs pravastatin 40 mg/day (standard regimen)	DB, DD, MC, PG, RCT Ambulatory patients 65 to 85 years of age with CAD, ≥1 episode of myocardial ischemia that lasted ≥3 minutes during a 48 hour ambulatory ECG at screening and baseline LDL-C 100 to 250 mg/dL	N=893 12 months	Primary: Absolute change from baseline in the total duration of myocardial ischemia on 48 hour Holter monitor Secondary: Absolute change from baseline to month three in the total duration of myocardial ischemia on 48 hour Holter monitor; percent change from baseline to months three and 12 in the total duration of myocardial ischemia; absolute and percent changes from baseline to months three and 12 in the number of ischemic episodes; percent change in ischemic burden; proportion of patients free of ischemia at months	Primary: After 12 months, the total duration of ischemia was significantly reduced from baseline with both treatments (*P*<0.001). There was no significant difference between the two treatments in terms of the primary endpoint (*P*=0.88). Secondary: There were no significant differences between the two treatments in any of the secondary endpoints assessing degree of ischemia at months three and 12 (*P* value not reported). Atorvastatin was associated with a significant 77% reduction in all-cause mortality compared to pravastatin (HR, 0.33; 95% CI, 0.13 to 0.83; *P*=0.014). Compared to pravastatin, atorvastatin was associated with significantly greater reductions in TC, LDL-C, TG and apo B at months three and 12 (*P*<0.001). Compared to atorvastatin, pravastatin was associated with a significantly greater increase in HDL-C at three (*P*<0.001) and 12 months (*P*=0.009). Atorvastatin was associated with a significantly higher incidence of liver test abnormalities (17.3 vs 13.9%; *P*<0.001). There were no significant differences between pravastatin and atorvastatin in treatment related adverse events (13.9 vs 17.3%; *P*=0.17).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			three and 12; percent changes in the levels of TC, LDL-C, HDL-C, TG and apo B	
Pitt et al[172] LUNAR Atorvastatin 80 mg/day vs rosuvastatin 20 mg/day vs rosuvastatin 40 mg/day	MC, OL, PG, PRO, RCT Patients 18 to 75 years of age with CAD who were hospitalized for ACS within 48 hours of ischemic symptoms with non–ST-segment elevation ACS or ST-segment elevation ACS who received optimal reperfusion therapy (successful treatment with a thrombolytic agent or primary catheter-based intervention initiated within 12 hours of symptom onset), LDL cholesterol level >70 mg/dL and a fasting TG level <500 mg/dL within 72 hours of symptom onset	N=825 12 weeks	Primary: Averaged LDL reduction measurements at six and 12 weeks Secondary: Percentage reduction from baseline in LDL at two, six and 12 weeks, percentage change in TC, HDL, Apo AI, Apo B, LDL/HDL cholesterol, TC/HDL, non-HDL/HDL-C, Apo B/Apo AI, change in CRP at six and 12 weeks and safety	Primary: The averaged week six and 12 LDL reduction from baseline was significantly greater with rosuvastatin 40 mg compared to atorvastatin 80 mg (46.8 vs 42.7%; *P*<0.05). The reduction from baseline with rosuvastatin 20 mg was -42.0%. Secondary: Compared to treatment with atorvastatin 80 mg, LDL was significantly reduced with rosuvastatin 20 mg at two weeks (*P*<0.01) and weeks six through 12 (*P*<0.05 for both). Similarly, rosuvastatin 40 mg significantly lowered LDL compared to atorvastatin 80 mg at weeks two, six and 12 (*P*<0.01 for all). The percent change in TC was significantly greater with rosuvastatin 20 mg compared to atorvastatin 80 mg (-28.6 vs 30.9%; *P*<0.05). Rosuvastatin 40 mg reduced TC from baseline by 32.2%. Both the 20 and 40 mg dose of rosuvastatin significantly increased HDL compared to atorvastatin 80 mg (9.7 and 11.9 vs 5.6%; *P*<0.01 for both rosuvastatin doses). Apo AI was significantly higher following treatment with rosuvastatin 20 and 40 mg compared to atorvastatin 80 mg (10.3 and 10.1 vs 4.2, respectively; *P*<0.01 for both rosuvastatin doses). There were no statistically significant differences between either dose of rosuvastatin and atorvastatin 80 mg with regard to decrease in Apo B over 12 weeks. The ratio of LDL/HDL decreased in all three groups, however, rosuvastatin

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				40 mg was associated with a greater percentage reduction compared to atorvastatin 80 mg (-51.5 vs 44.5%; *P*<0.001). Rosuvastatin 40 mg significantly reduced the ratio of TC/HDL compared to atorvastatin 80 mg (-38.2 vs 33.1%; *P*<0.001). Rosuvastatin 20 mg reduced the TC/HDL ratio by 34.0%. Rosuvastatin 40 mg also significantly improve the ratio of non-HDL/HDL compared to atorvastatin 80 mg (-47.3 vs -41.2%; *P*<0.001). Rosuvastatin 20 mg reduced the non-HDL/HDL ratio by -42.3%. The ratio of Apo B/Apo AI was significantly reduced with rosuvastatin 40 mg compared to atorvastatin 80 mg (*P*<0.001). The percent change in CRP at week 12 was >80% in all groups; however, there was no statistically significant difference between the treatments.
Pedersen et al[173] IDEAL Atorvastatin 80 mg/day vs simvastatin 20 to 40 mg/day	MC, OL, PG, RCT Patients ≤80 years of age with a history of an MI and qualifying for statin therapy based on NCEP ATP III guidelines	N=8,888 4.8 years	Primary: Incidence of a major coronary event (CHD death, nonfatal MI or cardiac arrest with resuscitation) Secondary: Major cardiovascular events (any primary event plus stroke), any CHD event (any primary event, any coronary revascularization procedure or	Primary: Atorvastatin was associated with a nonsignificant reduction in the risk of a major coronary event compared to simvastatin (9.3 vs 10.4%; HR, 0.89; *P*=0.07). Secondary: Atorvastatin was associated with a significant reduction in the risk of a nonfatal MI compared to simvastatin (6.0 vs 7.2%; HR, 0.83; *P*=0.02). Atorvastatin was associated with a significant reduction in the risk of major cardiovascular events compared to simvastatin (12.0 vs 13.7%; HR, 0.87; *P*=0.02). Atorvastatin was associated with a significant reduction in the risk of any CHD event compared to simvastatin (20.2 vs 23.8%; HR, 0.84; *P*<0.001). Atorvastatin was associated with a significant reduction in the risk of any cardiovascular events compared to simvastatin (26.5 vs 30.8%; HR, 0.84; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			hospitalization for unstable angina), any cardiovascular events (any of the former plus hospitalization with a primary diagnosis of CHF and peripheral artery disease), all individual endpoints, all-cause mortality	Atorvastatin was associated with a significant reduction in the risk of peripheral vascular disease compared to simvastatin (2.9 vs 3.8%; HR, 0.76; *P*=0.02). Atorvastatin was associated with a nonsignificant reduction in the risk of fatal or nonfatal stroke compared to simvastatin (3.4 vs 3.9%; HR, 0.87; *P*=0.20). Atorvastatin was associated with a nonsignificant reduction in the risk of hospitalization for nonfatal heart failure compared to simvastatin (2.2 vs 2.8%; HR, 0.81; *P*=0.11). Atorvastatin was associated with a nonsignificant reduction in the risk of death from cardiovascular or noncardiovascular cause compared to simvastatin (4.9 vs 5.0; HR, 1.03; 95% CI, 0.85 to 1.24; *P*=0.78 and 3.2 vs 3.5%; HR, 0.92; *P*=0.47). Atorvastatin was associated with a nonsignificant reduction in the risk of all-cause mortality compared to simvastatin (8.2 vs 8.4%; HR, 0.98; *P*=0.81). Atorvastatin was associated with a higher rate of drug discontinuations due to adverse effects compared to simvastatin (9.6 vs 4.2%; *P*<0.001). Atorvastatin was associated with a higher rate of liver transaminase elevations compared to simvastatin (*P*<0.001). There was no significant difference between the two treatments in the incidence of serious adverse events (*P*=0.42).
Tikkanen et al[174] Atorvastatin 80 mg/day	Post hoc analysis of IDEAL[141] Adult patients with a	N=8,888 4.8 years	Primary: Incidence of a major coronary event (coronary	Primary: There was no significant heterogeneity of treatment effect by age for any composite endpoint, indicating that the benefit of atorvastatin was similar for younger and older patients. Nevertheless, the cardiovascular risk

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs simvastatin 20 to 40 mg/day	history of an MI and qualifying for statin therapy based on NCEP ATP III guidelines; stratified by age (<65 years of age vs ≥65 years of age)		death, confirmed nonfatal acute MI or cardiac arrest with resuscitation) Secondary: Major cardiovascular events (any primary event and stroke), any CHD event (any primary event, any coronary revascularization procedure, any hospitalization for unstable angina), any cardiovascular events	reductions associated with atorvastatin tended to be numerically lower in the older than younger age group. Atorvastatin was associated with a 20% decrease in risk of the primary endpoint of major coronary events in patients <65 years of age (HR, 0.80; 95% CI, 0.66 to 0.98), with similarly significant reductions in secondary composite endpoints. Secondary: There were similarly significant reductions in secondary composite endpoints, the corresponding reductions in the risk in patients ≥65 years of age were four to 12%, and significance was achieved for only the endpoint of any cardiovascular event in older patients (HR, 0.88; 95% CI, 0.79 to 0.99).
Strandberg et al[175] Atorvastatin 80 mg/day vs simvastatin 20 mg/day	Post hoc analysis of IDEAL[141] Patients ≤80 years of age with a history of an MI and qualifying for statin therapy based on NCEP ATP III guidelines	N=8,888 4.8 years	Primary: Hospitalization for heart failure Secondary: Not reported	At baseline, a history of heart failure (NYHA class I to IIIa) was reported by 537 patients, 5.5 (n=244) and 6.6% (n=293) of patients receiving simvastatin and atorvastatin, respectively. Primary: During the trial, there were 222 new hospitalizations for heart failure. Incidences of hospitalization for heart failure were 10.6 (57/537) vs 2.0% (165/8,351) in patients with and without a history of heart failure. Of the new cases, most were not preceded by an in-trial MI. Of the 222 patients with new hospitalization for heart failure during the trial, 71 (32.0%) patients subsequently died. Among the 222 new hospitalizations, 123 (2.8%) occurred with simvastatin compared to 99 (2.2%) with atorvastatin (HR, 0.81; 95% CI, 0.62 to 1.05; *P*=0.11).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Of the 537 patients with heart failure at baseline, 104 died during the trial compared to 36 of the patients without a history of heart failure (HR, 2.66; 95% CI, 2.16 to 3.27; *P*<0.0001). After adjustments in the entire trial cohort, atorvastatin was associated with a 26% decrease (*P*=0.03) of new or recurrent heart failure events compared to simvastatin. Atorvastatin tended to be associated with fewer recurrent heart failure events in those with heart failure at baseline (n= 537; *P*=0.11) and in those without heart failure at baseline (n=8,351; *P*=0.15). Secondary: Not reported
Sakamoto et al[176] MUSASHI-AMI Lipophilic statins (mean daily doses; atorvastatin 9.3 mg, fluvastatin 26.8 mg, pitavastatin 2 mg, simvastatin 5 mg) vs hydrophilic statin (mean daily dose; pravastatin 9.4 mg) All medications were administered within 96 hours of hospital admission with an acute MI.	MC, RCT Adult patients randomized to statin or no statin therapy within 96 hours of an acute MI, with TC 190 to 240 mg/dL	N=486 416 days	Primary: Composite of ACS events (cardiovascular death, nonfatal MI, recurrent acute myocardial ischemia requiring emergency hospitalization) Secondary: Incidence of individual components of the primary endpoint, nonfatal stroke, heart failure requiring emergent rehospitalization, new Q-wave appearance on the	Primary: Hydrophilic statin therapy was associated with a nonsignificant lower incidence of ACS events compared to lipophilic statin therapy (3.6 vs 9.9%; *P*=0.053). Secondary: Hydrophilic statin therapy was associated with a significantly lower incidence of new Q-wave appearance on the ECG compared to lipophilic statin therapy (75% vs 89%; *P*=0.0056). There was no difference between the two treatments in any of the other secondary endpoints (*P*=0.339).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			ECG	
Afilalo et al[177] Moderate statin therapy (pravastatin ≤40 mg/day, lovastatin ≤40 mg/day, fluvastatin ≤40 mg/day, simvastatin ≤20 mg/day, atorvastatin ≤10 mg/day, rosuvastatin ≤5 mg/day) vs intensive statin therapy (simvastatin 80 mg/day, atorvastatin 80 mg/day, rosuvastatin 20 to 40 mg/day)	MA (6 RCTs) Patients with recent ACS or stable CHD randomized to an intensive statin therapy (intervention) or moderate statin therapy (control)	N=28,505 ≥6 months	Primary: All-cause mortality, CHD mortality, hospitalization for heart failure, major coronary event (cardiovascular death or ACS), stroke, adverse effects Secondary: Not reported	Primary: In patients with recent ACS, intensive statin therapy was associated with lower all-cause mortality (OR, 0.75; 95% CI, 0.61 to 0.93). By treating 90 people with intensive statin therapy, one death could be prevented. All-cause mortality was not reduced by intensive statin therapy among patients with stable CHD (OR, 0.99; 95% CI, 0.89 to 1.11). In patients with recent ACS, intensive statin therapy was associated with a reduction in the incidence of major coronary events (OR, 0.86; 95% CI, 0.73 to 1.01). In patients with stable CHD, intensive statin therapy was associated with a reduction in the incidence of major coronary events (OR, 0.82; 95% CI, 0.75 to 0.91). Treating 46 patients with intensive statin therapy may prevent one major coronary event. In patients with recent ACS, intensive statin therapy was associated with a reduction in the incidence of heart failure hospitalizations (OR, 0.63; 95% CI, 0.46 to 0.86). In patients with stable CHD, intensive statin therapy was associated with a reduction in the incidence of heart failure hospitalizations (OR, 0.77; 95% CI, 0.64 to 0.92). Treating 112 patients with intensive statin therapy may prevent one hospitalization for heart failure. Intensive statin therapy was associated with a threefold increase in adverse hepatic (OR, 3.73; 95% CI, 2.11 to 6.58) and muscular events (OR, 1.96; 95% CI, 0.50 to 7.63). Consequently, 96 people would need to be treated, for one patient to experience an adverse hepatic event.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Secondary: Not reported
Cannon et al[178] Intensive statin therapy (simvastatin 40 to 80 mg/day, atorvastatin 80 mg/day) vs moderate statin therapy (pravastatin 40 mg/day, simvastatin 20 mg/day, atorvastatin 10 mg/day)	MA (4 RCTs) Patients with recent ACS or stable CHD randomized to an intensive statin therapy (intervention) or moderate statin therapy (control)	N=27,548 (4 studies) Up to 5 years	Primary: Combined incidence of coronary death or nonfatal MI; the combined incidence of coronary death or any cardiovascular event (MI, stroke, hospitalization for unstable angina or revascularization); incidence of stroke; incidence of cardiovascular, noncardiovascular and all-cause mortality Secondary: Not reported	Primary: Intensive statin therapy was associated with a significant odds reduction of 16% for coronary death or MI compared to moderate statin therapy (9.4 vs 8.0%; OR, 0.84; 95% CI, 0.77 to 0.91; *P*<0.00001). Intensive statin therapy was associated with a significant odds reduction of 16% for coronary death or any cardiovascular event compared to moderate statin therapy (32.3 vs 28.8%; OR, 0.84; 95% CI, 0.80 to 0.89; *P*<0.0000001). Intensive statin therapy was associated with a nonsignificant reduction in cardiovascular mortality of 12% compared to moderate statin therapy (3.8 vs 3.3%; OR, 0.88; 95% CI, 0.78 to 0.1.00; *P*=0.054). Intensive statin therapy was associated with a nonsignificant lower rate of noncardiovascular mortality compared to moderate statin therapy (*P*=0.73). Intensive statin therapy was associated with a nonsignificant significant reduction in all-cause mortality compared to moderate statin therapy (6.2 vs 5.9%; *P*=0.20). Intensive statin therapy was associated with a significant overall odds reduction of 18% for stroke compared to moderate statin therapy (2.8 vs 2.3%; OR, 0.82; 95% CI, 0.71 to 0.96; *P*=0.012). Intensive statin therapy was associated with a significant odds reduction of 16.5% for CHD death or MI compared to moderate statin therapy (OR, 0.835; 95% CI, 0.77 to 0.91; *P*<0.0001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Murphy et al[179] Intensive statin therapy (simvastatin 40 to 80 mg/day, atorvastatin 80 mg/day) vs moderate statin therapy (pravastatin 40 mg/day, simvastatin 20 mg/day)	MA (2 RCTs) Patients with recent ACS, clinically stable for 12 to 24 hours, randomized to an intensive statin therapy (intervention) or moderate statin therapy (control)	N=8,658 Up to 2 years	Primary: Incidence of cardiovascular, non-cardiovascular and all-cause mortality Secondary: Not reported	Primary: Intensive statin therapy was associated with a significant 23% reduction in the risk of all-cause mortality compared to moderate statin therapy (3.6 vs 4.9%; HR, 0.77; 95% CI, 0.63 to 0.95; *P*=0.015). Intensive statin therapy was associated with a significant 24% reduction in the risk of cardiovascular mortality compared to moderate statin therapy (2.6 vs 3.5%; HR, 0.76; 95% CI, 0.59 to 0.97; *P*=0.025). Intensive statin therapy was associated with a nonsignificant reduction in the risk of noncardiovascular mortality compared to moderate statin therapy (1.0 vs 1.4%; HR, 0.82; 95% CI, 0.55 to 1.21; *P*=0.32). Secondary: Not reported
Hypercholesterolemia (Combination Products)				
Erdine et al[180] Gemini-AALA Amlodipine/ atorvastatin 5 or 10/10, 20, 40 or 80 mg/day All possible dosing combinations were evaluated. Patients were classified into 1 of 3 cardiovascular risk categories. Group 1:	OL, PRO Patients 18 to 80 years of age with concurrent hypertension and dyslipidemia	N=1,649 14 weeks	Primary: Proportion of patients achieving both BP and LDL-C goals Secondary: Absolute and percentage change from baseline in BP and lipid levels, BP and LDL-C goal attainment stratified by prior antihypertensive and lipid lowering medications	Primary: More than half (55.2%) of patients achieved both their BP and LDL-C goals at the end of 14 weeks. A higher proportion of patients in Groups 1 and 2 achieved both goals compared to patients in Group 3 (81.3 and 78.8 vs 40.3%). When patients in Group 3 without diabetes (N=407) were further analyzed using a BP goal <140/90 mm Hg, goal achievement for both BP and LDL-C in nondiabetic patients rose to 70.0%. Secondary: All doses achieved significant improvements in LDL-C, TG, HDL-C, TC, SBP and DBP (*P*<0.001 for all). The proportions of patients with no prior treatment for hypertension and dyslipidemia in the cardiovascular risk categories were 74.1 (95% CI, 53.7 to 88.9), 81.6 (95% CI, 72.7 to 88.5) and 39.8% (95% CI, 30.0 to 50.2) for Groups 1, 2 and 3. The corresponding proportions for patients with prior treatment for hypertension and dyslipidemia were 82.0 (95% CI, 68.6 to 91.4), 80.7 (95% CI, 73.1 to 87.0) and 39.5% (95% CI, 35.3 to 43.8). The

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
hypertension and dyslipidemia with no additional cardiovascular risk factors (BP goal: <140/90 mm Hg, LDL-C goal: <4.1 mmol/L). Group 2: hypertension and dyslipidemia with ≥1 additional cardiovascular risk factor, excluding CHD and diabetes (BP goal: <140/90 mm Hg, LDL-C goal: <3.4 mmol/L). Group 3: hypertension and dyslipidemia with CHD or CHD risk equivalent (diabetes or other atherosclerotic disease (BP goal: <130/80 mm Hg, LDL-C goal: <2.6 mmol/L).				corresponding proportions for patients with no prior treatment for dyslipidemia were 80.2 (95% CI, 69.9 to 88.3), 77.8 (95% CI, 73.0 to 82.2) and 40.9% (95% CI, 36.1 to 45.7). The corresponding proportions for patients with prior treatment for dyslipidemia were 82.8 (95% CI, 70.6 to 91.4), 80.9 (95% CI, 73.8 to 86.8) and 39.8% (95% CI, 35.9 to 43.9). The corresponding proportions for patients with no prior treatment for hypertension were 77.1 (95% CI, 59.9 to 89.6), 81.7 (95% CI, 73.6 to 88.1) and 41.1% (95% CI, 33.1 to 49.3). The corresponding proportions for patients with prior treatment for hypertension were 82.7 (95% CI, 74.0 to 89.4), 77.9 (95% CI, 73.3 to 82.0) and 40.1% (95% CI, 36.8 to 43.5). The corresponding proportions for patients with prior treatment for hypertension only were 83.3 (95% CI, 70.7 to 92.1), 76.2 (95% CI, 70.2 to 81.5) and 41.2% (95% CI, 35.8 to 46.8). The corresponding proportions of patients with prior treatment for dyslipidemia only were 87.5 (95% CI, 47.3 to 99.7), 82.4 (95% CI, 56.6 to 96.2) and 43.4% (95% CI, 29.8 to 57.7).
Flack et al[181] CAPABLE Amlodipine/	MC, OL African American patients 18 to 80	N=489 20 weeks	Primary: Proportion of patients in three cardiovascular risk	Primary: More patients in Groups 1 and 2 achieved both goals compared to patients in Group 3 (69.7, 66.7 and 28.2%, respectively; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
atorvastatin 5 or 10/10, 20, 40 or 80 mg/day All possible dosing combinations were evaluated.	years of age with uncontrolled hypertension and dyslipidemia		groups (Group 1: patients without additional risk factors; Group 2: patients with >1 additional risk factors, excluding CHD and diabetes and Group 3: patients with CHD or CHD risk equivalent) who achieved the JNC 7 and NCEP ATP III goals Secondary: Changes from baseline in SBP, DBP, LDL-C, TC, TG, HDL-C and apo B	Secondary: Combination therapy was associated with a 17.5 and 10.1 mm Hg decrease in the SBP and DBP, respectively (*P* value not reported). Combination therapy was associated with a 23.6% reduction in LDL-C (*P* value not reported). Combination therapy was associated with a 17% reduction in TC (*P* value not reported). Combination therapy was associated with a 2.2% increase in HDL-C (*P* value not reported). Combination therapy was associated with a 6.9% reduction in TG (*P* value not reported). Combination therapy was associated with a 19.3% reduction in apo B (*P* value not reported).
Hobbs et al (abstract)[182] Amlodipine/ atorvastatin 5 or 10/10, 20, 40 or 80 mg/day All possible dosing combinations were evaluated.	2 MC, OL Patients with uncontrolled BP and controlled/uncontrolled LDL-C qualifying for treatment according to local governing guidelines	N=2,245 16 weeks	Primary: Proportion of patients achieving country-specific BP and LDL-C goals, safety Secondary: Not reported	Primary: Within the two trials, 62.9 and 50.6% of patients achieved both country-specific BP and LDL-C goals. BP was reduced by 20.4/10.7 and 21.8/12.6 mm Hg in the two trials, respectively, and reductions in LDL-C were 34.8 and 42.2 mg/dL, respectively. The most common adverse events were peripheral oedema (11.0%), joint swelling (2.9%) and headache (2.9%), of which, only oedema was linked to trial medication. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Neutel et al[183] CUSP Amlodipine/ atorvastatin 5/20 mg/day vs placebo All patients also received lifestyle changes. After 4 weeks, add-on antihypertensive and/or lipid lowering therapy was permitted.	DB, MC, PC, RCT Patients ≥21 years of age with coexisting hypertension (140 to 168/90 to 105 mm Hg) and dyslipidemia (LDL-C 110 to 160 mg/dL), without a history of cardiovascular disease who have never received treatment in the 3 months prior to enrollment	N=130 8 weeks	Primary: Proportion of patients who achieved both BP (<140/90 mm Hg) and LDL-C (<100 mg/dL) goals at week four Secondary: Proportion of patients who achieved both BP and LDL-C goals at week eight; proportion of patients who achieved both BP and LDL-C goals at both weeks four and eight; proportion of patients who achieved the LDL-C goal at weeks four and eight; mean changes from baseline in SBP, DBP and LDL-C at weeks four and eight; 10 year Framingham risk of CHD at weeks four and eight	Primary: After four weeks, the proportion of patients who achieved both BP and LDL-C goals was significantly greater with combination therapy compared to placebo (47.6 vs 1.7%; OR, 59.8; 95% CI, 7.4 to 486.0; *P*<0.001). Secondary: After eight weeks, the proportion of patients who achieved both BP and LDL-C goals was significantly greater with combination therapy compared to placebo (55.6 vs 5.0%; OR, 23.8; 95% CI, 6.7 to 85.0; *P*<0.001). After four and eight weeks, the proportion of patients who achieved the BP goal was significantly greater with combination therapy compared to placebo (*P*=0.001 and *P*=0.006). After four and eight weeks, the proportion of patients who achieved the LDL-C goal was significantly greater with combination therapy compared to placebo (*P*<0.001 for both). Mean reductions in SBP (13.3 vs 5.6 mm Hg) and DBP (9.4 vs 4.2 mm Hg) at week four was significantly greater with combination therapy (*P*<0.001). The mean percentage change in LDL-C (35.6 vs +3.3%) at week four was significantly greater with combination therapy (*P*<0.001). These benefits were maintained throughout eight weeks of treatment. With placebo, 10 year Framingham risk of CHD increased by 4.1% both at weeks four and eight relative to baseline. With combination therapy, the risk of future cardiac events over the next 10 years decreased by 33 and 38% at weeks four and eight, respectively, relative to baseline (*P*<0.001 vs placebo).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Preston et al[184] RESPOND Amlodipine 5 or 10 mg QD plus atorvastatin 10, 20, 40 or 80 mg QD (all possible dosing combinations) vs amlodipine 5 or 10 mg QD vs atorvastatin 10, 20, 40 or 80 mg QD vs placebo	DB, RCT Patients 18 to 75 years of age with hypertension and dyslipidemia	N=1,660 8 weeks	Primary: Mean change from baseline in SBP and LDL-C Secondary: Augmentation of BP lowering with the addition of atorvastatin and augmentation of LDL-C lowering with the addition of amlodipine, reduction in 10 year Framingham risk scores, adverse effects	Primary: Regardless of dose, combination therapy was associated with significantly greater reductions in SBP compared to atorvastatin (*P*<0.001 for all comparisons). Overall, combination therapy and atorvastatin achieved comparable decreases in LDL-C. Only the combination of amlodipine 5 mg plus atorvastatin 10 mg achieved significant reductions in LDL-C compared to atorvastatin 10 mg (*P*=0.007). Secondary: Regardless of dose, there was no difference in terms of SBP lowering between combination therapy and amlodipine (*P*>0.05 for all comparisons). Regardless of dose, combination therapy significantly reduced LDL-C compared to amlodipine (*P*<0.001 for all comparisons). A maximal reduction in 10 year Framingham risk scores was observed with combination therapy (5/80 and 10/80 mg; *P* values not reported). The proportion of patients who discontinued therapy due to adverse effects was similar with all treatments (5.6 vs 5.4 vs 4.1, respectively; *P* value not reported).
Messerli et al[185] AVALON Amlodipine 5 mg/day for 8 weeks, followed by the addition of atorvastatin 10 mg/day for another 8 weeks vs	DD, MC, OL, RCT Patients with hypertension and dyslipidemia	N=847 28 weeks	Primary: Proportion of patients who reached the JNC 7 and NCEP ATP III goals, side effects Secondary: Not reported	Primary: A significantly greater proportion of patients receiving combination therapy achieved JNC 7 and NCEP ATP goals at eight weeks compared to patients receiving amlodipine or patients receiving atorvastatin monotherapy (45.0 vs 8.3 and 28.6%, respectively; *P*<0.001). The incidence of side effects was similar across all treatments (*P* value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
atorvastatin 10 mg/day for 8 weeks, followed by the addition of amlodipine 5 mg/day for an additional 8 weeks vs amlodipine/ atorvastatin 5/10 mg/day for 16 weeks vs placebo for 16 weeks All patients received an additional 12 weeks of OL treatment following the first 16 weeks of therapy.				
Grimm et al[186] TOGETHER Amlodipine/ atorvastatin 5 to 10/20 mg/day vs amlodipine 5 to 10	DB, DD, PRO, RCT Patients ≥21 years of age with hypertension, no history of cardiovascular disease or diabetes and ≥2 of the following risk factors: age ≥45 years if male and ≥55	N=245 6 weeks	Primary: Proportion of patients achieving both BP (<140/90 mm Hg) and LDL-C (<100 mg/dL) goals Secondary: Proportion of patients achieving	Primary: The proportion of patients achieving both BP and LDL-C goals at six weeks was 67.8 vs 9.6% with combination therapy and amlodipine (risk difference, 58.2; 95% CI, 48.1 to 68.4; *P*<0.001; OR, 19.0; 95% CI, 9.1 to 39.6; *P*<0.001). Secondary: The proportion of patients achieving both BP and LDL-C goals at four weeks was 62.9 vs 5.2% (risk difference, 57.7; 95% CI, 47.9 to 67.5; *P*<0.001; OR, 31.4; 95% CI, 12.6 to 78.1; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day All patients received therapeutic lifestyle changes.	years if female; current smoker; a family history of premature CHD in a first-degree relative; HDL-C <40 mg/dL; waist circumference 102 cm if male or 88 cm if female; all patients had been previously treated with amlodipine 5 or 10 mg with either controlled or Stage 1 hypertension, fasting LDL-C ≥100 to ≤170 mg/dL		both BP and LDL-C goals at four weeks; proportion of patients achieving the BP or LDL-C goal at weeks four and six; change from baseline in SBP, DBP, LDL-C, TC, TG and HDL-C at four and six weeks; predicted 10 year Framingham risk of CHD outcomes at four and six weeks; safety	LDL-C goal was achieved by 82.8 and 7.0% (risk difference, 75.8; 95% CI, 67.4 to 84.2; *P*<0.001; OR, 65.5; 95% CI, 27.1 to 158.3; *P*<0.001) at four weeks and 83.9 and 11.3% (risk difference, 72.6; 95% CI, 63.7 to 81.5; *P*<0.001; OR, 42.0; 95% CI, 19.4 to 91.0; *P*<0.001) at six weeks. The difference in the proportions of patients achieving the BP goal at weeks four and six were not significantly different between the two treatments (four weeks; OR, 1.1; *P*=0.785 and six weeks; OR, 1.5; *P*=0.171). There were significant mean percentage reductions from baseline in LDL-C, TC and TG with combination therapy compared to amlodipine at four and six weeks (*P*<0.001 for all comparisons). There was no difference in DBP between the two treatments and no difference in SBP at week four; however, at week six improvements in SBP were significantly greater with combination therapy compared to amlodipine (*P*=0.02). In patients receiving combination therapy, the 10 year Framingham risk for CHD at baseline was 8.2% and was reduced to 5.5 and 5.4% at weeks four and six compared to amlodipine (remained unchanged, 8.1%) (*P*<0.001). After four weeks, the percentage relative reduction from baseline in the 10 year Framingham risk for CHD in patients receiving combination therapy was 39.6% compared to 0.6% with amlodipine. After six weeks, the corresponding numbers were 42.0 and 4.5% (*P*<0.001). There were no deaths or serious adverse events reported during the trial. Overall, treatment-related adverse events occurred in 9.0 and 14.8% in patients receiving combination therapy and amlodipine, respectively. The majority of events with both treatments were mild. Changes in liver function test and creatinine phosphokinase were mild to moderate.
Bays et al[187] Ezetimibe/ simvastatin 10/10, 10/20, 10/40 or 10/80	DB, MC, RCT Patients 18 to 80 years of age with primary	N=1,528 24 weeks	Primary: Percent change from baseline in LDL-C	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day vs placebo	hypercholesterolemia with LDL-C >145 but ≤150 mg/dL and TG ≤350 mg/dL		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 hsCRP; proportion of patients reaching their NCEP ATP III LDL-C goal of <130, <100 or <70 mg/dL at 12 weeks	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 hsCRP 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, 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[188] Simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe/simvastatin 10/10, 10/20, 10/40 or 10/80 mg/day vs	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, hsCRP, LDL-C:HDL-C and TC:HDL-C; proportion of patients reaching LDL-C target (<100 or <70 mg/dL) Secondary:	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, hsCRP, 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
ezetimibe 10 mg/day vs placebo			Not reported	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[189] 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	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 hsCRP; 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 hsCRP 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). 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
Farnier et al[190] Fenofibrate 160 mg/day vs ezetimibe/ simvastatin10/20	DB, MC, PA, PC, RCT Patients 18 to 79 years of age with mixed hyperlipidemia and no CHD or CHD risk equivalent disease, or a 10 year CHD risk >20%	N=611 12 weeks	Primary: Percent change from baseline in LDL-C Secondary: Changes from baseline in TC, TG, non-HDL-C, HDL-	Primary: LDL-C was significantly reduced with triple therapy (-45.8%) compared to fenofibrate (-15.7%; *P*<0.01) or placebo (-3.5%; *P*<0.01), but not when compared to combination therapy (-47.1%; *P*>0.2). Secondary: HDL-C and apo AI were significantly increased with triple therapy (18.7 and 11.1%) compared to combination therapy (9.3 and 6.6%; *P*<0.01) or placebo (1.1 and 1.6%; *P*<0.01), but not when compared to fenofibrate

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day plus fenofibrate 160 mg/day vs ezetimibe/simvastatin 10/20 mg/day vs placebo	according to NCEP ATP III criteria		C, apo AI and apo B	(18.2 and 10.8%; *P*>0.2). TG, non-HDL-C and apo B were significantly reduced with triple therapy compared to all other active treatments (-50.0, -50.5 and -44.7%; *P*<0.01, respectively).
Ballantyne et al[191] VYVA Ezetimibe/ simvastatin 10/10, 10/20, 10/40 or 10/80 mg/day vs atorvastatin 10, 20, 40 or 80 mg/day	DB, MC, PG, RCT Patients ≥18 years of age with a LDL-C at or above drug treatment thresholds established by NCEP ATP III guidelines, with CAD or CAD risk equivalent, or with ≥2 risk factors conferring a 10 year risk >20% for CHD; with LDL-C ≥130 mg/dL, no CHD or its risk equivalent, and with ≥2 risk factors conferring a 10 year risk of <20% for CHD; with LDL-C ≥160 mg/dL and no CHD or its risk equivalent with <2 risk factors; with LDL-C	N=1,902 6 weeks	Primary: Mean percent change from baseline in LDL-C Secondary: Percent change from baseline in LDL-C at each mg-equivalent statin dose comparison, percent change from baseline in HDL-C, proportion of patients achieving NCEP ATP III LDL-C goal (<100 mg/dL)	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C compared to atorvastatin (53.4 vs 45.3%; *P*<0.001). Secondary: Combination therapy (10/20 mg) was associated with a significant reduction in LDL-C compared to atorvastatin 10 (50.6 vs 36.1%; *P*<0.001) and 20 mg (50.6 vs 43.7%; *P*<0.001). Combination therapy (10/40 mg) was associated with a significant reduction in LDL-C compared to atorvastatin 40 mg (57.4 vs 48.3%; *P*<0.001). Combination therapy (10/80 mg) was associated with a significant reduction in LDL-C compared to atorvastatin 80 mg (58.6 vs 52.9%; *P*<0.001). Averaged across all doses, combination therapy was associated with a significant increase in HDL-C compared to atorvastatin (7.9 vs 4.3%; *P*<0.001). Averaged across all doses, a significantly greater proportion of patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	≥190 mg/dL, TG ≤350 mg/dL, ALT or AST <1.5 times the ULN, serum creatinine ≤1.5 mg/dL, no active liver disease, CK <1.5 times the ULN and a HbA_{1c} <9.0% in patients with diabetes			receiving combination therapy achieved the NCEP ATP III LDL-C goal compared to atorvastatin (89.7 vs 81.1%; *P*<0.001). Averaged across all doses, a significantly greater proportion of patients with a CHD or a CHD risk equivalent receiving combination therapy achieved the NCEP ATP III LDL-C goals of <100 (85.4 vs 70.0%; *P*<0.001) and <70 mg/dL (45.3 vs 20.5%; *P*<0.001) compared to atorvastatin. Averaged across all doses, combination therapy was associated with a significant increase in the risk of ALT and AST elevation greater than three times the ULN compared to atorvastatin (*P*=0.006).
Ballantyne et al[192] Ezetimibe/ simvastatin 10/20 mg/day for weeks 1 to 6, titrated to 10/40 mg for weeks 7 to 18, titrated to 10/80 mg for weeks 19 to 24 vs ezetimibe/ simvastatin 10/10 mg/day for weeks 1 to 6, titrated to 10/20 mg/day for weeks 7 to 12, titrated to 10/40 mg/day for weeks 12 to 18, titrated to 10/80 mg/day for weeks 19 to 24	DB, MC, RCT Patients ≥18 years of age with a LDL-C at or above drug treatment thresholds established by NCEP ATP III guidelines, with CAD or CAD risk equivalent, or with ≥2 risk factors conferring a 10 year risk >20% for CHD; with LDL-C ≥130 mg/dL, no CHD or its risk equivalent, and with ≥2 risk factors conferring a 10 year risk of <20% for CHD; with LDL-C ≥160 mg/dL and no CHD or its risk equivalent with <2 risk factors; with LDL-C	N=788 24 weeks	Primary: Mean percent change from baseline in LDL-C and HDL-C Secondary: Percent change from baseline to the ends of the second and fourth six week treatment periods in LDL-C and HDL-C, safety	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C compared to atorvastatin (52.4 vs 45.1%; *P*<0.001). Averaged across all doses, combination therapy was associated with a significant increase in HDL-C compared to atorvastatin (12.3 vs 6.5%; *P*<0.001). Secondary: At the end of treatment period two, combination therapy was associated with a significant reduction in LDL-C compared to atorvastatin (50.2 and 54.3 vs 44.3%, respectively; *P*≤0.05). At the end of treatment period two, combination therapy (10/40 mg) was associated with a significant increase in HDL-C compared to atorvastatin (12.4 vs 6.9%; *P*≤0.05). At the end of treatment period four, combination therapy (10/40 mg) was associated with a significant reduction in LDL-C compared to atorvastatin (59.4 vs 52.5%, respectively; *P*≤0.05). At the end of treatment period four, combination therapy (10/40 mg) was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs atorvastatin 10 mg/day for weeks 1 to 6, titrated to 20 mg/day for weeks 7 to 12, titrated to 40 mg/day for weeks 12 to 18, titrated to 80 mg/day for weeks 19 to 24	≥190 mg/dL, TG ≤350 mg/dL, ALT or AST <1.5 times the ULN, serum creatinine ≤1.5 mg/dL, no active liver disease, CK <1.5 times the ULN and a HbA_{1c} <9.0% in patients with diabetes			associated with a significant increase in HDL-C compared to atorvastatin (12.3 vs 6.5%; *P*≤0.05). The safety of combination therapy was observed to be similar to that of atorvastatin (*P* value not reported).
Foody et al[193] VYTELD Ezetimibe/ simvastatin 10/20 mg/day vs atorvastatin 10 or 20 mg/day AND ezetimibe/simvastatin 10/40 mg/day vs atorvastatin 40 mg/day	DB, MC, PG, RCT Patients ≥65 years of age with hyperlipidemia at moderately high risk or high risk (with CHD or CHD risk equivalents) with or without atherosclerotic vascular disease with LDL-C ≥130 mg/dL, TC ≤350 mg/dL, liver transaminases ≤1.5 times the ULN with no active liver disease and creatinine kinase ≤2 times ULN	N=1,289 12 week	Primary: Percent change from baseline in LDL-C Secondary: Proportion of patients achieving an LDL-C <70 and <100 mg/dL; percent change from baseline in TC, TG, HDL-C, non-HDL-C, VLDL-C, apo B, apo AI, TC:HDL-C, LDL-C:HDL-C, apo B:apo AI, non-HDL-C:HDL-C and hsCRP; safety	Primary: Combination therapy achieved significantly greater percent decreases in LDL-C (-54.2 [10/20 mg] vs -39.5 [10 mg] and -46.6% [20 mg] and -59.1 [10/40 mg] vs -50.8% [40 mg]; *P*<0.001 for all). Secondary: A significantly greater proportion of combination therapy-treated patients achieved an LDL-C goal <70 mg/dL (51.3 [10/20 mg] and 68.2% [10/40mg]; *P*<0.05) and <100 mg/dL (83.6 and 90.3%; *P*<0.001). Analysis based on risk demonstrated that a significantly greater proportion of high risk patients reached target LDL-C levels <70 mg/dL with combination therapy compared to atorvastatin (*P*<0.001 for all comparisons). Combined analysis of LDL-C level attainment based on atherosclerotic vascular disease status (<100 mg/dL for patients without atherosclerotic vascular disease and <70 mg/dL for patients with atherosclerotic vascular disease) demonstrated that a significantly greater proportion of patients reached the specified target with combination therapy compared to atorvastatin (*P*<0.001 for ezetimibe/simvastatin 10/20 mg vs atorvastatin 10 mg, *P*<0.05 for ezetimibe/simvastatin 10/20 vs atorvastatin 20 mg and ezetimibe/simvastatin 10/40 mg vs atorvastatin 40 mg).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Improvements in non-HDL-C, TC, apo B and lipoprotein ratios were significantly greater with combination therapy (*P*<0.01 to *P*<0.001). Only ezetimibe/simvastatin 10/20 mg significantly improved HDL-C (*P*<0.001) levels compared to atorvastatin 20 mg and TG (*P*<0.01) and VLDL-C (*P*<0.05) levels compared to atorvastatin 10 mg. Improvements in apo AI and hsCRP levels did not differ among the various treatments (*P* values not reported). All doses of ezetimibe/simvastatin and atorvastatin were generally safe and well tolerated. The incidence of adverse events was similar between treatment groups. There were no serious drug-related adverse events observed during the trial.
Polis et al[194] Ezetimibe/ simvastatin 10/10, 10/20, 10/40 or 10/80 mg/day vs atorvastatin 10, 20, 40 or 80 mg/day or rosuvastatin 10, 20 or 40 mg/day	Post hoc analysis of VYVA and Catapano et al[152,161] Patients with hypercholesterolemia not attaining NCEP ATP III LDL-C goals in patients with diabetes, metabolic syndrome or neither disease	N=4,861 6 weeks	Primary: Percent change from baseline in LDL-C, proportion of patients achieving individual LDL-C goals Secondary: Safety	Primary: Changes in LDL-C were generally similar regardless of diabetes/metabolic syndrome status or CHD risk strata in both trials. There was a significant effect by dose level in both trials in all condition and risk subgroups (*P*<0.001), with greater reductions observed with higher doses. NCEP ATP III LDL-C goal attainment was lowest in the high risk group with atherosclerotic vascular disease (12 to 64%) and greatest in the moderate and low risk groups (84 to 100%). Secondary: All treatments were generally well tolerated, with overall similar safety regardless of disease and risk level.
Bardini et al[195] LEAD Ezetimibe/ simvastatin 10/20 mg/day vs simvastatin 40	DB, DD, MC, PG, RCT Patients 18 to 75 years of age with type 2 diabetes for ≥12 months and documented CHD, or symptomatic peripheral vascular	N=93 6 weeks	Primary: Percent change from baseline in LDL-C Secondary: Proportion of patients achieving LDL-C <100 mg/dL; percent	Primary: Combination therapy produced a significantly greater reduction in LDL-C compared to simvastatin 40 mg (-32.2 vs -20.8%; *P*<0.01). Secondary: A nonsignificantly greater proportion of patients receiving combination therapy achieved an LDL-C <100 mg/dL (78.4 vs 60.0%; OR, 2.81; *P*=0.052). Combination therapy produced a significantly greater change compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day	disease, who were taking a stable dose of simvastatin 20 mg/day for 6 weeks with good compliance and LDL-C ≥100 to ≤160 mg/dL		change from baseline in TC, HDL-C and TG	simvastatin 40 mg in TC (-20.6 vs -13.2%; *P*<0.01). Changes in HDL-C (0.85 vs 0.80%) and TG (-8.5 vs -1.8%) were similar between treatments (*P* values not reported).
Florentin et al[196] Ezetimibe/ simvastatin 10/10 mg/day vs simvastatin 40 mg/day	OL, RCT Patients with primary hypercholesterolemia with LDL-C levels above those recommended by the NCEP ATP III	N=100 3 months	Primary: Percent change from baseline in small density LDL-C Secondary: Percent change from baseline in lipid parameters, HOMA index and hsCRP	Primary: Both treatments decreased small density LDL-C (-42 vs -46%; *P*<0.000 vs baseline for both), with no significant difference between the two treatments (*P* value not reported). Secondary: Both treatments decreased TC (-31 vs -36%), LDL-C (-43 vs -49%), TG (-17 vs -19%), non-HDL-C (-40 vs -46%) and large LDL-C (-40 vs -44%) (*P*<0.000 vs baseline for all). Both treatments increased LDL particle size (0.5 vs 0.7%; *P*<0.05 vs baseline for both). Changes in TC, LDL-C and non-HDL-C were significantly greater with combination therapy (*P*<0.05 for all), while changes in TG, large LDL-C, and LDL particle size were similar (*P* values not reported). No significant changes were observed in HOMA index with either treatment, and hsCRP decreased by 23% (*P*<0.05 vs baseline) with both treatments.
Rotella et al[197] Ezetimibe/ simvastatin 10/20 mg/day vs simvastatin 40 mg/day	2 DB, MC, RCT Patients ≥18 to ≤75 years of age with documented CHD or symptomatic peripheral vascular disease, who were taking a stable dose of simvastatin 20 mg/day for 6 weeks with good	N=93 6 weeks	Primary: Percentage change from baseline in LDL-C; proportion of patients who achieved an LDL-C goal <100 mg/dL Secondary: Safety	Primary: Combination therapy resulted in significantly greater reductions in LDL-C, TC and TC:HDL-C (*P*<0.01 for all); and significantly more patients treated with combination therapy achieved the LDL-C goal <100 mg/dL (*P*<0.01). Secondary: There was no significant difference in the proportion of patients who reported adverse events between the two treatments (*P*=0.606). No significant differences between groups were observed in the number and rate of drug related adverse events, which were reported in 9.8 and 6.3% of patients treated with combination therapy and simvastatin 40 mg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	compliance			(*P*=0.500). There were few discontinuations due to treatment-related adverse events.
Farnier et al[198] IN-CROSS Ezetimibe/ simvastatin 10/20 mg/day vs rosuvastatin 10 mg/day	AC, DB, MC, PG, RCT Patients 18 to 80 years of age with hypercholesterolemia (LDL-C ≥100 and ≤190 mg/dL) and high cardiovascular risk who were taking a stable dose of none of the following statin medications for ≥6 weeks prior to trial randomization: atorvastatin (10 or 20 mg), fluvastatin (80 mg), pravastatin (40 mg), rosuvastatin (5 mg) or simvastatin (20 or 40 mg)	N=618 6 weeks	Primary: Percent change from baseline in LDL-C, HDL-C, non-HDL-C, TC, TG and apo B; proportion of patients achieving LDL-C <100 and <70 mg/dL Secondary: Adverse events	Primary: Combination therapy achieved greater reductions in LDL-C (27.7 vs 16.9%; *P*≤0.001), TC (17.5 vs 10.3%; *P*≤0.001), non-HDL-C (23.4 vs 14.0%; *P*≤0.001) and apo B (17.9 vs 9.8%; *P*≤0.001) compared to rosuvastatin. Both treatments achieved similar increases in HDL-C (2.1 vs 3.0%; *P*=0.433) and decreases in TG (11.0 vs 5.3%; *P*=0.056). A significantly greater proportion of patients receiving combination therapy achieved an LDL-C <100 (73 vs 56%) and <70 mg/dL (25 vs 11%) (*P*≤0.001 for both). Secondary: There were no between-group differences in the incidences of adverse events or liver transaminase and CK elevations (*P* values not reported).
Viigimaa et al[199] Ezetimibe/ simvastatin 10/20 mg/day vs rosuvastatin 10 mg/day	Post hoc analysis of Farnier et al[1159] Patients 18 to 80 years of age with hypercholesterolemia (LDL-C ≥100 and ≤190 mg/dL) and high cardiovascular risk who were taking a stable dose of none of the following statin medications for ≥6	N=618 6 weeks	Primary: Changes from baseline in lipid parameters stratified by statin potency prior to randomization; proportion of patients achieving LDL-C <100, <77 or <70 mg/dL; non-HDL-C <130 or <100 mg/dL; apo B	Primary: Significant treatment-by-subgroup interaction occurred for LDL-C (*P*=0.013), TC (*P*=0.025), non-HDL-C (*P*=0.032) and apo B (*P*=0.016) with greater between-treatment differences in favor of combination therapy observed in patients who were previously treated with a high potency statin vs a low potency. Individual and triple target attainment was higher with combination therapy compared to rosuvastatin in patients previously treated with a high or low potency statin (*P* values not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	weeks prior to trial randomization: atorvastatin (10 or 20 mg), fluvastatin (80 mg), pravastatin (40 mg), rosuvastatin (5 mg) or simvastatin (20 or 40 mg)		<90 or <80 mg/dL and LDL-C <100 mg/dL, non-HDL-C <130 mg/dL and apo B <90 mg/dL Secondary: Not reported	
Catapano et al[200] Ezetimibe/ simvastatin 10/20, 10/40 or 10/80 mg/day vs rosuvastatin 10, 20 or 40 mg/day	DB, MC, PG, RCT Patients 18 to 81 years of age with LDL-C ≥145 and ≤250 mg/dL; TG ≤350 mg/dL; ALT, AST and CK level <1.5 times the ULN, serum creatinine ≤1.5 mg/dL and HbA_{1c} <9.0% in patients with diabetes	N=2,959 6 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent changes from baseline in LDL-C at various dose comparisons, HDL-C, TC, apo B, TG, non-HDL-C, LDL-C:HDL-C, TC:HDL-C and hsCRP; proportion of patients who achieved an LDL-C goal <100, <130 or <160 mg/dL; safety	Primary: At all doses, combination therapy significantly reduced LDL-C compared to rosuvastatin (52 to 61 vs 56 to 57%; *P*≤0.001). Secondary: Significantly greater reductions in LDL-C with combination therapy were achieved with the 10/20 (*P*<0.001), 10/40 (*P*=0.001) and 10/80 mg (*P*<0.001) compared to rosuvastatin. Combination therapy produced significantly greater reductions in TC (*P*<0.001), non-HDL-C (*P*<0.001), all lipid ratios (*P*≤0.003), TG (*P*<0.001) and apo B (*P*<0.05) compared to rosuvastatin. Increases in HDL-C and decreases in hsCRP were similar between the two treatments (*P* values not reported). Significantly greater proportions of all patients (*P*<0.001) and high risk patients (*P*≤0.005) attained an LDL-C goal <70 mg/dL with combination therapy compared to rosuvastatin across all doses. Safety profiles were comparable between the two treatments. The percent of patients with proteinuria was significantly higher with rosuvastatin compared to combination therapy at doses of 10 vs 10/20 mg (*P*=0.004) and 40 vs 10/80 mg (*P*<0.001).
Fazio et al[201] Ezetimibe/ simvastatin 10/ 20	DB, MC, RCT Patients 18 to 79 years of age with	N=942 64 weeks	Primary: Safety and tolerability of ezetimibe/	Primary: The most frequent reason for discontinuation was clinical adverse events related to niacin-associated flushing with ezetimibe/simvastatin plus niacin (0.7% for ezetimibe/simvastatin vs 10.3% for ezetimibe/simvastatin plus

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day plus niacin ER 2 g/day vs niacin ER 2 g/day vs ezetimibe/simvastatin 10/ 20 mg/day At the end of 24 weeks, patients receiving niacin ER were rerandomized to either one of the other 2 treatment regimens.	hyperlipidemia (Types IIa and IIb) with LDL-C 130 to 190 mg/dL, TG ≤500 mg/dL, creatinine <2 mg/dL, creatine kinase ≤2 times the ULN, transaminases ≤1.5 times the ULN and HbA_{1c} ≤8.0%		simvastatin plus niacin ER Secondary: Changes in HDL-C, TG, non-HDL-C and LDL-C	niacin). A significant number of patients receiving ezetimibe/simvastatin plus niacin discontinued because of low LDL-C levels <50 mg/dL (1.5 vs 7.1%). The overall incidence of clinical adverse events was slightly greater for ezetimibe/simvastatin plus niacin compared to ezetimibe/simvastatin owing to the greater number of patients who experienced drug-related clinical adverse events and drug-related discontinuations with ezetimibe/simvastatin plus niacin, mainly attributed to niacin-associated flushing and pruritis. The percentage of patients with consecutive elevations in ALT or AST of at least three times or greater the ULN, and creatine kinase of at least ten times or greater the ULN were low and comparable between treatments. A total of 19 patients had adverse events of increased FPG levels, with eight receiving ezetimibe/simvastatin and 11 receiving ezetimibe/simvastatin plus niacin. Secondary: Ezetimibe/simvastatin plus niacin significantly improved baseline HDL-C, TG, non-HDL-C, LDL-C, apo B, apo A-I and Lp ratios compared to ezetimibe/simvastatin at week 64 (*P*<0.004). The changes in TC were comparable between the two treatment groups and the reduction in hsCRP was numerically greater with ezetimibe/simvastatin plus niacin (*P* value not reported). Ezetimibe/simvastatin plus niacin increased HDL-C considerably during the first 16 weeks of treatment, and at a lower, but significant, rate from 16 to 24 weeks, and then remained constant throughout 64 weeks. The HDL-C change was significantly greater with ezetimibe/simvastatin plus niacin vs ezetimibe/simvastatin throughout the 64 weeks (*P*<0.001). The reductions in LDL-C, non-HDL-C and TG observed after four weeks with ezetimibe/simvastatin plus niacin were maintained throughout the 64 weeks. In contrast, the levels remained relatively stable with ezetimibe/simvastatin throughout the 64 weeks (*P*<0.001) and became significant for non-HDL-C after eight weeks

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				(*P*=0.002) and LDL-C after 12 weeks (*P*<0.001).
Fazio et al[202] Ezetimibe/ simvastatin 10/ 20 mg/day plus niacin ER 2 g/day vs niacin ER 2 g/day vs ezetimibe/simvastatin 10/ 20 mg/day At the end of 24 weeks, patients receiving niacin ER were rerandomized to either one of the other 2 treatment regimens.	Subgroup analysis of Fazio et al[195] Hyperlipidemic patients with diabetes mellitus, metabolic syndrome without diabetes mellitus or neither	N=765 at 24 weeks N=574 at 64 weeks	Primary: Changes in HDL-C, TG, non-HDL-C, LDL-C, fasting glucose and uric acid Secondary: Not reported	Primary: The effect of triple therapy on efficacy variables across patient subgroups was generally consistent with the significantly greater improvements observed in the total population compared to niacin and combination therapy. Triple therapy improved levels of LDL-C, other lipids and Lp ratios compared to niacin and combination therapy at 24 and 64 weeks. Triple therapy also increased HDL-C and Lp(a) comparably to niacin and more than combination therapy. Triple therapy also decreased hsCRP more effectively than niacin and comparably to combination therapy. Fasting glucose trended higher for niacin compared to combination therapy. Glucose elevations from baseline to 12 weeks were highest for patients with diabetes (niacin, 24.9 mg/dL; triple therapy, 21.2 mg/dL and combination therapy, 17.5 mg/dL). Fasting glucose levels then declined to pretreatment levels at 64 weeks in all subgroups. New onset diabetes was more frequent among patients with metabolic syndrome than those without for the first 24 weeks and trended higher among those receiving niacin (niacin, 5.1%; combination therapy, 1.7% and triple therapy, 8.8%). Between weeks 24 and 64, five and one additional patient(s) receiving combination (cumulative incidence, 5.9%) and triple therapy (cumulative incidence, 9.2%) were diagnosed with diabetes. Treatment-incident increases in uric acid were higher among patients receiving niacin, but there were no effects on symptomatic gout. Secondary: Not reported
Karas et al[203] OCEANS <u>Group A:</u> Niacin	AC, MC, OL, PG, Phase III, RCT Patients ≥21 years of age with a diagnosis	N=641 24 weeks	Primary: Group A: mean percent change in non-HDL-C	Primary: In Group A, the mean percent changes in non-HDL-C at 24 weeks were significantly greater with niacin ER/simvastatin 1,000/20 and 2,000/20 mg than with simvastatin 20 mg (-13.6 and -19.5 vs -5.0%, respectively; *P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
ER/simvastatin 2,000/20 or 1,000/20 mg/day vs simvastatin 20 mg/day <u>Group B:</u> Niacin ER/simvastatin 1,000/40 or 2,000/40 mg/day vs simvastatin 80 mg/day All simvastatin monotherapy patients received niacin IR 50 mg/day to prevent unblinding due to flushing. All patients were instructed to take aspirin or ibuprofen to minimize flushing.	of primary type II hyperlipidemia or mixed dyslipidemia, proof of reasonable compliance with a standard cholesterol lowering diet for 4 weeks before screening and for the duration of the trial, and LDL and/or non-HDL levels above normal		Group B: non-inferiority of niacin ER/simvastatin 2,000/40 mg to simvastatin 80 mg in mean percent change in non-HDL Secondary: Mean percent change in LDL-C, TG and HDL-C	In Group B, the mean percent change in non-HDL-C at 24 weeks with niacin ER/simvastatin 2,000/40 mg was non-inferior to that of simvastatin 80 mg (-7.6 vs -6.0%; 95% CI, -7.7 to 4.5). Similar results were obtained in non-inferiority comparisons between niacin ER/simvastatin 1,000/40 mg and simvastatin 80 mg (-6.7 vs -6.0%; 95% CI, -6.6 to 5.3). Secondary: In Group A, the mean percent change in LDL-C at 24 weeks with niacin ER/simvastatin 1,000/20 and 2,000/20 mg were non-superior to simvastatin 20 mg (-11.9 and -14.3 vs -6.7%, respectively) (*P* value not provided). However, mean percent reduction in TG and mean percent increase in HDL-C with niacin ER/simvastatin 1,000/20 and 2,000/20 mg were "superior" to simvastatin 20 mg (TG, -26.5 and -38 vs -15.3%, respectively, HDL, 20.7 and 29% vs 7.8%, respectively) (*P* values not provided).
Ballantyne et al[204] SEACOAST 1 Niacin	AC, DB, MC, RCT High risk patients with primary or mixed	N=319 24 weeks	Primary: Percentage change from baseline in non-HDL-C	Primary: Combination therapy achieved significant improvements in non-HDL-C. Median change from baseline at week 24 in non-HDL-C was -13.9, -22.5 (*P*<0.01) and -7.4% (*P*<0.001) for niacin ER/simvastatin 1,000/20 mg/day,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
ER/simvastatin 1,000/20 or 2,000/20 mg/day vs simvastatin 20 mg/day All simvastatin monotherapy patients received niacin IR 50 mg/day to prevent unblinding due to flushing.	dyslipidemia		Secondary: Percent change from baseline in LDL-C, HDL-C, TC/HDL-C, TG, apo B and apo AI	niacin ER/simvastatin 2,000/20 mg/day and simvastatin. Secondary: Combination therapy was associated with nonsignificant additional decreases in LDL-C compared to simvastatin. Both combination therapy regimens had significantly greater decreases in TG, Lp(a), apo B and TC:HDL-C (*P* values not reported). Combination therapy also achieved significant increases in HDL-C and apo AI/apo B.
Charland et al[205] High potency dyslipidemia pharmacotherapy (niacin ER/lovastatin, niacin ER/simvastatin, rosuvastatin and ezetimibe/simvastatin	MA (120 unique reports) Patients with hyperlipidemia	N=43,974 Duration varied (≥4 weeks)	Primary: Percent change from baseline in lipid parameters, cardiovascular events Secondary: Not reported	Primary: All of the high potency therapies lowered LDL-C by ≥45%, with the higher doses of ezetimibe/simvastatin and rosuvastatin achieving the greatest LDL-C reduction of -60 and -54%, respectively. In general, percent lipid changes for ezetimibe/simvastatin and rosuvastatin increased in a significant dose dependent manner for TC and LDL-C. With niacin-containing therapies, percent changes in these parameters were flat, and no significant differences between moderate and high doses were observed. Ezetimibe/simvastatin and rosuvastatin did not demonstrate a significant difference in percent change in HDL-C throughout the doses evaluated. Non-niacin-containing therapies appeared to have a flat dose response curve, with weighted percent HDL-C changes between 5 and 9%. Niacin-containing therapies achieved a significant dose response effect. There was no significant difference in percent change in TG with any dose for ezetimibe/simvastatin or rosuvastatin (5, 20 and 40 mg/day). Niacin-containing therapies also demonstrated greater weighted percent changes

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				in TG lowering (-40%) compared to ezetimibe/simvastatin or rosuvastatin (-31 and -24%). In evaluating percent changes in TC between the therapies there was no significant difference between rosuvastatin 40 mg, ezetimibe/simvastatin 10/80 mg and niacin ER/simvastatin. For LDL-C, there were significant differences between many of the therapies at various doses of rosuvastatin, ezetimibe/simvastatin, niacin ER/lovastatin and niacin ER/simvastatin; however, there was no significant difference in percent change in LDL-C between rosuvastatin 40 mg, ezetimibe/simvastatin 10/40 or 10/80 mg or niacin ER/simvastatin 2,000/40 mg. All of the high-potency therapies are predicted to reduce cardiovascular event rates by >50%, except for the lowest dose of ezetimibe/simvastatin (10/10 mg) and niacin ER/lovastatin (500/20 mg). There was no significant difference in predicted event risk reduction between the largest dose of niacin ER/lovastatin (2,000/40 mg) and niacin ER/simvastatin (2,000/40 mg); however, there was a significant difference in predicted event reduction between either of the highest doses of niacin ER/lovastatin (2,000/40 mg) and niacin ER/simvastatin (2,000/40 mg) compared to all of the doses of rosuvastatin or ezetimibe/simvastatin. The average percent cardiovascular event reduction for ezetimibe/simvastatin, rosuvastatin, niacin ER/lovastatin and niacin ER/simvastatin was 60, 58, 61 and 72%, respectively. Secondary: Not reported
Adverse Events				
Newman et al[206] Atorvastatin 10 or 80 mg QD vs	MA (42 trials) Patients with various cardiovascular risks, LDL-C ≥130 mg/dL and TG ≤600 mg/dL	N=14,236 2 weeks to 52 months	Primary: Adverse effects Secondary: Not reported	Primary: Treatment-related side effects were similar between treatments (*P* value not reported). Treatment-associated myalgia was observed in 1.4, 1.5 and 0.7% of patients receiving atorvastatin 10 mg, 80 mg and placebo, respectively (*P* value not reported). No cases of rhabdomyolysis were reported with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
placebo				atorvastatin or placebo (*P* value not reported). Elevations in hepatic transaminases at least three times the ULN were observed in 0.1, 0.6 and 0.2% of patients receiving atorvastatin 10 mg, 80 mg and placebo, respectively (*P* value not reported). Secondary: Not reported
Shepherd et al[207] Rosuvastatin 5 to 40 mg QD vs atorvastatin 10 to 80 mg QD vs simvastatin 10 to 80 mg QD vs pravastatin 10 to 40 mg QD vs placebo	MA (33 RCTs) Patients with dyslipidemia	N=16,876 25,670 patient-years	Primary: Adverse events, elevation in transaminases, CK, myopathy, dipstick-positive proteinuria, estimated glomerular rate Secondary: Not reported	Primary: The incidence of adverse events was similar with rosuvastatin and placebo (52.1 vs 51.8%, respectively; *P* value not reported). The incidence of adverse events was similar across all the active treatments (*P* value not reported). The incidence of elevation in transaminases and CK, myopathy, dipstick-positive proteinuria and estimated glomerular rate was similar across all the active treatment groups (*P* value not reported). Secondary: Not reported
Silva et al[208] Statins (atorvastatin, pravastatin,	MA (18 PRO, RCTs) Patients receiving statin therapy or	N=71,108 Up to 317 weeks	Primary: Adverse events, cardiovascular events	Primary: Statin therapy significantly increased the risk of any adverse events by 39% compared to placebo (OR, 1.4; 95% CI, 1.09 to 1.80; *P*=0.008). Consequently, out of 197 statin-treated patients, one patient would

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
simvastatin, lovastatin, fluvastatin, rosuvastatin) vs placebo	placebo		Secondary: Not reported	experience an adverse event (95% CI, 24 to 37; *P* value not reported). Statin therapy was associated with a significant 26% reduction in the risk of a clinical cardiovascular event compared to placebo (OR, 0.74; 95% CI, 0.69 to 0.80; *P*<0.001). Consequently, the NNT to prevent one additional cardiovascular event was 27. Rosuvastatin trials were not included in the analysis of cardiovascular risk reduction due to inadequate data. The incidence of adverse effects during statin administration was observed in the following order, from highest to lowest: atorvastatin >pravastatin=simvastatin=lovastatin>fluvastatin. Secondary: Not reported
Kashani et al[209] Statins (atorvastatin 20 to 80 mg/day, fluvastatin 2.5 to 80 mg/day, lovastatin 10 to 80 mg/day, pravastatin 10 to 160 mg/day, rosuvastatin 1 to 80 mg/day, simvastatin 2.5 to 80 mg/day) vs placebo	MA (35 DB, RCTs) Patients ≥18 years of age with hyperlipidemia	N=74,102 Up to 65 months	Primary: Adverse events (myalgia, CK elevation, rhabdomyolysis, transaminase elevation), discontinuation due to adverse event Secondary: Not reported	Primary: Statin therapy was associated with a nonsignificant increase in the risk of myalgias (risk difference, 2.7; 95% CI, -3.2 to 8.7; *P*=0.37), CK elevation (risk difference, 0.2; 95% CI, -0.6 to 0.9; *P*=0.64), rhabdomyolysis (risk difference, 0.4; 95% CI, -0.1 to 0.9; *P*=0.13) or discontinuation due to adverse events (risk difference, -0.5; 95% CI, -4.3 to 3.3; *P*=0.80) compared to placebo. Statin therapy was associated with a significant risk of transaminase elevations (risk difference, 4.2; 95% CI, 1.5 to 6.9; *P*<0.01) compared to placebo. When individual statins were compared to placebo, atorvastatin was the only statin with a significant increase in the risk of myalgias (*P*=0.04). When individual statins were compared to placebo, fluvastatin (*P*<0.01) and lovastatin (*P*=0.05) were the only statins with a significant increase in the risk of transaminase elevations. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
McClure et al[210] Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin), stratified by ≤40 mg and >40 mg/day lovastatin equivalent dose vs placebo	MA (119 DB, RCTs) Patients ≥18 years of age with hyperlipidemia	N=86,000 Up to 65 months	Primary: Adverse events (myalgia, myositis, rhabdomyolysis), discontinuations due to adverse events Secondary: Not reported	Primary: Statin therapy was associated with a nonsignificant increase in the risk of myalgias (OR, 1.09; 95% CI, 0.97 to 1.23; *P*=0.471), rhabdomyolysis (OR, 1.59; 95% CI, 0.54 to 4.70; *P*=0.544) or myositis (OR, 2.56; 95% CI, 1.12 to 5.85; *P*=0.987) compared to placebo. Statin therapy was associated with a significantly lower incidence of discontinuations due to adverse events (OR, 0.88; 95% CI, 0.84 to 0.93; *P*<0.001) compared to placebo. Secondary: Not reported
Law et al[211] Statins (lovastatin, atorvastatin, pravastatin, simvastatin, fluvastatin) vs placebo	SR (2 cohort studies and 21 PC, RCTs) Patients receiving statin therapy or placebo	N=not reported Up to 6.1 years	Primary: Incidence of rhabdomyolysis, myopathy, renal failure, elevated ALT, renal failure, proteinuria and peripheral neuropathy Secondary: Not reported	Primary: The incidence of rhabdomyolysis associated with the use of statins in two cohort and RCTs was 3.4 (95% CI, 1.6 to 6.5) per 100,000 patient-years (*P* value not reported). The incidence of rhabdomyolysis associated with the use of statins in addition to gemfibrozil in two cohort studies was 35 (95% CI, 1 to 194) per 100,000 patient-years (*P* value not reported). The notification of rhabdomyolysis to the FDA adverse events reporting system was approximately four times higher in patients receiving lovastatin, simvastatin or atorvastatin compared to those receiving fluvastatin or pravastatin (*P*<0.001). The notification of rhabdomyolysis to the FDA adverse events reporting system was approximately 15 times higher in patients receiving statins in combination with gemfibrozil (21 per 100,000 patient-years; 95% CI, 17 to 25) compared to those receiving statin therapy (0.70 per 100,000 patient-years; 95% CI, 0.62 to 0.79; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				The incidence of myopathy associated with the statin therapy in RCTs was five (95% CI, -17 to 27) per 100,000 patient-years (*P* value not reported). The incidence of liver failure associated with statin therapy, reported to the FDA adverse events reporting system, was 0.1 per 100,000 patient-years of use (*P* value not reported). Statin therapy in patients with elevated ALT would lead to liver disease in less than one person (*P* value not reported). Statin therapy was not associated with a higher incidence of renal failure or proteinuria compared to placebo (*P* value not reported). Patients receiving statin therapy have 1.8 odds of experiencing peripheral neuropathy compared to placebo (95% CI, 1.1 to 3.0; *P*<0.001). Secondary: Not reported
Dale et al[212] Intensive statin therapy; hydrophilic (atorvastatin 80 mg/day) and lipophilic statins (simvastatin 40 to 80 mg/day, lovastatin 76 mg/day) vs moderate statin therapy; hydrophilic (atorvastatin 10 mg/day, pravastatin 40 mg/day) and lipophilic statins (simvastatin 20 to 40	MA (9 RCTs) Patients receiving statin therapy	N=21,765 Up to 5 years	Primary: Incidence of elevations in AST, ALT or CK Secondary: Not reported	Primary: Intensive statin therapy was associated with a significant increased risk of AST or ALT elevation compared to the moderate statin therapy (1.5 vs 0.4%; RR, 3.10; 95% CI, 1.72 to 5.58; *P*=0.002). Intensive statin therapy was associated with a nonsignificant risk of CK elevation compared to the moderate statin therapy (0.10 vs 0.02%; RR, 2.63; 95% CI, 0.88 to 7.85; *P*=0.89). In a subanalysis of hydrophilic and lipophilic statins, while no cases of CK elevation occurred in the hydrophilic intensive statin group, patients on lipophilic intensive statin therapy experienced a nonsignificant risk in CK elevation (RR, 6.09; 95% CI, 1.36 to 27.35; *P*≥0.11). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day, lovastatin 4 mg/day)				
Silva et al[213] Intensive statin therapy (atorvastatin 80 mg/day, simvastatin 80 mg/day) vs moderate statin therapy (atorvastatin 10 mg/day, simvastatin 20 mg/day, pravastatin 40 mg/day)	MA (4 RCTs) Patients with ACS or stable CAD receiving statins for the reduction of secondary cardiovascular events	N=27,548 3.4 years	Primary: CK ≥10 times the ULN, with or without myalgia; ALT or AST ≥3 times the ULN; rhabdomyolysis; drug-induced adverse effects requiring drug discontinuation; any drug-induced adverse event; all-cause mortality; cardiovascular death; nonfatal MI; and stroke Secondary: Not reported	Primary: Intensive statin therapy was associated with a significant increased risk of any adverse event compared to moderate statin therapy (OR, 1.44; 95% CI, 1.33 to 1.55; *P*<0.001). Consequently, out of 30 patients treated with intensive statin therapy, one patient would experience an adverse event (95% CI, 24 to 37; *P* value not reported). Intensive statin therapy was associated with a significant increased risk (absolute risk, 2.14%) of an adverse drug event requiring discontinuation of drug therapy (OR, 1.28; 95% CI, 1.18 to 1.39; *P*≤0.001). Intensive statin therapy was associated with a significant increased risk (absolute risk, 1.2%) of an elevation in AST and ALT at least three times the ULN (OR, 4.84; 95% CI, 3.27 to 6.16; *P*≤0.001). Consequently, out of 86 patients treated with intensive statin therapy, one patient would experience an elevation in AST and ALT at least three times the ULN (95% CI, 72 to 106; *P* value not reported). Intensive statin therapy was associated with a significant increased risk (absolute risk, 0.07%) of an elevation in CK ≥10 times the ULN (OR, 9.97; 95% CI, 1.28 to 77.92; *P*=0.028). Consequently, out of 1,534 patients treated with intensive statin therapy, one patient would experience an elevation in CK ≥10 times the ULN (*P* value not reported). There was no difference in the incidence of rhabdomyolysis between the treatments (*P* value not reported). Intensive statin therapy was associated with a nonsignificant reduction in all-cause mortality compared to moderate-dose statin therapy (*P*=0.185). Intensive statin therapy was associated with a significant reduction in the risk for cardiovascular death (*P*=0.031), nonfatal MI (*P*<0.001) and stroke (*P*=0.004). Consequently, the NNT to prevent one additional cardiovascular death, MI or stroke was 229, 99 and 166, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, DR=delayed-release, ER=extended-release, IR=immediate-release, QD=once-daily, SR=sustained-release, TID=three times daily
Study abbreviations: AC=active comparator, ARR=absolute risk reduction, CI=confidence interval, DB=double=blind, DD=double dummy, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NNT=number needed to treat, OL=open label, OR=odds ratio, PA=parallel arm, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized control trial, RETRO=retrospective, RR=relative risk, RRR=relative risk reduction, SE=standard error, SR=systematic review, XO=cross-over
Miscellaneous abbreviations: ACS=acute coronary syndrome, ALT=alanine aminotransferase, apo=apolipoprotein, AST=aspartate aminotransferase, BMI=body mass index, BNP=B-type natriuretic peptide, BP=blood pressure, CABG=coronary artery bypass graft, CAD=coronary artery disease, CHD=coronary heart disease, CHF=congestive heart failure, CIMT=carotid intima-media thickness, CK=creatine kinase, CKD=chronic kidney disease, CPK=creatine phosphokinase, DBP=diastolic blood pressure, EAS= European Atherosclerosis Society, ECG=electrocardiogram, eGFR=estimated glomerular filtration rate, FDA=Food and Drug Administration, FH=familial hypercholesterolemia, FPG=fasting plasma glucose, GFR=glomerular filtration rate, HAART=highly active antiretroviral therapy, HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, HIV=human immunodeficiency virus, HOMA=homeostatic model assessment, hsCRP=high-sensitivity C-reactive protein, IMT=intima-media thickness, IU=international units, JNC 7=Joint National Committee 7, LDL-C=low-density lipoprotein cholesterol, Lp(a)=lipoprotein(a), MI=myocardial infarction, NCEP ATP=National Cholesterol Education Program Adult Treatment Panel, NYHA=New York Heart Association, PAV=percent atheroma volume, PCI=percutaneous coronary intervention, SBP=systolic blood pressure, STEMI=ST-segment elevation myocardial infarction, TAV=total atheroma volume, TC=total cholesterol, TG=triglyceride, TIA=transient ischemic attack, ULN=upper limit of normal, VLDL-C=very low-density lipoprotein cholesterol, VTE=venous thromboembolism

Special Populations

Table 5. Special Populations[3-16,22]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single-Entity Agents					
Atorvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children 10 to 17 years of age for the treatment of heterozygous familial hyper-cholesterolemia. Safety and efficacy in children <10 years of age have not been established.	No dosage adjustment required.	Contraindicated in active liver disease or in patients with unexplained persistent elevations or serum transaminases.	X	Unknown; not re-commended.
Fluvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children 10 to 16 years of age for the treatment of heterozygous familial hyper-cholesterolemia (Lescol®, Lescol XL®). Safety and efficacy in children for other approved indications have not been established.	No dosage adjustment required in mild to moderate renal dysfunction. Use with caution in severe renal dysfunction.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases. Use with caution in severe hepatic dysfunction or heavy ethanol ingestion.	X	Yes (% not reported); not re-commended.
Lovastatin	No dosage adjustment required in the elderly. Approved for use in children 10 to 17	Renal dosage adjustment is required; for creatinine clearances <30	No dosage adjustment required.	X	Unknown; not re-commended.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	years of age for the treatment of heterozygous familial hyper-cholesterolemia (Mevacor®). Safety and efficacy in children <10 years of age have not been established (Mevacor®). Safety and efficacy in children have not been established (Altoprev®).	mL/minute, use with caution and carefully consider doses >20 mg/day.			
Pitavastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Renal dosage adjustment is required; for creatinine clearances 30 to 60 mL/ minute or end-stage renal disease, an initial dose of 1 mg once daily and a maximum dose of 2 mg/day is re-commended Not re-commended for creatinine clearances <30 mL/ minute with no hemodialysis.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	X	Unknown; not re-commended.
Pravastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children eight to 18 years of age for the	Renal dosage adjustment is required; an initial dose of 10 mg/day is re-commended.	Hepatic dosage adjustment is required; an initial dose of 10 mg/day is recommended.	X	Yes (% not reported); not re-commended.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	treatment of heterozygous familial hyper-cholesterolemia. Safety and efficacy in children <8 years of age have not been established.				
Rosuvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children 10 to 17 years of age for the treatment of heterozygous familial hyper-cholesterolemia. Safety and efficacy in children <10 years of age have not been established.	No dosage adjustment required in mild to moderate renal dysfunction. Renal dosage adjustment required; for creatinine clearances <30 mL/minute, an initial dose of 5 mg/day and a maximum dose of 10 mg/day are re-commended.	No dosage adjustment required in mild to moderate hepatic dysfunction. Hepatic dosage adjustment required in severe dysfunction; an initial dose of 5 mg/day and a maximum dose of 20 mg/day are recommended. Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	X	Unknown; not re-commended.
Simvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children 10 to 17 years of age for the treatment of heterozygous familial hyper-cholesterolemia.	No dosage adjustment required in mild to moderate renal dysfunction. Renal dosage adjustment required; for creatinine clearances <10 mL/ minute, an	No dosage adjustment required.	X	Unknown; not re-commended.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Safety and efficacy in children <10 years of age have not been established.	initial dose of 5 mg/day with close monitoring is re-commended.			
Combination Products					
Amlodipine/ atorvastatin	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	No dosage adjustment required.	Contraindicated in active liver disease.	X	Unknown; not re-commended.
Ezetimibe/ atorvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment required.	Contraindicated in active liver disease.	X	Unknown; not re-commended.
Ezetimibe/ simvastatin	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	No dosage adjustment required in mild to moderate renal dysfunction. Renal dosage adjustment required; in severe renal dysfunction, an initial dose of 5 mg/day with close monitoring is re-commended.	No dosage adjustment required in mild hepatic dysfunction. Use is not recommended in moderate to severe hepatic dysfunction.	X	Unknown; not re-commended.
Niacin extended release/ lovastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	No dosage adjustment required in mild to moderate renal dysfunction;	Contraindicated in active liver disease or unexplained persistent elevations in serum	X	Not studied in nursing mothers.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Safety and efficacy in children have not been established.	use with caution. Use caution with doses of lovastatin >20 mg/day with creatinine clearances <30 mL/minute.	transaminases.		
Niacin extended release/ simvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment required in mild to moderate renal dysfunction; use with caution. Use with extreme caution or avoid unless patient already tolerating simvastatin doses ≥10 mg in severe renal dysfunction.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	X	Unknown; not re-commended.

Adverse Drug Events

Table 6. Adverse Drug Events (%)[3-16,22]

Adverse Event	Single Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
Cardiovascular												
Angina pectoris	<2	-	-	-	3.1	-	-	-	-	-	-	-
Arrhythmia	<2	-	-	-	0.1 to 2.6	-	-	<2/✔	-	-	-	-
Bradycardia	-	-	-	-	-	-	-	-/✔	-	-	-	-
Chest pain	≥2	-	0.5 to 1.0	-	-	-	-	≥2.0/✔	-	-	-	-
Hypertension	<2	-	-	-	-	-	-	-	-	-	-	-
Hypotension	-	-	-		-	-	-	-/✔	-	-	-	-
Migraine	<2	-	-	-	-	-	-	-	-	-	-	-
Palpitation	<2	-	-	-	-	-	-	<2/0.7 to 4.5	-	-	-	-
Peripheral ischemia	-	-	-		-	-	-	✔/-	-	-	-	-
Postural hypotension	<2	-	-	-	-	-	-	<2/✔	-	-	-	-
Syncope	<2	-	-	-	-	-	-	<2/✔	-	-	-	-
Tachycardia	-	-	-	-	-	-	-	-/✔	-	-	-	-
Vasodilatation	<2	-	-	-	-	-	-	-/✔	-	-	-	-
Central Nervous System/Neurological												
Abnormal dreams	<2	-	-	-	-	-	-	<2/✔	-	-	-	-
Amnesia	<2	-	-	-	-	-	-	-	-	-	-	-
Anxiety	-	✔	✔	-	1	-	✔	-/✔	-	-	-	-
Chills	-	✔	✔	-	✔	-	✔	-	-	-	-	-
Cranial nerve dysfunction	-	✔	✔	-	✔	-	✔	-	-	-	-	-
Depersonalization	-	-	-	-	-	-	-	-/✔	-	-	-	-
Depression	<2	✔	✔	-	1	-	✔	<2/✔	-	-	-	-
Dizziness	≥2	✔	0.5 to 2.0	-	1.0 to 2.2	≤4	✔	≥2.0/1.1 to 3.4	2	-	-	-
Emotional lability	<2	-	-	-	-	-	-	-	-	-	-	-
Facial paralysis/paresis	<2	✔	-	-	✔	-	✔	-	-	-	-	-
Fever	<2	✔	-	-	<1	-	✔	-	-	-	-	-

Adverse Event	Single Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
Flushing	-	✔	✔	-	<1	-	✔	-/0.7 to 4.5	2	-	71	59
Headache	2.5 to 16.7	8.9/4.7	✔	✔	1.7 to 1.9	3.1 to 8.5	3.5	2.5 to 16.7/7.3	-	5.8	-	4.5
Hyperkinesia	<2	-	-	-	-	-	-	-	-	-	-	-
Hypertonia	<2	-	-	-	-	-	-	-	-	-	-	-
Hypesthesia	<2	-	-	-	-	-	-	-/✔	-	-	-	-
Impairment of extraocular movement	-	✔	-	-	✔	-	-	-	-	-	9	-
Incoordination	<2	-	-	-	-	-	-	-	-	-	-	-
Insomnia	≥2	2.7/0.8	0.5 to 1.0	-	1	-	✔	≥2/✔	-	-	-	-
Libido decreased	<2	✔	✔	-	<1	-	✔	-	-	-	-	-
Memory loss	-	✔	✔	-	<1	✔	✔	-	-	-	-	-
Neck rigidity	<2	-	-	-	-	-	-	-	-	-	-	-
Nervousness	-	-	-	-	-	-	-	-/✔	-	-	-	-
Paresthesia	<2	✔	0.5 to 1.0/-	-	<1	-	✔	<2/✔	-	-	-	-
Peripheral nerve palsy	-	✔	✔	-	<1	-	✔	-	-	-	-	-
Peripheral neuropathy	<2	✔	✔	-	<1	-	✔	-	-	-	-	-
Psychiatric disturbances	-	✔	✔	-	<1	-	✔	<2/✔	-	-	-	-
Somnolence	<2	-	-	-	-	-	-	<2.0/1.3 to 1.6	-	-	-	-
Tremor	-	✔	✔	-	<1	-	✔	-/✔	-	-	-	-
Vertigo	-	✔	✔	-	<1	-	✔	-/✔	-	-	-	-
Dermatological												
Acne	<2	-		-	-	-	-	-	-	-	-	-
Alopecia	<2	✔	0.5 to 1.0/-	-	<1	-	✔	-	-	-	-	-
Contact dermatitis	<2	-	-	-	-	-	-	-	-	-	-	-
Dry skin	<2	✔	✔	-	<1	-	✔	-	-	-	-	-
Eczema	<2	-	-	-	-	-	0.8	-	-	-	-	-
Erythema multiforme	<2	✔	✔	-	✔	-	✔	<2/✔	-	-	-	-
Pruritus	<2	✔	0.5 to 1.0/-	-	<1	<2	0.5	<2/✔	-	-	7	3.2
Rash	1.1 to 3.9	✔	0.8 to 1.3/-	-	1.3 to 2.1	<2	0.6	<2/✔	-	-	5	-

Adverse Event	Single Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
Rash erythematous	-	-	-	-	-	-	-	-/✔	-	-	-	-
Rash maculopapular	-	-	-	-	-	-	-	-/✔	-	-	-	-
Seborrhea	<2	-	-	-	-	-	-	-	-	-	-	-
Skin ulcer	<2	-	✔	-	-	-	-	-	-	-	-	-
Stevens-Johnson syndrome	✔	✔	-	-	✔	-	✔	-	-	-	-	-
Sweating	<2	-	-	-	-	-	-	<2/✔	-	-	-	-
Toxic epidermal necrolysis	✔	✔	✔	-	✔	-	✔	-	-	-	-	-
Urticaria	<2	✔	✔	-	-	<2	-	-	-	-	-	-
Endocrine and Metabolic												
Gout	<2	-	-	-	-	-	-	-	-	-	-	-
Hyperglycemia	<2	✔	-	-	-	-	-	<2/✔	-	-	4	-
Hypoglycemia	<2	-	-	-	-	-	-	-	-	-	-	-
Peripheral edema	≥2	-	-	-	-	-	-	<2/✔	-	-	-	-
Thirst	-	-	-	-	-	-	-	-/✔	-	-	-	-
Weight decrease	-	-	-	-	-	-	-	-/✔	-	-	-	-
Weight gain	<2	-	-	-	-	-	-	<2/✔	-	-	-	-
Gastrointestinal												
Abdominal pain	0.0 to 3.8	4.9/3.7	2.0 to 2.5/-	-	2.0 to 2.4	≤2.4	0.9 to 3.2	0 to 3.8/1.6	3	-	4	-
Acid regurgitation	-	-	0.5 to 1.0/-	-	-	-	-	-	-	-	-	-
Anorexia	<2	✔	✔	-	-	-	✔	0 to 3.8/1.6	-	-	-	-
Biliary pain	<2	-	-	-	-	-	-	-	-	-	-	-
Cheilitis	<2	-	-	-	-	-	-	-	-	-	-	-
Cholestatic jaundice	<2	✔	✔	-	✔	✔	✔	-	-	-	-	-
Cirrhosis	-	✔	✔	-	✔	-	✔	-	-	-	-	-
Colitis	<2	-	-	-	-	-	-	-	-	-	-	-
Constipation	0 to 2.5	-	2.0 to 3.5/-	1.5 to 3.6	1.2 to 2.4	2.1 to 4.7	2.3	0 to 2.5/✔	-	-	-	-
Decreased appetite	-	-	-	-	<1	-	-	-	-	-	-	-
Diarrhea	0 to 5.3	4.9/3.3	2.2 to 2.6	1.5 to 2.6	2	-	0.5 to 1.9	0 to 5.3/✔	-	2.8	6	3

Adverse Event	Single Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
			to 3.0									
Dry mouth	<2	-	0.5 to 1.0/-	-	-	-	-	<2/✔	-	-	-	-
Duodenal ulcer	<2	-	-	-	-	-	-	-	-	-	-	-
Dyspepsia/heartburn	1.3 to 2.8	7.9/3.5	1.0 to 1.6/-	-	2.0 to 3.5	-	0.6 to 1.1	1.3 to 2.8/✔	-	-	3	-
Dysphagia	<2	-	-	-	-	-	-	<2/✔	-	-	-	-
Enteritis	<2	-	-	-	-	-	-	-	-	-	-	-
Eructation	<2	-	-	-	-	-	-	-	-	-	-	-
Esophagitis	<2	-	-	-	-	-	-	-	-	-	-	-
Flatulence	1.1 to 2.8	2.6/1.4	3.7 to 4.5	-	1.2 to 2.7	-	0.9 to 1.9	1.1 to 2.8/✔	-	-	-	-
Fulminant hepatic necrosis	-	✔	✔	-	✔	-	✔	-	-	-	-	-
Gastritis	<2	-	-	-	-	-	-	-	-	-	-	-
Gastroenteritis	<2	-	-	-	-	-	-	-	-	-	-	-
Gingival hyperplasia	-	-	-	-	-		-	-/✔	-	-	-	-
Glossitis	<2	-	-	-	-	-	-	-	-	-	-	-
Gum hemorrhage	<2	-	-	-	-	-	-	-	-	-	-	-
Hepatitis	<2	✔	✔	-	✔	✔	✔	-	-	-	-	-
Hepatoma	-	✔	✔	-	✔	-	✔	-	-	-	-	-
Increased appetite	<2	-	-	-	-	-	-	-	-	-	-	-
Melena	<2	-	-	-	-	-	-	-	-	-	-	-
Mouth ulceration	<2	-	-	-	-	-	-	-	-	-	-	-
Nausea	≥2	3.2/2.5	-	-	1.6 to 2.9	0 to 6.3	0.4 to 1.3	≥2.0/2.9	3	-	7	3.2
Pancreatitis	<2	✔	✔	-	✔	<2	✔	<2/✔	-	-	-	-
Rectal hemorrhage	<2	-	-	-	-	-	-	-	-	-	-	-
Stomach ulcer	<2	-	-	-	-	-	-	-	-	-	-	-
Stomatitis	<2	-	-	-	-	-	-	-	-	-	-	-
Tenesmus	<2	-	-	-	-	-	-	-	-	-	-	-
Vomiting	<2	✔	0.5 to 1.0/-	-	1.6 to 2.9	-	✔	<2/✔	-	-	3	-
Genitourinary												
Abnormal ejaculation	<2	-	-	-	-	-	-	-	-	-	-	-

Adverse Event	Single Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
Albuminuria	≥2	-	-	-	-	-	-	-	-	-	-	-
Breast enlargement	<2	-	-	-	-	-	-	-	-	-	-	-
Cystitis	<2	-	-	-	-	-	-	-	-	-	-	-
Dysuria	<2	-	-	-	<1	-	-	-	-	-	-	-
Epididymitis	<2	-	-	-	-	-	-	-	-	-	-	-
Erectile dysfunction	-	✔	✔	-	<1	-	✔	-	-	-	-	-
Fibrocystic breast	<2	-	-	-	-	-	-	-	-	-	-	-
Gynecomastia	-	✔	✔	-	✔	-	✔	-	-	-	-	-
Hematuria	≥2	-	-	-	-	-	-	-	-	-	-	-
Impotence	<2	-	-	-	-	-	-	-	-	-	-	-
Kidney calculus	<2	-	-	-	-	-	-	-	-	-	-	-
Metrorrhagia	<2	-	-	-	-	-	-	-	-	-	-	-
Nephritis	<2	-	-	-	-	-	-	-	-	-	-	-
Nocturia	<2	-	-	-	<1	-	-	<2/ ✔	-	-	-	-
Urinary abnormality	-	-	-	-	0.7 to 1.0	-	-	-/ ✔	-	-	-	-
Urinary frequency	<2	-	-	-	<1	-	-	<2/ ✔	-	-	-	-
Urinary incontinence	<2	-	-	-	-	-	-	-	-	-	-	-
Urinary retention	<2	-	-	-	-	-	-	-	-	-	-	-
Urinary tract infection	≥2	1.6/2.7	-/2	-	-	-	-	-	-	-	-	-
Urinary urgency	<2	-	-	-	1	-	-	-	-	-	-	-
Uterine hemorrhage	<2	-	-	-	-	-	-	-	-	-	-	-
Vaginal hemorrhage	<2	-	-	-	-	-	-	-	-	-	-	-
Hematologic												
Anemia	<2	-	-	-	-	-	-	-	-	-	-	-
Ecchymosis	<2	-	-	-	-	-	-	-	-	-	-	-
Eosinophilia	-	✔	✔	-	✔	-	✔	-	-	-	-	-
Hemolytic anemia	-	✔	✔	-	✔	-	✔	-	-	-	-	-
Leukopenia	-	✔	✔	-	✔	-	-	-/ ✔	-	-	-	-
Lymphadenopathy	<2	-	-	-	-	-	-	-	-	-	-	-
Petechia	<2	-	-	-	-	-	-	-	-	-	-	-

Adverse Event	Single Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
Prolongation of prothrombin time	-	-	-	-	-	-	-	-	-	-	-	✔
Purpura	-	✔	✔	-	✔	-	✔	-/ ✔	-	-	-	-
Thrombocytopenia	<2	✔	✔	-		-	✔	2/ ✔	-	-	-	✔
Vasculitis	-	✔	✔	-	✔	-	✔	-/ ✔	-	-	-	-
Laboratory Test Abnormalities												
γ-glutamyl transpeptidase increase	-	-	-	-	-	-	-	-	-	-	-	✔
Abnormal thyroid function tests	-	-	-	-	-	-	-	-	-	-	-	✔
Bilirubin elevation	-	✔	✔	✔	-	✔	✔	-	-	-	-	✔
Creatine phosphokinase increased	<2	-	-	✔	-	2.6	✔	-	-	-	-	✔
Eosinophil sedimentation rate increase	-	✔	✔	-	✔	-	✔	-	-	-	-	-
Fasting glucose increase	-	-	-	-	-	-	-	-	-	-	-	✔
Hematuria	-	-	-	-	-	✔	-	-	-	-	-	-
Hyperkalemia	-	-	-	-	-	-	-	-	2	-	-	-
Lactate dehydrogenase decrease	-	-	-	-	-	-	-	-	-	-	-	✔
Liver enzyme abnormalities	-	✔	✔	✔	✔	2.2	✔	-	4 to 5	0.4 to 3.7	-	✔
Phosphorus decrease	-	-	-	-	-	-	-	-	-	-	-	✔
Positive antinuclear antibody	-	✔	✔	-	✔	-	✔	-	-	-	-	-
Proteinuria	-	-	-	-	-	✔	-	-	-	-	-	-
Thyroid level	-	✔	✔	-	✔	✔	✔	-	-	-	-	-

Adverse Event	Single Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
abnormality												
Uric acid increase	-	-	-	-	-	-	-	-	-	-	-	✔
Musculoskeletal												
Arthralgia	0 to 5.1	-/3.2	0.5 to 1.5/5.0	✔	6	10.1	✔	0 to 5.1/ ✔	3	-	-	-
Arthritis	≥2	2.1/1.3	0.5 to 6.0/5.0	-	✔	-	✔	-/ ✔	-	-	-	-
Back pain	0 to 3.8	-	-/5	1.4 to 3.9	-	-	-	0 to 3.8/ ✔	-	0.4	5	3.2
Bursitis	<2	-	-	-	-	-	-	-	-	-	-	-
Dermatomyositis	-	-	-	-	✔	-	-	-	-	-	-	-
Leg cramps	<2	-	0.5 to 1.0/-	-	-	-	-	-	-	-	-	-
Leg pain	-	-	-	-	-	-	-	-	-	-	-	-
Localized pain	-	-	-	-	1.4	-	-	-	-	-	-	-
Muscle cramps	-	✔	0.6 to 1.1/-	-	2	-	✔	-/ ✔	-	-	-	-
Muscle weakness	-	-	-	-	-	-	-	2	-	-	-	-
Musculoskeletal pain	-	-	-	-	-	-	-	4	-	-	-	-
Myalgia	0 to 5.6	5.0/3.8	1.8 to 3.0/3.0	1.9 to 3.1	0.6 to 1.4	1.9 to 12.7	1.2	0 to 5.6/ ✔	-	0.6 to 3.6	3	-
Myopathy	-	✔	-	-	✔	-	✔	-	-	-	-	-
Myositis	<2	-	-	-	-	-	-	-	-	-	-	-
Myasthenia	<2	-	-	-	<1	-	-	-	-	-	-	-
Pain in extremity	-	-	-	0.6 to 2.3	-	-	-	-	-	2.3	-	-
Polymyalgia rheumatica	-	✔	✔	-	✔	-	✔	-	-	-	-	-
Rhabdomyolysis	✔	✔	✔	-	✔	-	✔	-	-	-	-	-
Shoulder pain	-	-	0.5 to 1.0/-	-	-	-	-	-	-	-	-	-
Tendinous contracture	<2	-	-	-	-	-	-	-	-	-	-	-
Tenosynovitis	<2	-	-	-	-	-	-	-	-	-	-	-
Respiratory												
Asthma	<2	-	-	-	-	-	-	-	-	-	-	-
Bronchitis	≥2	1.2/2.6	-	-	-	-	-	-	2	-	-	-

Adverse Event	Single Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
Cough	-	-	-	-	0.1 to 1.0	-	-	-	2	-	-	-
Dyspnea	<2	✔	✔	-	1.6	-	✔	<2/ ✔	-	-	-	-
Epistaxis	<2	-	-	-	-	-	-	<2/ ✔	-	-	-	-
Pharyngitis	0 to 2.5	-	-	-	-	-	-	-	-	-	-	-
Pneumonia	<2	-	-	-	-	-	-	-	-	-	-	-
Rhinitis	≥2	-	-	-	0.1	-	-	-	-	-	-	-
Sinusitis	0 to 6.4	2.6/3.5	-/4	-	-	-	-	2	-	-	-	-
Upper respiratory infection	-	-	-	-	1.3	-	2.1	-	-	3.6	-	-
Other												
Abnormal vision	-	-	-	-	-	-	-	-/ ✔	-	-	-	-
Accidental injury	0 to 4.2	5.1/4.2	-/6	-	-	-	-	0 to 2.8/ ✔	-	-	-	-
Allergic reaction	0 to 2.8	2.3/1.0	-	-	<1	-	-	-	-	-	-	-
Amblyopia	<2	-	-	-	-	-	-	-	-	-	-	-
Anaphylaxis	✔	✔	✔	-	✔	-	✔	-	-	-	-	-
Angioedema	-	✔	✔	-	✔	<2	✔	-/ ✔	-	-	-	-
Angioneurotic edema	✔	-	-	-	-	-	-	-	-	-	-	-
Asthenia	0 to 3.8	✔	1.2 to 2.0/3.0	-	✔	0.9 to 4.7	1.6	0 to 3.8/ ✔	-	-	5	-
Blurred vision	-	-	0.9 to 1.2/-	-	-	-	-	-	-	-	-	-
Cataracts	-	✔	✔	-	-	-	0.5	-	-	-	-	-
Conjunctivitis	-	-	-	-	-	-	-	-/ ✔	-	-	-	-
Deafness	<2	-	-	-	-	-	-	-	-	-	-	-
Diplopia	-	-	-	-	-	-	-	-/ ✔	-	-	-	-
Dry eyes	<2	-	-	-	-	-	-	-	-	-	-	-
Eye hemorrhage	<2	-	-	-	-	-	-	-	-	-	-	-
Eye irritation	-	-	0.5 to 1.0/-	-	-	-	-	-	-	-	-	-
Eye pain	-	-	-	-	-	-	-	-/ ✔	-	-	-	-
Facial/general edema	<2	-	-	-	<1	-	-	-	-	-	-	-
Fatigue	✔	2.7/1.6	-	-	1.9 to 3.4	-	-	✔ /4.5	-	-	-	-

Adverse Event	Single Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
Flu syndrome	0 to 3.2	5.1/7.1	-/5	-	-	-	-	-	-	-	6	-
Glaucoma	<2	-	-/11	-	-	-	-	-	-	-	-	-
Hot flashes	-	-	-	-	-	-	-	-/✔	-	-	-	-
Infection	2.8 to 10.3	-	-	-	-	-	-	-	-	-	20	-
Influenza	-	-	-	✔	-	-	-	-	-	2.3	-	-
Lupus erythematosus-like syndrome	-	✔	✔	-	✔	-	✔	-	-	-	-	-
Malaise	<2	✔	✔	-	✔	-	✔	-	-	-	-	-
Nasopharyngitis	-	-	-	✔	-	-	-	-	-	-	-	-
Ophthalmoplegia	-	✔	✔	-	-	-	✔	-	-	-	-	-
Pain	-	-	-/3	-	-	-	-	-	-	-	-	-
Parosmia	<2	-	-	-	-	-	-	-	-	-	-	-
Photosensitivity reaction	<2	✔	-	-	✔	-	-	-	-	-	8	-
Refraction disorder	<2	-	-	-	-	-	-	-	-	-	-	-
Rigors	-	-	-	-	-	-	-	-/✔	-	-	-	-
Sexual dysfunction	-	-	-	-	-	-	-	-	-	-	-	-
Taste disturbance	<2	✔	-	-	✔	-	-	-/✔	-	-	-	-
Tinnitus	<2	-	-	-	-	-	-	<2/✔	-	-	-	-
Visual disturbances	-	-	✔	-	✔	-	-	-	-	-	-	-

ER=extended-release, IR=immediate-release
-Incidence not reported or incidence <0.1%.
✔ Percent not reported.

Contraindications

Table 7. Contraindications[3-16,22]

Adverse Event	Single Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
Active liver disease	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Active peptic ulcer disease	-	-	-	-	-	-	-	-	-	-	✔	✔
Arterial hemorrhage	-	-	-	-	-	-	-	-	-	-	✔	✔
Cyclosporine, concurrent use	-	-	-	✔	-	-	-	-	-	-	-	-
Cytochrome P450 inhibitors, concurrent use	-	-	✔	-	-	-	✔	-	-	✔	-	✔
Hypersensitivity to any component of the formulation	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
immune-mediated necrotizing myopathy	-	-	✔	-	-	-	-	-	-	✔	-	✔
Nursing Mothers	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Pregnancy	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Serum transaminase elevation (unexplained)	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔

Warnings and Precautions

Table 8. Warnings and Precautions[3-16,22]

Adverse Event	Single Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
Central nervous system effects (ataxia, loss of righting reflex, and ptosis) observed in animal studies.	✔	✔	-	-	-	-	-	✔	✔	-	-	-
Fasting blood glucose increases; monitor for increases in blood glucose	✔	-	-	-	-	✔	-	-	-	-	✔	✔
Flushing and pruritus; a gradual increase in dose and/or the administration of aspirin or a nonsteroidal anti-inflammatory drug 30 to 60 minutes before dosing may attenuate this effect	-	-	-	-	-	-	-	-	-	-	✔	✔

Adverse Event	Single Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
Fredrickson type I or III dyslipidemias; use has not been evaluated	-	-	-	-	-	-	-	-	-	-	✔	✔
Gallbladder disease, may be exacerbated	-	-	-	-	-	-	-	-	-	-	✔	✔
Hematuria (microscopic) and proteinuria; may be associated with use	-	-	-	-	-	✔	-	-	-	-	-	-
Hemorrhagic stroke, history of; patients may be at an increased risk for subsequent stroke	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Hyperuricemia; should be used with caution in patients with gout	-	-	-	-	-	-	-	-	-	-	✔	✔
Liver disease, history of ethanol use; caution should be used in these patients	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Primary dysbetalipoproteinemia; use in this condition has not been adequately studied	-	-	-	✔	-	-	-	-	-	-	-	-
Prothrombin time; may be increased	-	-	-	-	-	✔	-	-	-	-	✔	✔
Rhabdomyolysis, myopathy, and renal failure	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Secondary hyperlipidemia; should be ruled out prior to initiation of therapy	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔

Drug Interactions

Table 9. Drug Interactions[3-16,22]

Interaction	Single-Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
Amiodarone: Plasma concentrations of statins may be elevated, increasing the risk of toxicity. Use with amiodarone may be	✔	✔	✔	-	-	-	✔	✔	✔	✔	✔	✔

Interaction	Single-Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
associated with bradycardia, atrioventricular block and/or sinus arrest. Monitor for signs and symptoms of myopathy and rhabdomyolysis. Alternatively, consider the use of a statin that does not have a documented interaction with amiodarone.												
Azole antifungals: May elevate statin and dihydropyridine plasma concentrations, increasing pharmacologic effects and adverse reactions. Consider statin dose modification. Monitor for signs and symptoms of myopathy and rhabdomyolysis. Select statins are contraindicated with certain azole antifungals; concurrent use of these agents should be avoided.	✔	✔	✔	-	✔	-	✔	✔	✔	✔	✔	✔
Carbamazepine: Plasma concentrations of statins may be reduced, decreasing the therapeutic effect. Monitor cholesterol levels in patients receiving these agents concurrently. Dose adjustment may be necessary.	✔	-	✔	-	-	✔	✔	✔	✔	✔	✔	✔
Ciprofloxacin: Severe myopathy or rhabdomyolysis may occur. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	-	-	-	-	-	-	✔	-	-	✔	-	✔
Clopidogrel: Decreased antiplatelet effect and increased risk of thrombotic effects may occur. Use caution and monitor	-	-	-	-	-	-	-	✔	-	-	-	-

Interaction	Single-Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
patients for loss of clopidogrel efficacy.												
Cobicistat: increased statin concentration may occur. Lovastatin and simvastatin are contraindicated and use with cobicistat should be avoided. Consider atorvastatin dose modification. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	✔	-	✔	-	-	-	✔	✔	✔	✔	✔	✔
Colchicine: Severe myopathy or rhabdomyolysis may occur. Consider statin dose modification. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	✔	✔	✔	-	✔	-	✔	✔	✔	✔	✔	✔
Colesevelam: May be associated with decreased statin concentration. If concomitant use of colesevelam and statin is required, advise patient to take pravastatin 1 hour before or 4 hours after colesevelam.	-	-	-	-	✔	-	-	-	-	-	-	-
Conivaptan: increased amlodipine exposure may occur. Wait at least one week after the last conivaptan infusion before initiating treatment with a statin.	✔	-	✔	-	-	-	✔	✔	✔	✔	✔	✔
Cyclosporine: Increased plasma concentrations and adverse reactions of statins may occur. Plasma concentrations of ezetimibe and cyclosporine may be elevated, increasing the pharmacologic effects and adverse reactions. Avoid concurrent use or consider	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔

Interaction	Single-Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
statin dose modification. Monitor for signs and symptoms of myopathy and rhabdomyolysis.												
Danazol: Concurrent use may be associated with an increased risk of myopathy or rhabdomyolysis. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	✔	✔	✔	-	-	-	✔	✔	✔	✔	✔	✔
Daptomycin: Severe myopathy or rhabdomyolysis may occur. Consider statin discontinuation prior to daptomycin therapy if possible. If concurrent therapy is required, monitor for signs and symptoms of myopathy and rhabdomyolysis.	✔	✔	✔	-	✔	✔	✔	✔	✔	✔	✔	✔
Diltiazem: Plasma concentrations of statins may be elevated, increasing the risk of toxicity. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	✔	-	✔	-	-	✔	✔	✔	✔	✔	✔	✔
Dronedarone: May be associated with increased statin exposure. Consider statin dose modification. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	✔	✔	✔	-	-	-	✔	✔	✔	✔	✔	✔
Erlotinib: Severe myopathy or rhabdomyolysis may occur. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Everolimus: May be associated with increased statin toxicity. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	-	-	✔	-	-	-	✔	-	-	✔	✔	✔

Interaction	Single-Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
Fibric acid derivatives: Severe myopathy or rhabdomyolysis may occur. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Hepatitis C Virus protease inhibitors: Inhibition of the metabolism of statins may occur, increasing plasma concentrations and pharmacologic effects of statins. Consider statin dose modification. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Imatinib: Plasma concentrations of statins may be elevated, increasing the pharmacologic effects and risk of adverse reactions. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	✔	-	✔	-	-	✔	✔	✔	✔	✔	✔	✔
Lomitapide: may be associated with increased statin exposure. Consider statin dose modification. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	-	-	✔	-	-	-	✔	-	-	✔	✔	✔
Macrolides and related antibiotics: Severe myopathy or rhabdomyolysis may occur because of increased statin inhibitor plasma concentrations. Consider statin dose modification. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	✔	✔	✔	✔	-	✔	✔	✔	✔	✔	✔	✔
Mibefradil: Severe myopathy or rhabdomyolysis may occur.	✔	✔	✔	-	✔	-	✔	✔	✔	✔	✔	✔

Interaction	Single-Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
Monitor for signs and symptoms of myopathy and rhabdomyolysis.												
Mifepristone: Mifepristone may inhibit the metabolism of statins, increasing statin plasma concentrations and pharmacologic effects. Consider statin dose modification. Monitor for signs and symptoms of myopathy and rhabdomyolysis. Select statins are contraindicated with mifepristone; concurrent use of these agents should be avoided.	✔	✔	✔	-	-	✔	✔	✔	✔	✔	✔	✔
Nefazodone: The risk of rhabdomyolysis and myositis may be increased. Consider statin dose modification. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	✔	-	✔	-	-	✔	✔	✔	✔	✔	✔	✔
Niacin: The risk of rhabdomyolysis and myositis may be increased. Consider statin dose modification. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	✔	✔	✔	-	-	✔	✔	✔	✔	✔	✔	✔
Nonnucleoside reverse transcriptase inhibitors: Severe myopathy or rhabdomyolysis may occur because of increased statin plasma concentrations. Efavirenz and nevirapine may reduce statin plasma concentrations. Consider statin dose modification. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	✔	✔	✔	-	✔	-	✔	✔	✔	✔	✔	✔
Phenytoin: Concurrent use	✔	✔	-	-	-	-	-	✔	✔	-	-	-

Interaction	Single-Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
may be associated with increased statin exposure and increased risk of phenytoin toxicity. Consider statin dose modification. Monitor for signs and symptoms of myopathy and rhabdomyolysis.												
Primidone: Decreased statin concentration may occur. Consider statin dose modification. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	✔	-	✔	-	-	-	✔	✔	✔	✔	✔	✔
Protease inhibitors: Increased plasma concentrations and adverse reactions of dihydropyridines and statins may occur. Consider statin/dihyrdopyridine dose modification. Monitor for signs and symptoms of toxicity.	✔	-	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Quinpristine/dalfopristine: Severe myopathy or rhabdomyolysis may occur. Consider statin dose modification. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	✔	✔	✔	-	✔	-	✔	✔	✔	✔	✔	✔
Ranolazine: Ranolazine inhibits the metabolism of statins, statin plasma concentrations and increasing the risk of adverse events. Consider statin dose modification. Monitor for signs and symptoms of myopathy and rhabdomyolysis	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Rifamycins: Plasma concentrations of statins may be decreased, decreasing the	✔	✔	✔	✔	✔	-	✔	✔	✔	✔	✔	✔

Interaction	Single-Entity Agents							Combination Products				
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin	Amlodipine/ atorvastatin	Ezetimibe/ atorvastatin	Ezetimibe/ simvastatin	Niacin/ lovastatin	Niacin/ simvastatin
pharmacologic effect. Dose adjustment may be necessary.												
Risperidone: Severe myopathy or rhabdomyolysis may occur. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	-	-	-	-		-	✔	-	-	✔	-	✔
Simvastatin: Simvastatin plasma concentrations may be elevated, increasing the risk of toxicity. Consider statin dose modification. Monitor for signs and symptoms of myopathy and rhabdomyolysis	-	-	-	-	-	-	-	✔	-	-	-	-
Tadalafil: Severe myopathy or rhabdomyolysis may occur. Monitor for signs and symptoms of myopathy and rhabdomyolysis	-	-	-	-	-	-	✔	-	-	✔	-	✔
Warfarin: The anticoagulant effect of warfarin may increase. Dose adjustment of warfarin may be necessary. Monitor for signs and symptoms of myopathy and rhabdomyolysis	-	✔	✔	-	✔	✔	-	-	✔	✔	✔	✔
Verapamil: Plasma concentrations of statins and verapamil may be elevated, increasing the risk of toxicity. Consider statin dose modification. Monitor for signs and symptoms of myopathy and rhabdomyolysis.	✔	-	✔	-	-	✔	✔	✔	✔	✔	✔	✔

Dosage and Administration

Table 10. Dosing and Administration[3-16,22]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Single-Entity Agents			
Atorvastatin	Hyperlipidemia:	Hyperlipidemia:	Tablet:

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Adjunct to diet to reduce elevated TC, LDL-C, apo B and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia: Tablet: initial, 10 to 40 mg QD; maintenance, 10 to 80 mg/day Adjunct to diet for the treatment of patients with elevated serum TG levels, reduce TC and LDL-C in patients with homozygous FH as an adjunct to other lipid lowering treatments or if such treatments are unavailable, treatment of patients with primary dysbetalipoproteinemia*: Tablet: 10 to 80 mg/day Prevention of cardiovascular disease: In adult patients without clinically evident CHD to reduce the risk of angina, MI, revascularization procedures and stroke (primary prevention)‡, in patients with type 2 diabetes, and without clinically evident CHD, but with multiple risk factors for CHD, to reduce the risk of MI and stroke (primary prevention): Tablet: 10 to 80 mg/day In patients with clinically evident CHD to reduce the risk of angina, fatal and nonfatal stroke, hospitalization, nonfatal MI and revascularization procedures (secondary prevention): Tablet: 80 mg/day	Adjunct to diet to reduce TC, LDL-C and apo B levels in boys and postmenarchal girls, 10 to 17 years of age with heterozygous FH‡‡: Tablet: initial, 10 mg/day; maximum, 20 mg/day Safety and efficacy in children <10 years of age have not been established.	10 mg 20 mg 40 mg 80 mg
Fluvastatin	Hyperlipidemia: Adjunct to diet to reduce elevated TC, LDL-C, apo B and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia: Capsule: initial, 20 or 40 mg QD or 40 mg BID; maintenance, 20 to 80 mg/day Extended-release tablet: 80 mg QD Prevention of cardiovascular disease: In patients with clinically evident CHD, to reduce the risk of revascularization procedures and to slow the progression of coronary atherosclerosis (secondary prevention): Capsule: initial, 20 or 40 mg QD or 40 mg BID; maintenance, 20 to 80 mg/day	Hyperlipidemia: Adjunct to diet to reduce TC, LDL-C and apo B levels in adolescent boys and girls, who are ≥1 year post-menarche, 10 to 16 years of age with heterozygous FH‡: Capsule: 20 mg/day; maximum, 40 BID Extended-release tablet: maximum, 80 mg/day Safety and efficacy in children for other approved indications	Capsule: 20 mg 40 mg Extended-release tablet: 80 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Extended-release tablet: 80 mg QD	have not been established.	
Lovastatin	Hyperlipidemia: Adjunct to diet to reduce elevated TC, LDL-C, apo B and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia**: Extended-release tablet: initial, 20 to 60 mg QD; maintenance, 20 to 60 mg/day Tablet: initial, 20 mg QD; maintenance, 10 to 80 mg/day in single or two divided doses; maximum, 80 mg/day Prevention of cardiovascular disease: In adult patients without clinically evident CHD to reduce the risk of unstable angina, MI and revascularization procedures (primary prevention)††, in patients with clinically evident CHD, to slow the progression of coronary atherosclerosis (secondary prevention)‖: Extended-release tablet: initial, 20 to 60 mg QD; maintenance, 20 to 60 mg/day Tablet: initial, 20 mg QD; maintenance, 10 to 80 mg/day in single or two divided doses; maximum, 80 mg/day	Hyperlipidemia: Adjunct to diet to reduce TC, LDL-C and apo B levels in adolescent boys and girls, who are ≥1 year post-menarche, 10 to 17 years of age with heterozygous HF‡: Tablet: maintenance, 10 to 40 mg/day; maximum, 40 mg/day Safety and efficacy in children <10 years of age have not been established (Mevacor®). Safety and efficacy in children have not been established (Altoprev®).	Extended-release tablet: 20 mg 40 mg 60 mg Tablet: 10 mg 20 mg 40 mg
Pitavastatin	Hyperlipidemia: Adjunct to diet to reduce elevated TC, LDL-C, apo B and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia: Tablet: initial, 2 mg QD; maintenance, 1 to 4 mg/day; maximum, 4 mg/day	Safety and efficacy in children have not been established.	Tablet: 1 mg 2 mg 4 mg
Pravastatin	Hyperlipidemia: Adjunct to diet to reduce elevated TC, LDL-C, apo B and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia, adjunct to diet for the treatment of patients with elevated serum TG levels, treatment of patients with primary dysbetalipoproteinemia*: Tablet: initial, 40 mg QD; maintenance, 40 to 80 mg QD Prevention of cardiovascular disease: In patients without clinically evident CHD to reduce the risk of cardiovascular mortality	Hyperlipidemia: Adjunct to diet to reduce TC, LDL-C and apo B levels in children and adolescents 8 to 13 years of age with heterozygous FH‡: Tablet: initial, 20 mg QD; maximum, 20 mg/day Adjunct to diet to reduce TC, LDL-C and apo B levels in	Tablet: 10 mg 20 mg 40 mg 80 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	with no increase in death from noncardiovascular causes, MI and revascularization procedures, in patients with clinically evident CHD, to reduce the risk of MI, revascularization procedures, stroke and stroke/transient ischemic attack and total mortality by reducing coronary death; and to slow the progression or coronary atherosclerosis: Tablet: initial, 40 mg QD; maintenance, 40 to 80 mg QD	children and adolescents 14 to 18 years of age with heterozygous FH‡: Tablet: 40 mg QD; maximum, 40 mg/day Safety and efficacy in children <8 years of age have not been established.	
Rosuvastatin	Hyperlipidemia: Adjunct to diet to reduce elevated TC, LDL-C, apo B and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia, adjunct to diet for the treatment of patients with elevated serum TG levels, adjunct to diet for the treatment of primary dysbetalipoproteinemia: Tablet: initial, 10 to 20 mg QD; maintenance, 5 to 40 mg/day Reduce TC, LDL-C and apo B in patients with homozygous FH as an adjunct to other lipid lowering treatments or if such treatments are unavailable: Tablet: initial, 20 mg QD; maintenance, 5 to 40 mg/day Prevention of cardiovascular disease: In patients without clinically evident CHD to reduce the risk of MI, revascularization procedures and stroke§, in patients with clinically evident CHD to slow the progression of coronary atherosclerosis‖: Tablet: initial, 10 to 20 mg QD; maintenance, 5 to 40 mg/day	Hyperlipidemia: Adjunct to diet to reduce TC, LDL-C and apo B levels in adolescent boys and girls, who are at least one year post-menarche, 10 to 17 years of age with heterozygous FH‡: Tablet: maintenance, 50 to 20 mg/day; maximum, 20 mg/day Safety and efficacy in children <10 years of age have not been established.	Tablet: 5 mg 10 mg 20 mg 40 mg
Simvastatin	Hyperlipidemia: Adjunct to diet to reduce elevated TC, LDL-C, apo B and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia, adjunct to diet for the treatment of patients with elevated serum TG levels, treatment of patients with primary dysbetalipoproteinemia¶: Tablet: initial, 10 or 20 mg QD; maintenance, 5 to 40 mg/day Reduce TC and LDL-C in patients with homozygous FH as an adjunct to other lipid	Hyperlipidemia: Adjunct to diet to reduce TC, LDL-C and apo B levels in adolescent boys and girls, who are at least one year post-menarche, 10 to 17 years of age with heterozygous FH‡: Tablet: initial, 10 mg QD; maintenance, 10 to 40 mg/day; maximum, 40 mg/day	Tablet: 5 mg 10 mg 20 mg 40 mg 80 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	lowering treatments or if such treatments are unavailable: Tablet: 40 mg QD Prevention of cardiovascular disease: In patients at high risk of coronary events because of existing CHD, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, to reduce the risk of nonfatal MI and stroke, revascularization procedures and total mortality by reducing CHD death: Tablet: initial, 10 or 20 mg QD; maintenance, 5 to 40 mg/day	Safety and efficacy in children <10 years of age have not been established.	
Combination Products			
Amlodipine/ atorvastatin	Hyperlipidemia: Adjunct to diet to reduce elevated TC, LDL-C, apo B and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (atorvastatin): Tablet: initial, 10 to 40 mg QD; maintenance, 10 to 80 mg/day Adjunct to diet for the treatment of patients with elevated serum TG levels, reduce TC and LDL-C in patients with homozygous FH as an adjunct to other lipid lowering treatments or if such treatments are unavailable, treatment of patients with primary dysbetalipoproteinemia* (atorvastatin): Tablet: 10 to 80 mg/day Prevention of cardiovascular disease: In adult patients without clinically evident CHD to reduce the risk of angina, MI, revascularization procedures and stroke (primary prevention)[†], in patients with type 2 diabetes, and without clinically evident CHD, but with multiple risk factors for CHD, to reduce the risk of MI and stroke (primary prevention) (atorvastatin): Tablet: 10 to 80 mg/day In patients with clinically evident CHD to reduce the risk of angina, fatal and nonfatal stroke, hospitalization, nonfatal MI and revascularization procedures (secondary prevention) (atorvastatin): Tablet: 80 mg/day	Safety and efficacy in children have not been established.	Tablet: 2.5/10 mg 2.5/20 mg 2.5/40 mg 5/10 mg 5/20 mg 5/40 mg 5/80 mg 10/10 mg 10/20 mg 10/40 mg 10/80 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Other: Angiographically documented CAD, chronic stable angina, hypertension, vasospastic angina (amlodipine): Tablet: initial, 5 mg QD; maintenance, 5 to 10 mg/day; maximum, 10 mg/day		
Ezetimibe/ atorvastatin	Hyperlipidemia: Adjunct to diet to reduce elevated TC, LDL-C, apo B, TG levels and non-HDL-C and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia: Tablet: Tablet: initial, 10/10 to 40/10 mg once daily; maintenance, 10/10 to 80/10 mg mg/day; maximum, 80/10 mg/day Adjunct to diet for the treatment of patients with elevated serum TG levels, reduce TC and LDL-C in patients with homozygous FH as an adjunct to other lipid lowering treatments or if such treatments are unavailable: Tablet: Tablet: initial, 40/10 to 80/10 mg once daily; maintenance, 40/10 to 80/10 mg mg/day; maximum, 80/10 mg/day	Safety and efficacy in children have not been established.	Tablet: 10/10 mg 20/10 mg 40 mg/10 mg 80 mg/10 mg
Ezetimibe/ simvastatin	Hyperlipidemia: Adjunct to diet to reduce elevated TC, LDL-C, apo B and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia, reduce TC and LDL-C in patients with homozygous FH as an adjunct to other lipid lowering treatments or if such treatments are unavailable: Tablet: initial, 10/10 to 10/40 mg QD; maintenance, 10/10 to 10/40 mg/day	Safety and efficacy in children have not been established.	Tablet: 10/10 mg 10/20 mg 10/40 mg 10/80 mg
Niacin extended release/ lovastatin	Hyperlipidemia: Adjunct to diet to reduce elevated TC and LDL-C in patients with primary hypercholesterolemia[#] (lovastatin, niacin extended release), adjunct to diet for the treatment of patients with elevated serum TG levels[‡‡] (niacin extended release): Tablet: initial, 500/20 mg QD (in patients not currently on niacin); maintenance, increase by no more than 500 mg/day (based on the niacin component) every four weeks; maximum, 2,000/40 mg/day Prevention of cardiovascular disease: In patients without clinically evident CHD to reduce the risk of unstable angina, MI and	Safety and efficacy in children have not been established.	Tablet: 500/20 mg 750/20 mg 1,000/20 mg 1,000/40 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	revascularization procedures (primary prevention) (lovastatin)‡‡, in patients with clinically evident CHD, to slow the progression of coronary atherosclerosis (secondary prevention) (lovastatin)‖, in patients with a history of a MI and hypercholesterolemia to reduce the risk of recurrent nonfatal MI (niacin extended release): Tablet: initial, 500/20 mg QD (in patients not currently on niacin); maintenance, increase by no more than 500 mg/day (based on the niacin component) every four weeks; maximum, 2,000/40 mg/day		
Niacin extended release/ simvastatin	Hyperlipidemia: Adjunct to diet to reduce elevated TC, LDL-C, apo B and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia#, adjunct to diet for the treatment of patients with elevated serum TG levels#: Tablet: initial, 500/20 mg QD (in patients not currently on niacin) or 500/40 mg QD (in patients already taking simvastatin 20 to 40 mg who need additional management of their lipid levels); maintenance, 1,000/20 to 2,000/40 mg QD	Safety and efficacy in children have not been established.	Tablet: 500/20 mg 500/40 mg 750/20 mg 1,000/20 mg 1,000/40 mg

apo=apolipoprotein, CHD=coronary heart disease, FH=familial hypercholesterolemia, HDL-C=high density lipoprotein cholesterol, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, QD=once-daily, TC=total cholesterol, TG=triglyceride
*Who do not respond adequately to diet.
†Without clinically evident coronary heart disease (CHD) but with multiple risk factors for CHD such as age, smoking, hypertension, low high-density lipoprotein cholesterol (HDL-C) or a family history of early CHD.
‡If after an adequate trial of diet therapy the following findings are present: low density lipoprotein cholesterol (LDL-C) remains ≥190 or ≥160 mg/dL and there is a positive family history of premature cardiovascular disease or ≥2 other cardiovascular disease risk factors are present in the pediatric patient.
§ With an increased risk of cardiovascular disease based on age ≥50 years in men and ≥60 years in women; high-sensitivity C reactive protein ≥2 mg/L and the presence of ≥1 additional cardiovascular risk factor such as hypertension, low HDL-C, smoking or a family history of premature CHD.
‖ As part of a treatment strategy to lower TC and LDL-C to target levels.
¶ To reduce elevated triglycerides and very low density lipoprotein cholesterol levels.
# When treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.
** When response to diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate (extended- and immediate-release); reduction in elevated total cholesterol (TC) and LDL-C in patients with primary hypercholesterolemia (immediate-release only).
†† With average to moderately elevated TC and LDL-C, and below average HDL-C.
‡‡ In patients at risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them.

Clinical Guidelines

Current guidelines are summarized in Table 11. The guidelines addressing the management of hypercholesterolemia are presented globally, addressing the role of various medication classes in the management of this disease.

Table 11. Clinical Guidelines

Clinical Guideline	Recommendation
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)**[19]	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low density lipoprotein cholesterol (LDL-C) lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. • Standard hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statin) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • Fibrates may have an adjunctive role in the treatment of patients with high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins. • In high risk patients with high TG or low HDL-C levels, consideration 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>

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	• 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 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)**[1]	General recommendations • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of evidence is only moderate at present. National Cholesterol Education Program supports the American Heart Association's recommendation that fish be included as part of a CHD risk reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate LDL lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first line drugs when LDL lowering drugs are indicated to achieve LDL-C treatment goals. • After six weeks if LDL-C goal is not achieved, intensify LDL lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. Statins • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals. Bile acid sequestrants • Bile acid sequestrants should be considered as LDL lowering therapy for patients with moderate elevations in LDL-C, for younger patients with elevated LDL-C, for women with elevated LDL-C who are considering pregnancy and for patients needing only modest reductions in LDL-C to achieve target goals. • Bile acid sequestrants should be considered in combination therapy with statins in patients with very high LDL-C levels. Nicotinic acid • Nicotinic acid should be considered as a therapeutic option for higher risk patients with atherogenic dyslipidemia. • Nicotinic acid should be considered as a single agent in higher risk patients with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol lowering drugs in higher risk patients with atherogenic dyslipidemia combined with elevated LDL-C levels. • Nicotinic acid should be used with caution in patients with active liver disease, recent peptic ulcer, hyperuricemia, gout and type 2 diabetes. • High doses of nicotinic acid (>3 g/day) generally should be avoided in patients with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia. Fibric acid derivatives (fibrates) • Fibrates can be recommended for patients with very high TG to

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	reduce risk for acute pancreatitis. • They also can be recommended for patients with dysbetalipoproteinemia (elevated beta-very LDL). • Fibrate therapy should be considered an option for treatment of patients with established CHD who have low levels of LDL-C and atherogenic dyslipidemia. • They also should be considered in combination with statin therapy in patients who have elevated LDL-C and atherogenic dyslipidemia. 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)**[214]	Lipid management • Goal: treatment with statin therapy; use statin therapy to achieve LDL-C of <100 mg/dL; for very high risk patients an LDL-C <70 mg/dL is reasonable; if TG are ≥200 mg/dL, non-HDL-C should be <130 mg/dL, whereas non-HDL-C <100 mg/dL for very high risk patients is reasonable. • Lifestyle modifications (daily physical activity and weight management) are strongly recommended for all patients. • In addition to lifestyle modifications, statin therapy should be prescribed in the absence of contraindications or documented adverse events. • An adequate dose of statin should be used that reduces LDL-C to <100 mg/dL and achieves ≥30% lowering of LDL-C. • Patients who have TG ≥200 mg/dL should be treated with statins to lower non-HDL-C to <130 mg/dL. • Patients who have TG >500 mg/dL should be started on fibrate therapy in addition to statin therapy to prevent acute pancreatitis. • If treatment with a statin does not achieve the goal selected for an individual patient, intensification of LDL-C-lowering drug therapy with a bile acid sequestrant or niacin is reasonable. • For patients who do not tolerate statins, LDL-C-lowering therapy with bile acid sequestrants and/or niacin is reasonable. • It is reasonable to treat very high risk patients with statin therapy to lower LDL-C to <70 mg/dL. • In patients who are at very high risk and who have TG ≥200 mg/dL, a non-HDL-C goal of <100 mg/dL is reasonable.

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	• The use of ezetimibe may be considered for patients who do not tolerate or achieve target LDL-C with statins, bile acid sequestrants, and/or niacin. • For patients who continue to have an elevated non-HDL-C while on adequate statin therapy, niacin or fibrate therapy or fish oil may be reasonable. • For all patients, it may be reasonable to recommend omega-3 fatty acids from fist or fish oil capsules (1 g/day) for cardiovascular disease risk reduction.
Institute for Clinical Systems Improvement: **Lipid Management in Adults (2011)**[20]	Clinical highlights • Initiate a statin with patients who have a history of CHD or CHD risk equivalents. • Establish lipid goals based on risk level. • Instruct patients on healthy lifestyle and adjunctive measures. • Patient adherence with recommended therapy should be reinforced during scheduled follow-up. • An LDL goal <70 mg/dL can be considered for patients with established coronary artery disease, non-cardiac atherosclerosis, or coronary artery disease equivalent. Ongoing drug therapy • The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). • Combination therapy can be considered on an individual basis. • No primary prevention trials have addressed pharmacologic lipid treatment in patients at low risk for CHD, and there is no evidence to support drug treatment in this population. • Primary prevention trials of pharmacologic lipid-lowering have not shown a decrease in mortality, although most have shown about a 30% reduction in CHD events. Monotherapy • Patients with risk factors for CHD but no history of disease who receive lipid-lowering therapy are likely to experience a decreased risk of CHD. • Patients with a history of CHD often benefit from statin therapy, and trials have consistently shown a decrease in risk of death from CHD. • The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). • Statins are the drugs of choice for lowering LDL-C, and aggressive treatment with statins should be pursued. Statins also have a modest effect on reducing TG and increasing HDL-C. • Several trials with clinical endpoints support the use of statins in primary and secondary prevention. • If a patient is intolerant to a statin, patients should try another statin before ruling all of them out. • Incidence of muscle symptoms or signs is the most prevalent and important adverse effect of statin therapy.

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	• Specific statin and dose should be selected based on cost and amount of lipid-lowering required. • If patients are unable to take a statin, then bile acid sequestrants, niacin, fibric acid derivatives or fibrates, and ezetimibe are available. • Many crystalline (immediate-release) and sustained-release preparations of niacin are available over-the-counter. The extended-release preparation of niacin is a prescription drug. Niacin exerts favorable effects on all lipids and lipoproteins, and is good for mixed hyperlipidemia. • Long-term use of niacin is usually limited for many patients due to side effects (e.g., flushing and pruritus, liver toxicity, gastrointestinal complaints, etc). • Combination therapy with niacin and a statin may increase the risk of myopathy based on early experience with lovastatin. • Prior to initiating a fibric acid (gemfibrozil, fenofibrate, and fenofibrate micronized), lifestyle therapies should be intensified for moderately elevated TG. With fibric acids, TG are reduced 30 to 50%, HDL-C is increased 10 to 20%, TC is reduced 5 to 20% in patients without elevated TG, and the effect on LDL-C is variable. Fibric acids are good for severe hypertriglyceridemia (>500 mg/dL) in patients at risk for pancreatitis and for prevention of CHD (not proven for fenofibrate). • Myositis, cholelithiasis, and cholecystitis can occur with fibric acid, and caution should be exercised with a history of liver disease. • The long-term effects of ezetimibe on cardiovascular morbidity and mortality are unknown. Ezetimibe is associated with a LDL-C lowering of about 18%, and additive LDL-C lowering occurs when used in combination with a statin. • The short-term tolerability of ezetimibe is similar to placebo, and the long-term safety is unknown. • Bile acid sequestrants reduce LDL-C by 15 to 30% and TG may increase 15%; therefore, are these agents are useful for patients with moderately elevated LDL-C. The effects of the bile acid sequestrants are apparent within one week and maximum at two to three weeks. Bile acid sequestrants are good for combination therapy and are most potent with a statin. • Bile acid sequestrants are not systemically absorbed; therefore, side effects are limited to the gastrointestinal tract. In addition, drug interactions are minimized by taking other medications one hour before the sequestrant or four hours after. <u>Combination therapy</u> • It has become common practice to adjust medication therapy, including using combinations of medications, to achieve LDL-C goals. Common combinations include statin/fibrate, statin/niacin, and statin/ezetimibe. o A fibrate is commonly added to a statin, which results in enhanced lowering of LDL-C, as well as a higher incidence of myopathy. o No published clinical trial to date has evaluated the clinical benefit of combination therapy with a statin and niacin on vascular events. o The addition of ezetimibe to a statin significantly improves

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	LDL-C over either agent alone. To date no large clinical trials have been completed evaluating this combination therapy compared to statin monotherapy on clinical vascular endpoints. • Combinations of lipid-lowering agents do not improve clinical outcomes more than statin monotherapy. • Combination therapy can be considered on an individual basis, but the additional cost, complexity, and risk for side effects argue against routine use until further trials indicate what groups of patients might benefit. • There are negative trials of cholesterylester transfer protein inhibitors when used in combination with statins. • No randomized-controlled trials looking at clinical vascular endpoints are available for other agents such as fish oils or bile-acid sequestrants used in combination therapy. 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-C level is lowered to the target range. • A diet low saturated and trans fats, and high in soluble fiber, with consideration given to adding two grams of plant sterol/stanol is recommended. • Vitamin E supplementation should not be used. • Light to moderate consumption of alcohol may lower CHD rates. • Omega-3 fatty acids should be recommended in patients with dyslipidemia (one gram of EPA/DHA by capsule supplement, or by eating at least two servings per week of fatty fish).
American Heart Association: **Drug Therapy of High Risk Lipid Abnormalities in Children and Adolescents: A Scientific Statement From the American Heart Association (2007)**[215]	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high risk lipid abnormalities, the presence of additional risk factors or high risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high risk lipid abnormalities in children is needed to evaluate the long term efficacy and safety and impact on the atherosclerotic disease process. • Niacin is rarely used to treat the pediatric population. • Given the reported poor tolerance, the potential for very serious adverse effects, and the limited available data, niacin cannot be routinely recommended but may be considered for selected patients. • This guideline does not contain recommendations regarding the use of omega-3 acid ethyl esters.
European Society of Cardiology and Other Societies: **Guidelines on Cardiovascular Disease**	Drugs • Currently available lipid-lowering drugs include statins, fibrates, bile acid sequestrants, niacin, and selective cholesterol absorption inhibitors (e.g., ezetimibe).

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Prevention in Clinical Practice (2012)[21]	• Statins, by reducing LDL-C, reduce cardiovascular morbidity and mortality as well as the need for coronary artery interventions. • Statins should be used as the drugs of first choice in patients with hypercholesterolemia or combined hyperlipidemia. • Selective cholesterol absorption inhibitors are not used as monotherapy to decrease LDL-C. • Bile acid sequestrants also decrease TC and LDL-C, but tend to increase TG. • Fibrates and niacin are used primarily for TG lowering and increasing HDL-C, while fish oils (omega-3 fatty acids) in doses of 2 to 4 g/day are used for TG lowering. • Fibrates are the drugs of choice for patients with severely elevated TG, and prescription omega-3 fatty acids might be added if elevated TG is not decreased adequately. <u>Drug combinations</u> • Patients with dyslipidemia, particularly those with established cardiovascular disease, diabetes, or asymptomatic high risk patients, may not always reach treatment targets; therefore, combination treatment may be needed. • Combinations of a statin and a bile acid sequestrants or a combination of a statin and ezetimibe can be used for greater reduction in LDL-C than can be achieved with either agent used as monotherapy. • Another advantage of combination therapy is that lower doses of statins can be utilized, thus reducing the risk of adverse events associated with high dose statin therapy. However, statins should be used in the highest tolerable dose to reach LDL-C target level before combination therapy is initiated. • Combinations of niacin and a statin increase HDL-C and decrease TG better than either drug used as monotherapy, but flushing is the main adverse event with niacin, which may affect compliance. • Fibrates, particularly fenofibrate, may be useful, not only for decreasing TG and increasing HDL-C, but can further lower LDL-C when administered in combination with a statin. • If target levels cannot be reached with maximal doses of lipid-lowering therapy or combination therapy, patients will still benefit from treatment to the extent to which dyslipidemia has been improved. In these patients, increased attention to other risk factors may help to reduce total risk.
American Association of Clinical Endocrinologists: **Guidelines for the management of dyslipidemia and prevention of atherosclerosis (2012)**[216]	• Aggressive lipid-modifying therapy is recommended to lower LDL-C to <100 mg/dL in patients with average or elevated LDL-C. This has been shown to reduce vascular mortality in patients at high risk. • An LDL-C goal <70 mg/dL is recommended as an appropriate goal for *all* patients with established coronary artery disease. Current evidence indicates that LDL-C can be aggressively lowered with statin therapy regardless of baseline levels and suggests that there is no threshold below which LDL-C lowering ceases to be effective. • Patients for whom aggressive therapy is recommended: o Patients undergoing coronary artery bypass graft. o Patients with acute coronary syndrome (ACS). o Certain healthy and functional older patients at high risk. • Statins are the drug of choice for LDL-C reduction on the basis of

Clinical Guideline	Recommendation
	findings from morbidity and mortality outcome trials. Agents currently available are atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and pitavastatin. • Fibrates are recommended for treatment of severe hypertriglyceridemia (triglycerides >500 mg/dL). Adjunct use of 2 to 4 g of omega 3 acids can be used, if necessary, to achieve satisfactory triglyceride lowering. • Niacin is recommended for reducing triglycerides, increasing HDL-C, and reducing LDL-C. Adjunct use of 2 to 4 g of omega-3 fish oil can be used, if necessary, to achieve satisfactory triglyceride lowering. • Bile acid sequestrants are recommended for reducing LDL-C and apolipoprotein B and modestly increasing HDL-C, but they may increase triglycerides. Bile acid sequestrants have a glucose-lowering effect; colesevelam is now also approved for treatment of type 2 diabetes. Available agents in this drug class are chole-styramine, colestipol, and colesevelam. • Cholesterol absorption inhibitors are effective as monotherapy in reducing LDL-C and apolipoprotein B. Combination therapy with statins is recommended because current research indicates that this enhances these benefits and further improves the beneficial effects of statins on triglycerides and HDL-C. It is uncertain whether cholesterol absorption inhibitor therapy has a direct benefit on reducing cardiovascular events. • Combination therapy be considered in the following circumstances: o When the cholesterol level is markedly increased and monotherapy does not achieve the therapeutic goal. o When mixed dyslipidemia is present. o Niacin or fibrates in combination with statins may be appropriate options for many patients with hypertriglyceridemia and associated low HDL-C. o To reduce the risk of dosage-related adverse effects. • Recommendations for lipid management in children include: o Colesevelam has been approved for patients older than 8 years. o Atorvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin have been approved for the treatment of familial hypercholesterolemia in patients 10 years or older. Cholestyramine may also be used in children.
American Heart Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (2011)**[217]	• Risk factor control for all patients with transient ischemic attack (TIA) or ischemic stroke: • Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA who have evidence of atherosclerosis, an LDL-C level ≥100 mg/dL, and who are without known CHD. • For patients with atherosclerotic ischemic stroke or TIA without known CHD, it is reasonable to target a reduction of ≥50% in LDL-C or a target LDL-C level <70 mg/dL to obtain maximal benefit. • Patients with ischemic stroke or TIA with elevated cholesterol or comorbid coronary artery disease should be otherwise managed according to the National Cholesterol Education Program III guidelines (i.e., lifestyle modification, dietary guidelines, and medication recommendations). • Patients with ischemic stroke or TIA with low HDL-C may be

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	considered for treatment with niacin or gemfibrozil.
American Heart Association/American Stroke Association: **Guidelines for the Early Management of Patients With Acute Ischemic Stroke : A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association (2013)**[218]	• In addition to their LDL-C–lowering effects, statins, or statins, exert acute neuroprotective properties, including beneficial effects on endothelial function, cerebral blood flow, and inflammation. • Among patients already taking statins at the time of onset of ischemic stroke, continuation of statin therapy during the acute period is reasonable.
American College of Cardiology Foundation/American Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infraction (STEMI) (2013)**[219]	• Treatment with statins in patients stabilized after an ACS, including STEMI, lowers the risk of CHD death, recurrent MI, stroke, and the need for coronary revascularization. • Statin therapy after ACS is beneficial even in patients with baseline LDL-C levels <70 mg/dL. • High-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications to its use. • Among currently available statins, only high-dose atorvastatin (80 mg daily) has been shown to reduce death and ischemic events among patients with ACS. • It is reasonable to obtain a fasting lipid profile in patients with STEMI, preferably within 24 hours of presentation. • Longer-term lipid management after STEMI, including indications for targeting TGs and non–HDL-C are addressed in the "AHA/ACC Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Vascular Disease: 2011 Update."
American Heart Association/American College of Cardiology: **2012 Focused Update Incorporated Into the 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction (NSTEMI) (2012)**[220]	• Lipid management should include assessment of a fasting lipid profile for all patients, within 24 hours of hospitalization. • Statins, in the absence of contraindications, regardless of baseline LDL-C and diet modification, should be given to post-unstable angina/NSTEMI patients, including postrevascularization patients. • For hospitalized patients, lipid-lowering medications should be initiated before discharge. • For patients with elevated LDL-C (≥100 mg/dL), cholesterol-lowering therapy should be initiated or intensified to achieve an LDL-C <100 mg/dL. Further titration to <70 mg/dL is reasonable. • Treatment of triglycerides and non-HDL-C is useful, including the following: o If triglycerides are 200 to 499 mg per dL, non-HDL-C should be <130 mg/dL. o If triglycerides are >500 mg/dL, herapeutic options to prevent pancreatitis are a fibrate or niacin before LDL-lowering therapy is recommended. o It is also recommended that LDL-C be treated to goal after triglyceride-lowering therapy. o Achievement of a non-HDL-C <130 mg/dL, if possible, is recommended. • Therapeutic options to reduce non-HDL-C (after LDL-C lowering) include niacin or fibrate therapy. • Nicotinic acid (niacin) and fibric acid derivatives (fenofibrate,

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	gemfibrozil) can be useful as therapeutic options (after LDL-C–lowering therapy) for HDL-C <40 mg/dL. • Nicotinic acid (niacin) and fibric acid derivatives (fenofibrate, gemfibrozil) can be useful as therapeutic options (after LDL-C–lowering therapy) for triglycerides >200 mg/dL. • Encouraging consumption of omega-3 fatty (1 g/day) for risk reduction may be reasonable. • For treatment of elevated triglycerides, higher doses (2 to 4 g/day) may be used for risk reduction.

Conclusions

Atorvastatin (Lipitor®), fluvastatin (Lescol®), lovastatin (Mevacor®), pitavastatin (Livalo®), pravastatin (Pravachol®), rosuvastatin (Crestor®) and simvastatin (Zocor®) are the currently available hydroxymethylglutaryl coenzyme A reductase inhibitors (statins). The statins are the most effective class of medications available for reducing low density lipoprotein cholesterol (LDL-C) and all agents are Food and Drug Administration (FDA)-approved to manage primary hyperlipidemia, as well as other specific lipid abnormalities.[1,3-15] Of the single-entity statins, atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin are available generically. The combination products include amlodipine/atorvastatin (Caduet®), ezetimibe/atorvastatin (Liptruzet®), ezetimibe/simvastatin (Vytorin®), niacin extended-release/lovastatin (Advicor®) and niacin extended-release/simvastatin (Simcor®). Currently the amlodipine/atorvastatin combination is available generically.

Clinical trials consistently demonstrate the benefits of statins on serum lipid levels in patients with lipid disorders. In general, based on the amount of LDL-C lowering required for a particular patient, one statin may be preferred over another; however, all available statins produce significant improvements in baseline serum lipid levels.[23-98,180-205] Guidelines recommend the statins first line when LDL-C lowering is required, with no one agent preferred over another.[1,19-21] Statins have also demonstrated significant cardiovascular benefits in both primary and secondary prevention of coronary heart disease (CHD). Overall, decreases in the risk for acute coronary syndromes, coronary procedures, strokes and other coronary outcomes have been demonstrated.[1,99-179] Of the available statins, atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin have gained FDA approval for the prevention of cardiovascular disease in primary prevention, secondary prevention or both. In terms of preventing cardiovascular disease, guidelines again do not distinguish among the available statins. Statins are recommended in patients with established CHD or CHD risk equivalents and choice of statin, and dose, should be based on cost and the amount of lipid lowering required for a specific patient. Patients with risk factors for CHD, but with no history of disease, are likely to decrease their risk of CHD with lipid lowering therapy.[20]

Of note, in June 2011 the FDA issued a safety warning regarding the highest dose of simvastatin. Specifically, the FDA has recommended that simvastatin 80 mg be restricted due to an increased risk of muscle damage associated with the agent. Patients who have been receiving simvastatin 80 mg for more than 12 months without evidence of myopathy may continue treatment; however, this strength should not be initiated in new patients. In addition, new warnings regarding the use of simvastatin concurrently with certain medications have been made. As a result, the approved labeling for simvastatin (Zocor®) and simvastatin-containing medications (Simcor® [niacin extended-release/simvastatin] and Vytorin® [ezetimibe/simvastatin] have been updated to reflect these new recommendations.[17-18]

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