imaginable. But the technology will support and improve medical care only if it evolves in ways that help, rather than hinder, us in synthesizing, analyzing, thinking critically, and telling the stories of our patients.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

Dr. Rosenbaum is a national correspondent for the *Journal*.

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Reducing LDL with PCSK9 Inhibitors — The Clinical Benefit of Lipid Drugs

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In early June, the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration (FDA), on which we serve, met to consider marketing applications for the new molecular entities alirocumab and evolocumab on the basis of their ability to lower low-density lipoprotein (LDL) cholesterol levels and their effects on other lipid fractions in patients at risk for cardiovascular disease. These first-in-class medications are fully humanized monoclonal antibodies that inactivate proprotein convertase subtilisin–kexin type 9 (PCSK9). That inactivation results in decreased LDL-receptor degradation, increased recirculation of the receptor to the surface of hepatocytes, and consequent lowering of LDL cholesterol levels in the bloodstream. Statins, by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, similarly act by increasing LDL-receptor expression. This shared LDL cholesterol–lowering mechanism, combined with data on cardiovascular events from genetic studies of persons with PCSK9 gain- or loss-of-function mutations, has led to optimism regarding the potential — but as yet unproven — cardiovascular benefits of these agents.

Both alirocumab and evolocumab, which are given by injection, cause large reductions in LDL cholesterol levels, as compared with placebo (39 to 62% reduction for alirocumab and 47 to 56% for evolocumab). In the drugs' development programs, LDL cholesterol levels in approximately 37% of patients receiving evolocumab and 24% of patients receiving alirocumab dropped below 25 mg per deciliter on two consecutive measurements. Because such low plasma cholesterol levels can be attained with these medications, particularly when they're given in conjunction with a statin, the FDA raised concerns about possible gastrointestinal, metabolic, and neurocognitive adverse effects. The target populations considered for long-term use of either drug include adults with primary hypercholesterolemia (nonfamilial or heterozygous familial), patients with mixed dyslipidemia (including those with type 2 diabetes mellitus), and patients unable to take statins. The evolocumab studies also included patients with homozygous familial hypercholesterolemia.

Both drugs were submitted through the traditional FDA approval pathway, with LDL cholesterol reduction as the surrogate measure of clinical benefit. No efficacy data on cardiovascular outcomes were provided to the advisory committee, except for encouraging but preliminary analyses of cardiovascular adverse events with evolocumab. During the meeting, the FDA noted that if a medication is approved through this traditional pathway on the basis of a surrogate end point, the FDA can subsequently mandate postmarketing safety studies but cannot require postmarketing studies of benefits, such as cardiovascular event reduction. Thus, the principal issue before the advisory committee was whether the observed LDL cholesterol reduction provided sufficient evidence to substitute for

Selected Clinical Trials of Medications for Lowering LDL Cholesterol Levels Other Than Statins Alone and Their Effects on Cardiovascular Events.*

Trial	Study Drug	Comparison	Primary End Point	% Difference in LDL Cholesterol Levels†	Cardiovascular Outcome	
					Hazard Ratio (95% CI)	P Value
HERS	Estrogen (alone or in combination with medroxyprogesterone)	Placebo	Nonfatal myocardial infarction or death due to coronary heart disease	–11	0.99 (0.80–1.22)	0.91
FIELD	Fenofibrate	Placebo	Nonfatal myocardial infarction or death due to coronary heart disease	–12	0.89 (0.75–1.05)	0.16
ILLUMINATE	Torcetrapib–atorvastatin	Placebo plus atorvastatin	Nonfatal myocardial infarction, stroke, hospitalization for unstable angina, or death due to coronary heart disease	–27	1.25 (1.09–1.44)	0.001
HPS-2 THRIVE	Niacin–laropiprant	Placebo	Nonfatal myocardial infarction, death from coronary causes, stroke, or arterial revascularization	–16	0.96 (0.90–1.03)	0.29
IMPROVE-IT	Ezetimibe–simvastatin	Placebo plus simvastatin	Death due to cardiovascular causes, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization, or nonfatal stroke	–24	0.94 (0.89–0.99)	0.02

* CI denotes confidence interval, HERS Heart and Estrogen/Progestin Replacement Study,[2] FIELD Fenofibrate Intervention and Event Lowering in Diabetes,[3] ILLUMINATE Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events,[4] HPS-2 THRIVE Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events,[5] and IMPROVE-IT Improved Reduction of Outcomes: Vytorin Efficacy International Trial.[1]

† The percent difference is for the comparison, during treatment, of the study drug with a placebo or another drug.

demonstration of clinical cardiovascular benefit.

LDL cholesterol reduction was the basis for FDA approval in 1987 of the first statin (lovastatin), 7 years before the publication of the Scandinavian Simvastatin Survival Trial, the first trial to provide definitive evidence of a statin's clinical benefit. Subsequent statin approvals were also based on the LDL cholesterol surrogate, as was approval of the first-in-class drug ezetimibe in 2002. However, one subsequent randomized trial raised concerns about an increased risk of cancer or an increase in cancer-related deaths with ezetimibe, prompting additional review and communication by the FDA. These safety concerns appear to have been favorably resolved by the recently published results of the IMPROVE-IT study, which showed a modest reduction in rates of major cardiovascular events in comparison with the control group and no increase in cancer risk.[1]

These results could be interpreted as evidence that LDL cholesterol reduction will reduce cardiovascular risk regardless of a drug's mechanism of action. However, aside from IMPROVE-IT, several trials with other nonstatin medications that lower LDL cholesterol do not fully support this hypothesis (see table). The ILLUMINATE study and the HPS2-THRIVE study are of particular interest, given the relatively large percent differences in LDL cholesterol levels they revealed between the study drug and comparison groups. They also showed other salutary effects on lipid levels, including decreased triglycerides and increased high-density lipoprotein (HDL) cholesterol levels, but neither trial demonstrated a benefit in terms

of cardiovascular outcomes. In fact, ILLUMINATE was stopped early because of a significantly increased rate of major cardiovascular events in the torcetrapib group. These trials and others call into question whether LDL cholesterol reduction is a reliable surrogate end point for the approval of new nonstatin drugs.

There are benefits and risks in using LDL cholesterol reduction as a surrogate end point for drug approval before the completion of definitive outcome trials. One potential advantage is the ability to demonstrate a statistically significant beneficial effect of a novel medication on the surrogate while exposing relatively few patients to the drug for a short period. The desired outcome would be lower-cost drug development and accelerated availability of new therapies. However, the limited number of patient-years of randomized, controlled drug exposure makes it difficult to assess the safety of new agents, particularly in terms of uncommon but clinically important adverse events, and leaves unevaluated the safety of agents intended for long-term use. Adverse effects may not be anticipated and may be recognized only when a large number of patients are exposed to a drug over a long period. For example, an increased risk of death with torcetrapib was evident in a large trial (>15,000 patients) of cardiovascular event outcomes.[4] Had torcetrapib been approved on the basis of LDL cholesterol reduction alone, its association with an increased risk of death might not have been detected until it was in widespread use.

A second advantage of using LDL cholesterol as a surrogate is that it can facilitate evaluation of new medications in patients with uncommon disorders for which trials with a clinical end point would not be feasible. For example, cardiovascular outcomes trials are not possible in homozygous familial hypercholesterolemia, which is quite rare. Evolocumab was shown to significantly reduce LDL cholesterol levels in patients with this condition and, on the basis of the high prevalence of premature death associated with the disorder, was unanimously recommended for approval by the advisory committee.

Patients with existing cardiovascular disease and persistently high LDL cholesterol levels despite high-intensity statin therapy also have important unmet medical needs. For this much larger population, the FDA must weigh the benefits of early approval against the possibility that the drugs will be substituted for maximally tolerated statins, even though there's much better evidence of statins' clinical benefit. The proposed labeling for the PCSK9 inhibitors would support their use in patients unable to take statins — a matter of concern, since statin intolerance appears to be overdiagnosed (e.g., 70% of patients who were considered unable to take statins in blinded alirocumab studies tolerated 20 mg of atorvastatin daily for 24 weeks). Although unlikely, an additional theoretical concern is that widespread availability of PCSK9 inhibitors might prompt patients enrolled in ongoing endpoint trials to receive the medications outside the protocol, thereby compromising the trials' integrity.

Despite the limitations in the benefit and risk data raised in the discussion of both PCSK9 drugs, the advisory committee voted 13 to 3 to approve alirocumab and 11 to 4 to approve evolocumab. The committee members voting for approval were motivated by the goal of providing a potentially beneficial option to patients with very high risk of disease before large cardiovascular outcome trials are completed. Many committee members, including those who supported approval, emphatically stated that LDL cholesterol levels were not a reliable surrogate for cardiovascular benefit and acknowledged that approval could lead to widespread use before definitive efficacy and adequate safety data are available. This concern may be somewhat mitigated by the high cost and requirement for parenteral administration of PCSK9 inhibitors.

Establishing evidence of improved cardiovascular outcomes is key to evaluating medications from any new drug class intended to reduce such risk. As substantially as alirocumab and evolocumab reduce LDL cholesterol, definitive evidence of reduced cardiovascular event rates is essential. Ongoing trials designed to provide such evidence should elucidate the medications' true clinical benefits and possible risks.

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All three authors participated as voting members of the FDA Endocrinologic and Metabolic Drugs Advisory Committee meeting on alirocumab, and Drs. Smith and Hiatt participated as voting members of the Advisory Committee meeting on evolocumab.

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Specialty Pharmaceuticals for Hyperlipidemia — Impact on Insurance Premiums

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The Food and Drug Administration (FDA) recently approved alirocumab and evolocumab, PCSK9 inhibitors, for the treatment of hyperlipidemia. These novel biologic agents offer the promise of reductions in blood cholesterol levels. Specifically, the FDA approved alirocumab as an "adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL [low-density lipoprotein]-cholesterol."[1] This broad indication sets the practice of cardiology on a collision course with specialty pharmaceutical pricing models that were previously reserved for drugs that benefited relatively limited patient populations.

Alirocumab was launched at a list price of $14,600 per patient per year. Of course, as other products in this class are introduced, there may be price competition, in the form of either differences in list prices or exclusive commercial arrangements between manufacturers and pharmaceutical benefits managers. These therapies may also lead to savings down the road, by reducing rates of cardiovascular events, though the FDA label clearly states that "the effect of alirocumab on cardiovascular morbidity and mortality has not been determined." According to post hoc analyses, clinical trials of alirocumab and evolocumab revealed a relative reduction of approximately 50% in the risk of cardiovascular events, but the study populations had low absolute event rates of only 2 to 3%. Even if these findings are substantiated, our preliminary analysis suggests that the average cost offsets that stem from lower rates of cardiovascular events are likely to be nominal. Even if there were a 100% reduction in cardiovascular events (i.e., a 3% absolute risk reduction) at an average of $20,000 for each event, the annual cost reduction would be at most $600 — a small offset relative to alirocumab's list price.

There will surely be formal economic evaluations of these data, and there are long-term outcome studies under way to elucidate the potential effect of these therapies on cardiovascular event rates and survival. But it is apparent that the prices for these drugs will result in net costs to the health care system, even if they may eventually be found to offer good value for the money.

With expected total annual costs in the billions, it's important to ask who will bear these costs. In the current market, these products will most likely be considered as part of the drug benefits of insurance plans because they are self-administered. Patients will probably face some degree of cost sharing for the products, possibly including coinsurance, a variable payment amounting to 20 to 25% of the cost, subject to a maximum out-of-pocket cost threshold (although manufacturers are likely to reduce this financial burden with coupon programs to spur adoption and continuation of the therapy for non-Medicare patients). The balance of the cost will be supported through health insurance premiums.

We estimated the magnitude of additional costs per beneficiary in a typical insurance pool by applying a 25% reduction (negotiated discount, cost sharing, or both) to the list price of alirocumab, accounting for the estimated $600 in savings due to fewer cardiovascular events, and varying clinical criteria for use of these therapies. If 5% of the estimated 27% of U.S. adults 40 to 64 years of age who have high LDL cholesterol levels[2] were eli-