as low-density lipoprotein cholesterol (LDL-C) and the risk of disease within the context of a Mendelian randomization study can be complex. Indeed, it was initially unclear whether the much-larger-than-expected reduced risk of coronary heart disease (CHD) reported in the original PCSK9 studies was caused by the effect of lifelong exposure to lower LDL-C or to the combination of lower LDL-C and other pleiotropic effects mediated by this polymorphism (1). For this reason, we specifically sought to evaluate the association between lifelong exposure to lower LDL-C and the risk of CHD mediated by polymorphism in a variety of different genes, each of which presumably affects circulating LDL-C levels by a different mechanism or biological pathway.

We found that each polymorphism included in our study was associated with a highly consistent effect on the risk of CHD when measured per unit lower of LDL-C with no evidence for heterogeneity of effect (2). In addition, we found an essentially identical magnitude of effect when we estimated the association between lifelong exposure to lower LDL-C and the risk of CHD by using a genetic LDL-C score, which measures the effect of lifelong exposure to lower LDL-C mediated by the combined effect of the included polymorphism. The practice of combining multiple instruments for a modifiable exposure into a single instrument to estimate the magnitude of a causal effect is common in the field of econometrics (3). Indeed, the magnitude of the association between lifetime exposure to lower LDL-C and the risk of CHD observed in our study has now been independently confirmed using separate genetic LDL-C scores composed of different combinations of polymorphism in two other studies (4,5).

The repeated replication of the same magnitude of effect per unit of lower LDL-C for each individual polymorphism included in our study, and for multiple different genetic LDL-C scores measured in different populations, strongly argues that our estimate of the magnitude of the effect of lifelong exposure to lower LDL-C on the risk of CHD is unlikely to be confounded by population stratification, linkage disequilibrium, pleiotropy, or other systematic bias, such as attenuation of effect with age as suggested by Dr. Schooling and colleagues because it would be implausible that each of these associations was affected by 1 or more of these biases in the same direction with the same magnitude of effect. Furthermore, in multiple metaregression analyses, we found no evidence for effect modification of age on the association between circulating LDL-C levels and any of the polymorphism included in our study (including rs646776). Therefore, we believe that it is very unlikely that the results of our study were inflated by the potential attenuation of LDL-C genetic associations with age as suggested by Schooling et al. Instead, we believe that the results of our study, and those of other studies, provide robust naturally randomized evidence for the magnitude of the association between lifelong exposure to lower LDL-C and the risk of CHD.

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How to Balance Cardiometabolic Benefits and Risks of Statins

The paper by Waters et al. (1) is timely and important in delineating overall risk-benefit profiles of statin therapy in patients with risk factors for diabetes. However, this study reminds physicians of the important issue of risk-benefit concept in treating patients with drugs. Therefore, it is important to look over the hazard ratio (HR) of new onset diabetes (NOD) and cardiovascular events (CVE) in patients by lower dose (atorvastatin 10 mg or simvastatin 20 to 40 mg) versus higher dose (atorvastatin 80 mg) statin therapy according to the number of NOD risk factors: fasting blood glucose >100 mg/dl, fasting triglycerides >150 mg/dl, body mass index >30 kg/m², and history of hypertension. In Figure 1 of Waters et al. (1), in risk factor 0, HRs of NOD and CVE are 0.96 and 0.95 by lower dose versus higher dose statin therapy; in risk factor 1, HRs of NOD and CVE are 0.97 and 0.82 by lower dose versus higher dose statin therapy; in risk factor 2, HRs of NOD and CVE are 1.15 and 0.85 by lower dose versus higher dose statin therapy; in risk factor 3, HRs of NOD and CVE are 1.31 and 0.82 by lower dose versus higher dose statin therapy; in risk factor 4, HRs of NOD and CVE are 1.36 and 0.65 by lower dose versus higher dose statin therapy; and overall, HRs of NOD and CVE are 1.16 and 0.85 by lower dose versus higher dose statin therapy, respectively (1). Therefore, it is true that higher dose statin therapy significantly reduced CVE; however, when both HRs are considered simultaneously, it seems that higher dose statin therapy does not have any benefit compared with lower dose statin therapy.

Consistent with this observation, recent clinical and meta-analysis studies have demonstrated that the effect of statins to induce type 2 diabetes is dose-dependent (2,3). Hypercholesterolemic patients receiving high dose atorvastatin (80 mg) developed greater insulin resistance, higher fasting insulin levels, and higher HbA$_{1c}$ levels when compared with patients receiving the low-dose atorvastatin (10 mg) or placebo, suggesting that high-dose statin therapy may have greater adverse effects on glucose homeostasis than low-dose therapy (2). A recent meta-analysis demonstrated that intensive-dose statins increased the risk of developing type 2 diabetes by 1.12 (95%

confidence interval: 1.04 to 1.22) despite of reducing the risk of cardiovascular events by 0.84 (95% confidence interval: 0.75 to 0.94), compared with moderate-dose statins (3). I speculate that long-term adverse effects of NOD may generate a relative increase in deaths. Indeed, a recent large-scale randomized clinical trial confirms my speculation. In individuals with 1 or more risk factors for diabetes, statin was associated with a 39% reduction in the primary endpoint, but in individuals with no major diabetes risk factors, statin was associated with a 52% reduction in the primary endpoint (4). One should consider that higher dose statin therapy may cause more adverse effects and therefore lead to differences in routine clinical care between those treated with higher and lower dose regimens. Thus, it is important to consider the cardiovascular and metabolic context and natural history of diseases when choosing statin therapy for optimal individual patient health over the long term (5).

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Statin Treatment and Diabetes

Waters et al. (1) discuss further evidence relating to increased incidence of new diabetes with statins. Superficially, the message from these and other studies is reassuring: statins have transformed the management of atherosclerotic disease; intensive therapy shows greater benefit than "standard" therapy; the rate of incident diabetes with statins is relatively small; benefits of statins are still apparent in patients with diabetes. It is further reassuring from this study (using data from the TNT [Treating to New Targets] and IDEAL [Incremental Decrease in Endpoints through Aggressive Lipid-lowering] studies) that those who develop diabetes are those who appear to be at risk.

The authors imply, but do not state, that all 4 risk factors for diabetes considered were equally important, and that there was no difference in incident diabetes between those with no or 1 risk factor. It is surprising that age was not considered as a factor in their analysis. Recent analyses of data from major lipid trials have documented the incidence of diabetes based on fasting glucose, but postprandial data are not available. The rate of incident diabetes may thus be underestimated. The effect of statins on diabetes incidence may also be underestimated because many of the patients in lipid trials have already been exposed to statins prior to the trial. Also, the comparators in the TNT and IDEAL studies (10 mg atorvastatin or 20 mg simvastatin) may themselves increase incident diabetes, thus partially masking the influence of intensive therapy.

It is unlikely that statins cause diabetes, but rather exacerbate a pre-existing dysglycemic state. Their impact almost certainly goes beyond the reported annual 2% increase in new diabetes. In the TNT and IDEAL studies, around 17% of patients had diabetes at baseline (previously diagnosed or increased fasting plasma glucose [FPG]). Deterioration in glycemic control in diabetic patients using statins is well documented (2) but has not been as extensively studied as the increase in incident diabetes. The increase in HbA_{1c} with statins is similar in magnitude to the decrease seen with the newer classes of oral hypoglycemic agents. The mechanism is not known. Impaired β-cell function may well be involved (2), but impaired insulin sensitivity has also been documented (3). If impaired insulin secretion is the predominant mechanism, then increased FPG may be the earliest diagnostic criterion for diabetes to be satisfied. If the problem is impaired insulin sensitivity, then increased postprandial glucose may appear first. Postprandial insulin and lipid excursions are well known to contribute to progression of macrovascular disease.

Development of diabetes or worsening of its control has the potential to impair quality of life through increased need for treatment, increased clinic visits, side effects of treatment, and development of complications. These considerations are not minor but we should certainly not deny patients the considerable benefits of statins where they are indicated. Statins can be lifesaving, but it is noteworthy that intensive statin therapy was not associated with decreased overall or cardiovascular mortality in either the TNT or IDEAL studies. Careful consideration of the risks and benefits are needed in each case, and we need greater understanding of the differing effects of class members on glucose homeostasis.

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