Statins and the Risk of Diabetes: Evidence From a Large Population-Based Cohort Study

OBJECTIVE
To investigate the relationship between adherence with statin therapy and the risk of developing diabetes.

METHODS
The cohort comprised 115,709 residents of the Italian Lombardy region who were newly treated with statins during 2003 and 2004. Patients were followed from the index prescription until 2010. During this period, patients who began therapy with an antidiabetic agent or were hospitalized for a main diagnosis of type 2 diabetes were identified (outcome). Adherence was measured by the proportion of days covered (PDC) with statins (exposure). A proportional hazards model was fitted to estimate hazard ratios (HRs) and 95% CIs for the exposure-outcome association, after adjusting for several covariates. A set of sensitivity analyses was performed to account for sources of systematic uncertainty.

RESULTS
During follow-up, 11,154 cohort members experienced the outcome. Compared with patients with very-low adherence (PDC <25%), those with low (26–50%), intermediate (51–75%), and high (≥75%) adherence to statin therapy had HRs (95% CIs) of 1.12 (1.06–1.18), 1.22 (1.14–1.27), and 1.32 (1.26–1.39), respectively.

CONCLUSIONS
In a real-world setting, the risk of new-onset diabetes rises as adherence with statin therapy increases. Benefits of statins in reducing cardiovascular events clearly overwhelm the diabetes risk.

Hydroxymethylglutaryl-CoA reductase inhibitors, known as statins, are the most effective drugs for the treatment of hypercholesterolemia (1), and their important role in primary and secondary prevention of cardiovascular (CV) morbidity and mortality is well established (2), even among patients with type 2 diabetes (3). However, during the past decade, concern has been raised about the use of statins and the development of diabetes (4). This did not appear to be the case in the post hoc analysis of one of the earliest trials on the CV protective effects of statins, the WOSCOPS (West of Scotland Coronary Prevention Study), which suggested that pravastatin might reduce the risk of diabetes (5). In the more recent JUPITER (Jusificazione for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) trial, rosuvastatin was found to be associated with an increased risk of physician-reported diabetes as well as with a small, though significant, increase in HbA1c levels (6). Two meta-analyses of clinical trials found that among...
patients treated with statins, the risk of developing diabetes was higher than in those treated with placebo (7,8). It should be noted, however, that none of these trials were designed to look for diabetes and that the meta-analyses used a range of methods to detect the condition.

Because statins are among the most commonly prescribed drugs and diabetes affects a substantial and increasing proportion of the population worldwide, efforts aimed at elucidating the magnitude of the association between use of statins and diabetes risk have major implications for public health. To address this issue, we used the data provided by the health-care utilization databases of Lombardy, a region of Italy with ~10 million inhabitants. This large cohort study investigated whether increasing levels of adherence with statin therapy increases the risk of developing physician-diagnosed diabetes and estimated the magnitude of the dose-response relationship. Controlling for sources of systematic uncertainty was of particular concern in this study.

RESEARCH DESIGN AND METHODS
Health-care Utilization Database of Lombardy
The data used for the current study were retrieved from the health-care utilization databases of Lombardy, a region of Italy that accounts for ~16% of Italy’s population. The Italian population is covered by the National Health Service (NHS), and in Lombardy, an automated system of databases collects a variety of information, including 1) an archive of residents who receive NHS assistance, reporting demographic and administrative data; 2) a database on diagnosis at discharge from public or private hospitals of the region; 3) a database on outpatient drug prescriptions reimbursable by the NHS; and 4) a database on outpatient visits, including visits in specialist ambulatory care and diagnostic laboratories accredited by the NHS. For each patient, we linked these databases through a single identification code. Full details of the procedures are reported elsewhere (9).

Cohort Selection and Follow-up
The target population comprised all NHS beneficiaries aged 40–80 years living in Lombardy. According to the 2011 Italian census, this population was 5,097,075 individuals. Of these, we identified patients for whom at least one prescription of statins was dispensed during 2003 and 2004, and the first dispensation was defined as the index prescription. To make data relevant to the study aim, four patient categories were excluded: 1) patients who received one or more prescriptions of a statin within 3 years before the index prescription, 2) patients who received at least one antidiabetic agent or were hospitalized for a primary or secondary diagnosis of diabetes within 3 years before the index prescription, 3) patients who did not reach at least 1 year of follow-up, and 4) patients who received only one dispensation of statins during the first year after the date of index prescription. The remaining patients represented the study cohort. Each member of the cohort accumulated person-years of follow-up from the date of index prescription until the earliest among the dates of new-onset diabetes (see next section) or censoring (i.e., death from any cause, emigration, or 31 December 2010 [end of follow-up]).

Outcome Identification
Cohort members who experienced at least one sign suggestive of the occurrence of diabetes during follow-up were identified. The date of the first dispensation of an antidiabetic agent (Anatomical Therapeutic Chemical Classification System code A10) or of hospitalization with a primary diagnosis of diabetes (ICD-9 code 250) was assumed as the date of outcome onset, whichever was earlier. However, because of the possibility that one isolated dispensation of an antidiabetic agent might be an inappropriate initial drug treatment, in a secondary analysis, we used a more-specific diagnostic criterion by requiring that at least three antidiabetic prescriptions be dispensed to consider a patient as having the outcome.

Assessment of Exposure to Statins
We identified all prescriptions dispensed to the cohort members during follow-up. The period covered by a prescription was calculated from the number of tablets in the dispensed canisters, assuming a treatment schedule of one tablet per day (10). For overlapping prescriptions, the individual was assumed to have completed the former one before starting the second. Adherence to therapy was assessed as the cumulative number of days during which the medication was available divided by the number of days of follow-up, a quantity referred to as the proportion of days covered (PDC) (11). Patients were categorized as having very-low (PDC < 25%), low (PDC 25–49%), intermediate (PDC 50–74%), and high (PDC ≥ 75%) adherence. To avoid the arbitrary nature of this categorization, in a secondary analysis, we used quartile categories of PDC for the entire period of follow-up to define increasing levels of exposure to statins.

PDC categories were also considered according to the potency of the statins dispensed during follow-up. Based on a systematic review and meta-analysis of randomized controlled trials that quantified the effect of statins on serum LDL cholesterol concentration (12), treatment with high-potency statins was defined as 10 mg rosuvastatin, ≥ 20 mg atorvastatin, and ≥ 40 mg simvastatin, whereas all other statin treatments were defined as low potency.

Covariates
For each cohort member, data also included 2) sex, age, and type of statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin) at the index prescription; 2) concomitant use of other drugs during follow-up (antihypertensive, nitrate, digitalis, antiarrhythmic, corticosteroid, oral contraceptive, cyclosporine, antipsychotic, and antidepressant agents); 3) hospitalizations for CV diseases in the 3 years before the index prescription; 4) the Charlson comorbidity index score (13), which was calculated from the diagnostic information available from inpatient charts in the 3 years before and 1 year after the date of the index prescription; and 5) the number of serum cholesterol tests and specialist visits during the first year after the date of the index prescription.

Data Analysis
The $\chi^2$ test was used for the trend and linear regression model when appropriate to test differences in demographic and clinical characteristics with increasing levels of statin adherence. The incidence rate of diabetes was calculated by the ratio between the number of cases of incident diabetes and the number of person-years accumulated during follow-up.
Cox proportional hazard regression was used to estimate the hazard ratio (HR) and 95% CI for the association between exposure to statins and time of diabetes onset. The predictor variables of interest were the factors constructed according to the categories of PDC, using the very-low-adherence category as reference. Because drug exposure may vary over time, assessment of its value requires proper accounting for the cumulative and varying nature of the measure. This was done by including adherence categories as time-dependent variables in the model.

The relationship of the risk of diabetes with increasing exposure to statins as a whole as well as to low-potency and high-potency statins separately was assessed using both unadjusted and adjusted HRs. Adjustment included these reported covariates as time-fixed (i.e., those measured at index prescription) or time-dependent (concomitant use of other drugs) factors. Trends in HRs were tested, when feasible, according to the statistical significance of the regression coefficient of the recorded variables obtained by scoring the corresponding categories. The null hypothesis of equality in the regression coefficients of low-potency and high-potency statins was tested by the z score.

Sensitivity Analyses
To verify the robustness of the findings, the following sensitivity analyses were performed: 1) As mentioned previously, we adopted various ways for categorizing exposure to statins (predefined or quartile categories of PDC) or for identifying incident diabetes (one to three prescriptions of antidiabetic drugs during follow-up), and 2) we checked the possibility that our estimates were affected by detection bias (14) (i.e., that long-term exposure to statins and a more-regular prescription renewal imply a more regular use of primary care services, triggering the search for diabetes). Detection bias was investigated by estimating the statistic—incident diabetes relationship in the cohort members stratified according to the number of cholesterol tests and outpatient specialist visits during the first year of follow-up. The rationale is that the relationship would move toward that expected under the null among patients who did not use laboratory analysis services and/or attend specialist visits.

Finally, although our estimates were adjusted for a number of factors and because relevant clinical features were not available in the databases, we addressed the potential bias generated by unmeasured confounders. For example, we considered obesity as a potentially important unmeasured confounder because obesity is a major predictor of diabetes (15) and can influence adherence to statin therapy (16,17), which means that failing to adjust for its effects can move the results toward or away from the null. We made a quantitative assessment of the obesity-related bias by using the Monte Carlo sensitivity analysis (18). We set 1) the prevalence of the obesity among users of statins to 37.5% (19), 2) the risk of diabetes in obese patients to threefold higher than in normal weight patients (15), and 3) the odds of obese patients belonging to the highest PDC category from twofold lower to twofold higher than that of normal weight patients (16,17). The Monte Carlo sensitivity analysis corrected the observed HRs for the bias factor calculated from the previously mentioned data and took into account random uncertainty for adjusting estimates. Full details on the Monte Carlo sampling procedure and computing method are reported elsewhere (20). For all hypotheses tested, a two-tailed \( p < 0.05 \) was considered significant.

RESULTS
Patients
The distribution of the exclusion criteria is shown in Supplementary Fig. 1. The 115,709 patients included in the study cohort accumulated 748,049 person-years of observation, with an average follow-up of \(-6.4\) years per patient.

Table 1 shows the characteristics of the entire cohort as well as stratification by adherence to statin therapy. At the index date, the mean age was \(-62\) years, and 49\% were men. Almost one in three patients began therapy with atorvastatin or simvastatin. Most patients were cotreated with antihypertensive drugs, whereas cotreatment with other drugs was less frequent. More than 30\% of the cohort was hospitalized previously for CV diseases. Other chronic comorbidities were identified in more than one in four patients. During the first year of follow-up, almost one in five patients and \(-6\%\) of patients did not have a serum cholesterol test or attend a specialist visit, respectively.

During follow-up, 11,154 cohort members experienced the study outcome, with an incidence rate of 14.9 new cases of diabetes per 1,000 person-years. More than one-half (57.3\%) had very-low or low adherence to statin therapy. Very-low or low adherence was more common in women; in patients who began therapy with fluvastatin or pravastatin; and among patients who did not use other drugs, were not hospitalized previously for CV disease, or did not have other chronic comorbidities. Patients with a higher number of serum cholesterol tests and specialist visits had higher adherence to statin therapy.

Adherence to Statin Therapy and Risk of Diabetes
There was a continuous and significant trend toward an increase of diabetes risk as adherence to statin therapy increased both in the unadjusted and in the adjusted risk models (58\% [95\% CI 51–66\%] vs. 32\% [26–39\%] for high adherence vs. very-low adherence, respectively) (Fig. 1A and B). Although high-potency statins showed a greater action on diabetes risk than low-potency statins (Fig. 1C and D), there was no statistical evidence that the effect of statins on diabetes risk differed according to their potency (\( P_{\text{trend}} = 0.372 \)).

The relationship did not substantially change by 1) varying the criteria for categorization of adherence with statin therapy or 2) considering a more demanding criterion for diabetes diagnosis. In particular, taking the first category of exposure as the reference, the HR (95\% CI) of diabetes increased to 1.11 (1.00–1.23), 1.23 (1.16–1.31), and 1.37 (1.29–1.45) by increasing quartiles of PDC and to 1.19 (1.11–1.27), 1.35 (1.26–1.45), and 1.53 (1.44–1.64) by the alternative criterion for diabetes diagnosis.

Detection Bias
The combined action of adherence to statin therapy and frequency of cholesterol tests and outpatient specialist visits on the risk of diabetes is shown in Fig. 2. Among patients with very-low adherence to statin therapy, the risk of diabetes decreased with the number of serum cholesterol tests but increased as the number of specialist visits increased.
Of note, evidence of a trend toward increasing risk of diabetes as adherence to statin therapy increased was also observed in patients who did not receive cholesterol tests (top panel) or outpatient specialist visits (bottom panel).

**Unmeasured Confounding**

Figure 3 shows the risk of diabetes associated with treatment adherence (exposure-outcome HR) after adjustment for an unmeasured confounder expected to be from twofold less to twofold more frequent among patients with high treatment adherence (confounder-exposure odds ratio [OR]). As expected, the trend in exposure-outcome HR was progressively driven toward the null as the confounder-exposure OR increased (i.e., as the confounder prevalence progressively increased among patients with high adherence). The significant exposure-outcome excess risk associated with high adherence observed in the main analysis became nonsignificant (1.13 [1.00–1.28]) whether the confounder-exposure OR was $\geq 1.84$ (e.g., obese patients in the lowest adherence category had a prevalence odds 1.84-fold higher than those in the highest adherence category). However, the point estimate of exposure-outcome association was never annulled, even for the highest considered disparity of treatment adherence between obese and normal weight patients.

**CONCLUSIONS**

The results show that compared with patients who used statins for a small portion of the follow-up period, those who exhibited a more continuous use...
of statins had a 32% excess risk of new-onset diabetes. Furthermore, the results show that an increased risk of new-onset diabetes is related to all available statins at all doses. The results failed to show, however, significant evidence that high-potency statins exert a stronger action on diabetes development than low-potency statins. In summary, this population-based study supports the notion that continuous use of statins is associated with a nonmarginal increase in the risk of developing diabetes in a real-life setting.

Comparison With Available Evidence
The current findings confirm and extend the results of the JUPITER trial, which was the first to find that new-onset diabetes was 27% more common in patients treated with statins than in those receiving placebo (5), as well as the results of the PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) trial, which showed that new-onset diabetes increased by 30% in the pravastatin group compared with the placebo group (21). Even more clear-cut risk excesses (+20% and +48%) have been reported from observational investigations (8,19,23).

Meta-analyses of clinical trials, however, showed a weaker increased risk of new-onset diabetes by ~10% (7,8,23). Finally, the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial showed that high-dose atorvastatin treatment compared with placebo is associated with a 37% excess risk of diabetes (24).

The current findings differ from those of a large cohort study, bolstering the suggestion that statin-induced diabetes is likely a class effect (8), and of a meta-analysis of clinical trials showing that intensive- versus moderate-dose statin therapy is associated with a greater risk of diabetes (25). Two large randomized trials, however, consistently showed that atorvastatin 80 mg daily is associated with a weak and nonsignificant excess of diabetes compared with atorvastatin 10 mg daily (HR 1.10 [0.94–1.29]) or simvastatin 20 mg daily (HR 1.19 [0.98–1.43]) (24).

Plausibility
The mechanisms underlying the diabetogenic influence of statins are incompletely understood. Atorvastatin and simvastatin have been shown to decrease glucose uptake in adipocyte cell lines (26) and insulin sensitivity (27), respectively. Simvastatin and atorvastatin have been shown to decrease insulin secretion in β-cells (28). The inhibition of isoprenoid synthesis may explain some of the observed dysglycemic effects of statins (26). Finally, it has been hypothesized that statins may influence muscle or liver insulin sensitivity directly, but there is no specific experimental evidence to support this hypothesis (29).

Strengths and Weaknesses
The current study is unique in several respects. First, the investigation was based on data from a very large unselected population, which was made possible because of a cost-free health-care system for virtually all Italian citizens. Second, the drug prescription database provides highly accurate data because report of prescriptions by the pharmacies is essential for reimbursement, and filing of an incorrect report about dispensed drugs has legal consequences (30). Third, patients were identified from the point of the initial lipid-lowering therapy, and the complete sequence of the subsequent prescriptions for statins was available. Fourth, we were able to include patients

![Figure 1](https://care.diabetesjournals.org/)

**Figure 1**—Effect of adherence to statin therapy on the HRs for diabetes. HR was estimated according to Cox proportional hazard model. A and B: Crude and adjusted estimates of all statins. C and D: Adjusted estimates of high-potency and low-potency statins. Adjustments were made for age (continuous), sex, first-line statin therapy, concomitant use of other drugs, history of CV disease, and categories of the Charlson comorbidity index score (see Table 1 for the complete list of covariates included in the model).
without previous clinical evidence (drug treatment and/or hospitalization) of diabetes so that the data relate to the effect of statin use on new-onset of diabetes. Finally, a number of sensitivity analyses were performed, which increased the robustness of the findings.

The study has a number of potential limitations. First, evaluation of statin adherence was based on pharmacy-dispensing information. This method assumes that the PDC by a prescription corresponds to the proportion of days of medication use. Small, insignificant differences between the assessed number of dispensed pills and the actual pill count were reported by a study investigating adherence to statin therapy over 12 months (31). Furthermore, data on dispensing history have been shown to be consistent with other adherence measures, drug serum levels, and clinical drug effects (32). Nevertheless, the use of medication dispensing as a measure of adherence remains a source of uncertainty in our estimates.

Second, because of privacy regulations, identification codes of prescription records were not available for analysis, so drug-based diagnoses of diabetes cannot be scrutinized and validated. However, it seems highly unlikely that diagnostic errors could differentially affect patients according to their adherence to statins. Moreover, the adherence-diabetes relationship was confirmed, and indeed amplified, when a more stringent diagnostic criterion for new-onset diabetes was used, which raises the possibility that the statin-dependent risk of developing diabetes might be greater than that resulting from the primary diagnostic criterion we adopted. It should also be mentioned that the improved diagnostic specificity obtained with the stricter criterion minimizes bias of a risk estimate that includes diagnostic misclassification.

Third, our estimates might be affected by detection bias; that is, patients with long-term adherence to statin therapy may have been more likely to receive a diagnosis of diabetes. However, we found a clear relationship between adherence with statins and risk of diabetes, even among patients who did not undergo laboratory examinations or outpatient specialist visits. Thus, the excess risk of diabetes also concerned patients with low use of health services, making it unlikely that detection bias explains the main findings.

Finally, whether the observed findings are a result of our inability to fully account for higher adherence to statin therapy in patients at higher risk of diabetes is the more relevant question in interpreting the findings. Baseline fasting serum glucose and other components of the metabolic syndrome, such as triglyceride level, BMI, and hypertension (24), might be more frequent in
Figure 3—Changes in HRs (and 95% CIs) for the risk of diabetes (outcome) associated with high adherence to statin therapy (exposure) after external adjustment for obesity (confounder). External adjustment was performed by means of Monte Carlo sensitivity analysis. Adjusted estimates were obtained by means of setting 1) the prevalence of obesity among statin users to 37.5% (12); 2) the risk of diabetes in obese patients to threefold higher than in normal weight patients (25); and 3) the odds of obese patients in the highest PDC category from twofold lower to twofold higher than that of normal weight patients (26,27).

individuals with high rather than low adherence to statin treatment. Because our databases have a limited amount of clinical information, we dealt with confounding in several ways. First, only statin users were included in the cohort to compare the duration of statin therapy, whereas inclusion of nonusers would be for observational investigations (8,19). In this way, the potential for confounding is reduced by actively comparing patients with the same indication at baseline (33). Second, our estimates were adjusted for a number of available demographic, therapeutic, and clinical characteristics, such as cotreatment with antihypertensive and other agents, history of CV disease, and categories of Charlson comorbidity index score. Third, the statin-diabetes relationship was observed within each stratum of frequency of laboratory examinations and outpatient specialist visits. Because medical attention might be considered a proxy of clinical profile and other unmeasured risk factors for diabetes, this further protects our conclusions, although residual confounding cannot be excluded. For this reason, we also performed a sensitivity analysis and showed that the association between adherence to statin treatment and the risk of diabetes was not annulled after correction for an unmeasured confounder of great importance for the development of diabetes, obesity. It should be emphasized that beyond obesity, no other unmeasured factor is able to annul the investigated relationship, even if it is characterized by very-high prevalence (i.e., up to 37.5%), strongly affects the outcome (i.e., up to threefold increased diabetes risk), and is markedly more diffuse among adherent patients (i.e., up to twofold more than in those with little adherence to statin therapy). In such conditions, an increased risk of diabetes weaker than that found in our main analysis is expected. This possibly explains the stronger association generally reported by observational investigations than reported in clinical trials.

Implications for Benefits of Statin Treatment
Assuming that 1) the diabetes incidence rate among patients with very-low adherence to statin therapy represents the baseline rate of new-onset diabetes because diabetes is unlikely to develop during very-short-term statin use and 2) diabetes develops in patients with high adherence to statins at a rate 1.32-fold faster than the baseline rate, we expected that ~280 patients would have to be continuously treated to induce one case of diabetes every year. In a meta-analysis of seven randomized controlled trials of statin use versus control in patients with diabetes, statins decreased major CV and cerebrovascular events every 40 patients treated (34).

Consistent with our calculation, a meta-analysis reported that treating 255 patients with statins for 4 years would induce one case of diabetes, but in the meantime, it would prevent 5.4 coronary deaths or myocardial infarctions for each millimolar reduction in serum LDL cholesterol (6). Thus, the CV protection offered by statins appears to markedly outweigh the increased incidence of diabetes, although the adverse effect of diabetes on CV risk (35) suggests that the original statin-dependent protection might decline with time. The decline might be less than predicted based on epidemiological data on diabetes and CV morbidity and mortality, however, because whether the prognostic value of drug-induced diabetes is equivalent to that of native diabetes is still uncertain (36). This has been reported to be the case in some studies (37,38), whereas in other studies, a few years or even long-term exposure to diabetes induced by antihypertensive drugs was not found to increase CV morbidity or fatal events (24,39).

In conclusion, this large population-based cohort study extends earlier findings of an increased risk of diabetes with statin therapy by providing evidence of a clear-cut association between adherence to statin therapy and risk of new-onset diabetes in a real-world setting. It appears from event-based investigations that benefits of statins in
reducing CV events clearly overwhelm the diabetes risk.

**Duality of Interest.** G.M. discloses consultancy agreements with Boehringer Ingelheim and Novartis and participation in speakers bureaus for Bayer, Boehringer Ingelheim, Merck Sharp & Dohme, Manar International, Novartis, Recordati, Sanofi, Sankyo, and Servier. No other potential conflicts of interest relevant to this article were reported.

**Author Contributions.** G.C. contributed to the initial study idea, interpretation of the results, and drafting of the manuscript. B.I. contributed to the protocol, preparation of the data set for analysis, data analysis, and interpretation of the results. F.N. contributed to the sensitivity analysis and interpretation of the results. M.C. contributed to the protocol and interpretation of the results. G.G., and G.M. contributed to the interpretation of the pharmacological and clinical prospective results and review of the manuscript. G.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**References**