Lipid-Lowering Drugs

Lipid-lowering drugs should be taken indefinitely; when they are stopped, plasma lipoproteins return to pretreatment levels. HMG-CoA reductase inhibitors (statins) remain the drugs of choice for treatment of most patients who require lipid-lowering therapy.

**STATINS** — Statins block the rate-limiting step in cholesterol synthesis. The subsequent reduction in hepatic cholesterol causes upregulation of low-density lipoprotein (LDL) receptors, increasing uptake and clearance of LDL-cholesterol (LDL-C) from the blood. Statins also decrease very low-density lipoprotein cholesterol (VLDL-C) and triglyceride levels and modestly increase high-density lipoprotein cholesterol (HDL-C) levels. Other direct effects of statins or indirect effects of lowering cholesterol include improved endothelial function, decreased platelet aggregation, and reduced inflammation. Statins also decrease serum concentrations of C-reactive protein, a marker of inflammation.

**Efficacy** — Taken as an adjunct to diet modification, increased exercise, and smoking cessation, statins can reduce the risk of first cardiovascular events and death (primary prevention) in patients at high risk for atherosclerotic cardiovascular disease. Even in patients at lower risk for cardiovascular disease, treatment with a statin can significantly reduce the incidence of cardiovascular events.

Controlled trials in patients with cardiovascular disease (secondary prevention) have shown that high-intensity statin therapy (defined as reducing LDL-C by ≥50% on average) decreases the incidence of cardiac events, stroke, and coronary death significantly more than less intensive regimens. In one meta-analysis, each additional 1 mmol/L (39 mg/dL) reduction in LDL-C was associated with a 20% reduction in major vascular events and a 10% reduction in all-cause mortality. Combining a statin with another LDL-C lowering drug such as ezetimibe may reduce the incidence of cardiovascular events more than a statin alone.

**Choice of a Lipid-Lowering Drug**

- Statins are the lipid-lowering drugs of choice for treatment and prevention of cardiovascular disease in most patients.
- Statins can decrease the incidence of major coronary events and death in patients with atherosclerotic cardiovascular disease.
- Statins can also reduce the risk of a first cardiovascular event and death in patients with risk factors such as elevated levels of low-density lipoprotein cholesterol (LDL-C) or diabetes when taken as an adjunct to diet modification, increased exercise, and smoking cessation.
- Addition of ezetimibe to high-dose simvastatin can reduce the incidence of secondary cardiovascular events.
- Combining a statin with a PCSK9 inhibitor can reduce LDL-C levels much more than a statin alone, but to date no studies are available demonstrating that such combinations improve clinical outcomes.
- Limited evidence suggests that use of a bile acid sequestrant alone or in combination with a statin may reduce the incidence of cardiovascular events.
- Addition of niacin or a fibrate to a statin has not been shown to reduce cardiovascular risk and is no longer recommended.
- There is no convincing evidence that use of fish oil supplements prevents cardiovascular disease or improves outcomes in patients who already have it.

**Adverse Effects** — Statins are generally well tolerated. Some patients who cannot tolerate one statin may tolerate another.

Muscle pain and weakness with or without increased creatine kinase (CK) levels are commonly reported in patients taking statins in clinical practice, but in some randomized trials, muscle symptoms were reported just as often in patients taking placebo. Rarely, rhabdomyolysis and myoglobinemia leading to renal failure can occur. In one randomized trial (SEARCH) in 12,064 patients, the incidence of myopathy with a CK level >10 times the upper limit of normal (ULN) was 0.9% (53 of 6031) in patients taking simvastatin 80 mg daily and 0.03% (2 of 6033) in those taking simvastatin 20 mg daily. The maximum daily dose of simvastatin has since been lowered from 80 mg to 40 mg. CK levels should be measured at baseline and again if myalgia occurs. Most cases of CK elevation are mild to moderate in severity and can be managed by reducing the statin dose or switching to a less
An increase in plasma aminotransferase levels at least temporarily.11

If CK levels exceed 10 times the ULN and are unrelated to secondary causes such as unusual or excessive exercise, statin therapy should be stopped, at least temporarily.11

An increase in plasma aminotransferase levels to 3 times the ULN occurs in 1-2% of patients taking high doses of a statin. Patients who develop transaminase elevations with one statin may be able to tolerate lower doses of the same statin or another statin. Statin treatment is safe in patients with mild to moderate transaminase elevations (≤3 times ULN) and may reduce cardiovascular morbidity even more in these patients than in those with normal transaminase levels.12

In a meta-analysis of 13 trials including a total of 91,140 patients, the risk of new-onset diabetes mellitus was slightly higher with statin therapy compared to placebo.13 In another meta-analysis, the risk of new-onset diabetes was higher with more intensive statin therapy than with moderate-dose therapy.14

Table 1. Lipid-Lowering Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Usual Adult Dosage</th>
<th>Average LDL-C Reduction</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin – generic</td>
<td>10, 20, 40, 80 mg tabs</td>
<td>Initial: 10-20 mg once/d</td>
<td>35-40%</td>
<td>$8.60</td>
</tr>
<tr>
<td>Lipitor (Pfizer)</td>
<td>Maximum: 80 mg once/d</td>
<td>50-60%</td>
<td>228.40</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin – generic</td>
<td>20, 40 mg caps</td>
<td>Initial: 40 mg bid</td>
<td>20-25%</td>
<td>210.70</td>
</tr>
<tr>
<td>Lescol (Novartis) extended-release – generic</td>
<td>80 mg tabs</td>
<td>Maximum: 40 mg bid</td>
<td>30-35%</td>
<td>305.50</td>
</tr>
<tr>
<td>Lescol XL</td>
<td>Maximum: 80 mg once/d</td>
<td>35-38%</td>
<td>199.50</td>
<td></td>
</tr>
<tr>
<td>Lovastatin – generic</td>
<td>10, 20, 40 mg tabs</td>
<td>Initial: 20 mg once/d</td>
<td>25-30%</td>
<td>9.50</td>
</tr>
<tr>
<td>extended-release – Altoprev (Watson/Actavis)</td>
<td>20, 40, 60 mg tabs</td>
<td>Maximum: 80 mg once/d</td>
<td>35-40%</td>
<td>20-25%</td>
</tr>
<tr>
<td>Pitavastatin – Livalo (Kowa)</td>
<td>1, 2, 4 mg tabs</td>
<td>Initial: 2 mg once/d</td>
<td>35-40%</td>
<td>40-45%</td>
</tr>
<tr>
<td>Pravastatin – generic</td>
<td>10, 20, 40, 80 mg tabs</td>
<td>Initial: 40 mg once/d</td>
<td>30-35%</td>
<td>20.70</td>
</tr>
<tr>
<td>Pravachol (BMS)</td>
<td>Maximum: 80 mg once/d</td>
<td>35-40%</td>
<td>169.70</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin – generic</td>
<td>5, 10, 20, 40 mg tabs</td>
<td>Initial: 10-20 mg once/d</td>
<td>45-50%</td>
<td>37.20</td>
</tr>
<tr>
<td>Crestor (AstraZeneca)</td>
<td>Maximum: 40 mg once/d</td>
<td>50-60%</td>
<td>248.50</td>
<td></td>
</tr>
<tr>
<td>Simvastatin – generic</td>
<td>5, 10, 20, 40, 80 mg tabs</td>
<td>Initial: 10-20 mg once/d</td>
<td>35-40%</td>
<td>3.40</td>
</tr>
<tr>
<td>Zocor (Merck)</td>
<td>Maximum: 40 mg once/d</td>
<td>45-50%</td>
<td>130.50</td>
<td></td>
</tr>
<tr>
<td><strong>Cholesterol Absorption Inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe12 – Zetia (Merck)</td>
<td>10 mg tabs</td>
<td>10 mg once/d</td>
<td>15-25%</td>
<td>285.60</td>
</tr>
<tr>
<td><strong>Cholesterol Absorption Inhibitor/Statin Combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe/simvastatin – Vytorin (Merck)</td>
<td>10/10, 10/20, 10/40, 10/90 mg tabs</td>
<td>Initial: 10/10-10/20 mg once/d</td>
<td>40-50%</td>
<td>282.90</td>
</tr>
<tr>
<td>PCSK9 Inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alirocumab – Praluent (Sanofi/Regeneron)</td>
<td>75, 150 mg/mL single-use pens, prefilled syringes</td>
<td>Initial: 75 mg SC q2 wks</td>
<td>45-50%</td>
<td>1120.00</td>
</tr>
<tr>
<td></td>
<td>Maximum: 150 mg SC q2 wks</td>
<td>50-60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evolocumab – Repatha (Amgen)</td>
<td>140 mg/mL single-use prefilled syringes</td>
<td>Initial: 140 mg SC q2 wks or 420 mg SC once/month15</td>
<td>55-60%</td>
<td>1084.60</td>
</tr>
<tr>
<td>Repatha Sureclick (Amgen)</td>
<td>Maximum: 420 mg SC once/month</td>
<td>1084.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repatha Pushtronex (Amgen)</td>
<td>420 mg/3.5 mL single-use infuser with prefilled cartridge</td>
<td></td>
<td>1175.00</td>
<td></td>
</tr>
</tbody>
</table>

1. FDA-approved dosage. Some expert clinicians use lower doses for initial treatment of patients with only modest elevations of LDL-C or a history of poor tolerance to these drugs. For patients who require a large reduction in LDL-C, some would use higher doses initially. Statins are generally most effective when taken in the evening. Dosage adjustment may be needed for patients with renal or hepatic impairment.

2. The listed ranges correspond to the initial and maximum dosages. Statin dosages that lower LDL-C by 50% are considered moderate-intensity therapy. LDL-C reductions may vary significantly among individuals.

3. Approximate WAC for 30 days’ treatment at the lowest initial dosage unless otherwise specified. WAC = wholesaler acquisition cost or manufacturer’s published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. October 5, 2016. Reprinted with permission by First Databank, Inc. All rights reserved. ©2016. www.fdbhealth.com/policies/drug-pricing-policy.

4. Or 40 mg bid.

5. 10 mg initially for patients with significant renal impairment.

6. Higher serum concentrations of rosvuastatin have been reported in Asian patients; an initial dose of 5 mg once daily is recommended.

7. Patients with severe renal impairment not on hemodialysis should start with 5 mg and not exceed 10 mg/day.


9. Patients with severe renal impairment should start with 5 mg.

10. Patients who have taken 80 mg/day of simvastatin for ≥12 months without evidence of myopathy can continue at this dose.

11. The maximum dose of simvastatin is 10 mg if taken with diltiazem or verapamil and 20 mg if taken with amiodarone, amiodipine, or ranolazine.

12. A generic formulation of ezetimibe is expected to become available in December 2016.

13. Alone or when added to statin therapy.

14. Cost of 2 prefilled syringes or autoinjectors or 1 cartridge.

15. Dosage for patients with heterozygous familial hypercholesterolemia (HeFH) or atherosclerotic CVD. Dosage for patients with homozygous familial hypercholesterolemia (HoFH) is 420 mg SC once monthly.

potent statin. If CK levels exceed 10 times the ULN and are unrelated to secondary causes such as unusual or excessive exercise, statin therapy should be stopped, at least temporarily.11

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Table 1. Lipid-Lowering Drugs (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Usual Adult Dosage</th>
<th>Average LDL-C Reduction</th>
<th>Cost¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bile Acid Sequestrants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colesevelam¹⁶ – Welchol tablets (Daiichi Sankyo)</td>
<td>625 mg tabs</td>
<td>3750 mg once/d or 1875 mg bid</td>
<td>15-20%</td>
<td>$565.20</td>
</tr>
<tr>
<td>Welchol packets</td>
<td>3.75 g packets</td>
<td>3.75 g once/d or 1.875 g bid</td>
<td></td>
<td>565.20</td>
</tr>
<tr>
<td>Colestipol – generic</td>
<td>1 g tabs; 5 g packets; 5 g/scoop</td>
<td>10 g once/d or 5 g bid</td>
<td>15-20%</td>
<td>187.70¹⁷</td>
</tr>
<tr>
<td>Cholestyramine – packets – generic</td>
<td>4 g packets</td>
<td>8 g once/d or 4 g bid</td>
<td>15-20%</td>
<td>63.80</td>
</tr>
<tr>
<td><strong>Cholestryramine – packets – generic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questran (Par)</td>
<td>4 g/scoop</td>
<td>5-10%¹⁹</td>
<td>19</td>
<td>66.60</td>
</tr>
<tr>
<td>ternix (Upsher Smith)</td>
<td>5 g packets; 5 g/scoop</td>
<td>500 mg once/d</td>
<td>25.07</td>
<td></td>
</tr>
<tr>
<td><strong>Fibrates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil – generic Lopid (Pfizer)</td>
<td>600 mg tabs</td>
<td>600 mg bid</td>
<td>5-10%¹⁹</td>
<td>11.60</td>
</tr>
<tr>
<td>Lopid (Pfizer)</td>
<td>600 mg caps</td>
<td></td>
<td></td>
<td>307.70</td>
</tr>
<tr>
<td>Fenofobrate – non-micronized</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>generic¹⁶</td>
<td>54, 160 mg tabs</td>
<td>160 mg once/d</td>
<td>5-10%¹⁹</td>
<td>62.60</td>
</tr>
<tr>
<td>Fenoglide (Santarus)¹⁶</td>
<td>40, 120 mg tabs</td>
<td>120 mg once/d</td>
<td>964.40</td>
<td></td>
</tr>
<tr>
<td>Lipofen (Kowa)¹⁶</td>
<td>50, 150 mg caps</td>
<td>150 mg once/d</td>
<td>222.90</td>
<td></td>
</tr>
<tr>
<td>Lofibra (Gate)¹⁶</td>
<td>54, 160 mg tabs</td>
<td>160 mg once/d</td>
<td>139.00</td>
<td></td>
</tr>
<tr>
<td>Tricor (AbbVie)¹⁶</td>
<td>48, 145 mg tabs</td>
<td>145 mg once/d</td>
<td>91.00</td>
<td></td>
</tr>
<tr>
<td>Triglide (Shionogi)</td>
<td>160 mg tabs</td>
<td>160 mg once/d</td>
<td>259.70</td>
<td></td>
</tr>
<tr>
<td>micronized – generic¹⁶</td>
<td>200 mg once/d</td>
<td>200 mg once/d</td>
<td>82.40</td>
<td></td>
</tr>
<tr>
<td>Antara (Lupin)</td>
<td>90 mg once/d</td>
<td>90 mg once/d</td>
<td>507.90</td>
<td></td>
</tr>
<tr>
<td>Lipofra (Gate)¹⁶</td>
<td>200 mg once/d</td>
<td>200 mg once/d</td>
<td>241.40</td>
<td></td>
</tr>
<tr>
<td>Fenofobrate acid – generic Fibrin (Trubute)</td>
<td>35, 105 mg tabs</td>
<td>105 mg once/d</td>
<td>5-10%¹⁹</td>
<td>24.00</td>
</tr>
<tr>
<td>delayed-release – generic Triglide (AbbVie)</td>
<td>45, 135 mg delayed-release caps</td>
<td>135 mg once/d</td>
<td></td>
<td>241.40</td>
</tr>
<tr>
<td>Nicin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicin immediate-release – OTC extended-release²⁰ – generic Niaspan (AbbVie)</td>
<td>500 mg tabs</td>
<td>1000 mg tid</td>
<td>5-25%</td>
<td>11.20</td>
</tr>
<tr>
<td>Nicin immediate-release – OTC extended-release²⁰ – generic Slo-Niacin (Upsher-Smith)</td>
<td>500 mg tabs</td>
<td>1000 mg once/d</td>
<td>117.50</td>
<td></td>
</tr>
<tr>
<td>Nicin immediate-release – OTC extended-release²⁰ – generic USP-verified fish oil capsules²⁴</td>
<td>250, 500, 750 mg SR tabs</td>
<td>1000 mg tid</td>
<td>274.20</td>
<td></td>
</tr>
<tr>
<td>Nicin immediate-release – OTC extended-release²⁰ – generic USP-verified fish oil capsules²⁴</td>
<td>1, 1.2 g caps²⁶</td>
<td>4-4.8 g tid</td>
<td>24.00</td>
<td></td>
</tr>
<tr>
<td>Fish Oil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Icosapent ethyl – Vascepa (Amarin)¹⁵</td>
<td>1000 mg caps²¹</td>
<td>2000 mg bid²²</td>
<td>0-5%¹⁵</td>
<td>234.00</td>
</tr>
<tr>
<td>Omega-3 acid ethyl esters – generic Lovaza (GSK)</td>
<td>1000 mg caps²⁶</td>
<td>4000 mg once/d or 2000 mg bid²²</td>
<td>180.00</td>
<td></td>
</tr>
<tr>
<td>USP-verified fish oil capsules²⁴</td>
<td>1, 1.2 g caps²⁶</td>
<td>4-4.8 g tid</td>
<td>290.00</td>
<td></td>
</tr>
</tbody>
</table>

16. Should be taken with food.
17. Cost of 60 packets.
18. Contains aspartame instead of sucrose.
19. LDL-C may increase when triglyceride levels are decreased.
20. Should be taken with a low-fat snack at bedtime.
21. Each 1000-mg capsule contains 1000 mg EPA.
22. FDA-approved dose for treating hypertriglyceridemia (≥500 mg/dL).
23. Each 1000-mg capsule contains about 465 mg EPA and 375 mg DHA (total 900 mg polyunsaturated fatty acids [PUFAs]).
24. USP-verified fish oil products are manufactured by Berkley & Jensen, Kirkland, and Nature Made.
25. Most 1-gram capsules contain 300 mg PUFAs (180 mg EPA and 120 mg DHA). Nature Made 1.2-g capsules contain 360 mg PUFAs (216 mg EPA and 144 mg DHA); three capsules are approximately equal to one Lovaza capsule.

Guidelines estimate that the risk of new-onset diabetes is about 0.1 cases/100 patient-years with moderate-intensity statin therapy (defined as reducing LDL-C by 30-50%) and about 0.3 cases/100 patient-years with high-intensity therapy.¹ The benefits of statin therapy for patients with elevated cardiovascular risk would appear to outweigh the risk of developing diabetes.¹⁵

In a meta-analysis of 26 randomized controlled trials including a total of 169,138 patients followed for ≥2 years, there was no correlation between the use or intensity of statin therapy and the incidence of cancer or nonvascular death.⁶ An increased incidence of hemorrhagic stroke has been reported with statin therapy in some studies, but in one large meta-analysis, patients taking a statin had a similar hemorrhagic stroke rate and significantly lower overall stroke and all-cause mortality rates compared to those not taking a statin.¹⁶ Polyneuropathy, memory loss, sleep disturbances,
Table 2. Adverse Effects of Cholesterol-Lowering Drugs

**STATINS**
- Myalgia, myositis, transaminase elevations, hepatic dysfunction, increased risk of diabetes mellitus
- Rare: Rhabdomyolysis, hemorrhagic stroke

**EZETIMIBE**
- Diarrhea, arthralgia, rhabdomyolysis, hepatitis, pancreatitis, thrombocytopenia

**PCSK9 INHIBITORS**
- Nasopharyngitis, upper respiratory tract infection, influenza, back pain, injection-site reactions, rash, allergic skin reactions, cognitive effects, anti-drug antibodies

**BILE ACID SEQUESTRANTS**
- Constipation, heartburn, nausea, eructation, bloating (adverse effects are more common with colestipol and cholestyramine and may diminish over time)

**FIBRIC ACID DERIVATIVES**
- GI disturbances, cholelithiasis, hepatitis, myositis

**NIACIN**
- Skin flushing, pruritus, GI disturbances, blurred vision, fatigue, glucose intolerance, hyperuricemia, hepatic toxicity, exacerbation of peptic ulcers (adverse effects, especially flushing, occur more frequently with immediate-release products)
- Rare: Dry eyes, hyperpigmentation

**FISH OIL**
- Eruption, dyspepsia, unpleasant aftertaste

**Drug Interactions** – Statin-induced myopathy is often precipitated by drug interactions. Simvastatin and lovastatin undergo extensive first-pass hepatic metabolism by CYP3A4; their plasma concentrations can increase dramatically when used concurrently with a strong CYP3A4 inhibitor. Atorvastatin undergoes less first-pass metabolism by CYP3A4 and concurrent use of most CYP3A4 inhibitors produces only small increases in its plasma concentrations, but rhabdomyolysis has occurred. Fluvastatin is metabolized primarily by CYP2C9. Pravastatin, rosuvastatin, and pitavastatin are not metabolized to a clinically significant extent by CYP enzymes. Bile acid sequestrants interfere with the absorption of statins; they should be taken at least several hours apart.

Concurrent administration of cyclosporine (Neoral, and others) increases serum concentrations of all statins and the risk of rhabdomyolysis, probably through inhibition of drug transporters such as organic anion transporting polypeptide (OATP) and P-glycoprotein. Gemfibrozil (Lopid, and generics) also increases statin concentrations and the risk of rhabdomyolysis, possibly through inhibition of OATP. Rosuvastatin is a substrate of OATP and breast cancer resistance protein (BCRP) and should be used with caution with drugs that inhibit these transporters.

**Pregnancy** – Statins are contraindicated (category X) for use during pregnancy and lactation; congenital anomalies have been reported with lovastatin in some animals and infants.

**Choice of a Statin** – Lovastatin, pravastatin, simvastatin, atorvastatin, and rosuvastatin are available generically and have been shown to reduce cardiovascular risk. The reduction in cardiovascular events associated with statin use is related to the magnitude of LDL-C lowering. Atorvastatin and rosuvastatin at their highest approved doses are the most effective in lowering LDL-C levels and have had well-documented beneficial effects on clinical outcomes; doses of 40 and 80 mg/day of atorvastatin and 20 and 40 mg/day of rosuvastatin are considered “high intensity,” achieving average LDL-C reductions of ≥50%. Pitavastatin, the only statin still not available generically, has not been shown to decrease LDL-C more than 50% or to improve clinical outcomes.

**CHOLESTEROL ABSORPTION INHIBITOR** – Ezetimibe (Zetia) inhibits intestinal absorption of dietary and biliary cholesterol by blocking its transport at the brush border of the small intestine. It reduces LDL-C levels by about 15-25%. The fixed-dose combination of ezetimibe and simvastatin (Vytorin) reduces LDL-C levels more than a statin alone. A large, long-term secondary prevention trial (IMPROVE-IT) showed that adding ezetimibe to 40 or 80 mg/day of simvastatin resulted in additional small but statistically significant reductions in cardiovascular events.

**Adverse Effects** – Ezetimibe has generally been well tolerated. Diarrhea, arthralgia, rhabdomyolysis, hepatitis, pancreatitis, and thrombocytopenia have been reported. Patients with moderate to severe hepatic impairment (Child-Pugh B/C) should not take ezetimibe.

**Drug Interactions** – Ezetimibe may increase the anticoagulant effect of warfarin. Bile acid sequestrants interfere with the absorption of ezetimibe; they should be taken at least several hours apart. Concurrent use of ezetimibe and cyclosporine increases plasma levels of both drugs; the clinical significance of these effects is unknown.

**Pregnancy** – Ezetimibe is classified as category C (skeletal defects in animals; no adequate studies in women) for use during pregnancy.

**PCSK9 INHIBITORS** – Alirocumab (Praluent) and evolocumab (Repatha) have been approved by the FDA as an adjunct to diet and maximally tolerated treatments.
statin therapy for adults with clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C and for those with heterozygous familial hypercholesterolemia (HeFH). Evolocumab is also approved for use in adults with homozygous familial hypercholesterolemia (HoFH).23,24 Both alirocumb and evolocumab are subcutaneously injected monoclonal antibodies that bind to proprotein convertase subtilisin/kexin type 9 (PCSK9), preventing it from binding to LDL receptors and permitting rapid recycling of the LDL receptor and enhanced clearance of LDL-C from the circulation.

**Efficacy** – Alirocumb or evolocumab added to a statin can further reduce LDL-C levels by 50-60%,25-26 To date, PCSK9 inhibitors have not been shown to reduce cardiovascular events and mortality, but large clinical outcome trials are underway.27,28 Post-hoc analyses of alirocumab and evolocumab trials found that addition of either drug to standard therapy was associated with a 50% reduction in cardiovascular events, but the total number of such events in these trials was relatively low.25,26

**Adverse Effects** – Both alirocumab and evolocumab appear to be well tolerated. Muscle aches, rash, urticaria, and mild injection-site reactions have been reported. Cognitive adverse events including confusion, memory impairment, and dementia occurred more frequently with either drug than with placebo in clinical trials; a cause-and-effect relationship has not been established.25,26 Although the drugs can cause abnormally low LDL-C levels (<25 mg/dL), mostly when administered in addition to statins in patients with LDL-C levels close to 70 mg/dL, no associated adverse events have been reported.29

**Pregnancy** – No data are available on use of PCSK9 inhibitors during pregnancy; monoclonal antibodies are unlikely to cross the placenta in the first trimester, but may do so subsequently.

**BILE ACID SEQUESTRANTS** – The resins cholestyramine (Questran, and others) and colestipol (Colestid, and generics) and the hydrophilic polymer colesevelam hydrochloride (Welchol) prevent reabsorption of bile acids, increasing cholesterol conversion to bile acids, depleting intrahepatic cholesterol, and upregulating LDL receptor synthesis. Depending on the dose, these drugs can lower LDL-C levels by up to 20% and increase HDL-C levels, but they may further increase plasma triglyceride levels in patients with hypertriglyceridemia. Limited evidence suggests that use of a bile acid sequestrant alone or in combination with a statin may reduce the incidence of cardiovascular events.30

**Adverse Effects** – Constipation occurs frequently with colestipol and cholestyramine and may be accompanied by heartburn, nausea, eructation, and bloating. Colesevelam is better tolerated.

**Drug Interactions** – Bile acid sequestrants can interfere with the absorption of other oral drugs, including statins and ezetimibe; they should be taken at least 4 hours before or after other medications. Colesevelam does not appear to interfere with the absorption of most statins.

**FIBRIC ACID DERIVATIVES** – Fibrates activate the nuclear transcription factor peroxisome proliferator-activated receptor-alpha (PPAR-alpha), which regulates genes that control lipid and glucose metabolism, inflammation, and endothelial function. Gemfibrozil, fenofibrate, fenofibric acid, and bezafibrate (Bezalip – available in Canada, not in the US) lower triglyceride and VLDL-C levels, usually by 25-50%, and may increase HDL-C levels. They may also lower LDL-C levels in patients with low to normal triglycerides, but may increase LDL-C levels when they are used to treat elevated triglycerides. Fibrates are best used in patients with hypertriglyceridemia severe enough to increase the risk of pancreatitis.31

**Efficacy** – Gemfibrozil is the only fibrate with demonstrated beneficial effects on cardiovascular outcomes,32 but drug interactions with statins are a problem. Fenofibrate may be more effective than gemfibrozil in lowering LDL-C and triglyceride levels, but in a randomized trial (ACCORD) in 5518 patients with type 2 diabetes, adding fenofibrate to simvastatin did not improve cardiovascular outcomes.33 There is no evidence that addition of any fibric acid derivative to a statin improves cardiovascular outcomes.34 Fenofibric acid, the active metabolite of fenofibrate, is no longer FDA-approved for use with a statin to reduce triglyceride levels and raise HDL-C levels.35

**Adverse Effects** – Fibrates are generally well tolerated. Gastrointestinal adverse effects are common. Cholelithiasis, hepatitis, and myositis can occur. Fibrates are contraindicated in patients with liver or gallbladder disease. A paradoxical severe decrease in HDL-C has been reported; if this occurs, the fibrate should be...
stopped. Aminotransferase elevations have occurred with fibrate therapy. Fenofibrate can increase serum creatinine levels; the clinical significance of this effect is unknown.

**Drug Interactions** – Fibrates may potentiate the effects of warfarin and antihyperglycemics. Gemfibrozil can increase serum concentrations of statins, possibly through inhibition of OATP, increasing the risk of rhabdomyolysis. Fenofibrate is eliminated renally and should be used with caution in patients taking cyclosporine or other nephrotoxic drugs.

**Pregnancy** – Gemfibrozil and fenofibrate are classified as category C (teratogenic in animals; no adequate studies in women) for use during pregnancy.

**NIACIN** – Niacin (nicotinic acid) modifies all plasma lipoproteins and lipids favorably. Monotherapy increases HDL-C levels by 15-35%, decreases triglyceride levels by 22-33% compared to placebo.42 In a meta-analysis of 11 randomized controlled trials including 6616 patients, use of niacin was found to have a beneficial effect for secondary prevention of cardiovascular events, but the included trials varied in size and quality.36 In a study in patients with atherosclerotic cardiovascular disease (HPS2-THRIVE), addition of niacin and the prostaglandin inhibitor laropiprant (to reduce flushing) to statin therapy did not significantly reduce the incidence of major vascular events, but was associated with an increased incidence of diabetes, serious gastrointestinal events, infection, and bleeding.37 Similar adverse effects have been reported in other studies.38 There is no evidence that adding extended-release niacin to a statin improves cardiovascular outcomes, and it is no longer FDA-approved for use with a statin to improve cholesterol levels.35

**Adverse Effects** – Niacin can cause flushing, pruritus, gastrointestinal distress, blurred vision, fatigue, glucose intolerance, hyperuricemia, hepatic toxicity, exacerbation of peptic ulcers and, rarely, dry eyes or hyperpigmentation. Some adverse effects, particularly flushing, are more common with the immediate-release formulation. Cutaneous reactions to niacin can be diminished by starting with a low dose that is taken after meals and at least 30 minutes after aspirin (81-325 mg).

**Pregnancy** – Niacin is classified as category C (no adequate studies in women or animals) for use during pregnancy.

**FISH OIL** – Long-chain omega-3 polyunsaturated fatty acids (PUFAs) are present in algae and cold-water fish such as herring and salmon. They are commercially available in capsules and can decrease elevated fasting triglyceride concentrations by 20-50% by reducing hepatic triglyceride production and increasing triglyceride clearance.39 Long-term use may increase HDL-C levels.

**Efficacy** – The results of clinical trials do not offer any convincing evidence that fish oil supplements prevent cardiovascular disease or improve outcomes in patients who already have it.40,41 A combination of eicosapentaenoic acid and docosahexaenoic acid (EPA/DHA; Lovaza, and generics) was the first omega-3 PUF product to be approved by the FDA for treatment of severe hypertriglyceridemia. Daily doses of 3-12 g can lower triglycerides by 20-50%, but have not been shown to prevent pancreatitis, which is a major concern in patients with very high triglycerides. Vascepa, the second omega-3 PUF product to be approved by the FDA for treatment of severe hypertriglyceridemia, is the ethyl ester of EPA. In controlled trials, it has reduced triglyceride levels by 22-33% compared to placebo.44 Epanova, a third omega-3 PUF product, is FDA-approved for treatment of severe hypertriglyceridemia, but has yet to be marketed. It consists of both EPA and DHA in free fatty acid form.

**Adverse Effects** – Fish oil supplements are generally well tolerated. Adverse effects have included eructation, dyspepsia, and an unpleasant aftertaste. Worsening glycemic control has been reported in diabetic patients taking large doses. Fish oil in large doses can also inhibit platelet aggregation and increase bleeding time; whether it can cause clinically significant bleeding has not been established. DHA can increase LDL-C levels, but EPA apparently does not.

**Pregnancy** – The omega-3 PUFAs are classified as category C (embryocidal in rats; no adequate studies in women) for use during pregnancy.

**COMBINATIONS** – The fixed-dose combination of ezetimibe and simvastatin (Vytorin) reduces LDL-C levels more than a statin alone. In a large, long-term secondary prevention trial (IMPROVE-IT), adding ezetimibe to 40 or 80 mg/day of simvastatin resulted in additional small but statistically significant reductions in cardiovascular events.7
Addition of alirocumab or evolocumab to a statin can further reduce LDL-C levels by 50–60%. To date, PCSK9 inhibitors have not been shown to reduce cardiovascular events and mortality, but large clinical outcome trials are underway.27,28

Although concurrent use of ezetimibe and a fibrate may improve lipid profiles in patients with combined dyslipidemia, it may also cause gallbladder disease because both drugs increase biliary cholesterol excretion. In severe hypertriglyceridemia not adequately controlled by diet, niacin and a fibrate can be used together, possibly in combination with omega-3 PUFAs. Since treatment of hypertriglyceridemia with a fibrate may increase LDL-C levels, it sometimes becomes necessary to add a statin as well.

Combination products containing a statin and fenofibric acid or niacin are no longer available. The FDA withdrew approval of these products in April 2016 because large clinical trials had not demonstrated that supplementing statin therapy with triglyceride-lowering or HDL-raising drugs reduced cardiovascular risk.35

HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA — This rare inherited condition (estimated prevalence 1:300,000 to 1:1,000,000 persons) is most commonly caused by defects in the LDL receptor gene, causing very high LDL-C levels, cutaneous xanthoma soon after birth, and, without treatment, cardiovascular disease and death in childhood.

Two drugs have been approved solely for this disorder: mipomersen (Kynamro), which must be injected subcutaneously and is approved for use in persons ≥12 years old, and lomitapide (Juxtapid), which is taken orally and is approved for use in adults.43 Both drugs can lower LDL-C (25% with mipomersen; 40% with lomitapide) in patients with HoFH already taking maximum dosages of other lipid-lowering drugs.44 Whether either one could eliminate the need for apheresis remains to be determined. Serious side effects, particularly hepatotoxicity, can occur with both drugs; each is available only through a Risk Evaluation and Mitigation Strategy (REMS) program. The PCSK9 inhibitor evolocumab (Repatha) was also recently approved for treatment of HoFH in patients >13 years old based on a large randomized trial that showed it reduced LDL-C levels by 31% compared to placebo.45

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27. MS Sabatine et al. Rationale and design of the further cardiovascular outcomes research with PCSK9 Inhibition in subjects with elevated risk trial. Am Heart J 2016; 173:94.


