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RESEARCH ARTICLE

Comparative effectiveness of statins in secondary prevention among the older people aged 75 years and over

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Abstract

Background While there is clear evidence for the benefit of statins in the secondary prevention of cardiovascular and cerebrovascular events, there is a lack of research on the effects of statin regimens in older patients aged 75 years and over. *Objectives* To compare the effectiveness of statin regimens in the secondary prevention of ischemic cardiovascular and cerebrovascular events among patients aged 75 years and over. *Setting* Claims data from the South Korean National Health Insurance Database from 2006 to 2014. *Methods* This retrospective cohort study included patients aged 75–100 years with a prior history of cardiovascular or cerebrovascular disease who began statin therapy in 2009–2011. Propensity score matching and the Cox proportional hazards regression model were used to compare the effectiveness of the statin regimens in secondary prevention. *Main outcome measure* The hazard ratios for ischemic cardiovascular and cerebrovascular events and all-cause mortality. *Results* Neither high nor low-intensity statin therapy significantly differed from moderate-intensity statin therapy in preventing ischemic cardiovascular and cerebrovascular events or all-cause mortality. Of the moderate-intensity statin therapies, the use of 10 mg rosuvastatin was more strongly associated with a reduced risk of ischemic cardiovascular and cerebrovascular events than was 10 mg atorvastatin [HR 0.79 (95% CI 0.64–0.98), $p = 0.029$]. Subgroup analysis revealed that the protective effects of 10 mg rosuvastatin against ischemic cardiovascular and cerebrovascular events were more obvious for patients who were 75–79 years old, those who were statin-adherent, those who did not have diabetes mellitus at baseline, and those who were non-adherent to aspirin or antiplatelet drugs during the selection and follow-up periods. *Conclusion* The results of this study support the preferential prescription of moderate-intensity rosuvastatin over moderate-intensity atorvastatin for the secondary prevention of ischemic cardiovascular and cerebrovascular events in older patients aged ≥ 75 years.

Keywords Effectiveness · Ischemic event · Older people · Secondary prevention · South Korea · Statin

Impacts on practice

- Information about the effectiveness of statin regimens in terms of secondary prevention among patients aged 75 years and over will allow healthcare professionals to select the most appropriate statin therapy for older patients.
- The protective effect of 10 mg rosuvastatin against ischemic events is important for older patients, because it is no longer tenable to focus only on longevity and all-cause mortality, given that the expected lifespan and cardiovascular disease morbidity in this age group are continuously increasing.

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Introduction

Aging is a well-known risk factor for atherosclerotic cardiovascular disease (ASCVD) morbidity and mortality [1, 2]. It is estimated that, in the 60–79 age group, 69.1% of men and 67.9% of women have cardiovascular disease. This increases to 84.7% and 85.9%, respectively, among those > 80 years of age [3]. In addition, about two-thirds of cardiovascular deaths occur in people aged 75 and older [3]. Because the elderly population is increasing steadily worldwide, the number of incident strokes is expected to more than double between 2010 and 2050, with the majority of this due to increases among older people (i.e. those aged ≥ 75 years) and minority groups [3].

Statin therapy is well-known for its contribution to reducing the risk of cardiovascular and cerebrovascular events (CCEs) in secondary prevention. Recent guidelines have recommended low-, moderate-, or high-intensity statin therapy for the secondary prevention of CCEs based on a patient's risk factors. The intensity of statin therapy is defined according to the average expected low-density lipoprotein cholesterol (LDL-C) response to a specific statin and dose [4]. For patients older than 75 years of age with clinical ASCVD, the American College of Cardiology (ACC)/American Heart Association (AHA) recommends moderate-intensity statin therapy [4]. The National Lipid Association (NLA) also recommends moderate- or high-intensity statin therapy for patients who are 75–80 years old and moderate-intensity statin therapy for those who are older than 80 years of age [2].

Nevertheless, it is concerning that there is a limited amount of information regarding the effects of statin therapy for individuals over 75 years of age. This patient group is often underrepresented in randomized control trials (RCTs) for statins, and those who have participated in statin-focused RCTs do not necessarily accurately represent this age group, which contains patients with various co-morbidities and polypharmacy, leading to an increased risk of drug-drug interactions [5]. Consequently, the question still remains which statin regimen benefits this age group the most. Although drugs in the same class are generally thought to be therapeutically equivalent based on similar mechanisms of action, these class effects are limited in geriatric patients [6]. Given that different statins of equipotent doses may lead to significantly different event rates and that the characteristic pharmacokinetic and pharmacodynamic differences between statins are of even greater significance in older patients due to age-related factors, the specific statin regimen administered to this age group should be carefully selected [7].

Aim of the study

This observational study aimed to compare the effectiveness of statin regimens in reducing the risk of a secondary ischemic CCE and all-cause mortality for patients aged 75 years and over.

Ethics approval

This study was approved by the Institutional Review Board of Korea University (KU-IRB-16-29-A-1) and the Korea NHIS Medical Information Disclosure Committee (NHIS-2016-1-087).

Methods

Study design and data source

This retrospective cohort study used claims data from the South Korean National Health Information Database (NHID) to assess the preventive effect of statin therapy against ischemic CCEs and all-cause mortality in patients aged 75–100 years old in relation to the lipid-lowering intensity of the statins (with moderate-intensity statin therapy used as a control group) and to the moderate-intensity statin regimen used (with 10 mg atorvastatin used as a control group). The NHID is a public database compiled by the National Health Insurance Service (NHIS) containing information on health care utilization, health screening, sociodemographic variables, and mortality for the entire South Korean population [8]. This database contains longitudinal patient information regarding patient demographics, diagnoses [International Classification of Disease, Tenth Revision (ICD-10)], procedures, prescription drugs (brand name, generic name, prescription date, days of supply, dose, and administration route), and the type of medical utilization (outpatient, inpatient, or emergency department).

Study population

All patients aged 75–100 years who were prescribed at least one statin between January 1, 2009, and December 31, 2011, were identified and their claims data from January 1, 2006, through December 31, 2014, obtained from the NHID. A new statin user was defined as a patient who had not been prescribed statin from 2006 to the date of the first statin prescription (i.e. the index date). Patients were excluded if they had a history of cancer diagnosis or lipid-lowering drug use other than statins within 1 year prior to the index date. Given that the benefits in terms of reducing

vascular events are expected to start about 1 year after statin therapy, the 1-year interval between the index date and the start of the follow-up (i.e. the selection period) was considered. Patients who changed to another dose of the initial statin, who switched to another type of statin, or who discontinued statin therapy during this selection period were excluded. In this study, the discontinuation of statin therapy was defined as 12 consecutive weeks without any statin prescription. This 12-week period was set based on the half-life of statins and the prescription intervals for statin therapy in Korea. For the analysis of the secondary prevention effects of statin therapy, we selected patients who experienced a CCE (both prevalent and incident cases) within the period of 3 years before the index date to the end of the selection period. The study population was grouped into low-, moderate-, and high-intensity statin user groups according to their statin therapy regimen. The intensity of statin therapy was defined as presented in ACC/AHA guidelines [4]. A flowchart for cohort selection is presented in Fig. 1.

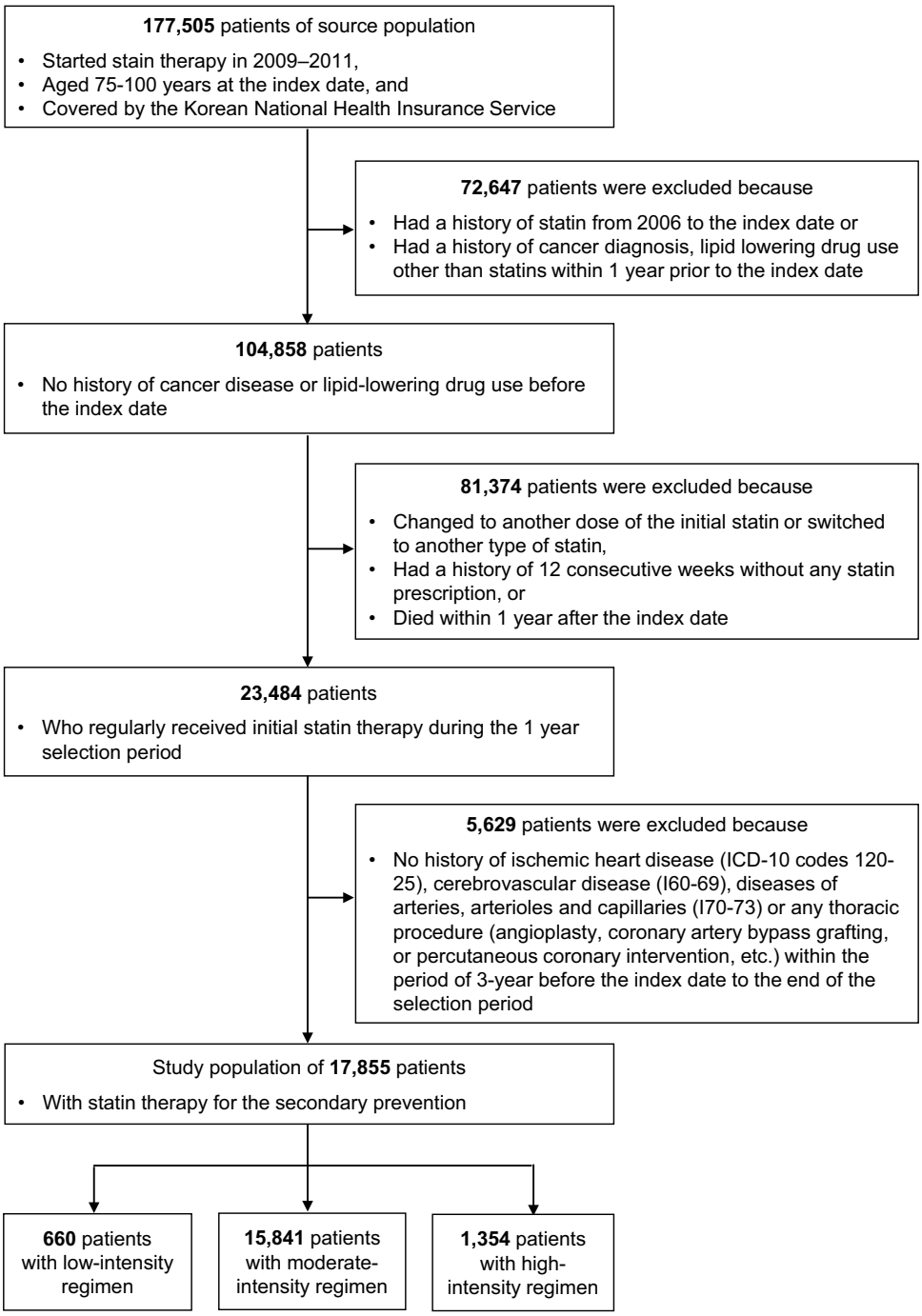

Fig. 1 Study population flow chart

Study outcomes and follow-up period

The follow-up period for outcomes started 1 year after the index date. The study outcomes assessed during the follow-up period were ischemic CCEs and all-cause mortality. An ischemic CCE was defined as any hospitalization with a primary diagnosis of acute ischemic heart disease (ICD-10 codes: I21-24), ischemic stroke (I63, I65, I66), or any procedure involving coronary artery bypass grafts or percutaneous coronary intervention. Patients were followed until one of these two outcomes occurred, until changes to or the discontinuation of statin therapy, or until December 31, 2014, whichever occurred first. If a patient changed or discontinued the initial statin therapy during the follow-up period, they were considered censored. In these cases, the discontinuation date for statin therapy was the anticipated final date of the most recent prescription of the statin.

Covariates

To control for potential confounding factors in the analyses, covariates were identified on the basis of previous literature, expert opinion, and the availability of covariates within the data. The covariates used in this study included age, gender, the Charlson Comorbidity Index (CCI), comorbidities at the index date, and adherence to statin therapy and co-medications during the selection and follow-up period (Table 1). The patients' CCI scores were estimated from their disease record using previously validated algorithms [9]. Comorbidities included hypertension, diabetes mellitus, and atrial fibrillation. Previous studies have shown a consistent direct association between poor statin therapy adherence and cardiovascular disease and mortality [10, 12]. This is particularly important for the older population, the majority of whom often have trouble adhering to the chronic disease medications they are prescribed. Therefore, adherence to statin therapy or co-medications was assessed by calculating the medication possession ratio (MPR, the ratio of the sum of the days of supply divided by the total number of days in the selection and follow-up periods). An MPR ratio equal to or higher than 80% was considered to represent adherence. This threshold is considered reasonable for identifying adherence to statin and other chronic disease medication therapies because this ratio is required to achieve a satisfactory clinical treatment effect based on the results of previous studies [11–13]. Co-medications included antihypertensive drugs (angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, β-adrenergic antagonists, calcium channel blockers or thiazide diuretics), antidiabetic drugs (metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, thiazolidinediones, or other hypoglycemic agents), aspirin, other antiplatelet drugs, and oral anticoagulants (warfarin and other anticoagulants).

Statistical analysis

Statistical analyses were performed separately to test the effect of changes to the lipid-lowering intensity of statin therapy and to test the effect of different types of moderate-intensity statin. In each analysis, propensity score (PS) matching was used to balance the comparative groups at a proportion of 1:1. For PS matching, clinical risk factors such as age, gender, CCI score, and comorbidities at the start of statin therapy were added to a non-parsimonious multivariable logistic regression model. Subjects were matched using a nearest neighbor-approach. All unsuccessfully matched subjects were excluded. In the comparison between different intensities of statin therapy, low-intensity statin users were matched to other intensity statin regimen users from the moderate-intensity and high-intensity statin groups. In the comparison between different types of moderate-intensity statins, 10 mg atorvastatin users were randomly matched to other statin regimen users in the 20 mg atorvastatin, 10 mg rosuvastatin, and 20 mg simvastatin groups.

To investigate the risk of ischemic CCEs or all-cause mortality, the Cox proportional hazards model was used to adjust the covariates (age, gender, CCI score, comorbidities at the start of statin therapy, adherence to statin therapy, and adherence to co-medications) before and after PS matching. Kaplan–Meier survival curves were plotted to determine the event-free survival rate for the target groups. Subgroup analyses were also performed to determine whether the results remained similar for different subgroups based on age, gender, comorbidities, adherence to statin therapy, and adherence to co-medications. Two-sided p values were reported for all analyses, and results were considered statistically significant for $p < 0.05$. All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Study population

Data from a total of 177,505 patients aged 75–100 years old who were prescribed statin therapy were collected from the NHID. Of these patients, 17,855 regularly received statin therapy for the secondary prevention of CCEs during the 1-year selection period and were thus included for further analysis. Moderate-intensity statins were the most commonly prescribed regimen for the study population (Fig. 1). Of these moderate-intensity users, 10 mg atorvastatin was the most common statin (7643 patients), followed by 20 mg atorvastatin, 10 mg rosuvastatin, and 20 mg simvastatin (3017 patients, 2536 patients, and 1315 patients, respectively).

Table 1 Baseline characteristics of the study population after propensity score matching

Variable, n (%)	Intensity of statin therapy				Types of moderate-intensity statin				
	Low intensity (n = 660)	Moderate intensity (n = 660)	High intensity (n = 660)	*p* value	Atorvastatin 10 mg (n = 1314)	Atorvastatin 20 mg (n = 1314)	Rosuvastatin 10 mg (n = 1314)	Simvastatin 20 mg (n = 1314)	*p* value
Age, years				0.335					0.815
75–79	371 (56.2)	371 (56.2)	394 (59.7)		791 (60.2)	809 (61.6)	793 (60.4)	786 (59.8)	
≥ 80	289 (43.8)	289 (43.8)	266 (40.3)		523 (39.8)	505 (38.4)	521 (39.6)	528 (40.2)	
Gender				0.985					0.978
Male	260 (39.4)	258 (39.1)	261 (39.5)		442 (33.6)	450 (34.2)	440 (33.5)	442 (33.6)	
Female	400 (60.6)	402 (60.9)	399 (60.5)		872 (66.4)	864 (65.8)	874 (66.5)	872 (66.4)	
Statin use[a]				0.500					< 0.001
Adherent	344 (52.1)	323 (48.9)	337 (51.1)		724 (55.1)	690 (52.5)	733 (55.8)	560 (42.6)	
Non-adherent	316 (47.9)	337 (51.1)	323 (48.9)		590 (44.9)	624 (47.5)	581 (44.2)	754 (57.4)	
CCI score				0.449					0.991
1	263 (39.9)	263 (39.8)	266 (40.3)		554 (42.2)	562 (42.8)	552 (42.0)	554 (42.2)	
2	185 (28.0)	186 (28.2)	161 (24.4)		322 (24.5)	319 (24.3)	336 (25.6)	330 (25.1)	
≥ 3	212 (32.1)	211 (32.0)	233 (35.3)		438 (33.3)	433 (32.9)	426 (32.4)	430 (32.7)	
Comorbidities									
Hypertension	570 (86.4)	570 (86.4)	582 (88.2)	0.526	1190 (90.6)	1187 (90.3)	1212 (92.2)	1182 (90.0)	0.188
Diabetes Mellitus	312 (47.3)	312 (47.3)	310 (47.0)	0.992	664 (50.5)	570 (51.0)	666 (50.7)	669 (50.9)	0.995
Atrial fibrillation	70 (10.6)	69 (10.5)	68 (10.3)	0.984	97 (7.4)	99 (7.5)	97 (7.4)	96 (7.3)	0.997
Co-medication[a]									
ACEI	89 (13.5)	125 (18.9)	174 (26.4)	< 0.001	264 (20.1)	249 (18.9)	370 (28.2)	187 (14.2)	< 0.001
ARB	247 (37.4)	257 (38.9)	304 (46.1)	0.003	524 (39.9)	532 (40.5)	623 (47.4)	453 (34.5)	< 0.001
ARB + Diuretics[b]	116 (17.6)	106 (16.1)	82 (12.4)	0.028	244 (18.6)	237 (18.0)	219 (16.7)	253 (19.3)	0.363
BB	235 (35.6)	264 (40.0)	330 (50.0)	< 0.001	567 (43.2)	567 (43.2)	739 (56.2)	449 (34.2)	< 0.001
CCB	334 (50.6)	332 (50.3)	282 (42.7)	0.005	667 (50.8)	618 (47.0)	643 (48.9)	739 (56.2)	< 0.001
CCB + ARB[b]	73 (11.1)	62 (9.4)	75 (11.4)	0.457	138 (10.5)	153 (11.6)	127 (9.7)	105 (8.0)	0.015
Diuretics	265 (40.2)	245 (37.1)	232 (35.2)	0.168	523 (39.8)	486 (37.0)	569 (43.3)	572 (43.5)	0.001
Metformin	57 (8.6)	45 (6.8)	42 (6.4)	0.243	115 (8.8)	112 (8.5)	119 (9.1)	122 (9.3)	0.090
Sulfonylurea	58 (8.8)	53 (8.0)	47 (7.1)	0.535	130 (9.9)	102 (7.8)	126 (9.6)	142 (10.8)	0.059
DPP4I	13 (2.0)	5 (0.8)	11 (1.7)	0.162	24 (1.8)	18 (1.4)	20 (1.5)	14 (1.1)	0.427
Thiazolidinedione	6 (0.9)	9 (1.4)	7 (1.1)	0.725	17 (1.3)	20 (1.5)	9 (0.7)	22 (1.7)	0.120
Other DM drugs	9 (1.4)	12 (1.8)	16 (2.4)	0.361	23 (1.8)	19 (1.4)	26 (2.0)	17 (1.3)	0.507
Anticoagulants	28 (4.2)	24 (3.6)	37 (5.6)	0.209	53 (4.0)	40 (3.0)	39 (3.0)	21 (1.6)	0.003
Aspirin	187 (28.3)	192 (29.1)	220 (33.3)	0.103	384 (29.2)	404 (30.7)	505 (38.4)	304 (23.1)	< 0.001
Other antiplatelet	201 (30.5)	237 (35.9)	307 (46.5)	< 0.001	436 (33.2)	600 (45.7)	533 (40.6)	421 (32.0)	< 0.001

ACEI angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BB* beta blocker, *CCB* calcium channel blocker, *CCI* Charlson comorbidity index, *DM* diabetes mellitus, *DPP4I* dipeptidyl peptidase-4 inhibitor, *PSM* propensity score matching

Clinical risk factors, such as age, gender, CCI score, comorbidities were added into a non-parsimonious multivariable logistic regression model for the propensity score matching

[a]Drug use for study subjects were considered if the MPR of each drug was ≥ 80% during the selection and follow-up periods

[b]Combination drugs

Comparison of the preventive effects of different statin intensity groups

To analyze the statin intensity effects, we selected a total of 1980 patients after PS matching (660 patients each from the low-, moderate-, and high-intensity statin groups). The mean age of this sample was 79.6 years (±4.1 years) and the mean observational period following the index date (i.e. the selection and follow-up periods) was 2.7 years (±0.6 years). After PS matching, most of the baseline characteristics between the comparative groups were well-balanced except adherence to co-medications (Table 1).

Cox proportional hazard regression analysis indicated that, before PS matching, high-intensity statin use was more strongly associated with the reduced risk of experiencing ischemic CCEs than was moderate-intensity statin use, and this difference was statistically significant [HR 0.79 (0.67–0.93), $p=0.004$]. After PS matching, however, high and low-intensity statin therapies were not significantly different from moderate-intensity statin use in preventing ischemic CCEs and all-cause mortality (Table 2, Supplementary Figure S1a).

Comparison of the preventive effects of different types of moderate-intensity statin

For the comparison between different types of moderate-intensity statin, a total of 5256 patients were selected after PS matching (1314 patients each in the 10 mg atorvastatin, 20 mg atorvastatin, 10 mg rosuvastatin, and 20 mg simvastatin groups). The mean age of the analytical sample was 79.2 years (±3.8 years) and the mean observational period from the index date (i.e. the selection and follow-up period) was 2.7 years (±0.6 years). After PS matching, most of the baseline characteristics between the comparative groups were well-balanced except adherence to statin therapy and adherence to co-medications (Table 1).

Cox proportional hazards regression analysis indicated that 10 mg rosuvastatin was more strongly associated with a reduced risk of experiencing an ischemic CCE than was 10 mg atorvastatin before PS matching, and this difference was significant [HR 0.78 (0.69–0.88), $p<0.001$; Table 3]. After PS matching, 10 mg rosuvastatin had a 0.793-fold lower risk of ischemic CCE compared to 10 mg atorvastatin ($p=0.029$) and the Kaplan–Meier survival curve showed that patients receiving 10 mg rosuvastatin therapy tended to have better ischemic CCE-free survival ($p=0.002$; Supplementary Figure S1b). For all-cause mortality, 20 mg simvastatin was more strongly associated with an increased risk of death compared with 10 mg atorvastatin before PS matching [HR 1.17 (1.01–1.35), $p=0.031$]. After PS matching, however, none of the statin therapies were significantly different from 10 mg atorvastatin in preventing all-cause mortality.

The preventive effects of the four moderate-intensity statin regimens for patient subgroups are summarized in Table 4. After PS matching, the protective effect of 10 mg rosuvastatin on ischemic CCEs was more obvious in patients aged 75–79 years old, those who were statin-adherent, those who did not have diabetes mellitus at baseline, and those who were non-adherent to aspirin or antiplatelet drugs. In contrast, the use of 20 mg simvastatin was significantly correlated with the experience of ischemic CCEs in the oldest-old group (≥80 years of age) and in statin-adherent patients. For all-cause mortality, 20 mg simvastatin use was found to have a higher risk of death in statin-adherent patients, but this was not statistically significant [HR 1.36 (1.00–1.86), $p=0.050$].

Table 2 Hazard ratios of developing ischemic CCE or all-cause mortality by each intensity statin regimen group, before and after propensity score matching

	Before PSM				After PSM			
	Number	Event (%)	HR[a] (95% CI)	*p* value	Number	Event (%)	HR[a] (95% CI)	*p* value
Ischemic CCE								
Moderate-intensity	15,841	2471 (15.6)	1.00 (reference)		660	96 (14.5)	1.00 (reference)	
Low-intensity	660	112 (17.0)	1.09 (0.90–1.32)	0.359	660	112 (17.0)	1.12 (0.85–1.48)	0.409
High-intensity	1354	184 (13.6)	0.79 (0.67–0.93)	0.004	660	85 (12.9)	0.80 (0.60–1.08)	0.145
All-cause mortality								
Moderate-intensity	15,841	1815 (11.5)	1.00 (reference)		660	86 (13.0)	1.00 (reference)	
Low-intensity	660	85 (12.9)	1.01 (0.83–1.23)	0.896	660	85 (12.9)	0.93 (0.71–1.21)	0.569
High-intensity	1354	154 (11.4)	0.97 (0.83–1.13)	0.662	660	87 (13.2)	0.90 (0.69–1.18)	0.455

CCE cerebrovascular and cardiovascular events, *PSM* propensity score matching, *HR* hazard ratio, *CI* confidence interval

[a]Adjusted hazard ratio calculated using Cox proportional hazard model adjusting for baseline gender, age, Charlson comorbidity index score, comorbidities (hypertension, diabetes mellitus, and atrial fibrillation) and adherence to statin and co-medications (antihypertensive drugs, antidiabetic drugs, aspirin, other antiplatelet and anticoagulants) during the selection and follow-up period

Table 3 Hazard ratios of developing ischemic CCE or all-cause mortality by each moderate-intensity statin regimen group, before and after propensity score matching

Group	Before PSM				After PSM			
	Number	Event (%)	HR[a] (95% CI)	*p* value	Number	Event (%)	HR[a] (95% CI)	*p* value
Ischemic CCE								
Atorvastatin 10 mg	7643	1205 (15.8)	1.00 (reference)		1314	195 (14.8)	1.00 (reference)	
Atorvastatin 20 mg	3017	486 (16.1)	0.95 (0.85–1.06)	0.331	1314	200 (15.2)	0.93 (0.76–1.14)	0.488
Rosuvastatin 10 mg	2536	333 (13.1)	0.78 (0.69–0.88)	< 0.001	1314	166 (12.6)	0.79 (0.64–0.98)	0.029
Simvastatin 20 mg	1315	240 (18.3)	1.12 (0.98–1.29)	0.106	1314	239 (18.2)	1.15 (0.95–1.39)	0.160
All-cause mortality								
Atorvastatin 10 mg	7643	828 (10.8)	1.00 (reference)		1314	144 (11.0)	1.00 (reference)	
Atorvastatin 20 mg	3017	372 (12.3)	1.10 (0.99–1.22)	0.091	1314	143 (10.9)	1.02 (0.83–1.24)	0.862
Rosuvastatin 10 mg	2536	271 (10.7)	0.90 (0.80–1.02)	0.100	1314	129 (9.8)	0.88 (0.72–1.08)	0.231
Simvastatin 20 mg	1315	170 (12.9)	1.17 (1.01–1.35)	0.031	1314	170 (12.9)	1.15 (0.95–1.40)	0.151

CCE cerebrovascular and cardiovascular events, *PSM* propensity score matching, *HR* hazard ratio, *CI* confidence interval

[a]Adjusted hazard ratio calculated using Cox proportional hazard model adjusting for baseline gender, age, Charlson comorbidity index score, comorbidities (hypertension, diabetes mellitus, and atrial fibrillation) and adherence to statin and co-medications (antihypertensive drugs, antidiabetic drugs, aspirin, other antiplatelet and anticoagulants) during the selection and follow-up period

Discussion

Main findings

Using South Korean real-world data, this study provides evidence that low, moderate, and high statin intensities are equally effective in preventing ischemic CCEs and that moderate-intensity rosuvastatin therapy can be more protective against ischemic CCEs compared with the same intensity of atorvastatin therapy in patients aged 75 years and older. Notably, the results of subgroup analysis showed that 10 mg rosuvastatin had more obvious protective effects in patients who were younger than 80 years old, those who were statin-adherent, those without diabetes mellitus, and those who were non-adherent to aspirin or antiplatelet drugs.

Comparison with other studies

Our results for the comparison between moderate- and high-intensity statin therapy were similar to those of previous studies. For example, a retrospective cohort analysis of elderly patients with acute coronary syndrome did not demonstrate the superiority of high-intensity over moderate-intensity statin treatment in preventing all-cause death or recurrent acute coronary syndrome [14]. In addition, subgroup analyses of a large meta-analysis of 26 randomized trials reported that more intensive statin therapy did not produce a significant reduction in major vascular events compared to less intensive therapy in patients 75 years and older [15]. Thus, our study supports the ACC/AHA recommendation of using moderate-intensity statin therapy for this age group [4].

The greater protective effect of moderate-intensity rosuvastatin compared with moderate-intensity atorvastatin found in this study is worth noting because no clinical trials have been conducted that directly compare the effect of these two statins on cardiovascular outcomes. There have only been some simulated trials which compared clinical outcomes in patients receiving the two statins [16–18]. The superiority of rosuvastatin in preventing CCEs can be explained by both lipid-dependent and independent mechanisms. In terms of lipid-dependent mechanisms, it is well-known that the reduction of CCEs is proportional to the absolute reduction in LDL-C, with the two exhibiting an approximately linear relationship [19]. A number of studies in various clinical settings have already confirmed that rosuvastatin has a greater LDL-C lowering effect and a greater high-density lipoprotein cholesterol (HDL-C) raising effect compared with atorvastatin [20–24], and it has been reported that these effects of rosuvastatin are as potent in older patients as they are in younger patients [25]. In terms of lipid-independent mechanisms, the anti-inflammatory effect via the reduction of C-reactive protein (CRP) is known to contribute to a decrease cardiovascular disease risk. Rosuvastatin has been found to be more effective in decreasing CRP and oxidative stress levels than atorvastatin [26, 27]. Similarly, it has been reported that rosuvastatin resulted in the more significant regression of coronary atherosclerosis than did atorvastatin in statin-naive patients [28].

The diminishing effect of statins with age found in the subgroup analyses is similar to a previous large-scale observational study [29]. It has been suggested that statins may be less effective in modifying cardiovascular outcomes in older age groups because the biological and

Table 4 Hazard ratios of developing ischemic CCE for different moderate-intensity statin regimens versus 10 mg atorvastatin: sub-group analysis

Characteristics	Number	Atorvastatin 20 mg		Rosuvastatin 10 mg		Simvastatin 20 mg	
		HR[a] (95% CI)	*p* value	HR[a] (95% CI)	*p* value	HR[a] (95% CI)	*p* value
Age, year							
75–79	3179	0.80 (0.62–1.03)	0.079	0.67 (0.51–0.87)	0.003	1.03 (0.81–1.31)	0.801
≥ 80	2077	1.23 (0.88–1.71)	0.231	1.10 (0.79–1.55)	0.570	1.40 (1.01–1.93)	0.042
Gender							
Male	1774	0.91 (0.67–1.24)	0.552	0.82 (0.59–1.13)	0.230	1.03 (0.76–1.39)	0.872
Female	3482	0.95 (0.73–1.22)	0.670	0.78 (0.59–1.02)	0.068	1.22 (0.96–1.56)	0.109
Statin use[b]							
Adherent	2707	1.03 (0.75–1.40)	0.866	0.65 (0.46–0.91)	0.013	1.39 (1.02–1.88)	0.035
Non-adherent	2549	0.88 (0.68–1.15)	0.355	0.91 (0.70–1.18)	0.470	1.03 (0.81–1.32)	0.803
HTN							
Yes	4771	0.93 (0.76–1.14)	0.483	0.78 (0.63–0.97)	0.027	1.11 (0.91–1.35)	0.325
No	485	0.89 (0.43–1.83)	0.746	0.85 (0.39–1.87)	0.692	1.58 (0.82–3.05)	0.172
DM							
Yes	2669	1.04 (0.79–1.37)	0.774	0.86 (0.65–1.15)	0.319	1.29 (0.99–1.68)	0.061
No	2587	0.81 (0.61–1.09)	0.165	0.71 (0.53–0.97)	0.029	1.01 (0.77–1.34)	0.924
A. Fib							
Yes	389	0.86 (0.46–1.61)	0.628	0.74 (0.39–1.41)	0.363	0.77 (0.39–1.49)	0.431
No	4867	0.93 (0.75–1.15)	0.503	0.79 (0.63–0.99)	0.037	1.19 (0.97–1.45)	0.096
AntiHTN drug[b]							
Adherent	3764	0.85 (0.67–1.08)	0.185	0.82 (0.65–1.04)	0.105	1.13 (0.90–1.41)	0.298
Non-adherent	1492	1.11 (0.78–1.58)	0.554	0.68 (0.44–1.06)	0.086	1.16 (0.81–1.65)	0.422
AntiDM drug[b]							
Adherent	600	0.92 (0.55–1.54)	0.744	0.98 (0.60–1.63)	0.950	1.28 (0.81–2.03)	0.287
Non-adherent	4656	0.94 (0.75–1.16)	0.542	0.77 (0.62–0.97)	0.028	1.12 (0.90–1.38)	0.307
Aspirin[b]							
Adherent	1597	0.72 (0.49–1.05)	0.085	0.86 (0.61–1.22)	0.391	0.98 (0.61–1.22)	0.905
Non-adherent	3659	1.03 (0.81–1.30)	0.837	0.74 (0.57–0.96)	0.024	1.21 (0.97–1.51)	0.097
Anti-platelet[b]							
Adherent	1990	0.94 (0.71–1.25)	0.683	0.90 (0.67–1.21)	0.484	0.99 (0.73–1.34)	0.928
Non-adherent	3266	0.92 (0.69–1.22)	0.538	0.70 (0.52–0.94)	0.019	1.27 (0.99–1.62)	0.060
Anticoagulation[b]							
Adherent	153	1.08 (0.37–3.15)	0.895	0.97 (0.34–2.76)	0.948	1.96 (0.62–6.17)	0.249
Non-adherent	5103	0.92 (0.75–1.13)	0.408	0.79 (0.63–0.97)	0.026	1.13 (0.93–1.37)	0.212

A. Fib atrial fibrillation, *CCE* cerebrovascular and cardiovascular events, *HR* hazard ratio, *HTN* hypertension, *CI* confidence interval, *DM* diabetes mellitus

[a]Adjusted hazard ratio calculated using Cox proportional hazard model adjusting for baseline gender, age, Charlson Comorbidity Index score, comorbidities and adherence to statin and co-medications (antihypertensive drugs, antidiabetic drugs, aspirin, other antiplatelet and anticoagulants) during the selection and follow-up periods

[b]Drug use for study subjects were considered if the MPR of each drug was ≥ 80% during the selection and follow-up periods

non-biological effects of aging may alter the relationship between cholesterol levels and cardiovascular outcomes [30–32]. In addition, individuals older than 75 years are more likely to be statin non-adherent than younger patients because of a number of sociodemographic, economic, and other treatment-related factors [33]. It is well known that there is a close relationship between poor adherence to statin therapy and worse clinical outcomes [34, 35]. Regarding the results from analyses stratified by comedications use, although the exact mechanisms are unclear, the differences observed between patients according to their non-adherence to co-medications could be explained by the protective effects of rosuvastatin being more

conspicuous when there was an absence of antiplatelet effects caused by the use of aspirin or other antiplatelet agents.

Strengths and limitations

The present study makes a number of contributions that are worth mentioning. First, to the best of our knowledge, this is the first study to compare the effectiveness of statins in secondary prevention in an elderly Asian population. Given that the direct application of recent Western population-based guidelines to Asian patients, who have possible differences in their genetics and ASCVD risk factors, remains controversial, the results of this study could be utilized as important evidence for the effectiveness of statin therapy in elderly Asian patients. Secondly, using a population-based, nationwide database, this study included nearly 100% of the older patients who started statin therapy over a 3-year period in South Korea. All comorbidities and medical interventions were recorded in detail in accordance with national health insurance regulations. Thirdly, the sample size was sufficiently large and the follow-up period sufficiently long to capture potential differences in actual cardiovascular event rates between different statin therapies [19].

However, the retrospective study design using national claims data employed in this study has some limitations. In this study, we only evaluated ischemic CCEs because there is conflicting evidence as to whether statin increases the risk of intracranial hemorrhage [36]. Therefore, the results of our study cannot be generalized to non-ischemic CCEs such as hemorrhagic stroke. Second, although we controlled for the most important risk factors for ischemic CCEs, other CCE risks such as obesity, smoking, family history, and physical inactivity were not considered in the model because the number of patients for whom this information was available was too small. Third, only all-cause mortality was considered because data on the cause of death was not available from the NHID. Finally, important adverse effects of statins such as renal toxicity, hepatic toxicity, rhabdomyolysis, and myopathy were not statistically analyzed in this study because only a small proportion of these adverse effects could be identified within the study population (30 patients with severe renal failure, 84 patients with hepatic failure, and 41 patients with rhabdomyolysis).

The impact of the findings on patients/society and professionals/practice

The results of this study based on real-world data can be used as the basis for selecting a statin regimen for the secondary prevention of cardiovascular events in patients aged 75 years and over. The protective effect of 10 mg rosuvastatin against ischemic events is important for older patients because focusing only on longevity and all-cause mortality is no longer sufficient given that the expected lifespan and cardiovascular disease morbidity of this age group continue to increase. Information about the effectiveness of statin regimens in secondary prevention among patients aged 75 years and older thus allows healthcare professionals to select the most appropriate statin therapy for their patients.

Conclusion

Using real-world data, we found that moderate-intensity rosuvastatin therapy can be more protective against ischemic CCEs compared with the same intensity of atorvastatin therapy in patients aged 75 years and older. Additional prospective studies are warranted to further clarify the efficacy and safety of statin therapy for this age group.

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