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RESEARCH

Risk of incident diabetes among patients treated with statins: population based study

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Abstract

Objective To examine the risk of new onset diabetes among patients treated with different HMG-CoA reductase inhibitors (statins).

Design Population based cohort study with time to event analyses to estimate the relation between use of particular statins and incident diabetes. Hazard ratios were calculated to determine the effect of dose and type of statin on the risk of incident diabetes.

Setting Ontario, Canada.

Participants All patients aged 66 or older without diabetes who started treatment with statins from 1 August 1997 to 31 March 2010. The analysis was restricted to new users who had not been prescribed a statin in at least the preceding year. Patients with established diabetes before the start of treatment were excluded.

Interventions Treatment with statins.

Main outcome measure Incident diabetes.

Results Compared with pravastatin (the reference drug in all analyses), there was an increased risk of incident diabetes with atorvastatin (adjusted hazard ratio 1.22, 95% confidence interval 1.15 to 1.29), rosuvastatin (1.18, 1.10 to 1.26), and simvastatin (1.10, 1.04 to 1.17). There was no significantly increased risk among people who received fluvastatin (0.95, 0.81 to 1.11) or lovastatin (0.99, 0.86 to 1.14). The absolute risk for incident diabetes was about 31 and 34 events per 1000 person years for atorvastatin and rosuvastatin, respectively. There was a slightly lower absolute risk with simvastatin (26 outcomes per 1000 person years) compared with pravastatin (23 outcomes per 1000 person years). Our findings were consistent regardless of whether statins were used for primary or secondary prevention of cardiovascular disease. Although similar results were observed when statins were grouped by potency, the risk of incident diabetes associated with use of rosuvastatin became non-significant (adjusted hazard ratio 1.01, 0.94 to 1.09) when dose was taken into account.

Conclusions Compared with pravastatin, treatment with higher potency statins, especially atorvastatin and simvastatin, might be associated with an increased risk of new onset diabetes.

Introduction

Hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are among the most widely prescribed drugs, with established benefits in patients at risk of cardiovascular events.[1] Although statins are tolerated well by most patients, an association with new onset diabetes has recently been suggested.[2] In the JUPITER (justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin) trial, rosuvastatin was associated with a 27% increased risk of new onset diabetes compared with placebo.[3] An increased risk compared with placebo was also observed with atorvastatin and simvastatin.[4-7] In contrast, the West of Scotland coronary prevention study (WOSCOPS) suggested that patients taking pravastatin faced a 30% lower risk of diabetes compared with placebo (relative risk 0.7, 95% confidence interval 0.5 to 0.99).[8]

In light of these discordant results, several meta-analyses have attempted to characterize the risk of new onset diabetes during treatment with statins.[9-13] Limited data, however, exist for direct comparisons of individual statins.[11 12 14] Despite these conflicting findings, some evidence supports the notion that different statins might impart differential risks of diabetes.[2 7 15] In animal models, pravastatin has been shown to increase adiponectin, improving insulin sensitivity and inhibiting gluconeogenesis, while simvastatin reduces insulin secretion, and atorvastatin and lovastatin impair glucose tolerance.[2 7 15 16] For these reasons, in February 2012 the United States Food and Drug Administration mandated labeling changes for all statins except pravastatin.[17 18]

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We examined the healthcare records of more than 1.5 million older people from Ontario, Canada, to examine the association between individual statin use and new onset diabetes.

Methods

Study design

We conducted a population based retrospective cohort study in patients aged 66 and older in Ontario, Canada, who started treatment with a statin from 1 August 1997 to 31 March 2010.

Data sources

We used linked administrative healthcare databases for identification of cohorts, assessment of comorbidity, and ascertainment of outcome. We used the Ontario Drug Benefit (ODB) database, a computerized pharmacy records system that records prescription drugs dispensed to Ontario residents aged over 65. Fluvastatin, lovastatin, pravastatin, and simvastatin were available from the provincial formulary before the start of our study period, while atorvastatin was added in 1997 and rosuvastatin in 2003. We used the Canadian Institute for Health Information discharge abstract database (CIHI-DAD) to identify inpatient admissions to hospital, including diagnostic and procedural information. Physician billing information was identified with the Ontario Health Insurance Plan (OHIP) database and demographic information, including vital statistics information, was obtained from the Ontario Registered Persons Database (RPDB). The Ontario Diabetes Database (ODD) was used to identify new onset diabetes.[19] These databases were anonymously linked by using encrypted individual health card numbers and are routinely used to study both diabetes [20 21] and drug safety.[22 23] Additionally, validation studies of the administration databases in Ontario have shown that the drug database used in this study has an error rate of <1%.[24]

Cohort definition

We identified statin treatment based on prescriptions for any of atorvastatin, fluvastatin, lovastatin, rosuvastatin, simvastatin, or pravastatin during the study period, restricting our analysis to new users by requiring a period of at least one year with no prescription for any statin. Cerivastatin was withdrawn from the market in 2001 and was not examined in our analyses; people who switched from another statin to cerivastatin, however, were censored at that point.

We defined the cohort entry date as the date of the first prescription for a statin after each patient's 66th birthday, excluding the first year of eligibility for prescription drug coverage (age 65) to avoid incomplete drug records. We excluded patients with established diabetes before the start of statin treatment, defined by any prescription for diabetes drugs (oral agents or insulin) or self monitoring blood glucose supplies in the previous year or a diagnosis of diabetes in the ODD at any time before the date of entry into the cohort.

Duration of exposure

For each patient, we defined a period of continuous use of each statin based on successive refills of prescriptions for the same statin within 1.5 times the duration of the preceding prescription. On discontinuation of a drug, each patient was followed for the duration of their final prescription to identify any events that could have precipitated stopping the treatment. People were censored if they experienced the primary outcome, discontinued treatment, switched to a different statin, died, reached the end of the study period (31 March 2010), or were followed up for a maximum of five years, whichever occurred first.

Outcomes

The primary outcome was incident diabetes, defined as a diagnosis of diabetes in the Ontario Diabetes Database, which is a validated registry of all Ontarians diagnosed with diabetes (sensitivity and specificity of 86-90% and 92-97%, respectively).[19] In a sensitivity analysis, we expanded the definition of diabetes to include any prescription for a diabetes drug or blood glucose test strips.

Subgroup analyses

We replicated our analyses according to whether the statin was prescribed for primary or secondary prevention. Secondary prevention patients were defined as those with any admission to hospital for acute coronary syndrome, ischemic heart disease, coronary artery bypass graft or angioplasty, stroke, or transient ischemic attack in the five years before statin treatment or any prescription for nitroglycerin in the previous year. All other patients were considered to receive a statin for primary prevention.[25] These subgroup definitions were defined with ICD-9 and ICD-10 (international classification of diseases, ninth and 10th revisions) and have been used previously.[25]

Statistical analysis

All analyses used patients treated with pravastatin as the reference comparison group as pravastatin has been shown to have favorable effects on incident diabetes in animal models and clinical trials.[2 7 15 16] We used standardized differences to examine baseline characteristics of patients treated with pravastatin compared with each of the other statin groups. Standardized differences of less than 0.1 are generally not considered meaningful.[26] We conducted time to event analyses using Cox proportional hazards regression to estimate the relation between use of statins and incident diabetes. The proportional hazards assumption was tested with log-log survival curves. We developed multivariable models adjusting for age, sex, year of cohort entry, history of cardiac disease and cardiac procedures, Charlson comorbidity index,[27] and history of drug use, including drugs with an impact on glycemic control in the past 12 months. We used adjusted Kaplan-Meier curves to compare the time to new onset diabetes in each statin cohort and calculated the number needed to treat to harm using absolute risk estimates at one year of follow-up.[28] Finally, we fitted two additional Cox proportional hazards models, including potency and time varying statin dose, to consider their independent impact on incident diabetes and to minimize survival bias. Doses were stratified into three categories (high dose: atorvastatin ≥80 mg and rosuvastatin ≥40 mg; moderate dose: atorvastatin 20-<80 mg, rosuvastatin 10 mg-<40 mg, and simvastatin ≥80 mg; and low dose: atorvastatin <20 mg, fluvastatin at all doses, lovastatin at all doses, pravastatin at all doses, rosuvastatin <10 mg, simvastatin <80 mg) as were the potency analyses (high potency: rosuvastatin, atorvastatin; moderate potency: simvastatin; low potency: fluvastatin, lovastatin, pravastatin).[29] All analyses were performed with SAS, version 9.2 (SAS Institute, Cary, NC).

Results

Patients' characteristics

Over the 14 year study period, we identified 471 250 patients with no history of diabetes who were newly treated with a statin. Of these, 227 994 (48.3%) received a statin for primary

prevention, while 243 256 (51.7%) received a statin for secondary prevention. The median age at the outset of treatment was 73 (interquartile range 69-78) and 254 915 (54.1%) were women. Atorvastatin accounted for more than half of all new statin prescriptions, followed by rosuvastatin, simvastatin, pravastatin, lovastatin, and fluvastatin. Tables 1 and 2 show the characteristics of people in the study⇓⇓. No major imbalances were apparent among the different statin cohorts.

Primary analysis

The crude event rate for incident diabetes was highest for atorvastatin (30.70 outcomes per 1000 person years) and rosuvastatin (34.21 outcomes per 1000 person years) compared with pravastatin (22.64 outcomes per 1000 person years). Simvastatin (26.22 outcomes per 1000 person years), fluvastatin (21.52 outcomes per 1000 person years), and lovastatin (21.80 outcomes per 1000 person years) had crude event rates similar to pravastatin (table 3⇓). After adjustment for known confounders, and compared with patients treated with pravastatin, those treated with atorvastatin faced a 22% increase in the risk of new onset diabetes (adjusted hazard ratio 1.22, 95% confidence interval 1.15 to 1.29). We also observed a significantly increased risk among those treated with rosuvastatin (1.18, 1.10 to 1.26) and simvastatin (1.10, 1.04 to 1.17) compared with pravastatin (table 3⇓). In contrast, treatment with fluvastatin (0.95, 0.81 to 1.11) or lovastatin (0.99, 0.86 to 1.14) was not significantly associated with an increased risk of incident diabetes.

The figure shows the cumulative incidence of diabetes according to individual statin use⇓. We observed consistent findings when the definition of diabetes included the initiation of antidiabetic drugs, a prescription for blood glucose test strips, or diagnosis in the Ontario Diabetes Database (table 4⇓).

Subgroup analyses

We found consistent results in subgroup analyses examining the use of statins for primary and secondary prevention. Relative to pravastatin, treatment with atorvastatin (adjusted hazard ratio 1.20, 95% confidence interval 1.10 to 1.30), rosuvastatin (1.12, 1.02 to 1.23), or simvastatin (1.12, 1.02 to 1.23) was associated with a significantly increased risk of new onset diabetes in the primary prevention cohort, while no increased risk was observed for patients treated with lovastatin (0.98, 0.79 to 1.22) or fluvastatin (1.01, 0.82 to 1.23). Similar findings were observed among the secondary prevention users (table 3⇓).

Overall, moderate (adjusted hazard ratio 1.22, 95% confidence interval 1.19 to 1.26) and high doses (1.30, 1.20 to 1.40) were associated with an increased risk of incident diabetes compared with low doses of statins (table 5⇓). At the individual statin level, our findings were largely consistent with our primary analyses after adjustment for dose. While we found similar risk estimates for simvastatin (1.11, 1.04 to1.17), we observed a slightly attenuated risk for atorvastatin (1.12, 1.05 to 1.18). The risk of incident diabetes among those treated with rosuvastatin, however, was no longer significant after adjustment for dose (1.01, 0.94 to 1.09). When we considered potency, our findings were consistent with our primary analyses (high potency statins (rosuvastatin, atorvastatin) adjusted hazard ratio 1.22, 1.15 to 1.29; moderate potency statins (simvastatin) 1.11, 1.04 to 1.18; low potency statins (fluvastatin, lovastatin) 0.97, 0.87 to 1.09; table 6⇓).

Discussion

In this population based study, we found that patients treated with atorvastatin, rosuvastatin, or simvastatin were at increased risk of new onset diabetes compared with those treated with pravastatin. No such risk was evident with fluvastatin or lovastatin. The risk associated with rosuvastatin could depend on dose and duration of treatment. The risk of incident diabetes was similar whether statins were being used for primary or secondary prevention.

Overall, we observed a 10-22% increased risk of diabetes for some statins that is consistent with findings from previously published meta-analyses of clinical trials. The increased risk with rosuvastatin significantly decreased after covariate adjustment and became non-significant once dose was taken into consideration. This could possibly represent greater use of rosuvastatin in patients with lower cardiovascular risk.[3] In 2009, an analysis of five placebo controlled trials (n=57 593) found a 13% (relative risk 1.13, 95% confidence interval 1.03 to 1.23) increased incidence of diabetes in people taking statins compared with placebo over an average 3.9 years of follow-up,[9] with a subsequent analysis of 13 placebo controlled trials (n=91 140) showing a 9% (odds ratio 1.09, 95% confidence interval 1.02 to 1.17) increased incidence of diabetes over four years of follow-up.[10] More recently, two meta-analyses have suggested a dose dependent effect for patients receiving high dose atorvastatin or simvastatin treatment versus moderate dose treatment (odds ratio 1.12, 95% confidence interval 1.04 to 1.22) and when considering only atorvastatin trials.[11 12] Our results differ from those of the Women's Health Initiative study, which showed a nearly 50% increase in new onset diabetes with statins compared with placebo (hazard ratio 1.48, 95% confidence interval 1.38 to 1.59), with no differential risk among low potency (fluvastatin, lovastatin, pravastatin) and high potency (simvastatin, atorvastatin) statins.[14] Our findings, however, are consistent with the findings of Zaharan and colleagues in 2012, who found an increased risk with atorvastatin (hazard ratio 1.25, 1.21 to 1.28), rosuvastatin (1.42, 1.33 to 1.52), and simvastatin (1.14, 1.06 to 1.23).[30] Our population based assessment adds to the discussion of risk when doctors are considering starting statin treatment in a patient for primary versus secondary prevention.

Possible mechanisms

Several factors could explain the increased risk of new onset diabetes among patients receiving certain statins.[2 7 15] The increased production of plasma derived low density lipoprotein (LDL) cholesterol as a compensatory response to de novo cholesterol synthesis inhibition might result in direct inflammation and oxidation within the β cell. Consequently, the functional and structural integrity of β cells is compromized, impairing insulin secretion as a result of cellular apoptosis.[15] Additionally, metabolic receptor effects interfere with cellular glucose uptake, energy production, and insulin secretion.[2 7 15 16] Statins can also inhibit calcium mediated pancreatic insulin release and decrease expression of the β cell glucose transporters GLUT-2 and GLUT-4.[15] Finally, statins are also known to interfere with the synthesis of ubiquinone (CoQ10), which could independently alter insulin secretion.[15 16] The degree to which statins are involved in these respective mechanisms of diabetes onset is variable and supports why some statins pose a higher risk than pravastatin.[7] As shown in our dose and potency analyses, the risk could be greater for atorvastatin and simvastatin, regardless of the dose prescribed.

Limitations and strengths

Some limitations of our study merit emphasis. We could not identify and account for potentially important risk factors for diabetes such as weight, ethnicity, and family history. Newer statins might be preferentially used in patients at higher risk of diabetes, though the characteristics of patients in our study were highly similar across study groups. Secondly, data on blood lipids, hemoglobin A_{1C} concentration, or triglyceride concentrations were unavailable, and therefore we could not use these measures for risk stratification or diagnostic purposes. The ODD, however, has been shown to be both sensitive (86-90%) and specific (92-97%).[19] Furthermore, we had no data on marketing or promotional efforts nor did we have data on physicians' preferences for particular statins. Although the statin groups were well balanced with respect to a wide variety of demographic and clinical variables, we cannot exclude the possibility of residual confounding.

Our study also had several strengths including a large sample size, use of pravastatin as an active comparator reference group, and a population based design. Our findings suggest that older patients treated with certain statins are at increased risk for incident diabetes, regardless of dose or whether treatment is used for primary or secondary prevention. The risk seems to be greatest with atorvastatin, rosuvastatin, and simvastatin. After adjustment for dose, however, the risk did not seem to persist among rosuvastatin users. Clinicians should consider this risk when they are contemplating statin treatment for individual patients. Preferential use of pravastatin, and potentially fluvastatin or lovastatin, while recognizing the limited efficacy data and increased risk of drug interactions with these two agents, might be warranted. Pravastatin might have a preferential benefit among primary prevention patients at high risk of diabetes.

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Contributors: AAC, TG, XC, and MMM were responsible for conception and design. All authors analyzed and interpreted data and drafted and revised the article. XC is guarantor.

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Ethical approval: The research ethics board of Sunnybrook Health Sciences Centre approved this study.

Data sharing: No additional data available.

1 Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670-81.
2 Preiss D, Sattar N. Statins and the risk of new-onset diabetes: a review of recent evidence. *Curr Opin Lipidol* 2011;22:460-6.
3 Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195-207.
4 Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Drugs* 2004;64(suppl 2):43-60.
5 Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA* 2005;294:2437-45.
6 LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425-35.
7 Koh KK, Sakuma I, Quon MJ. Differential metabolic effects of distinct statins. *Atherosclerosis* 2011;215:1-8.
8 Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, Ford I, et al. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation* 2001;103:357-62.
9 Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M, Ridker PM. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. *Diabetes Care* 2009;32:1924-9.
10 Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010;375:735-42.
11 Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA* 2011;305:2556-64.
12 Waters DD, Ho JE, DeMicco DA, Breazna A, Arsenault BJ, Wun CC, et al. Predictors of new-onset diabetes in patients treated with atorvastatin: results from 3 large randomized clinical trials. *J Am Coll Cardiol* 2011;57:1535-45.
13 Mills EJ, Wu P, Chong G, Ghement I, Singh S, Akl EA, et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials. *QJM* 2011;104:109-24.
14 Culver AL, Ockene IS, Balasubramanian R, Olendzki BC, Sepavich DM, Wactawski-Wende J, et al. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. *Arch Intern Med* 2012;172:144-52.
15 Sampson UK, Linton MF, Fazio S. Are statins diabetogenic? *Curr Opin Cardiol* 2011;26:342-7.
16 Goldfine AB. Statins: is it really time to reassess benefits and risks? *N Engl J Med* 2012;366:1752-5.
17 US Food and Drug Administration. FDA drug safety communication: important safety label changes to cholesterol-lowering statin drugs. 2012. www.fda.gov/Drugs/DrugSafety/ucm293101.htm.
18 Center for Drug Evaluation and Research. Approval package for: application number 019898Orig1s062. 2012. www.accessdata.fda.gov/drugsatfda_docs/nda/2012/019898s062.pdf.
19 Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care* 2002;25:512-6.
20 Juurlink DN, Gomes T, Lipscombe LL, Austin PC, Hux JE, Mamdani MM. Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study. *BMJ* 2009;339:b2942.
21 Gomes T, Juurlink DN, Shah BR, Paterson JM, Mamdani MM. Blood glucose test strips: options to reduce usage. *CMAJ* 2010;182:35-8.
22 Park-Wyllie LY, Juurlink DN, Kopp A, Shah BR, Stukel TA, Stumpo C, et al. Outpatient gatifloxacin therapy and dysglycemia in older adults. *N Engl J Med* 2006;354:1352-61.
23 Juurlink DN, Gomes T, Ko DT, Szmitko PE, Austin PC, Tu JV, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ* 2009;180:713-8.
24 Goel V, Williams J, Anderson G, Blackstein-Hirsch P, Fooks C, Naylor D. Patterns of health care in Ontario. 2nd ed. Canadian Medical Association, 1996.
25 Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA* 2002;288:462-7.
26 Mamdani M, Sykora K, Li P, Normand SL, Streiner DL, Austin PC, et al. Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding. *BMJ* 2005;330:960-2.
27 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-83.
28 Austin PC. Absolute risk reductions and numbers needed to treat can be obtained from adjusted survival models for time-to-event outcomes. *J Clin Epidemiol* 2010;63:46-55.
29 Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003;326:1423.
30 Zaharan NL, Williams D, Bennett K. Statins and risk of treated incident diabetes in a primary care population. *Br J Clin Pharmacol* 2013;75:11218-24.

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What is already known on this topic

Given the widespread use of statins to manage hypercholesterolemia, small effects in their efficacy and safety profiles can have important population impact.

Statins have previously been associated with an increased risk of incident diabetes, though there is controversy around whether this risk differs among drugs

What this study adds

When compared with pravastatin, atorvastatin, rosuvastatin, and simvastatin are associated with a greater risk of new onset diabetes, regardless of their use for primary or secondary prevention of cardiovascular events

The risk for rosuvastatin users might depend on the dose prescribed

Tables

Table 1| Baseline characteristics for new statin users. Figures are numbers (percentage) of patients unless stated otherwise

	Pravastatin (n=38 470)	Atorvastatin (n=268 254)	Fluvastatin/lovastatin (n=11 923)	Rosuvastatin (n=76 774)	Simvastatin (n=75 829
Age (years at start of cohort drug):					
Mean (SD)	73.04 (5.62)	73.97 (6.34)*	72.83 (5.49)	73.24 (6.20)	73.80 (6.06)*
Median (IQR)	72 (68-77)	73 (69-78)*	72 (68-76)	72 (68-77)	73 (69-78)*
Men	17 173 (44.6)	123 607 (46.1)	4 826 (40.5)	35 346 (46.0)	35 383 (46.7)
Median (IQR) year of cohort entry (fiscal)	1999 (1998-2001)	2004 (2001-06)*	1999 (1997-2000)*	2007 (2005-09)*	2002 (1999-2003)*
Secondary prevention†:					
History of cardiac disease/procedures	20 569 (53.5)	143 329 (53.4)	5616 (47.1)*	30 183 (39.3)*	43 559 (57.4)
Previous acute coronary syndrome	12 243 (31.8)	84 580 (31.5)	3110 (26.1)*	14 671 (19.1)*	26 854 (35.4)
Chronic coronary artery disease	18 399 (47.8)	121 600 (45.3)	4991 (41.9)*	24 592 (32.0)*	38 029 (50.2)
Stroke/transient ischemic attacks	5296 (13.8)	43 222 (16.1)	1433 (12.0)	9473 (12.3)	12 212 (16.1)
Charlson score‡:					
0	7057 (18.3)	48 527 (18.1)	2110 (17.7)	13 677 (17.8)*	13 715 (18.1)
1	4181 (10.9)	30 259 (11.3)	1150 (9.6)	5035 (6.6)*	8995 (11.9)
≥2	3918 (10.2)	28 767 (10.7)	1061 (8.9)	5266 (6.9)*	8526 (11.2)
No admissions to hospital	23 314 (60.6)	160 701 (59.9)	7602 (63.8)	52 796 (68.8)*	44 593 (58.8)
Daily statin dose (any ceiling dose)§	9201 (23.9)	11 051 (4.1)*	1753 (14.7)*	2056 (2.7)*	1931 (2.5)*
Fifth of income distribution:					
1	7807 (20.3)	51 356 (19.1)	2 510 (21.1)	14 255 (18.6)	14 933 (19.7)
2	8 414 (21.9)	56 596 (21.1)	2 607 (21.9)	16 246 (21.2)	16 127 (21.3)
3	7 891 (20.5)	53 070 (19.8)	2 518 (21.1)	15 333 (20.0)	15 336 (20.2)
4	7 088 (18.4)	51 411 (19.2)	2 095 (17.6)	15 339 (20.0)	14 161 (18.7)
5	7 155 (18.6)	54 922 (20.5)	2 143 (18.0)	15 378 (20.0)	15 042 (19.8)
Missing	115 (0.3)	899 (0.3)	50 (0.4)	223 (0.3)	230 (0.3)

*Standardized mean difference >0.1.

†Based on 5 years before cohort entry.

‡Based on 5 years of data from Canadian Institute for Health Information Discharge Abstract Database before cohort entry

§Defined as ≥80 mg/day (atorvastatin, simvastatin, fluvastatin) or 40 mg/day (lovastatin, pravastatin, rosuvastatin); daily doses: (quantity*strength)/days supplied.

Table 2| Previous drug use in year before cohort entry in new users of statins. Figures are numbers (percentage) of patients

	Pravastatin (n=38 470)	Atorvastatin (n=268 254)	Fluvastatin/lovastatin (n=11 923)	Rosuvastatin (n=76 774)	Simvastatin (n=75 829
Steroids	7054 (18.3)	48 155 (18.0)	1937 (16.2)	14 065 (18.3)	13 732 (18.1)
First generation antipsychotic	274 (0.7)	1415 (0.5)	91 (0.8)	310 (0.4)	413 (0.5)
Second generation antipsychotic	232 (0.6)	3838 (1.4)	39 (0.3)	1237 (1.6)	778 (1.0)
Immunosuppressants	31 (0.1)	127 (0.0)	15 (0.1)	15 (0.0)	18 (0.0)
Protease inhibitors	7 (0.0)	28 (0.0)	0 (0.0)	16 (0.0)	≤5 (0.0)
Lithium	60 (0.2)	578 (0.2)	18 (0.2)	146 (0.2)	159 (0.2)
β blockers	10 305 (26.8)	70 555 (26.3)	2824 (23.7)	17 107 (22.3)*	21 372 (28.2)
Thiazide diuretics	5532 (14.4)	51 141 (19.1)*	1600 (13.4)	15 755 (20.5)*	12 697 (16.7)
Other diuretics	3136 (8.2)	22 780 (8.5)	883 (7.4)	5028 (6.5)	6739 (8.9)
Niacin	≤5 (0.0)	≤5 (0.0)	0 (0.0)	31 (0.0)	≤5 (0.0)
Phenytoin	264 (0.7)	1978 (0.7)	67 (0.6)	447 (0.6)	539 (0.7)
Thyroid hormone	4510 (11.7)	33 410 (12.5)	1432 (12.0)	9672 (12.6)	9073 (12.0)
Hormones and analogues	3420 (8.9)	20 947 (7.8)	1130 (9.5)	4408 (5.7)*	6680 (8.8)
Isoniazid	≤5 (0.0)	19 (0.0)	≤5 (0.0)	≤5 (0.0)	7 (0.0)
Nitroglycerin	7063 (18.4)	36 908 (13.8)*	1739 (14.6)*	5909 (7.7)*	13 642 (18.0)
Angiotensin converting enzyme inhibitor	10 331 (26.9)	78 496 (29.3)	2715 (22.8)	21 397 (27.9)	22 183 (29.3)
Angiotensin receptor blocker	1526 (4.0)	24 619 (9.2)*	317 (2.7)	13 363 (17.4)*	4831 (6.4)*
Calcium channel blocker	10 481 (27.2)	68 389 (25.5)	2782 (23.3)	18 706 (24.4)	20 164 (26.6)

*Standardized mean difference >0.1.

Table 3| Analysis of primary outcome of diagnosis of diabetes in Ontario Diabetes Database in new users of statins

Statin	No of patients	No of outcomes	Median (IQR) follow-up (person days)	No of outcomes per 1000 person years	HR (95% CI)		Number needed to treat to harm
					Unadjusted	Adjusted*	
All users							
Pravastatin	38 470	1443	240 (90-1095)	22.64	Reference	Reference	—
Atorvastatin	268 254	15 261	369 (90-1283)	30.70	1.37 (1.30 to 1.44)	1.22 (1.15 to 1.29)	172
Fluvastatin	5636	167	190 (67-742)	21.52	0.94 (0.80 to 1.10)	0.95 (0.81 to 1.11)	—
Lovastatin	6287	211	210 (90-945)	21.80	0.96 (0.83 to 1.11)	0.99 (0.86 to 1.14)	—
Rosuvastatin	76 774	3732	308 (58-806)	34.21	1.50 (1.41 to 1.59)	1.18 (1.10 to 1.26)	210
Simvastatin	75 829	3727	331 (90-1384)	26.22	1.17 (1.10 to 1.24)	1.10 (1.04 to 1.17)	363
Primary prevention users							
Pravastatin	17 901	637	205 (72-975)	22.80	Reference	Reference	
Atorvastatin	124 925	6902	300 (64-1207)	31.45	1.39 (1.29 to 1.51)	1.20 (1.10 to 1.30)	181
Fluvastatin	3066	91	180 (63-799)	22.34	0.97 (0.77 to 1.20)	0.98 (0.79 to 1.22)	—
Lovastatin	3241	110	206 (90-945)	22.11	0.97 (0.79 to 1.18)	1.01 (0.82 to 1.23)	—
Rosuvastatin	46 591	2240	285 (37-772)	34.92	1.51 (1.39 to 1.65)	1.12 (1.02 to 1.23)	294
Simvastatin	32 270	1552	274 (80-1233)	27.41	1.21 (1.11 to 1.33)	1.12 (1.02 to 1.23)	294
Secondary prevention users							
Pravastatin	20 569	806	279 (90-1176)	22.51	Reference	Reference	—
Atorvastatin	143 329	8359	425 (90-1349)	30.11	1.35 (1.25 to 1.45)	1.25 (1.16 to 1.34)	162
Fluvastatin	2570	76	202 (71-787)	20.62	0.91 (0.72 to 1.15)	0.91 (0.72 to 1.15)	—
Lovastatin	3046	101	214 (90-941)	21.48	0.95 (0.77 to 1.16)	0.97 (0.79 to 1.20)	—
Rosuvastatin	30 183	1492	350 (60-858)	33.18	1.47 (1.34 to 1.60)	1.24 (1.13 to 1.36)	168
Simvastatin	43 559	2175	382 (90-1490)	25.44	1.14 (1.05 to 1.23)	1.10 (1.01 to 1.19)	407

*Adjusted for age, sex, year of cohort entry, recent acute coronary syndrome, chronic coronary artery disease, Charlson score, previous use of diuretic (thiazide), nitroglycerin, angiotensin receptor blocker, β blocker, hormones and analogues.

Table 4| Analysis of secondary outcomes (new prescriptions for antidiabetic drugs, self monitoring of blood glucose, diagnosis of diabetes in Ontario Diabetes Database) in new users of statins

Statin	No of patients	No of outcomes	Median (IQR) follow-up (person days)	No of outcomes per 1000 person years	HR (95% CI)		Number needed to treat to harm
					Unadjusted	Adjusted*	
Pravastatin	38 470	1713	236 (90-1080)	27.07	Reference	Reference	—
Atorvastatin	268 254	18 303	360 (89-1256)	37.28	1.39 (1.33 to 1.46)	1.21 (1.15 to 1.27)	140
Fluvastatin	5636	193	188 (66-732)	24.99	0.90 (0.78 to 1.05)	0.91 (0.79 to 1.06)	—
Lovastatin	6287	260	207 (90-927)	27.06	0.99 (0.87 to 1.13)	1.03 (0.90 to 1.17)	—
Rosuvastatin	76 774	4565	300 (50-796)	42.35	1.53 (1.45 to 1.62)	1.15 (1.08 to 1.22)	202
Simvastatin	75 829	4477	323 (90-1355)	31.84	1.19 (1.13 to 1.26)	1.11 (1.05 to 1.18)	261

*Adjusted for age, sex, year of cohort entry, recent acute coronary syndrome, chronic coronary artery disease, Charlson score, previous use of diuretic (thiazide), nitroglycerin, angiotensin receptor blocker, β blocker, hormones and analogues.

Table 5| Analysis of primary outcome of diagnosis of diabetes in Ontario Diabetes Database by drug and dose in new users of statins. Figures are hazard ratios (95% confidence intervals)

Statin	Unadjusted	Adjusted*
Pravastatin	Reference	Reference
Atorvastatin	1.21 (1.15 to 1.28)	1.12 (1.05 to 1.18)
Fluvastatin	0.94 (0.80 to 1.10)	0.94 (0.80 to 1.11)
Lovastatin	0.96 (0.83 to 1.11)	0.99 (0.85 to 1.14)
Rosuvastatin	1.21 (1.13 to 1.30)	1.01 (0.94 to 1.09)
Simvastatin	1.16 (1.09 to 1.24)	1.11 (1.04 to 1.18)
Dose grouping:		
Low dose†	Reference	Reference
Moderate dose‡	1.26 (1.22 to 1.30)	1.22 (1.19 to 1.26)
High dose§	1.39 (1.29 to 1.50)	1.30 (1.20 to 1.40)

*Adjusted for age, sex, year of cohort entry, recent acute coronary syndrome, chronic coronary artery disease, Charlson score, and previous use of diuretic (thiazide), nitroglycerin, angiotensin receptor blocker, β blocker, hormones and analogues.

†Atorvastatin <20 mg, fluvastatin all doses, lovastatin all doses, pravastatin all doses, rosuvastatin <10 mg, simvastatin <80 mg.

‡Atorvastatin 20-<80 mg, rosuvastatin 10-<40 mg, simvastatin ≥8 0mg.

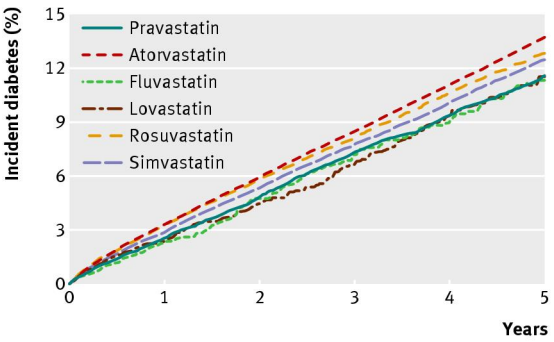
§Atorvastatin ≥80 mg, rosuvastatin ≥40 mg.

Table 6| Analysis of primary outcome of diagnosis of diabetes in Ontario Diabetes Database in new users of statins by statin potency

Statin	No of patients	No of outcomes	No of outcomes per 1000 person years	HR (95% CI)	
				Unadjusted	Adjusted*
Pravastatin	38 470	1443	22.64	Reference	Reference
High potency (atorvastatin, rosuvastatin)	345 028	18 993	31.34	1.39 (1.32 to 1.47)	1.22 (1.15 to 1.29)
Moderate potency (simvastatin)	75 829	3727	26.22	1.17 (1.1 to 1.24)	1.11 (1.04 to 1.18)
Low potency (fluvastatin, lovastatin)	11 923	378	21.68	0.95 (0.85 to 1.06)	0.97 (0.87 to 1.09)

*Adjusted for age, sex, year of cohort entry, recent acute coronary syndrome, chronic coronary artery disease, Charlson score and previous use of diuretic (thiazide), nitroglycerin, angiotensin receptor blocker, β blocker, hormones and analogues.

Figure



Adjusted survival curves for incident diabetes among new users of statins