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Statin and clinical outcomes of primary prevention in individuals aged > 75 years: The SCOPE-75 study

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HIGHLIGHTS

- Effect of statins for primary prevention was analyzed in individuals aged > 75 years.
- Statin was associated with lower cardiovascular risk and all-cause death.
- Rates of MI and coronary revascularization were lower in statin users.
- These results support a more active statin use in this population.

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ABSTRACT

Background and aims: Limited data is available on the benefit of statin for primary prevention in the elderly. The aim of this study is to investigate whether statin for primary prevention is effective in lowering the cardiovascular risk and all-cause death in individuals aged > 75 years.

Methods: This was a retrospective, propensity score-matched study and data were acquired between 2005 and 2016 in a tertiary university hospital. Of the 6414 patients screened, 1559 statin-naïve patients without a history of atherosclerotic cardiovascular disease before the index visit were included. After propensity score matching, 1278 patients (639 statin users, 639 statin non-users) were finally analyzed. Primary outcome variables included major adverse cardiovascular and cerebrovascular events (MACCE) and all-cause death. MACCE included cardiovascular death, nonfatal myocardial infarction, coronary revascularization, and nonfatal stroke or transient ischemic attack.

Results: At a median follow-up of 5.2 years, statin users had lower rates of MACCE (2.15 *vs.* 1.25 events/100 person-years; hazard ratio, 0.59; $p = 0.005$) and all-cause death (1.19 *vs.* 0.65 events/100 person-years; hazard ratio, 0.56; $p = 0.02$), as well as lower levels of low-density lipoprotein-cholesterol than did non-users. The Kaplan-Meier curves revealed lower event rates in statin users (hazard ratio: 0.59 for MACCE and 0.56 for all-cause death). The incidence of myocardial infarction and coronary revascularization were lower in statin users.

Conclusions: Statin therapy for primary prevention was clearly associated with lower risk of cardiovascular events and all-cause death in individuals aged > 75 years. These results support more active statin use in this population.

1. Introduction

Advanced age is recognized as a definite and strong risk factor for atherosclerotic cardiovascular disease, regardless of an individual's ethnicity [1,2]. Cardiovascular risk also increases with cholesterol levels in both elderly and young individuals [1]. There has been no doubt regarding the clinical benefit of statin use for secondary prevention, even in elderly patients [3–5]. In fact, as the absolute cardiovascular risk increases with age, the absolute benefit of lipid-lowering therapy may be greater in aged individuals [6]. Nevertheless, the statin prescription rates in elderly

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individuals are reportedly lower than those in younger individuals [7]. The latest versions of major guidelines on lipid-lowering therapy recommend personalized prescription of statins for primary prevention in individuals aged > 75 years [8–10]. The restriction is partly related to the risks associated with frailty [11] or geriatric-specific adverse events [12]. Importantly, very limited data are available regarding the outcomes and safety of statins in this population [5].

Previous studies focused on elderly individuals had mixed populations receiving statins for primary and secondary prevention. Meanwhile, the few studies focused on primary prevention generally enrolled mixed populations of elderly and non-elderly subjects. The JUPITER study focused on statin use for primary prevention and enrolled a population with a wide age range, reporting that the effect of statins did not differ between subjects aged > 65 years and those aged ≤65 years [13]. Likewise, the MEGA Study focused on statin use for primary prevention and enrolled a Japanese population with wide age range, reporting that pravastatin (10–20 mg daily) was associated with clinical benefit. This effect did not differ between patients aged ≥60 years and those aged < 60 years [14]. The HOPE-3 study reported that the benefit of rosuvastatin (10 mg daily) was similar in subjects aged > 65 years and those aged ≤65 years [15]. Despite these encouraging reports, clinical trials on statins have rarely enrolled subjects aged > 75 years, even when enrolling subjects aged > 65 years [15]. In a meta-analysis of trials on statin use for primary prevention in subjects aged ≥65 years, the statin group showed lower risk of myocardial infarction and stroke (by 39% and 24%, respectively), although there was no improvement in mortality. No analysis was conducted for individuals aged > 75 years [16].

Although some studies have reported data on the effect of statins in individuals aged > 75 years, these data have been inconsistent. The PROSPER study focused on statin use for primary and secondary prevention in subjects aged 70–82 years and reported only 6% risk reduction in a subgroup analysis focused on primary prevention alone [17]. A large meta-analysis reported that statin use was associated with 16% reduction in cardiovascular risk among subjects aged > 75 years, but this subgroup was much smaller than other subgroups. No age group-based analysis focused on primary prevention alone was conducted [18]. On the other hand, a post-hoc analysis of the ALLHAT-LLT study focused on statin use for primary prevention revealed that pravastatin was not beneficial and instead tended to increase all-cause mortality patients aged > 75 years [19]. Regarding all-cause mortality, the potential benefit of statin use for primary prevention in elderly individuals remains controversial [20,21]. In addition, a very recent retrospective study conducted in Spain demonstrated that statin use was not associated with cardiovascular and mortality benefit for primary prevention in people aged > 75 years, except for those with diabetes mellitus [22].

It is difficult to conduct a large clinical trial enrolling only with subjects aged > 75 years, for various reasons. Moreover, data on statin treatment and clinical outcomes in Asians are extremely limited, regardless of whether or not they originate from clinical trials [23]. However, there is an acute need for such data because Asian societies are aging at a fast rate, especially in East Asia, where medical care for elderly individuals has become a fundamental and pressing social issue. In the current SCOPE-75 study, we investigated whether statin use for primary prevention is associated with lower rates of cardiovascular events and all-cause mortality in 1559 Koreans aged > 75 years. We used propensity-score matching to obtain statin and no-statin (control) groups, which we compared in terms of clinical outcomes at a median follow-up of 5.2 years.

2. Materials and methods

2.1. Study population

The Institutional Review Board of Severance Hospital, Seoul, Korea approved this retrospective study (No. 4-2017-1178). The need for informed consent from the subjects themselves was waived for the following reasons: (i) the research involved no more than minimal risk to the subjects; (ii) the waiver did not adversely affect the rights and welfare of the subjects; and (iii) the research could not have been practicably carried out without the waiver. The subjects were selected from among the patients who visited the outpatient clinic of the Division of Cardiology, Severance Hospital, Seoul, Korea, between January 2005 and December 2016.

A total of 6414 consecutive patients who visited the outpatient clinic during the study period were initially screened. The inclusion criteria were: age > 75 years, at least one cardiovascular risk factor (hypertension, diabetes mellitus, or overweight), follow-up duration ≥12 months, and available data from regular laboratory work-ups. Patients fulfilling all four inclusion criteria were included in the study. Patients were excluded if they had a history of atherosclerotic cardiovascular disease, a history of statin use, low-density lipoprotein-cholesterol levels (LDL-C) > 190 mg/dL, or inconsistent dose of statins during follow-up (Fig. 1). Atherosclerotic cardiovascular disease included coronary artery disease, cerebrovascular disease, and peripheral artery disease. Inconsistent statin dose was defined as consistent statin intensity for < 80% of the follow-up period. We also excluded patients with cancers or those under dialysis. Finally, 1559 patients were analyzed. The number of patients enrolled at each year over the study period is presented in the Supplementary Fig. 1.

2.2. Study protocol

This was a retrospective, propensity score-matched cohort study. Clinical data including demographic parameters and medical history were collected by trained interviewers. Blood samples were collected after a 12-h fast and analyzed by the local laboratory, which was certified by the Korean Society of Laboratory Medicine. All patients received standard medical therapies at the physicians' discretion. When prescribing statins, physicians referred to updated guidelines [24–26] and judged clinically by weighing efficacy and safety. The patients who were prescribed statins were further classified according to the intensity of statin therapy received during ≥80% of the follow-up period. Statin therapy intensity was defined according to the 2013 American College of Cardiology/American Heart Association guidelines.

Most patients in our study were prescribed moderate-intensity statins, although some received low-or high-intensity statins. To determine whether the statin dose affected the clinical benefit in patients receiving different doses of moderate intensity statins, we further stratified these patients according to the statin dose: patients with low-moderate intensity statins (atorvastatin 10 mg/day or similar) and those with high-moderate intensity statins (atorvastatin 20 mg/day or similar).

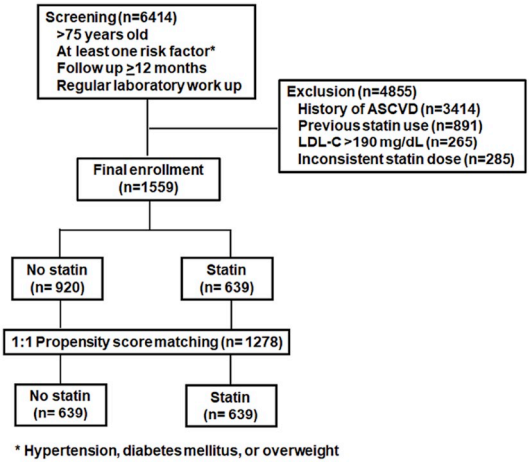

Fig. 1. Flowchart of patient inclusion.
ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein-cholesterol.

Table 1
Baseline characteristics of the matched study population.

	No statin (n = 639)	Statin (n = 639)	*p*
Age, years	78 (76, 80)	78 (76, 80)	0.90
Male	247 (38.7)	226 (35.4)	0.27
Hypertension	613 (95.9)	611 (95.6)	0.89
Diabetes mellitus	197 (30.8)	208 (32.6)	0.25
Congestive heart failure	148 (23.2)	137 (21.4)	0.50
Atrial fibrillation	155 (24.3)	140 (21.9)	0.35
Chronic thyroid disease	7 (1.1)	14 (2.2)	0.19
Chronic pulmonary disease	9 (1.4)	9 (1.4)	> 0.999
Renal insufficiency	20 (3.1)	20 (3.1)	> 0.999
Body mass index, kg/m^2	23.3 (22.0, 25.6)	23.4 (22.2, 25.8)	0.22
Laboratory values, mg/dL			
Total cholesterol	170 (149, 199)	172 (146, 200)	0.77
Triglycerides	107 (79, 151)	110 (82, 150)	0.71
HDL-C	46 (38, 55)	45 (39, 54)	0.91
LDL-C	107 (85, 129)	107 (85, 133)	0.31
Anticoagulant use	113 (17.7)	109 (17.1)	0.83
Antiplatelet use	166 (26.0)	179 (28.0)	0.45
Number of antihypertensive agents	2 (1, 3)	2 (1, 3)	0.14

Values are presented as median (interquartile range), number (%), or as indicated; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol.

The patients were followed up at the outpatient clinic every 3–6 months and underwent lipid profile examination every 3–12 months. The percent change in LDL-C at 12 months was calculated as follows: (12-month value − baseline value)/baseline value × 100. Clinical outcome data were obtained by reviewing the medical records maintained at the outpatient clinic or by telephone contact. Primary outcome variables included the rates of major adverse cardiovascular and cerebrovascular events (MACCE) and all-cause death. The MACCE outcome was defined as the composite outcome of cardiovascular death, nonfatal myocardial infarction, coronary revascularization, and nonfatal ischemic stroke or transient ischemic attack. Secondary outcome variables included the individual components of MACCE, new-onset diabetes mellitus, and cancer.

2.3. Statistical analysis

Continuous data are reported as medians (interquartile ranges), while categorical data are presented as frequencies and percentages. Data regarding clinical and laboratory parameters were compared using the chi-square test. Between-group comparisons were conducted using the Mann-Whitney *U* test, while within-group comparisons (before *vs.* after treatment) were conducted using the paired *t*-test. Cumulative survival curves for each group were built using the Kaplan-Meier method and compared using the log-rank test and Cox-proportional hazard regression. To reduce the effect of selection bias and potential confounders, we performed propensity-score matching. The following variables were used for matching: age, sex, hypertension, diabetes mellitus, chronic thyroid disease, chronic pulmonary disease, congestive heart failure, atrial fibrillation, renal insufficiency (estimated glomerular filtration rate < 60 mL/min/1.73 m^2), body mass index, baseline lipid profiles, and current medications (anticoagulant, antiplatelet, and number of antihypertensive agents). After matching, validation was performed according to the standardized mean difference of all baseline covariates, using a threshold of 0.1 to indicate imbalance. All analyses used two-tailed tests with a significance level of 0.05. R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for the analyses.

3. Results

3.1. Clinical characteristics

Of the 1559 patients enrolled, 639 received statins (statin group) and 920 did not (no-statin group). The median age in the study sample was 78 years, and 41% of patients were male. Most (96%) patients were hypertensive and the median LDL-C was 107 mg/dL. The prevalence of male sex, congestive heart failure, atrial fibrillation was lower, whereas that of diabetes mellitus was higher in the statin group (Table 1). After propensity-score matching, 1278 patients (639 per group) were included in the analysis (Fig. 1). In the matched statin group, 89% of patients received moderate-intensity statins (atorvastatin 10–20 mg/day or similar) and 54% received lower moderate intensity (atorvastatin 10 mg/day or similar). Patients receiving high- and low-intensity statins were just 1% and 9%, respectively (Supplementary Fig. S2).

3.2. Changes in lipid profiles and clinical outcomes

The patients were followed-up for a median of 5.2 years. At the 12-month follow-up, LDL-C was significantly lower in the statin group (92 *vs.* 84 mg/dL for no-statin *vs.* statin; $P < 0.001$), as was the median percentage change in LDL-C (−3.8% *vs.* −13.7%; $p < 0.001$) (Supplementary Table S1). During follow-up, the statin group had significantly lower rates of MACCE (2.15 *vs.* 1.25 events/100 person-years; hazard ratio [HR] 0.59; 95% confidence interval [CI] 0.41–0.85; $p = 0.005$) and all-cause death (1.19 *vs.* 0.65 events/100 person-years; HR 0.56; 95% CI 0.34–0.93; $p = 0.02$). The Kaplan-Meier curves revealed lower event rates in the statin group (hazard ratio 0.59 and $p < 0.001$ for MACCE; hazard ratio 0.56 and $p < 0.001$ for all-cause death) (Fig. 2). Among MACCE, myocardial infarction and coronary revascularization occurred less frequently in the statin

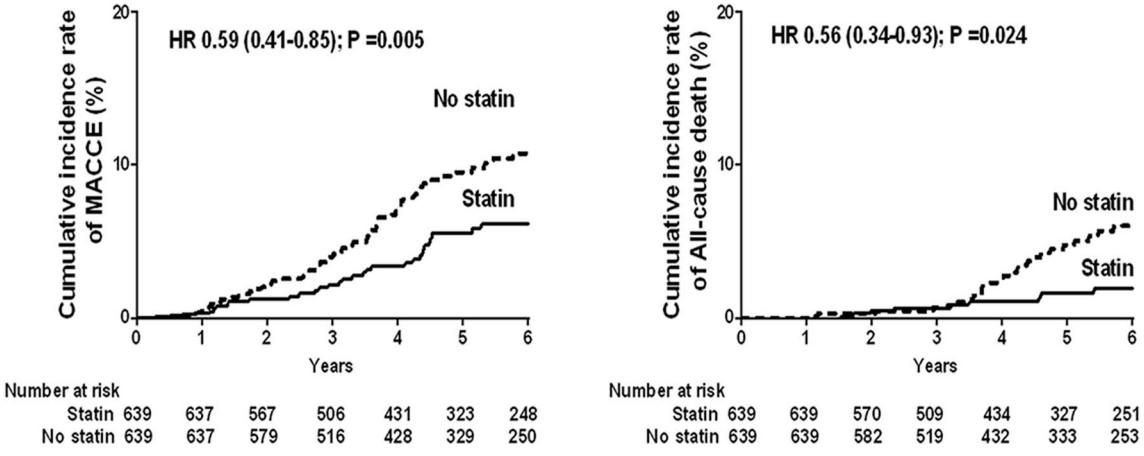

Fig. 2. Incidence of MACCE and all-cause death.
MACCE: major adverse cardio- and cerebrovascular events.

Table 2
Incidence of events in each group.

	Number of events (events/100 person-year)		HR (95% CI)	*p*
	No statin	Statin		
MACCE	77 (2.15)	44 (1.25)	0.59 (0.41–0.85)	0.005
Cardiovascular death	8 (0.22)	5 (0.14)	0.64 (0.21–1.95)	0.43
Myocardial infarction	13 (0.36)	4 (0.11)	0.32 (0.11–0.99)	0.047
Coronary revascularization	39 (1.09)	25 (0.71)	0.66 (0.40–1.09)	0.10
Ischemic stroke/TIA	17 (0.47)	10 (0.28)	0.61 (0.28–1.33)	0.22
All-cause death	43 (1.19)	23 (0.65)	0.56 (0.34–0.93)	0.02
New-onset DM	68 (3.38)	63 (2.39)	0.71 (0.51–1.01)	0.053
New-onset cancers	68 (2.01)	26 (1.99)	0.99 (0.71–1.40)	0.96

HR: hazard ratio; CI: confidence interval; MACCE: major adverse cardio- and cerebrovascular events; TIA: transient ischemic attack; DM: diabetes mellitus.

group. The incidence of new-onset diabetes mellitus and cancer did not differ significantly between the statin and no-statin groups (Table 2). Detailed statistics on cause of death are provided in Supplementary Table S2.

3.3. Subgroup analysis for clinical outcomes

On subgroup analyses that evaluated the differential effect of statins according to clinical factors, we found no significant factor affecting on the relationship between statin use and MACCE rate (including age ≥80 years and statin intensity). Regarding the effect of statins on all-cause death, potentially relevant differences were only noted between the subgroups defined according to diabetes mellitus, with the effect of statins tending to be more pronounced among diabetics than among non-diabetics ($p = 0.066$) (Fig. 3).

4. Discussion

Our present findings shed light on issues that have remained fairly controversial and insufficiently studied to date. (1) Statins, mostly with moderate intensity, had a clear clinical benefit in elderly Asians aged > 75 years. (2) All-cause mortality was significantly lower in the statin group, as was the risk of myocardial infarction and coronary revascularization which are components of the primary outcome. (3) The statin benefit was not affected by sex or other clinical conditions. (4) The rate of new-onset diabetes mellitus and cancer did not differ between statin users and non-users. Taken together, these findings indicate that statin therapy for primary prevention brought obvious clinical benefit in elderly individuals aged > 75 years. Our results provide evidence supporting the association between statin use and reduction in the risk of MACCE and all-cause mortality among individuals aged > 75 years.

In our study, although the patients' mean baseline LDL-C level was 107 mg/dL, lipid-lowering therapy might have been decided based on patients' cardiovascular risk (i.e. old age plus ≥1 cardiovascular risk factor). Mean LDL-C level after statin therapy was 84 mg/dL, but the dose was not escalated. The lack of dose escalation despite LDL-C > 70 mg/dL may be due to the following reasons: 1) One of the exclusion criteria was inconsistent dose of statins during the study period (as described in Methods section), and 2) When physicians prescribe statin, they consider both safety and efficacy, particularly for primary prevention in the elderly. In addition, physicians in Asia tend to use lower dose statins compared to those used in Western countries. These might have collectively influenced the dose of statins in our study. A previous study reported that, although statin therapy was largely beneficial in individuals aged > 75 years, the benefit tended to be smaller than that noted in younger age groups [18]. Of note, statin-associated reduction of cardiovascular risk has been reported to be smaller or uncertain for primary prevention than for secondary prevention [17,19]. The inconsistent clinical benefit in the elderly may be due to the statin effect not related to LDL-C reduction. The median LDL-C level changed from 107 to 91 mg/dL in the no statin group in our study. Although the exact cause of this finding is unclear, nonpharmacological treatment such as lifestyle change might have influenced the results. In previous reports including MEGA [14] and HOPE-3 [15] studies, modest reduction of LDL-C in the control group have not been uncommon.

A major finding of the SCOPE-75 study is that statin therapy reduces MACCE and all-cause mortality in the very elderly. In our study, the risk of myocardial infarction and coronary revascularization was significantly lower in the statin group than in the non-statin group.

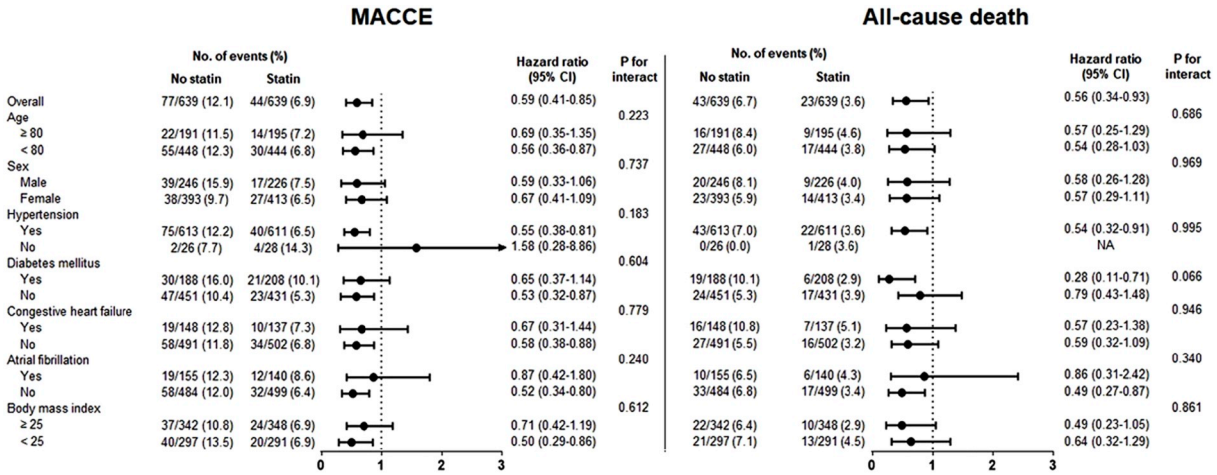

Fig. 3. Subgroup analysis for MACCE and all-cause death.
MACCE: major adverse cardio- and cerebrovascular events.

Conversely, the groups did not differ regarding the rate of cardiovascular death. These results are in line with those of a previous meta-analysis that reported reduced rates of myocardial infarction with no change in cardiovascular mortality among elderly individuals receiving statins for primary prevention [16]. Our results on clinical outcomes are discordant to those of a very recent study by Ramos et al. from Spain that showed lack of statin benefit for primary prevention in individuals aged > 75 years [22]. Although the reason for this disparity is not presently clear, some differences between the two studies may partly explain it. Our study population was all Koreans; their ethnic characteristics are different from those of Western Europeans [27], which might have influenced the results. Additionally, we excluded people who have ever used statins from the no statin group and those who took statins inconsistently or with inconsistent intensity from the statin group. The study by Ramos et al. may have some differences regarding these points in the study population.

Few studies have looked into the effect of statins on all-cause mortality in elderly populations. Meta-analyses suggested that statins would not have an effect on all-cause mortality (relative risk, 0.94–0.96) in individuals aged > 65 years in the setting of primary prevention [16,28]. Among the causes of non-vascular death in our study, pneumonia and other infections were less frequent in the statin group, although the difference between groups was not significant (Supplementary Table S2). Meanwhile, a large meta-analysis covering both primary and secondary prevention data reported that statin therapy was not associated with non-vascular death or cancer [18]. The PROSPER study, which focused on primary prevention in elderly individuals, found that pravastatin reduced the incidence of cardiovascular death but was not beneficial with regard to non-vascular or all-cause mortality [17]. Although it was not specifically focused on elderly individuals, a meta-analysis revealed that simvastatin decreased all-cause mortality mainly by reducing cardiovascular mortality [29]. In the JUPITER study, rosuvastatin showed a mortality benefit in the whole study population but not in the subgroup of individuals aged > 70 years [6]. However, a significant benefit in elderly individuals could not be ruled out in sufficiently large samples. In a study that enrolled a population with wide age range, atorvastatin was found to decrease all-cause and non-vascular mortality [30]. In a very recent French study regarding elderly subjects, statin use was associated with reduction of combined outcomes of acute coronary syndrome and all-cause death in those with risk factors, but not in those without risk factors [31]. This result is concordant to that of our study analyzing elderly subjects with > 1 risk factors, although the hazard ratio was relatively lower in ours. Regarding the cause of non-cardiovascular death, infection and respiratory disease were more common among the subjects of that study, whereas cancer and pneumonia were more common among the subjects of our study. Further work may be required to clarify whether the discrepancy between these studies regarding the relationship between statin effect and cause of death is clinically relevant.

We found dramatic risk reduction with relatively small statin-induced reduction in LDL-C. Our result is similar to that of the MEGA Study in Japanese patients, which reported reduced event rates, including total mortality, with a relatively small LDL-C reduction [14]. On the other hand, a previous study in Caucasians reported uncertain clinical benefit with small LDL-C reduction [32]. Currently, there is no satisfactory existing explanation to support our results. The differences in LDL-C lowering response to same statin dose between Asians and Caucasians were observed in a few studies [33]. However, the difference is not appropriate to clarify reason underlying the similar pharmacodynamic effects with different clinical outcomes in our study. However, further studies are needed to clarify this aspect, as currently available data on statin outcomes in Asians are very limited [14]. Furthermore, our present study differs from the MEGA Study in several aspects. First, statin intensity was higher and the outcome benefit was greater in our study even though the amount of LDL-C reduction was similar to that noted in the MEGA study. However, the MEGA study enrolled subjects aged 40–70 years, whereas we only enrolled older subjects (> 75 years). While the MEGA Study also reported a tendency of greater risk reduction by pravastatin in the subgroup of subjects older than 60 years, further investigation is required to determine whether this finding is relevant to patients older than 75 years.

In the SCOPE-75 study, the relative risk of all-cause death among statin users was remarkably lowered in patients with diabetes mellitus. This finding supports a more active use of statins in diabetic individuals aged > 75 years and is concordant with observations from the Reykjavik Study. That study enrolled subjects with a mean age of 77 years and reported a greater benefit of statins in the subgroup of diabetic subjects [34]. On the other hand, the PROSPER study, which enrolled elderly subjects, reported a higher incidence of new cancers in the pravastatin group [17]. In our study, new cancers tended to occur less frequently in the statin group.

Limited data on statin treatment and clinical outcomes are available for populations in Asia, where there is a steadily increasing need for primary prevention. Thus, we expect our present results will help clinicians who are treating Asian patients. In addition, we only enrolled statin-naïve subjects. Therefore, our findings will be relevant in elderly populations requiring first-time prescription of statins. At the same time, the current study has several potential limitations. First, our study has a retrospective design and the obtained results may have limited strengths for clinical application. Furthermore, collection of outcome data using medical records and/or telephone calls can be another limitation that can lead to unintentional bias. Second, the proportion of patients who used low- or high-intensity statins was too small, and we cannot rule out the possibility that different clinical outcomes may have been detected in these groups had they been larger. In addition, we could not obtain sufficient data on safety or treatment discontinuation rate. Some reports have suggested that drug discontinuation is more frequent in elderly populations. Safety data would help evaluate the net clinical benefit. Future research should account for these aspects. Third, since cardiovascular risk increases nonlinearly with age, particularly in age > 65 years, it is difficult to compare the results of groups from different trials and interpret them. This was another limitation of our study. We have summarized the characteristics and results of studies cited in our article in Supplementary Table S3. Fourth, our rate of MACCE was not lower than those of other studies [6,15,22]. However, the total number of events was small due to population size, and this can limit the strength of our data. Fifth, since the study population was enrolled over a 10-year period, changes in guidelines or major published trials might have influenced statin prescribing patterns. This can be a source for selection bias in our study. Finally, our analysis could have been more informative if we had collected data on nutritional status or nutraceuticals, which are easily found in common foods and can influence on lipid levels [35].

To conclude, we found that statin therapy for primary prevention is associated with a significantly lower risk of cardiovascular events and all-cause death in elderly individuals aged > 75 years. These results provide rare evidence on the clinical benefit of statins among elderly individuals, supporting more active use of statins in this population.

Conflicts of interest

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

Author contributions

S.-H.L. proposed the study design and provided funding; K.K. and S.-H.L. analyzed and interpreted the clinical data; C.J.L., C.-Y.S., J.-S.K., B.-K.K., S.P., H.-J.C., G.-R.H., Y.-G.K., S.-M.K., D.C., J.-W.H., M.-K.H., Y.J., and S.-H.L. provided clinical data. K.K. and S.-H.L. wrote the manuscript. All authors revised the manuscript.

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The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.02.026.

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