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# Lower and higher-potency statins on glycemic control in type 2 diabetes: A retrospective cohort study

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ABSTRACT

*Aims:* Evidences showed a link between statins and new-onset diabetes and large clinical trials in type 2 diabetes (T2DM) suggested a mild glycemic progression in statin treated. Since this effect has not yet elucidated in real world, we investigated the effects of different statins on glycemia in T2DM clinic outpatients.

*Methods:* In a retrospective cohort study, we recorded at 6 and 12 months modifications of fasting glucose (FPG), HbA1c, diabetes intensification therapy and target rate for HbA1c in 421 T2DM non-users and new statin users. Statins were categorized with low or high potency.

*Results:* Compared to statin users, no statin group showed a significant HbA1c reduction from 52.8 ± 14.0 mmol/mol to 48.2 ± 8.5 ($p = 0.003$) at 6 months and 48.6 ± 8.8 ($p = 0.007$) at 12 months. This trend without statins was also observed in FPG starting from 7.1 ± 2.0 mmol/l to 6.7 ± 1.6 ($p = 0.12$) at 6 months and 6.6 ± 1.5 ($p = 0.032$) at 12 months. Statins determined a significant diabetes treatment intensification: 48.7% vs 27.4% ($p = 0.002$) with hazard ratio 2.4 [95% CI 1.14–5.2], $p = 0.022$. HbA1c target was significantly lower in statin users 62.0% vs 75.4%, $p = 0.042$. Only lower-potency statins showed a significant reduction of HbA1c from 52.0 ± 11.1 mmol/mol to 50.7 ± 9.0 ($p = 0.017$) and 50.7 ± 9.5 ($p = 0.038$) at 6 and 12 months, respectively. The same effect for these statins was registered in FPG from 7.5 ± 2.2 mmol/l to 7.0 ± 1.6 ($p = 0.021$) at 6 months and 7.2 ± 1.5 ($p = 0.026$) at 12 months.

*Conclusions:* In patients receiving statin therapy a greater intensification diabetes therapy is need. This impact seems to be less pronounced by statins with lower potency.



*Abbreviations:* T2DM, type 2 diabetes; FPG, fasting plasma glucose; TC, total cholesterol; HDL-C, HDL cholesterol; TG, triglycerides; LDL-C, LDL cholesterol; HR, hazard ratio; CI, confidence interval

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## 1. Introduction

Hydroxy-methylglutaryl-CoA reductase inhibitors, known worldwide as statins, are the most effective drugs for the treatment of hypercholesterolemia, and their efficacy is well confirmed in several clinical trials for primary and secondary prevention of cardiovascular diseases [1], even among patients with type 2 diabetes mellitus (T2DM) [2]. On the other hand, statin therapy has been associated with incident diabetes [3]: a meta-analysis of 13 randomized trials showed that statin use increased the incidence of new cases of diabetes by 9% [3]. These observations were confirmed in subsequent observational studies [4–7]. In trials performed on patients with known diabetes, the initiation of statin therapy is associated with a small, although statistically significant, deterioration of glycemic control [8,9]. On the basis of these results, the increase of HbA1c determined by statin therapy is about 1–2 mmol/mol. However, the reliability of this estimate is limited by several methodological factors. First of all, randomized clinical trials select patients with a greater adherence to prescribed therapies than those visited in routine care; in addition, the higher number of visits associated with study protocol can enhance glycemic control. Because of those reasons, the effect of statin therapy on blood glucose could be underestimated by clinical trials. Furthermore, available trials with statins were designed for non-glycemic endpoints, and more typically for cardiovascular outcomes. As a consequence, data on glucose control were not collected in many studies. In fact, despite the remarkable number of randomized trials with statins, in a recent meta-analysis Erqou et al. [8] found only nine trails with a duration >12 weeks and a sample size >200 patients, which reported glycemic outcomes. In this context, observational studies performed in series of patients with known diabetes can add some relevant information.

Thus, we studied the effect of statin therapy on fasting glucose, HbA1c levels and modifications or intensification of diabetes therapy in clinical practice in T2DM patients.

## 2. Methods

### 2.1. Participants

This study was designed as a retrospective cohort study on a clinic-based sample of patients with diabetes. We retrospectively retrieved data from a consecutive series of T2DM outpatients, visited for the first time at the Diabetes Clinic of Careggi hospital, Florence, between January 1st, 2011, and February 28th, 2014,with a HbA1c <8% (64 mmol/mol), who were not already treated with statins, and who had provided their consent to the use of anonymized clinical data for epidemiological surveys. Patients treated with corticosteroids, or affected by chronic liver or kidney diseases were excluded, as those conditions could affect glycemic values. Insulin-treated patients were also excluded, in order to exclude the effect on glycemic control of variations of insulin doses, which were difficult to track during follow-up.

Given the observational nature of the study, no protocol was provided for the treatment of either diabetes or hypercholesterolemia. Current guidelines recommend statin treatment for all those with LDL cholesterol above 2.58 mmol/mol (1.81 mmol/mol in case of current or previous cardiovascular disease). The recommended goal for HbA1c is 53 mmol/mol (64 mmol/mol in older frail patients), with metformin as preferred first-line treatment and any other drug added in second-line [*www.siditalia.it*; *Standard Italiani SID/AMD per la cura del diabete mellito 2009–2010*].

### 2.2. Clinical and laboratory parameters

Data on current and previous diseases and current drug therapy at enrollment were retrieved from clinical records, together with height, weight, and waist circumference (measured in standing position with a flexible tape in the horizontal plane at the level just above the iliac crest, at minimal inspiration). Blood pressure was measured in sitting position, after a 5-min rest using a mercury sphygmomanometer with a cuff of appropriate size. Fasting plasma glucose (FPG), HbA1c, serum creatinine, total cholesterol (TC), HDL cholesterol (HDL-C) and triglyceride (TG) levels were measured at first visit in all subjects, as part of routine clinical assessment of new patients at the Diabetes Clinic. The lipid panel and serum creatinine were detected by an automated enzymatic method (Aeroset, Abbott Laboratories, USA). Glycated hemoglobin (HbA1c) was measured by high-performance liquid chromatography using DCCT-aligned method; plasma glucose, triglycerides, total and HDL cholesterol (HDL-C) were automatically measured (Beckman Instruments, Brea, USA). LDL cholesterol (LDL-C) was calculated by the Friedewald formula, when appropriated [10].

Data on new drug prescriptions at first visit, including statin prescription, are available in clinical records. In the routine clinical management type 2 diabetes at the time of enrolment, follow-up visits were regularly performed in all patients at least bi-annually, repeating the same measurements reported above for the first visit. All data reported above were retrieved after 6 and 12 months from enrolment. The same parameters were collected after 6 and 12 months. At the first visit, all patients received information on diet and regular physical exercise. Data on statin prescription were also retrieved from clinical records in the same observation period. Patients who initiated statin therapy after the first visit were excluded from the analysis.

Statins were categorized as higher or lower potency, according to whether they would produce a theoretical <45% or ⩾45% reduction of LDL-C levels. In particular, we considered higher-potency statins, rosuvastatin ⩾10 mg, atorvastatin ⩾20 mg, simvastatin ⩾40 mg and simvastatin + ezetimibe, while rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin ⩽20 mg and lovastatin, fluvastatin, pravastatin at any doses were defined as lower potency statins [11]. During the follow-up study, all patients maintained the same class of statin-potency.