OBSERVATIONS

Relationship of Sex to Diabetes Risk in Statin Trials

Statins appear to modestly increase the risk of incident diabetes. While an early trial (the West of Scotland Coronary Prevention Study [WOSCOPS]) suggested possible protection against diabetes (1), the JUPITER study (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) documented a 25% increase in diabetes risk with statin treatment (3 vs. 2.4%, $P = 0.01$) (2). A meta-analysis of 13 statin trials (>91,000 subjects) documented a statistically significant 9% increased risk for incident diabetes (3). Women may be more susceptible than men to develop diabetes while taking statins. While the overall increase in diabetes incidence was 25% in JUPITER, sex stratification revealed that the risk was increased by 49% in women and by only 14% in men (4). A retrospective analysis of the Women's Health Initiative (WHI) found that statin use was associated with a 71% increased risk of diabetes (95% CI, 1.61–1.83); after adjustment for potential confounders, the hazard ratio (HR) remained significant at 1.48 (1.38–1.59) (5). The effect of sex on incident diabetes has not been evaluated in recent meta-analyses (3).

To explore the relationship between the proportion of women in statin trials and diabetes risk, we obtained from the literature (3,6) the odds ratios (ORs) (and 95% CIs) of new-onset diabetes from 13 placebo-controlled statin trials (WOSCOPS, Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS], Long-Term Intervention with Pravastatin in Ischaemic Disease [LIPID], Heart Protection Study [HPS], Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm [ASCOT-LLA], Scandinavian Simvastatin Survival Study [4S], Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Heart Failure [GISSI HF], Controlled Rosuvastatin in Multinational Trial in Heart Failure [CORONA], JUPITER, Stroke Prevention by Aggressive Reduction in Cholesterol Levels [SPARCL], Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Lipid-Lowering Trial [ALLHAT-LLT], Prospective Study of Pravastatin in the Elderly at Risk [PROSPER], Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese [MEGA]) and reviewed the index publications to obtain the percent of women in each. Using SAS version 9.1, we conducted a random-effects meta-regression analysis between natural log-transformed OR of

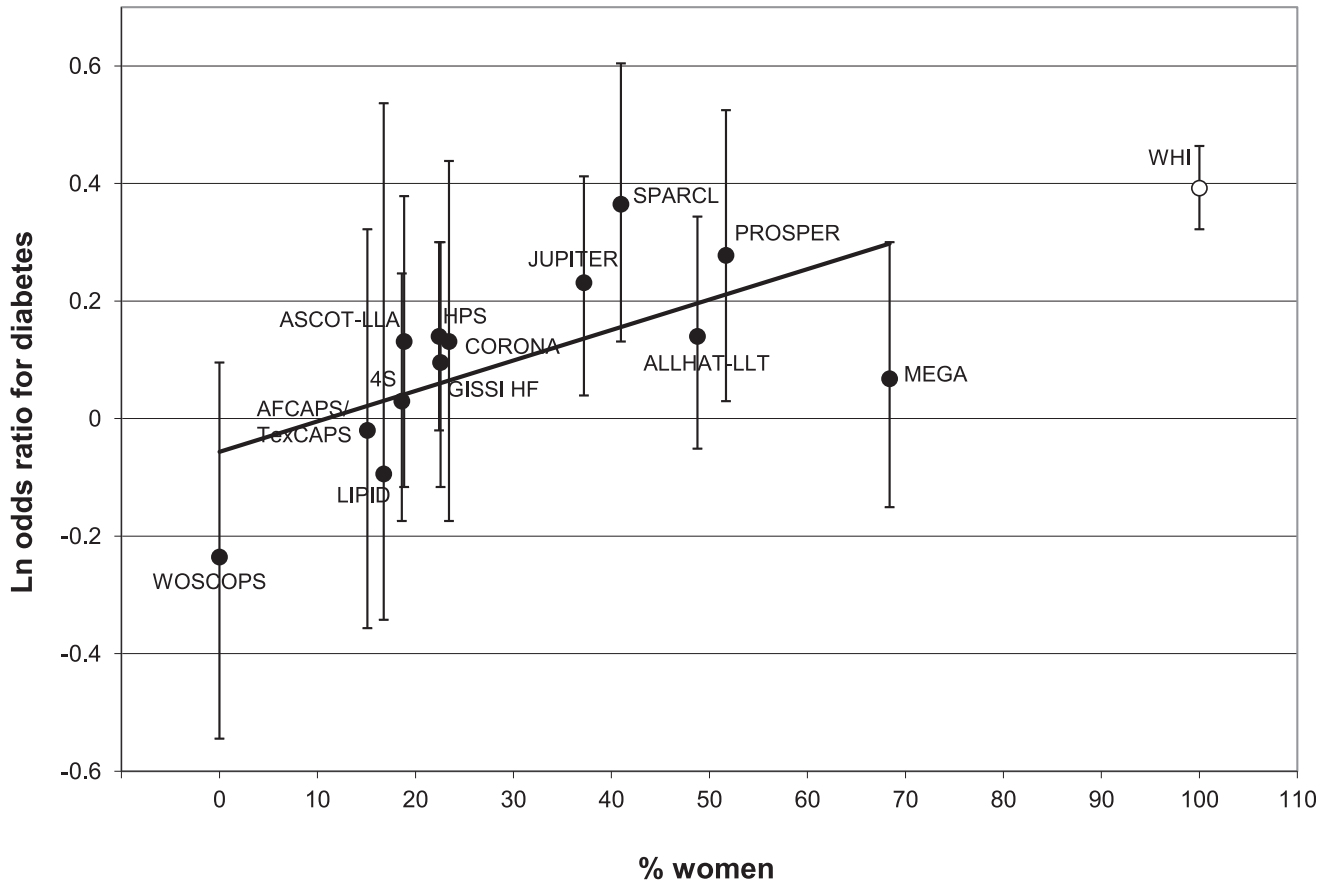

Figure 1—*Meta-regression of percent of women on OR for incident diabetes. Only trials examining statin vs. nonstatin placebo or control arms are represented. The percent of women in each trial was obtained from the index publications. When available, the percent of nondiabetic women was used (HPS, LIPID); otherwise, the percent of women in the trial as a whole was used. ORs (natural log-transformed, ln) for diabetes were obtained from the Sattar et al. meta-analysis (3) and from Waters et al. for SPARCL (6). The error bars represent the 95% CIs. The adjusted HR for diabetes from the WHI is plotted for comparison (open circle); its data were not used in the regression calculation.*

diabetes and proportion of females. A P value <0.05 for the likelihood ratio test for sex was considered statistically significant. We found a significant relationship ($r = 0.6$, $P = 0.036$) between the percent of women in statin trials and the OR of diabetes (Fig. 1). The three trials (JUPITER, PROSPER, SPARCL) that individually had significant rates of diabetes had higher proportions of women (>35%) than usually included in statin trials (<25%), while the one trial (WOSCOPS) suggesting reduced diabetes consisted only of men.

We found a provocative association of female sex with increased odds of diabetes. While the risk of statin-induced diabetes seen in WHI must be interpreted cautiously because it is an observational study, Fig. 1 reveals that the WHI HR for diabetes is consistent with the regression line derived from randomized trials. The possible greater risk of statin-induced diabetes in women is of substantial importance given that women tend to have lower cardiovascular risk than men (4), yet may be prescribed a statin based on lipid levels alone without calculation of cardiovascular risk. If this leads to statin administration to low-risk women, the risk of incident diabetes may outweigh the cardiovascular benefit.

As a meta-regression analysis, our findings are hypothesis generating. One possibility for higher risk in women is smaller body mass and hence greater effective statin dosage. Possibly, the effect of statins on diabetes has been noticed only recently because women have previously been underrepresented in statin trials. Appropriate monitoring for glycemic deterioration and encouragement of preventive lifestyle measures in patients commencing statin therapy may be particularly relevant for women.

Mark O. Goodarzi, md, phd[1,2]
Xiaohui Li, md, phd[2]
Ronald M. Krauss, md[3]
Jerome I. Rotter, md[2]
Yii-Der I. Chen, phd[2]

From the [1]Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, California; the [2]Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California; and the [3]Children's Hospital of Oakland Research Institute, Oakland, California.

Corresponding author: Mark O. Goodarzi, mark.goodarzi@cshs.org.

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