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Statins for primary prevention in adults aged 75 years and older: A nationwide population-based case-control study

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HIGHLIGHTS

- Current use of statin reduced the risk for a composite of MI, stroke, and all-cause death in subjects aged ≥75 years.
- Current use of statin reduced the risk for an individual event of stroke or all-cause death, but not MI in very eldery subjects.
- There was a graded reduction of these risks with increasing statin treatment durations.
- This study could support the appropriateness of statins for primary prevention in very elderly subjects aged ≥75 years.

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ABSTRACT

Background and aims: There is inadequate evidence to establish statin treatment for primary prevention in the elderly. This study evaluated whether statins are beneficial for primary prevention of cardiovascular disease (CVD) and all-cause death in adults aged ≥ 75 years.

Methods: A nationwide, nested case-control study was conducted in Korea. Individuals who developed CVD, including myocardial infarction (MI), stroke, or death from all causes, were matched to controls based on duration of follow-up, age, and sex at the index date. The statin administration data from both groups were retrospectively collected from the index date to five years before. Odds ratios (ORs) and 95% confidence intervals (CIs) for composite and individual outcomes associated with statin treatment were estimated by conditional logistic regression analyses.

Results: In total, 11,017 cases were matched to 55,085 control subjects. Current use of statins was significantly associated with a reduced risk of composite outcome (adjusted OR [AOR] 0.77; 95% CI 0.71–0.84), compared with non-users. Current use of statin also reduced the risk of stroke (AOR 0.74; 95% CI 0.61–0.89) and of all-cause death (AOR 0.73; 95% CI 0.66–0.81), but not of MI. However, former use of statins had no effect on CVD or all-cause death. There were significant decreasing trends in the incidence of composite outcomes and individual stroke or all-cause death with longer duration of statin treatment.

Conclusions: Current statin treatment has a beneficial effect as primary prevention for composite outcomes and individual event of stroke or all-cause death in Koreans aged ≥75 years.

1. Introduction

Low-density lipoprotein cholesterol (LDL-C) is a well-established risk factor for cardiovascular disease (CVD) by promoting plaque progression from an early-stage fatty streak to an advanced stage lipid-rich plaque [1]. Most guidelines highlight LDL-C reduction as primary and secondary prevention for CVD, and statins have served as the first-line therapy due to their strong potency in lowering LDL-C while having few adverse effects [2].

Until recently, decisions to initiate statins for primary prevention

Abbreviations: LDL-C, Low-density lipoprotein cholesterol; CVD, Cardiovascular disease; CHD, Coronary heart disease; MI, Myocardial infarction; NHIS-NSC, National health insurance service-national sample cohort; DM, Diabetes mellitus; SD, Standard deviation; OR, Odds ratio; AOR, Adjusted odds ratio; CI, Confidence interval

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were based on coronary heart disease (CHD) risk models from the Framingham Heart Study [3]. However, the American College of Cardiology/American Heart Association (ACC/AHA) guideline recommends neither for nor against statin initiation for primary prevention in individuals > 75 years of age [4], because of limited reliable evidence. Randomized controlled trials (RCTs) have shown that primary prevention with statins in an elderly population produced conflicting results. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial, which enrolled patients aged 70–82 years at high CVD risk without previous vascular disease, demonstrated that pravastatin reduces the combined incidence of CVD [5]. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT-LLT) trial failed to demonstrate that pravastatin prevented CVD in subjects aged more than 75 years [6]. Conversely, the Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study and the Heart Outomes Prevention Evaluation (HOPE-3) trial showed that rosuvastatin was protective for composite and individual CVD incidence in subjects who were older than 70 years and 65 years, respectively [7,8]. However, all-cause mortality did not significantly differ between the statin and control groups in any of these trials [5–8].

Although recent large RCTs revealed the benefit of primary prevention with statins in older subjects, these results are limited to subgroup analyses because the majority of the enrolled participants were younger than 75 years old. Furthermore, only a few studies have included Asian populations and investigated statins as primary prevention in elderly Asians. This study aimed to evaluate whether statins have significant benefits for primary CVD prevention and all-cause mortality in patients aged ≥75 years in a Korean population.

2. Materials and methods

2.1. Data source

The primary data for this study were obtained from the National Health Insurance Service-National Sample Cohort (NHIS-NSC) in the Republic of Korea from January 2002 to December 2015. The NHIS is a single-payer system for all residents in South Korea, composed of a stratified and random sample including 99% of the Korean population [9]. The information contains anonymized identification numbers, all inpatient and outpatient medical claims data, socioeconomic status, prescription drugs, diagnostic and treatment codes, and primary and secondary diagnosis codes. The diagnoses were classified using the International Classification of Disease, 10th Revision (ICD-10). Each unique de-identified number was linked to mortality information from the Korean National Statistical Office. Under universal medical coverage, all medical claims data are collected by the NHIS as the monopolistic health insurer in Korea, so that all individuals in the NHIS-NSC were followed until 2015, unless there was a death or disqualification for National Health Insurance such as emigration.

This study was approved by the Institutional Review Board of Kyung Hee University Hospital at Gangdong (IRB file number KHNMC 2016-06-015). An exemption from informed consent was granted by the board, because all data were analyzed anonymously.

2.2. Selection of cases and controls

A nested case-control design of this study is illustrated in Fig. 1; eligible subjects had first-time myocardial infarction (MI), stroke, or death from NHIS-NSC database records dated between January 2013 and December 2015.

The primary outcome was the combined endpoint of MI, stroke, and death from all causes; and the secondary outcomes were the separate components. MI was defined as hospitalization with a primary diagnosis code of I21−I22 (acute MI, I21; subsequent MI, I22). Stroke was defined as hospitalization with a primary diagnosis code of I63−I64 (cerebrovascular infarction, I63; cerebrovascular disease, not otherwise specified, I64) with brain magnetic resonance imaging or computed tomography. For all-cause mortality, death certificates from the National Statistical Office were identified via individual identification numbers, which are assigned to citizens at birth. Individuals who were younger than 75 years old on the index date, who were hospitalized with CVD before January 2015, and who were prescribed statins before five years from the index date were excluded. Controls who surviving subjects without incident CVD were selected through a 5:1 matching to the cases based on age, sex, and index date.

2.3. Classification of study subjects according to previous statin exposure

We classified all participants into three groups according to statin exposure within the five years prior to the index date. Non-statin users (the non-statin group) had not been prescribed statins within the five years before the index date. The subjects with a remote use of statin (the former user group) had redeemed no statin prescriptions within one year before the index date, but had > 90 days of prescription more than one year before the index date. Recent statin users (current user group) had been prescribed statins for at least 90 days until the index date, mandatorily including treatment within one year before the index date. In addition, the total duration of statin treatment until the index date was collected to evaluate the association between the duration of statin exposure and the outcomes.

2.4. Definition of comorbidities and other covariates

Patients with type 2 diabetes mellitus (DM) were defined as those who claimed DM as a principal or first additional diagnosis and had a prescription for anti-diabetic medications. The ICD-10 codes used to define patients with type 2 DM were as follows: E11, non-insulin dependent DM; E12, malnutrition-related diabetes; E13, diabetes associated with other disease, other diabetes; and E14, unknown diabetes. Hypertension was defined as ICD-10 codes I10, essential hypertension; I11, hypertensive heart disease; I12, hypertensive renal disease; I15, hypertensive heart and renal disease; and a prescription for anti-hypertensive drugs. Socioeconomic status was stratified into basic livelihood security recipients with Medicaid who pay a minimum or none of their medical bills and quartiles according to types of health insurance and amount of premium payment.

2.5. Statistical analysis

Descriptive data were presented as either the mean ± standard deviation (SD) or numbers with percentages. The difference between the case and control groups was evaluated by the *t*-test for normally distributed continuous variables, the Mann-Whitney *U* test for not normally distributed continuous variables, and the Chi-square test for categorical variables. The relative risk estimates of statin exposure for the outcomes were obtained using conditional logistic regression models that accounted for the matching variables of age, sex, income category, type 2 DM, hypertension, and previous use of other lipid-lowering drugs (fibrates or ezetimibe). SAS software (Version 9.3, SAS Institute, Cary, NC, USA) was used for statistical analyses. All of the statistical tests were two-sided, and p values < 0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

The demographic data for 11,017 cases and 55,085 controls are shown in Table 1. These two groups had similar distributions in the matching variables such as age at index date, sex, and duration of observation. Subjects were predominantly female (63.2%), and the mean

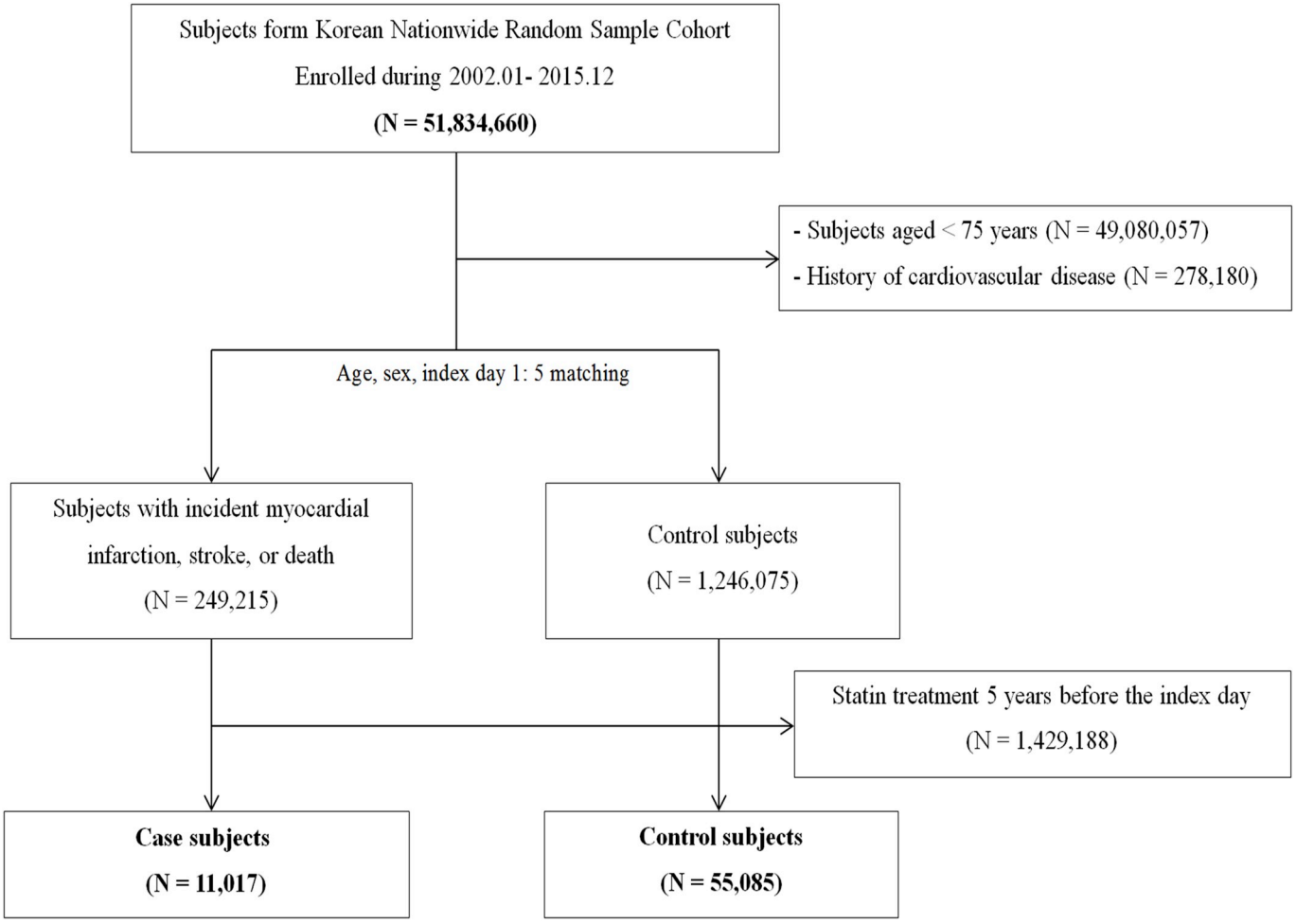

Fig. 1. Selection of study subjects.

Table 1
Baseline characteristics of study subjects.

Variables	Control (n = 55,085)	Case[a] (n = 11,017)	*p* value
Age (years)	83.7 ± 3.2	83.7 ± 3.2	1.000
Male sex, n (%)	20,255 (36.8%)	4051 (36.8%)	1.000
Urban resident, n (%)	18,961 (34.4%)	3699 (33.6%)	0.088
Income categories, n (%)			< 0.0001
Basic livelihood security recipients	5770 (10.5%)	1524 (13.8%)	
< 25 percentile (low)	12,032 (21.8%)	2374 (21.6%)	
≥25 and < 50 percentile (low-mid)	8841 (16.1%)	1736 (15.8%)	
≥50 and < 75 percentile (high-mid)	11,045 (20.1%)	2201 (20.0%)	
≥75 percentile (high)	17,397 (31.6%)	3182 (28.9%)	
Diabetes mellitus, n (%)	6321 (11.5%)	1614 (14.7%)	< 0.0001
Hypertension, n (%)	27,471 (49.9%)	4868 (44.2%)	< 0.0001
Dyslipidemia, n (%)	5792 (10.5%)	1498 (13.6%)	< 0.0001

[a] Case was defined as having a composite of myocardial infarction, stroke, and all-cause death.

age was 83.7 years. Compared to the control group, the patients with incident CVD or death included significantly higher numbers of the subjects with the lowest income, type 2 DM, and dyslipidemia, whereas the prevalence of hypertension was higher in the control group.

Throughout the study period, atorvastatin, simvastatin, and rosuvastatin were the most frequently prescribed statins (Supplementary Fig. 1). The proportions of patients prescribed atorvastatin and rosuvastatin increased over time, while that for simvastatin gradually decreased (Supplementary Fig. 1).

3.2. Primary outcome

The association between previous statin exposure and the risk of the primary outcome (the composite of MI, stroke and all-cause death) is shown in Table 2. Current statin use was significantly associated with a reduced risk for the primary outcome compared to non-users, before and after adjusting for age, sex, income categories, type 2 DM, hypertension, and previous use of fibrates or ezetimibe. There was a decreasing trend of risk, as shown by the AORs for the categories of statin exposure (former use, non-use, and current use of statin) in Fig. 2A,

Table 2
Odds ratios for incident cardiovascular disease and all-cause death in those aged ≥75 years according to statin exposure.

Statin exposure	Number (%)		OR (95% CI)	Adjusted OR (95% CI)		
	Control	Case	Crude Model	Adjusted Model 1	Adjusted Model 2	Adjusted Model 3
Overall events						
Non	48,601 (88.23)	9876 (89.64)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Former	1751 (3.18)	386 (3.5)	1.09 (0.97–1.21)	1.08 (0.97–1.21)	1.08 (0.97–1.21)	1.07 (0.95–1.20)
Current	4722 (8.59)	755 (6.85)	0.79 (0.73–0.85)	0.78 (0.72–0.85)	0.79 (0.73–0.85)	0.77 (0.71–0.84)
***p* for trend**			< 0.0001	< 0.0001	< 0.0001	< 0.0001
MI						
Non	4643 (88.61)	887 (84.64)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Former	157 (3.00)	41 (3.91)	1.37 (0.96–1.94)	1.38 (0.97–1.96)	1.16 (0.81–1.65)	1.11 (0.77–1.59)
Current	440 (8.40)	120 (11.45)	1.43 (1.15–1.77)	1.45 (1.17–1.80)	1.16 (0.93–1.45)	1.12 (0.90–1.41)
***p* for trend**			0.0015	0.0001	0.3257	0.5388
Stroke						
Non	8132 (87.72)	1604 (86.52)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Former	318 (3.43)	82 (4.42)	1.31 (1.02–1.68)	1.30 (1.01–1.67)	1.11 (0.86–1.43)	1.09 (0.84–1.40)
Current	820 (8.85)	168 (9.06)	1.04 (0.87–1.24)	1.03 (0.87–1.23)	0.77 (0.65–0.93)	0.74 (0.61–0.89)
***p* for trend**			0.1027	0.1156	0.0115	0.0037
All-cause death						
Non	36,125 (88.30)	7444 (90.98)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Former	1287 (3.15)	267 (3.26)	1.01 (0.88–1.15)	1.01 (0.88–1.15)	1.08 (0.94–1.24)	1.08 (0.94–1.23)
Current	3498 (8.55)	471 (5.76)	0.65 (0.59–0.72)	0.65 (0.59–0.72)	0.74 (0.66–0.81)	0.73 (0.66–0.81)
***p* for trend**			< 0.0001	< 0.0001	< 0.0001	< 0.0001

OR, odds ratio; CI, confidence interval; MI, myocardial infarction; DM, diabetes mellitus.
Model 1: Age, sex, and income category.
Model 2: Age, sex, income category, type 2 DM, and hypertension.
Model 3: Age, sex, income category, type 2 DM, hypertension, and previous use of other lipid-lowering drugs (fibrates or ezetimibe).

although the AOR for the primary outcome with former statin usage was not significant (Table 2).

3.3. Secondary outcomes

When we assessed MI, stroke, and all-cause mortality respectively, current statin users also had a significantly lower risk of stroke and all-cause death, compared to non-users (Table 2 and Fig. 2). However, current statin usage was not associated with MI. The relationship of former statin usage with secondary outcomes lost its statistical significance after adjusting for other covariates (Table 2 and Fig. 2).

3.4. CVD events and all-cause mortality according to the duration of statin exposure

The duration of statin exposure was classified into three groups in order to analyze the association between statin treatment and primary or secondary outcomes (Table 3). There was a tendency toward decreased odds for a composite outcome, for stroke, and for all-cause mortality with longer statin treatment. The longest duration of statin exposure (3–5 years) was significantly associated with a greater risk reduction of clinical outcomes except MI, compared to non-statin usage. However, less than 1 year of statin treatment did not affect the risk of any clinical outcomes.

4. Discussion

In this population-based case-control study, we analyzed the association between statin exposure and CVD events or all-cause death in individuals ≥75 years. The results indicated that current use of statin in the elderly was associated with a 23% reduction in a composite of CVD events and all-cause death, a 26% reduction in stroke risk, and a 27% reduction in all-cause death after adjusting for age, sex, income, and comorbidities including type 2 DM, dyslipidemia (as defined by previous use of fibrates or ezetimibe), and hypertension, compared to non-statin users. In addition, there was a decreasing tendency in the risk for clinical outcomes with longer duration of statin treatment.

Clinical practice guidelines currently do not adequately define “the elderly.” Some definitions specify a chronological age of 65 years or older, and others specify 75 years or older [10]. Therefore, the discrepancies among the results of the RCTs investigating statins as primary prevention for CVD may have partially resulted from these different definitions, as well as the endpoints across trials.

Pravastatin treatment (40 mg/day) had no significant effect on a composite of non-fatal MI, fatal CHD and death from CHD in the ALLHAT-LLT trial, in which the study patients were ≥75 years of age (mean 78 years) [6]. Conversely, rosuvastatin treatment (20 mg/day) was protective for a composite of nonfatal MI, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from CVD in the JUPITER study, in which the patients were ≥70 years of age (median 74 years) [7]. Pravastatin treatment (40 mg/day) also reduced combined events of coronary death, nonfatal MI, and fatal or nonfatal stroke in the PROSPER study, which enrolled patients aged 70–82 years (mean 75 years) [5]. In a subgroup analysis of patients aged ≥65 years (mean 71 years) in the HOPE-3 trial, rosuvastatin treatment (10 mg/d) was protective in terms of the composite outcomes of nonfatal MI, nonfatal stroke, or CVD death [8]. A meta-analysis of JUPITER and HOPE-3 also suggested that rosuvastatin prevented the composite outcomes of nonfatal MI, nonfatal stroke, and CVD death in those > 70 years of age, and there was no heterogeneity among age-stratified groups (< 65, 65– < 70, and > 70 years) [11]. Another meta-analysis, of eight RCTs including elderly subjects aged 69.0–75.5 years (mean 72.7 years), demonstrated that statin treatment only reduced the risk of nonfatal and total MI, but not fatal MI or fatal or nonfatal stroke [12].

Unlike the aforementioned RCTs, our study demonstrated that all-cause death significantly decreased in elderly current statin users, as did composite outcomes. In particular, the composite outcomes, stroke, and all-cause death were more effectively prevented in this study than observed in the PROSPER study. When the effect of pravastatin was compared to atorvastatin or rosuvastatin (high-potency statins), atorvastatin or rosuvastatin usage reduced the risk of composite events, stroke, and all-cause death in multivariate models, while pravastatin usage was not associated with any outcomes (data not shown). Only a smaller proportion (4.3%) of statin users used pravastatin compared to atorvastatin or rosuvastatin (72.0%), and some portion of the enrolled

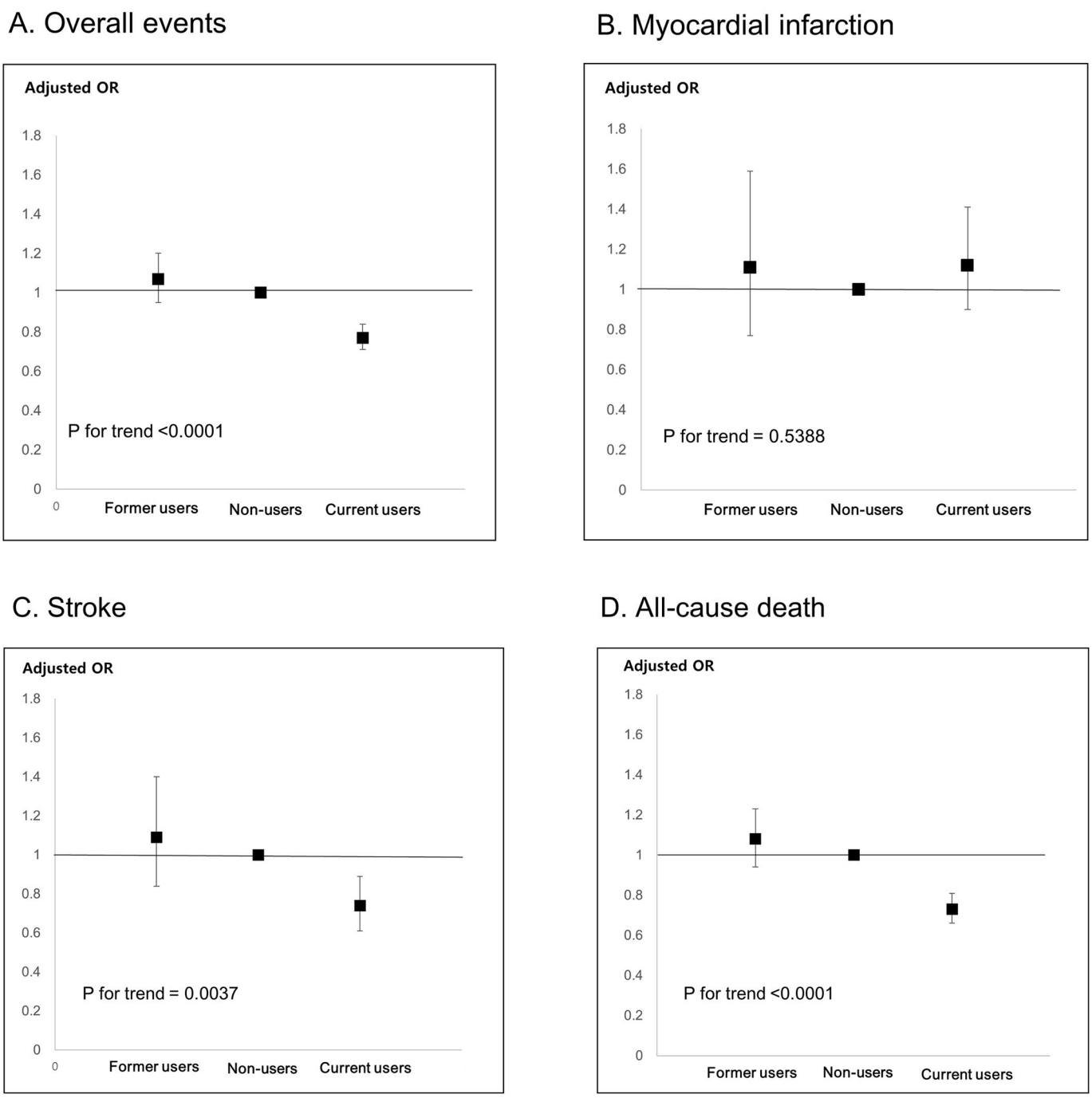

Fig. 2. The risks for composite and individual myocardial infarction, stroke, and all-cause death events in subjects aged ≥75 years.
(A) Adjusted odds ratios for a composite outcome including myocardial infarction, stroke, and all-cause death. (B) Adjusted odds ratios for incident myocardial infarction. (C) Adjusted odds ratios for incident stroke. (D) Adjusted odds ratios for incident all-cause death. All logistic regression analysis models were adjusted by age, sex, income categories, type 2 diabetes mellitus, hypertension, and previous use of other lipid-lowering drugs (fibrates or ezetimibe).

subjects changed statin type or dosage during the observation period. Therefore, the mixed effects of statins could have influenced the differences between our study and the PROSPER study which used a fixed dose of pravastatin during follow-up. However, it is also possible that the small number of events observed in pravastatin users made it difficult to reach statistical significance, particularly with regard to MI.

Furthermore, the significant association between statin treatment and the prevention of stroke but not of MI is surprising, because MI has been demonstrated to be a more statin-sensitive outcome compared to stroke. One possible explanation is the lack of clinical difference between high- and medium-intensity statins for reducing stroke over a course of up to 7 years [13,14]. In contrast, high-intensity statins are more effective at reducing non-fatal MI for up to 7 years despite their small effect size [14]. Considering the oldest old age of the enrolled patients, this cohort could be treated with low-to moderate-intensity statins or a low dose of high-intensity statins, especially Asian patients. Another explanation for these findings is that ischemic stroke occurs more frequently than MI in Asia [15]. In our study, MI incidence rate was 9.5% while the stroke incidence rate was 16.8%. Therefore, the effect size for MI incidence might be too small to be clinically important when evaluating primary prevention.

The non-significant trend in the increased risk for stroke or all-cause

Table 3
Odds ratios for incident cardiovascular disease and all-cause death in adults aged ≥75 years according to the duration of statin exposure.

Statin exposure	Number (%)		OR (95% CI)			
	Control	Case	Crude Model	Adjusted Model 1	Adjusted Model 2	Adjusted Model 3
Overall events						
Non	48,601 (88.23)	9876 (89.64)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
< 1 year	2556 (4.64)	510 (4.63)	0.98 (0.89–1.08)	0.98 (0.89–1.08)	0.98 (0.89–1.09)	0.97 (0.88–1.07)
1–3 years	2632 (4.78)	460 (4.18)	0.86 (0.78–0.95)	0.86 (0.78–0.95)	0.86 (0.78–0.95)	0.85 (0.76–0.94)
3–5 years	1296 (2.35)	171 (1.55)	0.65 (0.55–0.76)	0.65 (0.56–0.77)	0.65 (0.55–0.76)	0.63 (0.54–0.74)
***p* for trend**			< 0.0001	< 0.0001	< 0.0001	< 0.0001
MI						
Non	4643 (88.61)	887 (84.64)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
< 1 year	228 (4.35)	74 (7.06)	1.70 (1.29–2.23)	1.73 (1.32–2.27)	1.45 (1.10–1.92)	1.41 (1.06–1.86)
1–3 years	256 (4.89)	57 (5.44)	1.17 (0.87–1.57)	1.18 (0.88–1.59)	0.95 (0.70–1.29)	0.91 (0.67–1.24)
3–5 years	113 (2.16)	30 (2.86)	1.39 (0.92–2.09)	1.41 (0.94–2.12)	1.06 (0.70–1.61)	1.03 (0.67–1.56)
***p* for trend**			0.0007	0.0004	0.0639	0.0969
Stroke						
Non	8132 (87.72)	1604 (86.52)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
< 1 year	448 (4.83)	118 (6.36)	1.34 (1.08–1.65)	1.32 (1.07–1.63)	1.07 (0.86–1.32)	1.03 (0.83–1.28)
1–3 years	464 (5.01)	101 (5.45)	1.10 (0.88–1.38)	1.10 (0.88–1.37)	0.86 (0.68–1.08)	0.83 (0.66–1.04)
3–5 years	226 (2.44)	31 (1.67)	0.70 (0.48–1.02)	0.70 (0.48–1.02)	0.49 (0.34–0.73)	0.47 (0.32–0.69)
***p* for trend**			0.0081	0.0107	0.0018	0.0008
All-cause death						
Non	36,125 (88.30)	7444 (90.98)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
< 1 year	1894 (4.63)	322 (3.94)	0.83 (0.73–0.93)	0.82 (0.73–0.93)	0.90 (0.80–1.02)	0.90 (0.80–1.02)
1–3 years	1931 (4.72)	322 (3.94)	0.77 (0.68–0.87)	0.77 (0.68–0.87)	0.86 (0.76–0.98)	0.86 (0.76–0.97)
3–5 years	960 (2.35)	110 (1.34)	0.56 (0.46–0.68)	0.56 (0.46–0.68)	0.62 (0.51–0.76)	0.62 (0.51–0.76)
***p* for trend**			< 0.0001	< 0.0001	< 0.0001	< 0.0001

OR, odds ratio; CI, confidence interval; MI, myocardial infarction; DM, diabetes mellitus.
Model 1: Age, sex, and income category.
Model 2: Age, sex, income category, type 2 DM, and hypertension.
Model 3: Age, sex, income category, type 2 DM, hypertension, and previous use of other lipid-lowering drugs (fibrates or ezetimibe).

mortality among former statin users over non-users or current users in this study does not support the legacy effect. The West of Scotland Coronary Prevention Study (WOSCOPS) was the only trial to demonstrate a possible post-trial legacy effect on both all-cause and CVD-specific mortality. Unlike WOSCOPS, the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) trial observed no significant differences in the rate of cardiovascular death when administering 10 mg/day of atorvastatin during an extended follow-up of 11 years [16]. The ASCOT-LLA investigators speculated that the legacy effect of low-dose atorvastatin may have been limited to non-cardiovascular deaths, possibly due to its anti-inflammatory rather than its lipid-lowering properties. In other words, the legacy effect might vary according to the type, dose, or duration of statin use (5 years in WOSCOPS vs. a median of 3.3 years in ASCOT-LLA). In our study, most former users sustained statin treatment for less than 3 years, a relatively shorter duration than described in the aforementioned studies, and various types and doses of statin were administered during follow-up, possibly making mixed legacy effect. In addition, the participants of this study were much older and most were female (over 60%), while participants in the WOSCOPS trial were primarily middle-aged men aged 45–64 years. The legacy effect hypothesis for statins that the earlier patients begin usage, the lower their risk of a CVD event in the long term has not been tested directly in a RCT comparing statin commencement at an earlier versus later age [17]. Statins could have sex-specific legacy effects, but this has not yet been invastigated [17]. Lastly, anti-hypertensive, anti-coagulant, or anti-platelet medications also could affect CVD development when used in combination with statins.

Due to the conflicting results, there have been no clear recommendations for statin treatment in elderly people who are at a higher CVD risk defined by more frequent comorbidities such as DM, peripheral artery disease, or renal impairment, although recent guidelines broadened the indications for intensive statin treatment to subjects without established CVD but with factors indicating a high risk of CVD [18]. The ACC/AHA guidelines have recommended a clinician-patient discussion for statin initiation in patients older than 75 years of age without established CVD regardless of risk factors, even though the 10-year CVD risk already exceeds 7.5% in the elderly population [19]. There were no apparent recommendations for initiation of statins in the elderly in the Canadian Cardiovascular Society guidelines [20] and those of the U.S. Preventive Services Task Force [21]. Although the risk calculator Systematic COronary Risk Evaluation (SCORE) is not applicable to patients aged older than 65 years [22], statin treatment should be considered in older adults without established CVD, particularly in the presence of hypertension, smoking, DM and dyslipidemia (Class IIa recommendation), according to the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) guidelines [23]. Only the National Institute for Health and Care Excellence guideline provides a well-defined indication for statin treatment in individuals > 75 years of age, according to the 10-year risk of developing CVD: atorvastatin 20 mg can be offered as primary prevention in people 76–84 years of age, because all individuals > 75 years of age exceed the 10% risk threshold for treatment. This guideline also notes that even individuals > 85 years of age are likely to have a decreased CVD risk, even with a lack of confirmatory data [24,25].

There were several limitations in our study, which should be addressed. First, we were unable to define the daily dose of statin during the observation period. However, we expected at least a 30–50% reduction of LDL-C levels from baseline in the enrolled subjects, because high potency statins such as atorvastatin and rosuvastatin were mostly used in this study, and lower statin doses are typically sufficient to achieve lipid improvements in Asian patients comparable to those observed at higher doses in Caucasians [26]. Second, the administration of statins can be overestimated, because all of the dispensed statins were not actually taken by the enrolled subjects. Third, residual confounding factors including smoking status and family history of CVD could introduce error. The present cohort data were based on medical claims that did not include clinical laboratory results, medical history, or a physical examination. Data did not include cause-specific death [9], so we could not investigate CVD mortality. Forth, baseline CVD risk

stratification was also impossible due to lack of data and the absence of a validated cardiovascular risk assessment tool for older adults aged ≥75 years [27]. However, we expected our study populations to be at high-risk of CVD by virtue of their age alone. Fifth, this study only included Koreans, and thus it cannot be generalized to other ethnicities. Lastly, there was no information on the safety profiles of statins, even though statins have generally been safe and well tolerated in RCTs with patients up to 80 years of age [28]. Despite these limitations, this nationwide study includes a large sample of the Asian population of very old age, and demonstrates the efficacy of statin treatment for the reduction of not only stroke but all-cause mortality. RCTs for primary prevention with statin in elderly subjects aged ≥75 years might be difficult to perform due to the age itself and the need for a larger sample size compared to a secondary prevention trial. Therefore, this observational study could help support the appropriateness of statins for primary prevention in very elderly subjects.

In conclusion, persistent statin treatment was associated with significant risk reductions in composite outcomes and individual outcomes of stroke or all-cause death, but not in MI, in subjects aged ≥75 years without established CVD. In addition, there was a graded reduction of these risks with increasing statin treatment durations. Because the decision to initiate primary prevention with statins in people ≥75 years cannot be based directly on RCT evidence, treatment should be individualized according to comorbidities, polypharmacy, potential side effects, and the limited life expectancy of the patients, in line with current international guidelines. However, the significance of this observational study is that it serves as an alternative to RCTs in documenting the benefits of statins for primary prevention in elderly people, especially in an Asian population, for whom few data are available on the CVD risk reduction of statins.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

Concept and design of the study: YH; analysis and interpretation: IC, KH, JJE; drafting of the work or revising it critically: JJE, YH, IJ, KJA, HYJ.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.01.030.

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