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**Department of Vermont Health Access**

***Therapeutic Class Review  
Niacin Derivatives***

**Overview/Summary**

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

Niacin favorably affects all lipids and lipoproteins when given in pharmacological doses.<sup>1</sup> It has several effects on lipid metabolism including inhibition of hepatic production of very low density lipoprotein cholesterol (LDL-C) and consequently its metabolite LDL-C.<sup>1,2</sup> In addition, it decreases plasma concentrations of triglycerides (TGs), very LDL remnants and intermediate density lipoprotein. Administration of niacin also causes a shift in LDL composition from small, dense particles to larger, more buoyant particles.<sup>1</sup> Lastly, niacin increases high density lipoprotein cholesterol (HDL-C) (15 to 35%) both by reducing lipid transfer of cholesterol from HDL to very LDL, and by delaying HDL-C clearance.<sup>1,2</sup>

Use of niacin is effective in patients with hypercholesterolemia and in combined hyperlipidemia associated with normal and low levels of HDL-C (hypoalphalipoproteinemia). In general, increases in HDL-C and decreases in TGs can be achieved with lower doses of niacin, while decreases in very LDL- and LDL-C require higher doses. Additional LDL-C lowering can be attained by adding a bile acid sequestrant or a statin to treatment with niacin.<sup>1,2</sup>

The information provided in this review is for the two niacin products FDA approved for management of hyperlipidemia: Niacor<sup>®</sup> and Niaspan<sup>®</sup>.<sup>3,4</sup> Of note, there are several generic and over-the-counter formulations of niacin available with or without a prescription. Niacor<sup>®</sup> is available as a regular release tablet and Niaspan<sup>®</sup> is an extended-release tablet.<sup>5</sup> The extended-release formulation is associated with less flushing.<sup>1</sup> Niacor<sup>®</sup> is available generically, whereas Niaspan<sup>®</sup> is available brand only.

The specific FDA approved indications of the available niacin products are outlined in Table 2. In general, niacin is FDA approved for the treatment of hyperlipidemia and severe hypertriglyceridemia.<sup>3,4</sup> In addition, Niaspan<sup>®</sup> is approved to reduce the risk of recurrent myocardial infarction in patients with a history of myocardial infarction and hyperlipidemia and to slow progression or promote regression of atherosclerotic disease in patients with a history of coronary artery disease and hyperlipidemia.<sup>4</sup>

In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia.<sup>1,6,7</sup> When LDL lowering is required, initial treatment with a statin, a bile acid sequestrant or niacin is recommended.<sup>1</sup> However, in general, the statins are considered first line therapy for decreasing LDL-C levels.<sup>1,6-8</sup> If after six weeks of therapy lipid goals are not achieved on a statin alone, a dosage increase or the addition of a bile acid sequestrant or niacin should be considered.<sup>1</sup> In patients with an elevated triglyceride level ( $\geq 500$  mg/dL) a fibric acid derivative or niacin should be initiated before LDL-C lowering therapy to prevent pancreatitis.<sup>9</sup>

**Medications**

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**Table 1. Medications Included Within Class Review**

Generic Name (Trade name)	Medication Class	Generic Availability
Niacin (Niacor <sup>®*</sup> , Niaspan <sup>®</sup> )	Niacin	✓

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

## Indications

**Table 2. Food and Drug Administration (FDA) Approved Indications<sup>3,4</sup>**

Indication	Niacin
Adjunctive therapy for the treatment of adult patients with severe hypertriglyceridemia* who present risk of pancreatitis <sup>†</sup>	✓
Reduce total and low density lipoprotein cholesterol levels in adults with hyperlipidemia in combination with a bile acid binding resin <sup>‡§</sup>	✓
Reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hyperlipidemia	✓ (Niaspan <sup>®</sup> )
Reduce total and low density lipoprotein cholesterol levels in adult patients with hyperlipidemia in combination with a bile acid binding resin	✓ (Niaspan <sup>®</sup> )
Reduce total cholesterol, low density lipoprotein cholesterol, apolipoprotein B and triglyceride levels, and to increase high density lipoprotein cholesterol in patients with primary hyperlipidemia or mixed dyslipidemia	✓ (Niaspan <sup>®</sup> )
Slow progression or promote regression of atherosclerotic disease in combination with a bile acid binding resin in patients with a history of coronary artery disease and hyperlipidemia	✓ (Niaspan <sup>®</sup> )
Treatment of primary hyperlipidemia and mixed dyslipidemia in combination with simvastatin or lovastatin <sup>  </sup>	✓ (Niaspan <sup>®</sup> )

\*Types IV and V hyperlipidemia (Niacor<sup>®</sup>).

†And who do not respond adequately to a determined dietary effort to control them.

‡When the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate.

§Niacor<sup>®</sup> is indicated as adjunct to diet for the reduction of elevated total and low density lipoprotein cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) as monotherapy or in combination with a bile acid binding resin.

||When treatment with Niaspan<sup>®</sup>, simvastatin or lovastatin monotherapy is considered inadequate.

In addition to its Food and Drug Administration approved indications, niacin has the potential to be used off-label for prophylaxis treatment of coronary arteriosclerosis and can be used to treat a niacin deficiency.<sup>10</sup>

## Pharmacokinetics

**Table 3. Pharmacokinetics<sup>10</sup>**

Generic Name	Bioavailability (%)	Renal Elimination (%)	Active Metabolites	Serum Half-Life (hours)
Niacin	60 to 76*	60 to 76*	Nicotinamide adenine dinucleotide*	Not reported

\*Extended-release formulation.

## Clinical Trials

Clinical trials demonstrating the safety and efficacy of niacin in its Food and Drug Administration (FDA) approved indications are outlined in Table 4.<sup>11-36</sup> In general, niacin consistently demonstrated “superiority” over placebo in the management of hyperlipidemia.<sup>13-17</sup> In a trial comparing niacin extended-release and immediate-release formulations, doses  $\geq 1,500$  mg/day of niacin extended-release decreased low density lipoprotein cholesterol (LDL-C) 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 (HDL-C) ( $P < 0.04$  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 ( $P = 0.009$ ).<sup>18</sup> Direct

comparisons of niacin with other lipid modifying agents demonstrated that no one medication class is consistently “superior” to 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.<sup>19-30</sup>

In a trial conducted by Taylor et al, treatment with niacin extended-release in patients with coronary heart disease who were being treated with a hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) resulted in a smaller percentage of patients experiencing a clinical cardiovascular event (any hospitalization for an acute coronary syndrome, stroke, revascularization procedure or sudden cardiac death) compared to placebo (3.8 vs 9.6%;  $P=0.20$ ).<sup>32</sup> When niacin extended-release was added to statin therapy, no significant reduction in clinical cardiovascular outcomes (all-cause mortality, myocardial infarction, rehospitalization or revascularization) was observed between combination therapy and statin monotherapy (5.77 vs 7.14%; odds ratio, 0.78;  $P=0.052$ ).<sup>34</sup> With regards to niacin immediate-release, in the Coronary Drug Project Trial, treatment with niacin immediate-release resulted in some mortality benefits in secondary prevention of coronary heart disease (patients with a previous myocardial infarction); however, after a nine year follow up of these patients, niacin reduced the risk of all-cause mortality by 11% compared to placebo (52.0 vs 58.2%;  $P=0.0004$ ).<sup>31,33</sup> Of note, niacin immediate-release does not currently hold an FDA approved indication for the secondary prevention of myocardial infarction.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<b>Hypercholesterolemia</b>				
<p>Capuzzi et al<sup>11</sup></p> <p>Niacin ER (Niaspan<sup>®</sup>) 375 mg at bedtime for 1 week, followed by 500 mg at bedtime for 1 week, followed by 1,000 mg at bedtime for 1 week; then dosages were titrated to 1,000 to 3,000 mg/day for weeks 4 to 96 based on clinical response and adverse events</p> <p>Concomitant therapy with a statin, bile acid sequestrant or both was permitted if the patient did not achieve sufficient LDL-C reduction while taking a maximally tolerated dose or 2,000 mg of niacin ER.</p>	<p>ES, MC, OL</p> <p>Patients with primary hypercholesterolemia who were previously enrolled in a randomized short-term trial or in a placebo only qualification clinical trial</p>	<p>N=517</p> <p>Up to 96 weeks</p>	<p>Primary: Changes in LDL-C and apo B</p> <p>Secondary: Changes in TC, HDL-C, TC:HDL-C ratio, Lp(a) and TG; adverse events</p>	<p>Primary: Niacin achieved significant reductions in LDL-C by 18 and 20% at weeks 48 and 96. Similar reductions were seen with apo B (16 and 19% at weeks 48 and 96). The percent changes achieved at both 48 and 96 weeks of therapy were significant (<math>P&lt;0.001</math>).</p> <p>Secondary: Niacin achieved significant increases in HDL-C by 26 and 28% at weeks 48 and 96, with TC modestly decreasing (12 and 13%, respectively) (<math>P&lt;0.001</math> for all). The TC:HDL-C ratio decreased by almost one third (<math>P&lt;0.001</math>).</p> <p>Niacin achieved significant decreases in TG and Lp(a) levels by 27 and 30%, respectively, at week 48, and by 28 and 40%, respectively, at week 96 (<math>P&lt;0.001</math> for all).</p> <p>Treatment 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 <math>\leq 1.0</math> 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.</p> <p>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 significant increases in alkaline phosphatase, ALT, amylase, AST, direct bilirubin, glucose and uric acid, and a decrease in phosphorus (<math>P&lt;0.001</math> for all). These changes were considered small and not likely to be biologically or clinically significant since the majority of the changes occurred within the reference values for these analyses. Six patients had AST levels greater than two times the ULN and two patients had AST levels greater than three times the ULN on niacin monotherapy. Five patients had ALT levels greater than two times ULN and no patient had ALT levels greater than three times ULN.</p> <p>Mean platelet counts decreased by 10.1% at week 48 and 14.8% at week</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Guyton et al<sup>12</sup></p> <p>Niacin ER (Niaspan<sup>®</sup>) 375 mg at bedtime for 1 week, followed by 500 mg at bedtime for 1 week, followed by 1,000 mg at bedtime for 1 week; then dosages were titrated to 1,000 to 3,000 mg/day for weeks 4 to 96 based on clinical response and adverse events</p> <p>Concomitant therapy with a statin, bile acid sequestrant or both was permitted if the patient did not achieve sufficient LDL-C reduction while taking a maximally tolerated dose or 2,000 mg of niacin ER.</p>	<p>ES, MC, OL</p> <p>Patients with primary hypercholesterolemia who were previously enrolled in a randomized short-term trial or in a placebo-only qualification clinical trial</p>	<p>N=269 (patients treated up to 96 weeks)</p> <p>N=230 (cohort of patients treated for 3 months [safety data])</p> <p>Up to 96 weeks</p>	<p>Primary: Changes in TC, LDL-C, HCL-C, TG, apo B and Lp(a); safety</p> <p>Secondary: Not reported</p>	<p>96, whereas leukocyte counts increased by 6.5 and 6.8%, respectively, at weeks 48 and 96 (<math>P&lt;0.0001</math> for all).</p> <p>Primary: At week 96, niacin monotherapy (median dose 2,000 mg) significantly decreased LDL-C (18%), TC (10%) and TG (26%), and increased HDL-C (32%) (<math>P&lt;0.01</math> for all). Apo B and Lp(a) were significantly reduced by 26 and 36%, respectively, at week 48 (<math>P&lt;0.01</math> for both). Values for these parameters were not available at week 96.</p> <p>At week 96, niacin in combination with a statin significantly decreased LDL-C (32%), TC (24%) and TG (32%), and increased HDL-C (25%) (<math>P&lt;0.01</math> for all). Apo B (26%; <math>P&lt;0.01</math>) and Lp(a) (19%; <math>P</math> value not significant) were reduced at week 48. Values for these parameters were not available at week 96.</p> <p>At week 96, niacin in combination with a bile acid sequestrant significantly decreased LDL-C (28%) and TC (15%), and increased HDL-C (31%) (<math>P&lt;0.01</math> for all). Nonsignificant increases in TG (5%; <math>P</math> value not significant) were observed. Apo B and Lp(a) were significantly reduced by 19 and 24% (<math>P&lt;0.01</math>), respectively, at week 48. Values for these parameters were not available at week 96.</p> <p>Intolerance to flushing led 4.8% of patients (13/269) to discontinue niacin. Other medication-related adverse events leading to discontinuation from the 96 week trial included nausea (3.3%) 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.</p> <p>Overall, 9/499 (2.6%) patients experienced an ALT or AST elevation greater than two time ULN. 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</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>patient taking niacin with simvastatin.</p> <p>Secondary: Not reported</p>
<p>Elam et al<sup>13</sup> ADMIT</p> <p>Niacin IR (Niacor<sup>®</sup>) 3,000 mg/day or maximum tolerated dosage</p> <p>vs</p> <p>placebo</p>	<p>MC, PC, RCT</p> <p>Adult patients with peripheral arterial disease with or without diabetes</p>	<p>N=468 (N=125 diabetics)</p> <p>Up to 60 weeks (12 week active run in period plus 48 week DB period)</p>	<p>Primary: Change from baseline in lipid profile, glucose, HbA<sub>1c</sub>, ALT, uric acid; hypoglycemic drug use; compliance; adverse events</p> <p>Secondary: Not reported</p>	<p>Primary: Niacin 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 (<math>P&lt;0.001</math> for niacin vs placebo for all).</p> <p>Glucose levels were modestly increased by niacin (8.7 and 6.3 mg/dL; <math>P=0.04</math> and <math>P&lt;0.001</math>) in participants with and without diabetes, respectively.</p> <p>Baseline HbA<sub>1c</sub> levels were unchanged in participants with diabetes who received niacin; diabetics receiving placebo had a decrease of 0.3% (<math>P=0.04</math> for difference).</p> <p>There were no significant differences in niacin discontinuation, niacin dosage or hypoglycemic therapy in diabetics treated with niacin compared to placebo.</p> <p>Secondary: Not reported</p>
<p>Kuvin et al<sup>14</sup></p> <p>Niacin ER (Niaspan<sup>®</sup>) 500 mg at bedtime for 2 weeks, followed by 1,000 mg at bedtime</p> <p>vs</p> <p>placebo</p>	<p>PC, RCT</p> <p>Patients with stable CAD, a LDL-C &lt;100 mg/dL and receiving current statin therapy (&gt;80% atorvastatin)</p>	<p>N=60</p> <p>3 months</p>	<p>Primary: Changes in Lp, HDL and LDL particle distribution and inflammatory markers</p> <p>Secondary: Not reported</p>	<p>Primary: Niacin significantly increased total HDL-C by 7.5% and decreased TG by 15.0% compared to baseline (<math>P&lt;0.005</math> for both), whereas TC and LDL-C remained unchanged.</p> <p>Compared to baseline values, the addition of niacin resulted in a 32% increase in large particle HDL (<math>P&lt;0.001</math>) and an 8% decrease in small particle HDL (<math>P=0.0032</math>). Addition of niacin produced an 82% increase in large particle LDL (<math>P=0.09</math>) and a 12% decrease in small particle LDL (<math>P=0.008</math>).</p> <p>Niacin also favorably altered inflammatory markers with Lp associated phospholipase A2 and CRP levels decreasing by 20 and 15%, respectively,</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>compared to baseline (<math>P&lt;0.05</math> for both).</p> <p>No significant changes from baseline were observed in any tested parameter in patients receiving placebo.</p> <p>No major cardiovascular events were reported during the trial.</p> <p>Secondary: Not reported</p>
<p>Grundy et al<sup>15</sup> ADVENT</p> <p>Niacin ER (Niaspan<sup>®</sup>) 1,000 mg/day</p> <p>vs</p> <p>niacin ER (Niaspan<sup>®</sup>) 1,500 mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, RCT</p> <p>Patients with stable type 2 diabetes</p>	<p>N=148</p> <p>16 weeks</p>	<p>Primary: Change from baseline in HDL-C, TG and HbA<sub>1c</sub></p> <p>Secondary: Change from baseline in TC, LDL-C and FBG; adverse effects</p>	<p>Primary: Dose-dependent increases in HDL-C (13 to 19% for 1,000 mg/day and 22 to 24% for 1,500 mg/day; <math>P&lt;0.05</math> vs placebo for both) and reductions in TG levels (-15 to -20% for 1,000 mg/day; <math>P</math> value not significant and -28 to -36% for 1,500 mg/day; <math>P&lt;0.05</math>) were observed.</p> <p>Changes in HbA<sub>1c</sub> levels were small with all treatments. Mean HbA<sub>1c</sub> levels were 7.1 (0.13%), 7.4 (0.19%) and 7.5% (0.14%) with placebo, 1,000 mg/day and 1,500 mg/day, representing respective changes of -0.02, 0.07 and 0.29%. The 1,500 mg/day dose was the only to achieve a significant change from baseline (0.29%; <math>P=0.048</math>).</p> <p>Secondary: Mean LDL-C levels did not significantly change with placebo or 1,000 mg/day. With 1,500 mg/day, LDL-C levels decreased at all time points and the difference compared to placebo was significant at weeks 12 and 16 (<math>P&lt;0.05</math> for both). The mean changes from baseline at 16 weeks were 9, 5 and -7% with placebo, 1,000 mg/day and 1,500 mg/day, respectively.</p> <p>Similar trends were observed for TC with mean increases of 4% with placebo and 1,000 mg/day, and a decrease of 6% with 1,500 mg/day (<math>P</math> values not reported).</p> <p>For both 1,000 and 1,500 mg/day, an initial rise in FBG was observed between weeks four and eight which returned to baseline by week 16. Four patients receiving niacin (three at the 1,500 mg/day dose) discontinued participation because of inadequate glucose control.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>Rates of adverse events other than flushing were similar for niacin and placebo. Flushing was reported by approximately 67% of patients receiving niacin and approximately 10% of patients receiving placebo (<i>P</i> value not reported). Four patients, including one receiving placebo, withdrew from the trial due to flushing. No hepatotoxic effects or myopathy was observed.</p>
<p>Knopp et al<sup>16</sup></p> <p>Niacin IR TID, titrated up to 1.5 g/day for weeks 4 to 8, followed by 3 g/day for weeks 9 to 16</p> <p>vs</p> <p>niacin ER (Niaspan<sup>®</sup>) titrated up to 1.5 g/day at bedtime by week 4</p> <p>vs</p> <p>placebo</p> <p>All patients entered a 9 week run in period.</p>	<p>DB, MC, PG, RCT</p> <p>Adult patients with hypercholesterolemia</p>	<p>N=223</p> <p>25 weeks</p>	<p>Primary: Change in LDL-C, FPG and uric acid; drug tolerance</p> <p>Secondary: Change in TC, TG, HDL-C, HDL subfractions, apo B, apo A-I, apo E and Lp(a)</p>	<p>Primary: LDL-C was significantly reduced by 12, 12 and 22%, respectively, with niacin ER, niacin IR 1.5 g/day and niacin IR 3 g/day, respectively, compared to placebo (<i>P</i>≤0.05).</p> <p>At equal doses of 1.5 g/day, niacin ER vs niacin IR, AST increased 5.0 vs 4.8% (<i>P</i> value not significant), FPG increased 4.8 vs 4.5% (<i>P</i> value not significant) and uric acid concentration increased 6 vs 16% (<i>P</i>=0.0001), respectively.</p> <p>Flushing events were more frequent with niacin IR compared to niacin ER (1,905 vs 575; <i>P</i>&lt;0.001). Flushing severity was slightly greater with niacin ER, but still well tolerated.</p> <p>Secondary: Compared to placebo at week eight, niacin ER 1.5 g/day vs niacin IR 1.5 g/day demonstrated comparable efficacy in lowering TC, TG, apo B, apo E and Lp(a), and raising HDL-C, HDL2-C, HDL3-C and apo A-I (<i>P</i>≤0.05 for all).</p> <p>Niacin IR 3 g/day produced significantly greater changes in the above lipid parameters compared to niacin IR and ER 1.5 g/day (<i>P</i>≤0.05).</p>
<p>Superko et al<sup>17</sup></p> <p>Niacin IR 3,000 mg/day</p> <p>vs</p> <p>niacin ER (Niaspan<sup>®</sup>) 1,500 mg/day</p>	<p>PC, RCT</p> <p>Patients with hypercholesterolemia</p>	<p>N=218</p> <p>14 weeks</p>	<p>Primary: Changes in lipid profile and Lp subclass distribution</p> <p>Secondary: Not reported</p>	<p>Primary: Niacin IR and ER significantly decreased TG, LDL-C, apo B and Lp(a), and significantly increased HDL-C (<i>P</i>≤0.0001 for all).</p> <p>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 (<i>P</i>&lt;0.05 for all, except for LDL I; <i>P</i>=0.12 for niacin ER).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>vs placebo</p> <p>Results of 38 patients receiving niacin ER 3,000 mg/day from a previous trial were utilized in this analysis.</p>				<p>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).</p> <p>Compared to niacin IR, niacin ER 3,000 mg/day produced a smaller decrease in TG (-27 vs -47%; <math>P &lt; 0.001</math>), but had similar changes in LDL-C (-20 vs -22%; <math>P</math> value not reported), apo B (-22 vs -21%; <math>P</math> value not reported), HDL-C (27 vs 28%; <math>P</math> value not reported) and LDL peak particle diameter (0.90 vs 0.76 mm; <math>P</math> value not reported).</p> <p>Secondary: Not reported</p>
<p>McKenney et al<sup>18</sup></p> <p>Niacin IR BID, for a total daily dose of 500, 1,000, 1,500, 2,000 and 3,000 mg for 6 weeks each</p> <p>vs</p> <p>niacin ER BID, for a total daily dose of 500, 1,000, 1,500, 2,000 and 3,000 mg for 6 weeks each</p>	<p>DB, PG, RCT</p> <p>Patients with LDL-C &gt;160 mg/dL after 1 month on a NCEP ATP III-Step 1 diet</p>	<p>N=46</p> <p>36 weeks</p>	<p>Primary: Changes in LCL-C, HDL-C and TG; adverse events</p> <p>Secondary: Not reported</p>	<p>Primary: Niacin ER significantly decreased LDL-C more than niacin IR with doses of <math>\geq 1,500</math> mg/day (<math>P &lt; 0.04</math> or <math>P &lt; 0.001</math>).</p> <p>Niacin IR significantly increased HDL-C more than niacin ER with all doses (<math>P &lt; 0.04</math> or <math>P &lt; 0.001</math>).</p> <p>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 (<math>P = 0.009</math>).</p> <p>Nine of 23 patients (39%) receiving niacin IR withdrew before completing 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.</p> <p>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.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>None of the patients receiving niacin IR developed hepatotoxic effects, while 12 patients (52%) receiving niacin ER did.</p> <p>Secondary: Not reported</p>
<p>Wi et al<sup>19</sup></p> <p>Niacin ER 500 mg/day for 5 weeks, followed by 1,000 mg/day for 4 weeks, followed by 1,500 mg/day</p> <p>vs</p> <p>fenofibrate 160 mg/day</p> <p>After discontinuation of any lipid modifying drug, patients entered an 8 week dietary run in period.</p>	<p>OL, RCT</p> <p>Patients 20 to 79 years of age with TG 150 to 499 mg/dL and HDL-C &lt;45 mg/dL</p>	<p>N=201</p> <p>24 weeks (includes 8 week dietary run in period)</p>	<p>Primary: Percent change from randomization to week 16 in apo B/apo A-I</p> <p>Secondary: Percent changes in other lipid parameters, levels of glucose metabolism-related parameters, hsCRP</p>	<p>Primary: Apo B/apo A-I was reduced with both treatments with no difference between the two (<math>P=0.47</math>). The percent reduction in apo B was greater with niacin, whereas the percent elevation in apo A-I was higher with fenofibrate.</p> <p>Secondary: TC significantly decreased with both treatments, and TG decreased and HDL-C increased. LDL-C increased with fenofibrate but decreased with niacin. The percent reduction in TC was greater with niacin (<math>P=0.01</math>). TG decreased significantly more with fenofibrate (<math>P=0.045</math>), whereas the percent elevation in HDL-C was not different between the two treatments (<math>P=0.22</math>). The percent change in LDL-C was significantly different with the two treatments (<math>P&lt;0.001</math>). Lp(a) levels were reduced with niacin only, and the change was significantly different compared to fenofibrate (<math>P&lt;0.001</math>).</p> <p>FPG levels decreased with fenofibrate and increased significantly with niacin. HbA<sub>1c</sub> levels increased with both treatments; the increase was borderline with fenofibrate and significant with niacin. The percent changes in FPG (<math>P&lt;0.001</math>) and HbA<sub>1c</sub> (<math>P&lt;0.001</math>) 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 (<math>P&lt;0.001</math>) and HOMA-IR (<math>P&lt;0.001</math>) were significantly different between the two treatments.</p> <p>hsCRP levels were significantly lowered with both treatments, but the percent change was greater with niacin (<math>P=0.03</math>).</p>
<p>Guyton et al<sup>20</sup></p> <p>Niacin ER (Niaspan<sup>®</sup>)</p>	<p>DB, MC, PC, RCT</p>	<p>N=173</p> <p>8 weeks</p>	<p>Primary: Effect on HDL-C</p>	<p>Primary: Niacin 1,500 and 2,000 mg/day significantly increased HDL-C by 21 and 26%, respectively, compared to 13% with gemfibrozil (<math>P&lt;0.02</math>).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
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	Patients 21 to 75 years of age with HDL-C $\leq$ 40 mg/dL, LDL-C $\leq$ 160 mg/dL or $<$ 130 mg/dL with atherosclerotic disease and TG $\leq$ 400 mg/dL		Secondary: Change in other Lps, adverse effects	Secondary: Compared to gemfibrozil, niacin 1,500 and 2,000 mg/day significantly increased apo A-I (9 and 11 vs 4%), reduced TC:HDL-C ratio (-17 and -22 vs -12%), reduced Lp(a) (-7 and -20 vs no change) and had no adverse effect on LDL-C (2 and 0 vs 9%; $P < 0.001$ to $P < 0.02$ ).  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 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 ( $P = 0.009$ ).
Blankernhorn et al <sup>21</sup>  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 $\geq$ 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Illingworth et al <sup>22</sup>  Lovastatin 10 to 80 mg/day  vs  niacin IR 0.25 mg to 1.5 g TID	MC, OL, RCT  Patients 21 to 75 years of age with primary hypercholesterolemia and either an LDL-C >160 mg/dL and CHD or ≥2 CHD risk factors without CHD or LDL-C >190 mg/dL without CHD or ≥2 risk factors after rigorous diet	N=136  26 weeks	Primary: Change from baseline in lipid parameters  Secondary: Safety	<p>(<i>P</i>&lt;0.001 for all). Modifications in lipid parameters achieved with combination therapy were significant compared to baseline values (<i>P</i> values not reported).</p> <p>Primary:                      Lovastatin reduced TC, LDL-C and apo B significantly more than niacin (<i>P</i>&lt;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.</p> <p>The target treatment goal of LDL-C &lt;130 mg/day for patients with CHD or less than two risk factors was achieved in 14, 19 and 35% of patients receiving lovastatin compared to zero, 18 and 26% of patients receiving placebo at weeks 10, 18 and 26, respectively (<i>P</i> values not significant).</p> <p>For the majority of those patients with CHD or two or more risk factors in whom the LDL-C goal was &lt;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 (<i>P</i> value not reported).</p> <p>Niacin was more effective in decreasing TG at week 26 (<i>P</i>&lt;0.01 vs lovastatin).</p> <p>Both treatments were effective in reducing VLDL-C, with no significant difference observed between the two treatments (<i>P</i> value not reported).</p> <p>Niacin produced reductions in Lp(a) of 14, 30 and 35% at weeks 10, 18 and 26, whereas lovastatin had no effect (<i>P</i>&lt;0.05 or <i>P</i>&lt;0.01 between drugs at each time point).</p> <p>Niacin was significantly more effective at increasing HDL-C and apo A-I (<i>P</i>&lt;0.01 vs lovastatin), except for the change in apo A-1 at week 10 (<i>P</i> value not reported). Niacin increased HDL-C by 20, 29 and 33% and apo A-I by 11, 19 and 22% at weeks 10, 18 and 26. Lovastatin resulted in a modest increase in HDL-C and apo A-I of 7 and 6%, respectively, at week 26.</p> <p>Secondary:                      Four deaths occurred in the trial, one with niacin and three with lovastatin.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>All were related to atherosclerosis, and none were deemed to be drug-related.</p> <p>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 (<i>P</i> value not significant). The major reasons for discontinuation of niacin were cutaneous complaints, including flushing, pruritis and rash. One patient discontinued lovastatin because of myalgias.</p> <p>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.</p>
<p>Sharma et al<sup>23</sup></p> <p>Niacin ER/lovastatin 1,500 mg/20 mg/day</p>	<p>MC, OL</p> <p>Patients living in India with hypertension and dyslipidemia</p>	<p>N=131</p> <p>24 weeks</p>	<p>Primary: Percent change from baseline in LDL-C, HDL-C, TG and TC</p> <p>Secondary: Not reported</p>	<p>Primary: Combination therapy was associated with a significant reduction from baseline in LDL-C (38.0%), TG (21.0%) and TC (25.2%) (<i>P</i>&lt;0.01 for all).</p> <p>Combination therapy was associated with a significant increase from baseline in HDL-C (18.2%; <i>P</i>&lt;0.01).</p> <p>Secondary: Not reported</p>
<p>Brown et al<sup>24</sup></p> <p>Colestipol 5 to 10 g TID plus niacin 125 mg BID titrated to 1 to 1.5 g TID</p> <p>vs</p> <p>Colestipol 5 to 10 g TID plus lovastatin 20 mg BID titrated to 40 mg BID</p>	<p>DB, RCT</p> <p>Men ≤62 years of age with elevated apo B and a family history of CAD</p>	<p>N=120</p> <p>32 months</p>	<p>Primary: Average change in the percent stenosis for the worst lesion in each of the nine proximal segments</p> <p>Secondary: Average changes in all</p>	<p>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 (<i>P</i>&lt;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).</p> <p>Secondary: Placebo (conventional therapy) resulted in consistent worsening of disease</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo (or colestipol if LDL-C was elevated)			lesions measured in each patient and in proximal lesions causing ≥50% (severe) stenosis or <50% (mild) stenosis at baseline	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.
Karas et al <sup>25</sup> OCEANS  Group A: Niacin ER/simvastatin 2,000/20 or 1,000/20  vs simvastatin 20 mg daily  Group B: Niacin ER/simvastatin 1,000/40 or 2,000/40 mg daily  vs simvastatin 80 mg daily  All simvastatin monotherapy patients received niacin IR 50 mg/day to prevent unblinding due to flushing.  All patients were instructed	AC, MC, OL, PG, Phase III, RCT  Patients ≥21 years of age with a diagnosis of primary type II hyperlipidemia or mixed dyslipidemia, proof of reasonable compliance with a standard cholesterol lowering diet for 4 weeks before screening and for the duration of the trial, and LDL and/or non-HDL levels above normal	N=641  24 weeks	Primary: Group A: mean percent change in non-HDL-C  Group B: non-inferiority of niacin ER/simvastatin 2,000/40 mg to simvastatin 80 mg in mean percent change in non-HDL  Secondary: Mean percent change in LDL-C, TG and HDL-C	Primary: In Group A, the mean percent changes in non-HDL-C at 24 weeks were significantly greater with niacin ER/simvastatin 1,000/20 and 2,000/20 mg than with simvastatin 20 mg (-13.6 and -19.5 vs -5.0%, respectively; <i>P</i> <0.05).  In Group B, the mean percent change in non-HDL-C at 24 weeks with niacin ER/simvastatin 2,000/40 mg was non-inferior to that of simvastatin 80 mg (-7.6 vs -6.0%; 95% CI, -7.7 to 4.5). Similar results were obtained in non-inferiority comparisons between niacin ER/simvastatin 1,000/40 mg and simvastatin 80 mg (-6.7 vs -6.0%; 95% CI, -6.6 to 5.3).  Secondary: In Group A, the mean percent change in LDL-C at 24 weeks with niacin ER/simvastatin 1,000/20 and 2,000/20 mg were non-superior to simvastatin 20 mg (-11.9 and -14.3 vs -6.7%, respectively) ( <i>P</i> value not provided). However, mean percent reduction in TG and mean percent increase in HDL-C with niacin ER/simvastatin 1,000/20 and 2,000/20 mg were “superior” to simvastatin 20 mg (TG, -26.5 and -38 vs -15.3%, respectively, HDL, 20.7 and 29% vs 7.8%, respectively) ( <i>P</i> values not provided).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
to take aspirin or ibuprofen to minimize flushing.				
<p>Ballantyne et al<sup>26</sup> SEACOAST 1</p> <p>Niacin ER/simvastatin 1,000/20 or 2,000/20 mg/day</p> <p>vs</p> <p>simvastatin 20 mg/day</p> <p>All simvastatin monotherapy patients received niacin IR 50 mg/day to prevent unblinding due to flushing.</p>	<p>AC, DB, MC, RCT</p> <p>High risk patients with primary or mixed dyslipidemia</p>	<p>N=319</p> <p>24 weeks</p>	<p>Primary: Percentage change from baseline in non-HDL-C</p> <p>Secondary: Percent change from baseline in LDL-C, HDL-C, TC/HDL-C, TG, apo B and apo AI</p>	<p>Primary: Combination therapy achieved significant improvements in non-HDL-C. Median change from baseline at week 24 in non-HDL-C was -13.9, -22.5 (<math>P&lt;0.01</math>) and -7.4% (<math>P&lt;0.001</math>) for niacin ER/simvastatin 1,000/20 mg/day, niacin ER/simvastatin 2,000/20 mg/day and simvastatin.</p> <p>Secondary: Combination therapy was associated with nonsignificant additional decreases in LDL-C compared to simvastatin. Both combination therapy regimens had significantly greater decreases in TG, Lp(a), apo B and TC:HDL-C (<math>P</math> values not reported). Combination therapy also achieved significant increases in HDL-C and apo AI/apo B.</p>
<p>Fazio et al<sup>27</sup></p> <p>Ezetimibe/simvastatin 10/20 mg/day plus niacin ER 2 g/day</p> <p>vs</p> <p>niacin ER 2 g/day</p> <p>vs</p> <p>ezetimibe/simvastatin 10/20 mg/day</p> <p>At the end of 24 weeks, patients receiving niacin ER were rerandomized to either one of the other 2 treatment</p>	<p>DB, MC, RCT</p> <p>Patients 18 to 79 years of age with hyperlipidemia (Types IIa and IIb) with LDL-C 130 to 190 mg/dL, TG <math>\leq</math>500 mg/dL, creatinine <math>&lt;</math>2 mg/dL, creatine kinase <math>\leq</math>2 times the ULN, transaminases <math>\leq</math>1.5 times the ULN and HbA<sub>1c</sub> <math>\leq</math>8%</p>	<p>N=942</p> <p>64 weeks</p>	<p>Primary: Safety and tolerability of ezetimibe/simvastatin plus niacin ER</p> <p>Secondary: Changes in HDL-C, TG, non-HDL-C and LDL-C</p>	<p>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 <math>&lt;</math>50 mg/dL (1.5 vs 7.1%).</p> <p>The overall incidence of clinical adverse events was slightly greater for ezetimibe/simvastatin plus niacin compared to ezetimibe/simvastatin owing to the greater number of patients who experienced drug-related clinical adverse events and drug-related discontinuations with ezetimibe/simvastatin plus niacin, mainly attributed to niacin-associated flushing and pruritis.</p> <p>The percentage of patients with consecutive elevations in ALT or AST of at least three times or greater the ULN, and creatine kinase of at least ten times or greater the ULN were low and comparable between treatments.</p> <p>A total of 19 patients had adverse events of increased FPG levels, with eight receiving ezetimibe/simvastatin and 11 receiving ezetimibe/simvastatin plus</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
regimens.				<p>niacin.</p> <p>Secondary: Ezetimibe/simvastatin plus niacin significantly improved baseline HDL-C, TG, non-HDL-C, LDL-C, apo B, apo A-I and Lp ratios compared to ezetimibe/simvastatin at week 64 (<math>P&lt;0.004</math>). The changes in TC were comparable between the two treatment groups and the reduction in hsCRP was numerically greater with ezetimibe/simvastatin plus niacin (<math>P</math> 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 (<math>P&lt;0.001</math>). 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 (<math>P&lt;0.001</math>) and became significant for non-HDL-C after eight weeks (<math>P=0.002</math>) and LDL-C after 12 weeks (<math>P&lt;0.001</math>).</p>
<p>Fazio et al<sup>28</sup></p> <p>Ezetimibe/simvastatin 10/20 mg/day plus niacin ER 2 g/day</p> <p>vs</p> <p>niacin ER 2 g/day</p> <p>vs</p> <p>ezetimibe/simvastatin 10/20 mg/day</p> <p>At the end of 24 weeks, patients receiving niacin ER were rerandomized to either</p>	<p>Subgroup analysis of Fazio et al<sup>27</sup></p> <p>Hyperlipidemic patients with diabetes mellitus, metabolic syndrome without diabetes mellitus or neither</p>	<p>N=765 at 24 weeks</p> <p>N=574 at 64 weeks</p>	<p>Primary: Changes in HDL-C, TG, non-HDL-C, LDL-C, fasting glucose and uric acid</p> <p>Secondary: Not reported</p>	<p>Primary: The effect of triple therapy on efficacy variables across patient subgroups was generally consistent with the significantly greater improvements observed in the total population compared to niacin and combination therapy. Triple therapy improved levels of LDL-C, other lipids and Lp ratios compared to niacin and combination therapy at 24 and 64 weeks. Triple therapy also increased HDL-C and Lp(a) comparably to niacin and more than combination therapy. Triple therapy also decreased hsCRP more effectively than niacin and comparably to combination therapy.</p> <p>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.</p> <p>New onset diabetes was more frequent among patients with metabolic syndrome than those without for the first 24 weeks and trended higher</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
one of the other 2 treatment regimens.				<p>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.</p> <p>Treatment-incident increases in uric acid were higher among patients receiving niacin, but there were no effects on symptomatic gout.</p> <p>Secondary: Not reported</p>
<p>McKenney et al<sup>29</sup> COMPELL</p> <p>Rosuvastatin 10 mg/day for 4 weeks, followed by 20 mg/day for 4 weeks, followed by 40 mg/day</p> <p>vs</p> <p>atorvastatin 20 mg/day plus niacin SR 500 mg/day for 4 weeks, followed by atorvastatin 20 mg/day plus niacin SR 1,000 mg/day for 4 weeks, followed by atorvastatin 40 mg/day plus niacin SR 2,000 mg/day</p> <p>vs</p> <p>simvastatin 20 mg/day plus ezetimibe 10 mg/day for 8 weeks, followed by simvastatin 40 mg/day plus ezetimibe 10 mg/day</p>	<p>MC, OL, PG, RCT</p> <p>Patients ≥21 years of age with hypercholesterolemia, eligible for treatment based on the NCEP ATP III guidelines, with 2 consecutive LDL-C levels within 15% of each other and mean TG ≤300 mg/dL</p>	<p>N=292</p> <p>12 weeks</p>	<p>Primary: Change from baseline in LDL-C</p> <p>Secondary: Change from baseline in HDL-C non-HDL-C, TG, Lp(a) and apo B; side effects</p>	<p>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; <i>P</i>=0.093).</p> <p>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; <i>P</i>≤0.05).</p> <p>There was no significant differences in the reduction of non-HDL-C from baseline with any treatment (<i>P</i>=0.053).</p> <p>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; <i>P</i>≤0.05).</p> <p>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; <i>P</i>≤0.05).</p> <p>Atorvastatin plus niacin SR was associated with a significant reduction in apo B compared to rosuvastatin (43 vs 39%, respectively; <i>P</i>≤0.05).</p> <p>Side effects were similar across treatments (<i>P</i> values not reported). There were no cases of myopathy or hepatotoxicity reported.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
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				
Zhao et al <sup>30</sup>  Niacin 2.4±2.0 g/day (mean dose) plus simvastatin 13±6 mg/day (mean dose)  vs  antioxidants (vitamin E 800 IU/day, vitamin C 1,000 mg/day and selenium 100 µg/day)  vs  niacin plus simvastatin plus antioxidants  vs  placebo	ES of Brown et al <sup>35</sup>  Patients with clinical coronary disease (previous MI, coronary interventions or confirmed angina) including 25 with diabetes with mean LDL-C 128 mg/dL, HDL-C 31mg/dL and TG 217 mg/dL	N=160  38 months	Primary: Side effects, response to the question "Overall, how difficult is it to take the study medication?"  Secondary: Not reported	Primary: Patients receiving niacin plus simvastatin experienced similar frequencies of clinical or laboratory side effects compared to placebo; any degree of flushing (30 vs 23%; <i>P</i> value not significant), symptoms of fatigue, nausea and/or muscle aches (9 vs 5%; <i>P</i> value not significant), AST at least three times the ULN (3 vs 1%; <i>P</i> value not significant), CPK at least two times the ULN (3 vs 4%; <i>P</i> value not significant), new onset of uric acid ≥7.5 mg/dL (18 vs 15%; <i>P</i> value not significant) and homocysteine ≥15 µmol/L (9 vs 4%; <i>P</i> 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<b>Hypercholesterolemia Clinical Outcomes Trials</b>				
<p>Canner et al<sup>31</sup></p> <p>Niacin IR 3 g/day</p>	<p>ES of the Coronary Drug Project Trial<sup>33</sup></p> <p>Men 30 to 64 years of age with previous MI</p>	<p>N=8,341</p> <p>9 years</p>	<p>Primary: All-cause mortality</p> <p>Secondary: Cause-specific mortality (e.g., coronary mortality and sudden death)</p>	<p>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%; <math>P=0.0004</math> vs placebo).</p> <p>Secondary: The survival benefit with niacin was primarily evident for death caused by CHD (36.5 vs 41.3%; <math>P&lt;0.05</math> vs placebo).</p>
<p>Taylor et al<sup>32</sup></p> <p>Niacin ER (Niaspan<sup>®</sup>) 1,000 mg/day</p> <p>vs</p> <p>placebo</p> <p>All patients received background statin therapy.</p>	<p>DB, PC, RCT</p> <p>Adult patients with known CHD and low levels of HDL-C (&lt;45 mg/dL)</p>	<p>N=167</p> <p>1 year</p>	<p>Primary: Change in mean common CIMT after one year</p> <p>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</p>	<p>Primary: After one year, mean CIMT increased significantly with placebo (0.044±0.100 mm; <math>P&lt;0.001</math>) and was unchanged with niacin (0.014±0.104 mm; <math>P=0.23</math>).</p> <p>The overall difference in CIMT progression between placebo and niacin was not significant (<math>P=0.08</math>); however, a post hoc analysis revealed that niacin significantly reduced the rate of CIMT progression in subjects without insulin resistance (<math>P=0.026</math>).</p> <p>Secondary: HDL-C increased by 21% with niacin and did not change with placebo (<math>P&lt;0.003</math>).</p> <p>Clinical cardiovascular events occurred in three patients receiving niacin (3.8%) and seven receiving placebo (9.6%; <math>P=0.20</math>).</p> <p>Adherence to trial medication based on pill counts ranged from 90.3 to 94.5%, and was not different between the two treatments (<math>P</math> value not reported).</p> <p>No patient experienced significant (three times the ULN) 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 (<math>P&lt;0.001</math>).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>No authors listed<sup>33</sup> Coronary Drug Project Trial</p> <p>Niacin IR 3 g/day</p> <p>vs</p> <p>clofibrate* 1.8 g/day</p> <p>vs</p> <p>placebo</p> <p>Treatment arms also included estrogens and dextrothyroxine.</p>	<p>DB, MC, PC, RCT</p> <p>Men 30 to 64 years of age with previous MI</p>	<p>N=8,341</p> <p>5 years</p>	<p>Primary: All-cause mortality</p> <p>Secondary: Cause-specific mortality (e.g., coronary mortality and sudden death), nonfatal cardiovascular events</p>	<p>Primary: The incidence of all-cause mortality was comparable between niacin (24.4%), clofibrate (25.5%) and placebo (25.4%) (<i>P</i> values not significant).</p> <p>Secondary: Five year rates of death due to cardiovascular disease were comparable between niacin (18.8%), clofibrate (17.3%) and placebo (18.9%) (<i>P</i> values not significant).</p> <p>Major cardiovascular events were reduced with niacin; CHD events by 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%; <i>P</i>&lt;0.004).</p> <p>There was no evidence of significant efficacy of clofibrate with regard to all-cause and cause-specific mortality.</p> <p>Treatment with niacin for five years lowered TC by 10% and TG levels by 26% (<i>P</i> values not reported). Treatment with clofibrate lowered TC by 7% and TG levels by 22% (<i>P</i> values not reported).</p>
<p>Sang et al<sup>34</sup></p> <p>Atorvastatin 10 mg/day</p> <p>vs</p> <p>atorvastatin 10 mg/day plus niacin ER</p>	<p>RCT</p> <p>Patients with clinical and angiographic criteria for coronary disease, with ≥50% stenosis of 1 coronary artery with high TC</p>	<p>N=108</p> <p>12 months (plus a 12 month follow up)</p>	<p>Primary: All-cause mortality, MI, rehospitalization, revascularization with either PCI or CABG</p> <p>Secondary: Mean percent changes from baseline lipid parameters, effects on glucose metabolism,</p>	<p>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; <i>P</i>=0.052).</p> <p>Secondary: TC, TG, LDL-C and Lp(a) levels decreased significantly with both treatments (<i>P</i>&lt;0.01), with no significant difference between the two during the course of follow up (<i>P</i>&gt;0.05). Apo A increased significantly with both treatments (<i>P</i>&lt;0.01), with a more favorable effect observed with combination therapy (24.5 vs 40.8%; <i>P</i>&lt;0.01). During the follow up, apo B fell by 5.63 (<i>P</i>&lt;0.05 and 7.35% (<i>P</i>&lt;0.01) with atorvastatin and combination therapy; with no significant difference between the two (<i>P</i>&gt;0.05). During the trial, HDL-C</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			safety	<p>levels increased by 11.67 (<math>P&lt;0.05</math>) and 29.36% (<math>P&lt;0.01</math>) with atorvastatin and combination therapy, with a significant difference favoring combination therapy (<math>P&lt;0.01</math>).</p> <p>Niacin resulted in no significant increase in glucose levels at six or 12 months compared to baseline levels (<math>P&gt;0.05</math>). In the subgroup of diabetic patients (<math>n=28</math>), niacin resulted in a significant increase in glucose levels at six months (<math>P&lt;0.01</math>), and glucose levels increased more significantly at 12 months (<math>P&lt;0.01</math>), but the effect of niacin was not significant in nondiabetic patients (<math>P&gt;0.05</math>). HbA<sub>1c</sub> levels did not show a significant increase at six months in patient with diabetes, but levels increased significantly at 12 months (<math>P&lt;0.05</math>).</p> <p>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.</p>
<p>Brown et al<sup>35</sup></p> <p>Niacin 2.4±2.0 g/day (mean dose) plus simvastatin 13±6 mg/day (mean dose)</p> <p>vs</p> <p>antioxidants (vitamin E 800 IU/day, vitamin C 1,000 mg/day, beta carotene 25 mg/day and selenium 100 µg/day)</p> <p>vs</p> <p>niacin plus simvastatin plus antioxidants</p>	<p>DB, PC</p> <p>Patients with clinical coronary disease (previous MI, coronary interventions or confirmed angina) and with ≥3 stenosis ≥30% of the luminal diameter or 1 stenosis ≥50%, low HDL-C and normal LDL-C</p>	<p>N=160</p> <p>3 years</p>	<p>Primary:</p> <p>Changes in lipid profile, arteriographic evidence of change in coronary stenosis (percent of stenosis caused by most severe lesion in each of nine proximal coronary segments), occurrence of first cardiovascular event (death</p>	<p>Primary:</p> <p>The mean levels of LDL-C, HDL-C and TG were significantly altered by -42 (<math>P&lt;0.001</math>), 26 (<math>P&lt;0.001</math>) and -36% (<math>P&lt;0.001</math>), respectively, with niacin plus simvastatin, but were unaltered with antioxidants or placebo. Similar changes were observed when antioxidants were added to niacin plus simvastatin.</p> <p>The protective increase in HDL2 (considered to be the most protective component of HDL-C) with niacin plus simvastatin (65%) was attenuated by concurrent therapy with antioxidants (28%; <math>P=0.02</math>).</p> <p>The average stenosis progressed by 3.9% with placebo, 1.8% with antioxidants (<math>P=0.16</math> vs placebo) and 0.7% with niacin plus simvastatin plus antioxidants (<math>P=0.004</math>) and regressed by 0.4% with niacin plus simvastatin (<math>P&lt;0.001</math>).</p> <p>The frequency of the composite primary end point (death from coronary causes, MI, stroke or revascularization) was 24% with placebo, 3% with niacin plus simvastatin, 21% with antioxidants and 14% with niacin plus</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>vs placebo</p> <p>Niacin was initiated as ER niacin 250 mg BID and increased to 1,000 mg BID at 4 weeks.</p> <p>Patients whose HDL-C had not increased by 5 mg/dL at 3 months, 8 mg/dL at 8 months and 10 mg/dL at 12 months were switched to niacin IR (Niacor<sup>®</sup>) up to a maximum of 4 g/day.</p> <p>Placebo tablets contained niacin IR 50 mg.</p>			<p>from coronary causes, MI, stroke or re-vascularization)</p> <p>Secondary: Mean change in percent stenosis in lesions of varying degrees of severity, mean change in luminal diameter in proximal lesions and all lesions</p>	<p>simvastatin plus antioxidants. The risk of the composite primary end point was 90% lower with niacin plus simvastatin compared to placebo (<math>P=0.03</math>). The risk with the other treatments did not differ significantly from that with placebo (<math>P</math> values not reported).</p> <p>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.</p>
<p>Charland et al<sup>36</sup></p> <p>High potency dyslipidemia pharmacotherapy (niacin ER/lovastatin, niacin ER/simvastatin, rosuvastatin and ezetimibe/simvastatin</p>	<p>MA (120 unique reports)</p> <p>Patients with hyperlipidemia</p>	<p>N=43,974</p> <p>Duration varied (≥4 weeks)</p>	<p>Primary: Percent change from baseline in lipid parameters, cardiovascular events</p> <p>Secondary: Not reported</p>	<p>Primary: All of the high potency therapies lowered LDL-C by ≥45%, with the higher doses of ezetimibe/simvastatin and rosuvastatin achieving the greatest LDL-C reduction of -60 and -54%, respectively.</p> <p>In general, percent lipid changes for ezetimibe/simvastatin and rosuvastatin increased in a significant dose dependent manner for TC and LDL-C. With niacin-containing therapies, percent changes in these parameters were flat, and no significant differences between moderate and high doses were observed.</p> <p>Ezetimibe/simvastatin and rosuvastatin did not demonstrate a significant difference in percent change in HDL-C throughout the doses evaluated. Non-niacin-containing therapies appeared to have a flat dose response curve, with weighted percent HDL-C changes between 5 and 9%. Niacin-containing therapies achieved a significant dose response effect.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>There was no significant difference in percent change in TG with any dose for ezetimibe/simvastatin or rosuvastatin (5, 20 and 40 mg/day). Niacin-containing therapies also demonstrated greater weighted percent changes in TG lowering (-40%) compared to ezetimibe/simvastatin or rosuvastatin (-31 and -24%).</p> <p>In evaluating percent changes in TC between the therapies there was no significant difference between rosuvastatin 40 mg, ezetimibe/simvastatin 10/80 mg and niacin ER/simvastatin. For LDL-C, there were significant differences between many of the therapies at various doses of rosuvastatin, ezetimibe/simvastatin, niacin ER/lovastatin and niacin ER/simvastatin; however, there was no significant difference in percent change in LDL-C between rosuvastatin 40 mg, ezetimibe/simvastatin 10/40 or 10/80 mg or niacin ER/simvastatin 2,000/40 mg.</p> <p>All of the high-potency therapies are predicted to reduce cardiovascular event rates by &gt;50%, except for the lowest dose of ezetimibe/simvastatin (10/10 mg) and niacin ER/lovastatin (500/20 mg). There was no significant difference in predicted event risk reduction between the largest dose of niacin ER/lovastatin (2,000/40 mg) and niacin ER/simvastatin (2,000/40 mg); however, there was a significant difference in predicted event reduction between either of the highest doses of niacin ER/lovastatin (2,000/40 mg) and niacin ER/simvastatin (2,000/40 mg) compared to all of the doses of rosuvastatin or ezetimibe/simvastatin. The average percent cardiovascular event reduction for ezetimibe/simvastatin, rosuvastatin, niacin ER/lovastatin and niacin ER/simvastatin was 60, 58, 61 and 72%, respectively.</p> <p>Secondary: Not reported</p>

\*Not available in the United States.

Drug regimen abbreviations: BID=twice daily, ER=extended-release, IR=immediate-release, SR=sustained release, TID=three times daily

Study abbreviations: AC=active-controlled, DB=double-blind, ES=extension study, MA=meta analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial

Miscellaneous abbreviations: ALT=alanine aminotransferase, apo A-I=apolipoprotein A-I, apo B=apolipoprotein B, apo E=apolipoprotein E, AST=aspartate aminotransferase, CABG=coronary artery bypass grafting, CAD=coronary artery disease, CHD=coronary heart disease, CIMT=carotid intima-media thickness, CPK=creatinine phosphokinase, CRP=C-reactive protein, FBG=fasting blood glucose, FPG=fasting plasma glucose, HbA<sub>1c</sub>=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-IR=homeostatic model assessment of insulin resistance, hsCRP=high-sensitivity C-reactive protein, IU=international units, LDL-C=low density lipoprotein cholesterol, Lp(a)=lipoprotein(a), MI=myocardial infarction, NCEP ATP III=National Cholesterol Education Program Adult Treatment Panel III, PCI=percutaneous intervention, TC=total cholesterol, TG=triglycerides, ULN=upper limit of normal, VLDL-C=very low density lipoprotein cholesterol

**Special Populations****Table 5. Special Populations<sup>3-5</sup>**

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 ( $\leq 16$ years of age for Niaspan <sup>®</sup> ).	No dosage adjustment required; use with caution.	Contraindicated in patients with significant hepatic dysfunction.	C	Unknown; use with caution.

**Adverse Drug Events****Table 6. Adverse Drug Events<sup>3,4</sup>**

Adverse Event	Niacin
<b>Cardiovascular</b>	
Arrhythmia (including atrial fibrillation)	✓
Hypotension	✓
Migraine	✓ (Niaspan <sup>®</sup> )
Orthostasis	✓
Palpitations	✓ (Niaspan <sup>®</sup> )
Syncope	✓
Tachycardia	✓
<b>Central Nervous System</b>	
Dizziness	✓
Headache	✓ (Niacor <sup>®</sup> ), 5 to 11 (Niaspan <sup>®</sup> )
Insomnia	✓
Nervousness	✓
Paresthesia	✓
<b>Dermatologic</b>	
Acanthosis nigricans	✓
Dry skin	✓
Hyperpigmentation	✓
Mild-to-severe cutaneous flushing	✓
Pruritus	✓ (Niacor <sup>®</sup> ), $\leq 6$ (Niaspan <sup>®</sup> )
Rash	0 to 5 (Niaspan <sup>®</sup> )
Urticaria	✓
Sweating	✓
<b>Endocrine/Metabolic</b>	
Abnormal liver function tests	✓
Decreased glucose tolerance	✓
Edema (generalized)	✓
Face edema	✓

Adverse Event	Niacin
Gout	✓
Hyperglycemia	✓
Hyperuricemia	✓
Increased amylase	✓
Increased lactate dehydrogenase	✓
Peripheral edema	✓
Reductions in phosphorus	✓
<b>Gastrointestinal</b>	
Abdominal pain	2 to 5 (Niaspan <sup>®</sup> )
Diarrhea	✓ (Niacor <sup>®</sup> ), 6 to 8 (Niaspan <sup>®</sup> )
Dyspepsia	✓ (Niacor <sup>®</sup> ), 2 to 5 (Niaspan <sup>®</sup> )
Eructation	✓ (Niaspan <sup>®</sup> )
Flatulence	✓ (Niaspan <sup>®</sup> )
Hepatotoxicity	✓ (Niacor <sup>®</sup> )
Jaundice	✓
Nausea	2 to 8 (Niaspan <sup>®</sup> )
Peptic ulceration	✓
Vomiting	✓ (Niacor <sup>®</sup> ), 0 to 8 (Niaspan <sup>®</sup> )
<b>Hematologic/Lymphatic</b>	
Prolongation prothrombin time	✓
Slight reduction platelet count	✓
<b>Musculoskeletal</b>	
Asthenia	✓ (Niaspan <sup>®</sup> )
Leg cramps	✓ (Niaspan <sup>®</sup> )
Myalgia	✓ (Niaspan <sup>®</sup> )
Myasthenia	✓ (Niaspan <sup>®</sup> )
Pain	1 to 5 (Niaspan <sup>®</sup> )
Rhabdomyolysis	✓ (Niacor <sup>®</sup> )
<b>Respiratory</b>	
Dyspnea	✓ (Niaspan <sup>®</sup> )
Rhinitis	2 to 5 (Niaspan <sup>®</sup> )
<b>Other</b>	
Chills	✓ (Niaspan <sup>®</sup> )
Cystoid macular edema	✓
Hypersensitivity reactions	✓ (Niaspan <sup>®</sup> )
Toxoid amblyopia	✓

✓ Percent not specified.

### **Contraindications/Precautions**

Niacin is contraindicated in patients with hypersensitivity to niacin, niacinamide or any component of the formulations; in active hepatic disease or significant or unexplained persistent elevations in hepatic transaminases; in active peptic ulcer and in arterial hemorrhage.<sup>5</sup>

Prior to initiating therapy with niacin, secondary causes of hypercholesterolemia (e.g., poorly controlled diabetes, hypothyroidism) should be excluded. In addition, management with diet and nonpharmacologic measures (e.g., exercise or weight reduction) should be attempted prior to initiating therapy with niacin.<sup>5</sup>

A common adverse event of niacin is flushing and pruritis. A gradual increase in dose and/or the administration of aspirin or a nonsteroidal anti-inflammatory drug 30 to 60 minutes before dosing may attenuate the flushing and pruritis associated with niacin.<sup>5</sup>

Cases of severe hepatotoxicity, including fulminant hepatic necrosis, have occurred when niacin immediate-release products have been substituted with extended-release products at equivalent doses. Low doses should be used as initial therapy with titration to achieve the desired response. Additionally, liver function test should be monitored in all patients receiving lipid lowering doses of niacin. Caution should be exercised when administering niacin to patients with a past history of hepatic impairment and/or who consume substantial amounts of ethanol.<sup>5</sup>

Niacin should be used with caution in patients with unstable angina or myocardial infarction. Niacin should also be used with caution in patients with diabetes as the agent may increase fasting blood glucose levels, although clinical data suggest increases are modest (less than five percent). However, glucose should be monitored in patients receiving niacin and adjustments of hypoglycemic therapy may be required.<sup>5</sup>

Niacin can exacerbate gallbladder disease; therefore, the agent should be used with caution in patients with gallbladder disease. Use of niacin may also be associated with hyperuricemia; therefore, caution should be used in patients with gout.<sup>5</sup>

A slight increase in prothrombin time may be observed in patients receiving niacin. Patients receiving anticoagulation therapy should be cautioned of this before initiating therapy with niacin. In addition, rare cases of rhabdomyolysis have occurred during concurrent use with hydroxymethylglutaryl coenzyme A reductase inhibitors (statins). Patients receiving concurrent therapy or those who display symptoms suggestive of rhabdomyolysis should have their creatine phosphokinase and potassium monitored.<sup>5</sup>

Of note, niacin immediate-release products are not interchangeable with extended-release products as the bioavailability of the products varies. Use of niacin has not been evaluated in Fredrickson type I or III dyslipidemias.<sup>5</sup>

### **Drug Interactions**

No clinically significant drug interactions are associated with niacin.<sup>37</sup>

### **Dosage and Administration**

**Table 7. Dosing and Administration**<sup>3,4</sup>

<b>Generic Name</b>	<b>Adult Dose</b>	<b>Pediatric Dose</b>	<b>Availability</b>
Niacin	<p><u>Adjunct to diet for the reduction of elevated TC and LDL-C levels in patients with primary hypercholesterolemia (Types IIa and IIb) as monotherapy or in combination with a bile acid binding resin:*</u> Tablet: initial, 250 mg Daily after the evening meal; maintenance, 1 to 2 g BID to TID; maximum, 6 g/day</p> <p><u>Adjunctive therapy for the treatment of adult patients with severe hypertriglyceridemia<sup>†</sup> who present risk of pancreatitis:<sup>‡</sup></u> Extended-release tablet: initial, 500 mg Daily at bedtime; maintenance, 1,000 to 2,000 mg/day Daily at bedtime; maximum, 2,000 mg/day</p> <p>Tablet: initial, 250 mg Daily after the evening meal; maintenance, 1 to 2 g BID to TID; maximum, 6 g/day</p>	Safety and efficacy in children have not been established.	<p>Extended-release tablet (Niaspan<sup>®</sup>): 500 mg 750 mg 1,000 mg</p> <p>Tablet (Niacor<sup>®</sup>): 500 mg</p>

Generic Name	Adult Dose	Pediatric Dose	Availability
	<p><u>Reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hyperlipidemia:</u>                      Extended-release tablet: initial, 500 mg Daily at bedtime; maintenance, 1,000 to 2,000 mg/day Daily at bedtime; maximum, 2,000 mg/day</p> <p><u>Reduce TC and LDL-C levels in adult patients with hyperlipidemia in combination with a bile acid binding resin:*</u>                      Extended-release tablet: initial, 500 mg Daily at bedtime; maintenance, 1,000 to 2,000 mg/day Daily at bedtime; maximum, 2,000 mg/day</p> <p><u>Reduce TC, LDL-C, apo B and TG levels, and to increase HDL-C in patients with primary hyperlipidemia or mixed dyslipidemia:</u>                      Extended-release tablet: initial, 500 mg Daily at bedtime; maintenance, 1,000 to 2,000 mg/day Daily at bedtime; maximum, 2,000 mg/day</p> <p><u>Slow progression or promote regression of atherosclerotic disease in combination with a bile acid binding resin in patients with a history of coronary artery disease and hyperlipidemia:</u>                      Extended-release tablet: initial, 500 mg Daily at bedtime; maintenance, 1,000 to 2,000 mg/day Daily at bedtime; maximum, 2,000 mg/day</p> <p><u>Treatment of primary hyperlipidemia and mixed dyslipidemia in combination with simvastatin or lovastatin:§</u>                      Extended-release tablet: initial, 500 mg Daily at bedtime; maintenance, 1,000 to 2,000 mg/day Daily at bedtime; maximum, 2,000 mg/day</p>		

Apo B=apolipoprotein B, BID=twice daily, HDL-C=high density lipoprotein cholesterol, LDL-C=low density lipoprotein cholesterol, TC=total cholesterol, TG=triglycerides, TID=three times daily

\*When the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate.

†Types IV and V hyperlipidemia (Niacor®).

‡And who do not respond adequately to a determined dietary effort to control them.

§When treatment with Niaspan®, simvastatin or lovastatin monotherapy is considered inadequate.

**Clinical Guidelines**

Current guidelines are summarized in Table 8. The guidelines addressing the management of hypercholesterolemia are presented globally, addressing the role of various medication classes in the management of this disease.

**Table 8. Clinical Guidelines**

Clinical Guideline	Recommendations
National Cholesterol Education Program: <b>Implications of Recent Clinical Trials for the National Cholesterol</b>	<ul style="list-style-type: none"> <li>• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management.</li> <li>• When low density lipoprotein cholesterol (LDL-C) lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40%</li> </ul>

Clinical Guideline	Recommendations
<p><b>Education Program Adult Treatment Panel III Guidelines (2004)<sup>6</sup></b></p>	<p>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.</p> <ul style="list-style-type: none"> <li>• Standard hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statin) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols).</li> <li>• 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.</li> <li>• Fibrates may have an adjunctive role in the treatment of patients with high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins.</li> <li>• In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent.</li> <li>• Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of coronary heart disease (CHD) risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C.</li> </ul> <p><u>Treatment of heterozygous familial hypercholesterolemia</u></p> <ul style="list-style-type: none"> <li>• Begin LDL-C lowering drugs in young adulthood.</li> <li>• TLC indicated for all persons.</li> <li>• Statins, first line of therapy (start dietary therapy simultaneously).</li> <li>• Bile acid sequestrants (if necessary in combination with statins).</li> <li>• If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid).</li> </ul> <p><u>Treatment of homozygous familial hypercholesterolemia</u></p> <ul style="list-style-type: none"> <li>• Statins may be moderately effective in some persons.</li> <li>• LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia).</li> </ul> <p><u>Treatment of familial defective apolipoprotein B-100</u></p> <ul style="list-style-type: none"> <li>• TLC indicated.</li> <li>• All LDL-C lowering drugs are effective.</li> <li>• Combined drug therapy required less often than in heterozygous familial hypercholesterolemia.</li> </ul> <p><u>Treatment of polygenic hypercholesterolemia</u></p> <ul style="list-style-type: none"> <li>• TLC indicated for all persons.</li> <li>• All LDL-C lowering drugs are effective.</li> <li>• If necessary to reach LDL-C goals, consider combined drug therapy.</li> </ul>
<p>National Cholesterol Education Program: <b>Third Report of the</b></p>	<p><u>General recommendations</u></p> <ul style="list-style-type: none"> <li>• With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for</li> </ul>

Clinical Guideline	Recommendations
<p><b>National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report (2002)<sup>1</sup></b></p>	<p>CHD. This recommendation is optional because the strength of evidence is only moderate at present. National Cholesterol Education Program supports the American Heart Association's recommendation that fish be included as part of a CHD risk reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made.</p> <ul style="list-style-type: none"> <li>• Initiate LDL lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid.</li> <li>• Statins should be considered as first line drugs when LDL lowering drugs are indicated to achieve LDL-C treatment goals.</li> <li>• 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.</li> </ul> <p><u>Statins</u></p> <ul style="list-style-type: none"> <li>• Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals.</li> </ul> <p><u>Bile acid sequestrants</u></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Bile acid sequestrants should be considered in combination therapy with statins in patients with very high LDL-C levels.</li> </ul> <p><u>Nicotinic acid</u></p> <ul style="list-style-type: none"> <li>• Nicotinic acid should be considered as a therapeutic option for higher risk patients with atherogenic dyslipidemia.</li> <li>• Nicotinic acid should be considered as a single agent in higher risk patients with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol lowering drugs in higher risk patients with atherogenic dyslipidemia combined with elevated LDL-C levels.</li> <li>• Nicotinic acid should be used with caution in patients with active liver disease, recent peptic ulcer, hyperuricemia, gout and type 2 diabetes.</li> <li>• High doses of nicotinic acid (&gt;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.</li> </ul> <p><u>Fibric acid derivatives (fibrates)</u></p> <ul style="list-style-type: none"> <li>• Fibrates can be recommended for patients with very high TG to reduce risk for acute pancreatitis.</li> <li>• They also can be recommended for patients with dysbetalipoproteinemia (elevated beta-very LDL).</li> <li>• Fibrate therapy should be considered an option for treatment of patients with established CHD who have low levels of LDL-C and atherogenic dyslipidemia.</li> <li>• They also should be considered in combination with statin therapy in patients who have elevated LDL-C and atherogenic dyslipidemia.</li> </ul>

Clinical Guideline	Recommendations
	<p><u>Omega-3 fatty acids</u></p> <ul style="list-style-type: none"> <li>• Omega-3 fatty acids (e.g., linolenic acid, docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA]) have two potential uses.</li> <li>• In higher doses, DHA and EPA lower serum TGs by reducing hepatic secretion of TG-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3 to 12 g/day have been used depending on tolerance and severity of hypertriglyceridemia.</li> <li>• Recent trials also suggest that relatively high intakes of omega-3 fatty acids (1 to 2 g/day) in the form of fish, fish oils or high-linolenic acid oils will reduce the risk for major coronary events in persons with established CHD. Omega-3 fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1 to 2 g/day) for either primary or secondary prevention.</li> </ul>
<p>American Heart Association/American College of Cardiology/National Heart, Lung, and Blood Institute: <b>American Heart Association/American College of Cardiology Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update (2006)</b><sup>9</sup></p>	<p><u>Lipid management</u></p> <ul style="list-style-type: none"> <li>• For patients without atherosclerotic disease, including those with other risk factors, recommendations of the National Cholesterol Education Program guidelines and their 2004 update should still be considered current.</li> <li>• Therapeutic options to reduce non-HDL-C include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy).</li> <li>• If TGs are <math>\geq 500</math> mg/dL, therapeutic options to prevent pancreatitis are fibrate or niacin before LDL lowering therapy. Treat LDL-C to goal after TG lowering therapy.</li> <li>• Dietary supplement niacin must not be used as a substitute for prescription niacin.</li> </ul> <p><u>All patients with coronary and other atherosclerotic vascular disease</u></p> <ul style="list-style-type: none"> <li>• In addition to other lifestyle modifications, increased consumption of omega-3 fatty acids in the form of fish or in capsule form (1 g/day) for risk reduction is encouraged. For treatment of elevated TGs, higher doses are usually necessary for risk reduction.</li> </ul>
<p>Institute for Clinical Systems Improvement: <b>Lipid Management in Adults (2009)</b><sup>7</sup></p>	<ul style="list-style-type: none"> <li>• Diet and exercise are the cornerstones of treatment for asymptomatic patients with dyslipidemia. TLC may include diet, aerobic exercise, weight management, smoking cessation, evaluation of alcohol consumption, sterol and stanol ester nutritional supplement and fish oil (EPA-DHA).</li> <li>• Omega-3 fats do not affect LDL levels but may help protect the heart in other ways. Trials have suggested that omega-3 fats reduce the risk of heart attack and death from heart disease for those who already have heart disease.</li> <li>• No primary prevention trials have addressed pharmacologic lipid treatment in persons at low risk for CHD. The incidence of CHD in men &lt;40 years and premenopausal women is very low, and drug treatment in these groups is discouraged.</li> <li>• Primary prevention trials of pharmacologic lipid lowering have not shown a decrease in mortality, although most trials have shown a 30%</li> </ul>

Clinical Guideline	Recommendations
	<p>reduction in CHD events. Trial populations have consisted mostly of middle-aged men, some with other risk factors. Similar benefit in higher-risk women can be assumed but has not been demonstrated.</p> <p><u>Monotherapy</u></p> <ul style="list-style-type: none"> <li>• Patients with risk factors for CHD but no history of disease who receive lipid lowering therapy are likely to experience a decreased risk of CHD.</li> <li>• Patients with a history of CHD often benefit from statin therapy and trials have consistently shown a decrease in risk of death from CHD.</li> <li>• Specific statin and dose should be selected based on cost and amount of lipid lowering required.</li> <li>• Based on the information above, for patients with established CHD or CHD risk equivalents, the use of a statin is recommended.</li> <li>• Statins are the drugs of choice for lowering LDL-C, and aggressive treatment should be pursued. Statins also have a modest effect on reducing TGs and increasing HDL-C. Several trials with clinical endpoints support the use of statins in primary and secondary prevention.</li> <li>• In patients receiving a statin who experience myalgias, it is recommended that a lower dose or another statin be tried. A 10 to 14 day vacation from a statin can also be considered as a diagnostic maneuver to see if myalgia symptoms abate. The evidence is inconclusive at this time for treating myalgia with Vitamin D and coenzyme Q.</li> <li>• If patients are intolerant to a statin, they should try the other statins in reduced doses before the medication class is deemed inappropriate.</li> <li>• If patients are unable to take a statin, bile acid sequestrants, niacin, fibric acid derivatives and ezetimibe are available.</li> <li>• The bile acid sequestrants reduce LDL-C, but they can increase TGs so should only be used as monotherapy in patients with a baseline TG <math>\leq</math>200 mg/dL.</li> <li>• Niacin has a greater effect on HDL-C than other currently available lipid medications. To improve tolerability and compliance, doses of niacin need to be titrated.</li> <li>• Fibric acid derivatives have a variable effect on LDL-C. Fenofibrate may be more effective at lowering LDL-C than gemfibrozil. They are usually reserved for hypertriglyceridemia or for an isolated low HDL-C.</li> <li>• Ezetimibe mainly reduces LDL-C, with minimal effect on TGs or HDL-C. No clinical outcome trials are currently available, but ezetimibe appears useful for reducing LDL-C in patients who cannot take a statin and in combination with other LDL reducing medications.</li> </ul> <p><u>Combination therapy</u></p> <ul style="list-style-type: none"> <li>• Although combination therapy is not supported by outcome-based trials, some high risk patients will require combination therapy. These patients will most likely have CHD.</li> <li>• Using low doses of two complementary agents can often reduce LDL-C to a greater extent than a higher dose of either agent, with fewer side effects and possibly less cost.</li> <li>• In very resistant cases, triple therapy may be required.</li> <li>• Combination of a cholesterol lowering drug with a TG lowering drug to</li> </ul>

Clinical Guideline	Recommendations
	<p>achieve the non-HDL-C goal may be most warranted in patients with established coronary artery disease who are a very high risk of recurrent coronary events.</p> <ul style="list-style-type: none"> <li>• Combining nicotinic acid with a statin is favorable for improving LDL-C, HDL-C and TGs.</li> <li>• Use of fibric acid derivatives leads to effective decreases in TGs and increased HDL-C, but the effect on LDL-C is varied.</li> <li>• An increased incidence of severe myopathy has been reported when a statin was combined with nicotinic acid or fibric acid derivatives.</li> <li>• In general, the combination of a statin and a fibric acid derivative raises the risk of myopathy and rhabdomyolysis.</li> </ul> <p><u>Aspirin</u></p> <ul style="list-style-type: none"> <li>• Dosage appears unimportant, usually ranging from 60 mg every other day up to 325 mg/day.</li> <li>• Secondary prevention trials have demonstrated reduced cardiovascular and cerebrovascular endpoints.</li> <li>• Primary prevention trials in patients not selected for cardiovascular risk factors have shown minimal benefit.</li> <li>• Patients with hyperlipidemia are at intermediate risk and may derive greater benefit from aspirin than the lower risk populations evaluated in primary prevention trials. The recommendation of aspirin in hyperlipidemic patients is supported by this reasoning, and by the low cost and risk of this therapy.</li> </ul>
<p>American Heart Association: <b>Drug Therapy of High Risk Lipid Abnormalities in Children and Adolescents: A Scientific Statement From the American Heart Association (2007)</b><sup>38</sup></p>	<ul style="list-style-type: none"> <li>• 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.</li> <li>• 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 &lt;10 years of age.</li> <li>• Additional research regarding drug therapy of high risk lipid abnormalities in children is needed to evaluate the long term efficacy and safety and impact on the atherosclerotic disease process.</li> <li>• Niacin is rarely used to treat the pediatric population.</li> <li>• 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.</li> <li>• This guideline does not contain recommendations regarding the use of omega-3 acid ethyl esters.</li> </ul>
<p>European Society of Cardiology and Other Societies: <b>Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2007)</b><sup>8</sup></p>	<ul style="list-style-type: none"> <li>• Statins are first line drugs for lowering LDL-C.</li> <li>• Bile acid sequestrants can serve as effective lipid lowering alternatives.</li> <li>• Bile acid sequestrants tend to increase TG; therefore, should only be used when TG are &lt;180 mg/dL or given in conjunction with TG lowering agents.</li> <li>• Niacin is considered an effective lipid lowering agent but flushing may limit use.</li> <li>• Niacin is more effective in increasing HDL-C than fibrates.</li> <li>• When TGs are 450 to 900 mg/dL, either fibrates or statins may be</li> </ul>

Clinical Guideline	Recommendations
	<p>used as first line drugs, and niacin is considered a good drug for selected patients.</p> <ul style="list-style-type: none"> <li>• Fish oils are also TG lowering agents and might be useful as a third line therapy for patients with hypertriglyceridemia resistant to or intolerant of fibrates or niacin or in combination with other TG lowering drugs.</li> <li>• Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels.</li> </ul>

### Conclusions

Niacin favorably affects all lipids and lipoproteins when given in pharmacological doses.<sup>1</sup> Niacin acts to decrease very low density lipoprotein and low density lipoprotein cholesterol (LDL-C) and triglycerides, while causing an increase in high density lipoprotein cholesterol (HDL-C).<sup>1,2</sup> There are two Food and Drug Administration (FDA) approved niacin products: Niacor<sup>®</sup> (immediate-release) and Niaspan<sup>®</sup> (extended-release). In general, these products are FDA approved for the treatment of hyperlipidemia and severe hypertriglyceridemia.<sup>3,4</sup> Niaspan<sup>®</sup> is also FDA approved to reduce the risk of recurrent myocardial infarction in patients with a history of myocardial infarction and hyperlipidemia and to slow progression or promote regression of atherosclerotic disease in patients with a history of coronary artery disease and hyperlipidemia.<sup>4</sup> The extended-release formulation of niacin is associated with less flushing.<sup>1</sup> Niacor<sup>®</sup> is available generically, whereas Niaspan<sup>®</sup> is available brand only. Of note, niacin immediate-release products are not interchangeable with extended-release products as the bioavailability of the products varies.<sup>5</sup>

Clinical trial data has consistently demonstrated the “superiority” of niacin over placebo for the management of hyperlipidemia.<sup>13-17</sup> When comparing the two different formulations for the treatment of hyperlipidemia, both formulations are effective. However, it appears that in general niacin extended-release is associated with greater decreases in LDL-C, while immediate-release niacin is associated with greater increases in HDL-C.<sup>16-18</sup> Of note, greater increases in HDL-C occurred with all doses of niacin immediate-release compared to only higher doses of niacin extended-release achieving greater decreases in LDL-C.<sup>18</sup> Direct comparisons of niacin with other lipid modifying agents have demonstrated that significant increases or decreases in specific lipid parameters are not consistently achieved with any lipid modifying therapy, and when used in combination with other lipid modifying agents, the addition of niacin produces significant increases and decreases in lipid parameters.<sup>19-30</sup> In addition, clinical trial data exists to support the use of niacin extended-release for secondary prevention in patients with a previous myocardial infarction.<sup>31,33</sup>

Therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia.<sup>1,6,7</sup> When LDL lowering is required, initial treatment with a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin), a bile acid sequestrant or niacin is recommended; however, the statins are considered first line therapy for decreasing LDL-C levels.<sup>1,6-8</sup> If after six weeks of therapy lipid goals are not achieved on a statin alone, a dosage increase or the addition of a bile acid sequestrant or niacin should be considered.<sup>1</sup> In patients with an elevated triglyceride level ( $\geq 500$  mg/dL), a fibric acid derivative or niacin should be initiated, before LDL-C lowering therapy, to prevent pancreatitis.<sup>9</sup>

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

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Niaspan	190	368	100.00%	\$97,204.77	\$264.14
<b>Class Total:</b>	<b>190</b>	<b>368</b>	<b>100%</b>	<b>\$97,204.77</b>	<b>\$264.14</b>

### **Recommendations**

Currently, all niacin derivatives are preferred on the Department of Vermont Health Access (DVHA) preferred drug list (PDL) and are available without a prior authorization. No changes are recommended for this managed category.

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