Association of Mortality with Antiplatelet Treatment in Patients with Stent Placement or Angioplasty: A Population-Based Nested Case-Control Study

Ho Geol Woo[1,2]*, Hye Ah Lee[3]*, Dong-Ryeol Ryu[4], and Tae-Jin Song[1]

Departments of [1]Neurology and [4]Nephrology, Seoul Hospital, Ewha Womans University College of Medicine, Seoul;
[2]Department of Neurology, Kyung Hee University College of Medicine, Seoul;
[3]Clinical Trial Center, Mokdong Hospital, Ewha Womans University College of Medicine, Seoul, Korea.

Purpose: Antiplatelet drugs are essential in patients with cardiovascular disease who undergo stent placement. We hypothesized that risks of mortality would differ according to adherence to antiplatelet agents, number of antiplatelet agents, and antiplatelet regimens in patients undergoing stent placement or angioplasty.

Materials and Methods: Between 2002 and 2013, we initially enrolled 8671 subjects who underwent stent placement or angioplasty in the National Health Insurance Service-National Sample Cohort in Korea. Using the International Classification of Diseases, 10th revision, the incidence of all-cause death, including cardiovascular disease, cerebrovascular disease, and cancer, was defined. Using a nested case-control study design, controls were matched to cases at a ratio of 4:1, and a total of 5415 subjects were eligible for this study.

Results: During a median follow-up period of 3.51 years, the incidence rate of all-cause death was 40 per 1000 person-years. We found that adherence to antiplatelet monotherapy significantly decreased risk of death by cerebro-cardiovascular disease, compared with discontinuation of antiplatelets [adjusted odds ratio (OR) 0.62, 95% confidence interval (CI) (0.41–0.96)]. Compared with dual antiplatelet therapy (DAPT), aspirin and clopidogrel monotherapy significantly reduced death by cerebro-cardiovascular disease [adjusted OR 0.65, 95% CI (0.44–0.95) and adjusted OR 0.58, 95% CI (0.35–0.96), respectively]. There was no significant difference of mortality between aspirin monotherapy and clopidogrel monotherapy.

Conclusion: Our study demonstrated that adherence to antiplatelet therapy and antiplatelet monotherapy, compared with DAPT, in patients with stent placement or angioplasty may have a beneficial effect on mortality in cerebro-cardiovascular disease.

Key Words: Antiplatelet, stent, mortality

INTRODUCTION

Although mortality due to cardiovascular disease is generally

decreasing in both Asian and Western countries as a result of progress in medical and surgical treatments and prevention methods, including stent placement or angioplasty, cardiovascular disease remains a major cause of mortality worldwide.[1,2] Moreover, in individuals with coronary artery disease, stroke, and peripheral artery disease (PAD), mortality from non-cardiovascular etiologies can be as high as that from cardiovascular causes.[2-4] While recent clinical trials have sought to focus on morbidity and quality of life, such as recurrence of vascular disease, rather than mortality, mortality is an important outcome for both the physician and patient.[2-4]

In cardiovascular disease patients, especially patients with stent placement or angioplasty, antiplatelets are essential drugs.[5,6] Antiplatelet administration has been shown to reduce the risk

of stent thrombosis and to reduce the risk of composite cardiovascular outcomes in patients with a coronary stent placement.[7-9] In patients with PAD, treatment with high dose aspirin plus dipyridamole significantly reduced re-occlusion.[10,11] Meanwhile, dual antiplatelet therapy (DAPT) is recommended in intracranial cerebral artery atherosclerosis, regardless of best medical therapy or intracranial artery stent placement.[12] However, although previous randomized controlled trials provided high levels of evidence, the results do not necessarily reflect real-world outcomes, especially mortality, because only so-called stable or healthy patients are usually enrolled in randomized controlled studies. In a previous study of patients who underwent coronary stent placement, the rate of all-cause mortality was higher in patients on DAPT than those on mono-antiplatelet therapy (2.0% vs. 1.5%, respectively).[13] In contrast, a meta-analysis reported that extended duration DAPT was not associated with a difference in the risk of all-cause, cardiovascular, or non-cardiovascular death, compared with aspirin alone or short duration DAPT. Thus, the association between the number of antiplatelet agents or antiplatelet regimen and mortality is still unclear.

We hypothesized that risk of mortality would differ according to adherence to antiplatelet therapy, antiplatelet agent regimen, and number of antiplatelet agents in patients with stent placement or angioplasty. We, therefore, assessed the association between antiplatelet treatment strategy and mortality in cardiovascular disease patients with stent placement or angioplasty according to adherence, number of antiplatelet agents, and regimen of antiplatelet agents in the general population of South Korea using a nested case-control study design.

MATERIALS AND METHODS

Data source and study subjects

This study was conducted using data from the National Health Insurance Service (NHIS)-National Sample Cohort (NSC) version 2.0 for the Republic of Korea. A detailed description of data source of this study can be found in previous publications (Supplementary Material, only online).

For this study, we initially included subjects who underwent stent placement or angioplasty from 2002 to 2013 (n=8671) and were followed up to 2015 for enough follow up after stent placement or angioplasty. We excluded subjects aged <20 years; those who had only one-time prescription history for antiplatelet drugs after stent placement or angioplasty; those who were treated with warfarin and non-vitamin K antagonist oral anticoagulants; those with a history of atrial fibrillation [International Classification of Disease, 10th revision (ICD-10), I48]; and those who had an acute or subacute thrombus within 30 days of stent placement or angioplasty.[14] On the basis of the above criteria, a total of 5415 subjects were eligible for this study (Fig. 1). This study was approved by the Institutional Review Board of the College of Medicine, Ewha Womans University (approval number: EUMC 2018-01-056). Informed consent was waived because retrospective anonymized data were used.

Case-control selection for the nested case-control study design

In pharmacoepidemiologic studies, the nested case-control design makes it possible to quantify time-dependent drug exposure and to easily assess associations.[15] Considering the time-varying nature of antiplatelet drug use in a real setting, we selected subjects for a nested case-control study. Cases were defined as
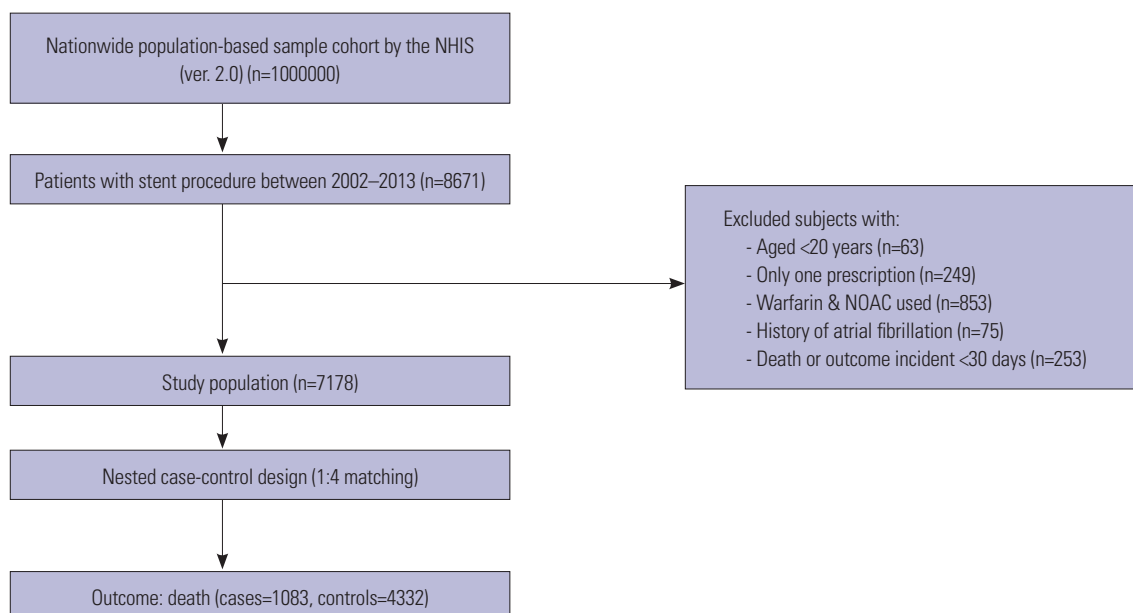

Fig. 1. Flowchart of the study participants. NHIS, National Health Insurance Service; NOAC, non-vitamin K antagonist oral anticoagulants.

subjects who died between 2002 and 2015 after stent placement or angioplasty. Date and cause of death in the NHIS-NSC version 2.0 dataset are linked to National Statistical Office/National Administrator's Data using identification numbers, such as social security numbers. This allows for accurate identification of date and cause of death. The date of death was defined as the index date of case. Controls were selected using the incidence density sampling with replacement; it chose controls among a risk set defined as non-cases who are still at risk when the case occurs. Due to the nature of this method, the index dates of controls was decided as that which provided the same follow-up period as those of the matched index cases. Moreover, studies have recommended that incidence density sampling with replacement for the nested case-control design is suitable for unbiased estimation.[16,17] For each case, we randomly selected four controls matched by sex, age at stent placement or angioplasty, and follow-up period (Fig. 1).

If a patient had more than two instances of stent placement or angioplasty between 2002 and 2013, the last procedure was used in the analysis. We used procedure codes (M6551-2 and M6561-4 for stent placement in the coronary artery, M6601-2 for stent placement in the intracranial and extracranial cerebral arteries, M6611-3 and M6603-5 for stent placement in other peripheral arteries, and M6593-7 for balloon angioplasty) and material codes (J5083 for drug eluting stent and J5231-2 for bare metal stent) to identify patients according to site of stent placement or angioplasty and type of procedure during 2002 to 2013. The ICD-10 codes used to define risk factors and concomitant diseases have been described previously.[18,19] Timing of stent placement or angioplasty was defined as the period of visit to an outpatient clinic or hospital admission shortly before stent placement or angioplasty until the time of stent placement or angioplasty. Also, intensive care unit (ICU) admission was defined as the presence of the physicians' procedure codes for intensive care (AJ001–3).[20] The primary outcome of interest was all-cause death (n=1083), whereas secondary outcomes were composite all-cause death, including death by cerebro-cardiovascular disease (n=555) and cancer (n=405). Death from cerebro-cardiovascular diseases included death due to cardiovascular disease (ICD-10, I00-I09, I11, I13, and I20-I51; n=434) and cerebrovascular disease (ICD-10, I60-I69; n=161). Cancer deaths were identified by ICD–10 underlying cause-of-death codes C00-C97. Diagnosis of cancer using the ICD-10 code had been validated by comparison with the Korean National Cancer Incidence Database.

Exposure assessments

For a total of 5415 subjects, we evaluated antiplatelet drug patterns for 2 years after stent placement or angioplasty. In the first year, the pattern was confirmed every 3 months. The pattern of antiplatelet use was defined based on the number of antiplatelet prescriptions (1 antiplatelet drug, 2 antiplatelet drugs, and ≥3 antiplatelet drugs) and drug regimen. All anti-

platelet prescriptions (aspirin, cilostazol, clopidogrel, ticlopidine, triflusal, ticagrelor, and prasugrel) for each subject were identified. To analyze the antiplatelet regimen taking into account the frequency of prescription of antiplatelets (except when the frequency of drug use was <1%), subjects were categorized according to the use of aspirin, clopidogrel, and cilostazol alone or in combination with each other. In terms of drug persistence, the "proportion of days covered" concept was applied. Thus, when the claimed prescription accounted for more than 80% of the antiplatelet drugs prescribed within the measurement period, it was defined as "continuous use" for the same drug or otherwise as "discontinuation."[21] When the claimed prescription accounted for less than 80% of the prescribed antiplatelet drugs within the measurement period, it was defined as "others or non-use." In the present study, measurement period was alternatively defined and evaluated according to the following criteria: Fig. 2A) medication pattern for 6 months from 6 months before the index date; Fig. 2B) medication pattern for 9 months starting 3 months before the index date (Fig. 2).

Statistical analysis

Basic characteristics of the study subjects are summarized as means with standard deviations for numerical variables and number of subjects with percentages for categorical variables. The significance of differences in basic characteristics between case and control groups was evaluated using independent Student's t-test and the chi-square test. To assess the effect of antiplatelet drug patterns (number and regimen) on adverse outcomes, we used logistic regression analysis and expressed the results as odds ratios (ORs) with 95% confidence intervals (CIs). Multivariable logistic regression was carried out by adjusting for covariates, including sex, age, income lev-
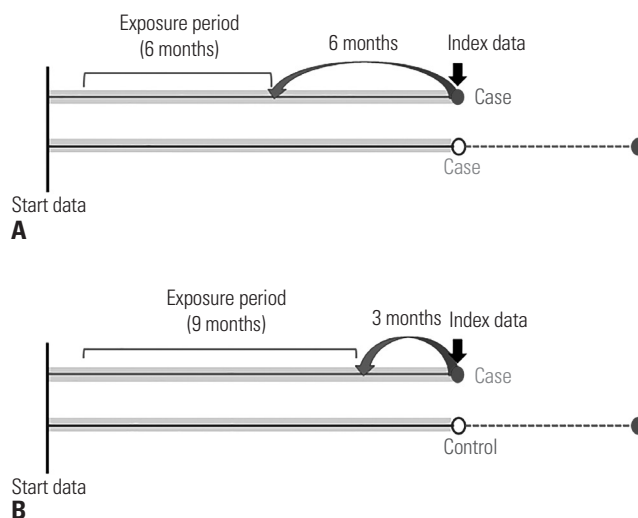

Fig. 2. Nested case-control study design. (A) Medication patterns for 6 months from 6 months before index data. (B) Medication patterns for 9 months from 3 months before index date.

el, procedure type, timing of stent replacement or angioplasty, ICU admission, baseline comorbidities (hypertension, diabetes mellitus, dyslipidemia, myocardial infarction, heart failure, stroke, chronic kidney disease, PAD, and cancer), and concomitant statin use. Moreover, adverse outcomes were compared between study patients according to number (mono, dual, and triple) and regimen (aspirin, clopidogrel, and DAPT) of medications for the periods 6 months from 6 months before the index data and 9 months from 3 months before the index date. Multicollinearity was assessed based on the variance inflation factor and had a value <6.0.

Because the majority of the included patients underwent coronary artery stent placement, subgroup analysis was performed on patients who underwent coronary artery stent placement. In addition, to reduce the possibility of grouping subjects into "others or non-use" by reducing the measurement period, the measurement period was redefined and analyzed as follows: medication pattern for 3 months from 1 month before the index date. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA), and statistical significance was set at $p>0.05$ in two-sided tests.

Table 1. Baseline Characteristics of All-Cause Mortality Cases and Their Matched Controls

| | Total (n=5415) | 1:4 matching | | p value |
		Cases (n=1083)	Controls (n=4332)	
Sex				
Male	3580 (66.11)	716 (66.11)	2864 (66.11)	>0.999
Female	1835 (33.89)	367 (33.89)	1468 (33.89)	
Age (yr)				
<45	70 (1.29)	14 (1.29)	56 (1.29)	>0.999
45–64	1095 (20.22)	219 (20.22)	876 (20.22)	
65–79	3500 (64.64)	700 (64.64)	2800 (64.64)	
≥80	750 (13.85)	150 (13.85)	600 (13.85)	
Income level				
Quintile 1	655 (13.20)	136 (13.95)	519 (13.02)	0.002
Quintile 2	589 (11.87)	137 (14.05)	452 (11.34)	
Quintile 3	659 (13.28)	151 (15.49)	508 (12.74)	
Quintile 4	1206 (24.31)	230 (23.59)	976 (24.49)	
Quintile 5	1852 (37.33)	321 (32.92)	1531 (38.41)	
Year in stent placement or angioplasty				
2002–2005	1173 (21.66)	122 (11.27)	1051 (24.26)	<0.001
2006–2009	2562 (47.31)	488 (45.06)	2074 (47.88)	
2010–2013	1680 (31.02)	473 (43.67)	1207 (27.86)	
Procedure type				
Drug eluting stent	4660 (86.06)	958 (88.46)	3702 (85.46)	<0.001
Bare metal stent	631 (11.65)	81 (7.48)	550 (12.70)	
Both (drug eluting and bare metal)	70 (1.29)	11 (1.02)	59 (1.36)	
Balloon angioplasty only	54 (1.00)	33 (3.05)	21 (0.48)	
Timing of stent placement or angioplasty	6.0 (0.0–30.0)	7.0 (0.0–62.0)	5.0 (0.0–27.0)	<0.001
Intensive care unit admission	1196 (22.09)	402 (37.12)	794 (18.33)	<0.001
Medical history				
Hypertension	3062 (56.55)	660 (60.94)	2402 (55.45)	0.001
Diabetes mellitus	1537 (28.38)	436 (40.26)	1101 (25.42)	<0.001
Dyslipidemia	538 (9.94)	87 (8.03)	451 (10.41)	0.019
Chronic kidney disease	77 (1.42)	54 (4.99)	23 (0.53)	<0.001
Peripheral artery disease	453 (8.37)	136 (12.56)	317 (7.32)	<0.001
Stroke	902 (16.66)	262 (24.19)	640 (14.77)	<0.001
Cancer	441 (8.14)	139 (12.83)	302 (6.97)	<0.001
Heart failure	279 (5.15)	91 (8.4)	188 (4.34)	<0.001
Myocardial infarction	1964 (36.27)	389 (35.92)	1575 (36.36)	0.788
Statin intake during 1 year from the index date	4442 (82.03)	806 (74.42)	3636 (83.93)	<0.001

Data are expressed as n (%).

RESULTS

Comparison of baseline characteristics

Baseline characteristics of selected cases and controls are shown in Table 1. There were no significant differences in sex or age at stent placement or angioplasty between cases and controls. Histories of hypertension, diabetes mellitus, chronic kidney disease, PAD, stroke, cancer, and heart failure were more prevalent in the all-cause death group than in the control group (all *p*<0.001). History of dyslipidemia and concomitant statin use was more prevalent in the control group than the all-cause death group (*p*=0.019 and *p*<0.001). According to site of stent placement among all included patients, 3.6% had undergone stent placement in an intracranial or extracranial artery, 88.4% had undergone coronary artery stent placement, and 7.9% had undergone stent placement in other peripheral arteries. Using drug eluting stent and ICU admission were more prevalent in the all-cause death group than in the control group (all *p*<0.001). Timing of stent placement or angioplasty was longer in the all-cause death group than in the control group (*p*<0.001).

Mortality and pattern of antiplatelet use

The incidence rate of all-cause death in this study was 40 per 1000 person-years (median follow-up: 3.51 years, interquartile range 1.64–6.00 years). Among patients with an all-cause death, 5.8% had undergone stent placement in an intracranial or extracranial artery, 80.3% had undergone coronary artery stent placement, and 13.9% had undergone stent placement in other peripheral arteries. Fig. 3 shows the pattern of antiplatelet treatment for the 2-year follow-up period after stent placement. Although 74.1% of patients at the 1-month follow-

up after stent placement were receiving DAPT, only 48.7% and 27.9% of patients at the 1-and 2-year follow-ups after stent placement were receiving DAPT. Although 3.8% of patients were on antiplatelet monotherapy and 15.6% of patients had discontinued antiplatelets at the 1-month follow-up after stent placement, these values increased to 8.9% and 38.3% of patients at 1-year follow-up and 20.3% and 49.8% of patients at 2-year follow-up after stent placement, respectively.

Mortality according to number of antiplatelet medications and treatment regimen

When analyzing adherence to medication, we found that adherence to antiplatelet monotherapy was negatively associated with risk of death by cerebro-cardiovascular disease, compared with discontinuation of antiplatelets, for 6 months from 6 months before the index date [crude OR 0.57, 95% CI (0.38–0.86), adjusted OR 0.60, 95% CI (0.38–0.96)]. This association was still evident for the 9-month time period from 3 months before the index date [crude OR 0.65, 95% CI (0.44–0.95), adjusted OR 0.62, 95% CI (0.41–0.96)] (Table 2). Moreover, we found that antiplatelet monotherapy was negatively associated with risk of all-cause death, compared with discontinuation of antiplatelets, for 9 months from 3 months before the index date [crude OR 0.75, 95% CI (0.58–0.98), adjusted OR 0.70, 95% CI (0.52–0.96)] (Supplementary Table 1, only online).

Aspirin monotherapy was negatively associated with risk of death by cerebro-cardiovascular disease, compared with discontinuation of antiplatelets, for 6 months from 6 months before the index date [adjusted OR 0.61, 95% CI (0.38–0.97)] and for 9 months from 3 months before the index date [adjusted OR 0.62, 95% CI (0.40–0.96)]. Moreover, we found that aspirin monotherapy was negatively associated with risk of all-cause
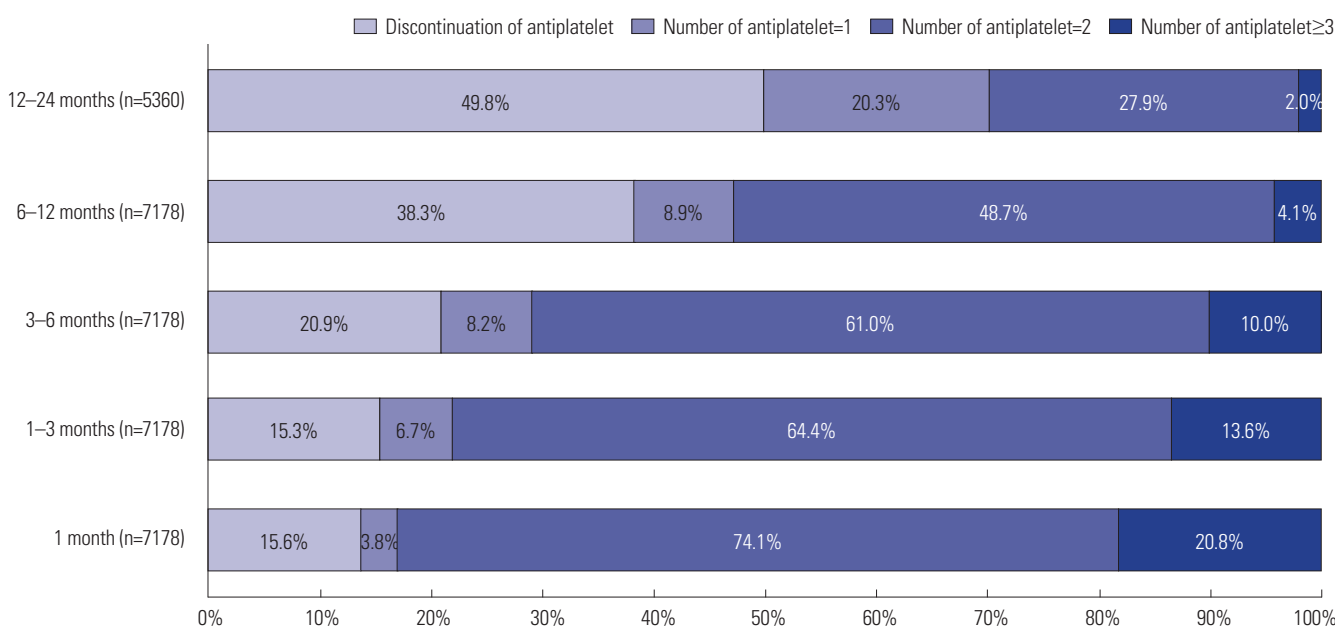

Fig. 3. Patterns of antiplatelet treatment for the 2-year follow-up period after stent placement.

death and death by cancer, compared with discontinuation of antiplatelets, for 9 months from 3 months before the index date [adjusted OR 0.71, 95% CI (0.52–0.98) and adjusted OR 0.55, 95% CI (0.33–0.91), respectively]. Clopidogrel monotherapy was negatively associated with risk of death by cerebro-cardiovascular disease, compared with discontinuation of antiplatelets, for 9 months from 3 months before the index date [adjusted OR 0.55, 95% CI (0.32–0.96)] (Table 2 and Supplementary Table 1 and 2, only online). There was no significant association between risk of death by cardiovascular disease and cerebrovascular disease and number and regimen of medication

(Supplementary Table 3 and 4, only online).

In comparisons of mortality according to number of antiplatelet agents (mono, dual, and triple) and regimen (aspirin, clopidogrel, and DAPT), we found that antiplatelet monotherapy was negatively related to risk of death by cerebro-cardiovascular disease compared with DAPT, for 9 months from 3 months before the index date [adjusted OR 0.72, 95% CI (0.52–0.99)]. Moreover, we found that aspirin monotherapy was negatively related to risk of all-cause death for 6 months from 6 months before the index date and for 9 months from 3 months before the index date [adjusted OR 0.74, 95% CI (0.57–

Table 2. Risk of Death by Cerebro-Cardiovascular Disease according to Number of Antiplatelet Medications and Regimen of Medications for 6 Months from 6 Months before the Index Date and for 9 Months from 3 Months before the Index Date

	Cases (n=555)	Controls (n=2220)	Univariable	Multivariable
	n (%)	n (%)	OR (95% CI)	OR (95% CI)
A. Medication patterns for 6 months from 6 months before the index date				
Number				
Discontinuation	42 (7.57)	141 (6.35)	Reference	Reference
1 antiplatelet drug	127 (22.88)	716 (32.25)	0.57 (0.38–0.86)*	0.60 (0.38–0.96)*
2 antiplatelet drugs	143 (25.77)	607 (27.34)	0.77 (0.52–1.14)	0.83 (0.53–1.30)
≥3 antiplatelet drugs	8 (1.44)	41 (1.85)	0.64 (0.28–1.49)	0.77 (0.30–1.93)
Others or non-use	235 (42.34)	715 (32.21)	1.68 (1.10–2.57)*	1.31 (0.78–2.19)
Regimen				
Discontinuation	48 (8.65)	156 (7.03)	Reference	Reference
Aspirin	79 (14.23)	488 (21.98)	0.50 (0.33–0.76)*	0.61 (0.38–0.97)*
Clopidogrel	37 (6.67)	187 (8.42)	0.62 (0.38–1.01)	0.63 (0.36–1.10)
Cilostazol	1 (0.18)	6 (0.27)	0.49 (0.06–4.19)	0.67 (0.07–6.38)
Aspirin+Clopidogrel	120 (21.62)	495 (22.3)	0.79 (0.54–1.15)	0.92 (0.59–1.42)
Aspirin+Cilostazol	17 (3.06)	63 (2.84)	0.83 (0.44–1.56)	0.93 (0.44–1.96)
Aspirin+Clopidogrel+Cilostazol	7 (1.26)	37 (1.67)	0.63 (0.26–1.52)	0.79 (0.30–2.07)
Others or non-use	246 (44.32)	788 (35.5)	1.33 (0.90–1.97)	1.16 (0.72–1.87)
B. Medication patterns for 9 months from 3 months before the index date				
Number				
Discontinuation	53 (9.55)	199 (8.96)	Reference	Reference
1 antiplatelet drug	123 (22.16)	701 (31.58)	0.65 (0.44–0.95)*	0.62 (0.41–0.96)*
2 antiplatelet drugs	132 (23.78)	575 (25.9)	0.86 (0.60–1.23)	0.87 (0.58–1.31)
≥3 antiplatelet drugs	7 (1.26)	37 (1.67)	0.70 (0.29–1.65)	0.78 (0.31–2.01)
Others or non-use	240 (43.24)	708 (31.89)	1.94 (1.31–2.86)*	1.33 (0.83–2.12)
Regimen				
Discontinuation	61 (10.99)	214 (9.64)	Reference	Reference
Aspirin	75 (13.51)	476 (21.44)	0.53 (0.36–0.78)*	0.62 (0.40–0.96)*
Clopidogrel	33 (5.95)	182 (8.2)	0.62 (0.38–1.00)	0.55 (0.32–0.96)*
Cilostazol	1 (0.18)	5 (0.22)	0.61 (0.07–5.32)	0.64 (0.07–6.04)
Aspirin+Clopidogrel	110 (19.82)	467 (21.04)	0.83 (0.59–1.19)	0.95 (0.64–1.42)
Aspirin+Cilostazol	16 (2.88)	61 (2.75)	0.87 (0.46–1.63)	0.90 (0.43–1.89)
Aspirin+Clopidogrel+Cilostazol	6 (1.08)	34 (1.53)	0.64 (0.25–1.61)	0.76 (0.28–2.08)
Others or non-use	253 (45.59)	781 (35.18)	1.51 (1.05–2.16)*	1.19 (0.77–1.84)

OR, odds ratio; CI, confidence interval.
Data of case and control subjects are shown as n (%). Data of regression are shown as ORs (95% CI). Multivariable model was adjusted for sex, age, income level, procedure type, timing of stent replacement or angioplasty, intensive care unit admission, baseline comorbidities (hypertension, diabetes mellitus, dyslipidemia, myocardial infarction, heart failure, stroke, chronic kidney disease, peripheral arterial disease, and cancer), and concomitant statin use.
*$p<0.05$.

0.97) and adjusted OR 0.72, 95% CI (0.55–0.95), respectively], death by cerebro-cardiovascular disease for 6 months from 6 months before the index date and for 9 months from 3 months before the index date [adjusted OR 0.66, 95% CI (0.45–0.96) and adjusted OR 0.65, 95% CI (0.44–0.95), respectively], compared with DAPT. Clopidogrel monotherapy was negatively related to risk of death by cerebro-cardiovascular disease for 9 months from 3 months before the index date [adjusted OR 0.58, 95% CI (0.35–0.96)], compared with DAPT. There was no significant difference in mortality between aspirin monotherapy and clopidogrel monotherapy (Table 3 and 4).

Subgroup analysis of patients who received stent placement in the coronary artery

We found that antiplatelet monotherapy was negatively related to risk of death by cerebro-cardiovascular disease in patients with coronary artery stent placement, compared with DAPT, for 6 months from 6 months before the index date [adjusted OR 0.69, 95% CI (0.48–0.99)]. Comparisons of mortality according to medication regimen (aspirin, clopidogrel, DAPT) in these patients revealed that aspirin was negatively related to risk of all-cause death for 6 months from 6 months before the index

date and for 9 months from 3 months before the index date [adjusted OR 0.73, 95% CI (0.54–0.98) and adjusted OR 0.72, 95% CI (0.53–0.98), respectively], death by cerebro-cardiovascular disease for 6 months from 6 months before the index date and for 9 months from 3 months before the index date [adjusted OR 0.58, 95% CI (0.38–0.88) and adjusted OR 0.58, 95% CI (0.38–0.90), respectively], compared with DAPT (Supplementary Table 5 and 6, only online).

Sensitivity analysis of medication patterns for 3 months from 1 month before the index date

To reduce the possibility of grouping subjects into "others or non-use," we analyzed medication patterns for 3 months from 1 month before the index date and found that antiplatelet monotherapy was negatively related to risk of death by cerebrovascular disease, compared with DAPT, for this time period [adjusted OR 0.41, 95% CI (0.21–0.82)]. Moreover, we found that aspirin monotherapy was negatively related to risk of all-cause death and death by cerebrovascular disease for 3 months from 1 month before the index date [adjusted OR 0.75, 95% CI (0.57–0.99) and adjusted OR 0.44, 95% CI (0.20–0.96), respectively]. Clopidogrel monotherapy was negatively related to risk of death

Table 3. Comparisons of Mortality between Study Patients according to Number (Mono, Dual, and Triple) of Medications for 6 Months from 6 Months Before the Index Data and for 9 Months from 3 Months before the Index Date

Cause of mortality	Medication patterns for 6 months from 6 months before the index date	Medication patterns for 9 months from 3 months before the index date
	Adjusted OR (95% CI)	Adjusted OR (95% CI)
All-cause		
Antiplatelet=1 vs. Antiplatelets=2 (Ref.)	0.83 (0.66–1.05)	0.83 (0.66–1.05)
Antiplatelet=1 vs. Antiplatelets≥3 (Ref.)	1.11 (0.56–2.20)	1.06 (0.52–2.15)
Antiplatelets=2 vs. Antiplatelets≥3 (Ref.)	1.34 (0.69–2.61)	1.27 (0.63–2.56)
Cerebro-cardiovascular disease		
Antiplatelet=1 vs. Antiplatelets=2 (Ref.)	0.73 (0.53–1.01)	0.72 (0.52–0.99)*
Antiplatelet=1 vs. Antiplatelets≥3 (Ref.)	0.78 (0.32–1.90)	0.80 (0.32–2.01)
Antiplatelets=2 vs. Antiplatelets≥3 (Ref.)	1.08 (0.46–2.55)	1.11 (0.45–2.76)
Cerebrovascular disease		
Antiplatelet=1 vs. Antiplatelets=2 (Ref.)	0.78 (0.38–1.58)	0.66 (0.31–1.40)
Antiplatelet=1 vs. Antiplatelets≥3 (Ref.)	0.63 (0.06–6.49)	0.46 (0.04–4.93)
Antiplatelets=2 vs. Antiplatelets≥3 (Ref.)	0.81 (0.08–8.40)	0.70 (0.06–7.53)
Cardiovascular disease		
Antiplatelet=1 vs. Antiplatelets=2 (Ref.)	0.77 (0.53–1.10)	0.76 (0.53–1.10)
Antiplatelet=1 vs. Antiplatelet≥3 (Ref.)	0.88 (0.35–2.26)	0.77 (0.30–1.97)
Antiplatelet=2 vs. Antiplatelet≥3 (Ref.)	1.15 (0.46–2.87)	1.01 (0.40–2.55)
Cancer		
Antiplatelet=1 vs. Antiplatelet=2 (Ref.)	1.01 (0.69–1.48)	1.10 (0.74–1.63)
Antiplatelet=1 vs. Antiplatelets≥3 (Ref.)	1.66 (0.52–5.31)	1.92 (0.51–7.20)
Antiplatelets=2 vs. Antiplatelets≥3 (Ref.)	1.63 (0.52–5.13)	1.75 (0.47–6.50)

OR, odds ratio; CI, confidence interval.
Data are shown as ORs (95% CI). Multivariable model was adjusted for sex, age, income level, procedure type, timing of stent replacement or angioplasty, intensive care unit admission, baseline comorbidities (hypertension, diabetes mellitus, dyslipidemia, myocardial infarction, heart failure, stroke, chronic kidney disease, peripheral arterial disease, and cancer), and concomitant statin use.
*p<0.05.

Table 4. Comparisons of Mortality between Study Patients according to Regimen (Aspirin, Clopidogrel, and Dual Antiplatelet) of Medication for 6 Months from 6 Months before the Index Date and 9 Months from 3 Months before the Index Date

Cause of mortality	Medication patterns for 6 months from 6 months before the index date	Medication patterns for 9 months from 3 months before the index date
	Adjusted OR (95% CI)	Adjusted OR (95% CI)
All-cause		
Aspirin vs. Clopidogrel (Ref.)	0.96 (0.68–1.34)	0.98 (0.69–1.40)
Aspirin vs. DAPT (Ref.)	0.74 (0.57–0.97)*	0.72 (0.55–0.95)*
Clopidogrel vs. DAPT (Ref.)	0.78 (0.56–1.08)	0.73 (0.52–1.04)
Cerebro-cardiovascular disease		
Aspirin vs. Clopidogrel (Ref.)	0.96 (0.59–1.55)	1.11 (0.67–1.86)
Aspirin vs. DAPT (Ref.)	0.66 (0.45–0.96)*	0.65 (0.44–0.95)*
Clopidogrel vs. DAPT (Ref.)	0.69 (0.43–1.11)	0.58 (0.35–0.96)*
Cerebrovascular disease		
Aspirin vs. Clopidogrel (Ref.)	1.01 (0.36–2.83)	1.95 (0.56–6.87)
Aspirin vs. DAPT (Ref.)	0.99 (0.43–2.26)	0.84 (0.35–1.99)
Clopidogrel vs. DAPT (Ref.)	0.97 (0.35–2.73)	0.43 (0.12–1.53)
Cardiovascular disease		
Aspirin vs. Clopidogrel (Ref.)	1.02 (0.59–1.74)	1.05 (0.60–1.82)
Aspirin vs. DAPT (Ref.)	0.67 (0.44–1.01)	0.66 (0.43–1.01)
Clopidogrel vs. DAPT (Ref.)	0.66 (0.39–1.12)	0.63 (0.37–1.09)
Cancer		
Aspirin vs. Clopidogrel (Ref.)	0.79 (0.46–1.37)	0.93 (0.96–1.64)
Aspirin vs. DAPT (Ref.)	0.82 (0.52–1.28)	0.82 (0.84–1.29)
Clopidogrel vs. DAPT (Ref.)	1.03 (0.60–1.75)	0.88 (0.87–1.55)

OR, odds ratio; CI, confidence interval; DAPT, dual antiplatelet therapy.
Data are shown as ORs (95% CI). Multivariable model was adjusted for sex, age, income level, procedure type, timing of stent replacement or angioplasty, intensive care unit admission, baseline comorbidities (hypertension, diabetes mellitus, dyslipidemia, myocardial infarction, heart failure, stroke, chronic kidney disease, peripheral arterial disease, and cancer), and concomitant statin use.
*p<0.05.

by cerebrovascular disease for 3 months from 1 month before the index date [adjusted OR 0.33, 95% CI (0.11−0.93)] (Supplementary Table 7 and 8, only online).

DISCUSSION

In the present study of patients who underwent stent placement or angioplasty, we found that antiplatelet monotherapy, including aspirin or clopidogrel, was negatively associated with risk of death by cerebro-cardiovascular disease, compared with discontinuation of antiplatelets and DAPT. Furthermore, aspirin monotherapy was negatively related to risk of all-cause death and death by cancer, compared with discontinuation of antiplatelets. In addition, aspirin monotherapy was negatively related to risk of all-cause death, compared with DAPT. However, there was no significant difference in mortality between aspirin monotherapy and clopidogrel monotherapy.

A previous study proposed that antiplatelet monotherapy among patients with high risk occlusive vascular events decreased vascular mortality.[22] Furthermore, aspirin treatment decreased risk of myocardial infarction and stroke, death by

cardiovascular disease, and all-cause death.[23,24] Additionally, clopidogrel treatment for secondary prevention with stroke resulted in greater relative-risk reduction than aspirin treatment.[25] With respect to cancer, a previous clinical trial demonstrated that aspirin monotherapy was associated with a reduction in overall cancer incidence between 3 and 5 years after treatment.[26] Because aspirin interrupts neoplastic transformation of normal colorectal epithelium to sporadic adenomas, aspirin monotherapy is associated with decreased mortality from colorectal cancer.[27] It has been shown to reduce cancer incidence by 10% during the first 10 years of treatment.[27] Recent study using registry data of the National Institute of Health showed that there were no differences in death occurrence from any cause, myocardial infarction, repeat percutaneous coronary intervention, stent thrombosis, and ischemic stroke between aspirin and clopidogrel monotherapy. Although previous observational study of patients who underwent drug-eluting stent showed that clopidogrel was associated with a reduced risk for cardiac death, myocardial infarction, or stroke, less than half of the patients enrolled in these studies were diagnosed with acute coronary syndrome.[28,29] These results are similar to our findings in patients on prolonged antiplatelet treatment due to stent place-

ment or angioplasty.

In real-world patients, long-term adherence to DAPT after stent placement might raise compliance issues. In one systemic review, adherence to DAPT after stent placement in the coronary artery was high at 1 month (about 90%), began to decline by 6 months, and was lower still at 12 months.[30] One clinical trial reported a rate of early discontinuation of antiplatelet medications as high as 30% after 12 months.[31] Furthermore, real-world practice is characterized by frequent, transient interruptions, alternative prescriptions, or complete cessation of DAPT, regardless of guidelines. Of note, the rate and clinical consequences of DAPT beyond 12 months after stent placement in real-world patients still need to be determined. Despite the benefits of DAPT or antiplatelet monotherapy, antiplatelet therapy is sometimes prematurely discontinued after stent placement by the patient or healthcare provider. In previous reports, discontinuation of aspirin for secondary prevention increased the risk of all-cause mortality.[32,33] Furthermore, discontinuation of DAPT within 6 months and 1 year after stent placement increased the risks of all-cause mortality, cardiovascular death, myocardial infarction, and all-cause mortality.[34,35] These results are similar to our findings showing that adherence to antiplatelet therapy with aspirin reduced all-cause deaths and death by cerebro-cardiovascular disease, and cancer and to that with clopidogrel reduced deaths by cerebro-cardiovascular disease.

Antiplatelet monotherapy, including aspirin or clopidogrel, significantly decreased the risk of death by cerebro-cardiovascular disease, compared with DAPT, in our study. In addition, aspirin monotherapy was significantly associated with reduced risk of all-cause death, compared with DAPT. Although one clinical trial reported that prolonged DAPT (30 months) after stent placement in the coronary artery reduced the risk of major adverse cerebro-cardiovascular and cerebrovascular events, myocardial infarction, and stent thrombosis, it was associated with an unexpected increase in all-cause death.[36] In addition, another trial demonstrated that there was no difference in cardiovascular or non-cardiovascular mortality, all-cause death, or stent thrombosis between prolonged DAPT (median period 33.4 months) and antiplatelet monotherapy.[37] Furthermore, in a systemic review and meta-analysis, prolonged DAPT, compared with antiplatelet monotherapy or short duration DAPT, was not associated with cardiovascular or non-cardiovascular death or all-cause mortality. Our results are not sensitive to the exclusion of any trial, and although the enrolled subjects varied, we found that antiplatelet monotherapy (median follow-up: 3.51 years) was negatively associated with risk of death by cerebro-cardiovascular disease and all-cause death, compared with prolonged DAPT, in a real-world setting.

Unlike stent placement in the coronary artery, data regarding the effects of antiplatelet strategies after stent placement in patients with PAD or cerebral artery disease are limited.[12,38] In patients with PAD, DAPT significantly reduced re-occlusion

and resulted in maintenance of target artery at 6 months after the procedure, compared to aspirin monotherapy.[10,11] It is recommended that patients who undergo procedures in the carotid artery receive DAPT (currently aspirin and clopidogrel) throughout the periprocedural period to decrease the risk of stent thrombosis/embolization; however, there is no evidence-based consensus as to how long DAPT should be continued or what kinds of antiplatelet drugs should be given.[39] Data regarding antiplatelet management in patients treated with stent placement in the intracranial cerebral artery are even more limited. Although our dataset included patients from the general population who underwent stent placement or angioplasty in a peripheral artery or intracranial or extracranial cerebral arteries, it was not possible to perform subgroup analysis due to the small number of patients who received stent placement or angioplasty in these vessels. Therefore, further study of these specific populations is needed.

Our current study has several limitations. First, case-control studies have several inherent limitations, particularly selection bias due to the retrospective nature of the study. Second, we used ICD coding to select study subjects. Although the accuracy of diagnosis of vascular risk factors using ICD-10 codes was 85.0−94.1% in previous studies using the NHIS-HEALS dataset and the overall sensitivity of cancer diagnosis using ICD-10 codes was previously found to be 92.8%, because we relied on ICD coding of the principal diagnosis, we were not able to validate individual ICD codes.[40-42] Third, because of the exclusion of patients who had an acute or subacute thrombus within 30 days after stent placement or angioplasty, we may have underestimated adverse outcomes. Fourth, due to the lack of detailed clinical information in health claims data, we were not able to collect data on the severity of stenosis of the artery into which the stent was implanted, radiological findings, blood pressure, glucose level, low-density lipoprotein level, or length of ICU stay, which are strong prognostic factors in patients with stent placement or angioplasty. Fifth, currently, because there is no standard for exposure period and washout period after stent placement or angioplasty, we cannot confirm that a proper washout period and exposure period were followed. Therefore, we used a nested case-control study design to analyze dynamic variations in patterns of antiplatelet treatment and evaluated whether relationships between the patterns of antiplatelet treatment and clinical outcomes were consistent considering variable exposure periods and washout periods or not. Finally, because of the nested case-control study design and the time-varying nature of antiplatelet drug use after stent placement or angioplasty among the patients in our study, we cannot provide recommendations on when prescriptions should be changed from antiplatelet monotherapy to DAPT. Despite these limitations, a major strength of this study is that we evaluated real-world prognoses of patients with stent placement or angioplasty according to treatment with antiplatelets using nationwide health insurance claims data. Because the

NHIS in Korea is a single payer insurer, we were able to access detailed prescription data for antiplatelets for an extended period after stent placement or angioplasty.

In conclusion, adherent antiplatelet therapy in patients with stent placement or angioplasty may have a beneficial inhibitory effect on mortality by cerebro-cardiovascular disease. Antiplatelet monotherapy, including aspirin or clopidogrel, appears to be associated with a lower risk of mortality by cerebro-cardiovascular disease than DAPT.

ACKNOWLEDGEMENTS

AUTHOR CONTRIBUTIONS

Conceptualization: Ho Geol Woo and Tae-Jin Song. Data curation: all authors. Formal analysis: Ho Geol Woo, Hye Ah Lee, and Tae-Jin Song. Funding acquisition: Tae-Jin Song. Investigation: all authors. Methodology: all authors. Project administration: Tae-Jin Song. Resources: all authors. Software: Ho Geol Woo and Hye Ah Lee. Supervision: Dong-Ryeol Ryu. Validation: all authors. Visualization: Ho Geol Woo, Hye Ah Lee, and Tae-Jin Song. Writing—original draft: Ho Geol Woo and Hye Ah Lee. Writing—review & editing: all authors. Approval of final manuscript: all authors.

ORCID iDs

Ho Geol Woo https://orcid.org/0000-0001-6489-0100
Hye Ah Lee https://orcid.org/0000-0002-4051-0350
Dong-Ryeol Ryu https://orcid.org/0000-0002-5309-7606
Tae-Jin Song https://orcid.org/0000-0002-9937-762X

REFERENCES

1. Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. N Engl J Med 2012;366:54-63.
2. Kim JY, Kang K, Kang J, Koo J, Kim DH, Kim BJ, et al. Executive summary of stroke statistics in Korea 2018: a report from the epidemiology research council of the Korean stroke society. J Stroke 2019;21:42-59.
3. Spoon DB, Psaltis PJ, Singh M, Holmes DR Jr, Gersh BJ, Rihal CS, et al. Trends in cause of death after percutaneous coronary intervention. Circulation 2014;129:1286-94.
4. Melfi R, Ricottini E. Antiplatelet therapy for peripheral artery disease. Cardiovasc Diagn Ther 2018;8:663-77.
5. Jeppsson A, Petricevic M, Kolh P, Valgimigli M. 2017 European Society of Cardiology (ESC) focused update on dual antiplatelet therapy in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2018;53:3-4.
6. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. Circulation 2016;134:e123-55.
7. Palmerini T, Benedetto U, Bacchi-Reggiani L, Della Riva D, Biondi-Zoccai G, Feres F, et al. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. Lancet 2015;385:2371-82.
8. Yin SH, Xu P, Wang B, Lu Y, Wu QY, Zhou ML, et al. Duration of dual antiplatelet therapy after percutaneous coronary intervention with drug-eluting stent: systematic review and network meta-analysis. BMJ 2019;365:l2222.
9. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39:213-60.
10. Robertson L, Ghouri MA, Kovacs F. Antiplatelet and anticoagulant drugs for prevention of restenosis/reocclusion following peripheral endovascular treatment. Cochrane Database Syst Rev 2012:CD002071.
11. Strobl FF, Brechtel K, Schmehl J, Zeller T, Reiser MF, Claussen CD, et al. Twelve-month results of a randomized trial comparing mono with dual antiplatelet therapy in endovascularly treated patients with peripheral artery disease. J Endovasc Ther 2013;20:699-706.
12. Barnard ZR, Alexander MJ. Update in the treatment of intracranial atherosclerotic disease. Stroke Vasc Neurol 2020;5:59-64.
13. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371:2155-66.
14. Wang F, Stouffer GA, Waxman S, Uretsky BF. Late coronary stent thrombosis: early vs. late stent thrombosis in the stent era. Catheter Cardiovasc Interv 2002;55:142-7.
15. Etminan M. Pharmacoepidemiology II: the nested case-control study--a novel approach in pharmacoepidemiologic research. Pharmacotherapy 2004;24:1105-9.
16. Richardson DB. An incidence density sampling program for nested case-control analyses. Occup Environ Med 2004;61:e59.
17. Wang MH, Shugart YY, Cole SR, Platz EA. A simulation study of control sampling methods for nested case-control studies of genetic and molecular biomarkers and prostate cancer progression. Cancer Epidemiol Biomarkers Prev 2009;18:706-11.
18. Bae SO, Kang GW. A comparative study of the disease codes between Korean National Health Insurance Claims and Korean National Hospital Discharge in-depth injury survey. Health Policy and Management 2014;24:322-9.
19. Pourhoseingholi MA, Vahedi M, Baghestani AR. Burden of gastrointestinal cancer in Asia; an overview. Gastroenterol Hepatol Bed Bench 2015;8:19-27.
20. Kim DY, Lee MH, Lee SY, Yang BR, Kim HA. Survival rates following medical intensive care unit admission from 2003 to 2013: an observational study based on a representative population-based

sample cohort of Korean patients. Medicine (Baltimore) 2019;98: e17090.

21. Song TJ, Kim J. Risk of post-stroke pneumonia with proton pump inhibitors, H2 receptor antagonists and mucoprotective agents: a retrospective nationwide cohort study. PLoS One 2019;14:e0216750.

22. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86.

23. Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849-60.

24. Gum PA, Thamilarasan M, Watanabe J, Blackstone EH, Lauer MS. Aspirin use and all-cause mortality among patients being evaluated for known or suspected coronary artery disease: a propensity analysis. JAMA 2001;286:1187-94.

25. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996;348:1329-39.

26. Rothwell PM, Price JF, Fowkes FG, Zanchetti A, Roncaglioni MC, Tognoni G, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet 2012;379:1602-12.

27. Thun MJ, Jacobs EJ, Patrono C. The role of aspirin in cancer prevention. Nat Rev Clin Oncol 2012;9:259-67.

28. Sim DS, Jeong MH, Kim HS, Gwon HC, Seung KB, Rha SW, et al. Clopidogrel versus aspirin after dual antiplatelet therapy in acute myocardial infarction patients undergoing drug-eluting stenting. Korean Circ J 2020;50:120-9.

29. Park TK, Song YB, Ahn J, Carriere KC, Hahn JY, Yang JH, et al. Clopidogrel versus aspirin as an antiplatelet monotherapy after 12-month dual-antiplatelet therapy in the era of drug-eluting stents. Circ Cardiovasc Interv 2016;9:e002816.

30. Czarny MJ, Nathan AS, Yeh RW, Mauri L. Adherence to dual antiplatelet therapy after coronary stenting: a systematic review. Clin Cardiol 2014;37:505-13.

31. Bonaca MP, Bhatt DL, Oude Ophuis T, Steg PG, Storey R, Cohen M, et al. Long-term tolerability of ticagrelor for the secondary prevention of major adverse cardiovascular events: a secondary analysis of the PEGASUS-TIMI 54 trial. JAMA Cardiol 2016;1:425-32.

32. Ho PM, Spertus JA, Masoudi FA, Reid KJ, Peterson ED, Magid DJ, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction. Arch Intern Med 2006;166:1842-7.

33. Newby LK, LaPointe NM, Chen AY, Kramer JM, Hammill BG, DeLong ER, et al. Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. Circulation 2006;113:203-12.

34. Cutlip DE, Kereiakes DJ, Mauri L, Stoler R, Dauerman HL; EDUCATE Investigators. Thrombotic complications associated with early and late nonadherence to dual antiplatelet therapy. JACC Cardiovasc Interv 2015;8:404-10.

35. Huber CA, Meyer MR, Steffel J, Blozik E, Reich O, Rosemann T. Post-myocardial infarction (MI) care: medication adherence for secondary prevention after MI in a large real-world population. Clin Ther 2019;41:107-17.

36. Kereiakes DJ, Yeh RW, Massaro JM, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Antiplatelet therapy duration following bare metal or drug-eluting coronary stents: the dual antiplatelet therapy randomized clinical trial. JAMA 2015;313:1113-21.

37. Helft G, Steg PG, Le Feuvre C, Georges JL, Carrie D, Dreyfus X, et al. Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: the OPTIDUAL randomized trial. Eur Heart J 2016;37:365-74.

38. Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J 2018;39:763-816.

39. Enomoto Y, Yoshimura S. Antiplatelet therapy for carotid artery stenting. Interv Neurol 2013;1:151-63.

40. Chang Y, Woo HG, Park J, Lee JS, Song TJ. Improved oral hygiene care is associated with decreased risk of occurrence for atrial fibrillation and heart failure: a nationwide population-based cohort study. Eur J Prev Cardiol 2020;27:1835-45.

41. Seo HJ, Oh IH, Yoon SJ. A comparison of the cancer incidence rates between the national cancer registry and insurance claims data in Korea. Asian Pac J Cancer Prev 2012;13:6163-8.

42. Lee SJ, Im JS, Choi JS. Sensitivity of medical insurance claims data using population-based cancer registry data. J Korean Soc Med Inform 2002;8:35-40.