Statin Use and Risk of Intracerebral Hemorrhage in Older patients: A Population-Based, Matched Cohort Study

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Abstract

Purpose: Statin therapy has been shown to prevent major vascular events in a wide range of individuals, but the risk of intracerebral hemorrhage (ICH) from statin use is unclear. We aimed to determine the ICH risk since statin initiation for older patients.

Methods: Based on 2011-2020 year data from the Yinzhou Regional Health Care Database, patients aged 50 years or older who have no history of ICH and statin use were included in the framework of target trial emulation, and then were categorized as statin initiators and non-initiators according to their initial statin assignment during 3-month recruitment periods. The statin initiators and non-initiators in each emulated trials were matched by using propensity score and then were stacked together. Cox proportional hazards model was used to estimate the association between ICH risk and statin treatment.

Results: With a median follow-up of 7.75 (interquartile range 6.75-8.75) years, 37,659 statins initiators and their 1:1 matched non-initiators were analysed where the hazard ratio of ICH between statin initiators and non-initiators were 1.09 (95% confidence interval: 0.92–1.29). The results are consistent across several subgroups and sensitivity analyses.

Conclusions: no association was found between ICH risk and statin use among older patients without prior ICH, suggesting no need to avoid potential statin prescribing due to concerns of evaluated ICH risk.

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of mortality worldwide (1). Especially, as a modifiable risk factor for ASCVD, elevated low-density lipoprotein cholesterol (LDL-C) has contributed to 3.81 million deaths overall in 2021 (2). While statins therapy has been proved to lower the risk of ASCVD (3,4), concerns for potentially increased risk of intracerebral hemorrhage (ICH) has been raised. It is possible that statins may weaken endothelial cells and inhibit platelet aggregation, enhance fibrinolysis, and thereby promotes vessels rapture and thrombogenesis (5).

Till now, no consensus has been reached with regard to statin use and ICH risk. A meta-analysis of 36 randomized trials suggest that statins increase the risk of ICH (6), while another meta-analysis of 31 randomized trials found no association between statin use and ICH risk (7). However, these randomized trials documented ICH as an adverse event rather than as a predetermined outcome, and underestimation may occur due to the strict inclusion/exclusion criteria. Observational studies showed divergent results which ranged from decreased to no association or increased risk (8–10). These observational studies (8–10) are limited to naïve study designs (groups are often assigned based on exposure status, i.e. users vs. non-users,
rather than initiators vs non-initiators) which cannot strictly avoid prevalent user and immortal time biases (11). Therefore, a greater degree of confidence could be achieved by replicating consistent adverse event relationships using different study designs across different health systems and prescribing patterns.

As the risk-benefit profile of statin therapy requires further investigation, this population-based cohort study aims to examine the association between statin use and ICH risk in older patients using target trial emulation design.

METHODS

Data source

A retrospective cohort was assembled based on the Yinzhou Regional Health Care Database (YRHCD) (12). Yinzhou is the largest district of Ningbo city in eastern China. YRHCD is a data warehouse established in 2006 by the Yinzhou District Centre for Disease Control and Prevention, which has enrolled nearly 99% (2.53 million) local residents by 2021. Personal information from different sources (population census, primary care, outpatient and inpatient electronic medical records, routine health check information and death reports) can be inherently linked by unique identifiers in the YRHCD. Of them, electronic medical records were collected from a regionally representative network of healthcare services, including 5 general hospitals, 24 community health centers, and 289 community health service stations. The following data were recorded in electronic medical records: (a) diagnoses data including diagnosis name, diagnosis type, diagnosis code (International Classification of Diseases, Tenth Revision, ICD-10) and diagnosis date, (b) prescription data including brand and generic names, ATC (Anatomical Therapeutic Chemical Classification of Medications) code, prescription date, filled amount and usage in natural text. All Death certificates in Yinzhou (no matter in hospital or out of hospital) were recorded in the death report system.

Study population and design

From January 1, 2011 to December 31, 2014, a sequence of 3-month emulated trials was created aligning with the framework of target trial emulation (Supplementary Table 1, Figure 1). For each trial, we included patients with age ≥50 years old. Any patients aged over 100 years old, with missing data on sex, had prior use of statin drugs within 365 days or a history of ICH were excluded (Supplementary Figure 1 and Supplementary Figure 2). Finally, a total of 37,661 statin initiators and 8,986,236 non-initiators were included in 16 sequential trials.

Exposure

For each trial, patients who initiated any statin treatment (i.e., rosuvastatin, atorvastatin, pitavastatin, simvastatin, pravastatin, fluvastatin, and lovastatin) during the recruitment period were categorized as statin initiators (statin intervention arm), while patients received none of above statins were categorized as non-initiators (usual care arm).

Covariates

In each trial, the following baseline characteristics of patients were extracted for further covariates balancing: demographic information (age and sex), comorbidities (e.g., ASCVD, pulmonary diseases, renal diseases, cancer and neurological conditions), concurrent medication use (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers [ACEi/ARB], diuretics, calcium channel blockers [CCB], other anti-hypertensive agents [alpha-blockers and beta-blockers], insulin, sulfonylurea, metformin, other anti-diabetic drugs [thiazolidinedione, glinide, alpha-glucosidase inhibitors, dipeptidyl peptidase 4 inhibitors [DPP-4i], glucagon-like peptide 1 receptor agonists [GLP-1 RA], and sodium-glucose cotransporter-2 inhibitors [SGLT-2i], antithrombotic drugs, nonsteroidal anti-inflammatory drug [NSAID]), lab test LDL-C (missing rate was 97.8%) and health care utilization (inpatient and outpatient visits). Details are shown in Supplementary Table 2.

Outcomes

The primary outcome was defined as the first, principal hospital diagnosis of ICH (ICD-10: I61). All-cause
mortality as the secondary outcome was identified from the death records. Patients were followed up from the last day of the recruitment period for each emulated trial, until the onset of ICH, death, or end of the study period (December 31st, 2020), whichever came first.

Statistical analyses

Continuous variables were presented as the mean±standard deviation (SD) or median with interquartile range (IQR), depending on the distribution, and categorical variables as number and percentage.

To balance the baseline characteristics between the statin intervention arm and usual care arm, 1:1 propensity score (PS) matching by the ‘nearest-neighbor’ approach with a caliper of 0.2 was performed for each trial (13). PS was estimated by logistic regression models, in which statin initiation was logistically regressed on the pre-treatment covariates (i.e., demographics, comorbidities, medication uses and healthcare utilization [LDL-C was excluded due to the high missing rate]). The balance of the baseline characteristics between the two arms was measured by the standardized mean difference (SMD) where SMD of less than 0.1 indicated a negligible difference. After PS matching, we increase the statistical power by stacking 16 PS-matched trials together as each single trial only has very few numbers of ICH events. Based on the stacked dataset, Kaplan-Meier curves were first plotted to compare the cumulative incidence of ICH and death between the two arms, and then hazard ratio (HR) was calculated by the proportional hazard Cox regression model. However, because patients may be included in multiple emulated trials, confidence interval (CI) of HR was re-estimated by robust method (14).

To test potential effect modification of sex, age (<65 vs. ≥65 years), antithrombotic drugs, ischemic stroke, and hypertension, subgroup analyses were performed. In addition, several sensitivity analyses were performed to examine the robustness of our results: (1) considering the lag of drug effect issue, only ICH events occurring 180 days after the start of follow-up would be counted to explore statin-associated ICH risk; (2) we further dichotomized the statin intervention arm into high (atorvastatin, rosuvastatin, pitavastatin) and low potency (lovastatin, fluvastatin, pravastatin, simvastatin) groups according to the LDL-C lowering efficacy of received statins (15), and to adjust for confounders by indication of non-initiators (16), high potency and low potency statin initiators, the inverse probability of treatment weighting (IPTW) was employed; (3) considering imperfect adherence in real world (17), an as-treated analysis was performed (18) where observations would be censored once statin initiators discontinued statin therapy for more than 30 days (grace period) or non-initiators initiated statin therapy; a dummy ‘statin initiation’ indicator in primary intention-to-treat analysis was replaced by ‘total duration of treatment’ to capture potential dose-response relationship in statin treatments. Statin initiators were further categorized into three groups (0-90 days, 90-365 days, and over 365 days) according to their duration of statin treatments.

Significance levels were set at a P value of <0.05 for 2-tailed tests. All statistical analyses were performed using R statistical software (R, version 4.2.2; R Project). This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Checklist (See STROBE Checklist in the Supporting Information).

RESULTS

Patient characteristics

Baseline characteristics of 37,661 statin initiators and 8,986,236 non-initiators from 16 emulated trials were summarized in Table 1. Among statin initiators, 17,394 (1,813 patients received rosuvastatin and 15,581 patients received atorvastatin) and 20,267 (19,879 received simvastatin and 388 patients received fluvastatin) patients received high and low potency statins (46.19% vs. 53.81% in total) respectively. Compared with non-initiators, the statin initiators were older (65 vs. 63 years), have fewer females (44.2% vs. 50.5%) and higher LDL-C levels (2.86 vs. 2.52) mg/dL. Statin initiators were more prone to comorbidities than non-initiators, where hypertension (67.6% vs. 13.3%), diabetes mellitus (22.5% vs. 3.8%), chronic obstructive pulmonary disease (19% vs. 4.3%) and ischemic heart disease (17.9% vs. 2.5%) are most common diseases. In terms of concurrent medication use, statin initiators reported higher prescription rates of other anti-
hypertensive agents (48.3% vs. 9.6%), ACEi/ARB (46.4% vs. 8%), CCB (45.9% vs. 7.8%), NSAID (42% vs. 9.1%), and diuretics (35% vs. 6.2%). Also, statin initiators utilize more outpatient services (median 12; IQR [4,23]), compared with non-initiators (median 0; IQR [0,0]). After PS matching, a total of 75,318 patients (37,659 statin initiators and 37,659 non-initiators) with well-balanced characteristics were included in the following analyses.

Comparison between statin initiators and non-initiators on risks of ICH and all-cause mortality

The incidence rates of ICH events and all-cause mortality for statin initiators and non-initiators were described in Table 2. There were 261 ICH events occurred in non-initiators, accounting for 9.1 (95% CI: 8.1-10.3) per 10,000 person-years. In contrast, 284 ICH events occurred among statin initiators, accounting for 9.9 (95% CI: 8.9-11.1) per 10,000 person-years. Overall HR of ICH risk for statin initiators compared to non-initiators is 1.09 (95% CI: 0.92-1.29), suggesting no statistically significant association between statin treatment and ICH risk. The incidence rate of all-cause mortality was 68.1 (95% CI: 65.1-71.1) and 70.1 (95% CI: 67.1-73.2) per 10,000 person-years for non-initiators and statin initiators respectively. The risk of all-cause mortality (HR: 1.03, 95% CI: 0.97-1.10) was also not statistically associated with statin initiation. Similar patterns of ICH risk and all-cause mortality were observed in survival curves (Figure 1).

Subgroup and sensitivity analyses

Supplementary Table 3 shows that no significant differences in the risks of ICH were observed between statin initiators and non-initiators with respect to sex, antithrombotic drugs, ischemic stroke, and hypertension. When we excluded ICH events occurring within first 180 days during follow-up, no statin-associated ICH risk was found (HR: 1.06, 95% CI: 0.89-1.27) (Supplementary Table 4). Compared with non-initiators, no statistically significant variation in ICH risk was found for either low potency statin (HR: 1.04, 95% CI: 0.85-1.28) or high potency statin (HR: 1.07, 95% CI: 0.97-1.32) initiators. But high potency statin initiators were found to be associated with a lower risk of all-cause mortality (HR: 0.90, 95% CI: 0.83-0.97) (Supplementary Table 5). In as-treated analysis, patients who received statin therapy from 0 to 90 days were associated with a higher ICH risk than non-initiators (HR: 1.65, 95% CI: 1.25-2.17) However, for those who were treated with statins for 90-365 days and > 365 days, no statistically significant results of ICH risks (HR: 1.47, 95% CI: 0.89-2.45; HR: 1.05, 95% CI: 0.55-1.89, respectively) were observed (Supplementary Figure 3).

DISCUSSION

By creating a sequence of emulated trials in a population-based cohort, our study showed that statin use was not associated with increased risk of ICH. This finding is consistent across different subgroups with respect to sex, age, antithrombotic drugs, ischemic stroke and hypertension. Hereafter, risk of all-cause mortality was found to be similar among statin initiators and non-initiators. To the best of our knowledge, this is the first study to explore the association between statin use and ICH using a target trial emulation design.

In line with our primary finding, a meta-analysis of 31 randomized controlled trials studies (7) and a population-based study conducted in Taiwan (8) found no association between statin use and ICH risk. Contrarily, two cohort studies in Denmark (19,20) and another cohort study in Korea (21) suggest a lower risk of ICH associated with statin use. We speculate that the inconsistency may be attributable to different study design, inclusion criteria and medication adherence. Target trial emulation is viewed methodologically superior to naive observational studies as it can bridge the gap between clinical trial and real-world data (22), which enhance the robustness of our study. Unlike the inclusion criteria from the studies in Denmark ([?]:45 years) (20) and Korea ([?]:40 years) (21), our study analyzed more vulnerable patients ([?]:50 years). Aging as an essential risk factor for ICH (23) possibly renders the effect of statin less pronounced. For medication adherence, Danish patients have been observed to have an medication possession ratio (MPR) of over 90% (24), while the Korean study only included patients with an MPR greater than 80% (21). Instead, poor medication adherence is more commonly seen in patients taking lipid-lowering medications in Asian areas (17,25), and may be a possible explanation for diverse trend.
Since statin intolerance (e.g., myalgia) is often observed in Asian population (26), high-intensity statin therapy (atorvastatin 40-80mg, rosuvastatin 20-40mg) is not recommended in Chinese guideline (27) and rarely prescribed as a consequence. A recent meta-analysis found that statins were associated with a higher risk of ICH in a dose-dependent manner (6). Low to moderate intensity statin prescription in clinical practice may diminish the potential effect of statin on ICH if any risk exists. In addition, risk of ICH was shown to decrease with increasing cholesterol levels (8,28). Given the unsatisfactory attainment of LDL-C as previously reported (29) and LDL-C levels shown in baseline, high LDL-C levels might be a protective factor for ICH in our population. In addition, genetic polymorphism among race and ethnic groups account for different responses to statins (30), which indicates that the effect of statins on ICH may also depend on genetic polymorphism.

Interestingly, an increased risk of ICH was identified in early statin initiators (¡90 days). Though presenting a different trend of ICH, the study by Ribe et al. (19) also showed that the risk of ICH decreased after six months of initiating statin use. One of the potential ways that statins offer protection is by changing the risk of developing cerebral small vessel disease in the long run, which is the main cause of spontaneous ICH (31,32). This finding suggests that the protection mechanism may be related to long-term effect of statin use. Besides, it is justifiable that statin initiators with ischemic stroke have higher ICH risk despite without statistical significance, as ischemic stroke is a commonly known factor of ICH (33). The result for ischemic stroke subgroup analysis further demonstrates the robustness of our study.

Our findings have important clinical implications. Despite variations in statin-related risk-benefit profile among people with different baseline features, the overall benefit well outweighs any potential risks. Our study suggested that the concerns for ICH should not be an obstacle for prescribing statins. However, caution should be taken during the early use of statin (¡90 days) and in subjects with previous ischemic stroke especially when patients exhibit clinical symptoms related to ICH.

Our study has some significant strength. Firstly, target trial emulation not only assigns study samples based on their initial treatment assignment, but also fixes application of eligibility of criteria, treatment initiation, and start of follow-up at time zero (22). Thus, this strategy solves prevalent user biases and immortal-time biases that are usually present in previous observational studies assessing the association of statin and ICH risk (11,22). Secondly, given the potential drug discontinuation and prescription change in clinical practice, as-treated analysis takes into account the actual treatment duration during the follow-up and thereby increases the robustness of our findings.

It is also important to note certain limitations in our study. Firstly, our data simply focuses on Asian population and caution should be warranted when extrapolating our findings to a different population. Secondly, records on statin doses were insufficient in the YRHCD, so we were unable to further conduct subgroup analysis with high-, moderate-, and low-intensity statin therapy according to definitions by American guidelines (4). Alternatively, we performed sensitivity analyses based on high and low potency groups to examine the robustness of our results. Thirdly, despite we implemented in target trial emulations, the efficacy of this depend on the data on a diverse set of confounders (22). Given that residual confounding remains possible as in all observational studies, we acknowledge that evidence provided from target trial emulation is not solid as in randomized controlled trials.

Collectively, our study using target trial emulation design shows that statin use over approximately 8 years does not increase the risk of ICH in older patients.

ETHICS STATEMENT

Not applicable.

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Yang Xu https://orcid.org/0000-0002-1074-608X
ACKNOWLEDGEMENTS

The corresponding author has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dongze Ji and Yang Xu conceived and designed the study, performed the statistical analysis. Dongze Ji, Yang Xu and Shujie Dong drafted and revised the manuscript, contributed to the study design. Tiansheng Wang, Jinkai Wei, and Xiaodong Guan critically revised the manuscript for intellectual content. Luwen Shi, Peng Shen and Hongbo Lin provide final approval of the version to be published. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPORTING INFORMATION

STROBE Checklist

Supplemental Figure 1-3

Supplemental Table 1-5

REFERENCES


**Table 1** Baseline Characteristics of Patients at Index Date From 16 Emulated Trials

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<tbody>
<tr>
<td></td>
<td>(n=8,986,236)</td>
<td>(n=37,661)</td>
<td>SMD</td>
<td>(n=37,659)</td>
<td>(n=37,659)</td>
<td>SMD</td>
</tr>
<tr>
<td>Age, years, mean ± SD</td>
<td>63 (10.1)</td>
<td>65 (9.41)</td>
<td>0.184</td>
<td>64 (10.20)</td>
<td>65 (9.41)</td>
<td>0.030</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Female</td>
<td>4,536,959 (50.5)</td>
<td>16,640 (44.2)</td>
<td>0.127</td>
<td>16,823 (44.7)</td>
<td>16,639 (44.2)</td>
<td>0.010</td>
</tr>
<tr>
<td>LDL-C level, mg/dL median [IQR]a</td>
<td>2.52 [2.05, 3.11]</td>
<td>2.86 [2.31, 3.43]</td>
<td>/</td>
<td>/</td>
<td>/</td>
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**Comorbidity, n (%)**

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<th>PS matched</th>
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<tbody>
<tr>
<td>Hypertension</td>
<td>1,199,569 (13.3)</td>
<td>25,469 (67.6)</td>
<td>1.327</td>
<td>25,896 (68.8)</td>
<td>25,467 (67.6)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>72,661 (0.8)</td>
<td>2,166 (5.8)</td>
<td>0.280</td>
<td>1,947 (5.2)</td>
<td>2,165 (5.7)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>227,830 (2.5)</td>
<td>6,754 (17.9)</td>
<td>0.525</td>
<td>6,085 (16.2)</td>
<td>6,752 (17.9)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>72,859 (0.8)</td>
<td>1,729 (4.6)</td>
<td>0.235</td>
<td>1,547 (4.1)</td>
<td>1,729 (4.6)</td>
</tr>
<tr>
<td>Peripheral arterial occlusion disease</td>
<td>42,756 (0.5)</td>
<td>1,460 (3.9)</td>
<td>0.235</td>
<td>1,247 (3.3)</td>
<td>1,460 (3.9)</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>225,511 (2.5)</td>
<td>6,608 (17.5)</td>
<td>0.517</td>
<td>5,998 (15.9)</td>
<td>6,606 (17.5)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>339,857 (3.8)</td>
<td>8,466 (22.5)</td>
<td>0.576</td>
<td>8,247 (21.9)</td>
<td>8,465 (22.5)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>383,926 (4.3)</td>
<td>7,165 (19.0)</td>
<td>0.473</td>
<td>7,255 (19.3)</td>
<td>7,165 (19.0)</td>
</tr>
<tr>
<td>Liver diseases</td>
<td>131,853 (1.5)</td>
<td>2,563 (6.8)</td>
<td>0.271</td>
<td>2,592 (6.9)</td>
<td>2,563 (6.8)</td>
</tr>
<tr>
<td>Condition</td>
<td>Unmatched</td>
<td>Unmatched</td>
<td>PS matched</td>
<td>PS matched</td>
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</tr>
<tr>
<td>Cancer</td>
<td>87,585 (1.0)</td>
<td>1,242 (3.3)</td>
<td>0.161</td>
<td>1,307 (3.5)</td>
<td>1,242 (3.3)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>8,245 (0.1)</td>
<td>182 (0.5)</td>
<td>0.073</td>
<td>176 (0.5)</td>
<td>182 (0.5)</td>
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<tr>
<td>Parkinson’s disease</td>
<td>12,105 (0.1)</td>
<td>258 (0.7)</td>
<td>0.086</td>
<td>249 (0.7)</td>
<td>258 (0.7)</td>
</tr>
<tr>
<td>Mood, stress, or anxiety</td>
<td>179,361 (2.0)</td>
<td>4,631 (12.3)</td>
<td>0.408</td>
<td>4,373 (11.6)</td>
<td>4,629 (12.3)</td>
</tr>
<tr>
<td><strong>Medication Uses, n (%)</strong></td>
<td></td>
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</tr>
<tr>
<td>ACEi/ARB</td>
<td>716,882 (8.0)</td>
<td>17,474 (46.4)</td>
<td>0.957</td>
<td>16,890 (44.8)</td>
<td>17,472 (46.4)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>555,434 (6.2)</td>
<td>13,198 (35.0)</td>
<td>0.764</td>
<td>13,009 (34.5)</td>
<td>13,197 (35.0)</td>
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<tr>
<td>CCB</td>
<td>704,019 (7.8)</td>
<td>17,284 (45.9)</td>
<td>0.951</td>
<td>16,743 (44.5)</td>
<td>17,282 (45.9)</td>
</tr>
<tr>
<td>Other anti-hypertensive agents</td>
<td>865,994 (9.6)</td>
<td>18,198 (48.3)</td>
<td>0.943</td>
<td>19,197 (51.0)</td>
<td>18,196 (48.3)</td>
</tr>
<tr>
<td>(Alpha-blocker, Beta-blocker)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Insulin</td>
<td>47,838 (0.5)</td>
<td>1,313 (3.5)</td>
<td>0.212</td>
<td>1,227 (3.3)</td>
<td>1,313 (3.5)</td>
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<tr>
<td>Sulfonylurea</td>
<td>209,928 (2.3)</td>
<td>5,399 (14.3)</td>
<td>0.445</td>
<td>5,175 (13.7)</td>
<td>5,398 (14.3)</td>
</tr>
<tr>
<td>Metformin</td>
<td>182,717 (2.0)</td>
<td>4,939 (13.1)</td>
<td>0.428</td>
<td>4,675 (12.4)</td>
<td>4,938 (13.1)</td>
</tr>
<tr>
<td>Other</td>
<td>154,821 (1.7)</td>
<td>4,256 (11.3)</td>
<td>0.396</td>
<td>3,963 (10.5)</td>
<td>4,255 (11.3)</td>
</tr>
<tr>
<td>anti-diabetic drugs (Thiazolidinedione, Glinides, Alpha-glucosidase inhibitor, DPP-4i, GLP-1 RA, SGLT-2i)</td>
<td></td>
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<td></td>
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<tr>
<td>Antithrombotic drugs</td>
<td>274,046 (3.0)</td>
<td>8595 (22.8)</td>
<td>0.614</td>
<td>7724 (20.5)</td>
<td>8594 (22.8)</td>
</tr>
<tr>
<td>NSAID</td>
<td>821,841 (9.1)</td>
<td>15,806 (42.0)</td>
<td>0.812</td>
<td>16,930 (45.0)</td>
<td>15,804 (42.0)</td>
</tr>
<tr>
<td><strong>Healthcare Utilization, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthcare Utilization, median</td>
<td>[IQR]</td>
<td>[IQR]</td>
<td>[IQR]</td>
<td>[IQR]</td>
<td>[IQR]</td>
</tr>
<tr>
<td>[IQR]</td>
<td>0 [0, 0]</td>
<td>0 [0, 0]</td>
<td>0.215</td>
<td>0 [0, 0]</td>
<td>0 [0, 0]</td>
</tr>
<tr>
<td>No. of inpatient visits</td>
<td>0 [0, 0]</td>
<td>12 [4, 23]</td>
<td>1.066</td>
<td>10 [2, 22]</td>
<td>12 [4, 23]</td>
</tr>
<tr>
<td>No. of outpatient visits</td>
<td>0 [0, 0]</td>
<td>12 [4, 23]</td>
<td>1.066</td>
<td>10 [2, 22]</td>
<td>12 [4, 23]</td>
</tr>
</tbody>
</table>
Abbreviations: SMD, standardized mean difference; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; ACEi/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CCB, calcium channel blockers; DPP-4i, dipeptidyl peptidase 4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonists; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; NSAID, nonsteroidal anti-inflammatory drugs.

Since 97.8% of observations (n=8,849,066) lack information on LDL-C level, it would not be included for covariates balancing.

**Table 2** Description of ICH Events and All-Cause Mortality for Statin Initiators and Non-initiators

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group</th>
<th>No.</th>
<th>Follow-up (year)</th>
<th>Event</th>
<th>Person-year</th>
<th>Incidence rate per 10,000 person-years (95% CI)</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH</td>
<td>Non-Statin</td>
<td>37659</td>
<td>7.75 [6.75-8.75]</td>
<td>261</td>
<td>286236</td>
<td>9.1 (8.1, 10.3)</td>
<td>Reference</td>
<td>/</td>
</tr>
<tr>
<td></td>
<td>Statin</td>
<td>37659</td>
<td>7.75 [6.75-8.75]</td>
<td>284</td>
<td>285719</td>
<td>9.9 (8.9, 11.1)</td>
<td>1.09 (0.92, 1.29)</td>
<td>0.32</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Non-Statin</td>
<td>37659</td>
<td>7.75 [6.75-8.75]</td>
<td>1949</td>
<td>286236</td>
<td>68.1 (65.1, 71.1)</td>
<td>Reference</td>
<td>/</td>
</tr>
<tr>
<td></td>
<td>Statin</td>
<td>37659</td>
<td>7.75 [6.75-8.75]</td>
<td>2002</td>
<td>285719</td>
<td>70.1 (67.1, 73.2)</td>
<td>1.03 (0.97, 1.10)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; CI, confidence interval; ICH, intracerebral hemorrhage.

**FIGURES**

**Figure 1** The Illustration of Study Design of 16 Emulated Trials

**Figure 2** Cumulative Incidence Curves for A) ICH and B) All-Cause Mortality for Statin Initiators and Non-initiators

Abbreviation: ICH, intracerebral hemorrhage.
**Figures**

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Figure 2 Cumulative Incidence Curves for A) ICH and B) All-Cause Mortality for Statin Initiators and Non-initiators

Abbreviation: ICH, intracerebral hemorrhage.