

Statin selection has just become more complicated. Will physicians be diverted from interventions that may be less costly and just as effective?

Statin Therapy: More Than Meets the Eye?

By Jack McCain
Contributing Editor

When Gertrude Stein famously wrote, “Rose is a rose is a rose is a rose,” she seemed to reveal an ignorance of, if not contempt for, the flowers. After all, any gardener knows some roses look like flabby cabbages and others sport flesh-ripping thorns. Do physicians, MCOs, and PBMs who act as though “statin is a statin is a statin is a statin” display a similarly uncritical attitude toward the drugs — and unwittingly show a certain disregard for their patients? Or are statins (and roses) really rather more similar than not?

Back in the early days of statin therapy, circa 1990, the notion of reducing the risk of morbidity and mortality from heart disease by lowering levels of cholesterol was still greeted with some skepticism. Cholesterol, after all, is a component of every human cell. It was thought that overly aggressive cholesterol reduction might trigger cancer or some kind of central nervous disorder. But since then several large clinical trials (See “Major statin trials” on page 41) seem to have established the overall safety and clinical value of statins. Their best-known effect is reducing the amount of cholesterol carried by low-density lipoprotein (LDL), thereby preventing the accumulation of LDL cholesterol (LDL-c) in atherosclerotic plaque.

Today, LDL-c reduction is well accepted as a means of reducing cardiovascular risk, and the manufacturers of a half dozen statins vie for the attention of physicians, patients, and P&T committees — and a chunk of the \$13.5 billion U.S. statin market. The entire market is supported by guidelines issued by the National Cholesterol Education Program (NCEP), which recommends statin therapy for patients at risk for coronary heart disease (CHD), and which physicians ignore at their legal peril. Armed with scientific studies — plus plenty of marketing savvy — each statin manufacturer seeks to demonstrate why its product should be preferred over the competition. If you haven’t yet heard presentations about the effects

of statins on high-density lipoprotein cholesterol (HDL-c) and inflammation, as measured by high-sensitivity C-reactive protein (hs-CRP), you soon will.

At the same time, all the statin manufacturers keep looking over their shoulder for the coming of the next blockbuster in cardiovascular drug therapy. It probably won’t be yet another statin, but it might be one or more products that improve levels of HDL-c. HDL is best known for its ability to transport cholesterol away from peripheral tissues, thereby reducing the cholesterol burden in atherosclerotic plaque.

Apolipoprotein A-I Milano

This past November, the Cleveland Clinic cardiologist Steven Nissen, MD, commanded a considerable amount of attention from the news media, owing to his recent work in these two areas — traditional statin therapy and novel HDL therapy.

First came the publication in *JAMA* of what Nissen dubbed his “Drano” study — a new method for rapidly reducing the atherosclerotic burden via infusions of a recombinant form of HDL. This agent, ETC-216, was developed by Esperion Therapeutics, a company specializing in novel HDL-based treatments. It is a naturally occurring variant of apolipoprotein A-I (apo A-I), which characterizes HDL. The variant was discovered among residents of a small village in northern Italy and hence has been named apo A-I Milano. Carriers have low levels of HDL-c, and low levels of atherosclerosis. In Nissen’s small study (N=47), images produced via intravascular ultrasound (IVUS) showed that the volume of atheroma was decreased in the patients who received ETC-216, whereas the atheroma volume was unchanged in patients receiving placebo. That is, ETC-216 caused regression of the atherosclerotic burden; whether that translates into improved clinical outcomes remains to be seen.

Further drama

Days later, Nissen was the center of attention again, this time as the result of a presentation at the American Heart Association’s annual scientific sessions with the results of his REVERSAL study.

TABLE 1 Major statin trials

Study Acronym	Statin	Year Published	Journal	Type of Study	Patients Enrolled	Principal Findings
4S	Simvastatin 10–40 mg	1994	<i>Lancet</i>	Secondary prevention	N = 4444 (81% male), with history of CHD (angina or MI) (TC mean, mg/dL; LDL-c mean, mg/dL)	<ul style="list-style-type: none"> • 30% reduction in relative risk of total mortality • 42% reduction in relative risk of coronary death • 35% reduction in LDL-c
WOSCOPS	Pravastatin 40 mg	1995	<i>New England Journal of Medicine</i>	Primary prevention	N = 6595 (100% male), with moderate hypercholesterolemia (TC mean, 272 mg/dL; LDL-c mean, 192 mg/dL)	<ul style="list-style-type: none"> • 31% reduction in relative risk of nonfatal MI or CHD death • 28% reduction in CHD death not statistically significant ($P=0.13$) • 26% reduction in LDL-c
CARE	Pravastatin 40 mg	1996	<i>New England Journal of Medicine</i>	Secondary prevention	N = 4159 (86% male), with history of MI and "average" lipid levels (TC mean, 209 mg/dL; LDL-c mean, 139 mg/dL)	<ul style="list-style-type: none"> • 24% reduction in relative risk of CHD death or MI • 28% reduction in LDL-c
AFCAPS/ TexCAPS	Lovastatin 20–40 mg	1998	<i>JAMA</i>	Primary prevention	N = 6605 (85% male), with average TC (mean, 221 mg/dL) and LDL-c (mean, 150 mg/dL) and below-average HDL-c (mean, 37 mg/dL)	<ul style="list-style-type: none"> • 37% reduction in relative risk of first acute major coronary event • No mortality benefit demonstrated • 25% reduction in LDL-c
LIPID	Pravastatin 40 mg	1998	<i>New England Journal of Medicine</i>	Secondary prevention	N = 9014 (83% male), with history of CHD and broad range of lipid levels (TC mean, 218 mg/dL; LDL-c mean, 150 mg/dL)	<ul style="list-style-type: none"> • 24% reduction in relative risk of CHD death • 25% reduction in LDL-c
HPS	Simvastatin 40 mg	2002	<i>Lancet</i>	High-risk patients; secondary, 35%	N = 20536 (75% male), with coronary disease, other occlusive arterial disease, or diabetes and TC >135 mg/dL	<ul style="list-style-type: none"> • 27% reduction in relative risk of major coronary event • 35% reduction in LDL-c
ASCOT-LLA	Atorvastatin 10 mg	2003	<i>Lancet</i>	High-risk patients; primary prevention	N = 10305 (81% male), without known CHD but with hypertension, ≥ 3 other CHD risk factors, and TC ≤ 250 mg/dL	<ul style="list-style-type: none"> • Trial stopped early because of benefit in atorvastatin arm • 36% reduction in nonfatal MI or CHD death • 33% reduction in LDL-c

AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm; CARE, Cholesterol and Recurrent Events; HPS, Heart Protection Study; LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease; 4S, Scandinavian Simvastatin Survival Study; WOSCOPS, West of Scotland Coronary Prevention Study.

REVERSAL pitted the highest marketed dosage of Lipitor (atorvastatin), 80 mg, against the highest dosage of Pravachol (pravastatin) then available, 40 mg. The study showed not only that high-dose Lipitor reduced LDL-c to a greater extent than high-dose Pravachol, but also that Lipitor brought the buildup of atherosclerotic plaque to a complete halt, unlike Pravachol. REVERSAL seemed to add to Lipitor's luster, helping to justify its lofty perch high atop the U.S. pharmaceutical market. But what the study didn't show, because it wasn't large enough or long enough, was whether Lipitor has any advantage over Pravachol in terms of the things that really matter — reducing the risk of mortality and morbidity from cardiovascular disease. That's why physicians prescribe statins and why patients take them, after all: to stave off heart attacks and, ultimately, death. Clearly, with U.S. physicians dispensing about 70 million prescriptions annually for Lipitor (more than twice as many as for Zocor, the second-leading statin), an awful lot of physicians already have been sold on Lipitor's value. Their acceptance of the product translates into annual U.S. sales exceeding \$6 billion for the past two years (See "U.S. statin sales since 1998" below).

Leap of faith

Physicians have made a certain leap of faith when they prescribe Lipitor. Well before the results of ASCOT-LLA became available, physicians had posited a "class effect" holding that the mortality and morbidity benefits demonstrated by pravastatin, simvastatin, and lovastatin in the major statin trials (table on page 41) would extend to other members of the class that lack such an evidence base. In other words, a statin *is* a statin is a statin.

"A lot of clinicians prescribe statins on the basis of the class effect," says Thom Schoenwaelder, managed care practice leader at IMS Health. "Physicians tend to be empirical and extrapolate from clinical trial data."

From this perspective, statins exert their primary effect on LDL-c, though to differing degrees, while also favorably affecting levels of HDL-c and triglycerides to more or less the same degree. So if a given statin is powerful enough, in terms of LDL-c reduction, the only meaningful variable is price.

Of course, when the safety problems with Baycol (cerivastatin) emerged a few years ago, manufacturers of the other

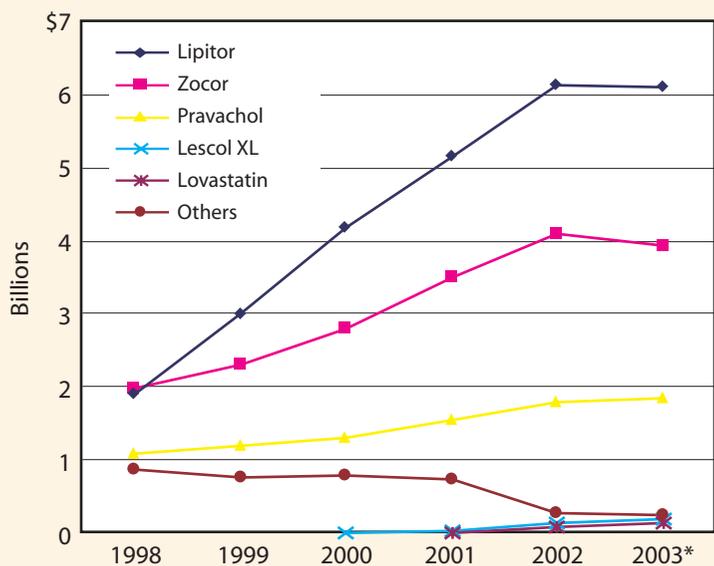
statins scrambled to point out how their products differed from cerivastatin. The newcomer Crestor is saddled with some of Baycol's baggage, too, and is being approached with a certain level of caution.

The Baycol problem notwithstanding, the other statins are widely accepted as very safe and well tolerated — more so, some say, than aspirin. And if statins were as inexpensive as aspirin, MCOs wouldn't be concerned about them. But statins aren't inexpensive, not at all. The class doesn't generate over \$13 billion in annual U.S. sales because a statin costs mere pennies a day. Even generic lovastatin costs about \$1 a day. Branded products are twice or thrice that amount.

Statin marketing strategy

Merck's Mevacor (lovastatin) was the first statin to be marketed in the United States. For four years, Mevacor had the class to itself. Because of the concerns that too much cholesterol reduction could be harmful, some thought that any gain in lives saved by reducing atherosclerotic mortality through statin therapy might be offset by an increase in deaths from noncoronary causes. Indeed, the primary endpoint in the first big statin trial, was total mortality, and the investigators watched closely for any hint of increased non-CHD mortality associated with simvastatin therapy. None was found. Likewise, the

FIGURE 1 U.S. statin sales since 1998



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investigators in the next two large statin studies, WOSCOPS and CARE, were alert for any excess of deaths from noncardiovascular causes, but pravastatin also emerged untainted. These reports increased the comfort level for physicians prescribing the four statins available then (Mevacor, Pravachol, Zocor, and Lescol).

Before Lescol (fluvastatin) was introduced as the fourth statin, the main competition was between Bristol-Myers Squibb's Pravachol and Merck's second statin, Zocor, which is more powerful than Mevacor in terms of LDL reduction. Launched a few months before Zocor, Pravachol was priced slightly below Mevacor. Merck's marketing strategy was to shift Mevacor prescribers over to Zocor to avoid having its own products competing with each other. Lescol couldn't claim greater efficacy, so it was promoted on the basis of a considerably lower price than the competition. So was Baycol, during its brief stay. Indeed, a news release heralding its launch touted Baycol as being "competitively priced," providing "particular value," and being "affordable." To drive home the point, the press release even provided the AWP for Baycol (0.3 mg, \$1.32) and the most commonly prescribed doses of the other statins (Lescol 20 mg, \$1.25; Lipitor 10 mg, \$1.82; Pravachol 20 mg, \$2.06; Zocor 10 mg, \$2.10; Mevacor 20 mg, \$2.33; Zocor 20 mg, \$3.66). Bear in mind that PBMs often negotiate steep discounts for products.

Lipitor's position in this list shows how an attractive price was important to the marketing strategy when it was launched. Being priced lower than Pravachol and Zocor, Lipitor captured market share rapidly on the strength of its superior efficacy in LDL-c reduction, and Pfizer also pointed to Lipitor's indication for triglyceride reduction.

Most recently comes AstraZeneca's attempt, a so-called "super" statin, Crestor, which is being portrayed as more powerful than Lipitor and hence able to get more patients to their LDL-c goals at the starting dose. Crestor also is said to improve HDL-c levels across its dose range, unlike Lipitor. To make it easier for physicians to embrace the newest statin, Crestor was introduced with flat pricing — with a price of \$2.62 for a tablet of any strength (5, 10, 20, or 40 mg). That is a little more than the \$2.47 list price for Lipitor 10 mg — but well below the \$3.64 for Lipitor 20 mg, 40 mg, or 80 mg. So if patients start on Lipitor 10 mg but end up on a higher dosage, they end up paying more overall for Lipitor than they would for Crestor. And if Crestor 10 mg and Lipitor 20 mg produce essentially the same amount of LDL-c reduction, why bother with the more expensive Lipitor? (Crestor looks even more favorable, price-wise, when compared with the costlier, and less efficacious, Zocor and Pravachol.)

REVERSAL data set the stage

That's why a study like REVERSAL could be important for Lipitor, from a marketing perspective. It's not that Pfizer needs to put any more distance between Lipitor and Pravachol. Rather, REVERSAL, and the recently released PROVE-IT findings (see "PROVE-IT proves ... what?" page 45) suggest there might be something special about Lipitor, something that distinguishes it from Pravachol, renowned for its solid evidence base (the WOSCOPS, CARE, and LIPID trials) — and that presumably distinguishes it from the new challenger, Crestor, too. Physicians who swear by evidence-based medicine probably won't be lured away from Pravachol or Zocor just yet, but Lipitor prescribers considering a switch to Crestor might be very interested in REVERSAL.

REVERSAL enrolled 654 patients with symptomatic coronary artery disease, documented with angiography showing stenosis greater than 20 percent. IVUS was used to make an image of a section of a target artery, 30 mm or more long. Patients were randomly selected to undergo 18 months of treatment with pravastatin 40 mg or atorvastatin 80 mg, after which IVUS images were produced again for the subjects remaining for follow-up. In the pravastatin group, the atheroma volume increased by 2.7 percent, while in the atorvastatin group it was essentially unchanged, decreasing by 0.4 percent. As would have been expected on the basis of the drugs' performance in clinical trials, these changes were accompanied by statistically significantly greater reductions in LDL-c and triglycerides in the atorvastatin group (See "Changes in lipid and hs-CRP levels in REVERSAL and PROVE-IT" page 44).

It would be tempting to attribute the changes in atheroma volume in REVERSAL to the substantial differences in LDL-c reduction (46 percent in the atorvastatin group vs 25 percent in the pravastatin group), but at least two other findings complicate the situation. First, a post-hoc analysis showed that 67 percent of the pravastatin group achieved an LDL-c level well below their goal of 100 mg/dL, per the NCEP guidelines — a mean LDL-c concentration of 88 mg/dL, nearly as low as the mean level achieved in the atorvastatin group. Nevertheless, atherosclerotic progression was observed in this pravastatin subgroup, too.

The second finding, which may explain the first, is that levels of hs-CRP were reduced considerably more in the atorvastatin group than in the pravastatin group — 36 percent versus 5 percent. Atherosclerosis is widely regarded as a disease of inflammation, of which hs-CRP is a measure; the high-sensitivity assay detects CRP at sub-clinical levels far below those associated with infection and inflammation. So if some property

of atorvastatin quiets inflammation in arterial walls, the reduction in inflammation could make atherosclerotic plaque less prone to rupture, which in turn could reduce the risk of morbidity and mortality, independently of atorvastatin's effects on LDL-c.

But that's not necessarily bad news for Crestor. Because if an anti-inflammatory effect proves to be a key to Lipitor's continued success, REVERSAL just might be making Crestor's path a little smoother. That's because AstraZeneca has a large trial in progress, JUPITER, designed to study the effects of Crestor in a population of patients with elevated hs-CRP.

JUPITER stands for "Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin." But it's a big trial, enrolling 15,000 patients, and it's an outcomes trial comparable to those that established the utility of statins. Patients will be randomized to Crestor 20 mg or placebo and followed for about three or four years (until the requisite number of cardiovascular events occur). The primary outcome is a composite of cardiovascular events (MI, stroke, hospitalization for unstable angina, coronary revascularization, or cardiovascular death). To qualify, patients must have no history of CAD, an LDL-c level below 130 mg/dL (i.e., meeting

the current NCEP goal), and have an hs-CRP level greater than 2 mg/L. So, unlike the REVERSAL population, the JUPITER population is essentially healthy from a cardiovascular perspective (it would be unethical to conduct a placebo-controlled statin trial if they were not), but they have a slight elevation in their hs-CRP suggestive of a budding problem.

If JUPITER shows a substantial reduction in cardiovascular events in the Crestor group, Crestor could get a big marketing boost. It seems to need one; at the beginning of January, Crestor accounted for 4.0 percent of new prescriptions for statins, down from 4.2 and 4.3 percent during the last two weeks of December and disappointing analysts' expectation that the newest statin would gain at least 5 percent of market share by the end of 2003 as it headed toward eventually acquiring perhaps 20 percent of the statin market.

Paul Thompson, MD, a nationally known dyslipidemia expert who directs the preventive cardiology program and cardiovascular research at Hartford Hospital in Connecticut, says it's virtually guaranteed that JUPITER will show positive results for Crestor — but not necessarily because of its effects on hs-CRP. LDL-c is inflammatory in its own right, so an agent that's as powerful at LDL-c reduction as Crestor

TABLE 3 Changes in lipid and hs-CRP levels in REVERSAL and PROVE-IT

	REVERSAL (mean values)			PROVE-IT (median values)		
	Pravastatin 40 mg (n=249)	Atorvastatin 80 mg (n=253)	P value	Pravastatin 40 mg (n=2063)	Atorvastatin 80 mg (n=2099)	P value
Baseline TC, mg/dL	232.6	231.8	0.80	180	181	NA
Final TC, mg/dL	187.5	151.3	<0.001	NA	NA	NA
Percent change, TC	-18.4%	-34.1%		NA	NA	
Baseline LDL, mg/dL	150.2	150.2	0.99	106	106	NA
Final LDL, mg/dL	110.4	78.9	<0.001	95	62	P<0.001
Percent change, LDL	-25.2%	-46.3%		-10.4%	-41.5%	
Baseline HDL, mg/dL	42.9	42.3	0.51	39	38	NA
Final HDL, mg/dL	44.6	43.1	0.06	42.1*	40.5*	P<0.001
Percent change, HDL	5.6%	2.9%		8.1%	6.5%	
Baseline triglycerides, mg/dL	197.7	197.2	0.96	154	158	NA
Final triglycerides, mg/dL	165.8	148.4	<0.001	NA	NA	NA
Percent change, triglycerides	-6.8%	-20.0%		NA	NA	
Baseline hs-CRP, mg/L	3.0	2.8	0.46	12.3	12.3	NA
Final hs-CRP, mg/L	2.9	1.8	P<0.001	2.1	1.3	P<0.001
Percent change, hs-CRP	-5.2%	-36.4%		-82.9%*	-89.4%*	

*Calculated from published values.

NA = not available.

Sources: Nissen 2004, Cannon 2004.

PROVE-IT Proves ... What?

It was a rough winter for the folks at Bristol-Myers Squibb, at least for those on the Pravachol team. First came the Pfizer-sponsored REVERSAL study (discussed in the main text). Then came PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy — Thrombolysis in Myocardial Infarction), sponsored by Bristol-Myers itself. Using the same dosages of Pravachol and Lipitor as were used in REVERSAL, PROVE-IT was intended to show that Pravachol is not inferior to Lipitor in patients with acute coronary syndromes (ACS) — unstable angina or MI. A modest-enough goal, it seemed. But that's not how things worked out. Much to Bristol-Myers's dismay, its own study showed that, in this patient population, Lipitor 80 mg was more efficacious than Pravachol 40. Worse still, the benefit was expressed in terms of clinical events: a 16 percent relative reduction in the risk of a major cardiovascular event or death from any cause after 2 years. The absolute rates of these events were 26.3 percent in the Pravachol group and 22.4 percent in the Lipitor group.

The results of PROVE-IT were announced at the meeting of the American College of Cardiology in March. Because of that, the *New England Journal of Medicine* made its article about the study available electronically, a month ahead of print, along with an editorial about the importance of the study. It made big news in the *New York Times* (headline: "Study Targets Should Be Set Far Lower, Study Finds") and the *Wall Street Journal* (headline: "For Bristol-Myers, Challenging Pfizer Was a Big Mistake"), and the *Times* even saw fit to opine editorially about how PROVE-IT "could certainly presage a significant change in the way heart disease patients are treated."

But does it really? Who stands to

benefit from PROVE-IT (with respect to patients, not drug companies)? Well, among patients meeting the entry criteria for this study, the clear winners would be patients aged less than 65 years old, those whose LDL-c levels were 125 mg/dL or higher to begin with, and patients who were not already receiving statin therapy (see 2-Year Event Rates, pg 47).

Put the other way, PROVE-IT did not show any substantial benefit of treatment with Lipitor 80 mg compared with Pravachol 40 mg for patients aged 65 or older, for patients already on statin therapy, or for patients whose LDL-c already was less than 125 mg/dL.

The 1,049 patients who previously had received statin therapy accounted for 25 percent of the study

If you already have a lot of members on a statin, PROVE-IT doesn't have a lot of applicability to your managed care organization.

population. Baseline LDL-c values were available for 990 of these patients. They deserve a closer look. Among those assigned to the Pravachol 40 mg group, their LDL-c levels remained essentially unchanged. Among those assigned to Lipitor 80 mg, LDL-c levels decreased by an additional 32 percent. But this additional 32 percent reduction provided virtually no additional clinical benefit. That is, if patients already were receiving a statin, providing those patients with Lipitor 80 mg was not more advantageous than keeping them on their previous statin.

The article doesn't say what the previous statins and their dosages were, but it says what they were not — and they were not Lipitor 80 mg (or 80 mg of any statin). So, at the most, these 1,049 patients had been taking Zocor 40 mg, Pravachol 40 mg, Lipitor 40 mg. So the overall find-

ing that LDL-c levels of 62 mg/dL were achieved in the Lipitor 80 mg group, compared with 95 mg/dL in the Pravachol group, does not speak to patients who already were taking a moderate dose of a statin (or to those whose LDL-c initially was less than 125 mg/dL). Rather than supporting the use of aggressive lipid-lowering to get LDL-c levels as low as possible, PROVE-IT (supported by the pooled results of LIPID and CARE) just as easily could be interpreted as demonstrating importance of reducing LDL-c to below 125 mg/dL.

Now, as noted, only 25 percent of this population was taking a statin to start with, but you might like to think, on the basis of their baseline characteristics, that had they been enrolled in your MCO, a higher per-

centage would have been on a statin. That's because about 37 percent were current smokers, about 50 percent had hypertension, the majority were men over the age of 45, and median HDL-c levels were less than 40 mg/dL — all major risk factors that could warrant lipid-lowering drug therapy if their 10-year CHD risk exceeded 20 percent, per the NCEP guidelines.

So if you already have a lot of your members on a statin, PROVE-IT doesn't have a lot of applicability to your MCO. Neither does it have a lot of applicability to the population at-large who experience heart attacks, John Abramson, MD, former head of family practice at Lahey Clinic in Massachusetts, points out.

In general, only about 1/3 of people who suffer MIs are under the age of 65 (vs 70 percent in PROVE-IT), and about 2/3 of MI patients have

PROVE-IT Proves ... What?

LDL-c levels above 125 mg/dL. So, simple arithmetic shows that about 2/9 of the MI population would meet these criteria.

Also, the study reported that 37 percent of the subjects were *current* smokers. However, risk reduction in terms of smoking status was reported in terms of *prior* smoking. Abramson thinks it would have been interesting to see risk reduction reported with respect to current smoking status. That's because quitting smoking, in and of itself, after an MI has been shown to reduce the risk of death by 46 percent, according to a meta-analysis published in 2000 in *Annals of Internal Medicine*. That's a relative risk reduction that compares quite favorably with those reported in PROVE-IT and which can be

achieved for considerably less cost than would be associated with intensive statin therapy.

If PROVE-IT has persuaded you to use drug therapy to reduce LDL-c as much as possible, Lipitor 80 mg isn't the only way to get there. Given that Lipitor reached its current lofty perch when people extrapolated from the outcomes studies conducted by Merck and Bristol-Myers, it would be only fair for people to use PROVE-IT to justify the use of, say, Crestor 40 mg or the new product combining Zocor and Zetia to achieve similar LDL-c reductions.

"In a population younger than 65, which describes 70 percent of the PROVE-IT subjects, lifestyle plays a huge role in patient's CHD risk," Abramson says. But he is concerned that all the media attention given to

studies like PROVE-IT focuses MCOs' and physicians' efforts to prevent heart disease primarily on choosing between different drug regimens.

He advises that preventive interventions ought to proportionately reflect the benefit shown by our best scientific evidence: regular exercise, smoking cessation, a healthy Mediterranean-style diet with minimal trans (partially hydrogenated) fats, proper body weight, and addressing feelings of anxiety and anger.

Each one of these interventions individually has the potential to be at least as effective at preventing heart disease as statin therapy. Together they can decrease the risk of heart disease by 80 to 90 percent. "This is the real breakthrough in helping our patients," says Abramson.

would be expected to differentiate itself from placebo. "The real question," Thompson says, "is should hs-CRP be used to decide whether or not to start a statin?" But JUPITER will provide no answer because it lacks an arm populated by patients with low hs-CRP. "JUPITER is primarily a marketing trial because it will almost certainly be positive," Thompson says.

CRP purportedly stronger predictor

Much of the theoretical foundation for JUPITER rests on the Women's Health Study, in which 27,939 healthy women were followed for a mean of eight years. It was found that, after adjustment for various risk factors, the relative risk of a first cardiovascular event among women who were in the highest quintile for CRP (greater than 4.19 mg/L) was 2.3 times that of women in the lowest CRP quintile (less than 0.49 mg/L). In contrast, the risk-adjusted relative risk of women in the highest LDL-c quintile (greater than 154 mg/dL) was only 1.5 times greater than the risk for women in the lowest LDL-c quintile (less than 98 mg/dL). This confirmed an observation from previous studies — that CRP is a stronger predictor of cardiovascular events than LDL-c.

The results were published in the *New England Journal of Medicine*. But when John Abramson, MD, former head of the family practice department at Lahey Clinic in Massachusetts, took a closer look at the study, he was dismayed by what he found. He noticed that the article discussed relative risk at length,

but failed to present the *absolute risk* of elevated CRP levels (the only mention of absolute risk was unadjusted risk in comparison to LDL-c levels, not the absolute risk of elevated CRP levels by themselves). Absolute risk, of course, is critical for evaluating the clinical importance of the results of any study that shows a change in risk. This oversight apparently escaped notice of the journal's editors and its peer reviewers, along with writers and editors at the *Times* and most other outlets.

Making the best of meager information, Abramson did his own calculations to assess the difference in absolute risk between the highest and lowest CRP quintiles. He estimated that among 1,000 women with the highest CRP levels, only 1.3 more cardiovascular events occurred annually than did among 1,000 women with the lowest CRP levels. In other words, the Women's Health Study enrolled some very healthy subjects.

Abramson went further. What if women with the highest CRP levels were treated with Pravachol for one year? At an annual cost of \$1,572 per patient (the price of Pravachol 40 mg at a regional chain of pharmacies) and assuming a 40 percent reduction in cardiovascular events owing to Pravachol, Abramson figures it would cost \$1.7 million to prevent one cardiovascular event in this population. That's exclusive of office visits and laboratory tests to check for adverse drug effects. That's also exclusive of the cost of tests to establish hs-CRP levels in the first place. (The number needed to treat [NNT] works out like this: If there

are 2.3 events per 1,000 patients each year, Pravachol treatment would reduce the rate to 1.4 events per 1,000, so 1,111 patients [1 divided by 0.0009] would need to be treated to prevent one event.)

But Abramson wonders whether hs-CRP assays even are warranted. He suspects much of the small absolute increase in the risk of CVD among women with the highest CRP concentrations could be explained by their smoking status (the NEJM study adjusted for current smoking, but not former smoking, which has been shown to elevate CRP levels and data from the Nurses Health Study show a significantly increased risk of CVD for 10 to 14 years after quitting).

Given that about half of all cardiovascular events occur in patients with normal or below-normal LDL-c levels, any positive results to JUPITER could be interpreted as justifying an expansion of the population

of patients who might benefit from statin therapy. But following Abramson's example, MCOs and PBMs might want to check the math for themselves.

The number of U.S. patients eligible for lipid-lowering drug therapy already is substantial — some 36 million under the most recent NCEP guidelines (up from 13 million previously). About 20 million of these patients have an LDL-c goal under 100 mg/dL. That concentration is the optimal level for anyone, but it's the specified goal for patients with the highest CHD risk — those with a history of CHD, diabetes, or other conditions posing a risk equivalent to that of CHD, or a set of various factors conferring a 10-year risk of CHD that exceeds 20 percent.

The massive Heart Protection Study is among recent trials suggesting that the NCEP goals should be more stringent. HPS showed that patients receiving Zocor 40 mg reduced their risk of CVD events regardless of their LDL-c level at baseline. Even patients whose LDL-c initially was below 100 mg/dL were found to benefit from Zocor therapy. The HPS results support the argument that statin therapy should be extended to anyone with elevated risk of CHD, regardless of LDL-c levels. According to HPS, there's no floor below which LDL-c reduction ceases to be beneficial, which argues for using the most powerful statin. And that would be Crestor, with Lipitor a close second.

OTC statin?

By the time the results of JUPITER are available, rosuvastatin and atorvastatin both could be looking for something to spur their sales. Both simvastatin and pravastatin could be available as generic products by then. Beyond that, some statins could be available as OTC products soon. In November, the *Wall Street Journal* reported that Merck and Johnson & Johnson are planning to ask the FDA for permission to sell Zocor and Pravachol over the counter, and that the FDA seems receptive to the idea of expanding the role of OTC products in general. This would mark a reversal of past policy, because in 2000 an FDA committee nixed the idea of selling either Mevacor 10 mg or Pravachol 10 mg over the counter. OTC statins could reach the British market even sooner; in November, the *Financial Times* of London reported that low-dose Zocor could be available OTC within six months. Thompson says he's not personally opposed to making statins available OTC, because that would make the drugs available to more patients, albeit with less physician supervision.

All these developments could make life easier for P&T committees but harder for statin manu-

TABLE 4 2-year event rates in PROVE-IT, according to baseline characteristics

Baseline characteristic	Number of patients (%)	2-year event rates		Relative risk reduction*
		Atorva- statin 80 mg	Prava- statin 40 mg	
Sex				
Male	3251 (78)	23.0	26.2	12.2
Female	911 (22)	20.3	27.0	24.8
Age				
≥65 years	1230 (30)	28.1	29.5	4.7
<65 years	2932 (70)	20.1	25.0	19.6
Diabetes				
Yes	734 (18)	28.8	34.6	16.8
No	3428 (82)	21.0	24.6	14.6
Prior smoking†				
Yes	3077 (74)	22.8	26.5	14.0
No	1085 (26)	21.3	25.9	17.7
Prior statin therapy				
Yes	1049 (25)	27.5	28.9	4.8
No	3112 (75)	20.6	25.5	19.2
LDL-c				
≥125 mg/dL	1091 (27)	20.1	28.2	28.7
<125 mg/dL	2885 (73)	23.5	25.6	8.2
HDL-c				
≥40 mg/dL	1776 (44)	21.7	26.7	18.7
<40 mg/dL	2219 (56)	23.1	26.0	11.1

* Calculated from values provided

† This group comprises the entire population, but the terminology — *prior* smoking — conflicts with information provided elsewhere in the study showing that 36.7% of subjects were *current* smokers. It is assumed that *ever* smoking was intended, instead of *prior* smoking.

SOURCE: Cannon 2004.

Oh, really?

The first sentence of the *New England Journal's* recent article about PROVE-IT sounds like a summary of conventional wisdom: "Several large, randomized, controlled trials have documented that cholesterol-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduces the risk of death or cardiovascular events across a wide range of cholesterol levels whether or not patients have a history of coronary artery disease.¹⁻⁷"

Everyone knows that, right? Well, no. The benefits of statins in primary prevention have not been *documented* to be quite this broad. That is, the seven references notwithstanding, it can't be claimed on the basis of these studies that statins have been shown to reduce the risk of death in patients without a history of CAD (i.e., in primary prevention). Perhaps later studies will show a reduction in mortality, but these seven don't.

References 1-3 lead the reader to 4S, CARE, and LIPID (see "Major statin trials," p. 41). All three are pure studies of statins in secondary prevention (i.e., patients with a history of CAD). Reference 4 is HPS, which enrolled high-risk patients with vascular disease or diabetes, or both.

The last three references are for WOSCOPS, AFCAPS/TexCAPS, and PROSPER. And none of these, alas, shows convincingly that statins reduce the risk of death in primary prevention. The only one that comes close to doing so is WOSCOPS, in which the relative risk of death from CHD was reduced by 28 percent in the pravastatin group (absolute rates of CHD death in the drug and placebo groups, 1.7 and 1.2 percent) but the difference wasn't statistically significant ($P=0.13$). Neither was the 22 percent reduction in the relative risk of death from any cause ($P=0.051$) (absolute rates of all-cause death, 4.1 and 3.2 percent).

In AFCAPS/TexCAPS, the rate of deaths from any cause was very low and virtually identical in the lovastatin (80/3304 = 2.4 percent) and placebo (77/3301 = 2.3 percent) groups.

And in PROSPER, the 22 fewer deaths from vascular disease in the pravastatin group were offset by an increase of 24 deaths from cancer.

facturers. With Crestor, the statin class may have reached the end of its line. "Once a market becomes crowded, it's hard to differentiate among products," says IMS's Schoenwaelder. "It's time to move on," he says.

Double-blind, randomized trials needed

Nissen's study is an example of attempts to find a faster approach to reduce the risk of atherosclerotic disease. Pfizer thinks enough of this approach to have agreed to purchase Esperion Therapeutics for \$1.3 billion, though it may be eyeing other products in Esperion's pipeline. But that's not all that's in Pfizer's cholesterol bag. It's also developing torcetrapib, which inhibits cholesteryl ester transfer protein (CETP), thereby increasing HDL-c levels by up to 50 percent. Torcetrapib would be used in combination with Lipitor, whose effects on HDL-c are modest.

But show-me-the-proof physicians like Abramson and Thompson are holding their applause for Nissen's

recent studies, intriguing though they may be. Each questions the utility of a surrogate marker like IVUS. Real clinical outcomes in randomized studies are what impress them.

Abramson remains skeptical about the body of evidence said to back statins as the most effective way to prevent heart disease. He'd be a lot more impressed with the big statin trials if they had contained not just a placebo arm but also an arm in which patients were randomized to lifestyle therapy — diet, exercise, smoking cessation. But in a world where biological reductionism combines synergistically with commercially sponsored research, he's not surprised that drug therapies haven't been tested against lifestyle intervention.

"No one demands it. They're not even asking the question," he says. And he says that's because, in his view, the unstated question is how best to sell a product, not how best to treat patients.

Lifestyle changes

Abramson cites the Lyon Diet Heart Study as an example of what can be accomplished with a better diet. This study enrolled a high-risk population and randomized them to either a Mediterranean-style diet or a prudent Western-type diet typically

prescribed after a heart attack. After a mean of four years of follow-up, total cholesterol was 239 mg/dL in the control group (Western) vs 240 mg/dL in the experimental group (Mediterranean). LDL-c likewise was very similar, 164 mg/dL in the control group vs 161 mg/dL in the Mediterranean group. Moreover, these and other biological parameters were similar to those obtained at randomization. So the trial was a total failure, right? Well, no. The risk of cardiac death was reduced by 65 percent in the experimental group relative to the control group, and the relative risk of cardiac death or nonfatal MI was reduced by 72 percent in the experimental group. Likewise, the relative risk of death from any cause was reduced by 56 percent in the experimental group. The absolute reduction of all-cause deaths was 6 percent in the Lyon Diet Heart Study, compared with 3 percent in LIPID.

"We've been tricked into looking at LDL-c as an end in itself," Abramson says.

“Lifestyle therapy *does* work,” Abramson says, pointing not just to the Lyon study but also to the Oslo Study in which more than 1,200 men without heart disease, but with cholesterol levels above 300 mg/dL, four fifths of whom also smoked, were randomized to receive counseling about diet (decrease saturated fats by more than half and increase polyunsaturated fats) and smoking. Over the subsequent 10 years, there were 44 percent fewer cases of heart disease and 39 percent fewer deaths among the men who had been counseled about diet and smoking than among the men in the control group.

For these high-risk men in Oslo, lifestyle counseling was half again *more effective* at preventing heart disease and premature death than was treatment with a statin in a similar group of high-risk men in WOSCOPS.

When he was practicing family medicine, Abramson followed the NCEP guidelines because to ignore them is to court a malpractice suit. But if he had a patient who was a candidate for statin therapy but had doubts about going that route, Abramson would walk the patient through the arithmetic, using the NNT from the appropriate statin trial. For example, if the patient matched the entry criteria for WOSCOPS, once he understood that in that trial 42 men had to be treated with Pravachol for 5 years to prevent one death from CHD or heart attack (that is, one man would benefit from 5 years of Pravachol treatment, and 41 would not), he might look at the benefit of statin therapy much differently.

Abramson would like people to make decisions on statin trials and statin therapy on the basis of all the evidence, not just part of it. That would include looking at serious adverse events and overall mortality, instead of focusing on changes in lipid profiles and coronary events. For example, he points out that PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) is touted as supporting the use of statins to reduce the risk of CHD events in high-risk elderly patients (aged 70–82). Indeed, PROSPER shows such a benefit — but only in patients with previous vascular disease. For those patients, the relative risk of CHD death, nonfatal MI, or fatal or nonfatal stroke was reduced by 22 percent; for patients without previous vascular disease, the relative risk reduction in this composite endpoint was not significant.

In addition, the study also showed no difference in all-cause mortality: after 3.2 years of follow-up, 10.3 percent of the patients in the pravastatin group had died, as had 10.5 percent of patients in the placebo group. And remember, the PROSPER study showed us that the statins may not be as benign as once thought: the risk of developing cancer was 25 percent higher in

the people who took the statin ($P=0.02$).

So is a statin a statin a statin? Maybe. Maybe not. “There’s nothing wrong with lovastatin,” Abramson says, and if you think the greater LDL-c reduction achieved with the newer statins is beneficial for some patients, go for it. But Abramson also might suggest that the rose isn’t the only flower in the garden.

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