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Use of statin for the primary prevention of cardiovascular outcomes in elderly patients: A propensity-matched cohort study

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ABSTRACT

Background and aims: Herein, we investigate whether statin treatment as primary prevention reduces cardiovascular outcomes in elderly Asian patients.
Methods: Data were obtained from the Korean National Health Insurance Service-Senior Cohort database (n = 558,147). A total of 81,729 elderly patients (≥75 years) without clinically recognized atherosclerotic cardiovascular disease (CVD) were included. The patients who did not have a history of statin use in year 2003 were followed from January 2004 to the end of 2012. New statin users (n = 3670) were matched on the basis of the propensity score in a 1:2 ratio with non-users. Incidences of myocardial infarction, ischemic stroke, and death from CVD were compared using the Cox proportional hazards model.
Results: The risk of cardiovascular death was significantly reduced in the statin treatment group compared with the non-user group (hazard ratio [HR] 0.34, 95% confidence interval [CI] 0.29 to 0.40; $p < 0.001$). This effect was observed in both patient groups with and without diabetes. In patients with diabetes, the HR for statin use was 0.85 (95% CI 0.55 to 1.33) for myocardial infarction and 0.75 (95% CI 0.60 to 0.93) for ischemic stroke. In participants without diabetes, the HR of statin use was 0.95 (95% CI 0.73 to 1.24) for myocardial infarction and 1.13 (95% CI 1.01 to 1.26) for ischemic stroke. The presence of hypertension was also a significant factor in the prevention of ischemic stroke by statin treatment.
Conclusions: In elderly patients without clinically recognized atherosclerotic CVD, the risk of cardiovascular mortality was significantly reduced with statin treatment than with non-users. In participants with type 2 diabetes, statin treatment was associated with a reduction in ischemic stroke.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide. In 2016, it was estimated that 17.9 million people have died from CVD, representing 31% of all global deaths [1]. Cardiovascular mortality has begun to decline in developed countries; however, it is still rapidly increasing in developing countries. For this reason, the incidence of CVD is expected to increase worldwide [2]. Among the modifiable risk factors, hypercholesterolemia is a major risk factor for atherosclerotic CVD, including coronary heart disease and ischemic stroke [3]. Owing to the rapidly rising mortality rate from CVD with age, it is crucial to manage hyperlipidemia, especially in old age [4].

Currently, the drugs of choice for the treatment of hypercholesterolemia are statins [5]. These drugs reduce morbidity and mortality of CVD with relatively few side effects in both primary and secondary prevention studies. However, the relationship between the low density lipoprotein (LDL) cholesterol level on CVD incidence and mortality rate has been controversial in the elderly population [6]. Most randomized

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clinical trials (RCTs) that determined the primary preventive effect of statins did not include the elderly (age over 75) population [7], limiting their validity to this population. Several concerns about the stability and adverse effects of statins in the elderly have also been raised [8]. For this reason, statin therapy in the elderly is not strongly recommended in the recent guidelines. The American College of Cardiology and American Heart Association guidelines on elderly patients have shown that there is little evidence to initiate or continue statin treatment for primary prevention and recommend that the decision to treat should be based on the clinical assessment of the benefit and risk status [9]. Similarly, the 2019 European Society of Cardiology and European Atherosclerosis Society guidelines have recommended that cardiovascular risk should be considered when initiating statins for primary prevention in an elderly population (aged 75 years and older); however, the exact criteria were not defined [10].

Previous studies have been conducted to verify the role of statins in the prevention of CVD in the elderly. In a recent meta-analysis, there was less direct evidence of benefit among patients older than 75 years who did not already have evidence of occlusive vascular disease [11]. In a population-based cohort study, statin therapy was effective for primary prevention in patients with modifiable risk factors [12]. Ramos et al. have also reported that the statin effect on primary prevention was significant in patients with diabetes [13]. These European studies based on their own cohort have shown that the effectiveness of statins could vary depending on the underlying medical condition. However, there is insufficient evidence regarding the long term effect of statin therapy on CVD incidence and mortality in those without cardiovascular disease, especially in Asian elderly individuals. In this study, we aimed to clarify the effect of statin use on the primary prevention of CVD in the elderly Korean population from cohort data.

2. Materials and methods

2.1. Data sources

We used the Korean National Health Insurance Service-Senior (NHIS-Senior) cohort, which included 558,147 Koreans. This cohort represents 10% of a random selection from a total of 5.5 million subjects aged 60+ years in the National Health Information Database in December 2002 and followed up until December, 2012 for all subjects, excluding the deceased ones. Since the pharmaceutical prescription record for 2002 covered only a small portion of the year, the existing statin user group was identified and excluded based on the statin prescription history for the year 2003. This database includes personal data, death records, and longitudinal information including prescribed medical records and disease diagnoses (International Classification of Diseases, 10th revision (ICD-10)). The cohort protocol has been described previously [14]. This study protocol was approved by the Institutional Review Board of Inha University Hospital (No. 2020-03-002), and the requirement for informed consent was waived by the board.

2.2. Patient selection

All individuals of the original database aged 75 years or older without a history of statin prescription from January 1, 2003 to December 31, 2003 were selected. The patients who did not have a history of statin use in 2003 were followed since January 2004. "New statin users" were enrolled from this period to the end of December, 2012 and was followed up to the end of 2012. We defined "new statin users" as those who initiated statin treatment with no statin prescription record during the previous 12 months or longer. For new statin users, the index date was three months after the first statin invoice. Only patients with statin cumulative prescription days exceeding 90 days during the follow-up period were finally defined as the statin group. For non-users, we selected the index date randomly according to the distribution of the index date for new statin users. We excluded those with a history of CVD, defined as a history of outpatient or inpatient visit with a primary diagnosis of ischemic heart disease (ICD-10 codes I21-25), stroke (I60, I61, I62, I63, I64), transient ischemic attack (G45), or any thoracic procedure (such as angioplasty/percutaneous coronary intervention [Z98.6] or coronary artery bypass grafting Z95.1) on at least two different dates before the index date.

After analyzing the whole population, we also stratified all analyses by diabetic status. The presence of diabetes mellitus was defined according to the following criteria: (1) at least one claim under ICD–10 codes E10–14 and (2) at least one claim for the prescription of antidiabetic medication.

2.3. Propensity score matching

The propensity score (PS) was estimated using the multiple logistic regression model of the baseline covariates for statin use. PS matching was performed to reduce the imbalance in the distribution of the baseline covariates between the two groups of statin use using the 1:2 greedy nearest-neighbor algorithm. In the whole study population, new statin users (n = 3670) were matched on the basis of the propensity score in a 1:2 ratio with non-users. After the stratification of participants by the presence of type 2 diabetes mellitus, new statin users of each group were matched on the basis of the propensity score in a 1:2 ratio with non-users, again. Potential risk factors related to the outcome and confounding variables associated with both treatment status and outcome were included as PS covariates. Covariates included age, sex, income decile, the Charlson comorbidity index (calculated from all hospitalization records one year prior to the index date) [15], major comorbidities at baseline with/without hospitalization record one year prior to the index date (chronic obstructive pulmonary disease [ICD-10 codes J44], hypertension [I10, I15], neoplasm [malignant, C00-97], atrial fibrillation [I48.x], and heart failure [I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0]), and drugs (anticoagulant, antiplatelet agent, other antithrombotic agent, and steroid) within one year before the index date. The covariate balance was calculated as standardized differences before and after propensity score matching. Significant imbalances were defined as standardized differences ≥10% [16].

2.4. Outcome measures and follow-up

The cardiovascular outcomes were: (1) newly diagnosed myocardial infarction, (2) ischemic stroke, or (3) cardiovascular death (death from ICD codes I00-I99). Myocardial infarction was defined as the recording of ICD-10 codes I21 or I22 during hospitalization. Ischemic stroke was defined as the recording of ICD-10 codes I63 or I64 during hospitalization with claims for brain magnetic resonance imaging or brain computerized tomography [17]. Each participant was followed up from the index date to the earliest occurrence of any study outcome, death, or end of the study period (December 31, 2012).

2.5. Statistical analysis

Continuous and categorical variables were presented as means (standard deviations) and numbers (percentages), respectively. Only the first occurrence of each outcome was included, and incidence rates per 1000 person-years with corresponding 95% confidence intervals were calculated for the individual outcomes. A marginal Cox proportional hazards regression model for a cluster in PS-matched pairs was used to estimate the hazard ratios (HRs) for study outcomes according to statin use. Analyses for all outcomes were then repeated across multiple patient subgroups to examine whether the associations differed on the basis of patient demographics or clinical and treatment characteristics. Characteristics for subgroup analysis included age (≥80, 75≤ <80 years), sex (men, women), income decile (1–5, 6–10), the Charlson comorbidity index (0, ≥1), preexisting type 2 diabetes, hypertension, and the use of antithrombotic agents and steroids.

To test the stability of the findings, a sensitivity analysis was done. First, the E-value, which is related to the evidence for causality in observational studies that are potentially subject to confounding bias, was calculated for sensitivity analysis using the E-value calculator [18, 19]. The E-value stands for the minimum strength of association that the unmeasured confounder should explain the association of the treatment outcome (ranged as 1 or more). The larger the E-value of the estimate (more extreme than 1), the more robust it is to the unmeasured covariate, and the stronger the evidence of causality. This is because the larger the E-value, the more difficult it is to describe the result as an unmeasured covariate, so the 'unmeasured confounder' that has not entered the model in causal relationship does not play a strong enough role. If the E-value is as small as close to 1, it means that the evidence of the effect is weak and there is a larger possibility of the influence of unmeasured covariates.

Further analysis was conducted to assess the possibility of confounding factors that may affect the results. First, to control for confounding by indication, a "user-only design" [20] was employed. The base cohort was restricted to those with statin prescription, excluding patients who did not receive any statin prescription. Only exposure during follow-up was assessed and short-term users (<3 or <6 months) were contrasted with users for >3 months (or >6 months) to <1 year, and long-term users (≥1year). In addition, we evaluated several "control" events to assess for any healthy-user bias. The outcomes not expected to be associated with statin exposure were chosen. Control events examined were any primary diagnosis of pneumonia, dental problem, food-borne bacterial infection, gallstone, migraine, skin infection, and open wound during inpatient and outpatient visits after the index date. Events and corresponding diagnostic codes are listed in the Supplementary Materials. The first occurrence of each event was assessed as outcomes.

Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC). A *p*-value less than 0.05 was considered to be statistically significant.

3. Results

A total of 81,729 elderly patients (≥75 years) without clinically recognized atherosclerotic CVD and no history of statin prescription in 2003 were included. Participants were first stratified on the basis of statin use (as new statin users or non-user). After PS matching, an analysis of the whole population was conducted. The participants were stratified further by the presence of type 2 diabetes mellitus and statin use. After PS matching of each group, each analysis was conducted repeatedly (Supplementary Fig. 1). The median follow-up was of eight years (interquartile range 6–8 years), and the median age of the study population was 78 years (interquartile range, 76–80 years). Of those participants, 3670 (4.5%) were new statin users and 7727 (9.9%) had type 2 diabetes.

Table 1 shows the baseline characteristics of new statin users and non-users. New statin users were younger and consisted of more females and had a higher income level and a higher prevalence of hypertension than non-users. Following propensity matching, the cohort included 11,007 patients: 3669 and 7338 patients in the new statin user and non-user group, respectively. Baseline characteristics were well-balanced between the groups.

Supplementary Table 1 shows the baseline characteristics for new statin users and non-users stratified by the presence of type 2 diabetes. The difference in characteristics between new statin users and non-users was similar in those with and without diabetes. There was no statistically significant standardized difference observed after propensity score matching (absolute standardized difference less than 0.1 after matching).

Table 2 shows the number of events, incidence rates per 1000 person-years, and hazard ratios (95% confidence intervals) of myocardial infarction, ischemic stroke, and death from CVD. The risk of cardiovascular death was significantly reduced in the statin treatment group compared with the non-statin group (HR 0.34, 95% CI 0.28 to 0.40; $p < 0.001$). No benefit was observed for myocardial infarction (HR 0.90, 95% CI 0.72 to 1.13) and ischemic stroke (HR 1.00, 95% CI 0.91 to 1.10).

In participants with diabetes, the HR for statin use was 0.85 (95% CI 0.55 to 1.33) for myocardial infarction, 0.75 (95% CI 0.60 to 0.93) for ischemic stroke, and 0.29 (95% CI 0.20 to 0.45) for cardiovascular death. Statin use was significantly associated with the decreased risk of ischemic stroke and cardiovascular death (all $p < 0.05$, Fig. 1). In participants without diabetes, the HR for statin use was 0.34 (95% CI 0.29 to 0.41) for cardiovascular death, 0.95 (95% CI 0.73 to 1.24) for myocardial infarction, and 1.13 (95% CI 1.01 to 1.26) for ischemic stroke. Statin use was associated with a significant decrease in cardiovascular death ($p < 0.001$) and an increase in the risk for ischemic stroke ($p = 0.038$). However, no significant benefit nor increased risk for

Table 1
Baseline characteristics of new statin users and non-users, using standardized differences of the mean before and after adjustment for propensity score.

	Before matching			After matching		
	Statin non-users	New statin users	Absolute standardized difference	Statin non-users	New statin users	Absolute standardized difference
	(n = 78,059)	(n = 3670)		(n = 7338)	(n = 3669)	
Mean (SD) age (years)	80.1 (4.4)	77.9 (3.0)	0.580	77.9 (3.0)	77.9 (3.0)	0.003
Men	25,860 (33.1)	888 (24.2)	0.199	1716 (23.4)	888 (24.2)	0.019
Mean (SD) income decile	6.2 (3.3)	6.7 (3.3)	0.124	6.8 (3.2)	6.7 (3.3)	0.038
Mean (SD) Charlson comorbidity index	0.1 (0.4)	0.1 (0.5)	0.076	0.1 (0.4)	0.1 (0.5)	0.037
Comorbidities						
Chronic obstructive pulmonary disease	190 (0.2)	8 (0.2)	0.005	8 (0.1)	8 (0.2)	0.027
Type 2 diabetes mellitus	7082 (9.07)	645 (17.57)	0.343	1329 (18.11)	644 (17.55)	0.043
Hypertension	9165 (11.7)	949 (25.9)	0.367	1921 (26.2)	948 (25.8)	0.008
Neoplasm, malignant	207 (0.3)	9 (0.3)	0.004	16 (0.2)	9 (0.3)	0.006
Atrial fibrillation	98 (0.1)	5 (0.1)	0.003	10 (0.1)	5 (0.1)	<0.001
Congestive heart failure	74 (0.1)	2 (0.1)	0.015	1 (<0.1)	2 (0.1)	0.022
Drugs						
Anticoagulant	43 (0.1)	1 (<0.1)	0.014	4 (0.1)	1 (<0.1)	0.014
Antiplatelet	2579 (3.3)	107 (2.9)	0.022	309 (4.2)	107 (2.9)	0.070
Other antithrombotics	83 (0.1)	3 (0.1)	0.008	8 (0.1)	3 (0.1)	0.009
Steroid	2984 (3.8)	136 (3.7)	0.006	259 (3.5)	135 (3.7)	0.008

Values are numbers (percentages) unless stated otherwise.

Table 2
Event rates and hazard ratios for myocardial infarction, ischemic stroke and cardiovascular death stratified by the presence of diabetes.

Variables	Statin non-users		New statin users		Hazard ratio (95% CI)	*p*-value	E-value	E-value of CI
	No of events	Incidence rate/1000 person-years (95% CI)	No of events	Incidence rate/1000 person-years (95% CI)				
Whole population								
Outcomes of interest:								
MI	206	4.5 (4.0–5.2)	116	4.2 (3.5–5.0)	0.90 (0.72–1.13)	0.377	1.46	1.00
Ischemic stroke	1025	23.3 (21.9–24.7)	637	24.3 (22.5–26.2)	1.00 (0.91–1.1)	0.983	1.00	1.00
Cardiovascular death	761	16.6 (15.5–17.8)	165	5.9 (5.1–6.9)	0.34 (0.28–0.4)	<0.001	5.33	4.44
Without diabetes								
Outcomes of interest:								
MI	147	3.9 (3.3–4.6)	87	3.8 (3.1–4.7)	0.95 (0.73–1.24)	0.712	1.29	1.00
Ischemic stroke	752	20.5 (19.1–22)	522	24.1 (22.1–26.3)	1.13 (1.01–1.26)	0.038	1.51	1.11
Cardiovascular death	628	16.6 (15.3–17.9)	137	6 (5.0–7.0)	0.34 (0.28–0.41)	<0.001	5.33	4.31
With diabetes								
Outcomes of interest:								
MI	54	7.0 (5.4–9.2)	30	6.3 (4.4–9.0)	0.85 (0.55–1.33)	0.489	1.63	1.00
Ischemic stroke	235	31.8 (28–36.1)	115	25 (20.9–30.1)	0.75 (0.60–0.93)	0.009	1.74	1.28
Cardiovascular death	140	17.9 (15.2–21.1)	28	5.8 (4.0–8.3)	0.29 (0.20–0.45)	<0.001	6.35	3.87

MI = myocardial infarction.

myocardial infarction was observed ($p = 0.712$).

As a sensitivity analysis for unmeasured confounding, the E-value was calculated. For cardiovascular death, the E-value of the HR estimate was larger than 5 in all categorized groups. This shows strong evidence for causality and robustness against the unmeasured covariates. For myocardial infarction or ischemic stroke, the E-values were closer to 1, implying a larger possibility of the influence of unmeasured covariates.

In the subgroup analysis of the whole population (with/without type 2 diabetes), statin treatment decreased the risk of myocardial infarction only in patients with one or more Charlson comorbidity indexes (HR 0.36, 95% CI 0.16 to 0.80, *p* for interaction = 0.023, Fig. 2A). Consistent with the results of the P-S matching analysis stratified by diabetic status, statin treatment lowered the risk of stroke only in the group with type 2 diabetes. In addition, the risk of stroke was found to be lower only in the group with hypertension ($p < 0.05$, Fig. 2B). In most subgroups, statin treatment was associated with a lower risk of cardiovascular death compared with the non-statin treatment group. There were no significant interactions for cardiovascular death (Fig. 2C).

When the study population was restricted to participants who received statins within the follow up duration, and participants treated for a short time (<3 months or <6 months) were chosen as comparators, longer duration of statin use was associated with a stronger effect on improving cardiovascular death risk (all *p* for trend < 0.05, Supplementary Tables 2 and 3). Several "control" events between new statin users and statin non-users were compared in the propensity matched whole population. There was no significant difference in risk between new-statin users and statin non-users (Supplementary Table 4). However, new-statin users tended to less likely have events in many of the outcomes analyzed than statin non-users: pneumonia (HR = 0.59; 95% CI, 0.24 to 1.47), dental problem (HR = 0.78; 95% CI, 0.24 to 2.50), food-borne bacterial infection (HR = 0.35; 95% CI, 0.08 to 1.61), gallstone (HR = 0.22; 95% CI, 0.03 to 1.74), migraine (HR = 0.98; 95% CI, 0.29 to 3.26), skin infection (HR = 0.72; 95% CI, 0.42 to 1.25), and open wound (HR = 0.76; 95% CI, 0.39 to 1.47), without statistical significance.

4. Discussion

In this propensity-matched cohort study of elderly patients without clinically recognized atherosclerotic CVD, the risk of cardiovascular mortality was significantly reduced with statin treatment. Only in participants with type 2 diabetes, statin treatment was significantly associated with a reduction in ischemic stroke. In the population without type 2 diabetes, the statin effect on primary prevention was not seen in both the risk of coronary heart disease and ischemic stroke. In the subgroup analysis, the presence of hypertension was also a significant factor in the prevention of ischemic stroke with statin treatment.

The majority of deaths from CVD occur in the elderly at a continuously increasing mortality rate with age [4]. The prevalence of dyslipidemia increases in the elderly, which often makes them fall into the high-risk group of coronary artery disease. The prevention of CVD in the elderly is an important clinical issue; however, previous studies raised concerns that an excessive decrease in cholesterol in the elderly may increase mortality [8]. Several RCTs, in which a number of guidelines are determined from studying the effect of statin, did not include the elderly population. As a result, the risk engines used by these guidelines are difficult to apply in the elderly population, limiting a strong recommendation for statin use as the primary prevention in the elderly [5,10,21,22]. Although a careful approach is needed, recent studies have evaluated the role of statin use in the elderly. A sub-analysis of the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin Trial has shown that statins may be useful for primary prevention in the elderly [23]. In a sub-study of the Collaborative Atorvastatin Diabetes Study in patients with type 2 diabetes, the use of statins significantly reduced the incidence of CVD in the elderly [24]. In the Prospective Study of Pravastatin in the Elderly at

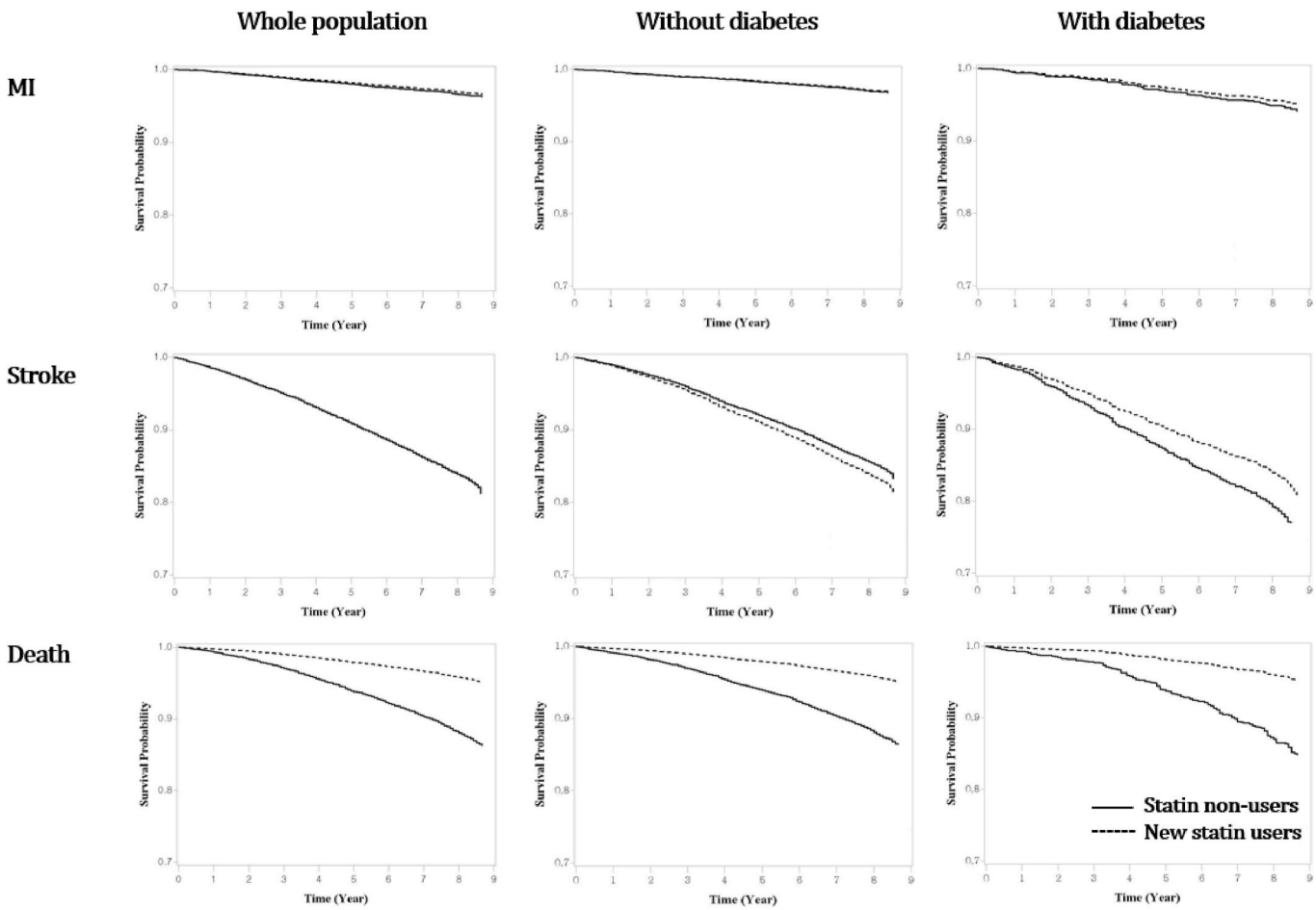

Fig. 1. Kaplan-Meier survival curves for myocardial infarction (top), ischemic stroke (middle), and cardiovascular death (bottom) between treatment groups (statin non-users = line, new statin users = dotted line).

Risk study, statin use was reported to significantly reduce the incidence and mortality of CVD in elderly patients. However, the benefit of statin use was not significant in the subgroup analysis for patients without previous vascular disease (statin use for primary prevention) [25]. In a recent meta-analysis, the benefit of primary prevention through statin use was not clearly seen in people over 75 years [11]. Some studies of the elderly show conflicting results depending on the underlying conditions of the participants [13].

Previous large-scale primary and secondary prevention trials were mainly conducted in Western populations with high cardiovascular risk, and little is known about the relationship between decreasing cholesterol concentrations and CVD risk reduction in Asian populations [26]. Further, higher plasma exposure to statin and its metabolites in Asian populations compared with Caucasian subjects can lead to the difference in both positive and adverse effects of statin treatment [27]. For this reason, study-based evidence to evaluate statin efficacy for the primary prevention of cardiovascular risk reduction in the elderly Asian population is necessary. In Korea, retrospective studies have reported on the secondary preventive effect of statins in the elderly population [28]. A nationwide population-based case-control study has shown the beneficial effect of statins for primary prevention, and "current statin treatment" was associated with reduced stroke or all-cause death in Koreans aged over 75 years [29]. Furthermore, in a retrospective study conducted in a tertiary university hospital, statin therapy for primary prevention was also associated with a lower risk of cardiovascular events and all-cause death in individuals aged over 75 years [30]. However, firm evidence to predict the effectiveness of initiating statins for primary prevention purposes in an elderly Asian population through previous studies is limited. Therefore, in this study, we attempted to confirm the long term effect of statin in a large-scale real-world setting, excluding the immortal and lag-time bias and correcting the related indicators as much as possible.

In the current study where the majority of the subjects were Asians, significant effects of prevention through statin use were confirmed in cardiovascular mortality. With or without several modifiable risks, statin treatment was associated with a lower risk of cardiovascular death compared with the non-statin treatment group. However, the effect of primary prevention on myocardial infarction and ischemic stroke was not consistent. Recent studies have reported that the benefit of using statins for the elderly was confirmed only in groups with modifiable risks [12], such as diabetes [13]. The greater beneficial effect in patients with diabetes observed is consistent with the results of other recently published studies [13]. Diabetes is a well-defined high-risk condition of CVD. Among patients with diabetes, LDL cholesterol is identified as the most important risk factor for developing atherosclerosis [31]. The results of this study suggest that the benefit of statins may be greater in patients with diabetes mellitus, even in elderly people. Concurrently, results have shown that statin treatment may be more effective in a group with hypertension or high comorbidity score. This reinforces the need to consider the risk factors, especially the presence of diabetes, in the decision to initiate or continue statins in elderly Asian patients. The currently underway RCT, the STAREE (STAtins for Reducing Events in the Elderly, NCT02099123) trial, will be able to provide further insights for the elderly population (aged over 70 years, atorvastatin *vs* placebo).

Despite the results, this study is limited by several elements. First, smoking and body mass index, among others, can act as major confounding factors which were not reflected despite minimizing the differences between new statin users and non-users by propensity matching

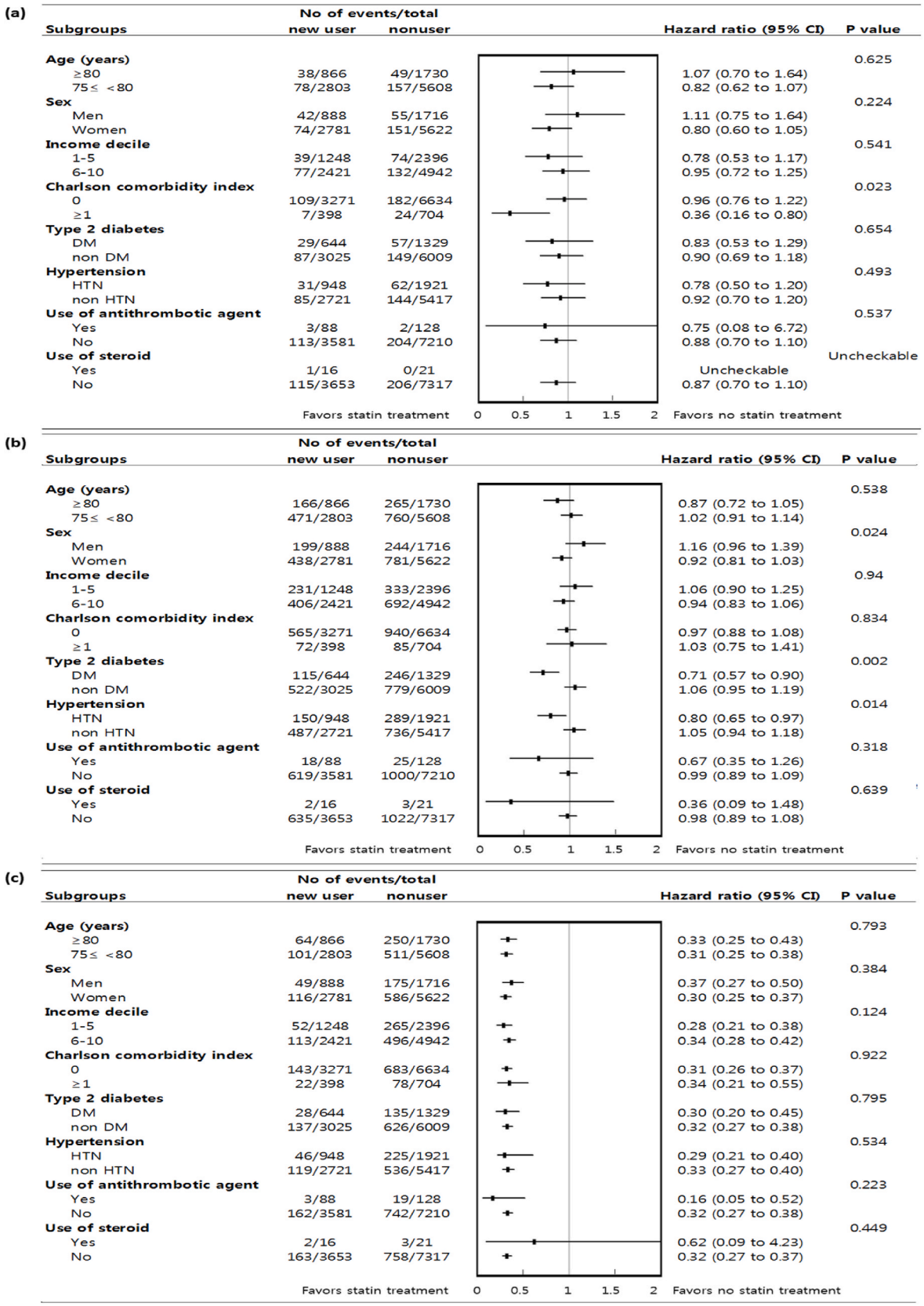

Fig. 2. Adjusted hazard ratio of cardiovascular outcomes by subgroups.
Subgroup analyses for (a) myocardial infarction, (b) ischemic stroke, and (c) cardiovascular death by age (≥80, 75≤ <80 years), sex (men, women), income decile (1–5, 6–10), the Charlson comorbidity index (0, ≥1), preexisting type 2 diabetes, hypertension, and the use of antithrombotic agents and steroids.
Age, sex, income decile, the Charlson comorbidity index, preexisting chronic obstructive pulmonary disease, hypertension, neoplasm, atrial fibrillation, heart failure, and the use of antithrombotic agents and steroids were adjusted.

based on the Charlson scoring, several major diseases, and drug usage records. Also, one year to trace comorbidities and co-treatments could not be enough to obtain a good characterization of patients. However, sensitivity analyses to assess for unmeasured confounding have shown the robustness of our findings. Second, we used a "new user design" to prevent survivor bias and covariate measurement bias. This is assuming that the history of statin treatment for at least 3 months may affect the long term outcome. However this design cannot fully reflect the duration of statin use or compliance of the patients. Third, LDL cholesterol levels prior to treatment and compliance with statin use could not be also reflected. Since the use of statins in the clinical setting is considered first in patients with hypercholesterolemia, this could suggest that the basal LDL cholesterol level might be higher in the statin use group. This can lead to an increase in MI and stroke risk in the new statin user group, possibly underestimating the preventive effect of statin use. In this study, the results have shown that MI and stroke risk were not reduced, and stroke risk was even increased in the statin use group in patients without diabetes mellitus. This may be the result of these factors. The design of this study is likely to blunt the preventive effects of statins on MI or stroke risk; nevertheless, significant effects have been identified in the group with diabetes. This strongly suggests that statin use can be beneficial in elderly patients with diabetes.

This study has shown that the use of statin drugs was more significantly beneficial in terms of improving cardiovascular mortality compared with other existing studies. There have been reports of the possibility of healthy user bias in the statin user group [32]. To evaluate the influence of unmeasured confounding factors on the stronger effect of statins in terms of improving survival compared to what was observed in other studies, additional analysis was done in several different ways. When control outcomes not influenced by statin therapy were analyzed, no statistically significant difference was found. However, a non-significant trend of overall risk reduction was found in the statin user group. This may suggest the possibility that a healthy user bias may act in the statin user group partially exaggerating the beneficial effect on cardiovascular mortality. The Charlson comorbidity index was used to adjust the possible bias arising from the underlying disease. Furthermore, the final outcome was defined as only "cardiovascular cause" mortality, although the data sources used may be subject to potential misclassification of causes of death in official death certificates. MI occurs frequently without typical symptoms or electrocardiographic changes in the elderly, often leading to misclassification [33]. On the other hand, MI development in the elderly is more fatal and can directly lead to death [34]. For this reason, the effect of statins preventing MI could be underestimated, and the effect on preventing cardiogenic death could be overestimated in the current study. Nevertheless, this study has several advantages. First, propensity matching was performed to correct for the major drug use history, underlying disease, and socioeconomic status that can be identified in this cohort. The patient group was further classified according to the presence or absence of diabetes to clearly identify the benefit of statin treatment. Second, the use of real-world data of Asian ethnic groups and people with similar cultures could confirm the benefits of statins in primary prevention in this group. Third, this study had a median follow-up period of eight years, which was longer than other existing studies conducted on the elderly population [12,25].

In conclusion, the risk of cardiovascular mortality was significantly decreased with statin treatment in elderly patients without clinically recognized atherosclerotic CVD. The beneficial role of statin was significantly associated with a reduction in ischemic stroke only in participants with type 2 diabetes or hypertension.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

YC conceptualized the study, provided the methodology, and wrote the manuscript. YJ provided the methodology, curated/validated data, and performed the analysis. DHS, SHA, and SH contributed to the discussion and reviewed/edited the manuscript. YJS provided the methodology, curated/validated data, performed analysis, and wrote the manuscript. SHK conceptualized the study, provided methodology, and wrote the manuscript. All authors have read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2021.05.022.

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