ulate that *SLCO1B1* variants cause a susceptibility to statin-induced myopathy, but the study by the SEARCH Collaborative Group shows an unequivocal association. Since approximately 60% of the cases of simvastatin-induced myopathy were attributed to variant *SLCO1B1*, avoiding the administration of high-dose simvastatin to those who are homozygous or heterozygous for the variant allele (about 30% of the population analyzed by the SEARCH group) could reduce the incidence of myopathy by nearly 60%. Alternatively, one might choose to avoid prescribing simvastatin only to those who are homozygous for the risk allele (nearly 2% of the population analyzed by the SEARCH group), which could reduce the incidence of myopathy by 25%, and prescribe a relatively low dose of the drug to patients who are heterozygous for the risk allele. Further investigation is required to identify the optimal therapeutic approach.

The degree of myopathy that occurred in these two trials was mild and reversible, in stark contrast to a form of statin-induced rhabdomyolysis that involves severe muscle damage accompanied by toxic effects in other organs such as the kidney. *SLCO1B1* variants must be tested for an association with this adverse drug reaction as soon as possible. However, severe adverse drug reactions are very rare, and the incidence of statin-induced rhabdomyolysis is reported to be as low as 0.000044 event per person per year.[13] Hence, a global network for the collection of data on persons with statin-induced rhabdomyolysis would be required to test for the association with a variant in *SLCO1B1*. Indeed, a global mechanism for collecting data on patients with severe adverse drug reactions would benefit the field of pharmacogenetics enormously and encourage the development of new technologies.[14]

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Preeclampsia — A Glimpse into the Future?

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Preeclampsia, a disorder of pregnancy characterized by elevated blood pressure and proteinuria, complicates approximately 5% of pregnancies.[1] Although several risk factors for this condition are well recognized, including nulliparity, extremes of maternal age, obesity, and preexisting diabetes or hypertension, the causes of preeclampsia remain uncertain; recent studies have suggested that circulating angiogenic factors, alterations in the renin–angiotensin system, and insulin resistance may be involved in pathogenesis.[1] Despite several trials examining various interventions,[1] no strat-

egy has proved effective in the prevention or treatment of preeclampsia other than delivery of the fetus. Complications include maternal stroke, renal failure, and placental abruption; offspring of mothers with preeclampsia are at risk for intrauterine growth restriction or death, as well as disorders related to prematurity.

Beyond these immediate complications, however, there is increasing evidence that the development of preeclampsia may be a marker for maternal disease risks later in life. Physiological adaptations necessary to support the growing fetus stress several systems; these stresses may result in expression of a woman's predisposition to the development of certain disorders.[2] Just as gestational diabetes is recognized as a strong predictor of the risk of the later development of diabetes, several reports have suggested that women with a history of preeclampsia have an increased risk of later hypertension and associated metabolic disturbances, including higher insulin levels and reduced endothelial function, as compared with women with uncomplicated pregnancies.[3-5] Long-term studies have also suggested increased risks of stroke,[5] ischemic heart disease,[6] and type 2 diabetes[7] later in life among women with a history of preeclampsia; higher relative risks of ischemic heart disease have been reported among women who have had more severe (as compared with milder) preeclampsia or recurrent hypertensive pregnancy.[8] However, reports have been limited by the uncertain validity of the diagnoses of preeclampsia and of the various outcomes, incomplete adjustment for potential confounders, small samples, and incomplete follow-up.

In this issue of the *Journal*, Vikse et al. report that preeclampsia may also portend an increased risk of future chronic kidney disease.[9] These investigators had previously reported that women with a history of preeclampsia are at increased risk for having a renal biopsy in the future.[10] In the present study, linking almost four decades of data from two large Norwegian registries — a national birth registry and an end-stage renal disease (ESRD) registry — the investigators identified a risk of the development of ESRD among women with a history of previous preeclampsia that was four times as high as the risk among women who had uncomplicated pregnancies. There appeared to be a "dose–response" effect, such that in women who had more than one pregnancy, recurrent preeclampsia conferred greater risk than did preeclampsia in only one pregnancy. An observation that might initially seem counterintuitive was that women with only one pregnancy who had preeclampsia seemed to be at particularly high risk. However, a plausible explanation is that women who had more severe preeclampsia were less likely to become pregnant again than were women with milder disease, and more severe preeclampsia may be a marker for a higher risk of subsequent disease.

The use of linked data from large national registries is a unique strength of the report and allows for a high rate of follow-up of large numbers of women, but drawbacks of these data should be recognized. Although the investigators noted that a registry diagnosis of preeclampsia implied that women met standard criteria for the diagnosis, the accuracy of coding was not validated. Random misclassification would be expected to bias toward the null and would not explain the findings, but the association between preeclampsia and chronic renal disease could be overestimated if women with preeclampsia had unrecognized chronic hypertension, given the strong association between hypertension and subsequent renal disease. It is reassuring that the authors report similar results after the exclusion of women who had a diagnosis of chronic hypertension before pregnancy and women who had prepregnancy diagnoses of diabetes mellitus, renal disease, or rheumatologic disease. However, these conditions may not have been comprehensively recorded or even clinically apparent. Information was not available on body-mass index, and obesity — a recognized risk factor for both preeclampsia and ESRD — may have confounded the observed association. Nonetheless, obesity is unlikely to explain the entire magnitude of the associations observed.

The report by Vikse et al. adds to the accumulating evidence linking complications of pregnancy with future disease, but these data cannot elucidate the critical question of mechanism. Does preeclampsia itself cause permanent renal injury? Do women with a history of preeclampsia in whom ESRD subsequently develops have a preexisting primary renal disease[11] or underlying risk factors predisposing to both preeclampsia and ESRD?

Evidence from other studies may help inform these questions. In case–control and cohort stud-

ies involving assessments in early or mid-pregnancy, women in whom preeclampsia subsequently developed have had higher blood pressures (even within the normal range), higher insulin levels, and higher cholesterol levels than women who remain normotensive, suggesting that derangements predisposing to hypertension, vascular disease, and renal disease antedated the preeclampsia.[12] Furthermore, a study involving postpartum renal biopsies of women who had severe preeclampsia indicated underlying (previously unrecognized) renal disease in more than 1 in 10 women, most frequently those with the early onset of preeclampsia (before 30 weeks of gestation).[13] At the same time, it is biologically plausible that long-term renal dysfunction might result from preeclampsia in some women. The characteristic renal findings in women with preeclampsia — endotheliosis (swelling of glomerular endothelial cells) and marked proteinuria — indicate acute glomerular damage. A "scar" after such damage might heal incompletely, or the injury might progress in a small percentage of subjects, particularly in the setting of associated hypertension and endothelial dysfunction, to the eventual development of chronic kidney disease.[14]

Whatever the basis of the association, the findings of Vikse et al. suggest the potential for early identification of women at increased risk for chronic kidney disease, which is itself a strong risk factor for cardiovascular disease. The number of patients starting treatment with long-term hemodialysis each year in the United States exceeds 100,000. Screening for chronic kidney disease by estimating the glomerular filtration rate and urine protein excretion represents the first major step. Improved control of hypertension and diabetes mellitus (both of which may be particular concerns in women who have had preeclampsia) reduces the risk of progression of renal disease.[15]

Although in the current report the relative risk of the development of ESRD was significantly elevated among women with a history of preeclampsia, the good news is that the absolute risk was quite low. Indeed, the likelihood that chronic renal failure did not develop, even among women with three previous episodes of preeclampsia, was greater than 99%. Nevertheless, the accumulation of data, including those from Vikse et al., suggests that a history of preeclampsia may provide a glimpse into the future, with attendant opportunities for reducing the risks of later disease.

Dr. Thadhani reports being named a coinventor on patents filed by Massachusetts General Hospital for the use of proteins, including angiogenic proteins, for the prediction and diagnosis of preeclampsia that have been licensed to multiple companies and receiving payments for patents related to diagnostics in preeclampsia; he also reports receiving consulting fees from Abbott Diagnostics, Beckman Coulter, Roche Diagnostics, and Ortho Clinical Diagnostics (related to the development of diagnostic tests for preeclampsia). No other potential conflict of interest relevant to this article was reported.

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