Original Investigation

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Association of Statin Therapy Initiation With Diabetes Progression

A Retrospective Matched-Cohort Study

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Key Points

Question What is the association of statin treatment initiation and diabetes progression in patients with diabetes?

Findings This large retrospective cohort study included 83 022 propensity-scored matched pairs of statin users and nonusers and found that the diabetes-progression composite outcome was significantly higher among patients with diabetes who used statins than among patients with diabetes who did not use statins. The study examined 12 years of data on patients covered by the Veterans Affairs health system and new-user and active-comparator designs to assess associations between statin initiation and

Meaning Statin use was associated with diabetes progression in patients with diabetes—statin users had a higher likelihood of insulin treatment initiation, developing significant hyperglycemia, experiencing acute glycemic complications, and being prescribed an increased number of glucose-lowering medication classes.

Importance Statin therapy has been associated with increased insulin resistance; however, its clinical implications for diabetes control among patients with diabetes is unknown.

Objective To assess diabetes progression after initiation of statin use in patients with diabetes.

Design, Setting, and Participants This was a retrospective matched-cohort study using new-user and active-comparator designs to assess associations between statin initiation and diabetes progression in a national cohort of patients covered by the US Department of Veterans Affairs from fiscal years 2003-2015. Patients included were 30 years or older; had been diagnosed with diabetes during the study period; and were regular users of the Veterans Affairs health system, with records of demographic information, clinical encounters, vital signs, laboratory data, and medication usage.

Interventions Treatment initiation with statins (statin users) or with H2-blockers or proton pump inhibitors (active comparators).

Main Outcomes and Measures Diabetes progression composite outcome comprised the following: new insulin initiation, increase in the number of glucose-lowering medication classes, incidence of 5 or more measurements of blood glucose of 200 mg/dL or greater, or a new diagnosis of ketoacidosis or uncontrolled diabetes.

Results From the 705 774 eligible patients, we matched 83 022 pairs of statin users and active comparators; the matched cohort had a mean (SD) age of 60.1 (11.6) years; 78 712 (94.9%) were men; 1715 (2.1%) were American Indian/Pacific Islander/Alaska Native, 570 (0.8%) were Asian, 17 890 (21.5%) were Black, and 56 633 (68.2 %) were White individuals. Diabetes progression outcome occurred in 55.9% of statin users vs 48.0% of active comparators (odds ratio, 1.37; 95% CI, 1.35-1.40; $P < .001$). Each individual component of the composite outcome was significantly higher among statin users. Secondary analysis demonstrated a dose-response relationship with a higher intensity of low-density lipoprotein-cholesterol lowering associated with greater diabetes progression.

Conclusions and Relevance This retrospective matched-cohort study found that statin use was associated with diabetes progression, including greater likelihood of insulin treatment initiation, significant

lowering medication classes. The risk-benefit ratio of statin use in patients with diabetes should take into consideration its metabolic effects.

Introduction

FULL TEXT

convert to mmol/L, multiply by 0.0259) for primary prevention of cardiovascular diseases (CVD).[1,2] However, statin use has been associated with increased insulin resistance and higher blood glucose levels. Several randomized controlled trials (RCTs)[3-5] and large prospective and retrospective observational studies[6-8] have noted that patients treated with statin therapy (hereafter, statin users) had increased insulin resistance, hemoglobin A_{1C} (HbA_{1C}) levels, and fasting plasma glucose levels. In a large observational study, statin use was associated with a 24% reduction in insulin sensitivity.[8] Despite the significant reduction in insulin sensitivity and the increase in fasting plasma insulin, the difference in fasting plasma glucose and HbA_{1C} between statin users and nonusers appears modest.[8] For example, a large RCT noted that an increase in HbA_{1C} was 0.30% in the rosuvastatin group and 0.22% in the placebo group ($P<.001$), and there was no significant difference in fasting serum glucose between the groups.[9]

A modest change in fasting blood glucose after statin initiation despite a relatively large change in insulin resistance and fasting insulin levels deserves further study. Clinicians might escalate antidiabetes therapy to offset the rising blood glucose; hence, HbA_{1C} levels may underestimate how statin therapy influences diabetes control. Yet increased insulin resistance is of concern because it may fuel diabetes disease progression.[10,11] It is important to understand the clinical importance of increased insulin resistance to actual patient care.

The statin Diabetes Safety Task Force has remarked on the paucity of data regarding how statin use affects glycemic control.[12] The present study's objective was to compare diabetes progression (by assessing new insulin treatment initiations, changes in the number of glucose-lowering medication classes, and new persistent hyperglycemia or acute glycemic complications) after statin initiation with progression among nonusers in a national cohort of patients covered by the US Department of Veterans Affairs (VA).

Methods

Study Design

This was a retrospective matched-cohort study that used new-user and active-comparator designs to assess associations between statin initiation and diabetes progression among a national cohort of pa-

Health Sciences Center. Informed consent was waived because the study used only preexisting deidentified data. The study followed the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline and the reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiologic research (RECORD-PE).

(October 1, 2002-September 30, 2015), which captures several domains under published protocols.[13] It includes inpatient and outpatient diagnoses and procedure codes, pharmacy and medication usage, vital signs records, and laboratory data. We used all available medical encounters for a national VA cohort of patients diagnosed with diabetes during the study period, identified using a validated algorithm.[14,15]

The overall cohort included patients who met these criteria, were age 30 years or older at the index date and were regular VA health system users. We defined regular VA system users as having the following during both the baseline and follow-up periods: (1) at least 1 VA encounter; (2) blood pressure and weight measurements; (3) VA pharmacy dispensing; and (4) laboratory data, including blood or serum glucose, creatinine, and LDL cholesterol measurements.

Study Groups

We used an active comparator, new user design, to minimize unmeasured confounders and confounding by indication.[16,17] The statin user group was composed of patients who initiated statin therapy within the study period. The active comparator group was composed of patients who initiated an H2-blocker or proton pump inhibitor (H2/PPI) and were not concurrently prescribed a statin. To exclude prevalent users, any patient who during the 12 months prior to cohort entry had filled a statin prescription was excluded from the statin user group and any patient who had filled an H2-blocker or PPI prescription was excluded from the active comparator group. For any patient in the active comparator group who filled a statin prescription during the follow-up period, their follow-up ended as a nonuser (on the date of statin initiation) and they were crossed over to the statin user group (the date of statin initiation became their new index date). This design mitigated confounding by indication and immortal time bias.[18]

The index date was the date on which the first prescription for statin therapy or an H2 or PPI was filled. Because the study data included all available encounters from FY 2003-FY 2015, regardless of when a patient was diagnosed with diabetes, the index date could precede, coincide with, or occur after the date of diabetes diagnosis.

Study Intervals

The baseline period, which was used to describe baseline characteristics, comprised the year preceding the index date. The follow-up period, which was used to ascertain outcomes, started at the index date

confounding, we excluded patients who had fewer than 60 days of follow-up because the study outcomes would be highly unlikely to occur with fewer than 60 days of statin exposure.[18-20]

Primary Outcome—Diabetes Progression

glucose-lowering medication classes that were ever used during follow-up in comparison with the baseline (eTable 1 in the **Supplement**) and (2) new persistent hyperglycemia or acute glycemic complications, including: (a) the presence of 5 or more measurements with blood glucose levels of 200 mg/dL or greater (to convert to mmol/L, multiply by 0.0555) during follow-up (not present during the baseline period) and (b) receiving a new diagnosis of diabetes with ketoacidosis or uncontrolled diabetes during the follow-up period (not present during the baseline period). The *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes were used to identify diabetic ketoacidosis or uncontrolled diabetes (eTable 2 in the **Supplement**)[21] and have been widely used in the literature.[22-24] Overall, administrative health databases have found *ICD-9-CM* codes to be useful for identifying diabetes and its complications, with specificity from 94.3% to 100%, although sensitivity can vary.[25,26]

Secondary Outcomes

The study had 4 secondary outcomes. The first was individual components of diabetes progression outcome; second, the difference in the number of glucose-lowering medication classes ever used during the follow-up period by each individual in comparison with the number during their baseline; third, the proportion of patients with a decreased number of glucose-lowering medication classes during follow-up vs baseline; and fourth, the change in mean blood glucose (mg/dL) during follow-up vs baseline.

Cohort Characterization

Patients' comorbidities were identified using *ICD-9-CM* codes as defined by the Agency for Health Research and Quality Clinical Classifications Software disease categories.[21] We calculated each patient's Charlson comorbidity index[27] score and cardiovascular risk (eTables 3 and 4 in the **Supplement**).[28-30] We created a propensity score (PS) to match statin users and active comparators (nonusers) at a ratio of 1:1 using 93 variables chosen a priori (**Table 1**).[31] We used the routine by Leuven and Sianesi[32] to perform multivariable logistic regression to estimate the PS and to perform nearest number matching using the logit model.[33] We subsequently examined the balance in baseline characteristics between treatment groups. A caliper of 0.00014 was found to balance differences between treatment groups and maximize sample size (eMethods in the **Supplement**).

In the primary analysis, we compared the primary and secondary outcomes in the PS matched cohort using conditional logistic regression to calculate odds ratios (OR) and 95% CI. For the secondary analyses, we compared the primary outcome in the following cohorts:

2. Healthy cohort: patients with no comorbidities in the Charlson comorbidity index at baseline.

3. High-intensity cholesterol-lowering statin users (decrease of ≥50% in mean LDL cholesterol during follow-up vs baseline) compared with nonusers in the overall cohort.[1]

4. Moderate-intensity cholesterol lowering statin users (decrease of <50% and ≥30% in mean LDL cholesterol during follow-up vs baseline) compared with nonusers in the overall cohort.

5. Low-intensity cholesterol lowering statin users (a decrease of <30% in mean LDL cholesterol during follow-up vs baseline) compared with nonusers in the overall cohort.

6. Ever user vs never user cohort: we excluded patients who started as active comparators and were crossed over to the statin user group.

Sensitivity Analysis

We excluded patients who were diagnosed with incident diabetes, diabetic complications, ketoacidosis or uncontrolled diabetes, or CVD events within 60 days from the index date. Because it is highly unlikely that statin use would influence these outcomes within 60 days of statin initiation, excluding these patients further mitigated confounding by indication or residual confounding.[18-20]

Post Hoc Analysis

We created another PS matched cohort that included only patients who had diabetes during the baseline period (PS matched prevalent diabetes cohort). All variables and techniques that were used in the primary analysis were included in this cohort. A caliper of 0.00002 was used to achieve balance-maximizing sample size (**Table 1**).

Statistical Analysis

Dichotomous variables were compared using χ^2, and continuous variables were compared using *t* tests. When the Kolmogorov-Smirnov test indicated unequal distribution, we used the Wilcoxon Mann-Whitney test. Statistical tests were 2-tailed, and significance was defined as $P < .05$.

formed using a separate logistic regression model for each dichotomous outcome adjusting for the PS. Data management and statistical analyses were conducted from September 2019 to October 2020 using STATA, version 15 (Stata Corp LLC).

pairs of statin users and active comparators; the matched cohort had a mean (SD) age of 60.1 (11.6) years; 78 712 (94.9%) were men; 1715 (2.1%) were American Indian/Pacific Islander/Alaska Native, 570 (0.8%) were Asian, 17 890 (21.5%) were Black, and 56 633 (68.2 %) were White individuals. To form the study cohort, we had excluded 441 778 patients who were prevalent users of statins, H2, or PPI; 6613 who were less than 30 years old; 36 085 whose follow-up period had been fewer than 60 days; 421 170 who were not regular VA users; and 1098 whose records were missing data on age (eFigure in the **Supplement**).

Statin users had filled prescriptions for statins for a mean (SD) duration of 5.3 (3.3) years; median (IQR) of 5.1 (2.6-8.0) years. Statin users filled 12 118 523 prescriptions for statins throughout the study; 63.4% of the prescriptions were for simvastatin, 12.4% for atorvastatin, 10.5% for rosuvastatin, and 9.5% for pravastatin. Among nonusers, 52 176 patients (47.4%) subsequently used a statin during the study period and 58 019 (52.7%) never used a statin.

Among the 83 022 matched pairs of statin users and nonusers (**Table 1**) there was only a small difference in race and ethnicity distribution. Based on the cohort characteristics, all patients had been diagnosed with diabetes by the end of the study period. At baseline, the statin user and nonuser groups in the PS matched cohort had similar proportions of patients with diabetes, diabetes complications, recurrent episodes of high blood glucose (≥200 mg/dL), and using glucose-lowering agents; they also had similar mean blood glucose levels and patient follow-up periods. During the follow-up period, the statin users decreased their mean LDL cholesterol by a mean (SD) of 25 (31.6) mg/dL compared with a 0.8 (23.7) mg/dL among nonusers (95% CI of mean difference, 23.9-24.4; $P < .001$), demonstrating that statin users had effectively used, not just filled, their statin prescriptions (eTable 5 in the **Supplement**). The mean (SD) number of outpatient encounters by the PS matched cohort during the follow-up period was 37.8 (43.1) for the statin user group and 41.4 (50.5) encounters for the nonuser group.

Primary Analysis

Statin users had significantly higher odds of diabetes progression (OR, 1.37; 95% CI, 1.35-1.40) compared with nonusers. There was significantly higher rate of each component of the diabetes progression outcome in statin users compared with nonusers (**Table 2**) including an increase in the number of glu-

1.12-1.19), presence of persistent hyperglycemia (OR, 1.13; 95% CI, 1.10-1.16), and new diagnosis of ketoacidosis or uncontrolled diabetes (OR, 1.24; 95% CI, 1.19-1.30).

Secondary Analysis

users in the healthy cohort were higher than the overall cohort (OR, 1.56 vs 1.40) (Table 3). Intensive cholesterol lowering was associated with highest odds of diabetes progression outcome among statin users in compared with nonusers.

Post Hoc Analysis

In the PS-matched prevalent diabetes cohort, we matched 51 467 pairs of statin users and nonusers with only a small difference in proportion of men and some racial and ethnic minority subgroups (Table 1). The odds of the primary and secondary outcomes were significantly higher among statin users (Table 2).

Discussion

This study of a national cohort of VA patients with diabetes found that statin use was associated with an escalation of diabetes treatment, including a higher risk of initiating insulin and the use of more glucose-lowering medication classes. This escalation of diabetes treatment was associated with worse diabetes control, including new persistent hyperglycemia and acute glycemic complications. Moreover, there was a dose-response association between intensity of lowering LDL cholesterol and risk of the study outcomes, with higher intensity of LDL cholesterol-lowering associated with higher odds of diabetes progression. For example, the odds of diabetes progression among statin users vs nonusers were 1.83, 1.55, and 1.45 for high-, moderate-, and low-intensity cholesterol lowering, respectively.

Using the Bender and Blettner formula,[34] the number needed to be exposed to statins for 1 additional person to experience diabetes progression outcome was 13. Although the mean difference between blood glucose during follow-up and baseline among statin users in contrast with nonusers was modest, there was significant escalation in diabetes therapy that was not associated with better clinical outcomes. This statin-associated metabolic cost was not measured by the RCTs, which instead focused mainly on cardiovascular benefits.[35] From 2009 to 2015, annual emergency department visits for hyperglycemic crisis almost doubled, hospitalization increased by 73%, and related deaths increased by 55%.[36] This resurgence in diabetes-specific complications deserves attention and a call to scrutinize our practices and goals.[37]

for secondary prevention. However, diabetes progression has long-term effects on quality of life and treatment burden, which warrant consideration when discussing the overall risk-benefit profile, especially when used for primary prevention. In this study, approximately 77% of the cohort had no known CVD at baseline. A recent cohort study[38] reported that patients with diabetes with 5 risk factors within

terol of risk of death from any cause. Moreover, some studies[39-42] have demonstrated that only patients who have had diabetes for at least 10 to 15 years have an increased risk of CVD events. In 1 of these studies,[39] only 31% of patients with diabetes and 66% of those with diabetes and coronary heart disease used statins at baseline.

Several RCTs,[3,4,43] Mendelian randomization studies,[44] observational studies,[5] and animal studies[45,46] have demonstrated that statin use increases insulin resistance. The association of statin use with diabetes progression may be explained by its effect on insulin resistance (eDiscussion in the **Supplement**). Insulin resistance has been shown to increase the risk of diabetic complications,[10,47] endothelial dysfunction, inflammation, and increased platelet reactivity.[48-52]

Strengths and Limitations

Strengths of this study are its large size and longitudinal follow-up period with detailed clinical data. Also of note, patients in the nonuser group did not receive statin therapy despite guidelines recommending statins, a finding consistent with other studies[53] that indicate that, in community practice, many patients do not receive statins according to guidelines. The present study's definitions of the intensity of cholesterol lowering is guided by, but not identical to, the definitions used by the American College of Cardiology/American Heart Association (ACC/AHA) and the American Diabetes Association.[1] The ACC/AHA identifies high-intensity statins based on their expected efficacy in lowering LDL cholesterol by 50% or more. For this study, we defined intensive cholesterol lowering among statin users as decreasing mean LDL cholesterol during the follow-up period by 50% or more compared with the baseline mean. Similarly, our definitions for low- and moderate-intensity cholesterol lowering used the same cutoff limits as the ACC/AHA guidelines but used the actual decrease in mean LDL cholesterol during follow-up. Our approach incorporates a measure of adherence to treatment, not simply filling of prescriptions.

This study also had some limitations inherent to retrospective observational data; hence, there is always a chance of unmeasured residual confounding. It may be argued that statin users have closer follow-up, resulting in ascertainment bias. However, the outpatient encounters of the PS matched cohort during the follow-up period were not more frequent among statin users than among nonusers. Prior studies[54] have shown that adjusting to number of encounters that took place during follow-up period did not af-

It could be argued that the physicians who prescribed statins may have also attempted to aggressively control diabetes by adding more glucose-lowering agents; however, this would not explain the increased persistent hyperglycemia nor the ketoacidosis, which would be expected to decrease. It may also be argued that confounding by indication may have played a part in the study findings, specifically

diabetic complications, ketoacidosis, uncontrolled diabetes, or CVD within fewer than 60 days from the index date, demonstrated an association of statin use with diabetes progression, with odds similar those of the primary analysis. We also could not ascertain whether the association of statin use with diabetes progression was because of the statin use or the lower LDL cholesterol—that is, statins are inseparable from their cholesterol-lowering effect. The definition of the study's composite outcome also had some limitations; an increase in the number of glucose-lowering agents assumed that all agents had similar potency. Also, selecting 5 or more episodes of blood glucose seems arbitrary; nevertheless, the outcome was applied equally to both statin users and nonusers and all components of the composite outcome were directionally the same. The study data could not reliably differentiate between diabetes types because there is no reliable algorithm to accomplish this in a data set such as this,[55] and regardless, there is no reason to believe that it would have differentially affected statin users vs nonusers. We expect that the extensive matching of the 2 groups on baseline characteristics, including microvascular and macrovascular diabetes complications, may have acted as a surrogate for diabetes severity and chronicity. Patients covered by the VA were predominantly men, which may limit generalization; however, research has shown that men covered by the VA have characteristics similar to those of individuals covered by other insurance.[56] Lastly, the study protocol was not prepublished.

Conclusions

This large retrospective matched-cohort study found that statin use was associated with a higher risk of diabetes treatment escalation and an increased risk of hyperglycemic complications. This metabolic cost was not considered in RCTs of statins. Further research is needed to form a risk-tailored approach to balancing the cardiovascular benefits of statin therapy with its risk of diabetes progression.

Article Information

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References

1. Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B):2889-2934. doi:10.1016/j.jacc.2013.11.002
PubMed | Google Scholar | Crossref

PubMed | Google Scholar | Crossref

3. Holman RR, Paul S, Farmer A, Tucker L, Stratton IM, Neil HA; Atorvastatin in Factorial with Omega-3 EE90 Risk Reduction in Diabetes Study Group. Atorvastatin in Factorial with Omega-3 [illegible] *Diabetologia*.

4. Erlandson KM, Jiang Y, Debanne SM, McComsey GA. Rosuvastatin worsens insulin resistance in HIV-infected adults on antiretroviral therapy. *Clin Infect Dis*. 2015;61(10):1566-1572. doi:10.1093/cid/civ554
PubMed | Google Scholar | Crossref

5. Koh KK, Quon MJ, Han SH, Lee Y, Kim SJ, Shin EK. Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients. *J Am Coll Cardiol*. 2010;55(12):1209-1216. doi:10.1016/j.jacc.2009.10.053
PubMed | Google Scholar | Crossref

6. Liew SM, Lee PY, Hanafi NS, et al. Statins use is associated with poorer glycaemic control in a cohort of hypertensive patients with diabetes and without diabetes. *Diabetol Metab Syndr*. 2014;6:53. doi:10.1186/1758-5996-6-53
PubMed | Google Scholar | Crossref

7. Sukhija R, Prayaga S, Marashdeh M, et al. Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients. *J Investig Med*. 2009;57(3):495-499. doi:10.2310/JIM.0b013e318197ec8b
PubMed | Google Scholar | Crossref

8. Cederberg H, Stančáková A, Yaluri N, Modi S, Kuusisto J, Laakso M. Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort. *Diabetologia*. 2015;58(5):1109-1117. doi:10.1007/s00125-015-3528-5
PubMed | Google Scholar | Crossref

9. Ridker PM, MacFadyen J, Cressman M, Glynn RJ. Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C-reactive protein: a secondary analysis from the JUPITER (Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin) trial. *J Am Coll Cardiol*. 2010;55(12):1266-1273. doi:10.1016/j.jacc.2010.01.020
PubMed | Google Scholar | Crossref

betes Care. 2007;30(3):707-712. doi:10.2337/dc06-1982
PubMed | Google Scholar | Crossref

11. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes*. 1615-1625. doi:10.2337/diabetes.54.6.1615

12. Maki KC, Ridker PM, Brown WV, Grundy SM, Sattar N, The Diabetes Subpanel of the National Lipid Association Expert Panel. An assessment by the Statin Diabetes Safety Task Force: 2014 update. *J Clin Lipidol*. 2014;8(3)(suppl):S17-S29. doi:10.1016/j.jacl.2014.02.012
PubMed | Google Scholar | Crossref

13. Health Services Research and Development. Accessed October 22, 2020. https://www.hsrd.research.va.gov/for_researchers/vinci/cdw.cfm

14. Miller DR, Safford MM, Pogach LM. Who has diabetes? Best estimates of diabetes prevalence in the Department of Veterans Affairs based on computerized patient data. *Diabetes Care*. 2004;27(suppl 2):B10-B21. doi:10.2337/diacare.27.suppl_2.B10
PubMed | Google Scholar | Crossref

15. Alvarez CA, Halm EA, Pugh MJV, et al. Lactic acidosis incidence with metformin in patients with type 2 diabetes and chronic kidney disease: A retrospective nested case-control study. *Endocrinol Diabetes Metab*. 2020;4(1):e00170. doi:10.1002/edm2.170
PubMed | Google Scholar

16. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Curr Epidemiol Rep*. 2015;2(4):221-228. doi:10.1007/s40471-015-0053-5
PubMed | Google Scholar | Crossref

17. Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. *Nat Rev Rheumatol*. 2015;11(7):437-441. doi:10.1038/nrrheum.2015.30
PubMed | Google Scholar | Crossref

18. Danaei G, Rodríguez LA, Cantero OF, Logan R, Hernán MA. Observational data for comparative effectiveness research: an emulation of randomised trials of statins and primary prevention of coronary heart disease. *Stat Methods Med Res*. 2013;22(1):70-96. doi:10.1177/0962280211403603
PubMed | Google Scholar | Crossref

19. Jee SH, Sull JW, Park J, et al. Body-mass index and mortality in Korean men and women. *N Engl J Med*. 2006;355(8):779-787. doi:10.1056/NEJMoa054017

20. Allison DB, Faith MS, Heo M, Townsend-Butterworth D, Williamson DF. Meta-analysis of the effect of excluding early deaths on the estimated relationship between body mass index and mortality. *Obes Res*. 1999;7(4):342-354. doi:10.1002/j.1550-8528.1999.tb00417.x
PubMed | Google Scholar | Crossref

Accessed August 30, 2021. https://www.hcup-us.ahrq.gov/toolssoftware/ccs/AppendixASingleDX.txt

22. Henderson DC, Cagliero E, Copeland PM, et al. Elevated hemoglobin A1c as a possible indicator of diabetes mellitus and diabetic ketoacidosis in schizophrenia patients receiving atypical antipsychotics. *J Clin Psychiatry*. 2007;68(4):533-541. doi:10.4088/JCP.v68n0407
PubMed | Google Scholar | Crossref

23. Wetterhall SF, Olson DR, DeStefano F, et al. Trends in diabetes and diabetic complications, 1980-1987. *Diabetes Care*. 1992;15(8):960-967. doi:10.2337/diacare.15.8.960
PubMed | Google Scholar | Crossref

24. Christakis DA, Feudtner C, Pihoker C, Connell FA. Continuity and quality of care for children with diabetes who are covered by medicaid. *Ambul Pediatr*. 2001;1(2):99-103. doi:10.1367/1539-4409(2001)001<0099:CAQOCF>2.0.CO;2
PubMed | Google Scholar | Crossref

25. Khokhar B, Jette N, Metcalfe A, et al. Systematic review of validated case definitions for diabetes in ICD-9-coded and ICD-10-coded data in adult populations. *BMJ Open*. 2016;6(8):e009952. doi:10.1136/bmjopen-2015-009952
PubMed | Google Scholar

26. Saydah SH, Geiss LS, Tierney E, Benjamin SM, Engelgau M, Brancati F. Review of the performance of methods to identify diabetes cases among vital statistics, administrative, and survey data. *Ann Epidemiol*. 2004;14(7):507-516. doi:10.1016/j.annepidem.2003.09.016
PubMed | Google Scholar | Crossref

27. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619. doi:10.1016/0895-4356(92)90133-8
PubMed | Google Scholar | Crossref

28. D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117(6):743-753. doi:10.1161/CIRCULA-

29. Quan H, Li B, Saunders LD, et al; IMECCHI Investigators. Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. *Health Serv Res*. 2008;43(4):1424-1441. doi:10.1111/j.1475-6773.2007.00822.x
PubMed | Google Scholar | Crossref

morbidities. *Paediatr Perinat Epidemiol*. 2012;26(5):421-429. doi:10.1111/j.1365-3016.2012.01303.x
PubMed | Google Scholar | Crossref

31. Stevens LA, Coresh J, Feldman HI, et al. Evaluation of the modification of diet in renal disease study equation in a large diverse population. *J Am Soc Nephrol*. 2007;18(10):2749-2757. doi:10.1681/ASN.2007020199
PubMed | Google Scholar | Crossref

32. Becker SO, Ichino A. Estimation of average treatment effects based on propensity scores. *Stata J*. 2002;2(4):358-377. doi:10.1177/1536867X0200200403
Google Scholar | Crossref

33. Leuven E, Sianesi B. PSMATCH2: Stata module to perform full Mahalanobis and propensity score matching, common support graphing, and covariate imbalance testing, v 4.0.5. 2003. Accessed August 27, 2021. https://ideas.repec.org/c/boc/bocode/s432001.html

34. Bender R, Blettner M. Calculating the "number needed to be exposed" with adjustment for confounding variables in epidemiological studies. *J Clin Epidemiol*. 2002;55(5):525-530. doi:10.1016/S0895-4356(01)00510-8
PubMed | Google Scholar | Crossref

35. Mansi IA. Statins in primary prevention: uncertainties and gaps in randomized trial data. *Am J Cardiovasc Drugs*. 2016;16(6):407-418. doi:10.1007/s40256-016-0190-3
PubMed | Google Scholar | Crossref

36. US Centers for Disease Control and Prevention. US diabetes surveillance system and diabetes atlas. Assessed December 9, 2020. https://www.cdc.gov/diabetes/data

37. Gregg EW, Hora I, Benoit SR. Resurgence in diabetes-related complications. *JAMA*. 2019;321(19):1867-1868. doi:10.1001/jama.2019.3471
Article | PubMed | Google Scholar | Crossref

38. Rawshani A, Rawshani A, Franzén S, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2018;379(7):633-644. doi:10.1056/NEJ-

39. Rana JS, Liu JY, Moffet HH, Jaffe M, Karter AJ. Diabetes and prior coronary heart disease are not necessarily risk equivalent for future coronary heart disease events. *J Gen Intern Med*. 2016;31(4):387-393. doi:10.1007/s11606-015-3556-3
PubMed | Google Scholar | Crossref

2001;161(14):1717-1723. doi:10.1001/archinte.161.14.1717
Article | PubMed | Google Scholar | Crossref

41. Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Impact of diabetes on cardiovascular disease risk and all-cause mortality in older men: influence of age at onset, diabetes duration, and established and novel risk factors. *Arch Intern Med*. 2011;171(5):404-410. doi:10.1001/archinternmed.2011.2
Article | PubMed | Google Scholar | Crossref

42. Idris I. Diabetes and cardiovascular risk equivalency: do age at diagnosis and disease duration affect risk stratification?: comment on "impact of diabetes on cardiovascular disease risk and all-cause mortality in older men". *Arch Intern Med*. 2011;171(5):410-411. doi:10.1001/archinternmed.2010.524
Article | PubMed | Google Scholar | Crossref

43. Colhoun HM, Betteridge DJ, Durrington PN, et al; CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364(9435):685-696. doi:10.1016/S0140-6736(04)16895-5
PubMed | Google Scholar | Crossref

44. Swerdlow DI, Preiss D, Kuchenbaecker KB, et al; DIAGRAM Consortium; MAGIC Consortium; InterAct Consortium. HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. *Lancet*. 2015;385(9965):351-361. doi:10.1016/S0140-6736(14)61183-1
PubMed | Google Scholar | Crossref

45. Henriksbo BD, Lau TC, Cavallari JF, et al. Fluvastatin causes NLRP3 inflammasome-mediated adipose insulin resistance. *Diabetes*. 2014;63(11):3742-3747. doi:10.2337/db13-1398
PubMed | Google Scholar | Crossref

46. Mitchell P, Marette A. Statin-induced insulin resistance through inflammasome activation: sailing between Scylla and Charybdis. *Diabetes*. 2014;63(11):3569-3571. doi:10.2337/db14-1059
PubMed | Google Scholar | Crossref

47. Buse MG. Hexosamines, insulin resistance, and the complications of diabetes: current status. *Am J Physiol Endocrinol Metab*. 2006;290(1):E1-E8. doi:10.1152/ajpendo.00329.2005
PubMed | Google Scholar | Crossref

Visseli CM Furie KL et al IRIS Trial Investigators Pioglitazone after ischemic

PubMed | Google Scholar | Crossref

49. Mather KJ, Steinberg HO, Baron AD. Insulin resistance in the vasculature. *J Clin Invest*. 2013;123(3):1003-1004. doi:10.1172/JCI67166
PubMed | Google Scholar | Crossref

50. Semenkovich CF. Insulin resistance and atherosclerosis. *J Clin Invest*. 2006;116(7):1813-1822. doi:10.1172/JCI29024
PubMed | Google Scholar | Crossref

51. Smith AG, Singleton JR. Obesity and hyperlipidemia are risk factors for early diabetic neuropathy. *J Diabetes Complications*. 2013;27(5):436-442. doi:10.1016/j.jdiacomp.2013.04.003
PubMed | Google Scholar | Crossref

52. Kissel JT, Smith AG. Understanding small fiber neuropathy: the long and short of it. *JAMA Neurol*. 2016;73(6):635-637. doi:10.1001/jamaneurol.2016.0256
Article | PubMed | Google Scholar | Crossref

53. Verma A, Visintainer P, Elarabi M, Wartak S, Rothberg MB. Overtreatment and undertreatment of hyperlipidemia in the outpatient setting. *South Med J*. 2012;105(7):329-333. doi:10.1097/SMJ.0b013e318259bad3
PubMed | Google Scholar | Crossref

54. Mansi IA, Frei CR, Halm EA, Mortensen EM. Association of statins with diabetes mellitus and diabetic complications: role of confounders during follow-up. *J Investig Med*. 2017;65(1):32-42. doi:10.1136/jim-2016-000218
PubMed | Google Scholar | Crossref

55. Raebel MA, Schroeder E, Goodrich G, et al Validating type 1 and type 2 diabetes mellitus in the Mini-Sentinel Distributed Database using the Surveillance, Prevention, and Management of Diabetes Mellitus (SUPREME-DM) DataLink. Accessed on March 4, 2021. https://www.sentinelsystem.org/sentinel/methods/validating-type-1-and-type-2-diabetes-mellitus-mini-sentinel-distributed-database

56. Wong ES, Wang V, Liu CF, Hebert PL, Maciejewski ML. Do Veterans Health Administration en-

PubMed | Google Scholar | Crossref

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