

Comparing different types of statins for secondary prevention of cardio-cerebrovascular disease from a national cohort study

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Abstract

Background

Statins have been recommended for use in atherosclerotic cardio-cerebrovascular disease (CCVD). The purpose of this study was to investigate the efficacy of five different types of statin in the secondary prevention of CCVD in patients.

Methods

This study has a retrospective design and utilised data from the Korean National Health Insurance Service-National Health Screening Cohort. Participants aged 40 to 69 years at baseline were categorized into five statin groups (atorvastatin, rosuvastatin, pitavastatin, simvastatin, and pravastatin). The primary composite outcome was defined as recurrence of CCVD or all causes of death. Cox proportional hazard regression models were adopted after stepwise adjustments for confounders to investigate the difference in efficacy among the different statins.

Results

Of the 755 final study participants (485: atorvastatin, 34: pitavastatin, 8: pravastatin, 96: rosuvastatin, and 132: simvastatin group), 48 patients experienced primary composite outcomes. The median follow-up duration was 12.4 years across all groups. After stepwise adjustments, the hazard ratios (95% confidence intervals) for primary composite outcomes of atorvastatin, pitavastatin, and rosuvastatin groups were 0.956 (0.456–2.005), 1.347 (0.354–5.116), and 0.943 (0.317–2.803), respectively, when compared with the simvastatin group.

Conclusions

There were no significant differences between the statins in their efficacy for preventing recurrence of CCVD events and/or death in CCVD patients. However, further large-scale clinical trials are required to confirm these results.

Introduction

According to the World Health Organization (WHO) fact sheet from 2017, atherosclerotic cardiovascular disease (ASCVD) is the number one cause of death worldwide. In addition, about 17 million people died from ASCVD in 2016, accounting for 31% of all global deaths. Of these deaths, 85% were reported to be due to a heart attack and/or stroke [1]. In Korea, the socioeconomic burden of cardio-cerebrovascular disease (CCVD) is rapidly increasing. CCVD is the second leading cause of death in Korea and accounted for one-quarter of total deaths in 2016 [2].

Strategies to prevent CCVD have important implications for substantially reducing mortality and related public health burdens. Dyslipidaemia is the most important controllable risk factor for atherosclerotic CCVD. According to several previously published cholesterol guidelines, statins, which are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are widely administered for primary and secondary prevention treatments of atherosclerotic CCVD in individuals with dyslipidaemia [3–6].

Various types of statins have been developed and approved for clinical use. Although most statins share common mechanisms of action, their pharmacokinetics and dynamics differ, and the clinical efficacy for improving patient lipid profiles and preventing ASCVD is unknown among different statins [7]. Additionally, in Korea, there is a lack of evidence on the efficacy of each statin for the secondary prevention of CCVD compared with other statins.

The purpose of this study was to investigate the relationship between the use of five different types of statins (atorvastatin, rosuvastatin, pitavastatin, simvastatin, and pravastatin) and the composite outcomes (all causes of death and/or CCVD events) in CCVD patients using the Korean National Health Insurance Service – National Health Screening Cohort (NHIS-HEALS) data set after adjusting for potential confounders.

Methods

Data source and study population

Data from the NHIS-HEALS cohort database, which was created based on general health screening examinations between 2002–2003, was used. The NHIS-HEALS cohort consists of 514794 persons and represents approximately 10% of the 5.15 million eligible health insurance holders aged 40 to 79 years. All the study participants received at least one health screening between January 2002 and December 2003. In 2015, the patients in the database received a follow-up health examination and submitted a lifestyle and behaviours survey at each screening, which included age, sex, income status, death information, medical use, and prescription details. A detailed description of the study design and methods was previously published [8].

The participants in this retrospective study were selected from the NHIS-HEALS cohort (Fig. 1). First, subjects were selected based on whether they attended a health screening since 2005 ($n = 479,959$). Next, participants were selected only if they satisfied all the following conditions: (1) a total cholesterol ≥ 250 mg/dL, (2) prescribed a statin since 2005, and (3) diagnosed with CCVD between 2002 and 2004 ($n = 5246$). For the purpose of maintain a homogeneous participant pool, subjects were excluded according to the following criteria: (1) prescribed two or more types of statins since 2005 ($n = 2403$), (2) prescribed a statin for ≤ 30 days since 2005 ($n = 395$), (3) prescribed statins which were not one of our target drugs since 2005 ($n = 18$), and (4) participants with missing data in the confounding values criterion between 2005 and 2008 ($n = 129$).

To evaluate the differences among the different types of statins, the subjects were divided into five groups: atorvastatin, pitavastatin, simvastatin, rosuvastatin, and pravastatin. Other types of statins were not considered due to their small sample population. All participants took only one type of statin in this study. Of a total of 5246 participants, 4491 subjects were excluded. Finally, 755 individuals were included in this analysis (Fig. 1).

This study was approved by the Institutional Review Board of Chungbuk National University Hospital (CBNUH-2019-07-013-001) and followed the guidelines of the Declaration of Helsinki (1975). The Ethics Committee of National Health Insurance Service waived the necessity for informed consent because data from NHIS-HEALS were anonymized at all stages, including during data clearing and statistical analyses.

Operational definition

In this study, we defined CCVD patients as those having had at least one inpatient or outpatient record with primary diagnostic codes, I20–I25 and I60–69, from the 10th edition of the International Classification of Disease codes (ICD-10th codes). The primary composite outcome in this study was defined as recurrence of CCVD with ICD-10th codes I21-24, I63, I65, and I66 and/or all causes of death since 2005. For further analysis, CCVD events were as considered as secondary outcomes.

Study period

The start date of the study was the first diagnosis date of CCVD. For subjects who had recurrence or death, the end date was the first recurrence date of CCVD or death date since 2005, whichever occurred earlier. For the other subjects, the study end date was the last date of the following events: (1) the most recent date of follow-up health screening, (2) the most recent date of hospital visit, or (3) the most recent date of statin administration.

Potential confounders

In this study, the following variables were considered as confounding variables: age, body mass index (BMI), systolic blood pressure (SBP), glucose, total cholesterol, alanine aminotransferase (ALT) levels, a past history of diabetes mellitus (DM), smoking status, drinking status, physical activity, and economic status. These confounding variables were obtained from the first health screening record. A past history of DM, smoking status, drinking status, physical activity, and economic status were classified as categorical variables; the remaining confounding variables were classified as continuous. The categorical variables, except for economic status, were extracted from self-reporting questionnaires and were recategorized for statistical analysis purposes: participants who answered “Yes” to “Have you ever been diagnosed with diabetes?” were classified as “DM”; smoking status was classified into two groups: “ever smokers” and “non-smokers”; drinking status was divided into three groups: “rare” (less than twice per month), “sometimes” (twice per month to twice per week), and “often” (more than twice per week); physical activity was classified into three groups: “rare” (individuals who did not exercise), “sometimes” (exercise between 1 and 4 days per week), and “regular” (exercise more than 4 days per week); economic

status was categorized into three groups: “low” (\leq 30th percentile), “middle” ($>$ 30th to \leq 70th percentile), and “high” ($>$ 70th percentile).

Statistical analysis

Continuous variables are expressed as mean \pm standard error (SE), while categorical variables are expressed as a percentage of the cohort. To evaluate the differences among the different types of statins, analysis of variance (ANOVA) and Fisher's exact tests were used. Kaplan-Meier methods and log rank test estimates were used to compare the prevention of CCVD effects by individual statin types. Cox proportional hazard (Cox-PH) models were performed to estimate the hazard ratios (HRs) for primary composite outcomes. In this study, the Cox-PH models were performed at three levels: model 1: age; model 2: age, smoking status, drinking status, and physical activity; and model 3: all variables in model 2 and included past history of DM, economic status, BMI, SBP, ALT, and total cholesterol. All statistical tests were two-sided, and p-values were defined as statistically significant if they were less than 0.05. The statistical package, SAS Enterprise Guide version 7.1 (SAS Inc., Cary, NC, USA), and R (R Core Team, Vienna, Austria) were used to perform the analyses in this study.

Results

Of the 755 final participants in this study (485: atorvastatin, 34: pitavastatin, 8: pravastatin, 96: rosuvastatin, and 132: simvastatin), 48 patients experienced the primary composite outcome during the study duration and accounted for 6.36% of the study population. The median follow-up duration was 12.4 years.

The baseline characteristics of the study participants according to their placement within five different statin groups are summarized in Table 1. All variables considered for this study were not significantly different among the five different statin groups. Although not statistically significant, individuals treated with simvastatin were the oldest, while patients in the pravastatin group were the youngest (Table 1). Total cholesterol levels were highest in pravastatin group and lowest in the rosuvastatin group. The prevalence of DM was more than 15% across all statin groups.

Table 1

Baseline characteristics according to statin type. Total number of participants in study: 755. BMI: body mass index; SBP: systolic blood pressure; ALT: alanine aminotransferase; DM: diabetes mellitus

	Atorvastatin	Pitavastatin	Rosuvastatin	Simvastatin	Pravastatin	p-value
Number of patients	485	34	96	132	8	
Age, years	55.4 ± 6.6	55.0 ± 6.5	54.3 ± 6.2	56.5 ± 7.1	52.3 ± 6.9	0.081
BMI, kg/m ²	24.8 ± 2.8	23.8 ± 2.6	24.0 ± 3.1	24.6 ± 2.9	24.6 ± 3.9	0.060
SBP, mmHg	126.4 ± 16.0	131.9 ± 17.0	124.8 ± 15.8	125.9 ± 15.8	126.3 ± 19.7	0.267
Glucose, mg/dL	96.5 ± 22.8	95.8 ± 15.5	96.2 ± 17.1	100.4 ± 31.0	94.4 ± 20.9	0.522
Total cholesterol, mg/dL	235.7 ± 50.1	240.1 ± 32.2	230.9 ± 32.4	240.7 ± 45.8	248.8 ± 27.7	0.504
ALT, IU/L	25.4 ± 14.8	22.5 ± 8.9	28.1 ± 26.6	28.5 ± 18.4	21.3 ± 13.2	0.151
DM, N (%)	99 (20.4)	10 (29.4)	15 (15.6)	39 (29.5)	2 (25.0)	0.066
Ever smokers, N (%)	101 (20.8)	7 (20.6)	25 (26.0)	33 (25.0)	1 (12.5)	0.669
Drinking status, N (%)						0.759
Rare	324 (66.8)	26 (76.5)	71 (74.0)	92 (69.7)	7 (87.5)	
Sometimes	125 (25.8)	7 (20.6)	18 (18.8)	28 (21.2)	1 (12.5)	
Often	36 (7.4)	1 (2.9)	7 (7.3)	12 (9.1)	0 (0.0)	
Physical activity, N (%)						0.741
Rare	229 (47.2)	18 (52.9)	49 (51.0)	66 (50.0)	3 (37.5)	
Sometimes	195 (40.2)	13 (38.2)	36 (37.5)	44 (33.3)	3 (37.5)	
Regular	61 (12.6)	3 (8.8)	11 (11.5)	22 (16.7)	2 (25.0)	
Economic status, N (%)						0.541
Low	103 (21.2)	5 (14.7)	19 (19.8)	32 (24.2)	3 (37.5)	
Middle	174 (35.9)	9 (26.5)	29 (30.2)	47 (35.6)	2 (25.0)	
High	208 (42.9)	20 (58.8)	48 (50.0)	53 (40.2)	3 (37.5)	

The findings of Cox-PH models for the primary composite outcomes are presented in Table 2. Compared with simvastatin group, the HRs (95% confidence intervals [CIs]) for the primary composite outcomes of atorvastatin, pitavastatin, and rosuvastatin group were 0.875 (0.426–1.794), 1.238 (0.339–4.521), and 0.788 (0.267–2.323), respectively, after adjusting for age (Cox-PH model 1). After fully adjusting for age, smoking status, drinking status, physical activity, BMI, SBP, total cholesterol, ALT, economic status, and DM, the HRs (95% CIs) of atorvastatin, pitavastatin, and rosuvastatin were 0.956 (0.456–2.005), 1.347 (0.354–5.116), and 0.943 (0.317–2.803), respectively (Cox-PH model 3). In the pravastatin group, the number of outcome events was insufficient; thus, there were no statistically reasonable results. The association between different statin types and recurrence of CCVD events are shown in Table 3. Compared with simvastatin, after fully adjusting for confounders, the HRs (95% CIs) in atorvastatin, pitavastatin, and rosuvastatin were 1.031 (0.479–2.220), 1.412 (0.366–5.449), and 1.031 (0.340–3.123), respectively.

Table 2

Cox-proportional hazard regression models for primary composite outcomes for each statin compared with simvastatin. HR: hazard ratio; CI: confidence interval

Model	Statin	HR (95% CI)
1	Atorvastatin	0.875 (0.426–1.794)
	Pitavastatin	1.238 (0.339–4.521)
	Rosuvastatin	0.788 (0.267–2.323)
	Pravastatin	N/A
2	Atorvastatin	0.900 (0.435–1.862)
	Pitavastatin	1.255 (0.342–4.603)
	Rosuvastatin	0.753 (0.254–2.232)
	Pravastatin	N/A
3	Atorvastatin	0.956 (0.456–2.005)
	Pitavastatin	1.347 (0.354–5.116)
	Rosuvastatin	0.943 (0.317–2.803)
	Pravastatin	N/A
Model 1: adjusted for age		
Model 2: adjusted for sex and smoking status (ever- and never-smokers), drinking status (rare, sometimes and often) and physical activity (rare, sometimes and regular) in addition to the age variable considered in Model 1		
Model 3: adjusted for body mass index, systolic blood pressure, total cholesterol, alanine aminotransferase, economic status (low, middle and high), and diabetes (yes or no), in addition to the variables considered in Model 2		

Table 3

Cox-proportional hazard regression models for the recurrence of cardio-cerebrovascular events for each statin compared with simvastatin. HR: hazard ratio; CI: confidence interval.

Outcome	Statin	HR (95% CI)
Cardio-cerebrovascular events	Atorvastatin	1.031 (0.479–2.220)
	Pitavastatin	1.412 (0.366–5.449)
	Rosuvastatin	1.031 (0.340–3.123)
	Pravastatin	N/A
Adjusted for age, sex, smoking status (ever and never smokers), drinking status (rare, sometimes, and often), physical activity (rare, sometimes, and regular), body mass index, systolic blood pressure, total cholesterol, alanine aminotransferase, economic status (low, middle, and high), and diabetes (yes or no)		

The survival analysis was performed by the Kaplan-Meier method and log rank test to estimate the five statins' effects on the primary composite outcomes and recurrence of CCVD events in Fig. 2. There were no statistically significant differences between different types of statin (p-values > 0.05).

Discussion

The present study is a retrospective national cohort study that compared the efficacy of secondary prevention for CCVD among different types of statins using claim data from the NHIS in Korea. This study shows that there was no significant difference to prevent the recurrence of CCVD and/or death among five different types of statin in CCVD patients.

Statins were classified into three groups according to their reported LDL-cholesterol lowering intensity. Its intensity will depend on the individual dose, but in general, atorvastatin, and rosuvastatin belong to moderate to high intensity groups, and the remaining statins are classified as low or moderate intensity groups [9]. The 2018 American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend that patients with clinical atherosclerotic CCVD should reduce their LDL-cholesterol with either a high-intensity statin therapy or via a maximum tolerated statin therapy [10]. Due to their efficacy and safety, statins are widely administered for primary and secondary prevention treatment of ASCVD in individuals with dyslipidaemia [3–6].

Different types of statins have different pharmacokinetics, as well as, varied clinical efficacies to improve patient lipid profiles and to prevent ASCVD [7]. In particular, the degree of LDL-cholesterol reduction achieved with statins appears different among Asian and Western patients. Asian CCVD patients often have an increased response to statins. As a result, recommended drug dosages often tend to be lower in Asian countries than in Western countries [11]. However, there is insufficient evidence to directly compare the efficacy of different statins in the secondary prevention of CCVD events [12]. Moreover, the efficacy of reducing LDL-cholesterol and increasing HDL-cholesterol varies from statin to statin. Pitavastatin is

classified as a moderate- to low-intensity statin [9], but its effect on HDL-cholesterol elevation is reported to be superior to those of atorvastatin, rosuvastatin, and simvastatin [13–15].

The results of this study show that there is no difference in secondary prevention effect between different types statins. This may be due to a more complex mechanism in which statins reduce recurrence of CCVD events in apparently healthy individuals beyond LDL-cholesterol reduction and HDL-cholesterol elevation [16, 17]. Statins inhibit HMG-CoA reductase activity in the mevalonate pathway. The mevalonate pathway produces mevalonic acids, which are precursors of cholesterol and some non-sterol isoprenoid derivatives. Isoprenoid derivatives play an important role in the regulation of various cellular functions including proliferation, differentiation, and survival [18, 19]. As a result, statins inhibit the production of isoprenoid intermediates in the cholesterol biosynthetic pathway. Therefore, statins are known to be pluripotent in their ability to modulate cell signalling and to reduce oxidative stress and pro-inflammation [20]. In addition, since the data used in this study was obtained in a real-world setting, it is necessary to interpret the results in consideration of the respective conditions of the participants included in this study. For example, high-intensity statins may be prescribed to participants with a higher risk of CCVD, while low-intensity statins may be prescribed to participants with relatively low risk of CCVD. Lastly, information about the participants' detailed lifestyle behaviours, such as dietary patterns, were not considered because they were not available in the NHIS-HEALS database. These factors can affect the efficacy of statins, and for this reason, there may be an confounding effect in secondary prevention between different types of statin that was not accounted for – future studies should consider dietary patterns in their analysis.

There are other limitations when interpreting the results of this study. First, several potentially confounding factors have been adjusted, but some residual confounding effects could not be completely controlled for in this study, and include lifestyle factors and/or underlying genetic or familial conditions. We also could not include the non-statin lipid-lowering agents as confounders due to the limited availability of data. Instead of non-statin lipid-lowering agents, we adopted total cholesterol as the second-best option. Second, since the operational definition of CCVD was determined based on ICD-10th codes, the participants in the study might not match actual CCVD patients in a real-world scenario. Third, because the number of participants in each statin group in this study is relatively small, large-scale clinical trials are needed to compare the main preventive effects of each statin type on CCVD. Fourth, we could not check that statin users took their medications as prescribed. Finally, a selection bias possibly exists because several participants of NHIS-HEALS were excluded according to the inclusion and exclusion criteria.

Nevertheless, there are several strengths that distinguish this study from previous studies. Of utmost importance, we used data from a large population provided by the NHIS-HEALS, which represents the entire Korean population based on real-world measurements in the clinical setting. In addition, since this study analysed claim data that included disease diagnosis, health and lifestyle questionnaires, some blood tests, such as lipid profiling, and prescriptions, recall bias is minimized. Finally, regarding the effort to evaluate the differences in efficacy between different types of statins, all participants in this study took

only one type of statin during a relatively long study period (median follow-up duration: 12.4 years). Thus, one type of statin's long-term effect of secondary prevention was confirmed.

Conclusion

In conclusion, in this Korean study, no significant differences were observed in the efficacies for preventing the recurrence of CCVD events and/or death according to different types of statins administered to CCVD patients. However, further large-scale clinical trials regarding the beneficial effects of secondary prevention of CCVD among individual statins are required.

Declarations

Ethics approval and consent to participate :

This study was approved by the Institutional Review Board of Chungbuk National University Hospital (CBNUH-2019-07-013-001). Informed consent was waived because data analyses were performed retrospectively with anonymous data derived from the South Korean National Health Insurance Service database.

Consent for publication :

Not applicable.

Availability of data and materials :

This study used NHIS-HEALS cohort data (REQ0000037182), which were released by the National Health Insurance Service (NHIS). Access to NHIS- HEALS data are available from the website of NHIS (<https://nhiss.nhis.or.kr>).

Competing interests :

This research was funded by a grant from JW Pharmaceutical. The authors maintain that this funding did not inappropriately affect the results of this study.

Conflict of Interest:

JW Lee received a research grant from JW Pharmaceutical.

Funding :

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Authors' contributions :

JW Lee contributed to concept formation and design of the study protocol and interpretation of data. J Kim designed the study, managed data and drafted the manuscript. HS Kim managed data, suggested the analytical strategy, performed data analysis, and drafted the article. HC Lee and HT Kang contributed to concept formation and project administration. YJ Bae contributed to data curation, methodology and validation. All other authors contributed to the study design and data acquisition.

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Figures

Figure 1. Flowchart of inclusion and exclusion criteria for participant selection method.

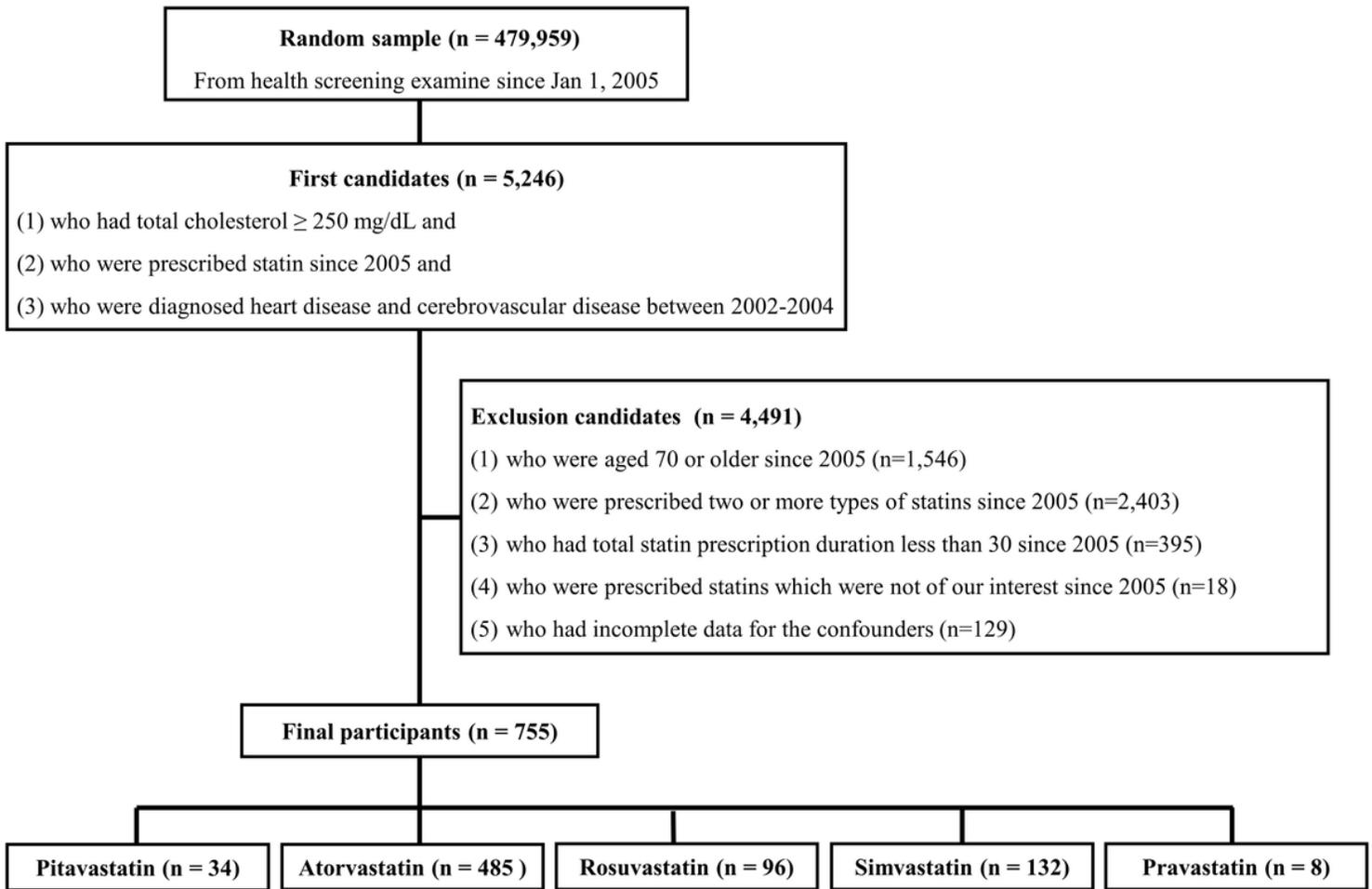
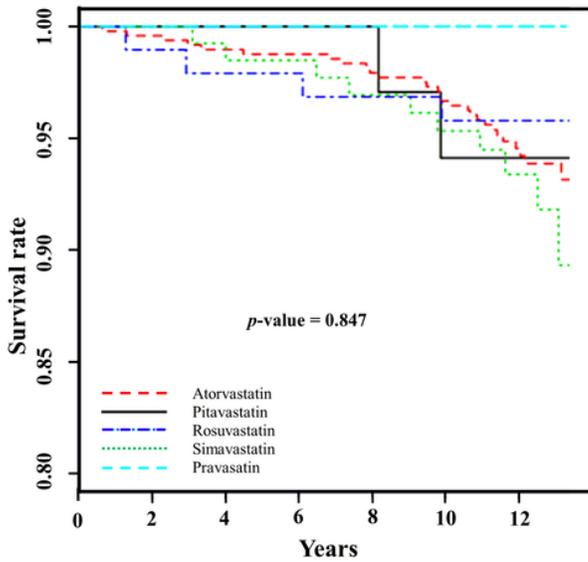


Figure 1

Flowchart of inclusion and exclusion criteria for participant selection method.

Figure 2. Kaplan-Meier estimates of primary composite outcomes and cardio-cerebrovascular events.

2A. Primary composite outcomes of all causes of death and/or recurrence of cardio-cerebrovascular disease.



2B. Recurrence of cardio-cerebrovascular events.

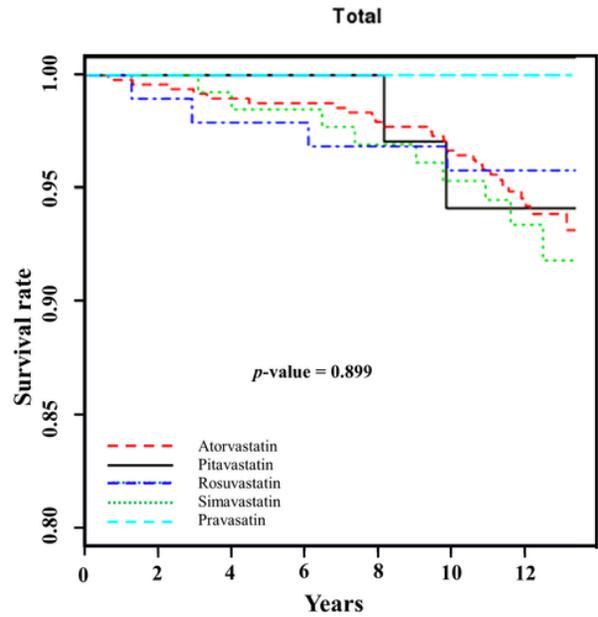


Figure 2

Kaplan-Meier estimates of primary composite outcomes and cardio-cerebrovascular events. A) Primary composite outcomes of all causes of death and/or recurrence of cardio-cerebrovascular disease (CCVD). B) Recurrence of cardio-cerebrovascular events.