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STATE-OF-THE-ART PAPER

## Safety of Aggressive Lipid Management

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Data from recent clinical trials of high- versus moderate-dose statin therapy support the recommendation to achieve a low-density lipoprotein (LDL) <100 mg/dl in high-risk patients and reveal that many patients will require a high-dose statin to achieve this goal. Overall, low rates of serious musculoskeletal (<0.6%) and hepatic (<1.3%) toxicity have been observed with high-dose statin therapy. In the long-term trials, atorvastatin 80 mg had higher rates of persistent transaminase elevations but rates of myopathy and rhabdomyolysis similar to lower doses of statins. The rate of myopathy and rhabdomyolysis for simvastatin 80 mg, although still low, was about 4× higher than for atorvastatin 80 mg and lower doses of statin. A similar margin of safety would be expected in properly selected patients with characteristics similar to those who participated in the clinical trials. High-dose statin therapy or combination therapy will be required for the large majority of very high-risk patients to achieve the optional LDL goal of <70 mg/dl. While the combination of ezetimibe, bile-acid sequestering agents, niacin, and fenofibrate with moderate dose statins appears to be reasonably safe, the long-term safety of combination with high-dose statins remains to be established. In order to optimize patient outcomes, clinicians should be aware of specific patient characteristics, such as advancing age, gender, body mass index, or glomerular filtration rate, which predict muscle and hepatic statin toxicity. (J Am Coll Cardiol 2007;49:1753–62) © 2007 by the American College of Cardiology Foundation

Recent clinical trials have demonstrated additional cardiovascular risk reduction with high-dose compared with moderate-dose statin therapy in subjects with coronary heart disease (CHD) (1–4). In the trials completed to date, those receiving high-dose (80 mg) atorvastatin or simvastatin had additional 11% to 21% reductions in the relative risk of cardiovascular events compared with those receiving a moderate statin dose (40 mg of pravastatin, 20 to 40 mg of simvastatin, or 10 mg of atorvastatin). In the high-dose statin groups, low-density lipoprotein (LDL) cholesterol levels were lowered on average to 62 to 81 mg/dl; in the moderate-dose statin groups, LDL levels were 77 to 104 mg/dl. In this review, we will address several safety issues

that may arise when considering more aggressive LDL-lowering therapy for a given patient.

The fundamental, if obvious, requirement for considering more aggressive LDL-lowering is that the patient has sufficiently elevated risk to benefit from more aggressive treatment. The third report of the National Cholesterol Education Program Adult Treatment Panel (NCEP) identified an LDL goal <100 mg/dl for high-risk patients (those with clinical cardiovascular disease, diabetes, or 10-year CHD risk >20%) (5). A subsequent 2004 report from the NCEP suggested an optional LDL goal <70 mg/dl for those at the highest risk, including those with established cardiovascular disease plus additional high-risk characteristics: diabetes mellitus, multiple cardiovascular risk factors, multiple risk factors of the metabolic syndrome, or severe or poorly controlled risk factors, especially continued cigarette smoking (6). An LDL goal <100 mg/dl was also extended as an option to moderately high-risk primary prevention patients who had 2 or more risk factors and a 10% to 20% 10-year CHD risk as well as other indicators of increased risk.

The 2004 NCEP report also recommended at least a 30% to 40% reduction in LDL in order to significantly lower cardiovascular risk. It should be noted, however, that many, if not most, patients will require at least a 50% reduction in LDL to achieve an LDL <100 mg/dl. In the TNT (Treating to New Targets) trial, based on the standard deviation of LDL at baseline, it can be estimated that approximately 90% of subjects in the atorvastatin 80 mg group had an LDL <100 mg/dl (2). Conversely, in the

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**Abbreviations and Acronyms**

- CHD** = coronary heart disease
- CI** = confidence interval
- CK** = creatine kinase
- CYP** = cytochrome
- FDA** = Food and Drug Administration
- HDL** = high-density lipoprotein
- HR** = hazard ratio
- LDL** = low-density lipoprotein
- NCEP** = National Cholesterol Education Program Adult Treatment Panel
- ULN** = upper limit of normal

atorvastatin 10 mg group, approximately 50% of patients had an LDL >100 mg/dl. The mean LDL in the atorvastatin 80 mg group in the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) trial was slightly higher at 81 mg/dl so slightly fewer subjects had an LDL <100 mg/dl. Notably, less than one-half of subjects in the atorvastatin 80 mg arms of TNT and IDEAL achieved the more aggressive LDL goal <70 mg/dl. Several conclusions can be drawn: 1) most moderately high and high-risk patients will require high-dose statin or combination statin therapy to achieve an LDL <100 mg/dl, especially since subjects with severe hypercholesterolemia

were excluded from these trials; 2) almost all very high-risk patients will require high-dose statin therapy or combination statin therapy to achieve an LDL <70 mg/dl; and 3) the TNT and IDEAL trials were a validation of the NCEP III goal <100 mg/dl rather than the 2004 NCEP report optional LDL goal <70 mg/dl. However, support for the more aggressive goal comes from the Heart Protection Study (7) and a retrospective analysis of the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) trial (1).

Safety will now be examined within the context of the requirement for high-dose statin or a statin used in combination with other lipid-lowering agents. It is very important to note that subjects who were most likely to experience statin toxicity were excluded from clinical trials. Therefore, the adverse event rates observed in clinical trials should not be generalized to an unselected patient population. High-dose statin monotherapy and combination therapy should be used very cautiously in patients having characteristics that predict statin toxicity including advanced age, small body size, diminished renal and hepatic function, or multiple comorbidities or medications, and avoided if glomerular filtration is <30 ml/min/1.73 m<sup>2</sup>. In appropriately selected patients (i.e., similar to those participating in clinical trials), high-dose statins would be expected, however, to have a similar margin of safety (1-4,8-13) (Table 1). The National Lipid Association Statin Safety Task Force has provided recommendations for management of muscle-related symptoms in patients receiving statin therapy (10) (Table 2).

**Safety of Moderate-Dose Statins**

Although statins have a 40% higher rate of adverse effects than placebo, the rates of significant musculoskeletal and

hepatic toxicity are very low for both moderate- and high-dose statin therapy (14). Nonurgent adverse events such as myalgia (muscle aches or pain with normal creatine kinase [CK]) and a single abnormal elevated liver function test constitute approximately two-thirds of reported adverse events. In a meta-analysis of over 70,000 subjects in 18 primary and secondary prevention placebo-controlled trials, the number needed to harm for any adverse event with statins was 197 versus the number needed to treat to prevent 1 cardiovascular event of 27 (14). In other words, treating 1,000 patients would prevent 37 cardiovascular events and cause 5 adverse events of any type. However, serious events such as CK >10× the upper limit of normal (ULN) or rhabdomyolysis are rare and have a number needed to harm of 3,400. Rhabdomyolysis alone was extremely rare with a number needed to harm of 7,428. In this analysis, fluvastatin, the least efficacious, also had the lowest rate of adverse events, and atorvastatin, the most efficacious, had the highest rate. Simvastatin, pravastatin, lovastatin, and rosuvastatin appeared to have similar odds of adverse events.

Excluding cerivastatin, post-approval surveillance reveals a rate of serious musculoskeletal toxicity no higher than the levels observed in pre-approval clinical trials, although the vast majority of prescriptions are for low or moderate doses of statin. In the Food and Drug Administration's (FDA) Adverse Event Reporting System database up until 2002, the reporting rates per million statin prescriptions was 0.38 cases for myopathy and 1.07 cases of rhabdomyolysis (15). Rates increased for all statins after the release of rosuvastatin suggesting changes in reporting rates rather than any changes in adverse effect profiles (15). An administrative database analysis also reported low rates of hospitalized rhabdomyolysis: 1.6 to 3.5 cases per 10,000 person-years of hospitalized patients on statins (16).

Post-approval surveillance also shows no evidence of serious hepatotoxicity with statins. The FDA's Adverse Event Reporting System database through 2004 reported a rate of 0.69 cases of liver failure/hepatitis in per million statin prescriptions, similar to the rate in the general adult population (15). Analysis of an administrative claims database reported 6.1 to 12.8 hospitalized hepatic events per 10,000 person-years of hospitalized patients on statins (17). None were hospitalized within 6 months of starting their statin. Furthermore, only 1 of the 51,741 patients who underwent liver transplantation between 1990 and 2002 was taking a marketed statin (18).

The drugs that most commonly increase the toxicity of statins are cyclosporine and those affecting metabolism via cytochrome (CYP) P450 or glucuronidation (19). Lovastatin, simvastatin, and atorvastatin are metabolized via the CYP P450 3A4 pathway. Fluvastatin is metabolized by the CYP 2C9, and cerivastatin is metabolized by dual 2C9 (or 2C8) and 3A4 pathways. Pravastatin and rosuvastatin are not significantly metabolized by the CYP pathway. The CYP 3A4 inhibitors most commonly re-

**Table 1** Patient Characteristics Likely to Enhance Safety of High-Dose\* Statins Based on Eligibility Criteria for Subjects Participating in End Point Clinical Trials, Adverse Event Reporting, and Package Inserts†

Patient Characteristics‡	Safety Criterion or Characteristic/Medication to Avoid
Age	<75 yrs§
Body size	Use with caution if small body frame, especially if female patient If frail, evaluate appropriate use in terms of life expectancy and goals of care
Race/ethnicity	Asian: rosuvastatin starting dose 5 mg due to decreased clearance
Statin use	Prior statin use No history of statin intolerance
Hepatic function	No active hepatic disease ALT and AST ≤2× ULN
Renal function	Creatinine ≤1.5× ULN Glomerular filtration rate >60 ml/min/1.73 m <sup>2</sup> No history of nephrotic syndrome Discontinue before intravenous dye administration
Thyroid function	TSH in normal range
Muscle function	CK <3× ULN unless explanation Use with caution if history of muscle disease Discontinue before strenuous exercise (e.g., marathon)
Immune function	No chronic immunosuppressive therapy (especially cyclosporine)
Cytochrome P450 inhibitors	No concomitant use of: Macrolide antibiotics (especially erythromycin and clarithromycin) Antiviral drugs (especially HIV protease inhibitors) Systemic azole antifungals (itraconazole and ketokonazole) Verapamil (simvastatin) Diltiazem (lovastatin, atorvastatin) Amiodarone (simvastatin) Nefazadone Grapefruit juice >1 quart/day
Other lipid-lowering therapy	No fibrates (especially gemfibrozil) No niacin?
Alcohol intake	<2 drinks per day Avoid if alcoholism present
Left ventricular ejection fraction	≥30%
Intercurrent illness, surgery, or trauma	If severe illness, major surgery, or major trauma, discontinue lipid-lowering medications until recovered
Multiple comorbidities or medications	Evaluate appropriate use in terms of life expectancy and goals of care

\*Atorvastatin 80 mg, simvastatin 80 mg, rosuvastatin 40 mg; †the risk-benefit ratio should be carefully evaluated for patients exceeding 1 or more criterion; patients should be carefully monitored for musculoskeletal and/or hepatic toxicity; ‡exclusion criteria for clinical trials also included blood pressure <160/<100 mm Hg, hemoglobin A<sub>1c</sub> <8.5%, hemodynamically important valvular heart disease, and cancer diagnosis other than nonmelanoma skin cancer less than 5 years ago; the relationship of these characteristics to increased risk of serious adverse muscle effects has not been established, but hypertension and diabetes were associated with an increased risk of serious hepatic adverse effects in one study (11); §age up to 80 years at baseline in IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering); others have recommended age <70 years at cut-point for safety (65); ||other concomitant lipid-lowering therapies excluded from high-dose statin trials; limited safety data with higher doses of statins although reported rates of rhabdomyolysis with moderate-dose statins used in combination with niacin are much lower than when statins are used with fibrates.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; HIV = human immunodeficiency virus; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

ported to increase the risk of myopathy and rhabdomyolysis are erythromycin, clarithromycin, the antifungals ketoconazole and itraconazole, protease inhibitors indinavir, nelfinavir, ritonavir, and saquinavir, and nefazadone. The antidepressants fluoxetine, fluvoxamine, and sertraline are also CYP 3A4 inhibitors and may have the potential to increase statin toxicity. Diltiazem, verapamil, and amiodarone are weak inhibitors of CYP 3A4 and have been reported to increase the risk of myopathy with simvastatin (9). Gemfibrozil inhibits glucuronidation thereby increasing statin serum levels. Fenofibrate is a weaker inhibitor and does not

significantly increase serum levels of simvastatin, pravastatin, or rosuvastatin.

Other very rare adverse effects such as peripheral neuropathy and cognitive dysfunction have been attributed to statins (20). In the 16 case reports of peripheral neuropathy in patients taking statins, symptoms generally appeared within 2 months of initiating statin therapy and dissipated after withdrawal of the statin. In clinical trials, however, peripheral neuropathy has been found to be no more common in the statin-treated group than the placebo group in long-term statin trials. Two trials have formally evaluated

**Table 2** Recommendations From the National Lipid Association Statin Safety Task Force for Muscle Issues

For Patients With Muscle Symptoms and/or an Asymptomatic CK Elevation or Both	
1.	First, rule out other etiologies (including increased physical activity, trauma, falls, accidents, seizure, hypothyroidism, infections, alcohol or drug abuse, and rheumatologic or other muscle disorders)
2.	CK monitoring <ul style="list-style-type: none"> <li>a. Obtain CK for unexplained muscle symptoms</li> <li>b. May obtain baseline CK in high-risk patients, optional for others</li> <li>c. No need to routinely monitor CK levels during therapy</li> </ul>
3.	Discontinue the statin if intolerable muscle symptoms occur, with or without CK increase <ul style="list-style-type: none"> <li>a. Rechallenge with same or lower dose of same or different statin once symptoms resolve</li> </ul>
4.	If tolerable muscle symptoms with CK <10× ULN, continue statin at same or lower dose until symptoms dictate otherwise
5.	Discontinue the statin and reconsider risk/benefit if: <ul style="list-style-type: none"> <li>a. CK &gt;10× ULN even with tolerable muscle symptoms</li> <li>b. CK &gt;10,000 IU/l</li> <li>c. Worsening serum creatinine and/or need for intravenous hydration therapy</li> </ul>

CK = creatine kinase; ULN = upper limit of normal.

cognitive function. The Heart Protection Study studied 20,536 patients over a 5-year period and found no difference in the rate of cognitive impairment between the simvastatin and placebo groups (7). Nor did the PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) Trial report any difference in cognitive function between placebo and pravastatin therapy in patients aged 70 to 82 years (21).

### Safety of High-Dose Statins

While, overall, high-dose statins were reasonably well tolerated in clinical trials, there was evidence of a higher rate of adverse effects leading to their discontinuation. In the long-term event trials of atorvastatin 80 mg, discontinuation rates due to unspecified drug-related adverse events were consistently higher in the high (7% to 10%) than moderate dose arms (4% to 5%) over the approximately 5 years of observation (2,4) (Table 3). Based on these rates, fewer than

1 in 20 to 1 in 50 properly selected patients would need to discontinue atorvastatin 80 mg therapy due to a drug-related adverse effect. In comparison, the number needed to treat to prevent 1 cardiovascular event was 19 to 23 for the 2 trials. For the 2-year trials in patients with acute coronary syndromes, discontinuation rates due to unspecified drug-related adverse effects were not reported (1,3). In the A to Z trial, simvastatin 80 mg had a slightly higher rate of treatment discontinuation due to muscle side effects (1.8%) than the simvastatin 20 mg group (1.5%) (3). In the PROVE-IT trial, the atorvastatin 80 mg group had a slightly higher rate (1.9% vs. 1.4% in the pravastatin 40 mg group) of dose decreases due to side effects or abnormal liver function tests.

For a number of reasons, discontinuation rates in clinical practice could be higher if patients naive to statin therapy are initially started on the 80 mg dose of atorvastatin or simvastatin. Both short- and long-term statin trials excluded individuals intolerant of statins, with impaired hepatic or renal function, or receiving treatment with other drugs that seriously affect the pharmacokinetics of statins. In addition, in the long-term event trials, subjects were selected for ability to tolerate statins. The TNT trial had a lead-in period with atorvastatin 10 mg during which 3.6% of subjects were excluded due to adverse effects (2), whereas in the IDEAL trial the large majority (75%) of subjects had been on statin therapy before study enrollment (4). In the A to Z trial, subjects were titrated up to 80 mg from 20 mg of simvastatin (3). In a retrospective analysis of over 14,000 subjects in 49 short-term trials of atorvastatin 10 mg versus 80 mg, similar rates of discontinuation due to drug-related adverse events occurred for placebo (3%) and both doses of atorvastatin (3.5% and 1.8%, for 10 and 80 mg, respectively) (22). Unfortunately, since rates of discontinuation were not presented separately for the 26 trials in which subjects were randomized directly to atorvastatin 80 mg rather than titrated, the tolerability of initiating atorvastatin at the 80 mg dose compared to up-titration to the 80 mg dose cannot

**Table 3** Reported Rates of Discontinuation of Study Medication Due to Any Drug-Related AE, NNH, and NNT

Study	Treatment	n	Mean Intent-to-Treat LDL (mg/dl)	Discontinued Study Drug Due to Drug-Related AE (%)	NNH to Result in Discontinuation Due to Drug-Related AE*	NNT to Prevent 1 Event* (Any CVD Event†/Hard Event‡)
TNT	Atorvastatin 10 mg	5,006	101	5.3		
	Atorvastatin 80 mg	4,995	77	7.2	53	19/44
IDEAL	Simvastatin 20-40 mg	4,449	104	4.2		
	Atorvastatin 80 mg	4,439	81	9.6	19	23/60
4S	Placebo	2,223	190	6		
	Simvastatin 20-40 mg	2,221	122	6	0§	NA  /10
CARE	Placebo	2,078	136	3.5		
	Pravastatin 40 mg	2,081	98	3.2	0‡	NA  /24

\*Atorvastatin 80 mg versus lower statin dose or active statin treatment versus control group; 4S and CARE were the only trials that reported discontinuations due to any drug-related adverse event (AE); this rate was not reported for other trials or only rate for muscle and/or hepatic AEs were reported; †nonfatal myocardial infarction, stroke, revascularization, documented or hospitalized angina, and cardiovascular death; ‡nonfatal myocardial infarction, stroke, and cardiovascular death; §rate of discontinuation due to AEs was higher in the placebo group; ||not applicable: documented or hospitalized angina was not reported.

CARE = Cholesterol and Recurrent Events trial; CVD = cardiovascular disease; IDEAL = Incremental Decrease in End Points Through Aggressive Lipid Lowering; LDL = low-density lipoprotein; NNH = numbers needed to result in drug discontinuation; NNT = numbers needed to treat to prevent 1 cardiovascular event; TNT = Treating to New Targets; 4S = Scandinavian Simvastatin Survival Study Group.

be addressed from this study. However, in 1 study of over 900 dyslipidemic subjects randomized to 1 of 4 atorvastatin doses, those who received an initial dose of atorvastatin 80 mg had a treatment-related discontinuation rate of 17% compared with a rate of 10% to 12% for doses of 10 to 40 mg (23). In a review of 4 studies where 1,393 of 1,586 subjects were randomized directly to simvastatin 80 mg, the discontinuation rate due to drug-related adverse effects in the 80-mg group (2.5%) was not significantly different compared to the simvastatin 40-mg group (1.9%) (24).

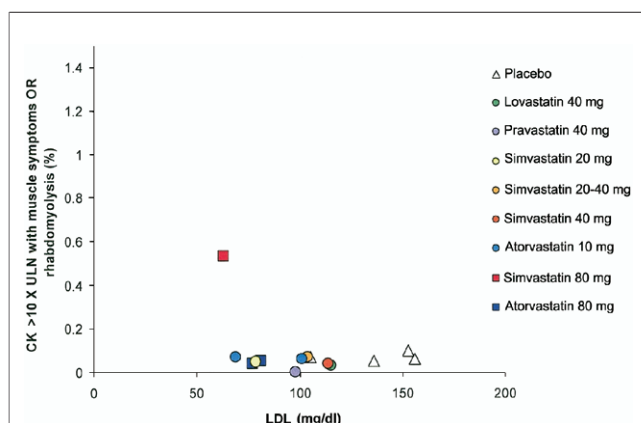
### Musculoskeletal Safety

Comparisons of the rates of significant muscle and liver adverse effects for both placebo and active-controlled statin cardiovascular end point trials is somewhat hampered by inconsistent reporting. With the exception of simvastatin 80 mg (0.53%) (3), rates of myopathy (or myositis, defined as CK elevation  $>10\times$  ULN with muscle symptoms) and rhabdomyolysis were quite low ( $\leq 0.7\%$ ) across the range of statin doses, including atorvastatin 80 mg, in the 7 trials for which these events were reported (2,4,7,25-27) (Fig. 1). Considered alone, rhabdomyolysis was very uncommon, with the highest rate (0.13%) in the simvastatin 80 mg arm of the A to Z trial (3). Rhabdomyolysis rates in other trials ranged from 0% to 0.07% for simvastatin 20 mg to 40 mg, pravastatin 40 mg or atorvastatin 10 mg, which was similar to the rates of 0% to 0.06% reported for placebo-treated subjects (1,2,4,7,21,25-29). Although 5 cases of rhabdomyolysis (2 in subjects receiving atorvastatin 80 mg) were reported by study investigators in the TNT trial, no cases of rhabdomyolysis met the criteria for rhabdomyolysis defined by the American College of Cardiology, American Heart

Association, and National Heart, Lung, and Blood Institute expert panel (11). In the IDEAL trial, 2 cases of investigator-reported rhabdomyolysis were reported for simvastatin 20 to 40 mg and 2 cases for atorvastatin 80 mg; comparison to the expert panel's criteria was not provided (4). The 1 case of rhabdomyolysis reported in the BELLES (Beyond Endorsed Lipid Lowering with Electron Beam Tomography Scanning) trial occurred after atorvastatin had been discontinued (30). No cases of rhabdomyolysis by the expert panel definition were reported in any of over 29,000 subjects in 51 other trials of atorvastatin given in doses of 10 to 80 mg (1,22,29). Elevated CK level and muscle symptoms consistent with the definition of myopathy given above occurred in 1 subject in each of the atorvastatin groups, for a rate of 0.01% in the atorvastatin 10 mg group and 0.02% in the atorvastatin 80 mg group. In contrast, in the pre-marketing database for simvastatin 80 mg, the rate of myopathy was 0.6% (24), similar to the rate observed in the A to Z trial (9). No cases of rhabdomyolysis were reported in these trials.

Rates of less serious muscle complaints such as myalgia (defined as muscle ache or pain), or CK elevations  $<10\times$  ULN with or without muscle symptoms were rarely reported in the event trials. In the review of 49 atorvastatin trials noted above, treatment-related myalgia occurred at a similar rate of 1.4% and 1.5% in subjects receiving 10 or 80 mg of atorvastatin compared with a rate of 0.7% with placebo (22). Persistent CK  $>10\times$  ULN without muscle symptoms was reported in 2 of 4,798 subjects (0.06%) who received atorvastatin 80 mg and none of the subjects receiving atorvastatin 10 mg or placebo. A retrospective analysis of safety from the PROVE-IT trial further suggests adverse effects are not related to LDL level (31). Adverse muscle, hepatic, and other adverse effects were found to occur at the same rate across the range of on-treatment LDL levels, including very low levels  $<40$  mg/dl.

The reason for the very low rate of myopathy for atorvastatin 80 mg remains speculative. Atorvastatin has a very low rate of renal clearance ( $<2\%$ ) (10), and therefore the pharmacokinetics would not be adversely affected in patients with renal impairment, which is not uncommon in a high-risk CHD population (32). Although atorvastatin is metabolized by CYP P450 3A4, inhibition of this pathway may not increase HMG CoA inhibition since net activity remains unchanged (33). The majority of cases of statin-related rhabdomyolysis have occurred when combined with gemfibrozil (34). Fewer reports of rhabdomyolysis with atorvastatin may be the result of lower plasma exposure after coadministration with gemfibrozil than occurs for other statins (35). The higher rate of myopathy and rhabdomyolysis for simvastatin may result in part from a decreased rate of plasma clearance in older compared with younger persons (9). Age does not appear to affect clearance rates for either atorvastatin or rosuvastatin (8,10).



**Figure 1** Incidence of Muscle Symptoms With CK Elevations  $>10\times$  ULN and Rhabdomyolysis

Included only cardiovascular event trials for which these data were reported (2-4,7,25-27). CK = creatine kinase; LDL = low-density lipoprotein; OR = odds ratio; ULN = upper limit of normal.

## Hepatic Safety

Although presentation of adverse event data again were not consistent across all the statin trials, 3 of 4 trials of high-versus moderate-dose statin therapy (2-4) and the largest placebo controlled statin trial (7) did present data on persistent significant elevations of hepatic transaminases (alanine aminotransferase [ALT] or aspartate aminotransferase  $>3\times$  ULN on 2 or more consecutive occasions) (Fig. 2). Although the rates of hepatic enzyme elevation were still quite low ( $<1.3\%$ ), achieving LDL levels below 100 mg/dl with 80 mg of atorvastatin or simvastatin resulted in a logarithmic increase in persistent hepatic enzyme elevations compared with lower doses of statins. These elevations were reversible; reduction in the dose or withdrawal of the statin resulted in a return of the elevated enzyme levels to normal.

In a review of over 14,000 patients in 49 trials lasting up to 52 months, cholecystitis and cholelithiasis were reported in 0.25% of subjects receiving atorvastatin 10 mg and 0.29% of subjects receiving atorvastatin 80 mg (22). No cases of hepatitis were reported with atorvastatin 10 mg ( $n = 7,258$ ). In the 5 subjects diagnosed with hepatitis as an adverse event in the atorvastatin 80 mg group ( $n = 4,798$ ), 4 cases were considered to be treatment related. The onset of symptoms occurred on average 4 weeks (range 1 to 8 weeks) after treatment initiation, and all cases resolved within 4 weeks of atorvastatin discontinuation. One case of acute hepatitis was reported in 1,586 subjects who received simvastatin 80 mg in pre-marketing studies (24), but no cases of severe hepatobiliary disease were reported for the 2,265 subjects who received simvastatin 80 mg for 2 years in the A to Z trial (3).

In clinical practice, baseline elevations of hepatic transaminases  $<3\times$  ULN are not a contraindication to statin therapy. Many patients with diabetes, metabolic syndrome, or obesity will have nonalcoholic fatty liver

disease, or nonalcoholic steatohepatitis, with transaminase levels fluctuating between 1.5 and  $3\times$  ULN (36). After establishing that no other etiologies are responsible for the transaminase elevations, a statin at a low-to-moderate dose can be started with close monitoring of alanine aminotransferase levels. Statin dose can be titrated upward, and additional LDL-lowering therapies can be added as tolerated, although in general niacin should be avoided in these patients due to concerns about hepatotoxicity. Transaminase level elevations due to fatty liver often improve with long-term statin therapy (37).

## Cancer

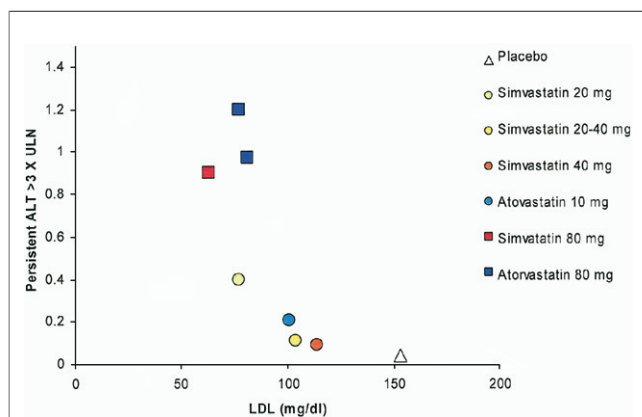
In a prospective meta-analysis of 14 trials of moderate-dose statin therapy, statin-treated subjects had the same rates of cancer as those receiving placebo over a period of follow-up of up to 6 years (hazard ratio [HR] 1.0 [95% confidence interval (CI) 0.95 to 1.06]) (38). Cancer rates in the approximately 5-year TNT trial were slightly higher in the atorvastatin 80 mg than in the atorvastatin 20 mg groups, although this did not reach statistical significance (HR = 1.13 [95% CI 0.83 to 1.55,  $p = 0.42$ ]) (2). Reassuringly, however, cancer rates were slightly lower in the atorvastatin 80 mg group compared with the simvastatin 20 to 40 mg in the IDEAL trial (HR 0.89 [95% CI 0.68 to 1.16],  $p = 0.38$ ), although again not reaching statistical significance, supporting a chance finding in the TNT trial (4).

## Safety of Other Agents That Lower LDL $>50\%$

On the basis of package insert information, only a few agents lower LDL cholesterol by  $\geq 50\%$ : atorvastatin 40 to 80 mg/day, rosuvastatin 20 to 40 mg/day, and simvastatin 20 to 80 mg combined with ezetimibe 10 mg/day (8,10,39). In both the TNT and IDEAL trials, despite recommendations for all clinical trial participants to follow a cholesterol-lowering diet and a  $>50\%$  reduction in LDL with atorvastatin 80 mg, fewer than half of patients had an LDL  $<70$  mg/dl. Many patients will therefore require further lifestyle changes as well as the addition of a second, or even third, LDL-lowering drug to achieve an LDL  $<70$  mg/dl. Therapeutic lifestyle changes (including stanol or sterol-containing products and increased soluble fiber intake added to restrictions in saturated and trans fats and cholesterol), ezetimibe, bile acid sequestrants, or niacin  $\geq 2$  g can provide an additional 10% to 20% LDL reduction in those on a stable dose of statin (5,40-44).

## Rosuvastatin

No cardiovascular end point studies have yet been completed for rosuvastatin preventing long-term safety comparisons with 80 mg of simvastatin or atorvastatin. Ongoing trials are evaluating 10 to 20 mg doses of rosuvastatin compared with placebo (45,46). In the open-label ASTEROID (Effect of Very High-Intensity Statin Ther-



**Figure 2** Incidence of ALT Elevations  $>3\times$  ULN on 2 or More Consecutive Occasions

Included only cardiovascular event trials for which these data were reported (2-4,7). Abbreviations as in Figure 1.

apy on Regression of Coronary Atherosclerosis) trial, in which 507 patients received rosuvastatin 40 mg for 2 years, 3.7% discontinued therapy due to drug-related muscle pain or weakness, a rate higher than in the atorvastatin 80 mg group in the IDEAL trial (2.2%) (4,47). All subjects in the ASTEROID trial were statin-naive although the open-label design may have influenced patient reports of adverse events, a phenomenon that may also have occurred in the IDEAL trial. No ASTEROID trial participant experienced persistent CK elevations  $>10\times$  ULN, myopathy, or rhabdomyolysis. Persistent ALT elevations were noted in only 1 subject (0.2%).

In regard to efficacy, rosuvastatin provides approximately an 8% additional lowering of LDL compared with atorvastatin, rosuvastatin at the same mg dose (48). Rosuvastatin 20 mg lowers LDL on average by about 52%, and 40 mg lowers LDL by 59% (49). With over 10,000 subjects in the drug development program, rosuvastatin has been shown to have rates of myopathy and liver function abnormalities of  $\leq 0.1\%$  at doses of up to 40 mg (50). No cases of hepatitis or liver failure were reported. Proteinuria occurred at the same rate as other statins at higher doses, and renal function actually improved (51). The 80 mg dosage of rosuvastatin was not approved due to an excess of rhabdomyolysis. Rosuvastatin has different pharmacokinetic properties than simvastatin and atorvastatin, which may have the potential to reduce musculoskeletal toxicity (52), although this remains to be proven in long-term clinical trials in a wider patient population. Some reassurance of safety can be found in the fact that over one-third of subjects in the rosuvastatin clinical database were over age 65 years and had significant levels of comorbidities or renal impairment (53). While rosuvastatin has a long half-life similar to atorvastatin, it has hydrophilicity similar to pravastatin and no significant CYP P450 interactions. However, gemfibrozil and cyclosporine still significantly increase rosuvastatin blood levels, and the dose of rosuvastatin should not exceed 10 mg when used in combination with these drugs. Persons of Asian ancestry have been found to have altered pharmacokinetics resulting in higher blood levels of rosuvastatin than persons of European ancestry (8). In such patients, rosuvastatin should be initiated at the 5 mg dosage and carefully titrated as required to maximum dose of 20 mg daily.

### Combination Therapies

**Ezetimibe.** Again, no long-term event trial data is available yet for ezetimibe used in combination with a statin, although several trials are ongoing (IMPROVE-IT [IMProved Reduction of Outcomes], Vytorin Efficacy International Trial, SEAS [Simvastatin and Ezetimibe in Aortic Stenosis], and SHARP [Study of Renal and Heart Protection]). Ezetimibe coadministered with or added to statin therapy results in additional 15% to 20% reductions in LDL (54,55). Ezetimibe coadministered with doses of simvastatin 20 mg or atorvastatin 10 mg results in approx-

imately 50% reductions in LDL, and an additional 5% reduction in LDL with each subsequent doubling of the statin dose. In a pooled analysis, ezetimibe + simvastatin 80 mg on average resulted in a 57% reduction in LDL, and ezetimibe + atorvastatin 80 mg in 60% reduction in LDL (55).

Ezetimibe + simvastatin resulted in a similar rate of discontinuance related to treatment compared with simvastatin monotherapy. No differences in muscle-related adverse events were found between 4,558 subjects receiving ezetimibe + simvastatin and 2,563 subjects who received simvastatin alone in an analysis of 17 12-week trials in the sponsor's database (56). Nor was any difference found in follow-up for as long as 48 weeks. Creatine kinase elevations  $>10\times$  ULN with muscle symptoms occurred only rarely ( $\leq 0.1\%$ ) with either therapy. Hepatic enzyme elevations  $\geq 3\times$  ULN on 2 or more consecutive occasions occurred in 1.4% of 925 ezetimibe + statin-treated subjects compared with 0.4% of 936 statin-only subjects (55). However, in an administrative database, hospitalization for hepatic events was no higher for statin + ezetimibe combinations than for statin monotherapy (16).

**Niacin.** Although niacin in doses of 1.0 to 1.5 g improves high-density lipoprotein (HDL) cholesterol and the total cholesterol/HDL cholesterol ratio, it does not improve LDL cholesterol when added to low-dose statin therapy unless larger doses are given (57). Niacin 2 g lowers LDL by an additional 9% to 24% when added to a statin (42-44). An adverse effect profile limits widespread use of niacin, although cutaneous effects are somewhat diminished with the use of extended-release formulations. The dose of niacin should not exceed 2 g per day for extended-release formulations because of reports of fulminant hepatotoxicity with higher doses of sustained-release niacin. Although a proprietary formulation of extended-release niacin and lovastatin is available, the maximum LDL-lowering LDL reduction that can be achieved is 42% with lovastatin 40 mg + extended-release niacin 2,000 mg (43). Extended-release niacin combined with lovastatin has higher rates of dose-related persistent elevated liver function tests (1%) compared with lovastatin alone (0.2%) (44). Myopathy and rhabdomyolysis have been reported with the combination of lovastatin and niacin  $\geq 1$  g per day, although in clinical studies of 1,079 subjects who received extended-release niacin/lovastatin (Advicor, Kos Pharmaceuticals, Cranbury, New Jersey), no cases of rhabdomyolysis and 1 case of myopathy were reported. The HATS Study (High-density cholesterol Atherosclerosis Treatment Study) randomized 160 subjects to placebo or to simvastatin + niacin (mean doses of simvastatin 13 mg and niacin 2.4 g) (58). No cases of persistent ALT or CK elevations were found, and no cases of myopathy or rhabdomyolysis were reported. The ongoing AIM-HIGH (Niacin Plus Statin to Prevent Vascular Events) trial will evaluate whether the addition of extended-release niacin to simvastatin will result in a cardiovascular risk reduction greater than expected due to the



degree of LDL lowering. Little data are available on the safety of extended-release niacin when added to high doses of simvastatin, atorvastatin, or rosuvastatin (59). The prescribing information for all 3 statins advises carefully weighing the benefit of further lipid alterations against the potential risk for combination therapy, especially with doses of niacin  $\geq 1$  g per day (8–10).

**Bile-acid binding agents.** The bile-acid binding agent, colestevam 2.3 to 3.8 g, lowers LDL by an additional 8% to 16% when added to statin monotherapy (60). Colestevam has several advantages over older bile-acid binding agents: fewer gastrointestinal side effects, minimal interference with the absorption of other drugs, and can be taken as 6 large tablets daily. Bile-acid binding agents are not systemically absorbed and therefore have no effect on muscle or liver. Bile-acid binding agents should be used with caution when triglyceride levels exceed 300 mg/dl since they can markedly exacerbate hypertriglyceridemia.

**Fibrates.** Fibrates are generally not considered effective LDL-lowering therapy and so should not be considered as add-on therapy for more aggressive LDL reduction. Addition of a fibrate could be considered in order to achieve more aggressive non-HDL goals and in those patients with severe hypertriglyceridemia ( $>500$  mg/dl) (38). Historically, however, fibrate combination therapy has been the greatest source of safety concerns for statin therapy. In the FDA's Adverse Event Reporting System database, 38% of all reported statin rhabdomyolysis cases occurred with statin + fibrate combinations, although the risk associated with gemfibrozil appears to be about 15 $\times$  higher than for fenofibrate when used with statins other than cerivastatin (20,34,61). Gemfibrozil has been shown to inhibit statin glucuronidation, a second pass effect for the hepatic metabolism of statins. Gemfibrozil is also an inhibitor of CYP P450 2C8, a major pathway for the metabolism of cerivastatin and other drugs such as pioglitazone and repaglinide. The net result is that gemfibrozil causes a 50% to 3-fold increase in statin areas under the curve, which most likely explains the increased propensity of the combination to cause myopathy (62). As statin doses escalate to achieve more aggressive LDL and non-HDL targets, combination with a fibrate will likely cause a multiplicative increase in the rate of myopathy. Fenofibrate does not affect statin glucuronidation or inhibit CYP 2C8 and may be a safer fibrate choice.

Data from approximately 1,000 subjects who received fenofibrate concomitantly with a statin in the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) trial suggest the combination does not significantly increase risk of myopathy in low-risk diabetic patients (63). The ongoing ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial will provide important insight into the additive cardiovascular risk reduction benefit and safety of fenofibrate when added to moderate-dose simvastatin therapy in a diabetic population.

Unfortunately, very little data are available for the combination of fenofibrate with the highest doses of statins, and

such therapy should be pursued only with extreme caution after establishing safety and efficacy at lower statin doses.

### Triple+ Drug Therapy

The average untreated LDL level for men with CHD is approximately 140 mg/dl (64). A 60% reduction in LDL, which could be achieved on average with ezetimibe 10 mg plus atorvastatin 80 mg or rosuvastatin 20 mg, would result in an LDL level of 84 mg/dl. About half of very high-risk patients would therefore need the addition of a third (or fourth) therapy to achieve the additional 17% reduction in LDL needed to reach the optional goal of 70 mg/dl. The safety of triple-drug combination therapy has been formally evaluated in only 1 randomized trial with a moderate dose of statin (65). Lovastatin 40 mg combined with niacin 200 mg and colestipol 20 g was evaluated in a cross-over trial in 29 middle-aged men with CHD. This regimen resulted in 54% to 60% reduction in LDL, depending on the niacin formulation. Only 21% of subjects reported the regimen was "very easy" to take, although 79% thought it was "fairly easy." The primary adverse effects were cutaneous, which were less when sustained release niacin formulations were used. No data on laboratory abnormalities or musculoskeletal complaints was reported. Low-density lipoprotein apheresis is the only other option for lowering LDL  $>65\%$  in CHD patients (66), although the vast majority of insurers currently limit reimbursement to those with LDL levels  $>200$  mg/dl despite maximal tolerated therapy.

### Conclusions

Since many patients with CHD or its equivalent will need a  $>50\%$  reduction in LDL to achieve the LDL goal  $<100$  mg/dl, it is reassuring that therapy with the highest doses of atorvastatin, simvastatin, and rosuvastatin appear to be well-tolerated in properly selected subjects. Low rates of serious musculoskeletal ( $<0.6\%$ ) or hepatic ( $<1.3\%$ ) adverse effects have occurred in randomized event trials with higher rates of persistent hepatic transaminase elevations occurring with atorvastatin 80 mg and higher rates of myopathy and rhabdomyolysis occurring with simvastatin 80 mg. Achievement of the more aggressive optional LDL goal  $<70$  mg/dl should be reserved for the very highest-risk patients who are most likely to experience benefit and least likely to experience toxicity. Although high-dose statin therapy or combination treatment will most likely be necessary to achieve an LDL level  $<70$  mg/dl, the long-term safety of other LDL, non-HDL, or triglyceride-lowering therapies added on to high-dose statin monotherapy has not been well established. Ezetimibe and colestevam appear unlikely to increase the risk of myopathy when used in combination with a high-dose statin; however, rates of hepatic enzyme elevation are slightly increased. Although the combination of niacin or fenofibrate with moderate-dose statins appears to be reasonably safe, the safety of combination with high-dose statins has yet to be deter-

mined. To enhance patient outcomes, clinicians need to be aware of specific patient characteristics, such as advancing age, gender, body mass index, diminished glomerular filtration rate, and other characteristics that predict muscle and hepatic statin toxicity, especially when considering the use of high-dose statin or combination therapy.

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## Safety of Aggressive Lipid Management

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