Diabetic dyslipidemia: A practical guide to therapy

Combination therapy is inevitable in many cases

Practice recommendations

- Low-density lipoprotein (LDL) should be the primary target of lipid-lowering therapy for patients with diabetes. Because of their robust reduction of LDL, statins are considered the agents of choice for these patients (A).

- Triglyceride (TG) and high-density lipoprotein (HDL) levels are also important targets. Combination therapy with fibrates or niacin is common due to concurrent high TG and low HDL levels in these patients (A).

- Data supporting an LDL goal <70 mg/dL for patients with diabetes are limited and contradictory at this time (B).

Strength of recommendation (SOR)

A Good-quality patient-oriented evidence
B Inconsistent or limited-quality patient-oriented evidence
C Consensus, usual practice, opinion, disease-oriented evidence, case series

Lipid-lowering therapy has proven to reduce cardiovascular morbidity and mortality in patients with diabetes, yet our efforts to achieve cholesterol goals appear to take a back seat to achieving blood pressure and A1C goals. Unfortunately, as seen in this study, we can overlook lipid goals in patients with chronic comorbidities such as hypertension and diabetes. Also, with the rise in obesity rates and number of physically unfit people in our country, achieving lipid goals is becoming increasingly more difficult. Meanwhile, the long list of medications these patients take places them at a high risk of not only adverse drug reactions, but also drug-drug and drug-disease interactions.

This article evaluates the evidence on treatment of abnormal lipid profiles in patients with diabetes, discusses special considerations that need to be taken into account before starting combination therapy, and recommends a practical strategy to achieve lipid goals.

How is dyslipidemia different in diabetes?

Dyslipidemia tends to be more atherogenic in diabetic patients than in individuals without diabetes. The dyslipidemia often consists of high TG, low HDL, and normal or slightly elevated LDL.

Does drug therapy improve outcomes?

Yes. Data are limited, but it appears that because lipids in patients with diabetes

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Our efforts to achieve cholesterol goals appear to take a back seat to achieving blood pressure and A1C goals, although lipid-lowering therapy has proven to reduce cardiovascular morbidity and mortality in patients with diabetes.

**FAST TRACK**

A 6% increase in HDL was associated with a 22% relative risk reduction in death from coronary disease, nonfatal MI, and stroke.

**What is the evidence?**

We’ll now look at the evidence on primary or secondary prevention of coronary heart disease (CHD) in patients with diabetes. All of these trials received some type of support or sponsorship from pharmaceutical manufacturers.

**Primary prevention**

The only primary prevention trial designed specifically for the diabetic population is CARDS.\(^3\) (ASPEN, while also designed to study the effect of statin therapy among these patients, was a mixed primary/secondary trial; more than half of the patients had CHD.) CARDS evaluated the effect of atorvastatin 10 mg/d among 2838 type 2 diabetic patients with no previous history of cardiovascular disease, but who had at least 1 cardiovascular risk factor (ie, hypertension, retinopathy, albuminuria, or smoking).

After a median follow-up of 3.9 years, the treatment group had a 37% reduction in risk for a major cardiovascular event. Because of the profound reduction in cardiovascular events, the trial was terminated 2 years early on ethical grounds. Over a 4-year period, the observed 30% reduction in LDL (baseline 116 mg/dL, end of study 81 mg/dL) was associated with a number needed to treat (NNT) of 31 to prevent 1 cardiovascular event (TABLE 1).

**Mixed primary/secondary prevention**

HPS. In a subgroup analysis of the approximately 5900 diabetic patients in the Heart Protection Study (HPS), simvastatin 40 mg/d prevented 49 patients per 1000 from having a major coronary event during the 5 years of follow-up.\(^6\) Patients achieved about a 31% reduction in LDL (123 mg/dL baseline, 85 mg/dL end of study) and, interestingly, the benefit of statin therapy was evident regardless of the patient’s baseline cholesterol level—as it was in the overall study population. Some have used this study as the basis for recommending that all patients
### Comparison of lipid-lowering trials that included a significant number of patients with diabetes

Number needed to treat (NNT) and number needed to harm (NNH)

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N</th>
<th>PATIENTS WITH DIABETES (%)</th>
<th>DURATION (Y)</th>
<th>INTERVENTIONS</th>
<th>PRIMARY ENDPOINT(S)</th>
<th>NNT</th>
<th>ADVERSE EVENT(S)</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARDSa</td>
<td>2838</td>
<td>100%</td>
<td>3.9</td>
<td>Atorvastatin 10 mg/d</td>
<td>Time to first occurrence of acute CHD events, coronary revascularization, or stroke</td>
<td>31</td>
<td>t AST/ALT &gt;3X ULN</td>
<td>303</td>
</tr>
<tr>
<td>Mixedb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALLHAT-LTTc</td>
<td>10,355</td>
<td>35%</td>
<td>4.8</td>
<td>Pravastatin 40 mg/d</td>
<td>All-cause mortality</td>
<td>NS</td>
<td>Not reported†</td>
<td>—</td>
</tr>
<tr>
<td>ASCOT-LLLTc</td>
<td>10,305</td>
<td>25%</td>
<td>3.3</td>
<td>Atorvastatin 10 mg/d</td>
<td>Nonfatal MI and fatal CHD</td>
<td>94</td>
<td>Not reported†</td>
<td>—</td>
</tr>
<tr>
<td>ASPEND</td>
<td>2410</td>
<td>100%</td>
<td>4.0</td>
<td>Atorvastatin 10 mg/d</td>
<td>Time to first occurrence of cardiovascular death, nonfatal MI, nonfatal stroke, recanalization, CABG, resuscitated cardiac arrest, or worsening of unstable angina</td>
<td>NS</td>
<td>Abnormal LFTs</td>
<td>500 (71)</td>
</tr>
<tr>
<td>FIELDf</td>
<td>9795</td>
<td>100%</td>
<td>5.0</td>
<td>Fenofibrate 200 mg/d</td>
<td>CHD death or nonfatal MI</td>
<td>NS</td>
<td>Rhabdomyolysis</td>
<td>2445 (980)</td>
</tr>
<tr>
<td>HPS-DMg</td>
<td>5903</td>
<td>100%</td>
<td>4.8</td>
<td>Simvastatin 40 mg/d</td>
<td>Coronary mortality</td>
<td>31</td>
<td>t AST/ALT &gt;3X ULN</td>
<td>980 (1480)</td>
</tr>
<tr>
<td><strong>Secondary prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A to Za</td>
<td>4497</td>
<td>23%</td>
<td>2.0</td>
<td>Simvastatin 20 mg/d</td>
<td>Cardiovascular death, readmission for acute coronary syndrome, nonfatal MI, and stroke</td>
<td>NS</td>
<td>1 AST/ALT &gt;3X ULN</td>
<td>200 (333)</td>
</tr>
<tr>
<td>CAREh</td>
<td>4159</td>
<td>14%</td>
<td>5.0</td>
<td>Pravastatin 40 mg/d</td>
<td>Fatal coronary event or nonfatal MI</td>
<td>33</td>
<td>1 CPK</td>
<td>416</td>
</tr>
<tr>
<td>PROVE-ITi</td>
<td>4162</td>
<td>17%</td>
<td>2.0</td>
<td>Pravastatin 40 mg/d</td>
<td>Death from any cause, MI, unstable angina requiring rehospitalization, revascularization, and stroke</td>
<td>26</td>
<td>1 LFTs &gt;3X ULN</td>
<td>46 (167)</td>
</tr>
<tr>
<td>TNTj</td>
<td>10,001</td>
<td>15%</td>
<td>4.9</td>
<td>Atorvastatin 10 mg/d</td>
<td>First occurrence of CHD death, nonfatal MI, fatal/nonfatal stroke, or resuscitation after cardiac arrest</td>
<td>44</td>
<td>Myalgias</td>
<td>44 (100)</td>
</tr>
<tr>
<td>VA-HITk</td>
<td>2531</td>
<td>25%</td>
<td>5.1</td>
<td>Gemfibrozil 1200 mg/d</td>
<td>Nonfatal MI or death from coronary causes</td>
<td>23</td>
<td>Not reported</td>
<td>—</td>
</tr>
</tbody>
</table>

**Trials:**
- ALLHAT-LTT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
- ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm
- ASPEN = Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus
- A to Z = Aggrastat to Zocor
- CARDS = Collaborative Atorvastatin Diabetes Study
- CARE = Cholesterol and Recurrent Events
- FIELD = Fenofibrate Intervention and Event Lowering in Diabetes
- HPS-DM = Heart Protection Study Diabetes Subgroup
- PROVE-IT = Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction
- TNT = Treating to New Target
- VA-HIT = Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial

**Terms:**
- ALT=alanine aminotransferase; AST=aspartate aminotransferase; CABG=coronary artery bypass graft; CHD=coronary heart disease; CPK=creatine phosphokinase; LFTs=liver function tests; NS=not statistically significant; ULN=upper limit of normal.
- Mixed group includes patients with established coronary heart disease or those with risk factors for coronary heart disease (ie, hypertension, diabetes mellitus, smoking).
- NNH indicates how many individuals must receive a high dose of a statin for 1 individual to experience an adverse event when compared with individuals receiving low doses of statins.

†Relevant adverse events not reported or reported as not being significantly different between the treatment and placebo groups.

‡NNH indicates how many individuals must receive a high dose of a statin for 1 individual to experience an adverse event when compared with individuals receiving low doses of statins.

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Because LDL is by far the most atherogenic lipoprotein, it is considered the primary target of therapy for most patients with diabetes. However, the average baseline LDL was 123 mg/dL; thus, HPS does not provide evidence that diabetic patients whose baseline LDL is <100 mg/dL will benefit from statin therapy.

**ALLHAT, ASCOT.** The lipid arms from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)\(^7\) and Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)\(^8\) reported conflicting results on the ability of statins to reduce cardiovascular morbidity and mortality. Both trials had a significant number of diabetic patients: 35% and 25%, respectively. ALLHAT found that pravastatin 40 mg/d did not reduce the primary endpoint of all-cause mortality. However, patients in ASCOT who received atorvastatin 10 mg/d saw a 35% relative risk reduction in the primary endpoint, composed of nonfatal myocardial infarction (MI) and fatal CHD. The disparity can be partially explained by the fact that >30% of usual care patients and placebo patients in ALLHAT started taking a lipid-lowering drug during the trial.

**ASPEN** randomized 2410 patients with type 2 diabetes to atorvastatin 10 mg or placebo. The primary endpoint was a composite of cardiovascular death, nonfatal MI, nonfatal stroke, recanalization, coronary artery bypass surgery, resuscitated cardiac arrest, or worsening of unstable angina requiring hospitalization. After 4 years of therapy, atorvastatin therapy failed to produce a statistically significant reduction in the primary endpoint. The lack of benefit from statin therapy might have been a result of the high number of placebo patients concomitantly taking a lipid-lowering medication (26.9%) compared with patients receiving atorvastatin (15.4%).\(^4\)

**FIELD,** the Fenofibrate Intervention and Event Lowering in Diabetes study, evaluated the effect of fenofibrate 200 mg/d among 9795 type 2 diabetic patients who were not taking a statin.\(^9\) Approximately 80% (7664) of patients did not have a history of CHD. After a median of 4.9 years, the study failed to meet the primary endpoint composed of CHD death or nonfatal MI. The apparent lack of benefit from fenofibrate therapy appears to have been due to a disproportionately higher number of patients in the placebo group taking a statin by the end of the study (36% placebo vs. 19% fenofibrate).

**Secondary prevention**

**CARE,** the Cholesterol and Recurrent Events trial, was a 5-year trial in which 4159 post-MI patients with an average baseline LDL of 139 mg/dL were randomized to pravastatin 40 mg/d or placebo.\(^10\) Diabetic patients accounted for 14.1% of the patients in the study. They achieved a 30% reduction in LDL, and had a 25% relative risk reduction in incidence of coronary events, a change that was statistically significant.

**TNT.** Results were similar among the subgroup of 1501 diabetic patients in the Treating to New Targets (TNT) study.\(^11\) After 4.9 years of therapy, atorvastatin 80 mg reduced the time to the first major cardiovascular event by 25%, compared to atorvastatin 10 mg.

**VA-HIT,** the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial: >2500 men with established CHD and low HDL (of which a quarter had diabetes) were randomized to gemfibrozil 600 mg twice daily or placebo and followed for approximately 5 years. A subgroup analysis of the patients with diabetes in this study found that raising HDL and decreasing TG with gemfibrozil decreased the incidence of both nonfatal MIs and coronary deaths by approximately 22% (\(P<.006\)).\(^12\)

What should be the initial drug for your patient?
The first step in determining what a patient's initial lipid-lowering drug should be is to establish goals. Given that nonfasting LDL and TG values are invalid,
Management of diabetic dyslipidemia

**FIGURE 1**

**Fasting Lipid Profile?**
- Yes
  - Are TG >500 mg/dL?
    - Yes
      - AST/ALT<3X ULN?
        - No
          - Not eligible for lipid-lowering therapy
          - Therapeutic lifestyle changes only*
        - Yes
          - Fibrates
            - Niacin
            - Omega-3-FA
            - 6 weeks
          - Are TG <500 mg/dL?
            - No
              - Not eligible for lipid-lowering therapy
              - Therapeutic lifestyle changes only*
            - Yes
              - Statins
                - Ezetimibe
                - Statins
                - Niacin
                - 6 weeks
    - Yes*
  - Is LDL >100 mg/dL?
    - Yes*
      - AST/ALT<3X ULN?
        - No
          - Not eligible for lipid-lowering therapy
          - Therapeutic lifestyle changes only*
        - Yes
          - Statins
            - Ezetimibe
            - Statins
            - Niacin
            - 6 weeks
  - No
  - Continue current therapy

Consider the following:
1. **Fibrates**
   - 1st line, gemfibrozil may be used in patients with moderate renal dysfunction
2. **Niacin**
   - 2nd line due to side effect profile, >HDL, give ASA and titrate slowly to avoid side effects
3. **Omega-3-FA**
   - 3rd line, no outcome data

When choosing a statin consider the following factors:
1. % LDL reduction that patient needs
2. if CYP450-drug interaction, use Pravachol
3. cost
4. statin on formulary
5. must achieve at least a 35% ↓ in LDL

ALT=alanine aminotransferase
ASA=acetylsalicylic acid (aspirin)
AST/aspartate aminotransferase
CYP450=cytochrome P450
HDL=high-density lipoprotein
LDL=low-density lipoprotein
Omega-3-FA=omega-3-fatty acids
TG=triglycerides
ULN=upper limit of normal.

*Institute therapeutic lifestyle changes.
†See discussion under "Hepatic adjustment," page 386
¶When using fibrate/statin combination, remember to monitor CPK and AST/ALT
Source: Adapted from Grundy*15
be sure to obtain a fasting lipid profile.
National Cholesterol Education Program guidelines recommend these goals for diabetic patients:13
- LDL <100 mg/dL (optional <70 mg/dL in “very-high-risk” patients)
- TG <150 mg/dL.
- HDL >40 mg/dL.

These amounts differ slightly from the American Diabetes Association (ADA) recommendation that all diabetic patients without overt CHD and at least 1 cardiovascular risk factor who are over the age of 40 receive a statin “regardless” of their baseline LDL level (Level of Evidence: A). The ADA also suggests that this treatment approach be considered in individuals younger than 40 who have an LDL >100 mg/dL, and in individuals with multiple cardiovascular risk factors (Level of Evidence: E).14

As there is some controversy about the 2 LDL recommendations, we used the National Cholesterol Education Program recommendations in the algorithm (FIGURE 1). Both National Cholesterol Education Program and ADA recommend the same TG goal, but for HDL, the ADA recommends a goal of >40 mg/dL in men and >50 mg/dL in women.14

Which lipoprotein to target first?
If more than 1 lipoprotein is not at goal, the next step is to determine which lipoprotein should be the primary target. Because LDL is by far the most atherogenic lipoprotein, it is considered the primary target of therapy for most patients with diabetes.

**TG levels.** Whenever TG levels exceed 500 mg/dL, however, focus should shift from LDL to TG because of the increased risk of pancreatitis observed among these patients.

- <500 mg/dL. Only when TG levels are <500 mg/dL should LDL become the primary target again (FIGURE 1).
- 150 to 199 mg/dL. For these patients, once the LDL goal has been attained, the focus should shift to decreasing TG and increasing HDL. While all patients should be encouraged to institute therapeutic lifestyle changes, patients with TG levels between 150 and 199 mg/dL should intensify any ongoing efforts to reduce weight, increase physical activity, and improve diabetes control.
- 200 to 499 mg/dL. In this range, non-HDL cholesterol (ie, very-low-density lipoprotein [VLDL] + LDL, or total cholesterol – HDL) becomes the secondary target of lipid-lowering therapy.

The non-HDL goal recommended is 30 mg/dL higher than the corresponding LDL goal; thus, in the case of most diabetic patients, it should be <130 mg/dL.

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**TABLE 2**

<table>
<thead>
<tr>
<th>APPROXIMATE LDL REDUCTION</th>
<th>FLUVASTATIN LESCOL XL</th>
<th>LOVASTATIN MEVACOR</th>
<th>PRAVASTATIN PRAVACHOL</th>
<th>SIMVASTATIN ZOCOR</th>
<th>ATORVASTATIN LIPITOR</th>
<th>ROSUVASTATIN CRESCORT</th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>30%</td>
<td>40</td>
<td>20</td>
<td>20</td>
<td>10</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>35%</td>
<td>80</td>
<td>40</td>
<td>40</td>
<td>20</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>40%</td>
<td>–</td>
<td>80</td>
<td>80</td>
<td>40</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>45%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>80</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>50%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>80</td>
<td>40*</td>
</tr>
</tbody>
</table>

* Rosuvastatin 40 mg may decrease LDL by up to 60%.

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There are 2 approaches to decreasing non-HDL cholesterol in patients with diabetes: decrease LDL further with higher doses of statins or addition of ezetimibe, or decrease VLDL by lowering TG with niacin or fibrates (ie, gemfibrozil and fenofibrate).

**Increasing the HDL level** is a challenge because available interventions do not significantly increase this lipoprotein. In a study of 111 sedentary, overweight men and women with mild-to-moderate dyslipidemia, approximately 8 months of high-amount, high-intensity exercise (the caloric equivalent of jogging 20 miles per week) resulted in only a 10% increase in HDL levels. Fibrates increase HDL by approximately 10% to 20%, whereas niacin may produce a more substantial increase, up to 35%. Nonetheless, it is important to keep in mind that in the VA-HIT, even a moderate increase in HDL (approximately 6%) was associated with a 22% relative risk reduction in the combined endpoint of death from coronary disease, nonfatal MI, and stroke.

**Statins to reduce LDL**
Statins are the drugs of choice for decreasing LDL. When deciding which statin to use for a particular patient, in addition to considering cost, drug interactions, and formulary issues, consider the percent reduction in LDL that the patient needs to achieve their goal (TABLE 2).

Regardless of which statin is used, if LDL exceeds 100 mg/dL, make every effort to reduce LDL by at least 30%, because such a reduction has been associated with an approximate 25% to 30% decrease in cardiovascular morbidity and mortality in clinical trials.

If a patient has not reached his or her goal despite maximizing the statin dose or if the patient cannot tolerate high doses of statins, ezetimibe (21% expected average additional reduction in LDL) may be added to the regimen. This combination has been questioned recently, as the addition of ezetimibe provided no improvement in surrogate markers.

**Fibrates or niacin to reduce triglyceride level**
The agents of choice to treat hypertriglyceridemia are fibrates (ie, gemfibrozil or fenofibrate) or niacin, which can reduce TG levels between 20% and 50%.

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**TABLE 3**

<table>
<thead>
<tr>
<th>Strategies to improve immediate-release niacin tolerability</th>
<th>SLOW TITRATION SCHEDULE (MG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Titrate dose slowly over a 12-week period to a target dose of 1.5-2 g/d.</td>
<td>WEEK</td>
</tr>
<tr>
<td>2. Instruct the patient to take over-the-counter nicotinic acid, not niacinamide. Niacinamide has no triglyceride-lowering properties.</td>
<td>1</td>
</tr>
<tr>
<td>3. Avoid over-the-counter extended- or sustained-release forms of niacin, as they have been associated with hepatotoxicity.</td>
<td>2</td>
</tr>
<tr>
<td>4. Tell the patient that side effects tend to decrease over time.</td>
<td>3</td>
</tr>
<tr>
<td>5. To minimize niacin’s side effects, instruct the patient to:</td>
<td>4</td>
</tr>
<tr>
<td>a. Take 1 aspirin tablet (81–325 mg) 30 minutes prior to taking the first daily dose</td>
<td>5</td>
</tr>
<tr>
<td>b. Take niacin with food</td>
<td>6</td>
</tr>
<tr>
<td>c. Avoid hot beverages</td>
<td>7</td>
</tr>
<tr>
<td>d. Avoid alcohol</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>250</td>
</tr>
<tr>
<td>10</td>
<td>500</td>
</tr>
<tr>
<td>11</td>
<td>500</td>
</tr>
<tr>
<td>12</td>
<td>500</td>
</tr>
</tbody>
</table>

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**FAST TRACK**

When choosing a lipid-lowering agent, consider the percent reduction in LDL that the patient needs to achieve.
Other options include statins or omega-3-fatty acids, but statins reduce TG only moderately and are generally insufficient alone.

Niacin has been discouraged by clinicians, due to patient intolerance and its capacity to cause hyperglycemia. Intolerance is more common with the immediate-release formulation, but may be overcome by patient/clinician education or the once-daily (extended-release) formulation. Strategies to improve immediate-release niacin tolerability can be found in Table 3. Hyperglycemia may occur with either formulation of niacin. Recent studies, however, have found that the once-daily formulation causes only minor, clinically insignificant changes in glycosylated hemoglobin and/or fasting blood glucose. Thus, niacin tends to be underused, but may be an effective alternative for these patients.

Omega-3-fatty acids (fish oils) have been used for years to treat hypertriglyceridemia, but lack of product standardization has limited their use. A prescription-only, highly purified, concentrated mixture of omega-3 polyunsaturated fatty acids is now available. At the maximum dose of 4 g/d, it can decrease TG by up to 40%. Until outcome data are available, omega-3-fatty acids should be reserved for patients whose TG levels fail to decrease while taking fibrates or niacin, or who still have elevated TG levels despite therapeutic doses of these agents.

What is “very high risk” and what is the LDL goal?
The National Cholesterol Education Program update defines patients at “very high risk” if they have established CHD plus any of these conditions:

- multiple major risk factors (especially diabetes)
- severe, poorly controlled risk factors (especially continued cigarette smoking)
- multiple risk factors of the metabolic syndrome (high TG plus non-HDL >130 mg/dL with low HDL)
- acute coronary syndrome (ACS).

For these patients, an optional LDL goal is <70 mg/dL. However, clinical trials fail to provide convincing evidence for such an aggressive goal. Only 2 clinical trials so far have evaluated the effect of lowering LDL to <70 mg/dL. These studies were conducted in patients with acute coronary syndrome and, besides yielding mixed results, less than a quarter of the patients had diabetes. Phase Z of the Aggrastat to Zocor (A to Z) Trial failed to meet its primary endpoint, which was a composite of cardiovascular death, nonfatal MI, readmission for ACS, and stroke. On the other hand, the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE-IT) study found a 16% relative risk reduction in the primary endpoint (composite of death from any cause, MI, documented unstable angina requiring rehospitalization, revascularization, and stroke) favoring the arm that achieved an LDL <70 mg/dL with a NNT of 26.

Thus, clinicians should understand that the data supporting this new goal are not only limited but also contradictory at this time.

Should all patients with diabetes take statins?
For years now, the ADA has granted a Level of Evidence A (well-conducted, generalizable, randomized controlled trials that are adequately powered) to the recommendation that all diabetic patients without overt CHD who are over the age of 40 receive a statin regardless of their baseline LDL level. The ADA pointed to 3 main clinical trials as the basis for this recommendation: HPS, CARDS, and PROVE-IT. Although these trials were well conducted, randomized, and adequately powered, their results are far from generalizable to all the diabetic patients described in this recommendation.

First, average baseline LDL levels...
for patients in HPS and CARDS were never <100 mg/dL (123 and 116 mg/dL, respectively). Second, although PROVE-IT found a benefit among patients in the intervention group who had a baseline LDL <100 mg/dL and end-of-study LDL <70 mg/dL, these findings were not confirmed by the A to Z Trial. Furthermore, only 17% of the patients in PROVE-IT had diabetes, and an evaluation of the effect of high doses of statins among this subgroup of patients has not been conducted. Thus, these trials fail to provide compelling evidence that statins are beneficial among diabetic patients with baseline LDL levels <100 mg/dL.

Moreover, despite a generally benign side effect profile, overuse of statins may unnecessarily put patients at risk of drug interactions and side effects, such as myopathies, while significantly increasing drug expenditures. If 25% of patients have baseline LDL levels <100 mg/dL, as pointed out by NHANES, treating these patients may lead to unnecessary and avoidable expense.

In 2008, the ADA modified its previous recommendation that everyone >40 without overt CHD receive a statin regardless of their baseline LDL level, to include only patients with at least 1 additional cardiovascular risk factor (Level of Evidence: A).

### What are the safety and dosing issues?

#### Combination therapy

Because of the particular lipid abnormalities often present in diabetic patients (high TG, low HDL, and elevated LDL), combination therapy is inevitable in many

**TABLE 4**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CREATININE CLEARANCE (ML/Min)</th>
<th>USUAL STARTING DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;30</td>
<td>30-60</td>
</tr>
<tr>
<td>Statins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lovastatin&lt;sup&gt;15,35&lt;/sup&gt;</td>
<td>Initial dose: 20 mg</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Pravastatin&lt;sup&gt;14,46&lt;/sup&gt;</td>
<td>Initial dose: 10 mg</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Simvastatin&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Initial dose: 5 mg</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Atorvastatin&lt;sup&gt;47&lt;/sup&gt;</td>
<td>No adjustment</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Rosuvastatin&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Initial dose: 5 mg&lt;sup&gt;*&lt;/sup&gt;</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Fibrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil&lt;sup&gt;16,35,46&lt;/sup&gt;</td>
<td>↓ to 50% or 25% of usual dose</td>
<td>No adjustment or may ↓ to 50% of usual dose</td>
</tr>
<tr>
<td>Fenofibrate&lt;sup&gt;16,49&lt;/sup&gt;</td>
<td>Use not recommended</td>
<td>Initial dose: TriCor 48 mg Antara 43 mg Lofibra 67 mg (capsule); 54 mg (tablet)</td>
</tr>
<tr>
<td>Ezetimibe&lt;sup&gt;17&lt;/sup&gt;</td>
<td>No adjustment</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Niacin&lt;sup&gt;16,30&lt;/sup&gt;</td>
<td>Use with caution may ↓ to 50% of usual dose</td>
<td>Use with caution</td>
</tr>
<tr>
<td>Omega-3-fatty acids&lt;sup&gt;23&lt;/sup&gt;</td>
<td>No adjustment</td>
<td>No adjustment</td>
</tr>
</tbody>
</table>

ER=extended-release; IR=immediate-release. *Not to exceed 10 mg/d rosuvastatin.
Use niacin with caution in patients with renal insufficiency

To effectively and safely combine lipid-lowering agents, it is important to understand benefits, risks, dosing, and monitoring.

**Statins used with niacin:** Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) should be monitored periodically because of the increased risk of hepatotoxicity.

**Statins used with fibrates:** Similarly, some precautions are needed. The incidence of rhabdomyolysis with statin or fibrate monotherapy is estimated to be 0.44 (95% confidence interval [CI], 0.20–0.84) and 2.82 (95% CI, 0.58–8.24) cases per 10,000 person-years, respectively. When these agents are combined, the incidence rises to an estimated 5.98 cases per 10,000 person-years. This risk seems to be higher with statin–gemfibrozil combinations. The number of cases reported to the Food and Drug Administration’s Adverse Event Reporting System is 33 times lower for the statin–fenofibrate combinations. Therefore, in combination with statins, gemfibrozil should generally be avoided and fenofibrate used instead. A baseline creatine phosphokinase (CPK) is recommended for patients who are started on statin–fibrate combinations, and that it be rechecked in patients who present with signs or symptoms of myopathy. It may also be prudent to maintain both the statin and fibrate at the lower end of their dosage range if possible. Particularly, the simvastatin and rosuvastatin doses should not exceed 10 mg/d when co-administered with gemfibrozil, and the lovastatin dose should not exceed 20 mg/d when co-administered with either fibrate.

Fibrates may be given with ezetimibe and niacin; however, AST/ALT should be closely monitored (at baseline, 4–6 weeks, yearly thereafter) in patients taking niacin.

**All ezetimibe combinations** have been found to be safe.

**Renal adjustment**

Ezetimibe and the omega-3-fatty acids do not undergo significant renal excretion; therefore, doses of these agents do not need to be adjusted in patients with renal impairment.

Although statins undergo only minimal renal excretion, doses need to be adjusted in patients with severe renal impairment (creatinine clearance <15 mL/min) to avoid toxicity due to a decrease in drug clearance. One exception is atorvastatin, which undergoes merely 1% to 2% renal excretion; it is safe for these patients. Fibrates should also be used with caution in patients with renal dysfunction and avoided in patients with severe renal impairment (creatinine clearance <15 mL/min). Although, about 60% to 76% of niacin is eliminated renally, its use in patients with renal insufficiency has not been studied, and current recommendations are to use niacin with caution in this population.

**TABLE 4** lists specific recommendations for each of these agents.

**Hepatic adjustment**

All lipid-lowering agents, except the omega-3-fatty acids, undergo significant hepatic metabolism and should not be used in patients with active liver disease. These agents should also be avoided in patients with chronic severe liver disease (Child-Pugh Class C), as they may inflict more damage to the liver and may place patients at risk for toxicity due to a decrease in drug clearance. Although liver disease is not a contraindication to omega-3-fatty acid therapy, no recommendations for its use in this population are available. It has been associated with increased levels of ALT in clinical trials, however. If used in patients with hepatic impairment, monitor both AST and ALT periodically.

In patients with chronic mild-to-moderate liver disease (Child-Pugh Class B), start statins at the lowest recommended dose and monitor AST/ALT regularly. Although no recommendations have been made regarding the use of niacin and fibrates in these patients, it would...
be prudent to monitor AST/ALT periodically (baseline, 4–6 weeks, at 6 months, yearly thereafter) and instruct patients to report any signs or symptoms of toxicity. Because the serum concentration of ezetimibe was significantly increased among these patients, the manufacturer recommends it only for patients with mild liver disease (Child-Pugh Class A).17

Financial Disclosures
Dr. Tovar discloses that he is on the speakers’ bureau for Merck & Co., Inc.; however, the subject of this manuscript is in no way related to his involvement with such entity. He currently speaks on The Role of the Human Papilloma Virus in the Development of Cervical Cancer, and Changing the Paradigm of Herpes Zoster Disease.

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Dr. Loffredo reported no financial relationships relevant to this article.

References


Combination therapy is inevitable in many cases


