search need. Evaluating the HBV viral load in HIV-infected pregnant women should be an essential step of prenatal evaluation, so that the mother's health can be managed appropriately.

Continued improvements in the coverage and timeliness of HBV vaccination and the education of clinicians about its importance should be priorities everywhere. Making such improvements will require substantial advocacy and political and financial commitment. Now is the time to provide the best care we can for coinfected people and to protect a future generation of children from the largely hidden epidemic of HBV-related liver disease, which is being further fueled by the HIV epidemic.

The opinions expressed in this article are those of the authors and do not necessarily reflect the position of the Centers for Disease Control and Prevention.

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Statins: Is It Really Time to Reassess Benefits and Risks?

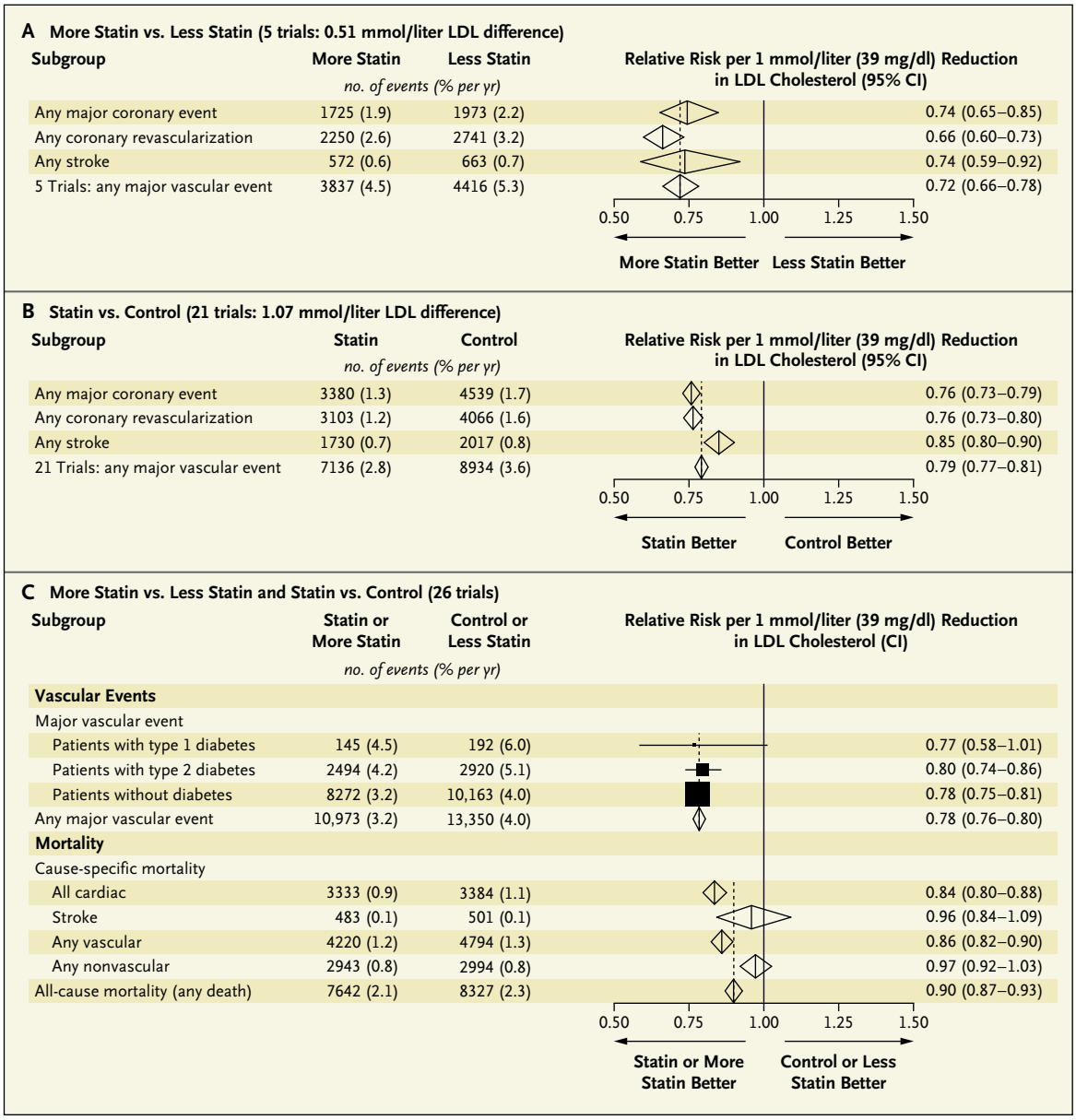
Allison B. Goldfine, M.D.

No drug provides health benefits without some degree of risk, and risk–benefit assessments require ongoing review as new data become available. This is certainly the case for the use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors — statins — and the risk of new-onset diabetes.

Cardiovascular disease is the leading cause of illness and death in patients with type 2 diabetes. There is no doubt that for persons who have had an acute coronary syndrome or who have other risk factors for atherosclerotic coronary artery disease, statins effectively reduce the risks of death from any cause, death due to cardiovascular disease, fatal myocardial infarction, the need for revascularization, and stroke (see figure). Over a period of 4 years of statin use, a reduction of 1 mmol per liter (39 mg per deciliter) in the level of low-density lipoprotein (LDL) cholesterol translates into a 9% reduction in the risk of death from any cause among patients with diabetes and a 13% reduction among those without diabetes.[1] Benefits are realized within the first year of use but increase over time. Few drugs have had such a dramatic effect on health outcomes.

In the JUPITER study (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; ClinicalTrials.gov number, NCT00239681), involving 17,802 participants without diabetes but with LDL cholesterol levels below 3.4 mmol per liter (130 mg per deciliter) and high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher, the hazard ratio for newly diagnosed diabetes was increased 25% in the rosuvastatin group than in the placebo group.[2] Despite the increase in the risk of new-onset diabetes, the participants previously considered to have low cardiovascular risk had clinically important health improvements over a median follow-up period of only 1.9 years, with a hazard rate 44% lower than that of the placebo group for the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. In addition, rates for the key secondary outcomes were lower in the treated participants: 54% lower for myocardial infarction, 48% for stroke, 46% for revascularization, and 20% for death from any cause.

A meta-analysis of six statin trials that included 57,593 participants revealed a 13% increase in the relative risk of new-onset diabetes[3] — a more modest effect than that seen in the JUPITER study, perhaps because the diagnostic criteria differed. Similarly, a meta-analysis of 13 randomized statin trials with 91,140 participants showed an odds ratio of 1.09 for a new diagnosis of



Effect of Statins on Cardiovascular Event Rates, According to Reduction in LDL Cholesterol of 1 Millimole per Liter.

Data are from a meta-analysis of 26 randomized trials, with 170,000 participants (Cholesterol Treatment Trialists' Collaboration, Lancet 2010;376:1670-81). Cardiovascular event rates were lower in the five trials comparing more with less statin therapy (Panel A) and in the 21 trials comparing statin therapy with control (Panel B). Patients with diabetes and those without diabetes had similar reductions in rates of major vascular events and mortality (Panel C). The studies enrolled fewer patients with type 1 diabetes than with type 2 diabetes, which contributed to greater uncertainty in this group; however, the point estimate is similar. Statins reduce cardiovascular mortality and all-cause mortality among patients with risk factors that are similar to those of trial participants. Open diamonds indicate 95% confidence intervals (CI), and horizontal lines indicate 99% CI.

diabetes, so that (on average) treatment of 255 patients with statins for 4 years resulted in one additional case of diabetes.[4] Given that statins are used by approximately 24 million Americans, the population-attributable risk is not small, but it must be considered in the context of the simultaneous prevention of 5.4 vascular events among those 255 patients.

Little to no heterogeneity in the risk of new-onset diabetes has been observed among trials.[3-5] Statins appear to have a class effect, unrelated to the individual statin, its potency, or its lipo-

philic or hydrophilic properties. Their effect also appears to be dose-dependent: the odds ratio for new-onset diabetes is 12% higher with intensive-dose therapy than with moderate-dose therapy, although there's also a 16% greater reduction in the risk of cardiovascular events. This difference in risk translates into two additional cases of diabetes but 6.5 fewer cardiovascular events per 1000 patient-years with intensive-dose statin therapy, as compared with moderate-dose therapy, among patients with risk factors similar to those of trial participants[5] — and we must consider whether the risk of diabetes and the risks of cardiovascular events and death should be weighted similarly. Women have been either underrepresented or not included in several large, randomized trials, but the increased incidence of new-onset diabetes with statin use has also been seen among postmenopausal women in the Women's Health Initiative observational study. Changes in the LDL cholesterol concentration do not account for the excess diabetes risk[4]; rather, the strongest predictors of new-onset diabetes, regardless of whether patients have received statins, include older age, higher baseline fasting glucose levels, and other features of the metabolic syndrome. Thus, statins may simply be unmasking disease in people who were likely to develop diabetes soon anyway.

The mechanism or mechanisms underlying the increased incidence of diabetes remain elusive. Genomewide studies have not identified associations between genes that regulate HMG-CoA reductase or LDL cholesterol metabolism and type 2 diabetes. Cellular studies have suggested that statins may interfere with beta-cell insulin secretion either by decreasing Ca^{2+}-dependent insulin secretion or by interfering with isoprenylation of guanosine triphosphate (GTP)–binding proteins. Statin inhibition of isoprenoid biosynthesis may lead to lower expression of insulin signaling proteins in adipocytes and to reduced glucose transporter expression or translocation. Fasting insulin levels may increase modestly, suggesting that insulin resistance may be increased, but euglycemic hyperinsulinemic clamp studies do not show consistent changes in insulin sensitivity. Other off-target effects may also be involved.

In light of the evidence, the Food and Drug Administration (FDA) recently added information to statin labels regarding an effect of these agents on diabetes, noting that "increases in glycosylated hemoglobin (HbA_{1c}) and fasting serum glucose levels have been reported with statin use," but adding that the "FDA continues to believe that the cardiovascular benefits of statins outweigh these small increased risks." Given the widespread use of statins, overestimating their clinical benefit or underestimating their risk is of potentially major importance to public health. The clinical trials that defined the diabetes risk have been relatively short-term, yet statin therapy is often continued for years; thus, it's possible that the risk of diabetes will increase with the duration of follow-up. Additional interventions for glycemic management might be warranted, and those interventions carry their own potential risks and additional costs.

Moreover, it remains unknown what effect, if any, statin-induced diabetes might have on the development of long-term microvascular complications. Current epidemiologic data are, however, reassuring. In recent years, with the lower target goals for lipid levels and the increasing use of statins, as well as improved screening, early detection, and multifactorial interventions, the age-adjusted prevalence rates of blindness and end-stage renal disease have decreased among patients with diabetes, according to the Centers for Disease Control and Prevention. Furthermore, the 10-year risk of myocardial infarction or stroke (25%) is markedly higher than that of blindness or renal failure (1 to 2%) for patients with recent-onset diabetes, according to the United Kingdom Prospective Diabetes Study (Current Controlled Trials number, ISRCTN75451837). Nonetheless, evaluation of the longer-term effects of statin-induced diabetes is warranted.

The net cardiovascular benefit for people at high cardiovascular risk strongly favors statin use. The greatest area of uncertainty is the use of statins for primary prevention among patients with a relatively low baseline risk of major adverse cardiovascular events, but multiple cardiovascular primary prevention trials have shown reductions in mortality even in this population. We lack data showing that any specific subgroup of patients is uniquely at increased risk for statin-induced diabetes and should therefore not use statins. Rather, the risk appears to be greatest among people in whom diabetes is most likely to develop anyway — at which point they would be treated with statins as part of their routine care. Although diabetes is a serious health concern, the management of dyslipidemia with statins substantially reduces cardiovascular risk and improves survival; thus, current data do not support the discontinuation of statins when diabetes is diagnosed, and

it remains prudent to target lipid levels according to established guidelines. Of course, it also remains important to recommend increased exercise, healthy food choices, and portion control and to help manage weight in patients with prediabetes levels of glycemia or metabolic syndrome.

Studies to define the risks of statin-induced diabetes and its underlying mechanisms are clearly necessary. But until more data are available, clinicians should monitor glucose or glycated hemoglobin in patients with multiple risk factors for diabetes who take statins, but they should continue to prescribe statins when indicated as part of a multifactorial approach to managing cardiovascular risk.

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Measles in the 21st Century

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Barely 20 years ago, such a high proportion of childhood deaths globally was attributable to measles that the going estimate of more than 1 million measles-related deaths per year was almost certainly an underestimate. Pediatric wards in the developing world were filled with patients with measles and its complications, and measles continued to be a major cause of blindness globally. All this occurred despite the remarkable progress that had been achieved during the 1980s in bringing routine immunizations, including a single dose of measles vaccine, to the poorest countries of the world, culminating in the achievement of the global Universal Childhood Immunization goals in 1990. In the United States, where measles had been effectively controlled since 1982, a minor resurgence of the disease occurred between 1989 and 1991, resulting in 123 deaths and more than 11,000 hospitalizations. Almost half of all cases were in older children or adults. The subsequent introduction of a two-dose vaccination strategy led to the elimination of measles in the United States by 2000, although imported cases continue to feed small outbreaks. In 2011, 90% of the 222 cases reported in the United States were associated with imported cases.

An interactive graphic showing incidence and vaccination rates is available at NEJM.org

During the 1990s, routine immunization stagnated in many parts of the developing world, especially Africa. The increasing emphasis on controlling poliovirus through focused campaigns may have been a factor in this stagnation, although it did enable some countries to undertake measles-vaccination campaigns that led to variable levels of control. By 2000, the countries of the African Region of the World Health Organization (WHO) were reporting more than 500,000 measles cases per year.[1] Global measles-related deaths were estimated at more than 700,000 per year, but there was considerable disagreement over these modeled estimates, and many experts believed they were too high. Between 2000 and 2008, measles control improved markedly in all regions (see the interactive graphic, available with the full text of this article at NEJM.org). Indigenous measles transmission was interrupted in the Americas by 2002, and the number of reported cases in Africa in 2008 was less than 10% of the 2000 level, despite improved reporting methods.[2] Control was being achieved through the addition of a second dose of measles vaccine, either within the routine schedule for countries with well-functioning programs or in targeted campaigns.

After 2005, a new pattern began to emerge, with some richer countries failing to maintain sufficient vaccination coverage to control the disease. In Western Europe, Switzerland, Germany, France, and Britain reported continuing measles transmission and declining vaccination coverage, associated with sensationalized reports of adverse events, objection to immunization among certain groups, and a marked in-