Therapeutic Class Overview
Niacin Derivatives

Therapeutic Class

- **Overview/Summary:** Niacin favorably affects all lipids and lipoproteins when given in pharmacological doses; however, the mechanism of action is not completely understood.[1-5] Niacin has several effects on lipid metabolism including inhibition of hepatic production of very low-density lipoprotein cholesterol, and consequently its metabolite low-density lipoprotein cholesterol. In addition, it decreases plasma concentrations of triglycerides (20 to 50%), very low-density lipoprotein remnants, and intermediate density lipoprotein. Administration of niacin also causes a shift in low-density lipoprotein composition from small, dense particles to larger, more buoyant particles. Lastly, niacin increases high density lipoprotein cholesterol (15 to 35%) both by reducing lipid transfer of cholesterol from high density lipoprotein cholesterol to very low-density lipoprotein cholesterol, and by delaying high density lipoprotein cholesterol clearance. Niacin can decrease low-density lipoprotein cholesterol by 5 to 25%.[1-5]

  There are over-the-counter niacin products that are currently available, and these products are labeled as dietary supplements. While these supplements are "generally recognized as safe", the Food and Drug Administration (FDA) does not examine the efficacy and safety of these products or regulate the manufacturing process. The FDA has imposed statutory restrictions prohibiting manufacturers of dietary supplements from claiming that their products "treat, cure, or prevent any disease". Without FDA regulation, the content of nicotinic acid in niacin products is not guaranteed.[6]

Table 1. Medications Included Within the Therapeutic Class Review[4-12]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Niacin (Niacor®, Niaspan®*)	To reduce elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B and triglycerides, and to increase high density lipoprotein cholesterol in patients with primary hyperlipidemia and mixed dyslipidemia; In combination with simvastatin or lovastatin: to treat primary hyperlipidemia and mixed dyslipidemia when treatment with niacin, simvastatin, or lovastatin monotherapy is considered inadequate; To reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hyperlipidemia.; In combination with a bile acid binding resin: slows progression or promotes regression of atherosclerotic disease in patients with a history of coronary artery disease and hyperlipidemia and as an adjunct to diet to reduce elevated total cholesterol and low-density lipoprotein cholesterol in adult patients with primary hyperlipidemia; To reduce triglycerides in adult patients with severe hypertriglyceridemia; Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia; nicotinic acid, alone or in combination with a bile-acid binding resin, is indicated as an adjunct to diet for the reduction of elevated total and low-density lipoprotein cholesterol	Extended-release tablet (Niaspan®):* 500 mg 750 mg 1,000 mg Tablet (Niacor®):* 500 mg	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	levels in patients with primary hypercholesterolemia (Types IIa and IIb), when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate; prior to initiating therapy with nicotinic acid, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure total cholesterol, high density lipoprotein cholesterol, and triglycerides; Adjunctive therapy for the treatment of adult patients with very high serum triglyceride levels (Types IV and V hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them; such patients typically have serum triglyceride levels over 2,000 mg/dL and have elevations of very low-density lipoprotein cholesterol as well as fasting chylomicrons (Type V hyperlipidemia); subjects who consistently have total serum or plasma triglycerides below 1,000 mg/dL are unlikely to develop pancreatitis; therapy with nicotinic acid may be considered for those subjects with triglyceride elevations between 1,000 and 2,000 mg/dL who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis; some Type IV patients with triglycerides under 1,000 mg/dL may, through dietary or alcoholic indiscretion, convert to a Type V pattern with massive triglyceride elevations accompanying fasting chylomicronemia, but the influence of nicotinic acid therapy on the risk of pancreatitis in such situations has not been adequately studied; drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low-density lipoprotein; inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV, and V hyperlipoproteinemia		

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

Evidence-based Medicine

- Clinical trials have demonstrated the safety and efficacy of the niacin derivatives.[7-35]
- In a trial comparing niacin extended-release and immediate-release formulations, doses ≥1,500 mg/day of niacin extended-release decreased low-density lipoprotein cholesterol to a significantly greater extent (P<0.04 or P<0.01); however, at all doses niacin immediate-release significantly increased high-density lipoprotein cholesterol (P<0.04 or P<0.01). Reductions in triglycerides were similar between the two formulations, except for niacin immediate-release 1,000 mg/day which led to significantly greater reductions (P=0.009).[4]

- Direct comparisons of niacin with other lipid modifying agents demonstrated that no one medication class is consistently more efficacious over another in achieving significant alterations in individual lipid parameters, and results support the use of the niacin as combination therapy with other lipid modifying agents.[7-35]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[36-43]
    - In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia.
    - When low-density lipoprotein cholesterol (LDL-C) lowering is required, initial treatment with a statin, a bile acid sequestrant or niacin is recommended. However, in general, the statins are considered first line therapy for decreasing LDL-C levels, and are recommended in patients with established coronary heart disease or coronary heart disease equivalents.
    - In patients with an elevated triglyceride level (≥500 mg/dL) a fibric acid derivative or niacin should be initiated before LDL-C lowering therapy to prevent pancreatitis.
    - Omega-3-acid ethyl esters represent an alternative to fibric acid derivatives and niacin for the treatment of hypertriglyceridemia.
- Other Key Facts:
    - Prescription niacin is approved by the Food and Drug Administration (FDA) for the treatment of hypertriglyceridemia.
    - Prescription niacin is also approved for the treatment of primary hypercholesterolemia and mixed dyslipidemia.[4-5]
    - Niacin is available over-the-counter in immediate-release and sustained-release formulations.
    - Niacin is also available by prescription as immediate-release (Niacor®) and extended-release (Niaspan®) formulations.

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Therapeutic Class Review
Niacin Derivatives

Overview/Summary

Niacin favorably affects all lipids and lipoproteins when given in pharmacological doses; however, the mechanism of action is not completely understood.[1-5] Niacin has several effects on lipid metabolism including inhibition of hepatic production of very low-density lipoprotein cholesterol, and consequently its metabolite low-density lipoprotein cholesterol. In addition, it decreases plasma concentrations of triglycerides (20 to 50%), very low-density lipoprotein remnants, and intermediate density lipoprotein. Administration of niacin also causes a shift in low-density lipoprotein composition from small, dense particles to larger, more buoyant particles. Lastly, niacin increases high density lipoprotein cholesterol (15 to 35%) both by reducing lipid transfer of cholesterol from high density lipoprotein cholesterol to very low-density lipoprotein cholesterol, and by delaying high density lipoprotein cholesterol clearance. Niacin can decrease low-density lipoprotein cholesterol by 5 to 25%.[1-5]

There are over-the-counter niacin products that are currently available, and these products are labeled as dietary supplements. While these supplements are "generally recognized as safe", the Food and Drug Administration (FDA) does not examine the efficacy and safety of these products or regulate the manufacturing process. The FDA has imposed statutory restrictions prohibiting manufacturers of dietary supplements from claiming that their products "treat, cure, or prevent any disease". Without FDA regulation, the content of nicotinic acid in niacin products is not guaranteed.[6]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Niacin (Niacor®, Niaspan®*)	Miscellaneous Antilipemic Agent	✔

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

Indications

Table 2. Food and Drug Administration Approved Indications[4-5]

Indication	Niacin Extended-Release*	Niacin Immediate-Release
To reduce elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B and triglycerides, and to increase high density lipoprotein cholesterol in patients with primary hyperlipidemia and mixed dyslipidemia	✔	
In combination with simvastatin or lovastatin: to treat primary hyperlipidemia and mixed dyslipidemia when treatment with niacin, simvastatin, or lovastatin monotherapy is considered inadequate	✔	
To reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hyperlipidemia.	✔	
In combination with a bile acid binding resin: • Slows progression or promotes regression of atherosclerotic disease in patients with a history of coronary artery disease and hyperlipidemia • As an adjunct to diet to reduce elevated total	✔	

Indication	Niacin Extended-Release*	Niacin Immediate-Release
cholesterol and low-density lipoprotein cholesterol in adult patients with primary hyperlipidemia		
To reduce triglycerides in adult patients with severe hypertriglyceridemia	✔	
Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia; nicotinic acid, alone or in combination with a bile-acid binding resin, is indicated as an adjunct to diet for the reduction of elevated total and low-density lipoprotein cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb), when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate; prior to initiating therapy with nicotinic acid, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure total cholesterol, high density lipoprotein cholesterol, and triglycerides		✔
Adjunctive therapy for the treatment of adult patients with very high serum triglyceride levels (Types IV and V hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them; such patients typically have serum triglyceride levels over 2,000 mg/dL and have elevations of very low-density lipoprotein cholesterol as well as fasting chylomicrons (Type V hyperlipidemia); subjects who consistently have total serum or plasma triglycerides below 1,000 mg/dL are unlikely to develop pancreatitis; therapy with nicotinic acid may be considered for those subjects with triglyceride elevations between 1,000 and 2,000 mg/dL who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis; some Type IV patients with triglycerides under 1,000 mg/dL may, through dietary or alcoholic indiscretion, convert to a Type V pattern with massive triglyceride elevations accompanying fasting chylomicronemia, but the influence of nicotinic acid therapy on the risk of pancreatitis in such situations has not been adequately studied; drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low-density lipoprotein; inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV, and V hyperlipoproteinemia		✔

*No incremental benefit of niacin extended release coadministered with simvastatin or lovastatin on cardiovascular morbidity and mortality over and above that demonstrated for niacin, simvastatin and lovastatin monotherapy, has been established. Niacin extended release, at doses of 1,500 to 2,000 mg/day, in combination with simvastatin, did not reduce the incidence of cardiovascular events more than simvastatin in a randomized controlled trial of patients with cardiovascular disease and mean baseline low-density lipoprotein cholesterol levels of 74 mg/dL.

Pharmacokinetics

Table 3. Pharmacokinetics[1-5]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (minutes)
Niacin	Extended release: 60 to 76	Not reported	Liver (rapid; percent not reported)	Renal (60 to 76)	Immediate release: 20 to 45

Clinical Trials

Clinical trials have demonstrated the safety and efficacy of the niacin derivatives.[7-35] In a trial comparing niacin extended-release and immediate-release formulations, doses ≥1,500 mg/day of niacin extended-release decreased low-density lipoprotein cholesterol to a significantly greater extent (P<0.04 or P<0.01); however, at all doses niacin immediate-release significantly increased high-density lipoprotein cholesterol (P<0.04 or P<0.01). Reductions in triglycerides were similar between the two formulations, except for niacin immediate-release 1,000 mg/day which led to significantly greater reductions (P=0.009).[4] Direct comparisons of niacin with other lipid modifying agents demonstrated that no one medication class is consistently more efficacious over another in achieving significant alterations in individual lipid parameters, and results support the use of the niacin as combination therapy with other lipid modifying agents.[7-35]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypercholesterolemia				
Elam et al.[7] (2000) Niacin IR (Niacor®) 3,000 mg per day or maximum tolerated dosage vs placebo	MC, PC, RCT Patients with peripheral arterial disease with or without diabetes, mean age 67 years for patients with diabetes and 65 years for those without diabetes	N=468 (N=125 patients with diabetes) Up to 60 weeks (12-week active run-in and 48-week DB)	Primary: Change in lipid profile, glucose, HbA_{1c}, ALT, uric acid; hypoglycemic drug use, compliance, adverse events Secondary: Not reported	Primary: Niacin use significantly increased HDL-C by 29 and 29% and decreased TG by 23 and 28% and LDL-C by 8 and 9%, respectively, in participants with and without diabetes compared to baseline (P<0.001 for niacin vs placebo for all). Glucose levels were modestly increased by niacin (8.7 and 6.3 mg/dL; P=0.04 and P<0.001) in participants with and without diabetes, respectively. HbA_{1c} levels were unchanged from baseline to follow-up in participants with diabetes treated with niacin. In participants with diabetes treated with placebo, HbA_{1c} decreased by 0.3% (P=0.04 for difference). There were no significant differences in niacin discontinuation, niacin dosage, or hypoglycemic therapy in participants with diabetes assigned to niacin vs placebo. Secondary: Not reported
Capuzzi et al.[8] (1998) Niacin ER (Niaspan®) titrated to 1 to 3 g per day Concomitant therapy with a statin, bile acid sequestrant or both was permitted if the patient did not achieve sufficient LDL-C reduction.	ES, MC, OL Patients with primary hyper-cholesterolemia who were previously enrolled in a randomized short-term study or in a placebo-only qualification clinical trial	N=517 Up to 96 weeks	Primary: Changes in LDL-C and apo B Secondary: Changes in TC, HDL-C, TC:HDL-C, Lp(a) and TG; adverse events	Primary: Patients receiving niacin experienced significant reductions in LDL-C by 18% at week 48 and 20% at week 96. Similar reductions were seen with apo B (16% at week 48 and 19% at week 96). The percent changes achieved by both 48 and 96 weeks of therapy were statistically significant (P<0.001). Secondary: HDL-C significantly increased by 26% at week 48 and 28% at week 96 in patients receiving niacin. TC modestly decreased (12 and 13%, respectively), whereas the TC:HDL-C ratio decreased by almost one third (P<0.001 for all). TG and Lp(a) levels were decreased by 27 and 30%, respectively, at

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				week 48, and by 28 and 40%, respectively, at week 96 (P<0.001 for all). Niacin was generally well tolerated. Flushing was common (75%); however, there was a progressive decrease in flushing with time from 3.3 episodes in the first month to ≤1 episode by week 48. Aspirin was used by one third of patients before niacin dosing to minimize flushing episodes. Six percent of patients discontinued therapy due to flushing. Serious adverse events occurred in about 10% of patients; however, none were considered probably or definitely related to niacin. No deaths or myopathy occurred. There were statistically significant increases in alkaline phosphatase, ALT, amylase, AST, direct bilirubin, glucose, and uric acid and a decrease in phosphorus (P<0.001 for all). Mean platelet counts decreased by 10.1% at week 48 and 14.8% at week 96, whereas leukocyte counts increased by 6.5 and 6.8%, respectively, at week 48 and week 96 of therapy (P<0.0001 for all).
Guyton et al.[9] (1998) Niacin ER (Niaspan®) titrated to 1 to 3 g per day Concomitant therapy with a statin, bile acid sequestrant or both was permitted if the patient did not achieve sufficient LDL-C reduction.	ES, MC, OL Patients with primary hyperlipidemia who were previously enrolled in an RCT or in a placebo-only qualification clinical trial	N=269 patients treated up to 96 weeks and a cohort of N=230 patients treated for 3 months (safety data)	Primary: Changes in TC, LDL-C, HCL-C, TG, apo B and Lp(a); safety Secondary: Not reported	Primary: The dosages of niacin attained by 269 patients were 1,000 mg (95% of patients), 1,500 mg (86%) and 2,000 mg (65%). After 96 weeks of treatment, niacin alone (median dose 2,000 mg) significantly reduced LDL-C (18%), TC (10%), and TG (26%), and increased HDL-C (32%). Apo B and Lp(a) were significantly reduced by 26 and 36%, respectively, at 48 weeks but values for these parameters were not available at 96 weeks (P<0.01 for all). At 96 weeks of the study, niacin plus a statin significantly lowered LDL-C (32%), TC (24%), and TG (32%) and increased HDL-C (25%) (P<0.01 for all values). Apo B (26%; P<0.01) and Lp(a) (19%; P value not significant) were also reduced at 48 weeks but values for these parameters were not available at 96 weeks. Niacin plus a bile acid sequestrant lowered LDL-C (28%) and TC (15%) and increased HDL-C (31%) (P<0.01 for all values). Niacin plus a bile acid sequestrant increased TG (5%; P value not significant). Apo B and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Lp(a) were significantly reduced by 19 and 24% (P<0.01), respectively, at 48 weeks but values for these parameters were not available at 96 weeks. Intolerance to flushing led 4.8% of participants (13 of 269) to discontinue niacin. (Combining all of the data, 7.3% of patients discontinued niacin due to flushing.) Other medication-related adverse events leading to discontinuation from the 96-week study included nausea (3.3% of patients) sometimes with vomiting, other gastrointestinal symptoms (1.5%) and pruritus (2.6%). One case each of acanthosis nigricans, elevated glucose, gout, headache, palpitations and shoulder pain led to patient withdrawal. Overall, nine of 499 (2.6%) patients experienced an ALT or AST elevation >2 times upper limit of normal. Five of these patients were on combination therapy, including four with a statin and one with a bile acid sequestrant. In five of the nine cases, the transaminase elevation resolved while niacin was continued without reduction in dose. Three cases led to niacin dosage reduction. One patient discontinued niacin because of transaminase elevations. Leg aches and myalgias with normal creatine kinase levels were described in one patient taking niacin with simvastatin. Secondary: Not reported
Gray et al.[10] (1994) Niacin SR (Slo-Niacin®) average maintenance dose of 1.67 g per day	RETRO Male veterans with dyslipoproteinemia who were treated with niacin	N=969 1 to 36 months	Primary: Changes in lipid profile, alterations in hepatic enzymes and blood chemistry tests, hepatotoxicity Secondary: Not reported	Primary: Lipoprotein responses were dose-related and favorable. Results included the following: TC,-19.1%; LDL-C , 24.0%; HDL-C, 5.7%; and TG, -32.5% (P≤0.0035 for all). Statistically but not clinically meaningful dose-related increases were seen in levels of liver enzymes and serum glucose (AST, 29%; ALT, 23%, alkaline phosphatase, 25%; and glucose, 7%; P=0.0001). Niacin was discontinued in 48.5% (435 of 896) of patients primarily because of adverse effects. The primary documented reasons for discontinuation included flushing and itching (8.9%), increased serum

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				glucose (4.8%), gastrointestinal complaints (3.7%) and increased liver function tests (3.7%). Poor glycemic controlled to discontinuation in 40.6% (43 of 106) patients with diabetes mellitus. Twenty of 896 (2.2%) and 42 of 896 (4.7%) patients met biochemical criteria for "probable" and for "possible or probable" niacin-induced hepatotoxicity, respectively. Predisposing factors included high dose, alcohol use, preexisting liver disease and concurrent oral sulfonylurea therapy. Secondary: Not reported
Grundy et al.[11] (2002) Niacin ER (Niaspan®) 1,000 mg per day vs niacin ER (Niaspan®) 1,500 mg per day vs placebo	DB, PC, RCT Patients with stable type 2 diabetes, 47% were receiving concomitant statin therapy	N=148 16 weeks	Primary: Change in HDL-C, TG, HbA_{1c} Secondary: TC, LDL-C, FBG, adverse effects	Primary: Dose-dependent increases in HDL-C (13 to 19% for the 1,000 mg dose and 22 to 24% for the 1,500 mg dose; both P<0.05 vs placebo) and reductions in TG levels (-15 to -20% for the 1,000 mg dose; P value not significant, and -28 to -36% for the 1,500 mg dose; P<0.05) were observed. Changes in HbA_{1c} levels from baseline to week 16 were no different for niacin 1,000 mg/day (7.28 and 7.35%; P=0.16) and placebo (7.13 and 7.11%) but were significantly different for niacin 1,500 mg/day (7.2 and 7.5%; P=0.048). Secondary: Mean LDL-C levels were not significantly different than baseline for the placebo and niacin 1,000 mg groups. In the niacin 1,500 mg group, LDL-C levels decreased at all time points and the difference vs placebo was statistically significant at weeks 12 and 16 (P<0.05). The mean changes from baseline at 16 weeks were 9, 5 and -7% in the placebo, niacin 1,000 mg and 1,500 mg groups, respectively. Similar trends were observed for TC with mean increases of 4% in both the placebo and niacin 1,000 mg groups and a decrease of -6% in the niacin ER 1,500 mg group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In both the niacin groups, an initial rise in FBG was observed between weeks four and eight which returned to baseline by week 16. Four patients in the niacin group (three patients were receiving 1,500 mg) discontinued participation because of inadequate glucose control. Rates of adverse events other than flushing were similar for the niacin and placebo groups. Flushing was reported by about 67% of patients receiving niacin ER and about 10% of patients receiving placebo. Four patients, including 1 patient in the placebo arm, withdrew from the study due to flushing. No hepatotoxic effects or myopathy was observed.
Kuvin et al.[12] (2006) Niacin ER (Niaspan®) initially 500 mg at bedtime for 2 weeks then 1,000 mg at bedtime vs placebo	PC, RCT Patients with stable CAD and LDL-C <100 mg/dL, all received concurrent statin therapy (>80% atorvastatin)	N=60 3 months	Primary: Changes in lipoproteins, HDL and LDL particle distribution and inflammatory markers Secondary: Not reported	Primary: Six patients did not complete the protocol, two discontinued treatment due to flushing, and four were lost to follow-up. Niacin significantly increased total HDL-C by 7.5% and decreased TG by 15% compared to baseline (P<0.005 for both), whereas TC and LDL-C remained unchanged. Compared to baseline values, the addition of niacin resulted in a 32% increase in large-particle HDL (P<0.001) and an 8% decrease in small-particle HDL (P=0.0032). Addition of niacin produced an 82% increase in large-particle LDL (P=0.09) and a 12% decrease in small-particle LDL (P=0.008). Niacin also favorably altered inflammatory markers with lipoprotein-associated phospholipase A2 and CRP levels decreasing by 20 and 15%, respectively, compared to baseline (P<0.05 for both). No significant changes from baseline were seen in any tested parameter in patients who received placebo. No major cardiovascular events were reported during the study in the treatment or placebo group. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Knopp et al.[13] (1998) Niacin IR titrated to 3 g per day vs niacin ER (Niaspan®) titrated to 1.5 g per day vs placebo	DB, MC, PG, RCT Patients with hyper-cholesterolemia, average age 54 years	N=223 25 weeks (9 week lead-in period)	Primary: Change in LDL-C, FPG, uric acid, drug tolerance Secondary: Change in TC, TG, HDL-C, HDL sub-fractions, apo B, apo AI, apo E, and Lp(a)	Primary: LDL-C was significantly reduced by 12, 12 and 22%, respectively, by niacin ER 1.5 g at bedtime, niacin IR 1.5 g/day, and niacin IR 3 g/day, respectively, compared to placebo (P≤0.05). At equal doses of 1.5 g/day of niacin ER vs niacin IR, AST increased 5.0 vs 4.8% (P value not significant), FPG increased 4.8 vs 4.5% (P value not reported), and uric acid concentration increased 6 vs 16% (P=0.0001), respectively. Flushing events were more frequent with niacin IR vs niacin ER (1,905 vs 575; P<0.001). Flushing severity was slightly greater with SR niacin, but still well tolerated. Secondary: Compared to placebo at eight weeks, niacin SR 1.5 g at bedtime vs niacin IR 1.5 g/day showed comparable efficacy in lowering TC, TG, apo B, apo E and Lp(a), and raising HDL-C, HDL2-C, HDL3-C and apo AI (P≤0.05 in all instances). Niacin IR 3 g/day produced significantly greater changes in the above lipid parameters compared to niacin IR 1.5 g/day and niacin ER 1.5 g at bedtime (P≤0.05).
McKenney et al.[14] (1994) Niacin IR BID, for a total daily dose of 500, 1,000, 1,500, 2,000 and 3,000 mg for 6 weeks each vs niacin ER BID, for a total daily dose of 500, 1,000,	DB, PG, RCT Patients with LDL-C >160 mg/dL after 1 month on a NCEP ATP III-Step 1 diet	N=46 36 weeks	Primary: Changes in LCL-C, HDL-C and TG; adverse events Secondary: Not reported	Primary: Niacin ER significantly decreased LDL-C more than niacin IR with doses of ≥1,500 mg/day (P<0.04 or P<0.001). Niacin IR significantly increased HDL-C more than niacin ER with all doses (P<0.04 or P<0.001). The reductions in TG levels were similar between niacin IR and ER with all doses, except for niacin IR 1,000 mg/day which led to significantly greater reductions (P=0.009). Nine of 23 patients (39%) receiving niacin IR withdrew before completing

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
1,500, 2,000 and 3,000 mg for 6 weeks each				the 3,000 mg/day dose. Four patients withdrew at 1,000 mg/day, one at 1,500 mg/day, three at 2,000 mg/day and one at 3,000 mg/day. The most common reasons for withdrawal were vasodilatory symptoms, fatigue and acanthosis nigricans. Eighteen of 23 patients (78%) receiving niacin ER withdrew before completing the 3,000 mg/day dose. Two patients withdrew at 1,000 mg/day, two at 1,500 mg/day, seven at 2,000 mg/day and seven at 3,000 mg/day. The most common reasons for withdrawal were gastrointestinal tract symptoms, fatigue and increases in liver function tests, often with symptoms of hepatic dysfunction. None of the patients receiving niacin IR developed hepatotoxic effects, while 12 patients (52%) receiving niacin ER did. Secondary: Not reported
Superko et al.[15] (2004) Niacin IR 3,000 mg/day vs niacin ER (Niaspan®) 1,500 mg/day vs placebo Results of 38 patients receiving niacin ER 3,000 mg/day from a previous trial were utilized in this analysis.	PC, RCT Patients with hyper-cholesterolemia	N=218 14 weeks	Primary: Changes in lipid profile and Lp subclass distribution Secondary: Not reported	Primary: Niacin IR and ER significantly decreased TG, LDL-C, apo B and Lp(a), and significantly increased HDL-C (P≤0.0001 for all). Niacin IR and ER significantly increased mean LDL peak particle diameter and percent distribution of large LDL I and IIa, with a significant decrease in small LDL IIIa, IIIb, and IVb (P<0.05 for all, except for LDL I; P=0.12 for niacin ER). In general, the effects were greater in patients with LDL pattern B (predominance of dense LDL) compared to those with LDL pattern A (predominance of buoyant LDL). Compared to niacin IR, niacin ER 3,000 mg/day produced a smaller decrease in TG (-27 vs -47%; P<0.001), but had similar changes in LDL-C (-20 vs -22%; P value not reported), apo B (-22 vs -21%; P value not reported), HDL-C (27 vs 28%; P value not reported) and LDL peak particle diameter (0.90 vs 0.76 mm; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Wi et al.[16] (2010) Niacin ER 500 mg/day for 5 weeks, followed by 1,000 mg/day for 4 weeks, followed by 1,500 mg/day vs fenofibrate 160 mg/day After discontinuation of any lipid modifying drug, patients entered an 8 week dietary run in period.	OL, RCT Patients 20 to 79 years of age with TG 150 to 499 mg/dL and HDL-C <45 mg/dL	N=201 24 weeks (includes 8 week dietary run in period)	Primary: Percent change from randomization to week 16 in apo B/apo AI Secondary: Percent changes in other lipid parameters, levels of glucose metabolism-related parameters, hsCRP	Primary: Apo B/apo AI was reduced with both treatments with no difference between the two (P=0.47). The percent reduction in apo B was greater with niacin, whereas the percent elevation in apo AI was higher with fenofibrate. Secondary: TC significantly decreased with both treatments, and TG decreased and HDL-C increased. LDL-C increased with fenofibrate but decreased with niacin. The percent reduction in TC was greater with niacin (P=0.01). TG decreased significantly more with fenofibrate (P=0.045), whereas the percent elevation in HDL-C was not different between the two treatments (P=0.22). The percent change in LDL-C was significantly different with the two treatments (P<0.001). Lp(a) levels were reduced with niacin only, and the change was significantly different compared to fenofibrate (P<0.001). FPG levels decreased with fenofibrate and increased significantly with niacin. HbA_{1c} levels increased with both treatments; the increase was borderline with fenofibrate and significant with niacin. The percent changes in FPG (P<0.001) and HbA_{1c} (P<0.001) levels were significantly different between the two treatments. Fasting insulin levels showed a borderline reduction with fenofibrate and a significant increase with niacin. HOMA-IR was decreased with fenofibrate and was increased with niacin. Percent changes of insulin (P<0.001) and HOMA-IR (P<0.001) were significantly different between the two treatments. hsCRP levels were significantly lowered with both treatments, but the percent change was greater with niacin (P=0.03).
Balasubramanyam et al.[17] (2011) Usual care vs	DB, PC, RCT Patients 21 to 65 years of age with hyper-triglyceridemia	N=191 24 weeks	Primary: Baseline changes in lipid parameters Secondary:	Primary: Patients receiving fenofibrate achieved significant improvements in TG (P=0.002), TC (P=0.02), and non-HDL-C (P=0.003), compared to patients receiving niacin who achieved significant improvements in HDL-C (P=0.03), and both groups of patients achieved significant improvements in TC:HDL-C (P=0.005 and P=0.01). The combination of D/E plus

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low saturated fat diet and exercise (D/E) vs D/E and fenofibrate 145 mg/day (Tricor®) vs D/E and niacin SR 2,000 mg/day (Niaspan®) vs D/E and fenofibrate 145 mg/day and niacin SR 2,000 mg/day	(fasting TG >150 mg/dL)		Baseline changes in insulin sensitivity, glycemia, adiponectin, CRP, energy expenditure, and body composition	fenofibrate plus niacin provided maximal benefit, reducing TG (-52% vs usual care; P=0.003), increasing HDL-C (12% vs usual care; P<0.001), and decreasing non-HDL-C (-18.5% vs usual care; P=0.003) and TC:HDL-C (-24.5% vs usual care; P<0.001). Secondary: Of the secondary endpoints evaluated, there was an effect of niacin on FPG (P=0.0002), oral glucose tolerance test area under the curve for glucose (P=0.02), fasting insulin (P=0.03), HOMA-IR (P=0.008), insulin sensitivity index (P=0.007), and adiponectin (P<0.0001), and an effect of fenofibrate on creatinine (P=0.002).
Guyton et al.[18] (2000) Niacin ER (Niaspan®) titrated up to 1,000 mg at bedtime for 4 weeks, followed by 1,500 mg at bedtime for 4 weeks, followed by 2,000 mg at bedtime for 8 weeks vs gemfibrozil 600 mg BID	DB, MC, PC, RCT Patients 21 to 75 years of age with HDL-C ≤40 mg/dL, LDL-C ≤160 or <130 mg/dL with atherosclerotic disease and TG ≤400 mg/dL	N=173 8 weeks	Primary: Effect on HDL-C Secondary: Change in other lipoproteins, adverse effects	Primary: Niacin 1,500 and 2,000 mg/day significantly increased HDL-C by 21 and 26%, respectively, compared to 13% with gemfibrozil (P<0.02). Secondary: Compared to gemfibrozil, niacin 1,500 and 2,000 mg/day significantly increased apo AI (9 and 11 vs 4%), reduced TC:HDL-C ratio (-17 and -22 vs -12%), reduced Lp(a) (-7 and -20 vs no change) and had no adverse effect on LDL-C (2 and 0 vs 9%; P<0.001 to P<0.02.). TG decreased by 40% with gemfibrozil compared to 16 and 29% with niacin 1,000 (P<0.001) and 2,000 mg/day (P<0.06). Effects on plasma fibrinogen levels were significantly favorable for niacin compared to gemfibrozil (-1 to -6% vs 5 to 9%, respectively; P<0.02). Flushing was significantly more frequent with niacin compared to

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				gemfibrozil at every point (78 vs 10%; P values not reported). Flu syndrome occurred more frequently with niacin (P=0.006). Dyspepsia was more frequent with gemfibrozil (P=0.009).
Alrasadi et al.[19] (2008) Protocol 1 Fenofibrate 200 mg/day for 8 weeks vs atorvastatin 20 mg/day for 8 weeks vs niacin SR 1 g BID for 8 weeks Protocol 2 Fenofibrate 200 mg/day and atorvastatin 20 mg/day for 8 weeks vs niacin SR 1 g BID and atorvastatin 20 mg/day for 8 weeks Patients in whom a statin was required were switched or maintained on atorvastatin 20 mg throughout the study	XO Men with HDL-C <5th percentile for age- and gender-matched patients and an identified genetic cause of HDL deficiency or ≥1 first degree relative affected with HDL deficiency	N=19 32 weeks	Primary: Percent changes in HDL-C and TC:HDL-C Secondary: Not reported	Primary: Protocol 1 The mean percent change in HDL-C was 6, -6, and 22% in patients receiving fenofibrate, atorvastatin, and niacin, respectively. Only niacin significantly raised HDL-C (P<0.05). The mean percent change in TC/HDL-C ratio was 19, -26, and -22% in patients receiving fenofibrate, atorvastatin, and niacin, respectively. Both niacin and atorvastatin significantly lowered TC/HDL-C (P<0.05 and P<0.01, respectively). Protocol 2 The mean percent change in HDL-C was -2 and 18% in patients receiving fenofibrate plus atorvastatin and niacin plus atorvastatin, respectively. Only the group receiving niacin experienced a significant increase in HDL-C (P<0.05). The mean percent change in TC:HDL-C was 32 and -32% in patients receiving fenofibrate plus atorvastatin and niacin plus atorvastatin, respectively. Only the group receiving niacin experienced a significant decrease in TC:HDL-C (P<0.01). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
in Protocol 2.				
Guyton et al.[20] (2008) Niacin ER 2 g (titrated) per day and ezetimibe-simvastatin 10 to 20 mg QD vs niacin ER 2 g (titrated) per day vs ezetimibe to simvastatin (E/S) 10 to 20 mg QD	DB, MC, RCT Patients 18 to 79 years of age with type IIa and IIb hyperlipidemia (LDL-C 130 to 190 mg/dL and TG ≤500 mg/dL)	N=1,220 24 weeks	Primary: Percent change from baseline in LDL-C, non-HDL-C, HDL-C, TG, TC, apo B, apo AI, and hsCRP Secondary: Not reported	Primary: After 24 weeks of therapy, the percent change from baseline in LDL-C, non-HDL-C, TG, apoB, TC:HDL-C, LDL-C:HDL-C, apo B:apo AI, and non-HDL-C:HDL-C were greater with niacin + E/S compared to treatment with niacin or E/S (P<0.001 for all). The percent change in HDL-C from baseline was significantly greater with niacin plus E/S compared to E/S (P<0.001). There was no significant difference with niacin plus E/S and niacin monotherapy (P>0.05). The percent change in TC from baseline was significantly greater with niacin plus E/S compared to niacin (P<0.001). There was no significant difference with niacin plus E/S and E/S monotherapy. The percent change in apoAI from baseline was significantly greater with niacin + E/S compared E/S (P<0.001). There was no significant difference with niacin + E/S and niacin monotherapy (P>0.05). Treatment with niacin + E/S led to a greater reduction in hsCRP compared to niacin monotherapy (P<0.005). Adverse events occurred more frequently in patients treated with niacin monotherapy and niacin + E/S compared to E/S monotherapy. This difference was due to flushing-related adverse events in the niacin groups. Secondary: Not reported
Zhao et al.[21] (2004) Niacin 2.4±2.0 g/day (mean dose) plus simvastatin 13±6 mg/day (mean dose)	ES Patients with clinical coronary disease (defined as previous MI, coronary	N=160 38 months	Primary: Side effects, response to the question “Overall, how difficult is it to take the study medication?”	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 upper limit of normal (3 vs 1%; P value not significant), CPK at least two times the upper limit of normal (3 vs 4%; P value not significant),

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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 Patients whose HDL-C had not increased by prespecified amounts were switched to niacin IR (Niacor®) titrated to 4 g per day.	interventions or confirmed angina) including 25 with diabetes mellitus with mean LDL-C 128 mg/dL, HDL-C 31mg/dL and TG 217 mg/dL		Secondary: Not reported	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
McKenney et al.[22] (2007) 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	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	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks, followed by atorvastatin 20 mg/day plus niacin SR 1,000 mg/day for 4 weeks, followed by atorvastatin 40 mg/day plus niacin SR 2,000 mg/day vs simvastatin 20 mg/day plus ezetimibe 10 mg/day for 8 weeks, followed by simvastatin 40 mg/day plus ezetimibe 10 mg/day vs rosuvastatin 10 mg/day plus niacin SR 500 mg/day for 4 weeks, followed by rosuvastatin 10 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	mg/dL			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.
Fazio et al.[23] (2010) Ezetimibe-simvastatin 10-20 mg/day plus niacin ER 2 g/day vs niacin ER 2 g/day	DB, MC, RCT Patients 18 to 79 years of age with hyperlipidemia (Types IIa and IIb) with LDL-C 130 to 190 mg/dL, TG ≤500 mg/dL, creatinine <2	N=942 64 weeks	Primary: Safety and tolerability of ezetimibe/ simvastatin plus niacin ER Secondary: Changes in HDL-C, TG, non-HDL-	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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.	mg/dL, creatine kinase ≤2 times the upper limit of normal, transaminases ≤1.5 times the upper limit of normal and HbA_{1c} ≤8.0%		C and LDL-C	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 upper limit of normal, and creatine kinase of at least ten times or greater the upper limit of normal 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 AI 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 (P=0.002) and LDL-C after 12 weeks (P<0.001).
Fazio et al.[24] (2010) Ezetimibe-simvastatin 10-20 mg/day plus niacin ER 2	Subgroup analysis Hyperlipidemic patients with diabetes mellitus,	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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.	metabolic syndrome without diabetes mellitus or neither		acid Secondary: Not reported	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
Trials Assessing Cardiovascular Outcomes				
Coronary Drug Project[25] (1975) Niacin IR 3,000 mg per day vs clofibrate 1.8 g per day vs	DB, MC, PC, RCT Men 30 to 64 years of age with previous MI	N=8,341 5 years	Primary: All-cause mortality Secondary: Cause-specific mortality (e.g., coronary mortality and sudden death), nonfatal	Primary: The incidence of all-cause mortality was comparable between niacin (24.4%), clofibrate (25.5%) and placebo (25.4%) (P values not significant). Secondary: Five year rates of death due to cardiovascular disease were comparable between niacin (18.8%), clofibrate (17.3%) and placebo (18.9%) (P values not significant). Major cardiovascular events were reduced with niacin; CHD events by

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			cardiovascular events	13%, nonfatal MI by 27% and cerebrovascular events by 21%. Niacin significantly reduced the incidence of nonfatal MI compared to placebo (8.9 vs 12.2%; P<0.004). There was no evidence of significant efficacy of clofibrate with regard to all-cause and cause-specific mortality. Treatment with niacin for five years lowered TC by 10% and TG levels by 26% (P values not reported). Treatment with clofibrate lowered TC by 7% and TG levels by 22% (P values not reported).
Canner et al.[26] (1986) Coronary Drug Project Niacin IR 3,000 mg per day vs placebo	ES of the Coronary Drug Project Men 30 to 64 years of age with previous MI	N=8,341 9 years	Primary: All-cause mortality Secondary: Cause-specific mortality (e.g., coronary mortality and sudden death)	Primary: A follow-up of patients nine years after completion of the Coronary Drug Project trial (total mean follow up of 15 years) revealed that niacin reduced the risk of all-cause mortality by 11% (52.0 vs 58.2%; P=0.0004 vs placebo). Secondary: The survival benefit with niacin was primarily evident for death caused by CHD (36.5 vs 41.3%; P<0.05 vs placebo).
Lee et al.[27] (2009) Niacin ER (Niaspan®) 2,000 mg per day vs placebo	DB, PC, RCT Patients with pre-existing atherosclerosis and low HDL-C (<40 mg/dL) in whom LDL-C was treated with statins	N=71 1 year	Primary: Absolute change in carotid artery wall area and change in carotid plaque index Secondary: Not reported	Primary: Patients receiving niacin had a significantly greater change in carotid wall area at 12 months compared to placebo (difference -1.64 mm^2; 95% CI, -3.12 to -0.16; P=0.03). After 12 months of therapy, the change in carotid plaque index was significantly reduced by niacin compared to placebo (difference -0.016; 95% CI, -0.03 to -0.0022; P=0.02). Niacin increased HDL-C by 23% and decreased LDL-C by 19%. TG, apo B, and Lp(a) were significantly decreased by niacin compared to placebo. CRP was decreased by niacin compared to placebo (P=0.03 at six months and P=0.1 at 12 months). Adiponectin was significantly increased at both six and at 12 months

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P<0.01). Secondary: Not reported
Taylor et al.[28] (2004) Niacin ER (Niaspan®) 1,000 mg/day vs placebo All patients received background statin therapy.	DB, PC, RCT Adult patients with known CHD and low levels of HDL-C (<45 mg/dL)	N=167 1 year	Primary: Change in mean common CIMT after one year Secondary: Changes in lipid concentrations, composite of clinical cardiovascular events (including any hospitalization for an acute coronary syndrome, stroke, revascularization procedure or sudden cardiac death), adverse events	Primary: After one year, mean CIMT increased significantly with placebo (0.044±0.100 mm; P<0.001) and was unchanged with niacin (0.014±0.104 mm; P=0.23). The overall difference in CIMT progression between placebo and niacin was not significant (P=0.08); however, a post hoc analysis revealed that niacin significantly reduced the rate of CIMT progression in subjects without insulin resistance (P=0.026). Secondary: HDL-C increased by 21% with niacin and did not change with placebo (P<0.003). Clinical cardiovascular events occurred in three patients receiving niacin (3.8%) and seven receiving placebo (9.6%; P=0.20). Adherence to trial medication based on pill counts ranged from 90.3 to 94.5%, and was not different between the two treatments (P value not reported). No patient experienced significant (three times the upper limit of normal) elevations of liver enzymes or developed myositis. At the end of the trial, skin flushing was reported in 69.2 and 12.7% of patients receiving niacin and placebo (P<0.001).
Illingworth et al.[29] (1994) Lovastatin 10 to 80 mg/day vs	MC, OL, RCT Patients 21 to 75 years of age with primary hyper-cholesterolemia and either an LDL-	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
niacin IR 0.25 mg to 1.5 g TID	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			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 AI (P<0.01 vs lovastatin), except for the change in apo AI 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. 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 to be drug-related in four and eight patients receiving lovastatin and niacin (P value not significant). The major reasons for discontinuation of niacin were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.
Sang et al.[30] (2009) Atorvastatin 10 mg/day vs atorvastatin 10 mg/day and niacin ER	RCT Patients with clinical and angiographic criteria for coronary disease, with ≥50% stenosis of 1 coronary artery with high TC	N=108 12 months (plus a 12 month follow up)	Primary: All-cause mortality, MI, rehospitalization, revascularization with either PCI or CABG Secondary: Mean percent changes from baseline lipid parameters, effects on glucose metabolism, safety	Primary: At 12 months, clinical events included rehospitalization due to angina pectoris and heart failure attack, respectively, revascularization with PCI and sudden death (7.14%) with atorvastatin. With combination therapy, the clinical events included rehospitalization due to heart failure attack, revascularization after PCI or CABG (5.77%). No significant reduction was observed with combination therapy (OR, 0.78; P=0.052). Secondary: TC, TG, LDL-C and Lp(a) levels decreased significantly with both treatments (P<0.01), with no significant difference between the two during the course of follow up (P>0.05). Apo A increased significantly with both treatments (P<0.01), with a more favorable effect observed with combination therapy (24.5 vs 40.8%; P<0.01). During the follow up, apo B fell by 5.63 (P<0.05 and 7.35% (P<0.01) with atorvastatin and combination therapy; with no significant difference between the two (P>0.05). During the trial, HDL-C levels increased by 11.67 (P<0.05) and 29.36% (P<0.01) with atorvastatin and combination therapy, with a significant difference favoring combination therapy (P<0.01). Niacin resulted in no significant increase in glucose levels at six or 12 months compared to baseline levels (P>0.05). In the subgroup of diabetic patients (n=28), niacin resulted in a significant increase in glucose levels at six months (P<0.01), and glucose levels increased more significantly at 12 months (P<0.01), but the effect of niacin was not significant in nondiabetic patients (P>0.05). HbA_{1c} levels did not show a significant increase at six months in patient with diabetes, but levels increased significantly at 12 months (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Both treatments were generally well tolerated. The most common side effect of niacin therapy was flushing which appeared in four patients receiving combination therapy; however, all patients continued the medication and the flushing disappeared.
Teo et al.[31] (2013) Simvastatin and placebo vs simvastatin and niacin ER	DB, RCT Patients with cardiovascular disease, low HDL-C, and high TG had no incremental benefit, despite increases in HDL-C	N=3,414 36 months	Primary: Fatal or nonfatal ischemic strokes Secondary: Not reported	Primary: There were 50 fatal or nonfatal ischemic strokes: 18 (1.06%) in placebo arm vs 32 (1.86%) in combination arm (HR, 1.78; 95% CI, 1.00 to 3.17; P=0.050). Multivariate analysis showed independent associations between ischemic stroke risk and >65 years of age (HR, 3.58; 95% CI, 1.82 to 7.05; P=0.0002), history of stroke/transient ischemic attack/carotid disease (HR, 2.18; 95% CI, 1.23 to 3.88; P=0.0079), elevated baseline Lp(a) (HR, 2.80; 95% CI, 1.25 to 6.27 comparing the middle with the lowest tertile; HR, 2.31; 95% CI, 1.002 to 5.30 comparing the highest with the lowest tertile; overall P=0.042) but a nonsignificant association with combination therapy (HR, 1.74; 95% CI, 0.97 to 3.11; P=0.063). Secondary: Not reported
Taylor et al.[32] (2009) Niacin ER (Niaspan®) 2 g (titrated) QD vs ezetimibe 10 mg QD	OL, PG, RCT Patients ≥30 years of age with atherosclerotic coronary or vascular disease or a CHD risk equivalent (diabetes mellitus, 10-year Framingham risk score ≥20%, coronary calcium score >200 for women or >400 for men who were receiving treatment	N=208 14 months	Primary: Change in CIMT after 14 months Secondary: Change in lipid values, composite of major adverse cardiovascular events (MI, myocardial revascularization, admission to the hospital for an acute coronary syndrome, and death from CHD),	Primary: Treatment with niacin led to a significant reduction in mean and maximal CIMT at eight months (P=0.001 and P=0.004, respectively) and 14 months (P=0.001 and P<0.001, respectively). There was no significant change in mean or maximal CIMT with ezetimibe at eight or 14 months compared to baseline. There was a significant difference between the niacin group and the ezetimibe group (P=0.003). Secondary: The change in LDL-C in the ezetimibe group was -17.6 mg/dL compared to -10.0 mg/dL in the niacin group (P=0.01). The change in HDL-C in the ezetimibe group was -2.8 mg/dL compared to 7.5 mg/dL in the niacin group (P<0.001). There were significant reductions in TG in both groups. Major adverse cardiovascular events occurred in 5% of patients receiving ezetimibe compared to 1% of patients receiving niacin (P=0.04). Adverse drug effects led to withdrawal from the study in three of nine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	with a statin (LDL-C <100 mg/dL and HDL-C <50 mg/dL for men or <55 mg/dL for women)		discontinuation of study drug due to adverse effects, health-related quality of life	patients receiving ezetimibe and 17 of 27 patients receiving niacin (P=0.12). There was no significant difference between the two groups in the quality of life at baseline or at 14 months.
Brown et al.[33] (2001) HATS Niacin SR (Slo-Niacin®) titrated to 1 g BID and simvastatin vs antioxidants vs niacin SR (Slo-Niacin®) titrated to 1 g BID, simvastatin, and antioxidants vs placebo Patients whose HDL-C had not increased by prespecified amounts were switched to niacin IR (Niacor®) titrated to 4 g per day.	DB, PC Patients with clinical coronary disease (defined as previous MI, coronary interventions or confirmed angina) and with ≥3 stenoses of ≥30% of the luminal diameter or 1 stenosis of ≥50%, low HDL-C, normal LDL-C	N=160 3 years	Primary: Changes in lipid profile, arteriographic evidence of change in coronary stenosis (percent 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 revascularization) Secondary: Mean change in percent stenosis in lesions of varying degrees of severity, mean change in luminal diameter in proximal lesions	Primary: The mean levels of LDL-C, HDL-C, and TG were significantly changed by -42% (P<0.001), 26% (P<0.001) and -36% (P<0.001), respectively, in the niacin plus simvastatin group but were unaltered in the antioxidant only and placebo groups. Similar changes were observed when antioxidants were added to niacin plus simvastatin. The protective increase in HDL_2 (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 compared to 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 end point (death from coronary causes, MI, stroke or revascularization) was 24% with placebos, 3% with niacin plus simvastatin, 21% with antioxidants and 14% with niacin plus simvastatin plus antioxidants. The risk of the composite primary end point was 90% lower in the niacin plus simvastatin group than placebo (P=0.03). The risk in the other treatment groups did not differ significantly from that in the placebo group. Secondary: In general, the treatment effects observed with respect to the primary angiographic end point were confirmed for the various subcategories of stenoses and were supported by the results for the mean minimal luminal diameter.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			and all lesions	
Blankernhorn et al.[34] (1987) Colestipol 30 g/day plus niacin 3 to 12 g/day vs placebo	DB, PC, RCT Nonsmoking men 49 to 59 years of age with progressive atherosclerosis who had coronary bypass surgery not involving valve replacement performed ≥3 months prior and a fasting blood cholesterol level 185 to 350 mg/dL	N=188 2 years	Primary: Coronary global change score Secondary: Change from baseline in lipid parameters	Primary: Deterioration in overall coronary status was significantly less with combination therapy compared to placebo (P<0.001). Atherosclerosis regression, as indicated by perceptible improvement in overall coronary status, occurred in 16.2 and 2.4% of patients receiving combination therapy and placebo (P=0.002). Combination therapy resulted in a significant reduction in the average number of lesions per patient that progressed (P<0.03) and the percentage of patients with new atheroma formation in native coronary arteries (P<0.03). The percentage of patients receiving combination therapy with new lesions (P<0.04) or any adverse change in bypass grafts (P<0.03) was significant reduced. Secondary: Large, significant decreases in TC (26 vs 4%), TG (22 vs 5%), LDL-C (43 vs 5%) and LDL-C/HDL-C (57 vs 6%), and a large, significant increase in HDL-C (37 vs 2%) were achieved with combination therapy compared to placebo (P<0.001 for all). Modifications in lipid parameters achieved with combination therapy were significant compared to baseline values (P values not reported).
Brown et al.[35] (1990) 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	DB, 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	Primary: On average, placebo (conventional therapy) increased the index of stenosis by 2.1 percentage points 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 3 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo (or colestipol if LDL-C was elevated)			measured in each patient and in proximal lesions causing ≥50% (severe) stenosis or <50% (mild) stenosis at baseline	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 difference from those receiving conventional therapy for each subset, demonstrating either a mean regression or no change in severity of disease.

Drug regimen abbreviations: BID=twice daily, ER=extended-release, IR=immediate release, QD=once daily, SR=sustained release, TID=three times daily
Study abbreviations: DB=double-blind, ES=extension study, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RETRO=retrospective, SB=single-blind, XO=crossover
Miscellaneous abbreviations: ALT=alanine aminotransferase, apo=apolipoprotein, AST=aspartate aminotransferase, CABG=coronary artery bypass graft, CAD=coronary artery disease, CHD=coronary heart disease, CI=confidence interval, CIMT=carotid intima-media thickness, CPK=creatinine phosphokinase, CRP=C-reactive protein, FBG=fasting blood glucose, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, HOMA-IR=homeostasis model assessment-insulin resistance, HR=hazard ratio, hsCRP=high sensitivity C reactive protein, LDL-C=low-density lipoprotein cholesterol, Lp(a)=lipoprotein(a), MI=myocardial infarction, NCEP ATP=National Cholesterol Education Program Adult Treatment Panel, OR=odds ratio, PCI=percutaneous coronary intervention, TC=total cholesterol, TG=triglycerides, VLDL-C=very low-density lipoprotein cholesterol

Special Populations

Table 5. Special Populations[4-5]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category*	Excreted in Breast Milk
Niacin	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 (tablet). Safety and effectiveness in children ≤16 years of age have not been established (extended-release tablet).	No dosage adjustment required; use with caution.	Contraindicated in patients with significant hepatic dysfunction.	C	Unknown; use with caution.

Adverse Drug Events

At usual antilipemic dosages, niacin is generally well tolerated and side effects are mild and transient. The most common adverse effects with niacin are gastrointestinal upset, flushing and pruritus. Flushing is more common with the immediate-release formulation and may be diminished by starting with a low dose, taking niacin after meals, and by pretreating with aspirin or ibuprofen. Sustained-release preparations have been shown to be hepatotoxic in doses ≥2 g per day. Cases of severe hepatic toxicity, including fulminant hepatic necrosis have occurred in patients who have substituted sustained-release niacin products for immediate-release products at equivalent doses.[1-5]

Table 6. Adverse Drug Events (%)[1-5]

Adverse Events	Niacin Extended-Release	Niacin Immediate-Release
Cardiovascular		
Angina pectoris	-	-
Arrhythmia	✔	✔
Atrial fibrillation	✔	✔
Bypass surgery	-	-
Cardiac arrest	-	-
Chest pain	-	-
Hypertension	-	-
Hypotension	✔	✔
Migraine	✔	-
Myocardial infarction	-	-
Myocardial ischemia	-	-
Occlusion	-	-
Orthostasis	✔	✔
Palpitations	✔	-
Peripheral edema	✔	-
Peripheral vascular disorder	-	-
Postural hypotension	✔	-
Syncope	✔	-
Tachycardia	✔	-

Adverse Events	Niacin Extended-Release	Niacin Immediate-Release
Central Nervous System		
Depression	-	-
Dizziness	✔	-
Emotional lability	-	-
Facial paralysis	-	-
Headache	-	✔
Insomnia	✔	-
Migraine	✔	-
Nervousness	✔	-
Paresthesia	✔	-
Vasodilatation	-	-
Vertigo	-	-
Dermatologic		
Acanthosis nigricans	-	✔
Alopecia	-	-
Dry skin	✔	✔
Eczema	-	-
Flushing	63 to 69	✔
Hyperpigmentation	-	✔
Pruritus	3 to 8	✔
Rash	0 to 5	-
Urticaria	✔	-
Skin burning sensation	✔	-
Skin discoloration	✔	-
Sweating	✔	-
Endocrine and Metabolic		
Gout	✔	✔
Gastrointestinal		
Abdomen enlarged	-	-
Anorexia	-	-
Colitis	-	-
Constipation	-	-
Diarrhea	7 to 14	✔
Dry mouth	-	-
Dyspepsia	-	✔
Dysphagia	-	-
Eructation	✔	-
Fecal incontinence	-	-
Flatulence	✔	-
Gastritis	-	-
Gastroenteritis	-	-
Increased appetite	-	-
Intestinal obstruction	-	-
Melena	-	-
Nausea	4 to 11	-
Pancreatitis	-	-
Peptic ulceration	✔	✔
Tenesmus	-	-
Vomiting	0 to 9	✔
Hematologic		
Prothrombin time increased	✔	-

Adverse Events	Niacin Extended-Release	Niacin Immediate-Release
Thrombocytopenia	✔	-
Hepatic		
Fulminant hepatic necrosis	-	✔
Hepatitis	✔	-
Hepatotoxicity	✔	✔
Jaundice	✔	✔
Laboratory Test Abnormalities		
Amylase increased	✔	-
Hyperglycemia	✔	✔
Hyperlipidemia	-	-
Hyperuricemia	✔	✔
Lactate dehydrogenase increased	✔	-
Liver function test abnormalities	✔	✔
Phosphorus decreased	✔	-
Musculoskeletal		
Arthralgia	-	-
Arthritis	-	-
Asthenia	✔	-
Back pain	-	-
Fracture	-	-
Malaise	-	-
Myalgia	✔	-
Myasthenia	✔	-
Myopathy	✔	-
Neck pain	-	-
Pain	-	-
Rhabdomyolysis	-	✔
Rheumatoid arthritis	-	-
Tendon rupture	-	-
Respiratory		
Asthma	-	-
Bronchitis	-	-
Cough	2 to 8	-
Dyspnea	✔	-
Epistaxis	-	-
Laryngitis	-	-
Pharyngitis	-	-
Pneumonia	-	-
Rhinitis	-	-
Sinusitis	-	-
Urogenital		
Cervix disorder	-	-
Endometrial carcinoma	-	-
Epididymitis	-	-
Impotence	-	-
Other		
Anaphylaxis	✔	-
Angioedema	✔	-
Blurred vision	✔	-
Body odor	-	-
Cataract	-	-

Adverse Events	Niacin Extended-Release	Niacin Immediate-Release
Chills	-	-
Edema	-	-
Facial edema	✔	-
Fever	-	-
Flu symptoms	-	-
Hemorrhagic diathesis	-	-
Hypersensitivity reactions	✔	-
Infection	-	-
Laryngismus	✔	-
Larynx edema	✔	-
Lymphadenopathy	-	-
Macular edema	✔	✔
Neoplasm	-	-
Sudden death	-	-
Suicide	-	-
Taste perversion	-	-
Tongue edema	✔	-
Toxoid amblyopia	-	✔

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

Contraindications

Table 7. Contraindications[4-5]

Contraindications	Niacin Extended-Release	Niacin Immediate-Release
Arterial bleeding	✔	✔
Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels	✔	
Active peptic ulcer disease	✔	✔
Known hypersensitivity to product or component	✔	✔
Significant or unexplained hepatic dysfunction		✔

Warnings/Precautions

Table 8. Warnings/Precautions[4-5]

Warning/Precaution	Niacin Extended-Release	Niacin Immediate-Release
Elevated uric acid levels have occurred with nicotinic acid therapy, therefore use with caution in patients predisposed to gout		✔
Liver enzyme abnormalities and monitoring: persistent elevations in hepatic transaminase can occur; monitor liver enzymes before and during treatment	✔	✔
Myopathy has been reported in patients taking sustained release niacin; the risk for myopathy and rhabdomyolysis are increased when lovastatin or simvastatin are coadministered with sustained release niacin, particularly in elderly patients and patients with diabetes, renal failure, or	✔	

Warning/Precaution	Niacin Extended-Release	Niacin Immediate-Release
uncontrolled hypothyroidism		
Patients with a past history of jaundice, hepatobiliary disease, or peptic ulcer should be observed closely during nicotinic acid therapy		✔
Rare cases of rhabdomyolysis have been associated with concomitant administration of lipid-altering doses of nicotinic acid and HMG-CoA reductase inhibitors		✔
Severe hepatic toxicity has occurred in patients substituting sustained release niacin for immediate-release niacin at equivalent doses	✔	✔
Sustained release niacin can increase serum glucose levels; glucose levels should be closely monitored in diabetic or potentially diabetic patients particularly during the first few months of use or dose adjustment	✔	✔
Use with caution in patients with unstable angina or in the acute phase of a myocardial infarction	✔	✔

Drug Interactions

There are no significant drug interactions reported with the niacin derivitives.[1]

Dosage and Administration

Table 9. Dosing and Administration[4-5]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Niacin	Treatment of hypertriglyceridemia, hypercholesterolemia and mixed dyslipidemia: Extended-release tablet: taken at bedtime with a low-fat snack; 500 to 2,000 mg once daily; must be initiated at 500 mg at bedtime in order to reduce the incidence and severity of side effects which may occur during early therapy and should not be increased by more than 500 mg in any four week period; maintenance dose, 1000 to 2000 mg once daily; doses greater than 2,000 mg daily are not recommended; concomitant therapy with lovastatin, initial dose of lovastatin is 20 mg once a day; combination therapy with lovastatin should not exceed doses of 2,000 and 40 mg daily, respectively; concomitant therapy with simvastatin, initial dose of simvastatin is 20 mg once a day; combination	Safety and efficacy in children have not been established (tablet). Safety and effectiveness in children ≤16 years of age have not been established (extended-release tablet).	Extended-release tablet (Niaspan®):* 500 mg 750 mg 1,000 mg Tablet (Niacor®):* 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	therapy with simvastatin should not exceed doses of 2,000 and 40 mg daily, respectively Tablet: the usual adult dosage is 1 to 2 g two or three times a day; doses should be individualized according to the patient's response; start with one-half tablet (250 mg) as a single daily dose following the evening meal; the frequency of dosing and total daily dose can be increased every four to seven days until the desired low density lipoprotein cholesterol and/or triglyceride level is achieved or the first-level therapeutic dose of 1.5 to 2 g/day is reached; if the patient's hyperlipidemia is not adequately controlled after two months at this level, the dosage can then be increased at two to four week intervals to 3 g/day (1 g three times per day); in patients with marked lipid abnormalities, a higher dose is occasionally required, but generally should not exceed 6 g/day		

*Product is also available over-the-counter.

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendation
American College of Cardiology/American Heart Association Task Force on Practice Guidelines: **Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2013)**[36]	Statin treatment • The panel makes no recommendations for or against specific low density lipoprotein cholesterol (LDL-C) or non-high density lipoprotein cholesterol (HDL-C) targets for the primary or secondary prevention of arteriosclerotic cardiovascular disease (ASCVD). • High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age that have clinical ASCVD, unless contraindicated. • In individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated. • In individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those

Clinical Guideline	Recommendation
	who are tolerating it. • Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required): use high-intensity statin therapy unless contraindicated. For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity. • For individual's ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction. • For individuals ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a nonstatin drug may be considered to further lower LDL-C. Evaluate the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and consider patient preferences. • Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus. • High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated 10-year ASCVD risk unless contraindicated. • In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy. • Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes and an estimated 10-year ASCVD risk ≥7.5% should be treated with moderate- to high-intensity statin therapy. • It is reasonable to offer treatment with a moderate intensity statin to adults 40 to 75 years of age, with LDL-C 70 to 189 mg/dL, without clinica ASCVD or diabetes and an estimated 10-year ASCVD risk of 5.0 to <7.5%. • Before initiating statin therapy for the primary prevention of ASCVD in adults with LDL-C 70 to 189 mg/dL without clinical ASCVD or diabetes it is reasonable for clinicians and patients to engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions, and patient preferences for treatment. • In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk based treatment decision is uncertain, additional factors may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluating the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and discussion of patient preference. <u>Statin safety</u> • To maximize the safety of statins, selection of the appropriate statin and dose in men and nonpregnant/nonnursing women should be based on patient characteristics, level of ASCVD risk,

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	and potential for adverse effects. • Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin associated adverse effects are present. • Characteristics predisposing individuals to statin adverse effects include, but are not limited to: o Multiple or serious comorbidities, including impaired renal or hepatic function. o History of previous statin intolerance or muscle disorders. o Unexplained alanine transaminase elevations >3 times upper limit of normal. o Patient characteristics or concomitant use of drugs affecting statin metabolism. o >75 years of age. • Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to: o History of hemorrhagic stroke. o Asian ancestry. • Creatine kinase should not be routinely measured in individuals receiving statin therapy. • Baseline measurement of creatinine kinase is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk for myopathy. • During statin therapy, it is reasonable to measure creatinine kinase in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue. • Baseline measurement of hepatic transaminase levels should be performed before initiating statin therapy. • During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark colored urine or yellowing of the skin or sclera). • Decreasing the statin dose may be considered when two consecutive values of LDL-C levels are <40 mg/dL. • It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily. • Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes screening guidelines. Those who develop diabetes mellitus during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events. • For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals that are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (e.g., those who have undergone solid organ transplantation or are receiving treatment

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	for human immunodeficiency virus (HIV). A review of the manufacturer's prescribing information may be useful before initiating any cholesterol-lowering drug. • It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm: o To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy. o If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating creatinine kinase, creatinine, and a urinalysis for myoglobinuria. • If mild to moderate muscle symptoms develop during statin therapy: o Discontinue the statin until the symptoms can be evaluated. o Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases). o If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy. o If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin. o Once a low dose of a statin is tolerated, gradually increase the dose as tolerated. o If, after two months without statin treatment, muscle symptoms or elevated creatinine kinase levels do not resolve completely, consider other causes of muscle symptoms listed above. o If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose. • For individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for nonstatin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy. <u>Monitoring and optimizing statin therapy</u> • Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This

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

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

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	• If estimated glomerular filtration rate is between 30 and 59 mL/min per 1.73 m^2, the dose of fenofibrate should not exceed 54 mg/day. • If, during follow-up, the estimated glomerular filtration rate decreases persistently to ≤30 mL/min per 1.73 m^2, fenofibrate should be discontinued. • If eicosapentaenoic acid and/or docosahexanoic acid are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)**[37]	• Therapeutic lifestyle changes remain an essential modality in clinical management. • When 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 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 and low HDL-C, especially in combination with statins. • In high risk patients with high triglycerides 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 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. • Therapeutic lifestyle changes 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).

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	Treatment of familial defective apolipoprotein B-100 • Therapeutic lifestyle changes indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. Treatment of polygenic hypercholesterolemia • Therapeutic lifestyle changes 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)**[38]	General recommendations • With regards to therapeutic lifestyle changes, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for coronary heart disease. 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 coronary heart disease 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

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	atherogenic dyslipidemia combined with elevated LDL-C levels. • Nicotinic acid should be used with caution in patients with active liver disease, recent peptic ulcer, hyperuricemia, gout and type 2 diabetes. • High doses of nicotinic acid (>3 g/day) generally should be avoided in patients with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia. <u>Fibric acid derivatives (fibrates)</u> • Fibrates can be recommended for patients with very high TG to reduce risk for acute pancreatitis. • They also can be recommended for patients with dysbetalipoproteinemia (elevated beta-very LDL). • Fibrate therapy should be considered an option for treatment of patients with established coronary heart disease 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. <u>Omega-3 fatty acids</u> • Omega-3 fatty acids (e.g., linolenic acid, docosahexaenoic acid, eicosapentaenoic acid) have two potential uses. • In higher doses, docosahexaenoic acid and eicosapentaenoic acid lower serum triglycerides by reducing hepatic secretion of triglyceride-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 coronary heart disease. 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**	<u>Lipid management</u> • Goal: treatment with statin therapy; use statin therapy to achieve LDL-C of <100 mg/dL; for very high risk patients an LDL-C <70 mg/dL is reasonable; if triglycerides 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

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(2011)[39]	<100 mg/dL and achieves ≥30% lowering of LDL-C. • Patients who have triglyceride ≥200 mg/dL should be treated with statins to lower non-HDL-C to <130 mg/dL. • Patients who have triglyceride >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 triglyceride ≥200 mg/dL, a non-HDL-C goal of <100 mg/dL is reasonable. • The use of ezetimibe may be considered for patients who do not tolerate or achieve target LDL-C with statins, bile acid sequestrants, and/or niacin. • For patients who continue to have an elevated non-HDL-C while on adequate statin therapy, niacin or fibrate therapy or fish oil may be reasonable. • For all patients, it may be reasonable to recommend omega-3 fatty acids from fist or fish oil capsules (1 g/day) for cardiovascular disease risk reduction.
Institute for Clinical Systems Improvement: **Lipid Management in Adults** **(2013)**[40]	• Clinicians should use a quantitative estimate of cardiovascular risk to guide lipid management decision-making for the adult population. • Clinicians should initiate statin therapy regardless of LDL in patients with established ASCVD. • Clinicians should initiate statin therapy in patients whose LDL is greater than 100 and have a 10-year coronary heart disease risk > 10% or diabetes. • Combination therapy should be initiated only on an individual basis as no studies have shown a benefit of use at this time, and some studies have shown an increased risk of harm over statin monotherapy. • If patients are intolerant to a statin, clinicians are encouraged to have the patient try the other statins in reduced doses before ruling out all statins. If patients are unable to take a statin, then bile-acid sequestrants, niacin, fibric acid derivatives or fibrates, and ezetimibe are available.
American Heart Association: **Drug Therapy of High Risk Lipid Abnormalities in Children and Adolescents: A Scientific Statement From the American Heart Association** **(2007)**[41]	• 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

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	efficacy and safety and impact on the atherosclerotic disease process. • Niacin is rarely used to treat the pediatric population. • Given the reported poor tolerance, the potential for very serious adverse effects, and the limited available data, niacin cannot be routinely recommended but may be considered for selected patients. • This guideline does not contain recommendations regarding the use of omega-3 acid ethyl esters.
European Society of Cardiology and Other Societies: **Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2012)**[42]	Drugs • Currently available lipid-lowering drugs include statins, fibrates, bile acid sequestrants, niacin, and selective cholesterol absorption inhibitors (e.g., ezetimibe). • Statins, by reducing LDL-C, reduce cardiovascular morbidity and mortality as well as the need for coronary artery interventions. • Statins should be used as the drugs of first choice in patients with hypercholesterolemia or combined hyperlipidemia. • Selective cholesterol absorption inhibitors are not used as monotherapy to decrease LDL-C. • Bile acid sequestrants also decrease total cholesterol and LDL-C, but tend to increase triglyceride. • Fibrates and niacin are used primarily for triglyceride lowering and increasing HDL-C, while fish oils (omega-3 fatty acids) in doses of 2 to 4 g/day are used for triglyceride lowering. • Fibrates are the drugs of choice for patients with severely elevated triglyceride, and prescription omega-3 fatty acids might be added if elevated triglyceride is not decreased adequately. Drug combinations • 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 triglyceride 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 triglyceride 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

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	improved. In these patients, increased attention to other risk factors may help to reduce total risk.
National Institute for Health and Clinical Excellence: **Lipid Modification (2010)**[43]	• Statin therapy is recommended as part of the management strategy for the primary prevention of cardiovascular disease for adults who have a ≥20% 10 year risk of developing cardiovascular disease. • Treatment for the primary prevention of cardiovascular disease should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. Higher intensity statins should not routinely be offered to people for the primary prevention of cardiovascular disease. • Fibrates, nicotinic acid or anion exchange resins should not routinely be offered for the primary prevention of cardiovascular disease. If statins are not tolerated, these treatments may be considered. • The combination of an anion exchange resin, fibrate, nicotinic acid or a fish oil supplement with a statin should not be offered for the primary prevention of cardiovascular disease. • Statin therapy is recommended for adults with clinical evidence of cardiovascular disease. People with acute coronary syndrome should be treated with a higher intensity statin. • Treatment for the secondary prevention of cardiovascular disease should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy if a total cholesterol of <4 mmol/L (<155 mg/dL) or LDL-C <2 mmol/L (<77 mg/dL) is not attained. • Fibrates, nicotinic acid and anion exchange resins may be considered for secondary prevention in people with cardiovascular disease who are not able to tolerate statins. • People with primary hypercholesterolemia should be considered for ezetimibe treatment.

Conclusions

Prescription niacin is approved by the Food and Drug Administration (FDA) for the treatment of hypertriglyceridemia. Prescription niacin is also approved for the treatment of primary hypercholesterolemia and mixed dyslipidemia.[4-5] Niacin is available over-the-counter in immediate-release and sustained-release formulations. Niacin is also available by prescription as immediate-release (Niacor®) and extended-release (Niaspan®) formulations.

In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When low-density lipoprotein cholesterol (LDL-C) lowering is required, initial treatment with a statin, a bile acid sequestrant or niacin is recommended. However, in general, the statins are considered first line therapy for decreasing LDL-C levels, and are recommended in patients with established coronary heart disease or coronary heart disease equivalents. In patients with an elevated triglyceride level (≥500 mg/dL) a fibric acid derivative or niacin should be initiated before LDL-C lowering therapy to prevent pancreatitis.

Omega-3-acid ethyl esters represent an alternative to fibric acid derivatives and niacin for the treatment of hypertriglyceridemia.[36-43]

Clinical trials have demonstrated that niacin positively impacts a variety of lipid/lipoprotein parameters.[7-35] Niacin has been shown to reduce the risk of recurrent nonfatal myocardial infarction in patients with hypercholesterolemia, as well as slow the progression or promote regression of atherosclerotic disease (in combination with bile acid sequestrants) in patients with a history of coronary artery disease and hypercholesterolemia.[25-26,33] There are limited head-to-head studies comparing the efficacy and safety of the different niacin formulations.[13-15] While flushing may be more common with the immediate-release formulation, it still occurs with the sustained-release and extended-release products. Cases of severe hepatic toxicity have occurred in patients who have substituted sustained-release niacin products for immediate-release niacin at equivalent doses.[4-5]

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