

RESEARCH ARTICLE

Association between Aspirin Therapy and Clinical Outcomes in Patients with Non-Obstructive Coronary Artery Disease: A Cohort Study

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Data Availability Statement: Due to ethical and legal restrictions, relevant data are available upon request from the Health Insurance Review and Assessment Service (HIRA) website by filling out the End User Agreement of the Patient Samples, or through the following contact information: HIRA website/government 3.0 information open/application for the use of medical information/sample data (<http://www.hira.or.kr/dummy.do?pgmid=HIRAA070001000312&cmsurl=/cms/open/02/01/02/index.html>). Tel: +82-2-2182-2601 E-mail: kshyun84@hiramail.net For more details, we added

Abstract

Background

Presence of non-obstructive coronary artery disease (CAD) is associated with increased prescription of cardiovascular preventive medications including aspirin. However, the association between aspirin therapy with all-cause mortality and coronary revascularization in this population has not been investigated.

Methods and Findings

Among the cohort of individuals who underwent coronary computed tomography angiography (CCTA) from 2007 to 2011, 8372 consecutive patients with non-obstructive CAD (1-49% stenosis) were identified. Patients with statin or aspirin prescription before CCTA, and those with history of revascularization before CCTA were excluded. We analyzed the differences of all-cause mortality and a composite of mortality and late coronary revascularization (>90 days after CCTA) between aspirin users (n=3751; 44.8%) and non-users. During a median of 828 (interquartile range 385–1,342) days of follow-up, 221 (2.6%) mortality cases and 295 (3.5%) cases of composite endpoint were observed. Annualized mortality rates were 0.97% in aspirin users versus 1.28% in non-users, and annualized rates of composite endpoint were 1.56% versus 1.48%, respectively. Aspirin therapy was associated with significantly lower risk of all-cause mortality (adjusted HR 0.649; 95% CI 0.492–0.857; p=0.0023), but not with the composite endpoint (adjusted HR 0.841; 95% CI 0.662–1.069; p=0.1577). Association between aspirin and lower all-cause mortality was limited to patients

the following manuscript on the guide for the utilization of HIRA claims data as a reference. - Kim L et al. *Epidemiol Health*. 2014 Jul 30;36:e2014008. - A guide for the utilization of Health Insurance Review and Assessment Service National Patient Samples.

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with age ≥ 65 years, diabetes, hypertension, decreased renal function, and higher levels of coronary artery calcium score, low-density lipoprotein cholesterol and high-sensitivity C-reactive protein.

Conclusions

Among the patients with non-obstructive CAD documented by CCTA, aspirin is associated with lower all-cause mortality only in those with higher risk.

Introduction

Coronary computed tomography angiography (CCTA) has been advocated as a useful diagnostic imaging test that provides anatomical evidence of coronary atherosclerosis. Especially among the patients with suspected coronary artery disease (CAD), CCTA could serve as a gate-keeper of downstream management including invasive coronary angiography or intervention.[1] With the increasing use of CCTA, more patients with non-obstructive CAD are being detected. Patients with non-obstructive CAD occupy 15%-30% of symptomatic subjects and 16% of asymptomatic subjects referred to CCTA.[2-4] Because non-obstructive CAD is frequently associated with the presence of vulnerable plaque, patients with non-obstructive CAD are at higher risk of mortality and cardiovascular events than those without.[2, 5-7] Despite the prevalence and the risk of non-obstructive CAD, appropriate management strategy is not established.

Several studies indicated that the detection of CAD by CCTA leads to more prescription of cardiovascular preventive therapies such as aspirin, statin, and anti-hypertensive medications.[8-10] Even without obstructive lesion that might cause myocardial ischemia, prescription of these preventive medications was significantly increased and intensified after CCTA in patients with non-obstructive CAD. The intensified statin and anti-hypertensive medications demonstrated improved cholesterol profile and blood pressure (BP), suggesting that the detection of non-obstructive CAD followed by increased preventive medications may lead the patients to better outcome.[9, 10] However, the effect of aspirin therapy in patients with non-obstructive CAD has not been established.[11-13]

In this study, we investigated the association between aspirin therapy and risk of all-cause mortality and a composite of mortality and coronary revascularization in patients with non-obstructive CAD (1-49% stenosis) documented by CCTA.

Methods

Ethics statement

This study followed the principles of the Declaration of Helsinki and was approved by the institutional review board of Seoul National University Hospital (H-1207-080-418). Because the records and information of study population were anonymized and de-identified for matching with the third party claims data, the requirement of informed consent for each individual was waived by the institutional review board.

Study population

A detailed study protocol was published in our previous paper.[14] In brief, we identified a total of 8,372 consecutive patients with non-obstructive CAD (1-49% stenosis) among the cohort of 47,708 consecutive individuals who underwent CCTA at Seoul National University

Hospital, Seoul National University Bundang Hospital, or Seoul National University Hospital Healthcare Gangnam Center from January 2007 to December 2011 (Fig 1). Patients for whom statin or aspirin was prescribed before CCTA (n = 10,316), and the patients who had prior coronary revascularization (n = 354) were excluded, to remove patients with existing coronary heart disease. We also excluded the patients with obstructive CAD ($\geq 50\%$ stenosis; n = 3,095) or normal CCTA results (0% stenosis; n = 25,571).

Source of data

Using the electronic medical records, we obtained the resident registration numbers of study population with demographic factors and laboratory test results. The medical record

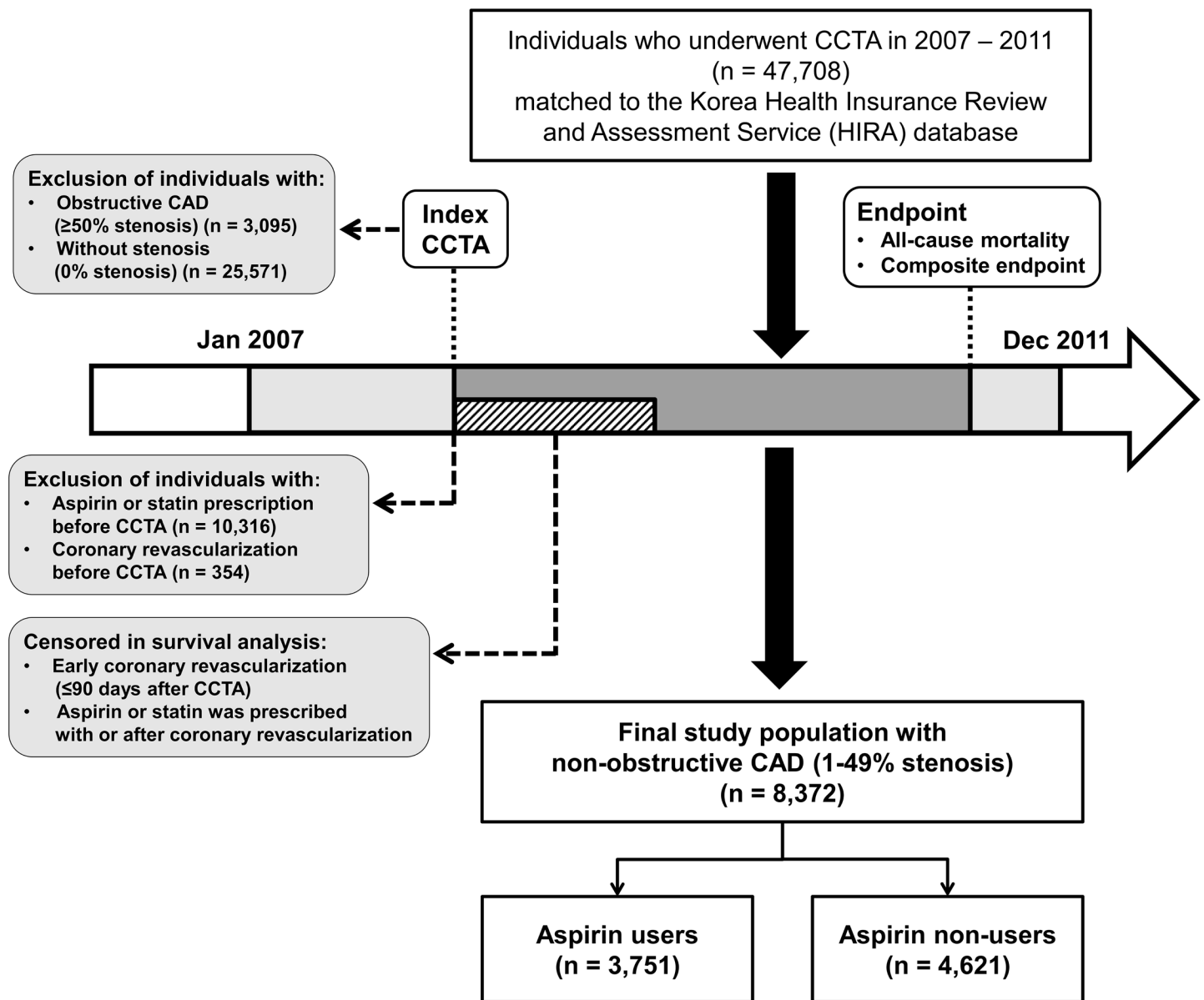


Fig 1. Selection of study population.

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information of study population was linked to the Health Insurance Review and Assessment Service (HIRA) claims data. Since HIRA has the universal coverage of the entire Korean population, it contains all information of medical service that was provided to each individual, including date, site, medications, diagnosis, procedures, hospitalization and survival.[14–17] Given that the novel antiplatelet agents such as ticagrelor and prasugrel were approved by Korean Food and Drug Association in 2013 after the study duration, information on these agents were not identified.

Personal information of study population was concealed, and an unidentifiable code was used for matching of the database. The matched data were kept securely at HIRA database. To confirm mortality cases and the accurate date of death, the HIRA data was cross-checked with the database from the Korean Ministry of Security and Public Administration.

Outcome measures

The primary outcome measure was all-cause mortality during follow-up period, and the secondary outcome was a composite of all-cause mortality and late coronary revascularization (>90 days after CCTA; including percutaneous coronary intervention and coronary artery bypass graft operation). The date of initial CCTA was used as the index date to calculate the time to study outcomes, and follow-up duration of each patient was counted according to the first to event occurrence order. To minimize verification bias, patients who underwent early coronary revascularization (≤ 90 days after CCTA) and the patients for whom statin or aspirin was prescribed with or after coronary revascularization were treated as censored at the time of revascularization.[18]

Coronary CT angiography

Patients underwent 64-slice multidetector CT (SOMATOM Sensation 64 and SOMATOM Definition, Siemens Medical Solutions, Forchheim, Germany; Brilliance 64, Philips Medical Systems, Best, The Netherlands). For patients with a prescanning heart rate of 65–70 beats/minute or higher, 50–100 mg of oral metoprolol or 10–30 mg of intravenous esmolol was given 45–60 minutes prior to the CT examination, unless the patient had any contraindication to beta-blockers. During the image acquisition, 60–80 mL of contrast was injected, followed by a saline flush. CCTA was performed using the retrospective electrocardiography (ECG)-gated mode with ECG dose modulation, covering from the diaphragm to the level of tracheal bifurcation in caudocranial direction. The results of CCTA transferred to an external workstation and analyzed by 2 experienced radiologists independently. Coronary artery calcium scores (CACs) were measured using the previously described scoring system by Agatston *et al.*[19] The results of CCTA were classified as normal (0% stenosis), non-obstructive (1–49% stenosis) and obstructive ($\geq 50\%$ stenosis), according to the maximal stenosis of left main, left anterior descending, left circumflex, and right coronary arteries.

Statistical analysis

Categorical variables were presented as frequencies with percentages, and continuous variables as means with standard deviations (SD) or medians with interquartile ranges (IQR). Group comparisons were performed by the use of Student's independent t-test for continuous variables and the chi-square test for categorical variables. Survival analysis was performed using Kaplan–Meier method with log-rank test and Cox proportional hazard regression analysis for comparison of time to event outcomes. Univariable Cox proportional hazard regression analyses were performed to identify independent predictors of study outcomes, and all baseline characteristics and the data of medication prescriptions were considered as covariates for

adjustment in multivariable Cox proportional hazard regression analyses. Data of laboratory tests were not entered into the multivariable regression model, because these parameters were incomplete in a small portion of the entire cohort. We performed subgroup analysis according to the age of 65 years, gender, and presence of diabetes or hypertension. For each subgroup, multivariable Cox proportional hazard regression analysis was performed using the baseline characteristics and medication prescriptions as covariates. Also, we added subgroup analysis according to CACS or results of laboratory tests among those each data was available: 7,488 patients for subgroup analysis by CACS; 7,015 patients by low-density lipoprotein cholesterol (LDL-C); 6,858 patients by high-sensitivity C-reactive protein (hsCRP); and 7,833 patients by glomerular filtration rate (GFR) calculated by the Modification of Diet in Renal Disease study equation. All statistical analyses were performed with software SAS 9.3 (SAS Institute Inc, Cary, NC, USA), and a P-value of <0.05 were considered statistically significant.

Results

Baseline characteristics

Demographic characteristics, the results of laboratory tests and CACS are summarized according to the use of aspirin (Table 1). Mean age of the total study population was 61.4 years (SD 10.9) and 70.3% were male. Aspirin was initiated after CCTA in 3751 (44.8%) patients. Compared to the aspirin non-users, aspirin users were older, with more frequent comorbidities and medication prescriptions, except the prevalence of liver cirrhosis and previous malignancies that were not different between the 2 groups. Of note, the proportion of patients with cerebrovascular disease was higher in the aspirin users (29.9% in aspirin users versus 13.8% in non-users; $P < 0.0001$), and the proportion of patients on clopidogrel was also higher in the aspirin users (20.8% versus 6.7%; $P < 0.0001$). Baseline fasting serum glucose and hemoglobin A1c were higher, and GFR was lower in aspirin-users. CACS was higher in the aspirin users.

Association between aspirin use and study outcomes

During the 828 days of follow-up duration (IQR 385–1,342), 221 (2.6%) cases of all-cause mortality and 295 (3.5%) cases of the composite of all-cause mortality and late coronary revascularization were observed (Table 1). Annualized mortality rate was 0.97% in aspirin users and 1.28% in non-users. Multivariable Cox proportional hazard regression analysis showed that the use of aspirin after CCTA was significantly associated with lower risk of all-cause mortality (adjusted hazard ratio [HR] 0.649; 95% CI 0.492–0.857; $P = 0.0023$; Fig 2A and Table 2). For the composite endpoint, annualized event rate was 1.56% in aspirin users and 1.48% in non-users. In total study population, aspirin therapy was not associated with lower risk of the composite endpoint (adjusted HR 0.841; 95% CI 0.662–1.069; $P = 0.1577$; Fig 2B and Table 3).

Subgroup analyses

Although aspirin therapy was associated with lower risk of all-cause mortality, the effects were not consistent among the dichotomous subgroups (Figs 3 and 4). Patients with age ≥ 65 years, diabetes, hypertension, CACS ≥ 100 , LDL-C ≥ 100 or ≥ 130 mg/dL, hsCRP ≥ 2 mg/L, or GFR < 60 mL/min/1.73m² showed significant association between aspirin therapy and lower risk of all-cause mortality, but the other subgroups did not. Similarly, overall beneficial effect of aspirin was not significant for the composite endpoint. However, prescription of aspirin after CCTA was significantly associated with lower risk of the composite endpoint among the patients with age ≥ 65 years, hypertension, higher hsCRP (≥ 2 mg/L) and lower GFR (< 60 mL/min/1.73m²), and also the diabetic patients with a trend for a lower risk of composite endpoint.

Table 1. Baseline characteristics of total study population.

	Total population (n = 8372)	Aspirin non-user (n = 4621)	Aspirin user (n = 3751)	P value
Age (years)	61.4±10.9	59.1±10.9	64.2±10.2	<0.0001
Male gender	5886 (70.3%)	3313 (71.7%)	2573 (68.6%)	0.0020
Diabetes mellitus	1272 (15.2%)	416 (9.0%)	856 (22.82%)	<0.0001
Hypertension	2621 (31.3%)	904 (19.6%)	1717 (45.8%)	<0.0001
Atrial fibrillation	678 (8.3%)	285 (6.4%)	393 (10.5%)	<0.0001
Heart failure	470 (5.8%)	154 (3.5%)	316 (8.4%)	<0.0001
Cerebrovascular disease	1732 (21.2%)	609 (13.8%)	1123 (29.9%)	<0.0001
COPD	2043 (25.0%)	997 (22.5%)	1046 (27.9%)	<0.0001
Liver cirrhosis	145 (1.8%)	82 (1.9%)	63 (1.7%)	0.5572
Chronic kidney disease*	122 (1.5%)	47 (1.1%)	75 (2.0%)	0.0005
History of malignancy	860 (10.3%)	470 (10.2%)	390 (10.4%)	0.7345
Medications				
Statin	1983 (23.7%)	673 (14.6%)	1310 (34.9%)	<0.0001
Clopidogrel	1089 (13.0%)	309 (6.7%)	779 (20.8%)	<0.0001
ACEi	304 (3.6%)	53 (1.2%)	251 (6.7%)	<0.0001
ARB	1126 (13.5%)	362 (7.8%)	764 (20.4%)	<0.0001
Beta blocker	839 (10.0%)	270 (5.8%)	569 (15.2%)	<0.0001
CCB	780 (9.3%)	274 (5.9%)	506 (13.5%)	<0.0001
Laboratory tests†				
Hemoglobin (g/dL)	14.5±1.6	14.6±1.7	14.4±1.6	<0.0001
Total cholesterol (mg/dL)	194.2±41.3	196.2±39.7	191.6±42.9	<0.0001
Triglyceride (mg/dL)	137.1±87.2	134.1±88.3	140.7±85.7	0.0012
HDL-C (mg/dL)	50.4±12.5	50.8±12.5	50.0±12.5	0.0133
LDL-C (mg/dL)	116.6±30.3	118.4±29.6	114.3±31.0	<0.0001
Fasting glucose (mg/dL)	102.8±29.5	100.2±26.9	106.0±32.1	<0.0001
Hemoglobin A1c (%)	6.0±1.0	5.9±0.9	6.2±1.1	<0.0001
hsCRP (mg/L)	0.6±2.3	0.6±2.4	0.6±2.2	0.9454
GFR (mL/min/1.73m ²)	77.3±17.8	79.4±18.5	74.6±16.2	<0.0001
CACS‡	94.1±221.5	67.5±163.0	128.8±276.3	<0.0001
Primary outcome				
All-cause mortality	221 (2.6%)	123 (2.7%)	98 (2.6%)	0.8891
Follow-up duration	828 (385–1342)	680 (289–1220)	1021 (522–1443)	<0.0001
Annualized mortality rate (% person-year)	1.12	1.28	0.97	
Secondary outcome				
All-cause mortality or late coronary revascularization‡	295 (3.5%)	143 (3.0%)	152 (4.1%)	0.0070
Follow-up duration	802 (367–1335)	677 (288–1220)	984 (485–1429)	<0.0001
Annualized event rate (% person-year)	1.52	1.48	1.56	

Data are mean±SD, median (IQR; Q1–Q3) or number (%).

*Chronic kidney disease was defined as estimated glomerular filtration rate (GFR) <60 mL/min/1.73m².

†Calculations of the laboratory tests and coronary artery calcium score were performed for those with available data of each component.

‡A composite of all-cause mortality and late coronary revascularization (>90 days after CCTA), including percutaneous coronary intervention and coronary artery bypass graft operation.

Abbreviations: COPD, chronic obstructive pulmonary disease; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; GFR, glomerular filtration rate; CACS, coronary artery calcium score; CCTA, coronary computed tomography angiography.

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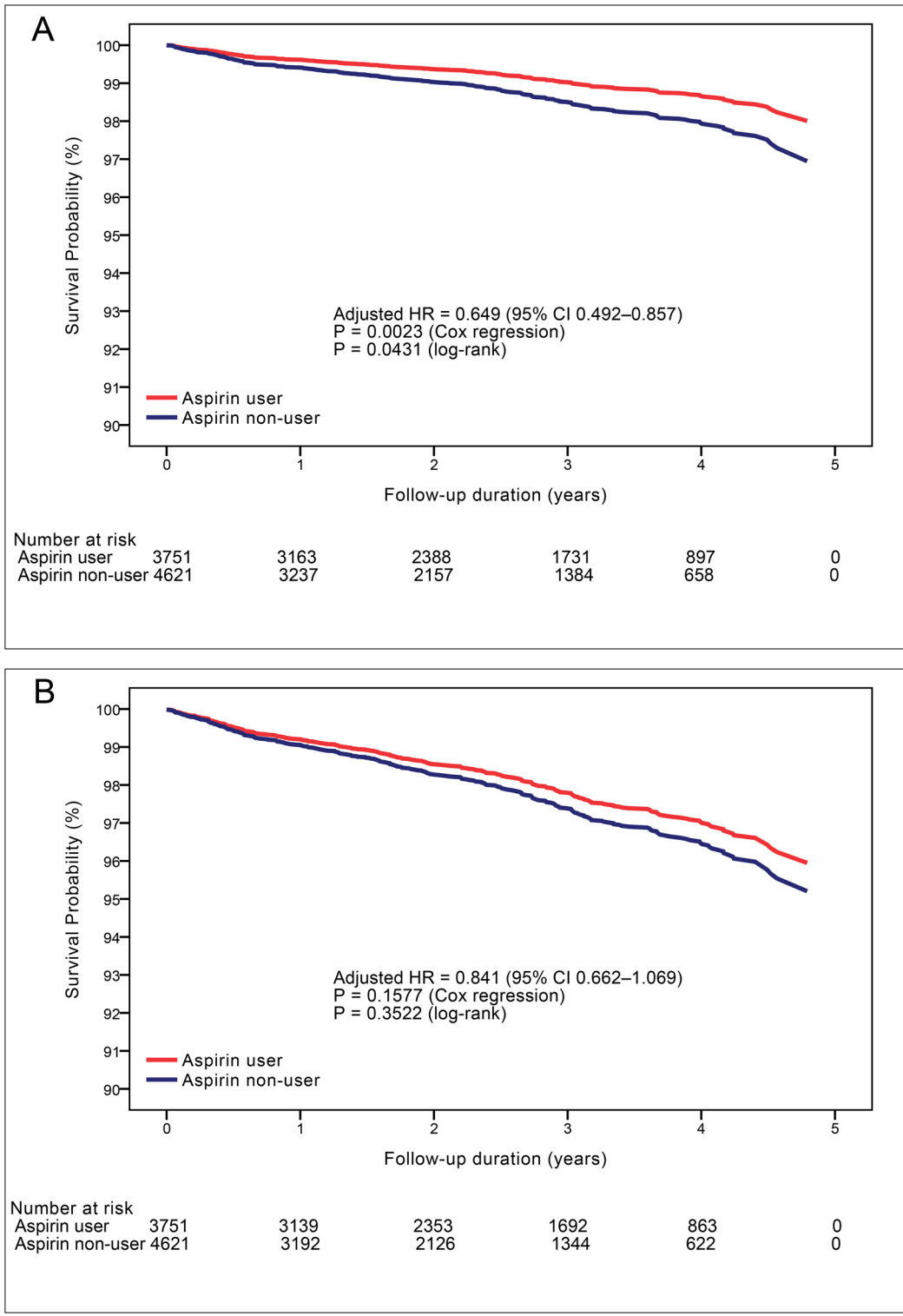


Fig 2. Risk-adjusted survival curves of aspirin users versus non-users. **A**, All-cause mortality-free survival by aspirin therapy in patients with non-obstructive coronary artery disease (1–49% stenosis). **B**, Composite endpoint (all-cause mortality or late coronary revascularization)-free survival by aspirin therapy. Survival analyses were performed using age, gender, comorbidities and concurrent medications as covariates.

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Table 2. Cox proportional hazard model for all-cause mortality.

Variables	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Age (per 1 year)	1.127 (1.113–1.142)	<0.0001	1.130 (1.115–1.144)	<0.0001
Male gender	1.880 (1.136–3.112)	0.0140	1.328 (1.003–1.758)	0.0475
Diabetes mellitus	1.257 (0.921–1.715)	0.1501	1.094 (0.793–1.511)	0.5839
Hypertension	0.724 (0.455–1.100)	0.1242	0.674 (0.411–1.103)	0.1166
Statin	0.323 (0.215–0.483)	<0.0001	0.397 (0.262–0.602)	<0.0001
Aspirin	0.760 (0.583–0.992)	0.0437	0.649 (0.492–0.857)	0.0023
Clopidogrel	0.998 (0.653–1.527)	0.9931	0.984 (0.692–1.400)	0.9303
Beta blocker	1.264 (0.784–2.038)	0.3364	1.352 (0.827–2.210)	0.2292
CCB	0.651 (0.410–1.033)	0.0683	0.665 (0.392–1.130)	0.1317
ACEi	1.035 (0.564–1.899)	0.9122	1.077 (0.556–2.087)	0.8252
ARB	0.761 (0.522–1.109)	0.1550	0.924 (0.567–1.507)	0.7526

Variables in the model are as follows: age, gender, diabetes, hypertension, and the use of statin, aspirin, clopidogrel, beta blocker, CCB, ACEi, and ARB. Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio.

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Discussion

We investigated the association between post-CCTA aspirin therapy and the risk of all-cause mortality and a composite of mortality and late coronary revascularization in 8,372 consecutive patients with non-obstructive CAD. Better clinical outcomes in aspirin users were observed in those with higher risk; the patients with age ≥ 65 years, diabetes, hypertension, decreased renal function, or higher CACS, LDL-C or hsCRP.

Currently, the use of CCTA is widely advocated not only for the detection of CAD in suspected patients but also as a reliable prognosticator and a gatekeeper for further management. [1, 20, 21] CCTA provides accurate detection of coronary atherosclerosis even in non-obstructive stage, [22] and more patients are being diagnosed as having non-obstructive CAD with the increasing use of CCTA. [2, 3, 5, 7] Because the presence of non-obstructive CAD indicates

Table 3. Multivariable Cox proportional hazard model for the composite endpoint*.

Variables	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Age (per 1 year)	1.095 (1.083–1.107)	<0.0001	1.096 (1.084–1.109)	<0.0001
Male gender	1.895 (1.213–2.961)	0.0050	1.409 (1.098–1.807)	0.0070
Diabetes mellitus	1.502 (1.160–1.945)	0.0020	1.301 (0.995–1.701)	0.0546
Hypertension	0.931 (0.734–1.180)	0.5533	0.728 (0.456–1.164)	0.1853
Statin	0.426 (0.310–0.586)	<0.0001	0.430 (0.310–0.597)	<0.0001
Aspirin	1.049 (0.834–1.319)	0.6808	0.841 (0.662–1.069)	0.1577
Clopidogrel	1.405 (0.995–1.986)	0.0537	1.200 (0.896–1.608)	0.2214
Beta blocker	1.123 (0.628–2.010)	0.6947	1.235 (0.767–1.988)	0.3853
CCB	0.747 (0.511–1.092)	0.1318	0.722 (0.472–1.104)	0.1325
ACEi	1.480 (0.929–2.358)	0.0991	1.451 (0.876–2.403)	0.1488
ARB	0.885 (0.649–1.207)	0.4390	1.028 (0.696–1.519)	0.8893

* Composite endpoint: a composite of all-cause mortality and late coronary revascularization.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio.

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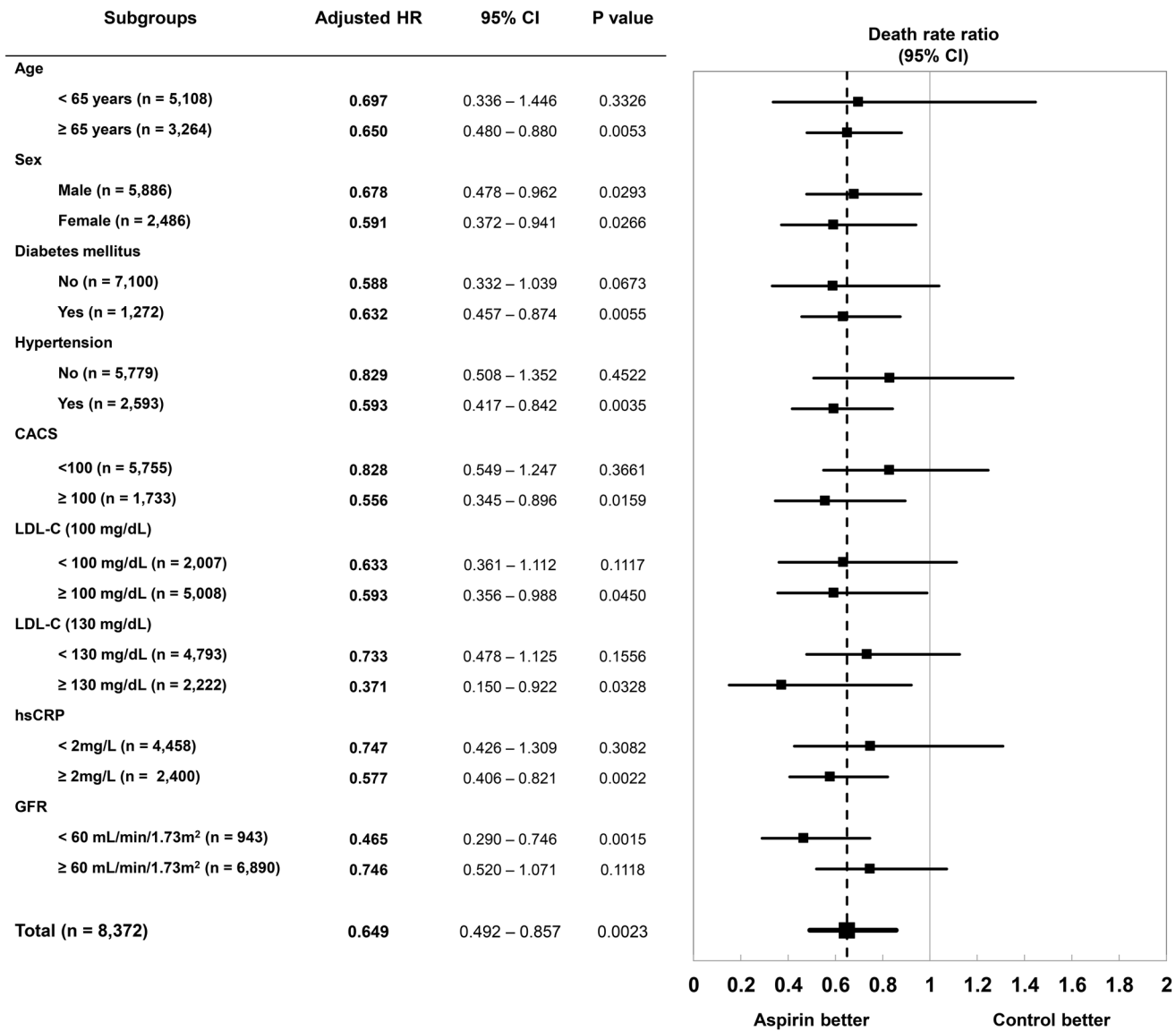


Fig 3. Association between post-CCTA aspirin therapy and all-cause mortality in subgroups. Risk-adjusted effects of aspirin therapy on all-cause mortality were analyzed in subgroups divided by age of 65 years, gender, presence of diabetes mellitus, presence of hypertension, and the results of CACS, LDL-C, hsCRP and GFR.

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higher risk of mortality and cardiovascular events,[2, 5–7] the management strategy in this population is of clinical importance.

Detection of non-obstructive CAD is associated with more prescriptions of cardiovascular preventive medications. [8–10] According to a study by *McEvoy et al*, coronary atherosclerosis detected by CCTA resulted in the increased prescription of aspirin (odds ratio [OR]; 6.8 at 90 days and 4.2 at 18 months after CCTA) and statin (OR; 4.6 at 90 days and 3.3 at 18 months after CCTA), however, the increased prescription of statin and aspirin did not reduce cardiac events.[8] Still without results on clinical outcome, *Cheezum et al* reported that the use of aspirin and statin was increased upon the detection of non-obstructive CAD (OR; 6.9 for aspirin and 6.6 for statin), followed by reductions in total cholesterol and LDL-C.[9] More recently, *Hulten and Bittencourt et al* showed the intensified preventive medical therapies with significant

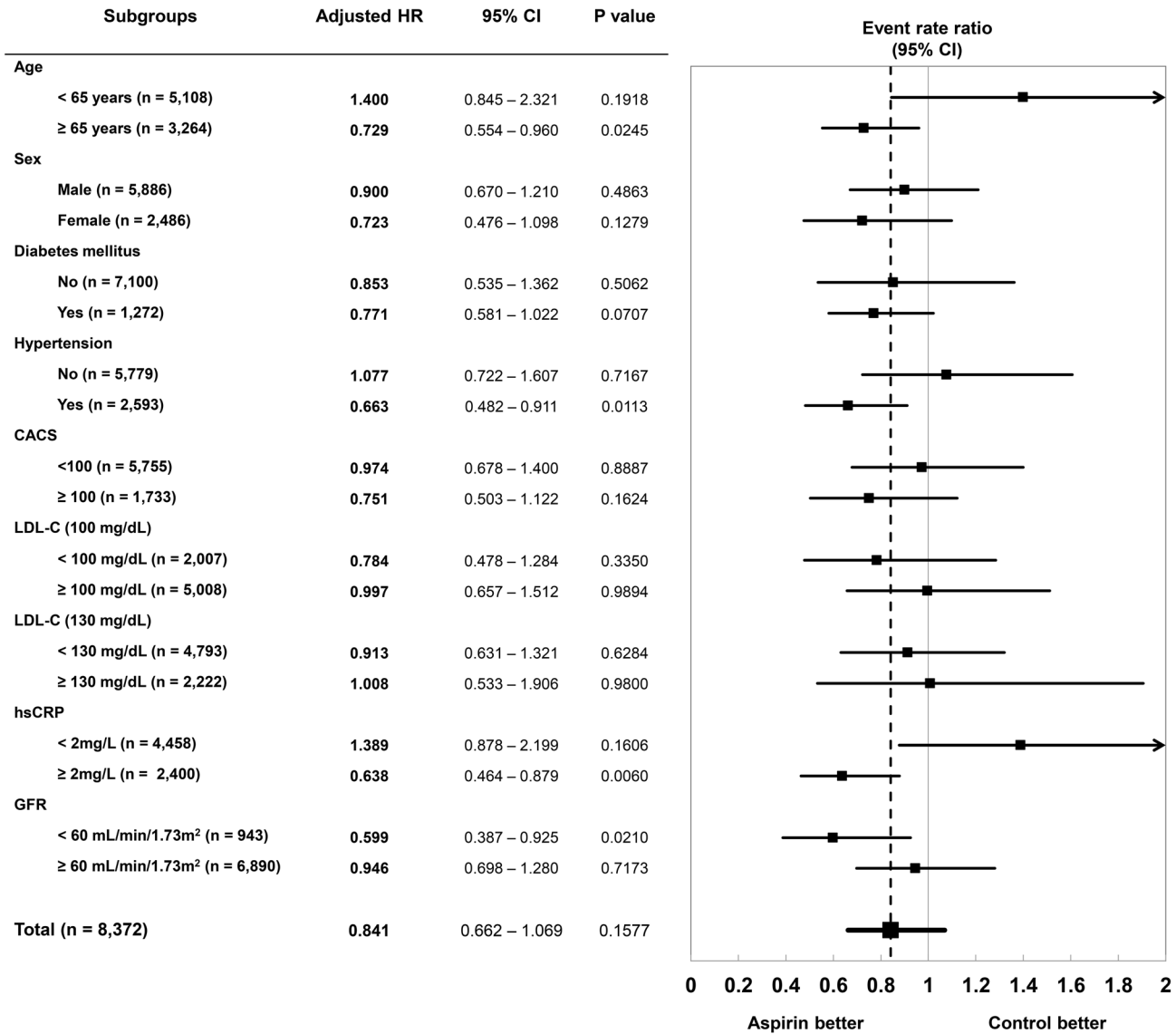


Fig 4. Association between post-CCTA aspirin therapy and the composite endpoint in subgroups. Risk-adjusted effects of aspirin therapy on the composite of mortality and late coronary revascularization (>90 days after CCTA) were analyzed in subgroups divided by age of 65 years, gender, presence of diabetes mellitus, presence of hypertension, and the results of CACS, LDL-C, hsCRP and GFR.

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improvements in lipid profile, and suggested that post-CCTA statin therapy may reduce cardiovascular events in the patients with non-obstructive CAD,[10] which was further clarified in our previous study.[14] However, there is no evidence regarding the use of aspirin in this population, which might be attributable to the lack of appropriate surrogate marker for aspirin therapy. Also, the use of aspirin confers increase in major bleeding and the net benefit of aspirin needs to be weighed between the bleeding risk and cardiovascular preventive effect, especially in patients with low risk.

Of note, the effect of aspirin for primary prevention is under debate and current guidelines advocate conflicting recommendations, because of the relatively lower event rates in the primary preventive setting and the unavoidable risk of major bleeding.[13, 23–26] Recent meta-analyses showed the benefit of aspirin on prevention of non-fatal myocardial infarction (MI), but

reductions in cardiovascular mortality or all-cause mortality were not observed, and the risk of hemorrhagic stroke or gastrointestinal bleeding was significant.[27–29] Moreover, the Japanese Primary Prevention Project (JPPP) that assessed the effect of aspirin in patients with atherosclerotic risk factors was terminated early based on a futility assessment.[30] These results indicate that the use of aspirin for primary prevention should be individualized.[23, 31]

However, the benefit of aspirin for primary prevention is obvious in certain population. A recent report from the Multi-Ethnic Study of Atherosclerosis (MESA) demonstrated the potential of CAC measurement to guide aspirin therapy for primary prevention in low risk individuals, showing the ratio of benefit on reduction of coronary heart disease versus the risk of major bleeding was favorable in those with CACS ≥ 100 but not in those with zero CAC.[32] That study emphasized the net benefit of aspirin against the bleeding risk is higher in those with higher cardiovascular risk, and also implicated the clinical application of CACS to guide the use of aspirin.[31] Long term follow-up data of the Women's Health Study also indicated that the risk of major bleeding increases with age, but the net benefit of aspirin for CVD risk is also greater at higher age.[33]

In this study, association between the use of aspirin and lower risk of mortality was observed only in subgroups with age ≥ 65 years, diabetes, hypertension, CACS ≥ 100 , LDL-C ≥ 100 or 130 mg/dL, hsCRP ≥ 2 mg/L, or GFR < 60 ml/min/1.73m². These findings suggest that aspirin therapy in patients with non-obstructive CAD is beneficial only when they are at higher risk, [34–36] which is concordant with previous studies.[37] Given the consistent benefit of aspirin on non-fatal MI as shown in previous trials,[13, 27–29] it might be reasonable to use aspirin in primary prevention for patients with higher cardiovascular risk and with evidence of coronary atherosclerosis. On the other hand, the use of aspirin in patients with non-obstructive CAD is not justifiable among those with lower risk. For these lower risk patients, the absolute benefit from aspirin therapy would be far less than those with higher risk, while the risk of bleeding outweighs the net benefit.[13] Given the increased use of preventive medical therapies upon the detection of abnormal CCTA findings without evidence in light of clinical outcomes,[8–10] our results could be applied to not only the selection of patients for aspirin therapy after CCTA, but also the prevention against unwarranted aspirin prescription as well as potential bleeding risk.

The patients with cerebrovascular disease and the patients on clopidogrel were more frequent in aspirin users. According to the major clinical guidelines that were available before or during our study period, clopidogrel monotherapy was an acceptable option for secondary prevention of ischemic stroke, and the addition of aspirin to clopidogrel was not routinely recommended for patients with ischemic stroke or transient ischemic attack because of the risk of hemorrhage, unless they have a specific indication such as coronary stent or acute coronary syndrome.[38–41] In this study, the patients for whom aspirin was prescribed before the index CCTA and the patients who had prior coronary revascularization were excluded, and the patients for whom aspirin was prescribed with or after coronary revascularization were treated as censored at the time of revascularization. Therefore, the “clopidogrel users” would mainly indicate the patients with cerebrovascular events for whom dual antiplatelet therapy was initiated after the detection of non-obstructive CAD by CCTA. Regarding the combination of aspirin and clopidogrel for secondary prevention of stroke, previous trials demonstrated no significant benefit,[42, 43] and moreover, showed higher all-cause mortality because of the increased bleeding risk.[44] Because our study mainly focused on the all-cause mortality where the risk of fatal hemorrhagic event was reflected, the inclusion of the patients with cerebrovascular disease and those on clopidogrel could enhance the practical relevance and facilitate the further studies.

Limitations

Interpretation of our results needs caution, given the following limitations. First, we could not provide information on symptomatic status, which might affect the event rates of study end-points. However, we investigated the associations between aspirin therapy and clinical outcomes in primary preventive setting through exclusion of the patients with prior history of coronary revascularization, or prescription of statin or aspirin, the patients who underwent early coronary revascularization, and those for whom statin or aspirin was prescribed with or after coronary revascularization. Together with the selection of homogenous patients with non-obstructive CAD, our results provide hypothesis-generating evidence in real-world practice. Second, cardiovascular risk estimation was not available. Although we selected homogenous patients with non-obstructive CAD and it has been suggested that the presence of coronary atherosclerosis detected by CCTA might be discordant with the estimated cardiovascular risk,^[45] the lack of 10-year risk scores limits the generalization of our study in part. Third, we could not provide data on any occurrence of major bleeding event, and therefore, quantitative comparison between the preventive effect and risk of bleeding by aspirin therapy was not possible. Because our study included the patients for whom the combination of aspirin and clopidogrel was used, our results should be interpreted with caution. However, we adopted the all-cause mortality as the main study outcome in which the fatal events from coronary heart disease or major bleeding would have been reflected. And it should be noted that, although the patients with dual antiplatelet therapy were included in the “aspirin users”, there was no reflection on the all-cause mortality, respectively the risk of bleeding. Fourth, certain information on the medications was not available, such as the compliance to aspirin therapy, the dosage of aspirin, and the use of anticoagulation. Given the recommendations from the guidelines that were available during the study period,^[38–41] and the protocol of our study that excluded the patients for whom aspirin was prescribed before the index CCTA, the majority of aspirin users would have been prescribed for low dose aspirin. However, we recognize that the specific roles of aspirin therapy among the patients with coronary atherosclerosis should be further clarified.

Conclusions

Among the patients with non-obstructive CAD (1–49% stenosis) documented by CCTA, aspirin therapy was associated with lower risk of all-cause mortality only in those with age ≥ 65 years, diabetes, hypertension, CACS ≥ 100 , LDL-C ≥ 100 or 130 mg/dL, hsCRP ≥ 2 mg/L, and GFR < 60 ml/min/1.73m².

Author Contributions

Conceived and designed the experiments: ICH JS YJK. Performed the experiments: ICH JYJ YK. Analyzed the data: ICH JYJ YK. Contributed reagents/materials/analysis tools: YJK JS. Wrote the paper: ICH YJK. Literature search: ICH HMK. Review and revise of manuscript: ICH JYJ YK HMK YEY SPL HKK DWS JS YJK.

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