Previous Antithrombotic Therapy, Particularly Anticoagulant, Is Associated with Unfavorable Outcomes in Patients with Primary Spontaneous Intracerebral Hemorrhage Receiving Craniotomy: A Nationwide Population-Based Cohort Study

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■ OBJECTIVE: **The impact of antithrombotic agents on patients with primary intracerebral hemorrhage (ICH) remains controversial, especially patients who require emergent craniotomy. This study was undertaken to evaluate clinical outcomes in operated patients with ICH with and without previous antithrombotic agents.**

■ METHODS: **This is a retrospective cohort study. Between January 2001 and December 2013, all patients with ICH who received emergent craniotomy and who were present in Taiwan's National Health Insurance Research Database were screened and divided into those with previous antiplatelet therapy, anticoagulant therapy, and nonantithrombotic therapy according to their health care claims data within 3 months of index admission. The primary end points included in-hospital mortality and complications and short-term outcome.**

■ RESULTS: **Of 18,872 eligible patients, 16,251 (87.1%) did not receive any antithrombotic therapy, 2267 patients had antiplatelet therapy, and 354 patients had anticoagulation therapy. After propensity score matching, significantly more blood transfusions and craniectomies were identified in the patients with previous antithrombotic treatment compared with those undergoing nonantithrombotic therapy. Compared with the nonantithrombotic treatment cohort, patients under previous anticoagulant treatment had significantly higher in-hospital mortality (odds ratio, 2.12; 95% confidence interval, 1.45–3.10). Furthermore, during the 6-month follow-up period, previous anticoagulant therapy was independently associated with a greater risk of all-cause mortality ($P = 0.001$). The in-hospital and 6-month all-cause mortality of patients with previous antiplatelet treatment was not significantly different from patients with nonantithrombotic treatment.**

■ CONCLUSIONS: **These findings suggested an increased risk of in-hospital mortality and poor short-term outcome among operated patients with ICH with previous antithrombotic therapy, particularly anticoagulant therapy, but not with antiplatelet therapy.**

INTRODUCTION

Spontaneous intracerebral hemorrhage (ICH) accounts for 10%–15% of all cerebrovascular accident and shows a higher mortality than either ischemic stroke or subarachnoid hemorrhage.[1] Recently, antithrombotic agents, including

Key words
- Anticoagulant
- Antiplatelet
- Antithrombotic agents
- Cohort study
- Craniotomy
- *ICD-9*
- Intracerebral hemorrhage

Abbreviations and Acronyms
CI: Confidence interval
GEE: Generalized estimating equation
ICD-9-CM: *International Classification of Diseases, Ninth Revision, Clinical Modification*
ICH: Intracerebral hemorrhage
NHIRD: National Health Insurance Research Database
NIHSS: National Institutes of Health Stroke Scale
NOAC: New oral anticoagulant
OR: Odds ratio
PSM: Propensity score matching

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antiplatelet therapy such as aspirin and anticoagulants such as warfarin, have been widely prescribed for patients as secondary prevention of coronary heart-related or thrombotic-related disease.[2,3] Therefore, it is becoming more common for patients before ICH to have previously been exposed to antithrombotic agents. It has been previously suggested that patients with exposure to antithrombotic agents before ICH have a higher risk of secondary hematoma expansion and an increased risk of death or poor functional outcome.[4,5] Therefore, one essential problem frequently encountered clinically is how to manage patients on antithrombotic agents after spontaneous ICH, especially those requiring craniotomy.

Craniotomy is a life-saving procedure regularly carried out in selected patients with spontaneous ICH, but the presence of antithrombotic agents may increase the possibility of postoperative hemorrhage, as well as complications and mortality after craniotomy.[6] Therefore, the dilemma in treating patients with ICH on antithrombotic agents is the risk of increasing blood loss during surgical intervention versus the risk of further secondary brain damage if the hematoma is not removed.

The impact of antithrombotic effect on mortality and complication rate after surgical intervention in spontaneous ICH has not been sufficiently assessed because of the limited number of operated patients with ICH. According to national cohort studies, only 6.9%–7.9% of patients with ICH receive hematoma evacuation.[7,8] The incidence of ICH is higher in Asian than in non-Asian populations,[9] which provides us with an opportunity to evaluate the impact of antithrombotic agents on the clinical outcomes of Asian patients with ICH requiring hematoma evacuation. In this study, we examined the hypothesis that antithrombotic agents provide unfavorable in-hospital and short-term outcomes for patients with ICH requiring craniotomy from the National Health Insurance Research Database (NHIRD) of Taiwan.

METHODS

Data Source

This retrospectively collected and observational cohort study involved data obtained from Taiwan's NHIRD, which contains all health care claims data between January 1997 and December 2013, including demographic data, records of clinical visits, hospital admissions, prescriptions, and disease status for >99% of the Taiwanese population. Data were anonymized, encrypted, and maintained by the National Health Research Institutes of Taiwan for research purposes. Diagnostic codes used in the database are based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes (**Supplementary Table 1**). The NHIRD data involving cerebrovascular accident have been validated in several studies by the National Health Insurance Bureau.[10,11] This study was exempt from approval requirements by the institutional review board of Chang Gung Memorial Hospital in Taiwan (institutional review board number 201601518B0) and without patients' consent, given that it was an epidemiologic study with no definable patient information.

Patients

Study patients were identified from the NHIRD as those admitted for first event of cerebrovascular accident from January 1, 2001 to December 31, 2013 (ICD-9-CM codes 430–437) (**Supplementary Table 1**). Of these patients with cerebrovascular accident, those who were diagnosed with a spontaneous ICH (ICD-9-CM code 431) were identified. The date of the first admission for ICH was assigned as the index date. Patients younger than 20 years, and those diagnosed with cerebral vascular lesion, such as arteriovenous malformation or aneurysm, were excluded (ICD-9-CM codes 437.3, 747.81, 4470). We also excluded comorbidities in which the conditions can possibly interfere with coagulation conditions, such as coagulopathy (ICD-9-CM codes 286.0–286.9, 287.1, 287.3–287.5, and 289.81–289.82), liver cirrhosis (ICD-9-CM codes 571.2, 571.5, and 571.6), malignancy (ICD-9-CM codes 140.xx–208.xx) predating the index date. To ensure that ICH was not secondary to other events, we also excluded those who had head injury (ICD-9-CM codes 800.xx–804.xx and 850.xx–854.xx), hemorrhage stroke (ICD-9-CM codes 430.xx–432.xx), and brain surgery events within 6 months before the index date. Overall, patients who received craniotomy during the index ICH admission data were eligible for selection into our study.

Exposure of Antithrombotic Therapy and Study Design

To compare the impact of antiplatelet and anticoagulant regiment on those receiving craniotomy, we retrieved the patient's health care claims data within 3 months of index admission. According to the prescription record system, we excluded those receiving dual antiplatelet treatment. Eligible patients were further divided into 3 groups according to the exposure to antithrombotic agents, including 1) no antithrombotic therapy, 2) antiplatelet therapy (e.g., aspirin, clopidogrel, and ticlopidine), and 3) anticoagulant therapy (e.g., warfarin and new oral anticoagulants [NOACs], including dabigatran and rivaroxaban). To balance all possible confounding factors between groups, propensity score matching (PSM) with 1:1 matching between groups was performed before analysis of clinical outcomes (**Figure 1**).

Outcome Measures and Comorbidities

Baseline comorbidities, in-hospital complications, and short-term outcomes were identified based on ICD-9-CM diagnosis codes recorded during hospitalization or clinic visit (**Supplementary Table 1**). The Charlson Comorbidity Index was calculated to measure the patient's underlying condition. Selected comorbidities were ascertained based on 1 in-patient diagnosis or ≥2 outpatient diagnoses 1 year before index date. History of event (i.e., stroke or myocardial infarction) was verified using in-patient diagnosis before index date and tracked back to 1997. To assess the severity of hemorrhagic stroke, the estimated National Institutes of Health Stroke Scale (NIHSS) was applied. The estimated NIHSS score was calculated from the Stroke Severity Index (SSI), which was obtained from 7 variables, comprising airway suctioning, bacterial sensitivity test, general ward stay, intensive care unit stay, nasogastric intubation, osmotherapy (mannitol or glycerol), and urinary catheterization. The estimated NIHSS score was highly correlated to the Stroke Severity Index score and the modified Rankin Scale score after discharge.[12] The primary outcome of this study was in-hospital mortality during the index admission. In-hospital treatment (including neurosurgical procedure and volume of blood transfusion) and postoperative conditions (including ischemic stroke, pneumonia, septicemia, surgical wound infection, pulmonary embolism, deep venous thrombosis,

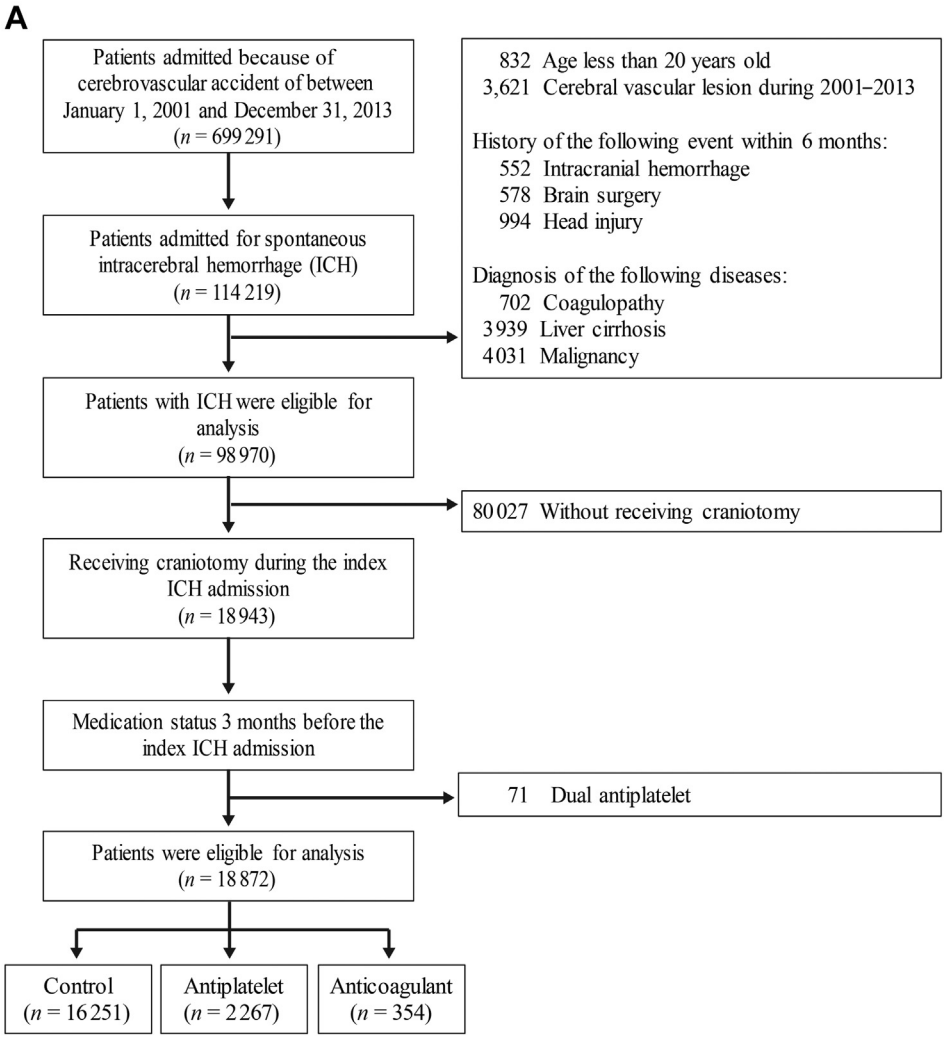

Figure 1. Flowchart showing the patient selection included in the study. (**A**) Patients with spontaneous intracerebral hemorrhage receiving craniotomy were divided into 3 groups (control, antiplatelet, and anticoagulant) according to the previous antithrombotic therapy. Patients with cerebrovascular accident admitted for hemorrhage stroke were included after relevant exclusions. (**B**) Propensity score matching with a 1:1 ratio enables 3 groups of comparisons with their number of patients.

acute kidney injury, and massive blood transfusion) during the index admission were secondary outcomes. The short-term 6-month all-cause mortality was identified according to withdrawal from the National Health Insurance system.[13] Patients were followed until the date of event occurrence, date of death, or 31 December, 2013.

Ascertainment of ICH, Comorbidities, and Outcomes

Most comorbidities based on ICD-9-CM have previously been validated.[14,15] The study patients with ICH were selected when their principal diagnosis of index hospitalization was ICH (ICD-9-CM code 431). The high accuracy of the diagnosis of ICH

based on ICD-9-CM coding in the NHIRD was confirmed in a previous study.[16] Furthermore, a validation study was conducted in 1 center by randomly sampling the records of 119 hospitalized patients whose principal diagnosis of hospitalization was coded as ICD-9-CM 431. A positive predictive value of 98% (117/119) was obtained when their medical records and images were independently reviewed by a physician (C.-H.L.).

Statistical Analysis

The distributions of demographic and clinical characteristics were compared between the 3 study groups using a χ^2 test for categorical variables or 1-way analysis of variance for continuous variables. Bonferroni adjustment was performed for the pairwise comparisons when the overall test was significant. Risk factors associated with in-hospital mortality were studied using multivariable logistic regression analysis. A PSM analysis was performed before comparing outcomes among the previous antiplatelet, anticoagulant, and nonantithrombotic groups, to ensure that the baseline characteristics among these 3 groups were comparable (**Supplementary Tables 2–4**). The selected covariates used to calculate the propensity scores were gender, age, level of hospital at which the operation was performed, coexisting diseases, history of event, Charlson Comorbidity Index, estimated NIHSS score, and index date. A 1:1 matching ratio was chosen in which greedy nearest neighbor algorithm was adopted and the caliper was set as 0.2 times the standard deviation of the logit of propensity score.[17] Comparison in blood transfusion volume between any 2 PSM groups was made using generalized estimating equation (GEE) type linear regression. Furthermore, comparison of risk of in-hospital treatment (neurosurgical procedures), in-hospital complications, and mortality between any 2 PSM groups was made using GEE type logistic regression. The correlation of patients among the same match pair was adjusted in the GEE model. The risk of time to all-cause mortality was compared within the 3 study groups before PSM using a pairwise log-rank test. Likewise, the survival curves during the 6-month follow-up were compared between any 2 PSM groups by using a log-rank test stratified by match pair. The level of statistical significance was set as 0.05 and no adjustment of multiple testing (multiplicity) was made in this study. The data analysis was conducted using SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Patient Characteristics

From an initial sample of 699,291 patients with cerebrovascular accident events during the 13-year period between January 1, 2001 and December 31, 2013, 114,219 patients were admitted for spontaneous ICH in Taiwan. After applying a series of excluding criteria, a total eligible 18,872 adult patients with ICH were included, of whom 2267 (12%) and 354 (1.9%) received antiplatelet or anticoagulant treatment, respectively, before surgical intervention (**Figure 1** and **Table 1**). The mean age for the overall cohort was 59.7 years, with a predominant male gender (66.5%).

There were several significant differences in the baseline demographics and clinical characteristics of the study patients (**Table 1**). The mean age in the control group (58.6 years) was significantly younger compared with that in the antiplatelet group (66.6 years) and anticoagulant group (65.3 years). Patients with anticoagulant therapy (54.5%) were significantly more likely to receive craniotomy in a teaching hospital than were the antiplatelet group (38.9%) or control group (36.9%). In general, patients who underwent antithrombotic or anticoagulant regimens had a significantly higher prevalence of all major medical comorbidities (i.e., atrial fibrillation, hypertension, and chronic kidney disease), and history of event (i.e., ischemic stroke) compared with control patients. The prevalence of atrial fibrillation was significantly higher in the anticoagulant group (46.3%) than in the antiplatelet group (6.4%).

Events During Index Hospitalization

In addition to craniotomy, further neurosurgical intervention and in-hospital blood transfusion were studied (**Tables 2** and **3**). There was a trend toward increasing number of craniectomy after craniotomy in patients receiving antiplatelet treatment compared with no previous antithrombotic therapy. Patients receiving anticoagulants were significantly more likely to undergo craniectomy than were those with previous antiplatelet treatment (odds ratio [OR], 2.21; 95% confidence interval [CI], 1.25–3.93) (**Table 3**). No significant difference was observed among the 3 groups with respect to other further surgical interventions (i.e., repeated brain surgery and extraventricular drainage) during the index admission. In contrast, a greater amount of platelet during blood transfusion was required in the antiplatelet group than in the control group (regression coefficient, 0.70 units; 95% CI, 0.28–1.12) (**Table 3**). Furthermore, administration of fresh frozen plasma was significantly less in the antiplatelet than the other 2 groups. Packed red blood cell use was significantly higher in the anticoagulant than in the antiplatelet group, and that in both groups was greater than in the nonantithrombotic (control) group.

To understand the in-hospital complications, complications after craniotomy were divided into the following categories: pulmonary, septicemia, wound infection, thromboembolic, postoperative hemorrhage, neurologic, and renal issues (**Tables 2** and **4**). The order of greatest common complication (greatest number first with percentage of occurrence $\geq$4%) was pneumonia, septicemia, and ischemic stroke. Compared with the control group, there was no significant difference between surgical-related complications in the 2 antithrombotic groups. Patients in the anticoagulant group were significantly more likely to have septicemia compared with those in the antiplatelet group (OR, 2.29; 95% CI, 1.10–4.76) (**Table 4**). Furthermore, patients under anticoagulant treatment had a significantly higher in-hospital mortality compared with the antiplatelet group (OR, 1.60; 95% CI, 1.12–2.30) and the control group (OR, 2.12; 95% CI, 1.45–3.10). However, the in-hospital mortality was not significantly different between the antiplatelet group and the control group.

Additional analysis was carried out to investigate risk factors of in-hospital mortality by using the whole cohort. The result identified the following variables as potential risk factors: male gender, age >80 years (compared with 20–39 years), operation in nonteaching hospital, atrial fibrillation, epilepsy, hypertension, diabetes mellitus, coronary artery disease, chronic kidney disease, and history of ischemic stroke (**Figure 2**).

Table 1. Baseline and Clinical Characteristics of the Study Patients Before Propensity Score Matching

Variable	Total (n = 18,872)	Control (n = 16,251)	Antiplatelet (n = 2267)	Anticoagulant (n = 354)
Gender				
Male	12,548 (66.5)	10,939 (67.3)	1413 (62.3)[a]	196 (55.4)[ab]
Female	6324 (33.5)	5312 (32.7)	854 (37.7)[a]	158 (44.6)[ab]
Age (years)	59.7 ± 13.8	58.6 ± 13.8	66.6 ± 11.7[a]	65.3 ± 13.5[a]
Age group				
20–39 years	1404 (7.4)	1349 (8.3)	35 (1.5)[a]	20 (5.6)[b]
40–59 years	8430 (44.7)	7721 (47.5)	613 (27.0)[a]	96 (27.1)[a]
60–79 years	7670 (40.6)	6123 (37.7)	1354 (59.7)[a]	193 (54.5)[a]
≥80 years	1368 (7.2)	1058 (6.5)	265 (11.7)[a]	45 (12.7)[a]
Operation in teaching hospital				
No	11,796 (62.5)	10,249 (63.1)	1386 (61.1)	161 (45.5)[ab]
Yes	7076 (37.5)	6002 (36.9)	881 (38.9)	193 (54.5)[ab]
Coexisting disease				
Atrial fibrillation	470 (2.5)	161 (1.0)	145 (6.4)[a]	164 (46.3)[ab]
Dementia	242 (1.3)	164 (1.0)	70 (3.1)[a]	8 (2.3)
Epilepsy	425 (2.3)	334 (2.1)	84 (3.7)[a]	7 (2.0)
Hypertension	5939 (31.5)	3945 (24.3)	1731 (76.4)[a]	263 (74.3)[a]
Diabetes mellitus	1907 (10.1)	1159 (7.1)	669 (29.5)[a]	79 (22.3)[ab]
Coronary artery disease	1915 (10.1)	947 (5.8)	844 (37.2)[a]	124 (35.0)[a]
Peripheral arterial disease	269 (1.4)	131 (0.8)	111 (4.9)[a]	27 (7.6)[a]
Dialysis	476 (2.5)	382 (2.4)	80 (3.5)[a]	14 (4.0)
Chronic kidney disease	898 (4.8)	680 (4.2)	184 (8.1)[a]	34 (9.6)[a]
History of event				
Ischemic stroke	750 (4.0)	466 (2.9)	244 (10.8)[a]	40 (11.3)[a]
Intracranial hemorrhage	427 (2.3)	340 (2.1)	79 (3.5)[a]	8 (2.3)
Myocardial infarction	206 (1.1)	98 (0.6)	94 (4.1)[a]	14 (4.0)[a]
Charlson Comorbidity Index	2.0 ± 1.3	1.9 ± 1.2	2.5 ± 1.5[a]	2.7 ± 1.7[ab]
Estimated National Institutes of Health Stroke Scale	22.5 ± 3.5	22.4 ± 3.5	22.9 ± 3.5[a]	22.8 ± 3.4

Values are number (%) except where indicated otherwise. Superscript a and b denote a significant post hoc comparison versus control and antiplatelet, respectively.

Outcomes During Follow-Up

The mortality of the 3 groups of patients during the 6-month follow-up period was studied in the whole cohort (Figure 3A). The all-cause mortality at 6 months follow-up of control, antiplatelet, and anticoagulant patients was 9.9%, 13.6%, and 19.9%, respectively. Large significant differences in the survival curves between all 3 groups were observed (Figure 3A). Furthermore, the 6-month mortality was significantly higher in the anticoagulant group compared with the control and the antiplatelet groups when using the PSM cohorts ($P = 0.001$, $P = 0.007$, respectively) (Figure 3B and C). However, the 6-month mortality was not significantly different between the antiplatelet and the control groups when using the PSM cohorts ($P = 0.773$; Figure 3D).

DISCUSSION

The use of antithrombotic agents in the general population is ever increasing because of their preventive use for a variety of diseases, such as cardiovascular disease. Therefore, it is important to understand their impact in emergency neurologic surgery. In this study, we compared 18,872 patients who received craniotomy after spontaneous ICH in a 13-year period with a matched control group by using Taiwan's nationwide health database. Our study showed that the incidence of ICH receiving craniotomy was 16.5%. This is the largest cohort study of craniotomy for ICH. Furthermore, this study compares the admission events, in-hospital mortality and 6-month outcome of patients receiving previous antithrombotic therapy with those of a matched control group. We found significant increased

Table 2. Descriptive Statistics of In-Hospital Treatment, Complications, and Mortality of The Study Patients

	Propensity Score Matched Cohort					
	Antiplatelet vs. Control (n = 1626 for Each Cohort)		Anticoagulant vs. Control (n = 281 for Each Cohort)		Anticoagulant vs. Antiplatelet (n = 293 for Each Cohort)	
Outcome	Antiplatelet	Control	Anticoagulant	Control	Anticoagulant	Antiplatelet
Neurosurgical procedure						
Repeated craniotomy	17 (1.0)	13 (0.8)	2 (0.7)	1 (0.4)	2 (0.7)	3 (1.0)
Craniectomy	148 (9.1)	121 (7.4)	34 (12.1)	27 (9.6)	39 (13.3)	19 (6.5)
Repeated brain surgery	165 (10.1)	132 (8.1)	36 (12.8)	27 (9.6)	41 (14.0)	22 (7.5)
Extraventricular drainage	290 (17.8)	299 (18.4)	55 (19.6)	54 (19.2)	61 (20.8)	57 (19.5)
Ventriculoperitoneal shunt	56 (3.4)	56 (3.4)	6 (2.1)	11 (3.9)	6 (2.0)	8 (2.7)
Blood transfusion, U						
Platelet	1.8 ± 7.1	1.1 ± 4.9	2.1 ± 6.0	2.1 ± 7.8	2.2 ± 6.4	2.8 ± 9.1
Fresh frozen plasma	2.5 ± 6.8	2.0 ± 4.7	5.6 ± 6.2	2.3 ± 4.9	5.5 ± 6.1	3.0 ± 9.1
Packed red blood cells	1.6 ± 2.5	1.4 ± 2.2	2.1 ± 2.7	1.9 ± 3.2	2.2 ± 2.8	1.9 ± 3.0
Complications						
Ischemic stroke	78 (4.8)	64 (3.9)	18 (6.4)	10 (3.6)	19 (6.5)	25 (8.5)
Pneumonia	398 (24.5)	412 (25.3)	82 (29.2)	68 (24.2)	84 (28.7)	69 (23.5)
Septicemia	80 (4.9)	78 (4.8)	22 (7.8)	14 (5.0)	24 (8.2)	11 (3.8)
Wound infection	11 (0.7)	20 (1.2)	4 (1.4)	3 (1.1)	5 (1.7)	1 (0.3)
Pulmonary embolism	4 (0.2)	2 (0.1)	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
Deep vein thrombosis	5 (0.3)	5 (0.3)	3 (1.1)	1 (0.4)	3 (1.0)	0 (0.0)
Acute kidney injury	62 (3.8)	66 (4.1)	10 (3.6)	11 (3.9)	11 (3.8)	11 (3.8)
Massive blood transfusion (packed red blood cells >10 U)	22 (1.4)	14 (0.9)	5 (1.8)	9 (3.2)	5 (1.7)	4 (1.4)
Any complications	630 (38.7)	629 (38.7)	127 (45.2)	112 (39.9)	136 (46.4)	113 (38.6)
In-hospital mortality	384 (23.6)	372 (22.9)	97 (34.5)	56 (19.9)	98 (33.4)	70 (23.9)

in-hospital mortality in operated patients with ICH receiving previous anticoagulant treatment, but not in patients with previous antiplatelet treatment.

Impact of Antiplatelet Therapy

The influence of previous antiplatelet therapy on ICH expansion or neurologic outcome remains controversial.[5,18,19] A recent study reported that a prehospital antiplatelet regimen was associated with hematoma expansion, increased mortality, and poor functional outcome in spontaneous ICH.[5,8] In contrast, other studies have failed to detect differences in outcome or hematoma growth.[18,19] The reason for this discrepancy is not clear, but it could be caused by the heterogeneous clinical presentations of ICH, different treatment strategies, and low incident rate.

A recent study reported a significantly higher risk of in-hospital mortality after hematoma evacuations in patients with previous antiplatelet treatment compared with patients without previous antiplatelet treatment.[20] From our real-world data, the in-hospital mortality and short-term outcome of patients with previous antiplatelet treatment were significantly increased compared with the control group (Figure 3A). However, in-hospital and 6-month mortality showed no significant difference after matched control comparison (Figure 3D). This finding implies that the underlying condition of patients receiving antiplatelet treatment plays a vital role in the clinical outcome.

Impact of Anticoagulation Therapy

Mortality and neurologic outcome are worse for anticoagulant-associated ICH. This situation could be to the result of larger hemorrhage volumes,[21,22] higher risk of hematoma expansion,[4] and higher comorbidities among anticoagulated patients.[23] This worsening in neurologic outcome may be associated with the patients' race, because a recent study[24] reported that hemorrhagic stroke rates were higher in Asians compared with non-Asians on warfarin. In line with previous studies,[25,26] our study observed that pretreatment with oral anticoagulant was a strong predictor of increased in-hospital mortality. Furthermore, we found that the rate of complications was significantly higher among patients receiving

Table 3. In-Hospital Treatment of the Study Patients

	Antiplatelet vs. Control (n = 1626 for Each Cohort)		Anticoagulant vs. Control (n = 281 for Each Cohort)		Anticoagulant vs. Antiplatelet (n = 293 for Each Cohort)	
Outcome	**OR/*B* (95% CI)**	***P***	**OR/*B* (95% CI)**	***P***	**OR/*B* (95% CI)**	***P***
Neurosurgical procedures						
Craniectomy	1.25 (0.97—1.60)	0.086	1.30 (0.76—2.21)	0.344	2.21 (1.25—3.93)	0.007
Repeated brain surgery	1.28 (1.01—1.63)	0.045	1.38 (0.81—2.35)	0.230	2.00 (1.16—3.46)	0.013
Extraventricular drainage	0.96 (0.81—1.15)	0.682	1.02 (0.67—1.55)	0.915	1.09 (0.73—1.63)	0.680
Ventriculoperitoneal shunt	1.00 (0.69—1.46)	1.000	0.54 (0.20—1.47)	0.225	0.75 (0.26—2.17)	0.590
Blood transfusion, U						
Platelet	0.70 (0.28—1.12)	0.001	−0.04 (−1.20 to 1.12)	0.945	−0.55 (−1.82 to 0.72)	0.393
Fresh frozen plasma	0.51 (0.10—0.91)	0.014	3.30 (2.38—4.22)	<0.001	2.59 (1.33—3.85)	<0.001
Packed red blood cells	0.23 (0.07—0.39)	0.006	0.23 (−0.26 to 0.71)	0.358	0.32 (−0.15 to 0.78)	0.185

CI, confidence interval; OR, odds ratio; *B*, regression coefficient.

previous anticoagulant therapy compared with the control and antiplatelet groups. A recent study[27] reported that oral anticoagulants did not increase in-hospital mortality in patients with ICH receiving hematoma evacuation because the international normalized ratio could be normalized before surgical intervention. This discrepancy could be explained by the racial difference in warfarin pharmacokinetics. The Asian population in particular have a higher risk for warfarin-related ICH.[28] The optimal range of international normalized ratio for Asians might be narrower than for non-Asians, which could lead to difficulty in control of anticoagulation quality.[29] Current data suggest that the NOACs are not associated with a higher risk of spontaneous ICH.[30] However, because this is a relatively new therapy, the number of patients who have received NOACs in our study was too low for any meaningful statistical analysis.

Surgical Outcome of ICH with Previous Antithrombotic Treatment

The findings from our study show that patients taking previous antithrombotic treatment required a greater number of decompression craniectomies. Our finding suggested that the brain edema developed more frequently in the patients who received

Table 4. In-Hospital Complications and Mortality of the Study Patients

	Antiplatelet vs. Control (n = 1626 for Each Cohort)		Anticoagulant vs. Control (n = 281 for Each Cohort)		Anticoagulant vs. Antiplatelet (n = 293 for Each Cohort)	
Outcome	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Complications						
Ischemic stroke	1.23 (0.88—1.72)	0.230	1.86 (0.84—4.09)	0.126	0.74 (0.40—1.38)	0.348
Pneumonia	0.96 (0.82—1.12)	0.570	1.29 (0.89—1.88)	0.182	1.31 (0.90—1.89)	0.159
Septicemia	1.03 (0.75—1.41)	0.870	1.62 (0.81—3.24)	0.172	2.29 (1.10—4.76)	0.027
Wound infection	0.55 (0.26—1.15)	0.110	1.34 (0.30—6.03)	0.705	5.07 (0.59—43.66)	0.140
Pulmonary embolism	2.00 (0.37—10.95)	0.423	NA	NA	NA	NA
Deep vein thrombosis	1.00 (0.29—3.46)	1.000	3.02 (0.31—29.22)	0.340	NA	NA
Acute kidney injury	0.94 (0.66—1.34)	0.718	0.91 (0.38—2.17)	0.824	1.00 (0.43—2.34)	1.000
Massive blood transfusion (packed red blood cells >10 U)	1.58 (0.81—3.10)	0.184	0.55 (0.18—1.66)	0.286	1.25 (0.33—4.72)	0.737
Any complications	1.003 (0.87—1.16)	0.971	1.24 (0.89—1.74)	0.201	1.38 (0.99—1.92)	0.055
In-hospital mortality	1.04 (0.89—1.23)	0.618	2.12 (1.45—3.10)	<0.001	1.60 (1.12—2.30)	0.011

OR, odds ratio; CI, confidence interval.

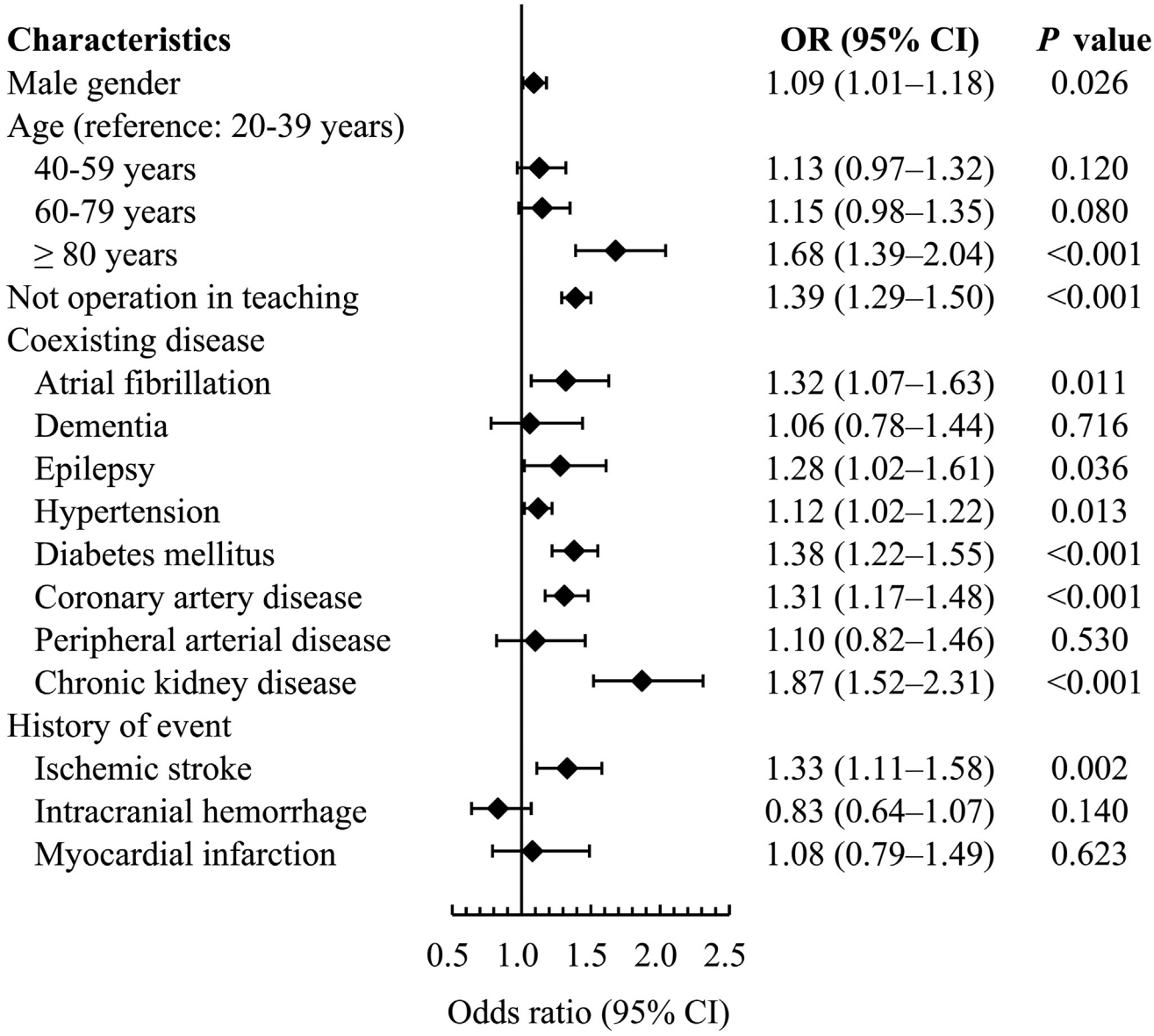

Figure 2. Association of patient characteristics with risk of in-hospital mortality. This multivariable logistic regression analysis was adjusted for all variables listed in **Table 1**. CI, confidence interval; OR, odds ratio.

antithrombotic treatment. Another possible reason could be related to the fact that significantly more blood transfusion was performed in these patients. Although complications of blood transfusion are rare, it can be life threatening because massive blood transfusions can result in abnormalities of coagulation status, vascular permeability, acid-base balance, and temperature hemostasis.[31] Previous studies have shown that a large number of blood transfusions can cause complications such as reversible posterior leukoencephalopathy syndrome.[32-34] Furthermore, blood transfusion may cause a rapid increase in total blood volume, which further leads to cerebral blood flow overload. It has been suggested[34] that an abrupt or acute cerebral hyperperfusion exceeding the capacity of autoregulation of cerebral capillary perfusion pressure could result in vasogenic edema.

Surgical Complications Associated with Antithrombotic Treatment

The 3 most common surgical complications in our study were pneumonia, septicemia, and gastrointestinal bleeding. This finding was not surprising, because patients with stroke have been shown to be more susceptible to infection as a result of immune system suppression.[35] Pneumonia was the most common complication in our study, which is consistent with other

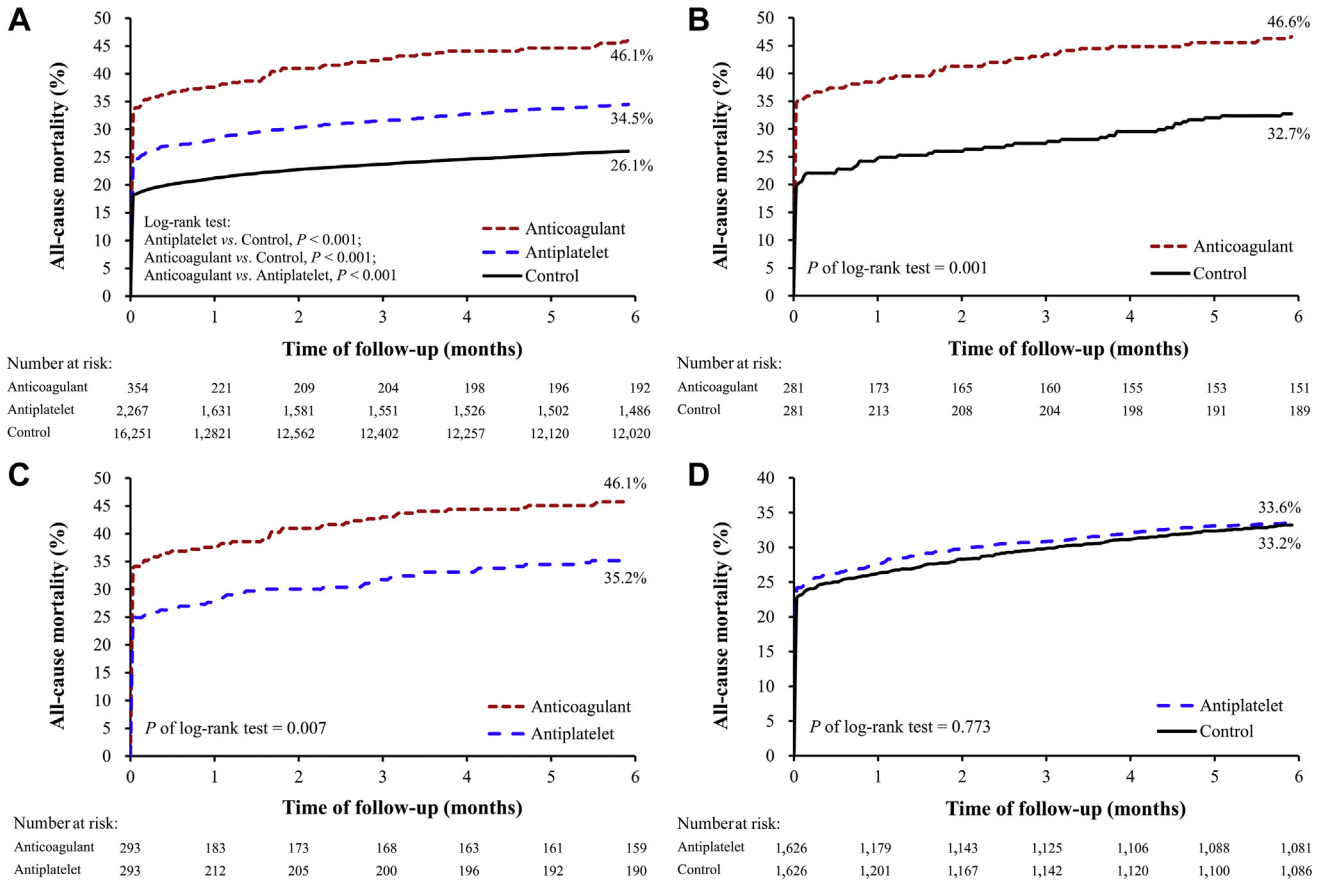

Figure 3. Kaplan-Meier survival curves of all-cause mortality. (**A**) The unadjusted Kaplan-Meier survival curves of all-cause mortality that estimated the mortality in operative patients with intracerebral hemorrhage using real-world data. Log-rank test showing $P < 0.001$ for all antiplatelet versus control, anticoagulant versus control, anticoagulant versus antiplatelet, and antiplatelet versus control. (**B**–**C**) The matched control Kaplan-Meier survival curves of all-cause mortality estimated the mortality of patients between different cohorts. Adjusted incidence curves were adjusted for all covariates listed in Table 1. *P* of log-rank test showing $P = 0.001$ for anticoagulant versus control (**B**), $P = 0.007$ for anticoagulant versus antiplatelet (**C**), and $P = 0.773$ for antiplatelet versus control (**D**).

studies of patients with stroke.[36] Pneumonia and septicemia that required medical treatment were present more often in patients with previous anticoagulant treatment. Overall, patients receiving previous anticoagulant therapy have higher complication rates compared with patients receiving either antiplatelet or nonantithrombotic therapy.

Limitations of the Study

The presented data were analyzed from Taiwan's nationwide database and the study was not a randomized trial for operative treatment patients with ICH. Therefore, there was no prospective document to suggest the reason why a craniotomy was necessary, so it was presumed that hemorrhage enlargement led to a worse neurologic examination result, such as a potential brain herniation. In addition, the database does not include neurologic or functional outcome measures, such as the Glasgow Coma Scale or modified Rankin Scale, respectively. However, the absence of such data does not lessen our data interpretation. Another consideration is that clinicians may not be blinded to antiplatelet or anticoagulant treatment before ICH development, so these data reflect an association between these medical treatments and the perceived need for craniotomy. The strengths of our study include 1) it is a large population-based follow-up study comprising all adults living in Taiwan, 2) the estimated NIHSS was used, which has already been well assessed to correlate severity of patients with ICH, and 3) the integrated details of prescription records before admission, complications, mortality, and clinical follow-up were well recorded. Furthermore, PSM analysis was applied to eliminate confounding factors among these patients.

CONCLUSIONS

This study provides a comprehensive national perspective on in-hospital complications and mortality in operative patients with ICH in Taiwan. Previous antithrombotic agent treatment in patients with ICH receiving craniotomy was associated with an increased risk of repeated brain surgery. Furthermore, our study also identified the significantly higher in-hospital mortality and 6-month all-cause mortality in patients with previous anticoagulant

therapy, but not in patients with previous antiplatelet therapy. Physicians should be more aware of the potential risk with previous antithrombotic therapy, especially anticoagulant treatment, and the negative association with life-saving surgical intervention for spontaneous ICH. This is valuable information for surgeons faced with difficult decisions in managing patients taking antithrombotic drugs but requiring neurosurgical intervention.

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SUPPLEMENTARY DATA

Supplementary Table 1. *International Classification of Diseases, Ninth Revision, Clinical Modification Code* Used in the Current Study

Variable	Code
Cerebrovascular accident	430.xx—437.xx
Intracerebral hemorrhage	431.xx
Coagulopathy	286.0—286.9, 287.1, 287.3—287.5, 289.81—289.82
Liver cirrhosis	571.2, 571.5, 571.6
Malignancy	140.xx—208.xx (Catastrophic illness card)
Cerebral vascular lesion	437.3, 747.81, 4470
Head injury	800.xx—804.xx, 850.xx—854.xx
Atrial fibrillation	427.31
Dementia	290.xx, 294.xx and intelligence assessment such as Clinical Dementia Rating (CDR)
Epilepsy	345.xx, 780.3x
Hypertension	401.xx—405.xx
Diabetes mellitus	250.xx
Coronary artery disease	410.xx—414.xx
Peripheral arterial disease	440.0x, 440.2x, 440.3x, 440.8x, 440.9x, 443.xx, 444.0x, 444.22, 444.8x, 447.8x, 447.9x
Dialysis	585.xx (catastrophic illness certificate)
Chronic kidney disease	580.xx—589.xx, 403.xx—404.xx, 016.0x, 095.4x, 236.9x, 250.4x, 274.1x, 442.1x, 447.3x, 440.1x, 572.4x, 642.1x, 646.2x, 753.1x, 283.11, 403.01, 404.02, 446.21
Ischemic stroke	433.xx, 434.xx, 435.xx, 436.xx, 437.xx
Intracranial hemorrhage	430.xx, 431.xx, 432.xx
Myocardial infarction	410.xx, 412.xx
Pneumonia	480.xx—486.xx
Septicemia	038.xx
Wound infection	998.0, 998.1, 998.2
Pulmonary embolism	415.1x
Gastrointestinal bleeding	530.21, 530.7, 530.82, 531.xx—534.xx, 535.xx, 537.83, 537.84, and 578.xx
Deep vein thrombosis	453.xx
Acute kidney injury (acute renal failure or de novo dialysis)	584.xx, 585.xx (catastrophic illness certificate)

Supplementary Table 2. Baseline and Clinical Characteristics in the Antiplatelet and Control Groups After Propensity Score Matching

Variable	Antiplatelet (n = 1626)	Control (n = 1626)	P Value
Gender			1.000
Male	1003 (61.7)	1003 (61.7)	
Female	623 (38.3)	623 (38.3)	
Age (years)	66.1 ± 11.5	65.9 ± 11.3	0.611
Age group			0.569
20—39 years	28 (1.7)	28 (1.7)	
40—59 years	465 (28.6)	464 (28.5)	
60—79 years	968 (59.5)	992 (61.0)	
≥80 years	165 (10.1)	142 (8.7)	
Operation in teaching hospital			0.160
No	977 (60.1)	1016 (62.5)	
Yes	649 (39.9)	610 (37.5)	
Coexisting disease			
Atrial fibrillation	13 (0.8)	13 (0.8)	1.000
Dementia	42 (2.6)	37 (2.3)	0.569
Epilepsy	61 (3.8)	44 (2.7)	0.092
Hypertension	1175 (72.3)	1175 (72.3)	1.000
Diabetes mellitus	382 (23.5)	374 (23.0)	0.740
Coronary artery disease	382 (23.5)	352 (21.6)	0.208
Peripheral arterial disease	39 (2.4)	44 (2.7)	0.578
Dialysis	58 (3.6)	54 (3.3)	0.700
Chronic kidney disease	127 (7.8)	110 (6.8)	0.251
History of event			
Ischemic stroke	150 (9.2)	123 (7.6)	0.088
Intracranial hemorrhage	63 (3.9)	50 (3.1)	0.213
Myocardial infarction	29 (1.8)	24 (1.5)	0.489
Charlson Comorbidity Index	2.4 ± 1.5	2.3 ± 1.4	0.107
Estimated National Institutes of Health Stroke Scale	22.8 ± 3.5	22.7 ± 3.5	0.187

Values are number (%) except where indicated otherwise.

Supplementary Table 3. Baseline and Clinical Characteristics in the Anticoagulant and Control Groups After Propensity Score Matching

Variable	Anticoagulant ($N = 281$)	Control ($N = 281$)	*P* Value
Gender			1.000
Male	153 (54.4)	153 (54.4)	
Female	128 (45.6)	128 (45.6)	
Age (years)	65.0 ± 13.6	64.4 ± 12.2	0.593
Age group			0.107
20—39 years	15 (5.3)	8 (2.8)	
40—59 years	81 (28.8)	85 (30.2)	
60—79 years	151 (53.7)	167 (59.4)	
≥80 years	34 (12.1)	21 (7.5)	
Operation in teaching hospital			0.063
No	136 (48.4)	158 (56.2)	
Yes	145 (51.6)	123 (43.8)	
Coexisting disease			
Atrial fibrillation	95 (33.8)	95 (33.8)	1.000
Dementia	8 (2.8)	8 (2.8)	1.000
Epilepsy	7 (2.5)	8 (2.8)	0.794
Hypertension	195 (69.4)	195 (69.4)	1.000
Diabetes mellitus	61 (21.7)	62 (22.1)	0.919
Coronary artery disease	86 (30.6)	71 (25.3)	0.158
Peripheral arterial disease	19 (6.8)	14 (5.0)	0.370
Dialysis	12 (4.3)	14 (5.0)	0.688
Chronic kidney disease	27 (9.6)	29 (10.3)	0.778
History of event			
Ischemic stroke	28 (10.0)	20 (7.1)	0.227
Intracranial hemorrhage	8 (2.8)	10 (3.6)	0.632
Myocardial infarction	11 (3.9)	12 (4.3)	0.831
Charlson Comorbidity Index	2.7 ± 1.7	2.7 ± 1.9	0.908
Estimated National Institutes of Health Stroke Scale	22.7 ± 3.4	22.6 ± 3.3	0.954

Values are number (%) except where indicated otherwise.

Supplementary Table 4. Baseline and Clinical Characteristics in the Anticoagulant and Antiplatelet Groups After Propensity Score Matching

Variable	Anticoagulant (*N* = 293)	Antiplatelet (*N* = 293)	*P* Value
Gender			1.000
Male	167 (57.0)	167 (57.0)	
Female	126 (43.0)	126 (43.0)	
Age (years)	65.8 ± 13.0	66.8 ± 12.7	0.365
Age group			0.772
20—39 years	12 (4.1)	11 (3.8)	
40—59 years	82 (28.0)	74 (25.3)	
60—79 years	165 (56.3)	167 (57.0)	
≥80 years	34 (11.6)	41 (14.0)	
Operation in teaching hospital			0.869
No	141 (48.1)	143 (48.8)	
Yes	152 (51.9)	150 (51.2)	
Coexisting disease			
Atrial fibrillation	107 (36.5)	106 (36.2)	0.932
Dementia	7 (2.4)	7 (2.4)	1.000
Epilepsy	6 (2.0)	6 (2.0)	1.000
Hypertension	216 (73.7)	212 (72.4)	0.710
Diabetes mellitus	69 (23.5)	59 (20.1)	0.317
Coronary artery disease	109 (37.2)	111 (37.9)	0.865
Peripheral arterial disease	23 (7.8)	22 (7.5)	0.877
Dialysis	12 (4.1)	12 (4.1)	1.000
Chronic kidney disease	29 (9.9)	30 (10.2)	0.891
History of event			
Ischemic stroke	31 (10.6)	36 (12.3)	0.516
Intracranial hemorrhage	8 (2.7)	8 (2.7)	1.000
Myocardial infarction	13 (4.4)	16 (5.5)	0.568
Charlson Comorbidity Index	2.7 ± 1.8	2.7 ± 1.6	0.767
Estimated National Institutes of Health Stroke Scale	22.8 ± 3.4	23.0 ± 3.5	0.322

Values are number (%) except where indicated otherwise.