Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

# Clinical significance of diabetes likely induced by statins: Evidence from a large population-based cohort

Giovanni Corrao [a,b,*], Matteo Monzio Compagnoni [a,b], Federico Rea [a,b], Luca Merlino [c], Alberico L. Catapano [d,e], Giuseppe Mancia [f]

[a] Interuniversity Centre of Healthcare Research & Pharmacoepidemiology, Laboratory of Healthcare Research & Pharmacoepidemiology, University of Milano-Bicocca, Milan, Italy
[b] Department of Statistics and Quantitative Methods, Division of Biostatistics, Epidemiology and Public Health, University of Milano-Bicocca, Milan, Italy
[c] Operative Unit of Territorial Health Services, Lombardy Region, Milan, Italy
[d] Department of Pharmacological and Biomolecular Sciences, Centre of Epidemiology and Preventive Pharmacology (SEFAP), University of Milano, Milan, Italy
[e] IRCSS Multimedica, Sesto San Giovanni, Milan, Italy
[f] Faculty of Medicine, University of Milano-Bicocca, Milan, Italy

ARTICLE INFO

*Article history:*
Received 6 April 2017
Received in revised form
13 July 2017
Accepted 14 August 2017
Available online 19 August 2017

*Keywords:*
Adherence
Cohort study
Healthcare utilization database
Macrovascular outcomes
Statins
Type 2 diabetes

ABSTRACT

*Aim:* To provide information on the extent to which type 2 diabetes more likely induced by statins affects the risk of macrovascular complications compared to diabetes unlikely induced by statins.

*Methods:* The 84,828 residents in the Italian Lombardy Region who were newly treated with statins between 2003 and 2005 were followed from the index statin prescription until 2009 (step-1 follow-up) to identify those starting antidiabetic therapy. The proportion of days of follow-up covered by statins measured adherence with statins. Cohort members who experienced diabetes were 1:3 matched with those who did not developed diabetes for gender, age and previous adherence with statin treatment. The 3321 diabetic - non-diabetic sets, were followed from the initial antidiabetic therapy until 2012 (step-2 follow-up) to estimate the hazard ratio (HR), and 95% Confidence Interval (CI), for macrovascular complications (proportional hazard models) associated with diabetes separately in each category of adherence with statins.

*Results:* During the step-1 follow-up, the risk of new-onset diabetes increased progressively with increasing adherence with statins. During the step-2 follow-up, the risk of macrovascular complications associated with diabetes decreased progressively from 1.70 (1.18–2.44), 1.41 (1.17–1.70), 1.30 (1.07–1.57) until 1.10 (0.40–2.80) as adherence with statins during the step-1 follow-up increased.

*Abbreviations:* CI, confidence interval; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HF, heart failure; MI, myocardial infarction; NHS, National Health Service; NSAIDs, non-steroidal anti-inflammatory drugs; PDC, proportion of days covered; HR, hazard ratio

* Corresponding author at: Dipartimento di Statistica e Metodi Quantitativi, Università degli Studi di Milano-Bicocca, Via Bicocca degli Arcimboldi, 8, Edificio U7, 20126 Milano, Italy.
E-mail address: giovanni.corrao@unimib.it (G. Corrao).

http://dx.doi.org/10.1016/j.diabres.2017.08.008

*Conclusions:* Type 2 diabetes lost its association with increasing macrovascular risk when previous adherence with statins was very high, and thus the chance of its induction by the drug greater. Statin-dependent type 2 diabetes might be prognostically less adverse than diabetes unlikely induced by statins.


## 1. Introduction

A large number of studies has shown that use of statins is accompanied by an increased risk of developing type 2 diabetes [1–5], which is thus currently listed as an inconvenience of these drugs that may attenuate in some patients their protective effect. However, several aspects of the statin-induced diabetes have not been adequately clarified. For example, albeit several hypotheses have been advanced, the mechanisms through which statins favour the alteration of glucose metabolism that leads to the appearance of hyperglycaemia and diabetes remain unclear [4,6]. Furthermore, although statin-induced diabetes is generally believed not to offset the protective lipid-lowering effect of statins on the cardiovascular (CV) system [7–9], limited information exists on whether statin-induced diabetes has the same adverse prognostic significance of diabetes unlikely induced by statins, i.e., whether it is associated with a similar increasing risk of diabetes-related macrovascular complications. This information is of fundamental importance to reliably quantify the impact of statin-induced diabetes on the role played by statins on primary and secondary CV prevention [10,11].

We have previously shown that at the population level an increasing adherence with statin treatment is accompanied by a clear-cut progressive increase in the risk of new onset type 2 diabetes [12]. The purpose of the present study was to provide information on the extent to which diabetes more likely to be induced by statins affects the risk of macrovascular complications to a similar or different degree compared to diabetes unlikely induced by statins.

## 2. Subjects, materials and methods

### 2.1. Setting

The data used for this study were retrieved from the healthcare utilization databases of Lombardy, a Region of Italy which accounts for about 16% (almost ten million) of its population. In Italy, the whole population is covered by the National Health Service and in Lombardy this has been associated since 1997 with an automated system of databases to collect a variety of information. A detailed description of the healthcare utilization databases of the Lombardy Region for studying the association between lipid lowering and antidiabetic treatments is available in previous studies [12,13].

### 2.2. Cohort selection and follow-up – step-1

The study was designed according to the procedure shown in Fig. 1, upper part. All the 651,552 beneficiaries of the National Health Service who had their residence in Lombardy were identified, provided that their age was between 40 and 80 years and at least one prescription of statins had been dispensed between 2003 and 2005. The date of the first dispensation was considered as the step-1 index date.

Four patient categories were excluded: (i) the 372,302 patients who received one or more statin prescriptions within three years prior the step-1 index date; (ii) the 51,912 patients who received at least one antidiabetic agent, or were hospitalized with a diagnosis of diabetes, within the three years before the step-1 index date; (iii) the 70,827 patients who were hospitalized for CV disease or received prescriptions of CV drugs such as nitrates or digitalis within the three years before the step-1 index date; and (iv) the 71,683 patients who did not renew the initial prescription of statins and/or did not reach at least one year of follow-up.

The remaining 84,828 patients represented the step-1 cohort, each of its members accumulating person-years of follow-up from the step-1 index date until the earliest among the dates of starting antidiabetic drug therapy (step-1 outcome, see below) or censoring, e.g. death from any cause, emigration or step-1 phase stopping (i.e., December 31st 2009). The step-1 outcome was the appearance of diabetes as diagnosed by the prescription of antidiabetic drugs. To minimize the risk of false positive diabetic cases, three antidiabetic drug prescriptions were required for the ascertainment of step-1 outcome onset.

### 2.3. Cohort selection and follow-up – step-2

As shown in Fig. 1, lower part, the 4391 step-1 cohort members who experienced the step-1 outcome and the 77,893 statin-treated patients who did not have any antidiabetic drug dispensation were considered eligible for inclusion in the step-2 cohort. For each cohort members who experienced the step-1 outcome (who we assumed to be diabetics), up to three patients without signs of diabetes were randomly selected from the corresponding cohort to be matched for gender, age at cohort entry (±1 year), step-1 index date (±30 days) and adherence with statin therapy (see below). Patients without signs of diabetes were assumed to be at risk of diabetes when the matched patient with diabetes suffered from it. To minimize the chance of outcomes (see below) unrelated to diabetes, the 1070 sets (each formed by 1 patient

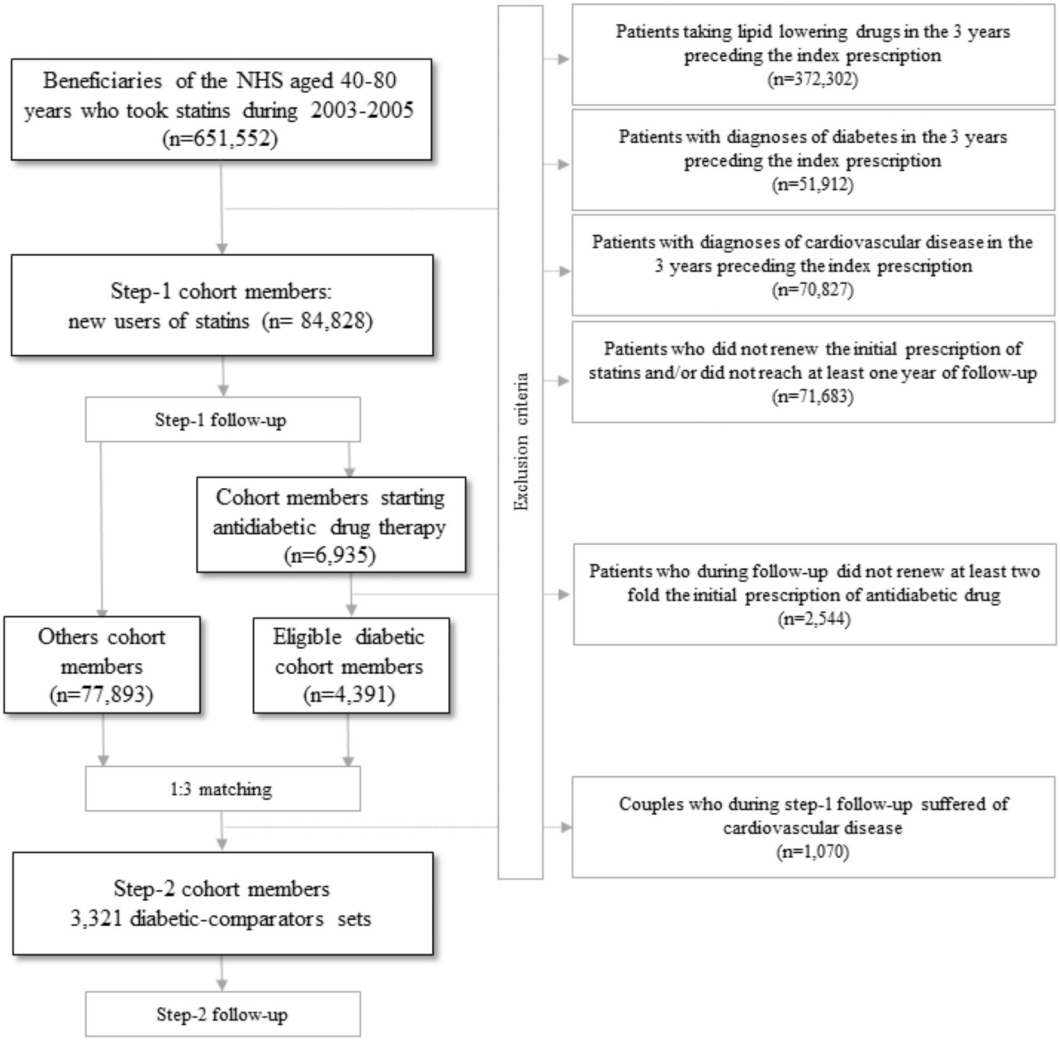


**Fig. 1 – Flow-chart of selection of the cohorts.**
***Footnote*: NHS: National Health Service; CV: Cardiovascular.**

with diabetes and 3 matched patients without diabetes) who experienced a hospitalization for CV disease during the step-1 follow-up were excluded. The remaining 3321 diabetic and non-diabetic matched sets represented the step-2 cohort, each of its members accumulating person-years of follow-up from the date of the first antidiabetic drug prescription (i.e., the step-2 index date), until the earliest among the dates of step-2 outcome (first admission to public or private hospitals for macrovascular complications), death from any cause, emigration, or December 31st 2012. Macrovascular complications included myocardial infarction, peripheral vascular disease, myocardial revascularization, heart failure and cerebrovascular disease requiring hospitalization, as reported by the diagnosis at discharge from hospital. The diagnostic codes employed are reported in the Supplementary Table S1.

### 2.4. *Adherence with medications*

All prescriptions of statins dispensed to the cohort members during the step-1 follow-up were identified. 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 [14]. For overlapping prescriptions, a patient was assumed to have used all tablets of the previous canister before starting to use the newer one. Adherence with therapy was quantified as the cumulative number of days during which the medication was available divided by the number of days of follow-up, i.e., the "proportion of days covered" (PDC) by treatment [15]. The antidiabetic and antihypertensive drugs dispensed to the statin-treated patients with diabetes during their follow-up were identified as well, and adherence with these treatments was also quantified through the PDC calculation. The codes used to identify therapeutic categories are reported in the Supplementary Table S1.

### 2.5. *Additional information*

At the step-1 index date, data included (1) the type of the prescribed statin (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin or simvastatin); (2) previous use of antihypertensive, antiarrhythmic, antithrombotic and

antidepressant agents, fibrates, as well as of non-steroidal anti-inflammatory drugs and drugs used for chronic obstructive lung disease; and (3) the Charlson comorbidity index score [16], which was calculated from the diagnostic information available from inpatient charts in the three years prior the step-1 index date. At the step-2 index date information also included adherence with statins during the step-1 follow-up as well as with antidiabetic agents during the step-2 follow-up.

### 2.6. Data analysis

A two-stage data analysis was employed. In the first stage, we looked for replication of our previous findings [12] that increasing the level of adherence with statins increases the risk of developing diabetes (the step-1 outcome), using the step-1 cohort. The Cox proportional hazard regression was used to estimate the hazard ratio (HR), and the 95% CI, of diabetes associated with adherence with statins. Adherence was quantified by four PDC categories, i.e. a very low (PDC $\leq$ 10%), low (PDC from 11% to 50%), intermediate (PDC from 51% to 89%) and high (PDC $\geq$ 90%) adherence with statins. The first category included patients who almost never used statins while the last one those who almost always used these drugs, which made the chance for new onset diabetes to be drug dependent very low and very high, respectively. Because drug exposure may vary over time, adherence categories were included in the model as time-dependent variables, thereby accounting for their cumulative and varying nature. The model included as covariates those above listed as additional information considered at step-1 index date.

The second-stage data analysis focused on whether the greater or lesser chance for diabetes to be induced by statins translated into a different risk of macrovascular complications. To this aim, the 3321 matched sets forming the step-2 cohort were stratified according to the four categories of adherence with statins used for the step-1 follow-up. The overall risk of macrovascular complications associated with the diabetic condition was calculated for the entire cohort, as well as separately in each category of adherence with statins, using the HR, and 95% CI, derived from the Cox proportional hazard model. The risk of each specific macrovascular complication was also estimated provided that the incidence at least 200 cases was available (being the limitation adopted to ensure against a two-sided type I error of 0.05 and a HR of at least 1.5, with a power of 0.80). Aforementioned covariates (with the exclusion of matching variables), both as time-fixed (those measured at the step-1 index date) and time dependent (those measured during the step-2 follow-up) variables, were included in the model.

We assumed that: (i) the likelihood that diabetes was induced by statins would increase from the lowest to the highest category of adherence with statins; (ii) because diabetic and non-diabetic patients were matched for statin adherence, the HRs of macrovascular complications would not be affected by statins and (iii) if the adverse prognostic significance of statin-induced diabetes was similar to that of diabetes not due to statin, the risk of macrovascular complications associated with diabetes would be similar in all categories of adherence with statins. It would, on the other hand, show a progressive attenuation of the risk of macrovascular complications associated with diabetes along categories of increasing adherence with statins if the adverse prognostic significance of statin-induced diabetes was less adverse than that of diabetes unlikely due to statins. Statistically talking, this is equivalent to test the null hypothesis that the HRs of macrovascular complications (on logarithmic scale) do not vary linearly along the categories of adherence with statins.

Two ancillary analyses were performed to check whether interpretation of the risk of macrovascular complications in diabetic patients with a different adherence with statins might be affected by (i) a delayed protective effect of statins dispensed during the step-1 follow-up and/or (ii) the exclusion of patients with CV events during the step-1 follow-up or before the inclusion in the study, with thus a selection of those less susceptible to the protective effect of the drug. The former possibility was addressed by calculating the risk of macrovascular complications at different degrees of adherence with statins starting 3 or 6 years after the initial drug dispensation in order to verify whether the CV outcomes observed in the step-2 follow-up may be affected by the adherence with statins during the step-1 follow-up. The latter possibility was addressed by including in the analysis also patients experiencing hospitalizations for CV events during the step-1 follow-up or in the 3 years before the step-1 index date.

The Statistical Analysis System Software (version 9.4; SAS Institute, Cary, North Carolina, USA) was used to perform the analyses. For all hypotheses tested, two-tailed p-values less than 0.05 were considered to be significant.

## 3. Results

### 3.1. New onset diabetes under statin treatment – step-1

The 84,828 patients belonging to the step-1 cohort accumulated 467,317 person-years of follow-up, on average 5.5 years per patient. During this period 6935 patients exhibited new onset diabetes (the step-1 outcome) with an incidence of 14.8 cases every 1000 person-years. The characteristics of step-1 cohort members according to whether they developed or did not develop diabetes are reported in Table 1. Compared with patients who did not develop diabetes, those developing diabetes were older, more often males, and more often under atorvastatin, as well as other drug treatments (antihypertensive, antithrombotic, anti-inflammatory and respiratory agents). Patients who developed diabetes also exhibited an overall higher adherence with statins than patients who did not develop diabetes.

As shown in Fig. 2, the risk of developing diabetes raised progressively and significantly as adherence with statins increased. Compared to patients with very low adherence, the increase was 24% (95% CI: 12–37%), 72% (95% CI: 56–90%), and 95% (95% CI: 60–139%) for patients with low, intermediate and high adherence, respectively. Assuming that among patients with very low adherence, diabetes was entirely unrelated to use of statins, the proportion of diabetes attributable to use of statins [17,18] was 19% (95% CI: 11–27%), 42% (36–47%) and 49% (38–58%) for patients with low,

**Table 1 – Characteristics of the 84,828 step-1 cohort members according to whether they developed or did not develop diabetes (antidiabetic drug therapy initiation) during the step-1 follow-up.**

| | New onset diabetes (n = 6935) | No new onset diabetes (n = 77,893) | p-Value[a] |
|---|---|---|---|
| **Baseline** | | | |
| Men | 3300 (47.6%) | 31,718 (40.7%) | <0.0001 |
| Age: mean (SD) | 62.4 (8.7) | 61.4 (9.2) | <0.0001 |
| *Initial therapy with statins* | | | |
| Atorvastatin | 2224 (32.0%) | 24,082 (30.9%) | 0.0021 |
| Fluvastatin | 804 (11.6%) | 8782 (11.3%) | |
| Lovastatin | 46 (0.7%) | 530 (0.7%) | |
| Pravastatin | 1024 (14.8%) | 11,927 (15.3%) | |
| Rosuvastatin | 896 (12.9%) | 11,397 (14.6%) | |
| Simvastatin | 1941 (28.0%) | 21,175 (27.2%) | |
| *Previous use of other drugs* | | | |
| Fibrates | 12 (0.2%) | 51 (0.1%) | 0.0963 |
| Antihypertensive agents | 4756 (68.6%) | 44,037 (56.5%) | <0.0001 |
| Antiarrhythmic agents | 145 (2.1%) | 1668 (2.1%) | 0.7803 |
| Antithrombotic agents | 2137 (30.8%) | 19,988 (25.7%) | <0.0001 |
| Drugs for COPD | 1582 (22.8%) | 16,331 (21.0%) | 0.0003 |
| NSAIDs | 3966 (57.2%) | 41,950 (53.9%) | <0.0001 |
| Antidepressant agents | 931 (13.4%) | 9866 (12.7%) | 0.0693 |
| Charlson comorbidity index score $\geq 1$ | 220 (3.2%) | 2312 (3.0%) | 0.3384 |
| **During the step-1 follow-up** | | | |
| *Categories of PDC*[b] | | | |
| $\leq$10% | 1091 (15.7%) | 17,732 (22.8%) | <0.0001 |
| 11–50% | 2868 (41.4%) | 32,094 (41.2%) | |
| 51–90% | 2830 (40.8%) | 26,957 (34.6%) | |
| >90% | 146 (2.1%) | 1110 (1.4%) | |

[a] Value according to chi-square (gender, initial therapy with statins, previous use of other drugs and Charlson comorbidity index score), its version for the trend (categories of PDC) or *t* test for independent samples (mean age).
[b] PDC: proportion of days covered by treatment with statins.

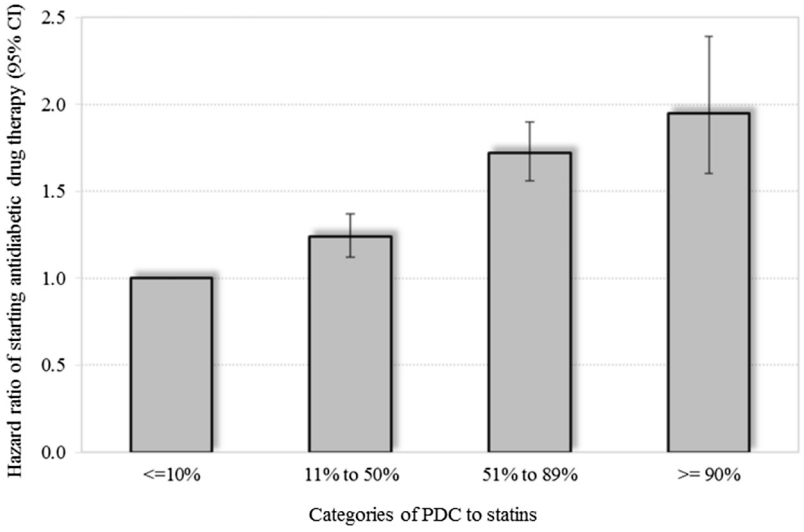


**Fig. 2 – Effect of adherence with statin therapy on the hazard ratio (HR) of new onset diabetes during the step-1 follow-up.** ***Footnote.*** **Adherence with statins therapy is categorized as very low ($\leq$10%), low (11–50%), intermediate (51–89%) and high ($\geq$90%) proportion of days covered (PDC) by statin prescription. HR of diabetes onset, and corresponding 95% CI, was estimated according to Cox proportional hazard model. Adjustments were made for age (continuous), gender, type of statin therapy, concomitant use of other drugs, history of CV disease and categories of Charlson comorbidity index score.**

intermediate and high adherence with statins, respectively. This means that the greater is the adherence with statins the greater is the likelihood of the diabetic condition to be induced by statin use.

### 3.2. Diabetes complications in patients with new onset diabetes – step-2

The 3321 matched sets of diabetic and non-diabetic patients belonging to the step-2 cohort accumulated 65,833 person-years of follow-up, on average 5.1 years per patient. During this period 376 and 760 diabetic and non-diabetic patients respectively experienced the step-2 outcome, the corresponding incidence being 22.8 and 15.4 hospitalizations every 1000 person-years (6.5 and 4.6 for myocardial infarction, 2.2 and 1.2 for peripheral vascular disease, 10.0 and 6.6 for myocardial revascularization, 3.7 and 1.9 for heart failure and 8.2 and 6.2 for cerebrovascular disease). Among the 3321 diabetics, 381, 1422, 1433 and 85 had very low, low, intermediate and high adherence with statins, respectively.

As step-1 adherence with statins increased, diabetics included in step-2 follow-up were trendily older, started lipid-lowering therapy with rosuvastatin (and less with pravastatin and simvastatin) and were on treatment with antihypertensive and antithrombotic agents (Supplementary Table S4).

The step-2 adherence with antidiabetic drugs was similar regardless the adherence with statins exhibited in the previous step-1 follow-up, the mean PDC (SD) values being 50% (26), 49% (26), 53% (25) and 55% (26) for diabetic patients with very low, low, intermediate and high adherence with statins, respectively. This was also the case for the step-2 adherence with antihypertensive drugs, the mean PDC (SD) values being 68% (31), 76% (28), 69% (31) and 71% (22), respectively. Furthermore, the mean age (SD) at the cohort entry (i.e., when statin treatment started) in the four groups of step-1 statin adherence was, respectively, 60.8 (8.9), 61.5 (8.4), 61.8 (8.0) and 62.6 (8.4) years.

In the entire cohort, patients with diabetes had a risk of macrovascular complications 39% (95% CI, 23–57%) higher than that of patients without diabetes. As shown in Supplementary Table S5, cotreatment with antihypertensive, antithrombotic agents, and presence of comorbidities, significantly contributed to increase the risk of the macrovascular complications. As shown in the top panel of Fig. 3, the potential of diabetes for inducing macrovascular complications in step-2 follow-up, decreased with the increasing adherence to statins in step-1 follow-up, the risk excess being 70% (95% CI: 18–144%), 41% (17–70%), 30% (7–57%) and 10% (−60% to 180%) for very low, low, intermediate and high adherence, respectively (p-trend = 0.0384). This trend was similar for the specific events separately considered, for all of which the diabetes-related risk was much less in patients with a high as compared to low adherence: 112% vs. 15% for myocardial infarction, 65% vs. 28% for myocardial revascularization and 40% vs. 13% for cerebrovascular disease (Fig. 3, bottom panel).

### 3.3. Ancillary analyses

Supplementary Table S2 shows that the difference in the risk of CV events along categories of adherence with statins in the step-1 follow-up, decreased and disappeared by delaying the start of follow-up, respectively by 3 and 6 years from the initial statin dispensation. This suggests that the risk of CV outcomes is probably not affected by the previous adherence with statins.

Supplementary Table S3 shows that the difference in the diabetes-related excess CV risk between the categories of very low and high adherence with statins (large and small or absent excess risk, respectively) was similar regardless the exclusion or inclusion of patients with events in the step-1 follow-up. This suggests that our main finding was not affected by the selective inclusion of patients who did not experience CV events before the step-2 index date.

## 4. Discussion

To obtain information on the prognostic significance of statin-induced diabetes vs. diabetes not due to statins we assumed that the probability for diabetes to be induced by statins would increase progressively as adherence with statins increased. We further assumed that, this being the case, in statin-treated patients developing diabetes the risk of macrovascular complications would exceed that of statin-treated patients without diabetes (1) similarly at all levels of adherence with statin treatment, if statin-induced diabetes and diabetes not due to statins are prognostically similar and (2) less as adherence with statin treatment increases if statin-induced diabetes is prognostically less adverse than diabetes not due to statins. Our finding that, compared to statin-treated patients without diabetes, statin-treated patients developing diabetes exhibited a progressively lower macrovascular risk as adherence with statins increased, is compatible with the latter possibility, leading to the suggestion that the adverse prognostic consequences of diabetes may be attenuated if this condition is induced by or associated with statins, its clinical nature thus being more benign. This finds a particularly clear support in the observation that in patients with an almost complete adherence with statins (>90%) new onset diabetes did not differ prognostically from the non-diabetes status whereas in patients with very low adherence (<10%) with statins the excess risk of new diabetic patients was about two fold higher than that of non-diabetic patients.

Other possible explanations of our findings need to be discussed. One explanation is that, adherence with statins reflected adherence to other drugs, i.e. to antidiabetic and antihypertensive agents, whose progressively greater therapeutic coverage during the step-2 follow-up might have been responsible for the results. However, the antidiabetic drugs that were prescribed in the Lombardy population have shown only modest beneficial effects on macrovascular complications [19–22], which have recently been shown to be substantially reduced by the administration of antidiabetic drugs [23–

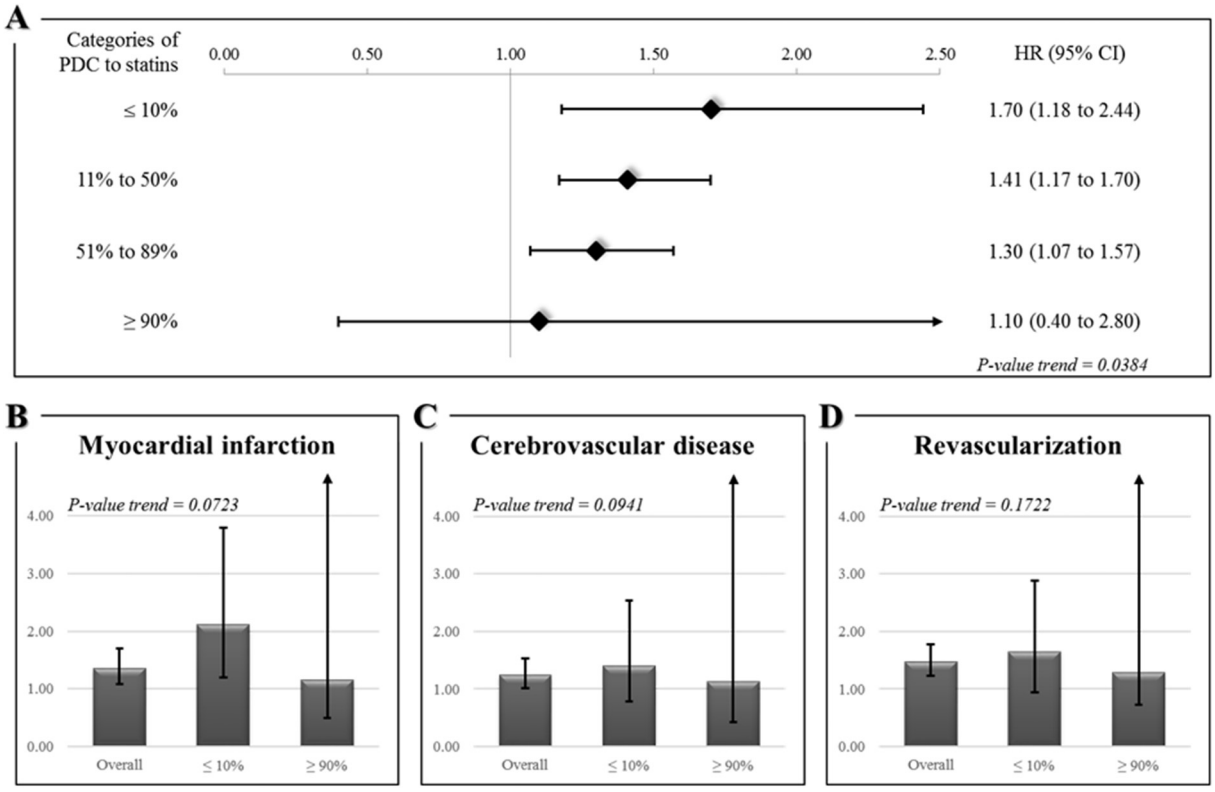


**Fig. 3 – Effect of diabetes on the hazard ratio (HR) of hospitalization for macrovascular complications according to step-1 adherence with statin therapy. Macrovascular complications on the whole and specific macrovascular outcomes (i.e., myocardial infarction, cerebrovascular disease and myocardial revascularization) are shown in top and bottom panel respectively.**

***Footnote.* Hazard ratio (HR) of hospitalization for macrovascular complications, and 95% CI, was estimated according to the Cox proportional hazard model. Adjustments were made for covariates measured at the step-1 index date. Explanations and symbols as in Fig. 2.**

25] not available at the time of our patients' follow-up. Furthermore, and more importantly, we did not find that adherence with antidiabetic agents during the step-2 follow-up differed substantially among the categories of step-1 adherence with statins that were analysed. This was the case also for adherence with antihypertensive drug treatment, i.e. a treatment with a documented protective effect in the large fraction of the diabetic population with a blood pressure elevation [26].

A second possible explanation is that the outcome patterns seen in the step-2 follow-up were accounted for by an extension of the protective effects of adherence with statins in the step-1 phase of the study [27]. However, this should have affected both diabetic and non-diabetic patients, with no progressive attenuation and final disappearance of their CV risk difference as adherence with statins increased, as it was indeed the case. Moreover, patients included in the step-2 cohort were those who did not experience CV hospitalizations during the step-1 follow-up, making it unlikely that an increased effect on the risk could appear later (see Supplementary Table S2).

A third explanation is that the progressive reduction of the excess risk of outcomes exhibited by newly diabetic patients as adherence with statins increased reflects a greater protective effect of statins in patients with diabetes compared to those without diabetes. This might find support in the observation that in the step-2 follow-up the risk attenuation associated with the increasing step-1 follow-up adherence was greater in patients with diabetes than in those without diabetes, this being the case both in individuals without and in individuals with hospitalization for CV events for several years before as well as during the step-1 follow-up (i.e., low and high risk categories in which the benefit of statins would be expected to be small and large, respectively) (Supplementary Table S3, ancillary analysis). In this context, it should be mentioned that in clinical trials the CV benefits of statins have been found to be evident both with and without diabetes [28,29]. It should also be mentioned that a greater protective effect of statins in diabetes implies that the continuing use of these drugs can therapeutically attenuate or even counterbalance the risk associated with their diabetogenic influence, thereby somehow coping with such specific inconvenience of their administration.

Our study has strengths and limitations. It is one of the largest cohort studies on the association between statins and new onset diabetes. This study has also examined the CV consequences of this phenomenon on a large variety of CV events over a reasonably long follow-up (on average 5.1 years

per patient). On the other hand, although the patients' clinical status can be inferred (and the data adjusted for) from knowledge of hospitalizations, treatments for CV disease and assumption of non-CV drugs, information does not include fasting serum glucose, lipid values, blood pressure and other clinical variables, e.g. baseline LDL-C levels. In addition, because the step-1 follow-up was not too long to influence the effect of novel statin therapy (in average 5.5 years), it is plausible that conventional risk factors of diabetes (i.e., those unavailable in the database, such as high BMI and unhealthy diet), may play an undetected (residual) role. However, we must assume that these factors are positively associated with statin adherence, in order they may act as confounders. Another limitation of our study is that antidiabetic medication may be started for indications different to diabetes (i.e., metformin for prediabetes or polycystic ovarian syndrome), albeit this misclassification would be likely small. Finally, our conclusion that, compared to diabetes unlikely due to statins, statin-induced diabetes is prognostically more benign holds for the follow-up of our study, leaving the possibility that in a longer run the CV risk of these two conditions becomes similar opening to further investigations. This is the case also for the possibility that the lower CV risk of statin-induced diabetes is accounted for a large protective effect of the drug, whose persistence over periods longer than those available in our study must be tested.

In summary, our data confirm that there is a definite increase in the development of diabetes with statin therapy. They suggest, however, that a diabetes that is likely to be induced by statins is not associated with a clear modification of macrovascular risk. Trials reflecting the clinical relevance of treatment-induced diabetes mellitus regarding macrovascular complications are required to confirm this finding.

## Funding source

This study was funded by grants from the Italian Ministry of the Education, University and Research ("Fondo d'Ateneo per la Ricerca" portion, year 2015).

## Duality of interest

G.C. received research support from the European Community (EC), the Italian Agency of Drug (AIFA), and the Italian Ministry for University and Research (MIUR). He took part to a variety of projects that were funded by pharmaceutical companies (i.e., Novartis, GSK, Roche, Amgen and BMS). He also received honoraria as member of Advisory Board from Roche. 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 contribution

G.C. contributed to the initial study idea, interpretation of the results, and drafting of the manuscript. M.M.C. and F.R. were responsible for the preparation of the dataset for the analysis, data analysis and review the manuscript. L.M. was responsible for data integrity, contributed to abstracting data and authorized their use. A.L.C. and G.M. contributed to the interpretation of pharmacological and clinical prospective results and to review the manuscript. All the authors contributed to the critical revision of the manuscript and approved the final manuscript to be published. 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.

## Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2017.08.008.

## REFERENCES

[1] Dormuth CR, Filion KB, Paterson JM, et al. Canadian Network for Observational Drug Effect Studies Investigators. Higher potency statins and the risk of new diabetes: multicentre, observational study of administrative databases. BMJ 2015;348:g3244.
[2] Navarese EP, Szczesniak A, Kolodziejczak M, Gorny B, Kubica J, Suryapranata H. Statins and risk of new-onset diabetes mellitus: is there a rationale for individualized statin therapy? Am J Cardiovasc Drugs 2014;14:79–87.
[3] Beckett RD, Schepers SM, Gordon SK. Risk of new-onset diabetes associated with statin use. SAGE Open Med 2015;3. 2050312115605518.
[4] Shah RV, Goldfine AB. Statins and risk of new-onset diabetes mellitus. Circulation 2012;126:e282–4.
[5] Bang CN, Okin PM. Statin treatment, new-onset diabetes, and other adverse effects: a systematic review. Curr Cardiol Rep 2014;16:461–5.
[6] Banach M, Malodobra-Mazur M, Gluba A, Katsiki N, Rysz J, Dobrzyn A. Statin therapy and new-onset diabetes: molecular mechanisms and clinical relevance. Curr Pharm Des 2013;19:4904–12.
[7] Ridker PM, Danielson E, Fonseca FA, et al. JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.
[8] Bell DS, DiNicolantonio JJ, O'Keefe JH. Is statin-induced diabetes clinically relevant? A comprehensive review of the literature. Diabetes Obes Metab 2014;16:689–94.
[9] Whayne Jr TF. Problems and possible solutions for therapy with statins. Int J Angiol 2013;22:75–82.
[10] Wang KL, Liu CJ, Chao TF, et al. Risk of new-onset diabetes mellitus versus reduction in cardiovascular events with statin therapy. Am J Cardiol 2014;113:631–6.
[11] Belalcazar LM, Raghavan VA, Ballantyne CM. Statin-induced diabetes: will it change clinical practice? Diabetes Care 2009;32:1941–3.
[12] Corrao G, Ibrahim B, Nicotra F, et al. Statins and the risk of diabetes: evidence from a large population-based cohort study. Diabetes Care 2014;37:2225–32.
[13] Arfè A, Corrao G. Tutorial: strategies addressing detection bias were reviewed and implemented for investigating the statins-diabetes association. J Clin Epidemiol 2015;68:480–8.

[14] Helin-Salmivaara A, Lavikainen P, Korhonen MJ, et al. Long-term persistence with statin therapy: a nationwide register study in Finland. Clin Ther 2008;30:2228–40.
[15] Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. Pharmacoepidemiol Drug Saf 2006;15:565–74.
[16] Charlson ME, Charlson RE, Peterson JC, Marinopoulos SS, Briggs WM, Hollenberg JP. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. J Clin Epidemiol 2008;61:1234–40.
[17] Greenland S, Robins JM. Conceptual problems in the definition and interpretation of attributable fractions. Am J Epidemiol 1988;128:1185–97.
[18] Rothman KJ, Greenland S, Lash TL. Modern epidemiology. 3rd ed. Philadelphia: Lippincott, Williams & Wilkins; 2008.
[19] Gerstein HC, Miller ME, Byington RP, et al. ACCORD Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–59.
[20] Patel A, MacMahon S, Chalmers J, et al. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–72.
[21] UK Prospective Diabetes Study (UKPDS). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853.
[22] Duckworth W, Abraira C, Moritz T, et al. VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–39.
[23] Zinman B, Wanner C, Lachin JM, et al. EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128.
[24] Marso SP, Daniels GH, Brown-Frandsen K, et al. LEADER Steering Committee, LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–22.
[25] Marso SP, Bain SC, Consoli A, et al. SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–44.
[26] Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA 2015;313:603–15.
[27] Corrao G, Conti V, Merlino L, Catapano AL, Mancia G. Results of a retrospective database analysis of adherence to statin therapy and risk of nonfatal ischemic heart disease in daily clinical practice in Italy. Clin Ther 2010;32:300–10.
[28] Kohli P, Waters DD, Nemr R, et al. Risk of new-onset diabetes and cardiovascular risk reduction from high-dose statin therapy in pre-diabetics and non-pre-diabetics: an analysis from TNT and IDEAL. J Am Coll Cardiol 2015;65:402–4.
[29] Ferrannini E, DeFronzo RA. Impact of glucose-lowering drugs on cardiovascular disease in type 2 diabetes. Eur Heart J 2015;36:2288–96.