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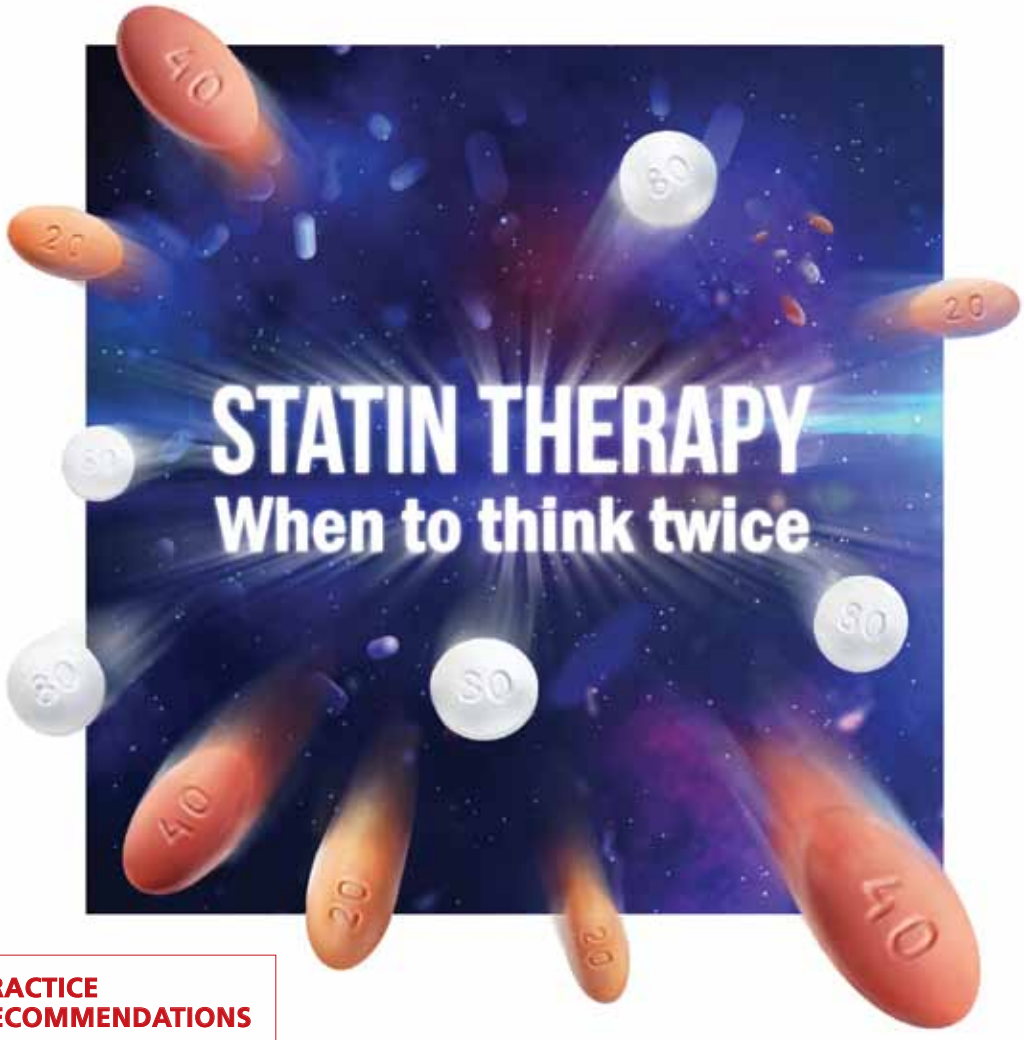

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PRACTICE RECOMMENDATIONS

› *Avoid adding niacin to statin therapy, as it does not appear to provide any added benefit and may increase the risk of stroke.* (B)

› *Continue statin therapy in a patient who has chronic kidney disease progressing to end-stage renal disease, but do not initiate it in patients on dialysis.* (B)

› *Do not add statins to the medication regimen of patients with heart failure; focus on optimizing therapies known to reduce mortality in this patient population instead.* (C)

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

While statins lower the risk of morbidity and mortality for millions of Americans, recent findings help clarify when a statin—or a statin and another lipid-lowering agent—is unlikely to help.

Morbidity and mortality from atherosclerotic disease have decreased significantly in the last several decades, in large part because of advances in therapies targeting serum lipids—including statins.[1] Since their introduction in 1987, HMG Coenzyme A inhibitors have been intensively studied, and their use has increased dramatically. A recent report from the National Center for Health Statistics reveals that in the years 1999 to 2002, 26% of men ages 65 to 74 years were taking statins; several years later (2005-2008), that number had soared to 50%. In the same time frame, statin use among women ages 65 to 74 went from 24% to 36%.[2]

Statins lower serum low-density lipoprotein cholesterol (LDL-C) and triglycerides, raise high-density lipoprotein cholesterol (HDL-C), and improve surrogate markers for

cardiovascular events. Most importantly, statins reduce the risk for major cardiovascular events, such as myocardial infarction (MI) and death from cardiovascular disease (CVD), in select populations. Yet doubts about the benefits of statins, alone or in combination with other lipid-lowering agents, for certain patient populations remain.

Primary care physicians need to know when, or whether, to add a second lipid-lowering agent to the drug regimen of patients whose response to a statin is less than hoped for, and which patient populations and clinical indicators statins have not been found to help. You'll find answers, the results of the latest studies, and details of the 2013 cholesterol guideline released last month by the American Heart Association/American College of Cardiology and in this evidence-based update.

A statin is not enough? Don't add these drugs

In patients with very elevated LDL-C or mixed dyslipidemias that fail to reach the desired lipid levels on statin monotherapy, other classes of lipid-modifying agents are often added in an attempt to improve clinical outcomes.[3] Fibrates, extended release (niacin, and n-3 polyunsaturated fatty acids have been frequently used for this purpose. But it is only in the last several years that large, well-designed studies have looked closely at patient-oriented outcomes associated with statins in combination with other lipid-modifying drugs.[4-9]

Fenofibrate + a statin yields little benefit

The ACCORD lipid placebo-controlled trial studied fenofibrate as a simvastatin add-on in patients with diabetes.[4] Its findings? While the lipid levels of patients receiving this drug combination improved significantly, the primary endpoint (MI, stroke, or death from cardiovascular causes) was no different from that of the controls, who were taking the statin alone.

Sub-group analysis suggested that the simvastatin-fenofibrate combination benefitted only one particular group: patients with high triglyceride levels (≥204 mg/dL) and low HDL-C (≤34 mg/dL). This finding prompted the US Food and Drug Administration to call for an additional clinical trial to evaluate the effectiveness of add-on therapy with fenofibrate in patients who meet this criteria.[10] The status of such a study is uncertain.

Adding niacin to a statin does more harm than good

The HATS trial, published in 2001, found the addition of niacin to a statin regimen to be beneficial.[7] But because of the wide confidence interval associated with the clinical endpoints and the small number of subjects (N=160) in that study, larger trials were needed to confirm the positive results. In fact, they found the opposite.

Niacin increases stroke risk. In both the AIM-HIGH[5] (N=3414) and HPS2-THRIVE[6] (N=25,673) trials, the addition of extended release niacin not only failed to reduce the risk of major cardiovascular events, it was shown to increase the risk of stroke.

n-3 polyunsaturated fatty acids don't help much

Studies evaluating the addition of n-3 polyunsaturated fatty acids to statin therapy have had mixed results. The JELIS[8] trial had more than 18,000 participants, 20% of whom had known coronary artery disease. All were taking statins and randomized to either open-label eicosapentaenoic acid (EPA) 600 mg 3 times daily or placebo. The primary endpoint, a composite of sudden cardiac death, fatal or nonfatal MI, unstable angina, angioplasty, and stenting or coronary artery bypass grafting, was lower in the intervention group: (2.8% vs 3.5%; number needed to treat [NNT]: 143).

It is important to note, however, that only one of the individual components of the primary endpoint—unstable angina—was significantly reduced by EPA (2.1% vs 1.6%; *P*=.014).[8] In the Alpha Omega trial,[9] various n-3 polyunsaturated fatty acids were tested in combination with statins. None was found to be superior to placebo in reducing cardiovascular outcomes.

Based on the evidence, the new cholesterol guideline does not support the routine use of these agents to reduce atherosclerotic CVD (See "The new cholesterol guideline: Beyond the headlines" on page 730.)[11]

CONTINUED

Among patients with heart failure, statin therapy substantially reduced LDL-C, but the time to death or hospitalization for cardiovascular causes was not significantly reduced.

Statins and kidney disease: Factors to consider

More than half of the deaths in patients with end-stage renal disease (ESRD) are from cardiovascular causes.[12] The relationship between renal dysfunction and cardiovascular events is independent of other risk factors, including a history of CVD. Risk rises with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2, with a sharp increase when the rate <45 mL/min/1.73m.^{2} Thus, strategies known to reduce major cardiovascular events in the general population, including statins, have the potential to offer substantial benefit for patients with chronic kidney disease (CKD).

Statin use in patients with CKD has been evaluated in post-hoc and subgroup analyses of large clinical trials and, more recently, in RCTs targeting patients with both moderate and end-stage disease (**TABLE**).[13-18]

Three post-hoc analyses of large multicenter, double-blind RCTs[13-15,19] compared patients with normal renal function with those with CKD. All 3 found that moderate or high-intensity statin therapy significantly reduced the incidence of the primary outcome—a composite of major cardiovascular events—compared with either placebo or a lower-intensity statin.

For patients with CKD, drug combo lowered the risk

The SHARP trial[17] (N=9270) was the first large prospective, double-blind, multicenter RCT to compare the effect of a statin plus a second lipid-lowering drug (simvastatin plus ezetimibe) vs placebo in patients with CKD. A third of the participants were on dialysis at the start of the trial (ESRD was defined as starting long-term dialysis or requiring kidney transplantation).

Patients in the intervention group were significantly (17%) less likely to experience a major atherosclerotic event compared with those on placebo. This translated into an NNT of 47 over a period of 4.9 years. (Since no group received only simvastatin, it is not known what role ezetimibe had in the reduction of cardiovascular events.) Although no difference in outcomes was found when the results were stratified based on whether participants were on dialysis, this trial was not adequately powered for this subgroup analysis.[17]

Little benefit from statins in patients with end-stage disease

Two major prospective randomized, double-blinded, placebo-controlled, multicenter trials evaluating the effects of statin use on cardiovascular outcomes in ESRD patients on dialysis have been published.[18,19] Both found a significant decline in LDL-C in patients receiving statin therapy. But neither found a significant difference in mortality rates in the statin vs placebo groups.

One group of researchers speculated that the lack of effect may be due to a difference in the pathogenesis of vascular events in patients with and without ESRD. Delayed use of statins until patients have ESRD will offer limited benefit, they concluded, and recommended against routine statin treatment in an attempt to reduce the incidence of CVD in this patient population.[18] Based on these results, the new cholesterol guideline indicates that this group of patients may not benefit from statin therapy.

For patients with heart failure, statins offer limited benefit

More than half of the heart failure (HF) in the United States is caused by ischemic heart disease.[20] Improvements in post-MI survival have increased the prevalence of chronic HF.

Statins have a well-established role in the prevention and treatment of atherosclerosis because of their ability to modify the natural course of the disease and reduce major adverse cardiovascular events. Thus, it seems reasonable to assume that, in patients who have or are at high risk for coronary heart disease, statins would help to prevent the occurrence or slow the progression of HF.

Early studies of statins either excluded patients with HF or enrolled so few HF patients that no conclusions could be reached regarding the safety or efficacy of statin use in this population.[21-25] More recently, 2 large RCTs have studied the effect of statins in patients with HF. Both have found them to be ineffective.[26,27]

The CORONA trial enrolled elderly patients with HF of ischemic causes and ejection fraction ≤40% (≤35% in patients with

TABLE

Statins for patients with chronic kidney disease: A look at cardiovascular outcomes

Study	Type	Study population/ purpose (N)	Intervention(s)	Renal function	Primary endpoint	HR (95% CI)
PPP[13]	Subgroup analysis of 3 RCTs	Men and women with or without CAD, divided into 3 groups based on renal function (19,700)	Pravastatin 40 mg/d	Normal Mild reduction* Moderate reduction†	Death from CHD or nonfatal myocardial or coronary revascularization	Normal RF: 0.77 (0.6-0.86) Mild reduction of RF: 0.76 (0.7-0.83) Moderate reduction of RF: 0.78 (0.65-0.94)
TNT- post hoc[14]	Subgroup analysis of 1 RCT	Men and women/ secondary prevention (9656)	Atorvastatin 10 mg/d or 80 mg/d	eGFR <60 mL/min/1.73 m^2	Death from CHD, nonfatal MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke	0.68 (0.55-0.84)
CARDS – post hoc[15]	Post hoc subgroup analysis of 1 RCT	Men and women with Type 2 diabetes/ primary prevention (2838)	Atorvastatin 10 mg/d	eGFR <60 mL/min/1.73 m^2	First MI, unstable angina, death from CHD, resuscitated after cardiac arrest, coronary revascularization, or stroke	0.58 (0.36-0.96)
SHARP[16]	RCT	Men and women with CKD (9270)	Simvastatin 20 mg/d or simvastatin 20 mg plus ezetimibe 10 mg/d	Serum creatinine ≥1.7 mg/dL in men and ≥1.5 mg/dL in women	Nonfatal MI or death from CHD, nonhemorrhagic stroke, or arterial revascularization‡	0.83§ (0.74-0.94)
4D[17]	RCT	Men and women with Type 2 diabetes on hemodialysis <2 y (1255)	Atorvastatin 20 mg/d	ESRD	Death from cardiac causes, nonfatal MI, fatal or nonfatal stroke	0.92 (0.77-1.10)
AURORA[18]	RCT	Men and women on hemodialysis ≥3 mo (2776)	Rosuvastatin 10 mg/d	ESRD	Death from cardiac causes, nonfatal MI, or nonfatal stroke	0.96 (0.84-1.11)

*Mild reduction=eGFR 60-89.99 ml/min/1.73 m^2. †Moderate reduction=eGFR 30-59.99 ml/min/1.73 m^2. ‡Excluding dialysis access procedures.

§ Reported as a risk ratio.

AURORA, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events; CAD, coronary artery disease; CARDS, Collaborative Atorvastatin Diabetes Study; CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; 4D, Die Deutsche Diabetes Dialyse Studie; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio; MI, myocardial infarction; PPP, Prospective Pravastatin Pooling; RCT, randomized controlled trial; SHARP, Study of Heart and Renal Protection; RF, renal function; TNT, Treating to New Target.

New York Heart Association [NYHA] Class II), randomized to either rosuvastatin 10 mg/d or placebo.[25] More than 40% of the participants had a history of MI, and more than 60% were NYHA Class III or IV. HF medications were well-managed; more than 90% of the patients were being treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; 75%, with beta-blockers; and 39%, with aldosterone antagonists.

The researchers found no significant difference between the rosuvastatin and placebo groups in the primary outcome of death from cardiovascular causes, nonfatal

The new cholesterol guideline: Beyond the headlines

Helen Lippman, MA, Managing Editor, The Journal of Family Practice

When the American Heart Association/American College of Cardiology (AHA/ACC) released the new cholesterol guideline last month—the first since a 2004 update—headlines like "Millions more to take statins" and "Doctors urge much wider use of statins" abounded.

Within a day, controversy erupted and was synthesized in a *New York Times* op-ed titled "Don't give more patients statins."[1] The authors—the editor of *JAMA Internal Medicine* and the author of "Overdosed America: The Broken Promise of American Medicine" (HarperCollins; 2004)—wrote that expanding the definition of who should take the drugs "will increase the number of healthy people for whom statins are recommended by nearly 70%."[1]

For its part, the ACC does indeed expect prescribing habits to change, and it stands by the guideline that may advance that change. "I would expect that the number of patients placed on statins will increase because the guideline has focused on the identification of additional groups at risk," John G. Harold, MD, president of the ACC, told *The Journal of Family Practice*. African Americans and women—among other variables—are included in a "global risk assessment," Dr. Harold said. And, for the first time, the guideline addresses the risk of stroke as well as heart disease.

The AHA/ACC guideline shifts the focus away from specific cholesterol targets and defines 4 groups for whom statin therapy is recommended:

- Patients who already have cardiovascular disease (CVD)
- Patients who have Type 2 diabetes and are between the ages of 40 and 75 years
- Patients who have extremely high LDL-C (≥190 mg/dL), typically because of genetic factors
- Individuals between the ages of 40 and 75 who have a 10-year risk of CVD ≥7.5%, based on the guideline's risk calculator.

It is the last criterion that has generated the most controversy. Notably, it represents a departure from the previous guideline, which recommended statins for those with a 10-year risk of CVD of 10% to 20%. The authors of *The New York Times* article see that shift as a big mistake. For people whose 10-year risk is less than 20%, they contend, "statins not only fail to reduce the risk of death, but also fail even to reduce the risk of serious illness."[1]

Questions of the validity of the risk calculator itself have been raised, as well. Two Harvard researchers tested it on participants in long-running studies and reported that it overestimates risk, sometimes by 75% to 150%.[2] And Steven Nissen, MD, a past president of the ACC, entered his own figures—and found that simply being a male age 60 or older could put a patient into a group for whom statins are recommended. "Something is terribly wrong," he told a *Times* reporter.[3]

Dr. Harold points out, however, that the risk calculator is not meant to be used in isolation. It really is intended to follow a doctor-patient discussion of individual risks that includes things like salt intake, smoking, obesity, and exercise, he said, so the patient can see the difference such variables can make."Within this context, statins become part of the armamentarium used to fight heart disease, which still kills one in 3 Americans," Dr. Harold said.

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MI, or nonfatal stroke (11.4% in the rosuvastatin group vs 12.3% among those on placebo; 95% confidence interval, 0.83-1.02; *P*=.12). No difference was found in patients with a history of MI (13.9% placebo event rate vs 12.7% rosuvastatin arm; *P*=not significant [NS]). Neither death from worsening HF nor sudden death was reduced.[26]

There were fewer hospitalizations among those taking rosuvastatin, however (NNT=17 per year). And there was a trend towards a benefit among those with more advanced HF (NYHA III/IV), with primary outcome rates of 12.7% for those in the rosuvastatin group vs 14.2% in the placebo group. (*P*=NS). Rosuvastatin was safe for HF patients, as most types of adverse events were more common in the placebo group. Assessments of muscle toxicity were similar in both groups.

The GISSI-HF study, another RCT of rosuvastatin vs placebo in HF patients, also showed a lack of benefit from statin treatment.[27] Researchers enrolled more than 4500 patients with NYHA Class II to IV HF, from both ischemic and nonischemic causes.[26] Similar to the findings in the CORONA trial,

LDL-C was substantially reduced by rosuvastatin 10 mg/d (-32% vs no change for those in the placebo group), but this did not translate into clinically relevant endpoints. After 3.9 years of therapy, the primary endpoints of time to death and time to death or hospitalization for cardiovascular causes were not significantly reduced, nor were any of the secondary endpoints.[26]

The similar lack of benefit in these 2 trials is striking in view of the benefit of statins in patients with coronary heart disease but without HF. Given these findings, focusing on optimizing therapies known to reduce mortality in patients with HF rather than adding a statin in an attempt to alter the atherosclerotic process appears to be a better approach. Thus, the recently published cholesterol guideline does not advocate the initiation or continuation of statin therapy in patients with NYHA Class II-IV HF. JFP

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"We think it is important that primary care as well as specialty organizations be included in guideline development so that special interests do not interfere with good science."
—Jeff Cain, MD
Board chair, AAFP

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