TITLE PAGE

Title

Statin Use and Risk of Intracerebral Hemorrhage in Chinese Population: a Target Trial Emulation Study.

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ABSTRACT

Objective: Statin has been shown to prevent major vascular events in a wide range of individuals, but the risk of intracerebral hemorrhage (ICH) from statin use remains unclear. Thus, we evaluated the influence of statins on the risk of ICH in Chinese population.

Study Design and Setting: Using 2011-2020 year data from the Yinzhou Regional Health Care Database (YRHCD), patients aged 50 years or older with no history of ICH and statin use were included. In the framework of target trial emulation. 60 sequential target trials were emulated each month from 2011 to 2015. Within each trial, patients were categorized as statin initiators or non-initiators based on their first prescription during the one-month enrollment period. Patients in different groups of each emulated trial were matched using propensity scores (PS) and then stacked together into one dataset. On this dataset, Cox proportional hazards model was used to estimate the effect of statin on ICH risk.

Results: 53,413 statin initiators and 35,033,455 non-initiators from 60 emulated trials were included into analysis. After PS matching, with a median follow-up of 6.67 (interquartile range 5.59-8.08) years, the hazard ratio of ICH of statin initiators compared with non-initiators was 1.18 (95% confidence interval: 1.04-1.35). The results are consistent across multiple subgroup and sensitivity analyses.

Conclusion: Increased ICH risk was found for ICH-free patients when they received statin treatment.

Plain Language Summary: Statins are commonly used to lower cholesterol and are beneficial for patients with cardiovascular diseases. However, concerns for potentially increased risk of brain hemorrhage have been raised. This study aims to determine whether statin treatment

increases brain hemorrhage. We included 35,086,868 patients aged 50 years or older without previous brain hemorrhage from Yinzhou Regional Health Care Database, and compared the incidence of brain hemorrhage between patients with statin use and those without statin use. Increased risk of brain hemorrhage was observed for statin users.

Keywords: causal inference; target trial emulation; sequential design; propensity score; statin; intracerebral hemorrhage.

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WHAT IS NEW?

Key findings

- In the framework of target trial emulation, we emulated 60 sequential trials and found that statin use increases the risk of ICH in Chinese population.

What this adds to what was known?

- The majority of observational studies evaluating the effect of statins on intracerebral hemorrhage (ICH) risk were plagued by various biases (immortal time bias, indication bias and etc.) from naïve observational designs, and thus false results were obtained.
- By using the framework of target trial emulation, observational studies can yield findings similar to RCTs, in our case, we observed an increased risk of ICH from statin use, which is consistent with results from previous RCTs.

What is the implication and what should change now?

- In China, healthcare providers should exercise caution when prescribing statins to patients with high risks of ICH.

1. 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 statin therapy proved to lower the risk of ASCVD [3,4], no consensus has been reached with regard to statin use and intracerebral hemorrhage (ICH) risk. Statins may weaken endothelial cells and inhibit platelet aggregation, enhance fibrinolysis, and thereby promote vessel rapture and thrombogenesis [5].

A recently updated meta-analysis of 36 randomized control trials (RCTs) suggests that statins increase ICH risk in a dose-response manner [6], whereas lower or non-statistically significant ICH risk is associated with statins in population-based observational studies [7–15]. The inconsistency between the results of RCTs and observational studies could be attributed to their study designs. Firstly, statin trials were criticized for the underrepresentation of patients managed in clinical practice [16]. The unreasonable exclusion of patients aged over 75 years old, females, patients with more than 2 chronic conditions, or patients with certain conditions (e.g., severe chronic kidney diseases and heart failure, which are not contraindicated for statins) can lead to biased outcomes due to possibly more side effects in those groups [16]. Secondly, naïve observational study designs are not methodologically sound and thus are plagued with a variety of biases. For example, in case-control studies, the analysis adjusted for covariates assessed at the time of ICH (for cases) or sampling (for controls), which will underestimate or even reverse the sign of the effect of statins on ICH [17,18]. In studies with cohort design, immortal time bias, selection bias and indication bias arise due to the specification of the eligibility criteria, the determination of statin exposure and the start of follow-up are not synchronized [19]. To avoid the limited transportability of results and causality pitfalls from existing statin studies, we employed the framework of target trial emulation by Hernán et al.

[20] using data from the regional healthcare database.

Thus, our study aims to (1) examine the effect of statin use on ICH risk in the Chinese population using a target trial emulation design, and (2) test whether the effect displays in a dose-response manner.

2. METHODS

2.1 Data source

A retrospective cohort was assembled based on the Yinzhou Regional Health Care Database (YRHCD) [21]. 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) of 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.

2.2 Study population and design

In the framework of target trial emulation [20], we specified the protocol of a target trial to estimate the effect of statins on the risk of ICH (**Supplementary Table 1**). We chose January 1st 2011 as the index date (the whole month of January as the baseline period), and included patients with age ≥50 years old. Any patients aged over 100 years old, with missing data on sex, had prescriptions of statin within 365 days prior to the index date or a diagnosis of ICH were excluded (**Fig. 1**). In this emulated 'trial', a total of 507,632 individuals in YRHCD met eligibility criteria. After controlling for confounders (See statistical analysis section for details) by propensity score (PS) matching, 1,176 subjects were finally included and among them, 12 developed ICH during the follow-up, which makes it impossible to conduct a meaningful analysis. Thus, by using sequential design, we chose the first date of every month between January 2011 and December 2015 as the index date, and applied the same eligibility criteria in a sequence of 60 emulated trials (**Supplementary Fig. 1**). Finally, a total of 53,413 statin initiators and 35,033,455 non-initiators were included in the sequential 'trials' (**Supplementary Fig. 2**).

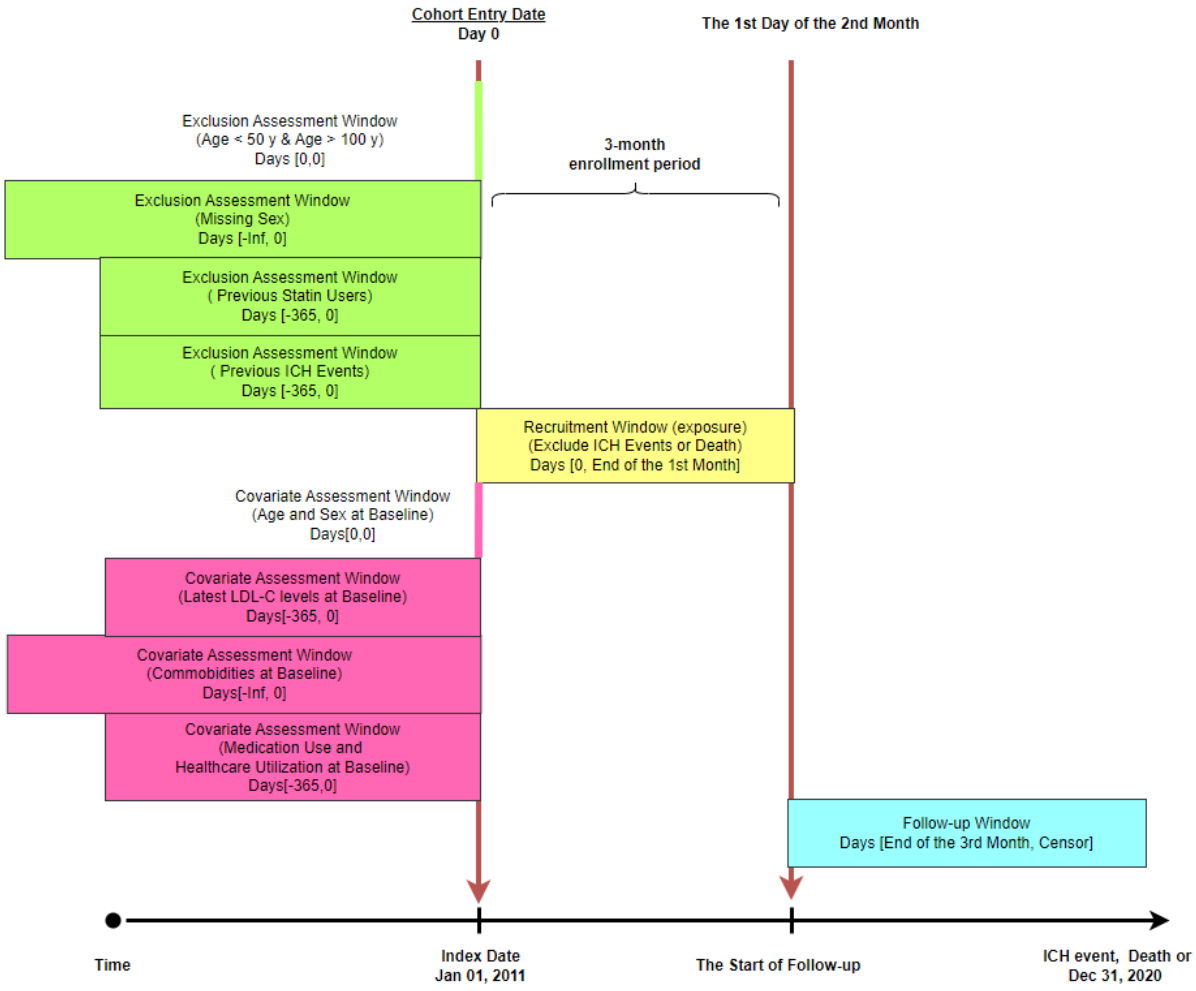


Fig. 1. The Illustration of Study Design for the January 2011 'trial'.

Abbreviations: ICH, Intracerebral Hemorrhage.

2.3 Exposure

In each emulated trial, patients who initiated any statin treatment (i.e., rosuvastatin, atorvastatin, simvastatin, pravastatin, and fluvastatin) at the baseline period (the month of the index date) were categorized as statin initiators, while patients received none of above statins were categorized as non-initiators.

2.4 Covariates

For each trial, the following baseline covariates were extracted: demographic information (age and sex), comorbidities (e.g., ASCVD, pulmonary diseases, renal diseases, cancer and neurological conditions), concurrent medication use within 1 year prior to the index date (e.g., 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 of 90.60%) and health care utilization (inpatient and outpatient visits) within 1 year prior (**Supplementary Table 2**).

2.5 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 baseline period of each emulated trial, until the onset of ICH, death, or end of the study period (December 31st, 2020), whichever came first.

2.6 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 covariates between statin initiators and non-initiators, 1:1 PS matching by the 'nearest-neighbor' approach with a caliper of 0.2 was performed for each trial [22]. 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 baseline covariates between the two groups was measured by the standardized mean difference (SMD), and an SMD of less than 0.1 indicated a negligible difference. As aforementioned, to increase the number of ICH events, the PS-matched dataset of each emulated trial was stacked together and analyzed as a whole. On the stacked dataset, Kaplan–Meier curves were first plotted to compare the cumulative incidence of ICH and death between statin initiators and non-initiators, and then the hazard ratio (HR) was calculated by the proportional hazard Cox regression model. However, because one individual may be included in multiple emulated trials, the confidence interval (CI) of HR was re-estimated by robust method [23].

To test potential effect modification of age (<65 vs. ≥65 years), sex, antithrombotic drugs, ischemic stroke, and hypertension, subgroup analyses were performed. In addition, several sensitivity analyses were performed to test the robustness of our results: (1) we repeated our analyses by shortening the target emulation period from 5 years to 4 years (January 2011 to December 2014) and extending it to 6 years (January 2011 to December 2016); (2) we further dichotomized statin initiators into high (atorvastatin, rosuvastatin, pitavastatin) and low potency (lovastatin, fluvastatin, pravastatin, simvastatin) statin groups according to the LDL-C lowering efficacy of statins [24], and to balance the baseline covariates between non-initiators, high potency and low potency statin initiators, the inverse probability of treatment weighting (IPTW) was further employed [25]; In the PS-matched dataset, we estimated the

probability of initiating high vs. low potency statin ($PS_{potency}$) as a function of all pre-treatment covariates mentioned previously. Patients in the high potency statin group were weighted by $1/PS_{potency}$ and in the low potency statin group by $1/(1-PS_{potency})$, while non-initiators were unweighted. (3) we performed a per-protocol analysis on the stacked dataset, in which patients were censored once statin initiators discontinued statin treatment for more than 30 days (grace period) or non-initiators initiated statin treatment. Because this censoring is likely to be informative, we used the inverse probability of censoring weighting (IPCW) to adjust for this [26].

All analyses were performed using R 3.6.3 software (The R Project for Statistical Computing).

3. RESULTS

3.1 Patient characteristics

Baseline characteristics of 53,413 statin initiators and 35,033,455 non-initiators from 60 emulated trials before and after PS matching were summarized in **Table 1**. Among statin initiators, 28,149 (4,200 patients received rosuvastatin and 23,949 patients received atorvastatin) and 25,264 (24,600 patients received simvastatin, 22 patients received pravastatin, and 642 patients received fluvastatin) patients received high and low potency statins (52.70% vs. 47.30% in total) respectively. Compared with non-initiators, statin initiators were older (65 vs. 63 years), had fewer females (44.5% vs. 50.5%) and had higher LDL-C levels (2.64 vs. 2.86) mg/dL. Statin initiators had a higher prevalence of hypertension (69 % vs. 14.1%), diabetes mellitus (23.7% vs. 4.1%) and chronic obstructive pulmonary disease (23.6% vs. 5.2%) than did non-initiators. For concurrent medication use, statin initiators reported higher prescription rates of ACEi/ARB (49.6% vs. 8.8%), CCB (48.5% vs. 8.6%), NSAID (45.5% vs. 10.4%), and diuretics (37.8% vs. 7.0%). Moreover, 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 106,818 patients (53,409 statin initiators and 53,409 non-initiators) with well-balanced characteristics were included in the following analyses.

	Unmatched			PS matched		
	Non-initiators (N=35,033,455)	Statin initiators (N=53,413)	SMD	Non-initiators (N=53,409)	Statin initiators (N=53,409)	SMD
Age, years, mean ± SD	63 (10.19)	65 (9.46)	0.204	65 (10.35)	65 (9.46)	0.014
Sex, N (%)						
Female	17,690,962 (50.5)	24,326 (45.5)	0.099	24,730 (46.3)	24,932 (46.7)	0.008
LDL-C level, mg/dL median [IQR]*	2.64 [2.14, 3.19]	2.86 [2.29, 3.45]	0.009	/	/	/
Comorbidity, N (%)						
Hypertension	4,955,532 (14.1)	36,861 (69.0)	1.340	37,892 (70.9)	36,857 (69.0)	0.042
Ischemic stroke	319,957 (0.9)	3,947 (7.4)	0.329	3,420 (6.4)	3,946 (7.4)	0.039
Ischemic heart disease	1,022,413 (2.9)	10,971 (20.5)	0.569	10,319 (19.3)	10,968 (20.5)	0.030
Congestive heart failure	325,417 (0.9)	2,883 (5.4)	0.257	2,713 (5.1)	2,880 (5.4)	0.014
Peripheral arterial occlusion disease	217,109 (0.6)	3,017 (5.6)	0.292	2,691 (5.0)	3,017 (5.6)	0.027
Cerebrovascular diseases	1,085,931 (3.1)	11,782 (22.1)	0.597	10,889 (20.4)	11,779 (22.1)	0.041
Diabetes mellitus	1,436,254 (4.1)	12678 (23.7)	0.592	12,434 (23.3)	12,676 (23.7)	0.015

Chronic obstructive pulmonary disease	1,828775 (5.2)	12,597 (23.6)	0.542	12,747 (23.9)	12,595 (23.6)	0.007
Liver diseases	604,736 (1.7)	4,345 (8.1)	0.299	4,302 (8.1)	4,344 (8.1)	0.003
Cancer	406,605 (1.2)	2,081 (3.9)	0.175	2,296 (4.3)	2,081 (3.9)	0.020
Epilepsy	38,755 (0.1)	314 (0.6)	0.081	286 (0.5)	314 (0.6)	0.007
Parkinson's disease	54,254 (0.2)	426 (0.8)	0.093	415 (0.8)	425 (0.8)	0.002
Mood, stress, or anxiety	835,695 (2.4)	7,584 (14.2)	0.439	7,242 (13.6)	7,582 (14.2)	0.018
Medication Uses, N (%)						
ACEi/ARB	3,077,109 (8.8)	26,511 (49.6)	1.006	26,358 (49.4)	26,507 (49.6)	0.006
Diuretics	2,453,420 (7.0)	20,188 (37.8)	0.795	20,257 (37.9)	20,184 (37.8)	0.003
CCB	3,001,314 (8.6)	25,925 (48.5)	0.987	25,671 (48.1)	25,921 (48.5)	0.009
Other anti-hypertensive agents (Alpha-blocker, Beta-blocker)	3,800,769 (10.8)	27,530 (51.5)	0.978	28,867 (54.0)	27,526 (51.5)	0.050
Insulin	207,031 (0.6)	1,963 (3.7)	0.215	1,808 (3.4)	1,963 (3.7)	0.016
Sulfonylurea	889,587 (2.5)	8,211 (15.4)	0.461	7,902 (14.8)	8,209 (15.4)	0.016
Metformin	773,523 (2.2)	7,461 (14.0)	0.442	7,159 (13.4)	74,59 (14.0)	0.016

Other anti-diabetic drugs (Thiazolidinedione, Glinides, Alpha-glucosidase inhibitor, DPP-4i, GLP-1 RA, SGLT-2i)	677,244 (1.9)	6,702 (12.5)	0.418	6,430 (12.0)	6,699 (12.5)	0.015
Antithrombotic drugs	1,210,332 (3.5)	13,805 (25.8)	0.668	12,774 (23.9)	13,804 (25.8)	0.045
NSAID	3,658,392 (10.4)	24,312 (45.5)	0.849	25,674 (48.1)	24,309 (45.5)	0.051
Healthcare Utilization, median [IQR]						
No. of inpatient visits	0 [0-0]	0 [0-0]	0.274	0 [0-0]	0 [0-0]	0.019
No. of outpatient visits	0 [0-0]	12 [4-23]	1.060	11 [2-22]	12 [4-23]	0.067

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 90.60% (n= 31,788,667) of patients lack information on LDL-C, it would not be included for covariates adjustment.

Table 1. Baseline Characteristics of Patients From 60 Emulated Trials before and after Propensity Score Matching

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

During a median follow-up time of 6.7 (IQR: 5.5-8.2) years, 478 ICH events occurred among 53,409 statin initiators and 404 ICH events among the PS-matched non-initiators, corresponding to incidence rates of 13.2 (95% CI: 12.1-14.4) and 11.2 (95% CI: 10.1-12.3) per 10,000 person-years, respectively (**Table 2**). The HR of ICH risk for statin initiators compared with non-initiators was 1.18 (95% CI: 1.04-1.35). The cumulative incidence curves were shown in **Fig. 2A**, which showed an early separation that was sustained throughout follow-up.

For the secondary outcome all-cause mortality, the HR was 1.00 (95% CI: 0.95-1.06, **Table 2**), and the cumulative incidence curves for statin initiators and non-initiators were overlapped (**Fig. 2B**).

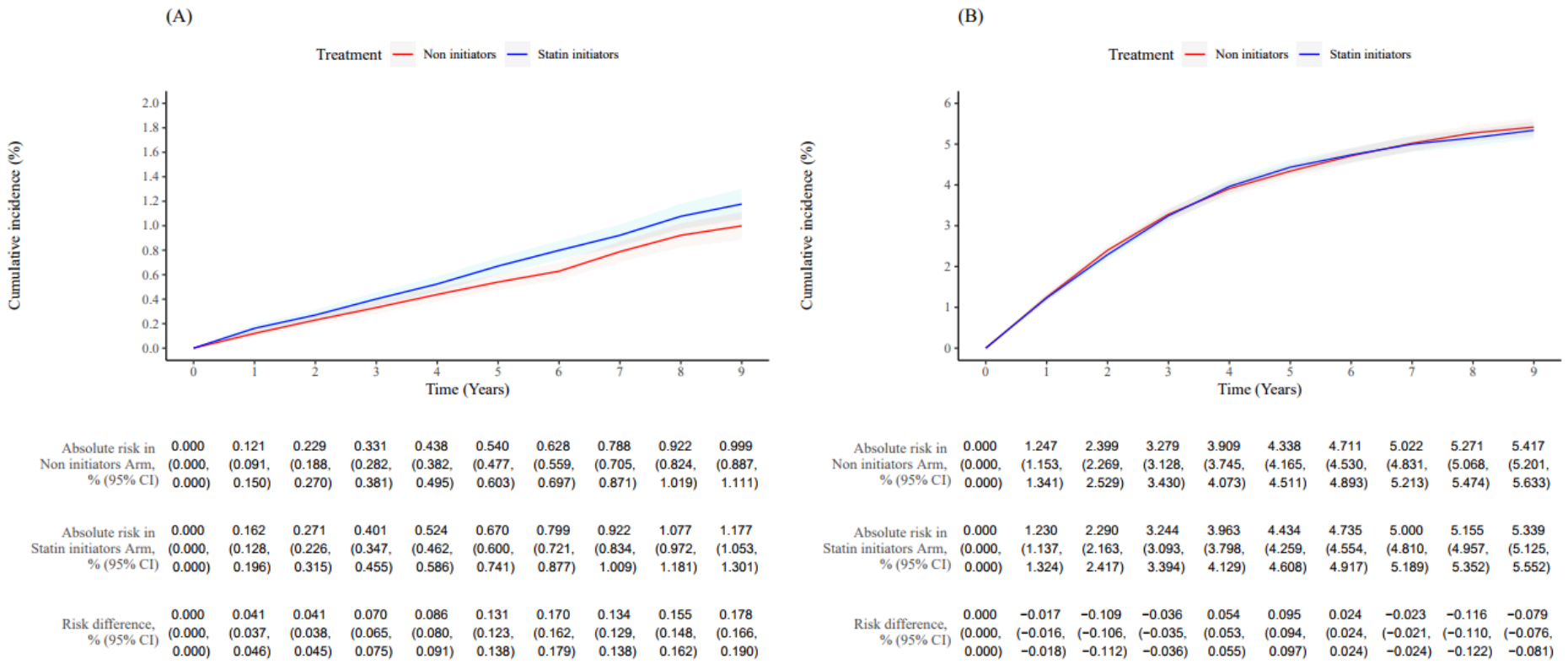
Outcome	Group	No. of patients	Follow-up (year), median (IQR)	No. of events	Person-years	Incidence rate per 10,000 person-years (95% CI)	HR*
ICH	Non-initiators	53409	6.6 [5.5-8.1]	404	361819	11.2 (10.1-12.3)	Reference
	Statin initiators	53409	6.7 [5.6-8.2]	478	361555	13.2 (12.1-14.4)	1.18 (1.04-1.35)
	Non-initiators	53409	6.7 [5.7-8.3]	2649	366141	72.3 (69.6-75.1)	Reference

All-cause mortality	Statin initiators	53409	6.8 [5.6-8.3]	2647	365877	72.3 (69.6-75.1)	1.00 (0.95-1.06)

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

* Analyses were adjusted for the following 27 covariates: age, sex, hypertension, ischemic stroke, ischemic heart disease, congestive heart failure, peripheral arterial occlusion diseases, cerebrovascular diseases, diabetes mellitus, chronic obstructive pulmonary disease, liver diseases, cancer, epilepsy, Parkinson's disease, mood, stress, or anxiety, angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers, diuretics, calcium channel blockers, other anti-hypertensive agents, insulin, sulfonylurea, metformin, other anti-diabetic drugs, antithrombotic drugs, nonsteroidal anti-inflammatory drugs, (number of inpatient visits and outpatient visits.

Table 2. Hazard ratios for ICH and All-Cause Mortality among Statin Initiators and Non-initiators.



	0	1	2	3	4	5	6	7	8	9
Absolute risk in Non initiators Arm, % (95% CI)	0.000 (0.000, 0.000)	0.121 (0.091, 0.150)	0.229 (0.188, 0.270)	0.331 (0.282, 0.381)	0.438 (0.382, 0.495)	0.540 (0.477, 0.603)	0.628 (0.559, 0.697)	0.788 (0.705, 0.871)	0.922 (0.824, 1.019)	0.999 (0.887, 1.111)
Absolute risk in Statin initiators Arm, % (95% CI)	0.000 (0.000, 0.000)	0.162 (0.128, 0.196)	0.271 (0.226, 0.315)	0.401 (0.347, 0.455)	0.524 (0.462, 0.586)	0.670 (0.600, 0.741)	0.799 (0.721, 0.877)	0.922 (0.834, 1.009)	1.077 (0.972, 1.181)	1.177 (1.053, 1.301)
Risk difference, % (95% CI)	0.000 (0.000, 0.000)	0.041 (0.037, 0.046)	0.041 (0.038, 0.045)	0.070 (0.065, 0.075)	0.086 (0.080, 0.091)	0.131 (0.123, 0.138)	0.170 (0.162, 0.179)	0.134 (0.129, 0.138)	0.155 (0.148, 0.162)	0.178 (0.166, 0.190)

	0	1	2	3	4	5	6	7	8	9
Absolute risk in Non initiators Arm, % (95% CI)	0.000 (0.000, 0.000)	1.247 (1.153, 1.341)	2.399 (2.269, 2.529)	3.279 (3.128, 3.430)	3.909 (3.745, 4.073)	4.338 (4.165, 4.511)	4.711 (4.530, 4.893)	5.022 (4.831, 5.213)	5.271 (5.068, 5.474)	5.417 (5.201, 5.633)
Absolute risk in Statin initiators Arm, % (95% CI)	0.000 (0.000, 0.000)	1.230 (1.137, 1.324)	2.290 (2.163, 2.417)	3.244 (3.093, 3.394)	3.963 (3.798, 4.129)	4.434 (4.259, 4.608)	4.735 (4.554, 4.917)	5.000 (4.810, 5.189)	5.155 (4.957, 5.352)	5.339 (5.125, 5.552)
Risk difference, % (95% CI)	0.000 (0.000, 0.000)	−0.017 (−0.016, −0.018)	−0.109 (−0.106, −0.112)	−0.036 (−0.035, −0.036)	0.054 (0.053, 0.055)	0.095 (0.094, 0.097)	0.024 (0.024, 0.024)	−0.023 (−0.021, −0.024)	−0.116 (−0.110, −0.122)	−0.079 (−0.076, −0.081)

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

Abbreviation: ICH, intracerebral hemorrhage; CI, confidence interval.

3.3 Subgroup and sensitivity analyses

The high risks for statin initiators on ICH were observed across subgroups of age (<65 vs. ≥65 years), sex, antithrombotic drugs and ischemic stroke, with all P values > 0.05 for interaction, although a significant interaction was observed according to hypertension at baseline. In patients with hypertension, the HR for ICH was lower than that in patients without hypertension (1.04 (95% CI: 0.90-1.21) vs. 2.46 (95% CI: 1.72-3.52); P < 0.001 for interaction) (**Supplementary Table 3**). When the target trial emulation period was shortened to 4 years or extended to 6 years, results were consistent with our main analyses (**Supplementary Tables 4-5**). A positive dose-response relationship between the LDL-C lowering efficacy of statins and ICH risk was observed, when compared with non-initiators, the HR for ICH of high potency statin initiators (HR: 1.16, 95% CI: 0.99-1.36) was higher than that of low potency statin initiators (HR: 1.14, 95% CI: 0.96-1.34) (**Supplementary Table 6**). By per-protocol analysis, the HR of ICH risk for statin initiators compared with non-initiators was 1.03 (95% CI: 0.81-1.31), indicating a slightly increased ICK risk associated with statins even without statistical significance.

4. DISCUSSION

Based on data from the YRHCD, emulating a sequence of 60 target trials, we found that statin use increased ICH risk among patients without ICH history. This finding was consistent across various subgroups of sex, age, history of comorbidity and medication use, and multiple sensitivity analyses. Further analyses examining the relation between statin potencies and ICH suggested that high-potency statins may contribute to higher increased risks of ICH. Our study raises the concern that statins increase ICH risk in Chinese population.

Existing statin RCTs have explored the association between statin use and ICH risk. For example, Nakamura et al. [27] randomly assigned diet or diet plus 10-20 mg pravastatin daily to patients with hypercholesterolemia, and found a statistically non-significant relationship between statins and ICH risk (HR: 1.18, 95% CI: 0.58-2.42). Similarly, Fellström et al. [28] compared the impacts of 10 mg rosuvastatin with placebo among patients undergoing maintenance hemodialysis, and an increased but no statistically significant ICH risk (relative risk [RR] 1.19, 95% CI: 0.67-2.11) was found from atorvastatin therapy. But most of them are limited to a small number of events (only between 0 and 25 events in the statin group) [27–32]. Thus, aforementioned RCTs can't conclude with statistically significant results on statin-ICH causality. Based on 33 statin RCTs (statins vs. placebo, and high dose vs. low dose statins) with 203,305 subjects enrolled, Cheng et al. [33] claimed that the statin group reported higher "ICH" risk than the control group (RR: 1.15, 95% CI: 1.00-1.32). However, 7 of 33 included studies misclassified hemorrhagic stroke as ICH events, and the former includes both ICH and subarachnoid hemorrhage [33]. Furthermore, the majority of the included RCT studies reported ICH events as adverse events rather than predefined outcomes, leading to low sensitivity of ICH event identification (Detailed in **Supplementary Table 7**). Thus, the true association between statins and ICH could be biased. A similar issue is also found in the meta-analysis exploring the association of high dose/potency statin on ICH risk [34].

On the other hand, existing population-based, observational studies showed opposite results which indicated no association or lower risk of ICH associated with statin use (**Supplementary Table 8**) [7–15]. This heterogeneity raises the concern of methodological biases from their naïve observational designs. For example, the study by Jung and Lee [12] followed hyperlipidemia patients in Korea with a mean follow-up of 6.4 years, and reported a protective effect against ICH from statin therapy (HR: 0.78, 95% CI: 0.65-0.94). It is noteworthy that the

index date for non-users was set as the date when hyperlipidemia was first diagnosed, whereas, for statin users, it was the date when they initiated statin therapy. Thus, this finding is subject to confounding by indication since as the severity of hyperlipidemia may differ between statin users and non-users at the index date. A Danish cohort study revealed the neuroprotection in ICH from statins (HR: 0.77, 95% CI: 0.72-0.82), but this could be explained by wrongly assuming the censorship to be non-informative. In fact, 40% to 75% of patients discontinue their statin therapy within 1 year of initiation [35], which could potentially lead to an overestimation of survival in statin users. Another Danish cohort study reporting lower ICH risk (HR: 0.61, 95% CI: 0.53-0.69) from statin therapy not only has the same issue in censorship, but also was plagued with immortal time bias [10]. Time since first-stroke as time scale, rather than time since statin initiation, further inflated the survival rates of statin users. Hackam et al. [15] analysed patients aged 65 years or older from Ontario, Canada, and found no association between ICH risk from statin use (HR: 0.87, 95% CI: 0.65-1.17). In their study, statin users were identified by at least 1 statin prescription within a 120-day interval following discharge from the stroke hospitalization, suggesting some patients could have already undergone a period of statin treatment. This group of patients, known as prevalent users, could potentially lead to the introduction of selection bias. Additionally, there are also three case-control studies found decreased ICH after statin therapy (OR: 0.68, 95% CI: 0.63-0.74 [9] and OR: 0.74, 95% CI: 0.71-0.78 [8] and OR: 0.83, 95% CI: 0.75-0.92 [7]). For these case-control studies, the analysis adjusted for covariates assessed at the time of ICH (for cases) or sampling (for controls). From a target trial perspective, this is equivalent to adjusting for variables measured at or after the end of follow-up, and will underestimate or even reverse the sign of the effect of statins on ICH [17,18].

Our findings also suggest that the ICH risk may increase with higher potency of statin therapy.

This finding is in agreement with the abstracted findings of 7 statin dose/potency RCTs, where subjects with high dose/potency statin reported magnified ICH risk than the placebo group (RR: 1.53, 95% CI: 1.16-2.01) [34]. As for observational studies, the study by Chang et al. [14] found that subjects with the highest potency statin have higher ICH risk than those with lowest potency statin (HR: 1.06, 95% CI: 0.94-1.19).

Our findings have important clinical implications as it suggested that the concerns for ICH risk could be an obstacle when prescribing statins among Chinese population. Especially, more caution should be taken in non-hypertensive patients, which is also an alarm given by another study conducted in Chinese population [14].

Our study has some significant strengths. First, target trial emulation not only assigned study samples based on their initial treatment assignment, but also fixed application of eligibility of criteria, treatment initiation, and start of follow-up at time zero [37]. Thus, this strategy solved prevalent user biases, immortal-time biases and et al. that are usually present in previous observational studies assessing the association of statin and ICH risk [19,37]. Secondly, given the potential drug discontinuation and prescription change in clinical practice, per-protocol analysis takes into account the actual treatment duration during the follow-up and thereby increases the robustness of our findings.

There are also some limitations in our study. Firstly, our data simply focuses on Chinese 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 analysis with high-, moderate-, and low-intensity statin therapy according to definitions by American guidelines [4]. Thirdly, despite target trial emulations, the efficacy of this study design depends on the data on a diverse set of confounders [37]. For example, considering the potential relationship between LDL-C and ICH risk, we acknowledge that lacking sufficient LDL-C records make our emulated trials is not as solid as RCTs.

5. CONCLUSIONS

Collectively, in the framework of target trial emulation, our study shows that statin use increase ICH risk in Chinese patients without previous history of ICH.

ETHICS STATEMENT

Not applicable.

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DECLARATION OF INTEREST

None.

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