Journal of the American Heart Association

ORIGINAL RESEARCH

Dual Antiplatelet Therapy with Clopidogrel and Aspirin Versus Aspirin Monotherapy in Patients Undergoing Coronary Artery Bypass Graft Surgery

Jianyu Qu, MD; Heng Zhang, MD, PhD; Chenfei Rao, MD, PhD; Sipeng Chen, MS, MPH; Yan Zhao, MD; Hansong Sun, MD, PhD; Yunhu Song, MD; Sheng Liu, MD, PhD; Liqing Wang, MD, PhD; Wei Feng, MD, PhD; Shuiyun Wang, MD, PhD; Shengshou Hu, MD; Zhe Zheng, MD, PhD

BACKGROUND: The optimal antiplatelet therapy after coronary artery bypass grafting remains unclear. We evaluated the association of dual antiplatelet therapy (DAPT) with clopidogrel plus aspirin and clinical outcomes among patients undergoing coronary artery bypass grafting.

METHODS AND RESULTS: A total of 18 069 consecutive patients who underwent primary isolated coronary artery bypass grafting between 2013 and 2017 were identified from a contemporary registry, and 10 854 (60.1%) received DAPT with clopidogrel plus aspirin as determined by claimed prescriptions after surgery. Cox regression models with inverse probability of treatment weighting were used to examine the associations between DAPT and outcomes. Patients who received DAPT, compared with those who received aspirin monotherapy, had a lower incidence of a composite of all-cause death, myocardial infarction, stroke, or repeat revascularization at 6 months (2.9% versus 4.2%; inverse probability of treatment weighting–adjusted hazard ratio [HR], 0.65; 95% CI, 0.55–0.77; $P<0.001$) as well as death (HR, 0.61; 95% CI, 0.41–0.90), myocardial infarction (HR, 0.55; 95% CI, 0.40–0.74), and stroke (HR, 0.58; 95% CI, 0.46–0.74). The incidence of major bleeding did not differ significantly between the 2 groups (HR, 1.11; 95% CI, 0.69–1.78). Similar results were noted across multiple subgroups as well as when using different analytic methods.

CONCLUSIONS: Among patients undergoing coronary artery bypass grafting, DAPT with clopidogrel plus aspirin as secondary prevention was associated with reduced risk of major adverse cardiovascular and cerebrovascular events within 6 months as compared with aspirin monotherapy, and there was no significant increase in major bleeding.

Key Words: aspirin ■ clopidogrel ■ coronary artery bypass grafting ■ dual antiplatelet therapy ■ secondary prevention

Coronary artery bypass grafting (CABG) has been established as an effective treatment for patients with extensive coronary artery disease.[1] Aspirin is recommended as a fundamental secondary prevention medication for patients with CABG to maintain the benefits of revascularization and prevent major adverse cardiovascular events.[2] However, patients treated with CABG still have a notable risk of subsequent major ischemic cardiac and cerebrovascular events, which may exceed 10% in the first 6 to 12 months after the surgery.[3] Reduced postoperative responsiveness to aspirin, platelet activation, and thrombosis results in systemic hypercoagulability and early graft failure. These have been identified as vital contributing factors in this context.[4–7]

Correspondence to: Zhe Zheng, MD, PhD, National Clinical Research Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, and Department of Cardiovascular Surgery, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 167 Beilishi Rd, Xicheng District, 100037, Beijing, People's Republic of China. E-mail: zhengzhe@fuwai.com

Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.020413.

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- The present study is one of the largest analyses that primarily focused on the association of dual antiplatelet therapy and major outcomes in patients who underwent coronary artery bypass grafting.
- We found that post–coronary artery bypass grafting dual antiplatelet therapy with clopidogrel plus aspirin was associated with reduced risk of major adverse cardiovascular and cerebrovascular events within 6 months as compared with aspirin monotherapy, and there was no significant increase in major bleeding.
- The association of dual antiplatelet therapy with fewer clinical events was consistent across key clinical subgroups, including age, sex, clinical presentations, diabetes mellitus, and bypass techniques.

What Are the Clinical Implications?

- Dual antiplatelet therapy with clopidogrel plus aspirin could be a promising secondary prevention strategy that may improve the outcome of patients who had coronary artery bypass grafting, including those with acute coronary syndrome or stable angina, presence or absence of diabetes mellitus, or had on-pump or off-pump bypass.

Nonstandard Abbreviations and Acronyms

DAPT	dual antiplatelet therapy
IPTW	inverse probability of treatment weighting
MACCE	major adverse cardiac and cerebrovascular events

Dual antiplatelet therapy (DAPT) with aspirin plus a $P2Y_{12}$ receptor antagonist (eg, clopidogrel or ticagrelor) to enhance the antiplatelet effect[8,9] has been reported to slow down native coronary stenosis progression[10] and increase graft patency[11–16] in patients who underwent CABG as well as prevent recurrent stroke in patients with ischemic cerebrovascular disease.[17,18] However, the question of whether the benefits associated with DAPT, especially the potential improvement in graft patency, translate into better clinical outcomes remains inadequately investigated with mixed results,[16,19–23] and DAPT may increase the risk of bleeding.[9,23] Clinical practice guidelines recommend that DAPT may be considered for selected patients who are at high risk of recurrent ischemic events, including those who presented with acute coronary syndrome (ACS) or received coronary stent implantation within 1 year before CABG, or underwent off-pump CABG.[2,24–26] However, they also acknowledge the need for more evidence in this area because these recommendations are merely based on expert consensus or underpowered secondary data (level C of evidence).[2,24–26] There is even less evidence available on the efficacy and safety of DAPT in specific patient populations, such as patients with stable angina who constitute the majority of CABG procedures and those who underwent on-pump CABG.

Therefore, the present study examined the association between post-CABG DAPT with clopidogrel plus aspirin and clinical outcomes in a large all-comer clinical practice registry. We hypothesized that DAPT may be associated with reduced risk of major adverse cardiac and cerebrovascular events (MACCE) when compared with aspirin monotherapy.

METHODS

Study Design and Data Source

The data, analytical methods, and study materials that support the findings of this study may be made available from the corresponding author on reasonable request. This retrospective cohort analysis used data from a contemporary registry of consecutive patients who underwent CABG at Fuwai Hospital (Beijing, China). Data on patient characteristics, procedures, and medications were extracted from the registry and supplemented with electronic medical records. All data were collected by experienced clinical researchers, and clinical definitions followed those of the Society of Thoracic Surgeons National Adult Cardiac Database (http://www.sts.org). The accuracy and completeness of these data were ensured through multiple procedures described previously.[27,28]

Patients were followed up by routine outpatient visit or via telephone by trained cardiovascular research nurses as part of standard institutional procedures. At follow-up, patients were asked to enumerate all of their current medications to the interviewer, including drug name, dose, and schedule.[27] If any adverse events were reported during the follow-up process, patients were asked to provide related medical records for further confirmation. Details on aspirin and clopidogrel use were obtained by review of in-hospital medication dispensing records, discharge summaries, and follow-up. The institutional review board at Fuwai Hospital approved the use of clinical data for this study and waived the requirement of informed consent.

Study Population

All adult patients who underwent primary CABG between January 1, 2013 and December 31, 2017 were

considered for the analysis. Patients were excluded if they had a concomitant cardiac surgery (eg, valve replacement or ventricular aneurysm resection), received simultaneous or staged hybrid coronary revascularization, were exposed to antiplatelet agents other than aspirin and clopidogrel (eg, ticagrelor or prasugrel) or treated with clopidogrel alone post-CABG, required vitamin K antagonist therapy, or died before the initiation of any antiplatelet therapy. Patients with DAPT were defined as those who had at least 1 postoperative prescription for aspirin plus clopidogrel. The aspirin monotherapy cohort was defined as patients who received aspirin alone post-CABG. Patients were considered exposed to the treatment (DAPT or aspirin monotherapy) through the end of follow-up, analogous to an intention-to-treat design.

Clinical Management

Patients were managed in accordance with local practice guidelines, and all procedures were performed using standard bypass techniques (Data S1).[27,29] The choice between on-pump and off-pump CABG was at the discretion of the principal surgeon. Whenever possible, the internal thoracic artery was preferentially used for revascularization of the left anterior descending artery. The perioperative antiplatelet therapy was also left to the individual surgeon's evaluation and decision, though clopidogrel should have been discontinued at least 5 days before surgery if clinically feasible. Local guidelines and regulatory authorities do not specify rules or restrictions for the selection of patients who receive post-CABG DAPT administration. Routinely, aspirin was started within 24 hours (ideally within 6 hours) after CABG in a daily dose of 100 mg and recommended to continue indefinitely. For patients who received DAPT, 75 mg of clopidogrel was added to 100 mg of aspirin daily without a loading dose, preferably within 48 hours after CABG, but when clinical stability was ensured and chest tube output was <30 mL/hour for at least 2 hours.[11] The duration of DAPT was determined by the treating physician, with the treatment typically maintained for a minimum of 1 month. Additional secondary prevention therapies (eg, statins, β-blockers, or renin-angiotensin system blockade) were recommended for all patients, if indicated, following clinical guidelines.

Outcomes

The primary outcome was the first occurrence of MACCE, defined as a composite of all-cause mortality, myocardial infarction, stroke, and repeat revascularization within 6 months after CABG. Secondary outcomes included individual components of the primary outcome and major bleeding, which was defined as a composite of in-hospital reoperation because of bleeding and hospitalization for bleeding after discharge. All outcome measures were prespecified, rigorously verified, and adjudicated by independent clinicians. Detailed definitions of the outcomes are provided in Data S1.

Statistical Analysis

Detailed statistical methods are available in the Data S1. We used inverse probability of treatment weighting (IPTW) based on propensity scores to construct a weighted cohort of patients who differed with respect to postoperative antiplatelet therapy but were similar with respect to other measured characteristics.[30] A propensity score for the predicted probability of receiving DAPT in each patient was calculated from a nonparsimonious multivariable logistic regression model fitted with patient characteristics that may confound the relationship between antiplatelet therapy and clinical outcomes (ie, demographic characteristics, medical history, concurrent medication use, procedure-related characteristics, and year of surgery; the full list of the 33 variables included in the propensity model is provided in the Data S1). The IPTW analysis was performed to estimate the average treatment effect, that is, the effect of treatment on the entire population eligible for isolated CABG.[30] Stabilized weights were used to reduce the variability in the IPTW models.[31] Balance among covariates was assessed using standardized differences, and a difference of ≤10% was considered the ideal balance.[31] To account for missing data (1.3% for preoperative hemoglobin and platelet count; <0.3% for height, weight, and preoperative creatinine), a single mean imputation stratified by study groups was used.

Time-to-event analyses for MACCE and all-cause mortality were performed using weighted Cox proportional hazards models. Cardiovascular death, myocardial infarction, stroke, repeat revascularization, and major bleeding were analyzed in the weighted population, accounting for death (or noncardiovascular death) as a competing risk using the Fine and Gray method.[32] Hazard ratios (HRs) and 95% CIs were estimated with a robust variance estimator to account for the weighted nature of the population. The proportional hazards assumption was confirmed by Schoenfeld residuals plots. Survival curves were constructed using the IPTW-adjusted Kaplan-Meier method and compared using the IPTW-adjusted log-rank test.[33] For each outcome analyzed, the follow-up period began upon initiation of DAPT or aspirin monotherapy (time 0). Patients were censored on first occurrence of the event, death, loss to follow-up, or reaching 180 days of follow-up. Prespecified

subgroup analyses were performed by refitting separate IPTW survival models for each subgroup and conducting tests for interaction.

We performed several sensitivity analyses to assess the robustness of our findings (Data S1). First, alternative analytic strategies (ie, propensity score matching, multivariable Cox regression, and doubly robust estimation combining the propensity score and outcome regression)[34,35] were used to compare outcomes between study groups. Second, the primary analyses were repeated after adjusting for other secondary prevention medications at discharge (ie, statin, β-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker) or including principal surgeon as a random effect to confirm that the observed associations were not the result of differences in the use of postoperative medications or unobserved characteristics between surgeons, respectively. Third, analyses of study outcomes were performed after excluding those who were treated with $P2Y_{12}$ inhibitors within 5 days before CABG to ensure that treatment-related outcome differences were not confounded by preoperative antiplatelet therapy.[36] Fourth, because a proportion of patients in the DAPT group started clopidogrel a few days after the initiation of aspirin rather than starting the 2 medications simultaneously, we repeated the primary analysis after exclusion of patients from the DAPT group who did not start clopidogrel and aspirin on the same day to minimize possible immortal time bias.[37,38] Finally, we calculated the *E*-value to quantify the potential for unmeasured confounders to explain the effect of DAPT on estimated HRs.[39]

All tests were 2-tailed, with *P* values <0.05 indicating statistical significance. Data were analyzed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Between 2013 and 2017, there were 22 819 patients who met the study inclusion criteria. After the exclusion criteria were applied, 18 069 (79.2%) patients were included in the analysis; 10 854 (60.1%) received DAPT with clopidogrel plus aspirin after surgery, and 7215 (39.9%) received aspirin monotherapy (Figure S1). Table 1 summarizes selected baseline characteristics of study patients before propensity score weighting (a list of all characteristics is provided in Table S1). Patients who received DAPT, as compared with those who received aspirin monotherapy, were younger; had a higher prevalence of insulin-dependent diabetes mellitus, peripheral artery disease, and previous percutaneous coronary intervention; and were more likely to be treated

Table 1. Selected Characteristics of Patients Before Inverse Probability Weighting

Characteristics	DAPT (N=10 854)	Aspirin Monotherapy (N=7215)	*P* Value
Age, y, mean (SD)	60.8 (8.6)	61.9 (8.5)	<0.01
Age ≥65 y, n (%)	3542 (32.6)	2651 (36.7)	<0.01
Female sex, n (%)	2441 (22.5)	1715 (23.8)	0.04
BMI*, kg/m^2, mean (SD)	25.7 (3.0)	25.7 (3.0)	0.21
Medical history, n (%)			
Smoking	6029 (55.5)	3944 (54.7)	0.24
Diabetes mellitus	4201 (38.7)	2782 (38.6)	0.84
Insulin-treated diabetes mellitus	903 (8.3)	409 (5.7)	<0.01
Hypertension	7091 (65.3)	4700 (65.1)	0.79
Hyperlipidemia	7134 (65.7)	4553 (63.1)	<0.01
Peripheral artery disease	1051 (9.7)	454 (6.3)	<0.01
Previous myocardial infarction	2880 (26.5)	1852 (25.7)	0.20
Previous PCI	1485 (13.7)	708 (9.8)	<0.01
Previous CVA	1248 (11.5)	781 (10.8)	0.16
Clinical presentation, n (%)			0.06
Stable angina	4810 (44.3)	3051 (42.3)	
Unstable angina	5341 (49.2)	3683 (51.0)	
NSTEMI	310 (2.9)	215 (3.0)	
STEMI	393 (3.6)	266 (3.7)	
LVEF, n (%)			0.11
≥50%	10183 (93.8)	6713 (93.0)	
40%–49%	528 (4.9)	379 (5.3)	
30%– 39%	135 (1.2)	115 (1.6)	
<30%	8 (0.1)	8 (0.1)	
EuroSCORE†, n (%)			<0.01
0–2	7000 (64.5)	4453 (61.7)	
3–5	3135 (28.9)	2194 (30.4)	
≥6	719 (6.6)	568 (7.9)	
Medication use before surgery, n (%)			
Aspirin	4128 (38.0)	2868 (39.8)	0.02
Clopidogrel	3868 (35.6)	2511 (34.8)	0.25
Clopidogrel within 5 days	770 (7.1)	540 (7.5)	0.32
Intravenous nitrate	1533 (14.1)	817 (11.3)	<0.01
β-blocker	9699 (89.4)	6346 (88.0)	0.01
Statin	9194 (84.7)	5622 (77.9)	<0.01
ACEI/ARB	4362 (40.2)	3022 (41.9)	0.02
Surgical procedure characteristics			
Emergency surgery‡, n (%)	330 (3.0)	126 (1.7)	<0.01
On pump, no. (%)	5561 (51.2)	3272 (45.3)	<0.01
LIMA to LAD graft, n (%)	10067 (92.7)	6844 (94.9)	<0.01
No. of grafts, mean (SD)	3.3 (0.9)	3.4 (0.9)	<0.01

(*Continued*)

Table 1. Continued

Characteristics	DAPT (N=10 854)	Aspirin Monotherapy (N=7215)	*P* Value
No. of arterial grafts	1.0 (0.4)	1.0 (0.2)	<0.01
No. of venous grafts	2.3 (0.9)	2.4 (0.9)	<0.01

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CVA, cerebrovascular accident; DAPT, dual antiplatelet therapy; EuroSCORE, European System for Cardiac Operative Risk Evaluation I; LAD, left anterior descending artery; LIMA, left internal mammary artery; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

*Calculated as weight in kilograms divided by height in meters squared.

†The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is a risk model for predicting the risk of death after cardiac surgery; scores range from 0 to 100%, with higher scores indicating greater risk.

‡Operation before the beginning of the next working day after decision to operate.

with intravenous nitrate or statins before surgery. Emergency surgery and use of cardiopulmonary bypass were more common in the DAPT group. The overall proportion of DAPT prescriptions increased over the 5-year study period but varied substantially across surgeons (Figures S2 and S3). Details on the administration of antiplatelet regimens are provided in Table S2. For patients who received DAPT, 87.6% of them maintained the therapy at discharge and 54.5% at 6 months (calculated by dividing the total on-treatment patients at the 2 time-points by the corresponding surviving patients). Covariates were well balanced in the propensity-weighted cohort, with all standardized differences <10% (Figure S4).

Study Outcomes

Table 2 shows the incidences of the primary and secondary outcomes, and Figure 1 and Figure S5 show the weighted Kaplan–Meier curves of the study outcomes for the DAPT and aspirin monotherapy groups. The primary composite outcome occurred in 312 (2.9%) patients who received DAPT during the 6-month follow-up period as compared with 305 patients (4.2%) who received aspirin monotherapy (unadjusted HR, 0.67; 95% CI, 0.58–0.79; *P*<0.001). After adjustment using the IPTW approach, DAPT was associated with lower risks of MACCE (HR, 0.65; 95% CI, 0.55–0.77; *P*<0.001) and all-cause mortality (0.6% versus 0.9%; HR, 0.61; 95% CI, 0.41–0.90; *P*=0.012) (Table 2). The DAPT group also had lower cumulative incidences of myocardial infarction (0.9% versus 1.3%; HR, 0.55; 95% CI, 0.40–0.74; *P*<0.001) and stroke (1.3% versus 2.3%; HR, 0.58; 95% CI, 0.46–0.74; *P*<0.001) in analyses accounting for the competing risk of death. The risk of major bleeding was similar for the DAPT and aspirin monotherapy groups (0.5% versus 0.4%), with an IPTW-adjusted HR of 1.11 (95% CI, 0.69–1.78; *P*=0.67). In a post hoc analysis evaluating the net clinical benefit of MACCE offset by major bleeding, a composite of MACCE and major bleeding occurred in 355 (3.3%) patients with DAPT and 330 (4.6%) patients with aspirin monotherapy (HR, 0.68; 95% CI, 0.58–0.80; *P*<0.001). DAPT with clopidogrel would lead to 136 fewer MACCE per 10 000 patients at the expense of 8 additional major bleeding events, with a number needed to treat of 74 and a number needed to harm of 1380.

Subgroup Analyses

The association of DAPT and primary outcome was consistent across predefined clinical subgroups defined by age (older or younger than 65 years), sex, clinical presentation (acute coronary syndrome [ACS] or stable angina), presence or absence of diabetes mellitus, presence or absence of hyperlipidemia, surgery risk (European System for Cardiac Operative Risk Evaluation I [EuroSCORE] ≥3 or ≤2), off-pump or on-pump bypass, and number of venous grafts (≥3 or ≤2) as well as in post hoc subsets defined by year of surgery (2013 to 2015, 2016 to 2017) (Figure 2). The difference between DAPT and aspirin monotherapy was less pronounced in the subgroup of patients who presented with ACS (HR, 0.75; 95% CI, 0.61–0.94) than it was in the subgroup of patients with stable angina (HR, 0.53; 95% CI, 0.40–0.69; *P*=0.04 for interaction), although DAPT was favored in both (Table 3 and Figure 2). Similarly, the association of DAPT and patient outcome tended to attenuate among patients with diabetes mellitus as opposed to among those without diabetes mellitus (Table 3, *P*=0.23 for interaction). No heterogeneity was noted among other subgroups (Figure 2).

Sensitivity Analyses

Propensity score matching created a well-balanced cohort of 6635 patient pairs (Table S3). Findings from the propensity score–matched analyses were consistent with the primary IPTW-adjusted analyses, demonstrating lower risk of MACCE with DAPT (HR, 0.68; 95% CI, 0.57–0.82; *P*<0.001) and comparable risk of major bleeding (HR, 1.14; 95% CI, 0.69–1.90; *P*=0.60) (Table S4). Both multivariable Cox regression and double robust estimation yielded nearly identical results with the original IPTW analysis (Tables S5).

In the primary propensity score–weighted cohort, the risk of MACCE remained lower in the DAPT group compared with the aspirin monotherapy group after further adjustment for other secondary prevention medications (HR, 0.67; 95% CI, 0.57–0.80; *P*<0.001), incorporation of principal surgeon as a random effect (HR, 0.65; 95% CI, 0.54–0.78; *P*<0.001), and exclusion of 1368 patients who were treated with $P2Y_{12}$

Table 2. Association of DAPT Versus Aspirin Monotherapy With Outcomes Within 6 Months After Coronary Artery Bypass Graft Surgery

	DAPT (N=10 854)	Aspirin Monotherapy (N=7215)	Adjusted HR (95% CI)*	*P* Value
Primary outcome, n (%)				
MACCE†	312 (2.9)	305 (4.2)	0.65 (0.55–0.77)	<0.001
Secondary outcomes, n (%)				
All-cause death	61 (0.6)	66 (0.9)	0.61 (0.41–0.90)	0.012
Cardiovascular death	44 (0.4)	49 (0.7)	0.57 (0.36–0.90)	0.015
MI	95 (0.9)	96 (1.3)	0.55 (0.40–0.74)	<0.001
Stroke‡	142 (1.3)	165 (2.3)	0.58 (0.46–0.74)	<0.001
Repeat revascularization	34 (0.3)	21 (0.3)	1.06 (0.61–1.86)	0.83
Cardiovascular death, MI, or ischemic stroke	263 (2.4)	282 (3.9)	0.59 (0.49–0.70)	<0.001
Cardiovascular death or MI	132 (1.2)	124 (1.7)	0.62 (0.48–0.81)	<0.001
Major bleeding	53 (0.5)	30 (0.4)	1.11 (0.69–1.78)	0.67
In-hospital reoperation for bleeding	16 (0.1)	9 (0.1)	1.27 (0.55–2.94)	0.57
Hospitalization for bleeding	37 (0.3)	21 (0.3)	1.17 (0.66–2.08)	0.59
Net clinical benefit outcome, n (%)				
MACCE, major bleeding	355 (3.3)	330 (4.6)	0.68 (0.58–0.80)	<0.001

DAPT indicates dual antiplatelet therapy; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; and MI, myocardial infarction.
*Estimated using inverse probability of treatment-weighted Cox regression or Fine and Gray model.
†A composite of all-cause mortality, MI, stroke, and repeat revascularization.
‡Seven patients in the DAPT group and 2 patients in the aspirin-alone group had hemorrhagic stroke.

inhibitors within 5 days before CABG (HR, 0.67; 95% CI, 0.56–0.79; *P*<0.001) (Table S6). The exclusion of patients who started clopidogrel and aspirin on different days after CABG in the DAPT group (*N*=5484; analysis conducted to account for potential immortal time bias) did not alter the findings substantially (Table 4). The *E*-value corresponding to the lower bound was 1.92 for MACCE (*E*-value for point estimate, 2.45) and 1.00 for major bleeding (*E*-value for point estimate, 1.46).

DISCUSSION

In this large cohort study comparing outcomes of DAPT with aspirin monotherapy in patients undergoing isolated CABG, the use of DAPT was associated with significantly lower risk of a composite outcome of death, myocardial infarction, stroke, or repeat revascularization as well as 3 individual components of the outcome—death, myocardial infarction, and stroke—at 6 months after the surgery. The association was apparent across clinically important subgroups, including patients with preoperative ACS or stable angina, those with or without diabetes mellitus, and those who underwent on-pump or off-pump bypass. There was no evidence of a higher risk of major bleeding among patients who received DAPT.

Inhibition of platelet activation and aggregation is crucial for maintaining graft patency and improving outcomes for patients with CABG, especially considering the continued popularity of saphenous vein grafts as the secondary bypass conduit supplement to the left internal mammary artery.[1,6] DAPT with a $P2Y_{12}$ inhibitor added to aspirin is an appealing secondary prevention strategy for patients who had CABG because its potent synergistic antithrombotic effects might help to overcome resistance to aspirin and prevent thrombosis in grafts, native coronary arteries, and even cerebrovascular arteries.[4,8,10,18] A recent randomized controlled trial that compared the effect of ticagrelor plus aspirin versus aspirin alone on saphenous vein graft patency[14] and 3 comprehensive meta-analyses incorporating data from both randomized controlled trials and observational studies[15,16,23] found that adding a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) to aspirin after CABG reduced the risk of saphenous vein graft failure. However, this benefit was not confirmed in another newly published randomized study on the same topic.[40]

Limited data are available to determine whether DAPT improves patient outcomes.[19,20,22] In a meta-analysis of 20 315 patients from 11 randomized controlled trials and 11 observational studies,[23] 7481 (37%) patients received postoperative DAPT (97% with clopidogrel), and DAPT was associated with lower cardiovascular mortality in the pooled observational sample (odds ratio, 0.67; 95% CI, 0.49–0.93). However, a subanalysis limited to patients from randomized controlled trials failed to demonstrate

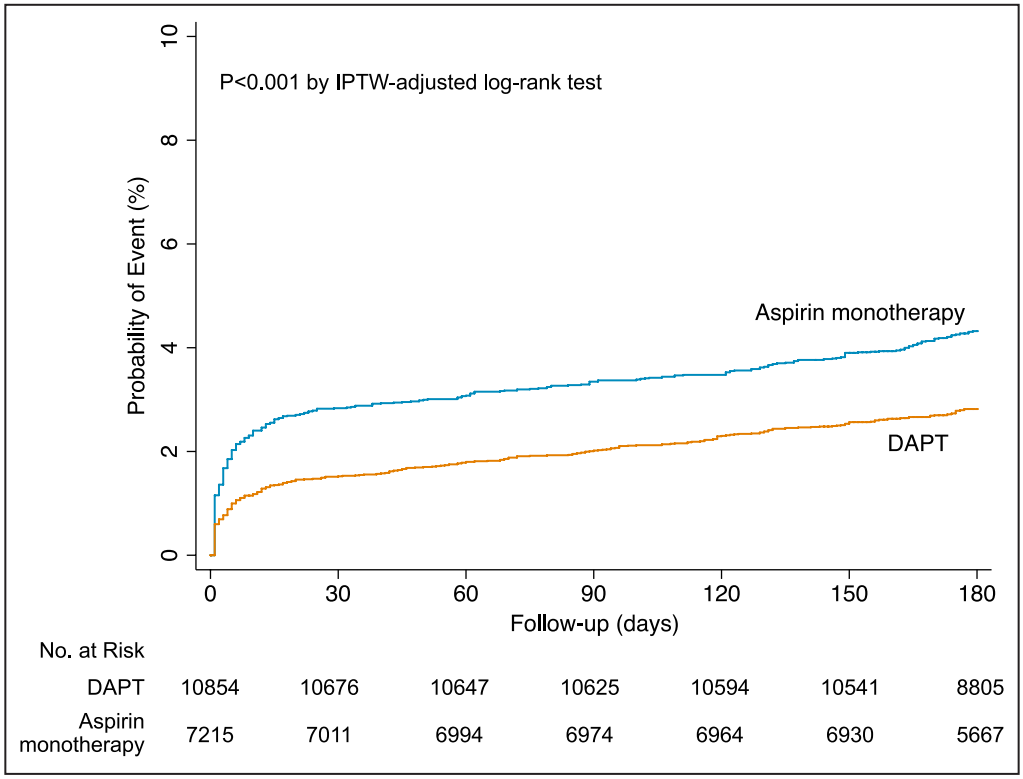


Figure 1. Inverse probability of treatment weighting-adjusted Kaplan-Meier analysis for the primary outcome.
The at-risk table shows the actual number of patients at risk. DAPT indicates dual antiplatelet therapy; and IPTW, inverse probability of treatment weighting.

a reduction in mortality (odds ratio, 0.84; 95% CI, 0.56–1.26). Moreover, DAPT was associated with a 31% higher risk of bleeding in the overall study population. It is noteworthy that almost all of the studies involved were designed to evaluate the efficacy of DAPT on graft patency rather than its effects on clinical outcomes, were underpowered,[15,16,23] had substantially heterogeneous populations,[14,40] and used different DAPT definitions, thereby precluding conclusive inference and resulting in inconsistent guideline recommendations[2,24,25] and variation in real-world clinical practice patterns.[41]

In the present study, 60% of patients were prescribed DAPT after CABG, which is considerably higher than the proportions reported in previous studies (20%–50%).[23] This finding may reflect differences in institutional practice experiences[11] or the removal of financial barriers to clopidogrel because the drug was covered for patients in our study by local healthcare insurance. We noted substantial variation in DAPT prescription rates (26% to 95%) across the 74 surgeons involved in our study, which is consistent with a survey among Canadian cardiac surgeons.[41] Only half of the patients in our DAPT group started therapy on postoperative day 0 or 1, and maintenance to DAPT rapidly declined to 54.5% by 6 months, similar to previous studies.[20–22,40,42] These findings suggest potential hesitation by surgeons regarding routine use of DAPT in patients who had CABG.

To our knowledge, the present study is the largest to date to principally investigate the association between DAPT and clinical outcomes in a contemporary CABG population. Our findings suggest that post-CABG DAPT with clopidogrel is an effective and safe secondary prevention regimen that can improve patient outcomes. We found a 39% reduction in mortality among patients treated with DAPT, an effect similar to 2 thorough meta-analyses.[23,43] This improvement in survival could be the cumulative result of better graft patency, as previously demonstrated[10,15,16,23] and supported by the lower incidences of myocardial infarction and cardiovascular death in the current analysis, and potential pleiotropic benefits of clopidogrel.[44] Additionally, for the first time, we observed a 50% lower risk of stroke at 6 months after CABG for patients taking DAPT with clopidogrel versus aspirin monotherapy. This finding is consistent with a trial of 5170 patients with recent transient ischemic attack or minor stroke that showed a combination of clopidogrel and aspirin was superior to aspirin alone in reducing the risk of stroke.[17] Collectively, the findings indicate that post-CABG DAPT contributed to a significantly lower risk of MACCE when compared with aspirin monotherapy.

	No. of Events/Total Patients (%)		HR (95% CI)	P Value	P for Interaction
	DAPT	Aspirin Monotherapy			
Age					0.87
≥65, years	136/3542 (3.8)	146/2651 (5.5)	0.67 (0.53, 0.86)	0.002	
<65, years	176/7312 (2.4)	159/4564 (3.5)	0.65 (0.52, 0.82)	<0.001	
Sex					0.69
Male	230/8413 (2.7)	221/5500 (4.0)	0.67 (0.55, 0.81)	<0.001	
Female	82/2441 (3.4)	84/1715 (4.9)	0.72 (0.52, 0.99)	0.043	
Clinical presentation					0.04
Acute coronary syndrome	195/6044 (3.2)	177/4164 (4.3)	0.75 (0.61, 0.94)	0.010	
Stable angina	117/4810 (2.4)	128/3051 (4.2)	0.53 (0.40, 0.69)	<0.001	
Diabetes mellitus					0.23
Yes	139/4201 (3.3)	120/2782 (4.3)	0.76 (0.59, 0.99)	0.040	
No	173/6653 (2.6)	185/4433 (4.2)	0.59 (0.47, 0.73)	<0.001	
Hyperlipidemia					0.86
Yes	200/7134 (2.8)	192/4553 (4.2)	0.64 (0.52, 0.79)	<0.001	
No	112/3720 (3.0)	113/2662 (4.2)	0.64 (0.49, 0.85)	0.002	
EuroSCORE					0.30
≥3	141/3854 (3.7)	160/2762 (5.8)	0.62 (0.49, 0.79)	<0.001	
≤2	171/7000 (2.4)	145/4453 (3.3)	0.71 (0.56, 0.89)	0.004	
Cardiopulmonary bypass					0.96
Off-pump	141/5293 (2.7)	158/3943 (4.0)	0.67 (0.52, 0.85)	0.001	
On-pump	171/5561 (3.1)	147/3272 (4.5)	0.66 (0.52, 0.84)	<0.001	
Venous graft					0.29
≥3	115/4492 (2.6)	134/3213 (4.2)	0.61 (0.47, 0.80)	<0.001	
≤2	197/6362 (3.1)	171/4002 (4.3)	0.69 (0.55, 0.86)	<0.001	
Year of surgery					0.93
2013 to 2015	161/5817 (2.8)	220/5220 (4.2)	0.70 (0.56, 0.87)	0.001	
2016 to 2017	151/5037 (3.0)	85/1995 (4.3)	0.60 (0.45, 0.80)	<0.001	

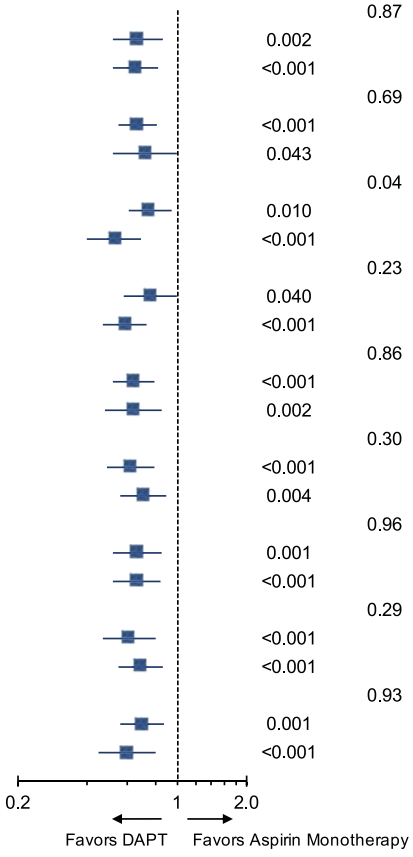


Figure 2. Subgroup analyses for the primary outcome.
Separate propensity score models were fitted to predict the probability of DAPT for each subgroup, and hazard ratios were estimated using inverse probability of treatment-weighted Cox proportional hazards models. DAPT indicates dual antiplatelet therapy; EuroSCORE, European System for Cardiac Operative Risk Evaluation I; and HR, hazard ratio.

In this study, the addition of clopidogrel to aspirin was associated with a risk of major bleeding that was comparable to aspirin monotherapy. This result was not unexpected given the conservative daily dose of DAPT (clopidogrel 75 mg plus aspirin 100 mg), relatively young and healthy patient population, and strict definitions of major bleeding. We developed a composite major bleeding outcome of roughly similar severity to the composite ischemic outcome to aid clinicians in evaluating the risk/benefit tradeoff of antiplatelet therapy, but omitting other minor bleeding events. Notably, previous studies indicated that DAPT was more likely to introduce minor bleeding rather than major bleeding requiring surgical intervention or intense hospitalization care,[7,14,40,45] and a lower-than-expected incidence of major bleeding under current definitions may have biased the result toward the null. In addition, the low number of major bleeding events precluded evaluation of the impact of DAPT in patients at higher risk for bleeding, such as those of older age, with diabetes mellitus, or with renal dysfunction.[25,26]

DAPT may offer specific benefits in subsets of the CABG patient population who are in a prothrombotic state or have residual cardiovascular risk, such as those presenting with ACS or diabetes mellitus and those who underwent off-pump bypass surgery. Current guidelines recommend post-CABG DAPT in patients with ACS[25,26] based on data from secondary analysis of DAPT trials in the setting of non-ST- or ST-segment–elevation myocardial infarction, in which only a small proportion (≈10%) of participants underwent CABG at 20 to 100 days after the initiation of DAPT.[19,23] The present study adds credibility to the recommendation in a large contemporary CABG cohort. However, unlike for ACS, scarce data exist on the effect of DAPT after surgical revascularization for stable angina, and it remains unclear whether the presenting symptoms result in clinical differences relevant to secondary antiplatelet therapy.[11,13,23,46] We observed a greater benefit

of DAPT in patients with stable angina, possibly because of these patients having fewer factors linked to low responsiveness to clopidogrel.[47] Our results also support the strategy of intensifying platelet inhibition with DAPT after off-pump CABG and expanding the use of DAPT to those who underwent on-pump bypass surgery. Given the continued debate on off-pump versus on-pump bypass grafting as well as the aforementioned response variability to clopidogrel,[1,3,47] the underlying mechanisms explaining the variation in DAPT-related benefits warrant further exploration.[44]

In our study, most of the events of interest occurred within 30 days after CABG, which is similar to previous analyses[15] and indicates that combined antiplatelet

Table 3. Association of DAPT vs Aspirin Monotherapy With Outcomes in Selected Subsets of Patients

	DAPT (N=10 854)	Aspirin Monotherapy (N=7215)	Adjusted HR (95% CI)*	*P* Value
Clinical presentation, n (%)				
Acute coronary syndrome	N=6044	N=4164		
MACCE†	195 (3.2)	177 (4.3)	0.75 (0.61–0.94)	0.010
All-cause death	42 (0.7)	39 (0.9)	0.85 (0.53–1.39)	0.52
Stroke	81 (1.3)	88 (2.1)	0.64 (0.47–0.89)	0.007
MACCE, major bleeding	219 (3.6)	195 (4.7)	0.77 (0.62–0.94)	0.011
Stable angina	N=4810	N=3051		
MACCE†	117 (2.4)	128 (4.2)	0.53 (0.40–0.69)	<0.001
All-cause death	19 (0.4)	27 (0.9)	0.42 (0.22–0.81)	0.010
Stroke	61 (1.3)	77 (2.5)	0.48 (0.34–0.69)	<0.001
MACCE, major bleeding	136 (2.8)	135 (4.4)	0.58 (0.45–0.75)	<0.001
Diabetes mellitus status, n (%)				
Diabetes mellitus	N=4201	N=2782		
MACCE†	139 (3.3)	120 (4.3)	0.76 (0.59–0.99)	0.040
All-cause death	27 (0.6)	26 (0.9)	0.68 (0.37–1.24)	0.21
Stroke	79 (1.9)	77 (2.8)	0.71 (0.51–0.99)	0.044
MACCE, major bleeding	152 (3.6)	133 (4.8)	0.75 (0.59–0.96)	0.024
No diabetes mellitus	N=6653	N=4433		
MACCE†	173 (2.6)	185 (4.2)	0.59 (0.47–0.73)	<0.001
All-cause death	34 (0.5)	40 (0.9)	0.54 (0.32–0.90)	0.018
Stroke	63 (0.9)	88 (2.0)	0.45 (0.32–0.63)	<0.001
MACCE, major bleeding	203 (3.1)	197 (4.4)	0.65 (0.53–0.80)	<0.001
Cardiopulmonary bypass, n (%)				
Off-pump	N=5293	N=3943		
MACCE†	141 (2.7)	158 (4.0)	0.67 (0.52–0.85)	0.001
All-cause death	26 (0.5)	30 (0.8)	0.72 (0.39–1.32)	0.28
Stroke	58 (1.1)	90 (2.3)	0.51 (0.36–0.73)	<0.001
MACCE, major bleeding	165 (3.1)	168 (4.3)	0.74 (0.59–0.93)	0.010
On-pump	N=5561	N=3272		
MACCE†	171 (3.1)	147 (4.5)	0.66 (0.52–0.84)	<0.001
All-cause death	35 (0.6)	36 (1.1)	0.52 (0.31–0.87)	0.014
Stroke	84 (1.5)	75 (2.3)	0.64 (0.46–0.88)	0.007
MACCE, major bleeding	190 (3.4)	162 (5.0)	0.66 (0.53–0.83)	<0.001

DAPT indicates dual antiplatelet therapy; HR, hazard ratio; and MACCE, major adverse cardiac and cerebrovascular events.

*Separate propensity-score models were fitted to predict the probability of DAPT for each subgroup, and HRs were estimated with the use of inverse probability of treatment-weighted Cox regression or Fine and Gray model.

†A composite of all-cause mortality, myocardial infarction, stroke, and repeat revascularization.

Table 4. Association of DAPT vs Aspirin Monotherapy With Outcomes After Exclusion of Patients in the DAPT Group Who Started Clopidogrel and Aspirin on Different Days

	DAPT (N=5370)	Aspirin Monotherapy (N=7215)	Adjusted HR (95% CI)*	*P* Value
Primary outcome, n (%)				
MACCE†	175 (3.3)	305 (4.2)	0.75 (0.61–0.92)	0.005
Secondary outcomes, n (%)				
All-cause death	21 (0.4)	66 (0.9)	0.48 (0.27–0.84)	0.010
Cardiovascular death	15 (0.3)	49 (0.7)	0.47 (0.24–0.90)	0.024
MI	70 (1.3)	96 (1.3)	0.88 (0.63–1.23)	0.46
Stroke	79 (1.5)	165 (2.3)	0.65 (0.48–0.86)	0.003
Repeat revascularization	19 (0.4)	21 (0.3)	1.01 (0.52–1.96)	0.97
Cardiovascular death, MI, or ischemic stroke	154 (2.9)	282 (3.9)	0.72 (0.58–0.89)	0.003
Cardiovascular death or MI	81 (1.5)	124 (1.7)	0.85 (0.63–1.15)	0.29
Major bleeding	31 (0.6)	30 (0.4)	1.47 (0.87–2.50)	0.15
In-hospital reoperation for bleeding	11 (0.2)	9 (0.1)	1.59 (0.64–3.97)	0.32
Hospitalization for bleeding	20 (0.4)	21 (0.3)	1.46 (0.77–2.77)	0.25
Net clinical benefit outcome, n (%)				
MACCE, major bleeding	201 (3.7)	330 (4.6)	0.81 (0.67–0.98)	0.028

DAPT indicates dual antiplatelet therapy; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; and MI, myocardial infarction.
*Estimated using inverse probability of treatment-weighted Cox regression or Fine and Gray model.
†A composite of all-cause mortality, MI, stroke, and repeat revascularization.

therapy may be most beneficial in the early post-CABG phase when thrombosis plays a predominant role in graft failure.[6] Use of DAPT for 1 to 3 or 6 months followed by conversion to monotherapy with $P2Y_{12}$ inhibitors or aspirin, which have been proven safe in patients with ACS and coronary stent implantation,[48] might also be a clinically feasible strategy to avoid potential excess bleeding in the CABG population. However, no specific study has examined the optimal treatment duration of DAPT after CABG, although an arbitrary 1-year treatment has been suggested for ACS and off-pump patients.[2,26] The optimal dose of DAPT and the appropriate postoperative initiation time require further investigation.

Several limitations of our analysis should be considered. First, as an observational study, the analyses are subject to selection bias, and residual unmeasured confounding may persist despite adjustment for a variety of known patient variables using propensity scores to approximate randomization. Second, our study was based on the experience of a single high-volume center. The conclusions may be influenced by patient referral patterns and local medical management, and therefore may not generalize to the larger CABG population. Third, detailed data on discontinuation time and on-treatment duration were unavailable for the present analyses, which were based on the intention-to-treat principle, and we were unable to conduct time-dependent Cox regression analyses to account for the impact of the variation in DAPT exposure over time on the association of interest. Instead, we delineated the proportion of "on-treatment" participants in the 2 groups at discharge and at 6 months. We observed a high rate of DAPT discontinuation, but the reasons were not documented in patient records. Nevertheless, noncompliance should favor a type II error, which cannot explain the findings of the present study. Fourth, the 6-month event rates in our analysis were lower than those in previous studies.[3,21] One potential explanation is that our study population tended to be younger and had fewer coexisting conditions. However, we cannot exclude the possibility of underreporting, although this is unlikely because a standardized case report form was used for the adjudication of all events and careful study oversight of outcomes; we anticipate that any problems would have impacted both groups equally. Fifth, low clopidogrel responsiveness has been reported in up to 30% of patients,[25,47] but we were unable to consider this information in our study because of lack of data on the platelet function test and CYP2C19 gene polymorphisms. Finally, novel $P2Y_{12}$ inhibitors (eg, ticagrelor) were not widely prescribed for patients with CABG in our center during the study period; therefore, the results of this study cannot be translated to patients given these agents.

CONCLUSIONS

Among patients undergoing primary isolated CABG, the use of DAPT with clopidogrel plus aspirin compared with aspirin monotherapy was associated with

significant reduction in the risks of MACCE, mortality, myocardial infarction, and stroke, without a significant increase in major bleeding. These findings suggest that DAPT with clopidogrel could be a promising secondary prevention strategy for CABG to improve patient outcomes. Future studies are needed to provide an optimal and personalized post-CABG DAPT strategy.

ARTICLE INFORMATION

Received December 13, 2020; accepted March 23, 2021.

Affiliations

National Clinical Research Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease (J.Q., H.Z., C.R., S.C., Y.Z., H.S., Y.S., S.L., L.W., W.F., S.W., S.H., Z.Z.); Department of Cardiovascular Surgery (J.Q., H.Z., C.R., H.S., Y.S., S.L., L.W., W.F., S.W., S.H., Z.Z.); and Information Center (S.C.); Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China.

Acknowledgments

The most important acknowledgments are to the participants in the study and to the doctors and nurses at Fuwai Hospital who assisted with its undertaking. We also thank Li He and Yuyan Zhou from the National Clinical Research Center of Cardiovascular Diseases and Wei Zhao, Xue Zhang, and Weinan Chen from the Information Center, Fuwai Hospital for their extraordinary help with data collection and follow-up.

Sources of Funding

This study was supported by grants from the Beijing Municipal Science and Technology Commission (D171100002917001). The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Disclosures

None.

Supplementary Material

Data S1
Table S1–S6
Figure S1–S5

REFERENCES

1. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87–165. DOI: 10.1093/eurheartj/ehy394.
2. Kulik A, Ruel M, Jneid H, Ferguson TB, Hiratzka LF, Ikonomidis JS, Lopez-Jimenez F, McNallan SM, Patel M, Roger VL, et al. Secondary prevention after coronary artery bypass graft surgery: a scientific statement from the American Heart Association. *Circulation*. 2015;131:927–964. DOI: 10.1161/CIR.0000000000000182.
3. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, Straka Z, Piegas LS, Akar AR, Jain AR, et al. Effects of off-pump and on-pump coronary-artery bypass grafting at 1 year. *N Engl J Med*. 2013;368:1179–1188. DOI: 10.1056/NEJMoa1301228.
4. Zimmermann N, Wenk A, Kim U, Kienzle P, Weber AA, Gams E, Schror K, Hohlfeld T. Functional and biochemical evaluation of platelet aspirin resistance after coronary artery bypass surgery. *Circulation*. 2003;108:542–547. DOI: 10.1161/01.CIR.0000081770.51929.5A.
5. Hankey GJ, Eikelboom JW. Aspirin resistance. *Lancet*. 2006;367:606–617. DOI: 10.1016/S0140-6736(06)68040-9.
6. Gaudino M, Antoniades C, Benedetto U, Deb S, Di Franco A, Di Giammarco G, Fremes S, Glineur D, Grau J, He G-W, et al. Mechanisms, consequences, and prevention of coronary graft failure. *Circulation*. 2017;136:1749–1764. DOI: 10.1161/CIRCULATIONAHA.117.027597.
7. Gasparovic H, Petricevic M, Kopjar T, Djuric Z, Svetina L, Biocina B. Impact of dual antiplatelet therapy on outcomes among aspirin-resistant patients following coronary artery bypass grafting. *Am J Cardiol*. 2014;113:1660–1667. DOI: 10.1016/j.amjcard.2014.02.024.
8. Cadroy Y, Bossavy JP, Thalamas C, Sagnard L, Sakariassen K, Boneu B. Early potent antithrombotic effect with combined aspirin and a loading dose of clopidogrel on experimental arterial thrombogenesis in humans. *Circulation*. 2000;101:2823–2828. DOI: 10.1161/01.CIR.101.24.2823.
9. Mega JL, Simon T. Pharmacology of antithrombotic drugs: an assessment of oral antiplatelet and anticoagulant treatments. *Lancet*. 2015;386:281–291. DOI: 10.1016/S0140-6736(15)60243-4.
10. Une D, Al-Atassi T, Kulik A, Voisine P, Le May M, Ruel M. Impact of clopidogrel plus aspirin versus aspirin alone on the progression of native coronary artery disease after bypass surgery: analysis from the clopidogrel after surgery for coronary artery disease (cascade) randomized trial. *Circulation*. 2014;130:S12–S18. DOI: 10.1161/CIRCULATIONAHA.113.008227.
11. Gao G, Zheng Z, Pi Y, Lu B, Lu J, Hu S. Aspirin plus clopidogrel therapy increases early venous graft patency after coronary artery bypass surgery a single-center, randomized, controlled trial. *J Am Coll Cardiol*. 2010;56:1639–1643. DOI: 10.1016/j.jacc.2010.03.104.
12. Sun JCJ, Teoh KHT, Lamy A, Sheth T, Ellins ML, Jung H, Yusuf S, Anand S, Connolly S, Whitlock RP, et al. Randomized trial of aspirin and clopidogrel versus aspirin alone for the prevention of coronary artery bypass graft occlusion: the preoperative aspirin and postoperative antiplatelets in coronary artery bypass grafting study. *Am Heart J*. 2010;160:1178–1184. DOI: 10.1016/j.ahj.2010.07.035.
13. Mannacio VA, Di Tommaso L, Antignan A, De Amicis V, Vosa C. Aspirin plus clopidogrel for optimal platelet inhibition following off-pump coronary artery bypass surgery: results from the CRYSSA (prevention of Coronary arteRY bypaSS occlusion After off-pump procedures) randomised study. *Heart*. 2012;98:1710–1715. DOI: 10.1136/heartjnl-2012-302449.
14. Zhao Q, Zhu Y, Xu Z, Cheng Z, Mei J, Chen X, Wang X. Effect of ticagrelor plus aspirin, ticagrelor alone, or aspirin alone on saphenous vein graft patency 1 year after coronary artery bypass grafting: a randomized clinical trial. *JAMA*. 2018;319:1677–1686. DOI: 10.1001/jama.2018.3197.
15. Deo SV, Dunlay SM, Shah IK, Altarabsheh SE, Erwin PJ, Boilson BA, Park SJ, Joyce LD. Dual anti-platelet therapy after coronary artery bypass grafting: is there any benefit? A systematic review and meta-analysis. *J Card Surg*. 2013;28:109–116. DOI: 10.1111/jocs.12074.
16. Solo K, Lavi S, Kabali C, Levine GN, Kulik A, John-Baptiste AA, Fremes SE, Martin J, Eikelboom JW, Ruel M, et al. Antithrombotic treatment after coronary artery bypass graft surgery: systematic review and network meta-analysis. *BMJ*. 2019;367:l5476. DOI: 10.1136/bmj.l5476.
17. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, Wang C, Li H, Meng X, Cui L, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med*. 2013;369:11–19. DOI: 10.1056/NEJMoa1215340.
18. Del Brutto VJ, Chaturvedi S, Diener HC, Romano JG, Sacco RL. Antithrombotic therapy to prevent recurrent strokes in ischemic cerebrovascular disease: JACC scientific expert panel. *J Am Coll Cardiol*. 2019;74:786–803. DOI: 10.1016/j.jacc.2019.06.039.
19. Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, Yusuf S; Clopidogrel in Unstable angina to prevent Recurrent ischemic Events T. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the clopidogrel in unstable angina to prevent recurrent ischemic events (cure) trial. *Circulation*. 2004;110:1202–1208. DOI: 10.1161/01.CIR.0000140675.85342.1B.
20. Sørensen R, Abildstrøm SZ, Hansen PR, Hvelplund A, Andersson C, Charlot M, Fosbøl EL, Køber L, Madsen JK, Gislason GH, et al. Efficacy of post-operative clopidogrel treatment in patients revascularized with coronary artery bypass grafting after myocardial infarction. *J Am Coll Cardiol*. 2011;57:1202–1209. DOI: 10.1016/j.jacc.2010.09.069.
21. van Diepen S, Fuster V, Verma S, Hamza TH, Siami FS, Goodman SG, Farkouh ME. Dual antiplatelet therapy versus aspirin monotherapy in diabetics with multivessel disease undergoing CABG: freedom insights. *J Am Coll Cardiol*. 2017;69:119–127. DOI: 10.1016/j.jacc.2016.10.043.
22. Benedetto U, Altman DG, Gerry S, Gray A, Lees B, Flather M, Taggart DP, Investigators ART. Impact of dual antiplatelet therapy after coronary artery bypass surgery on 1-year outcomes in the arterial

revascularization trial. *Eur J Cardiothorac Surg*. 2017;52:456–461. DOI: 10.1093/ejcts/ezx075.
23. Cardoso R, Knijnik L, Whelton SP, Rivera M, Gluckman TJ, Metkus TS, Blumenthal RS, McEvoy JW. Dual versus single antiplatelet therapy after coronary artery bypass graft surgery: an updated meta-analysis. *Int J Cardiol*. 2018;269:80–88. DOI: 10.1016/j.ijcard.2018.07.083.
24. Sousa-Uva M, Storey R, Huber K, Falk V, Leite-Moreira AF, Amour J, Al-Attar N, Ascione R, Taggart D, Collet JP, et al. Expert position paper on the management of antiplatelet therapy in patients undergoing coronary artery bypass graft surgery. *Eur Heart J*. 2014;35:1510–1514. DOI: 10.1093/eurheartj/ehu158.
25. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, 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;39:213–260. DOI: 10.1093/eurheartj/ehx419.
26. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, 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. *Circulation*. 2016;134:e123–155.
27. Zhang H, Yuan X, Zhang H, Chen S, Zhao Y, Hua K, Rao C, Wang W, Sun H, Hu S, et al. Efficacy of long-term beta-blocker therapy for secondary prevention of long-term outcomes after coronary artery bypass grafting surgery. *Circulation*. 2015;131:2194–2201.
28. Rao C, Zhang H, Gao H, Zhao Y, Yuan X, Hua K, Hu S, Zheng Z; Chinese Cardiac Surgery Registry Collaborative G. The Chinese cardiac surgery registry: design and data audit. *Ann Thorac Surg*. 2016;101:1514–1520. DOI: 10.1016/j.athoracsur.2015.09.038.
29. Zheng Z, Jayaram R, Jiang L, Emberson J, Zhao Y, Li QI, Du J, Guarguagli S, Hill M, Chen Z, et al. Perioperative rosuvastatin in cardiac surgery. *N Engl J Med*. 2016;374:1744–1753. DOI: 10.1056/NEJMoa1507750.
30. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. *BMJ*. 2019;367:l5657. DOI: 10.1136/bmj.l5657.
31. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34:3661–3679. DOI: 10.1002/sim.6607.
32. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Stat Med*. 2014;33:1242–1258. DOI: 10.1002/sim.5984.
33. Xie J, Liu C. Adjusted Kaplan–Meier estimator and log-rank test with inverse probability of treatment weighting for survival data. *Stat Med*. 2005;24:3089–3110. DOI: 10.1002/sim.2174.
34. Elze MC, Gregson J, Baber U, Williamson E, Sartori S, Mehran R, Nichols M, Stone GW, Pocock SJ. Comparison of propensity score methods and covariate adjustment: evaluation in 4 cardiovascular studies. *J Am Coll Cardiol*. 2017;69:345–357. DOI: 10.1016/j.jacc.2016.10.060.
35. Funk MJ, Westreich D, Wiesen C, Sturmer T, Brookhart MA, Davidian M. Doubly robust estimation of causal effects. *Am J Epidemiol*. 2011;173:761–767. DOI: 10.1093/aje/kwq439.
36. Qu J, Zhang D, Zhang H, Rao C, Chen S, Zhao Y, Zheng Z. Preoperative clopidogrel and outcomes in patients with acute coronary syndrome undergoing coronary artery bypass surgery. *J Thorac Cardiovasc Surg*. 2020;S0022-5223(20)30818-7. DOI: 10.1016/j.jtcvs.2020.03.118.
37. Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol*. 2008;167:492–499. DOI: 10.1093/aje/kwm324.
38. Levesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ*. 2010;340:b5087. DOI: 10.1136/bmj.b5087.
39. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the e-value. *Ann Intern Med*. 2017;167:268–274. DOI: 10.7326/M16-2607.
40. Willemsen LM, Janssen PWA, Peper J, Soliman-Hamad MA, van Straten AHM, Klein P, Hackeng CM, Sonker U, Bekker MWA, von Birgelen C, et al. Effect of adding ticagrelor to standard aspirin on saphenous vein graft patency in patients undergoing coronary artery bypass grafting (POPular CABG): a randomized, double-blind, placebo-controlled trial. *Circulation*. 2020;142:1799–1807. DOI: 10.1161/CIRCULATIONAHA.120.050749.
41. Yanagawa B, Ruel M, Bonneau C, Lee MM, Chung J, Al Shouli S, Fagan A, Al Khalifa A, White CW, Yamashita MH, et al. Dual antiplatelet therapy use by Canadian cardiac surgeons. *J Thorac Cardiovasc Surg*. 2015;150(6):1548–1554.e3. DOI: 10.1016/j.jtcvs.2015.08.066.
42. Ebrahimi R, Gupta S, Carr BM, Bishawi M, Bakaeen FG, Almassi GH, Collins J, Grover FL, Quin JA, Wagner TH, et al. Comparison of outcomes and costs associated with aspirin +/- clopidogrel after coronary artery bypass grafting. *Am J Cardiol*. 2018;121:709–714.
43. Agarwal N, Mahmoud AN, Patel NK, Jain A, Garg J, Mojadidi MK, Agrawal S, Qamar A, Golwala H, Gupta T, et al. Meta-analysis of aspirin versus dual antiplatelet therapy following coronary artery bypass grafting. *Am J Cardiol*. 2018;121:32–40. DOI: 10.1016/j.amjcard.2017.09.022.
44. Schnorbus B, Daiber A, Jurk K, Warnke S, Koenig J, Lackner KJ, Munzel T, Gori T. Effects of clopidogrel vs. prasugrel vs. ticagrelor on endothelial function, inflammatory parameters, and platelet function in patients with acute coronary syndrome undergoing coronary artery stenting: a randomized, blinded, parallel study. *Eur Heart J*. 2020;41:3144–3152. DOI: 10.1093/eurheartj/ehz917.
45. Saw J, Wong GC, Mayo J, Bernstein V, Mancini GB, Ye J, Skarsgard P, Starovoytov A, Cairns J. Ticagrelor and aspirin for the prevention of cardiovascular events after coronary artery bypass graft surgery. *Heart*. 2016;102:763–769. DOI: 10.1136/heartjnl-2015-308691.
46. Choi KH, Song YB, Jeong DS, Jang YH, Hong D, Lee SY, Youn T, Bak M, Min KM, Lee JM, et al. Differential effects of dual antiplatelet therapy in patients presented with acute coronary syndrome vs. stable ischaemic heart disease after coronary artery bypass grafting. *Eur Heart J Cardiovasc Pharmacother*. 2020. DOI: 10.1093/ehjcvp/pvaa080.
47. Siller-Matula JM, Trenk D, Schror K, Gawaz M, Kristensen SD, Storey RF, Huber K. Response variability to p2y12 receptor inhibitors: expectations and reality. *JACC Cardiovasc Interv*. 2013;6:1111–1128. DOI: 10.1016/j.jcin.2013.06.011.
48. O'Donoghue ML, Murphy SA, Sabatine MS. The safety and efficacy of aspirin discontinuation on a background of a p2y12 inhibitor in patients after percutaneous coronary intervention: a systematic review and meta-analysis. *Circulation*. 2020;142:538–545.

SUPPLEMENTAL MATERIAL

Data S1.

SUPPLEMENTAL METHODS

Revascularization Procedures

As part of standard institutional requirements, all surgeons had to have specialized in congenital or valve heart surgery for more than 3 years before undertaking any coronary artery bypass grafting (CABG) procedures. With respect to off-pump CABG, the surgeon had to perform at least 100 on-pump CABG procedures before being considered qualified to carry out the off-pump procedure. Once qualified, the choice of off-pump CABG or on-pump CABG for a particular patient was generally at the discretion of the individual surgeons.

Anesthesia was managed by inhalation of isoflurane with the addition of fentanyl or sufentanil, and propofol was administered continuously until the end of the procedure if necessary. Surgical revascularization was performed using standard bypass techniques. For on-pump CABG, a standard cardiopulmonary bypass was established, and moderate systemic hypothermia (28°C to 32°C) and perfusion with antegrade intermittent cold crystalloid cardioplegia were used. Heparin was given to achieve activated clotting times of 480 seconds or above before institution of cardiopulmonary bypass. For off-pump CABG, stabilization devices were used to provide a motionless anastomosis site, and heparin was administered before the start of the first distal anastomosis to achieve an activated clotting time of 300 to 350 seconds. On-pump CABG involved aortic cross-clamping and cardioplegic arrest, while off-pump CABG was performed with a partial occlusion clamp. Whenever possible, complete revascularization was attempted, and the internal thoracic artery was used preferentially for revascularization of the left anterior descending artery. The remaining vessels were to be bypassed either using another arterial conduit or the saphenous vein in the configuration decided by the surgeon. During reperfusion, the bypass grafting was completed with proximal anastomoses to the ascending aorta. The decision to switch to cardiopulmonary bypass during the procedure was based on significant hemodynamic instability or ventricular arrhythmia. After separation from cardiopulmonary bypass or on completion of all anastomoses, protamine was given to reverse the effects of heparin. All patients received tranexamic acid intraoperatively if not contraindicated. Postoperatively, starting within the first 24 hours, aspirin therapy (100 mg/day) is recommended and should be continued indefinitely. Routinely, re-exploration was performed if the bleeding exceeded 200 mL/hour in the first 3 hours or 300 mL/hour at any time, or in the presence of typical hemodynamic or echocardiographic features of cardiac tamponade.

Outcome Definitions

All-cause death was defined as death from any cause.

Cardiovascular death was defined as any death due to proximate cardiac cause (e.g., myocardial infarction, low-output failure, fatal arrhythmia), unwitnessed death, death of unknown cause, all procedure-related deaths (including those related to concomitant treatment), and death due to noncoronary vascular causes (e.g., cerebrovascular disease, ruptured aortic aneurysm, pulmonary embolism) or other vascular diseases.

Myocardial infarction occurred when there were clinical signs and symptoms of ischemia that were distinct from the presenting ischemic event and met at least one of the following criteria:

1) Spontaneous (before or without revascularization, >48 hours after CABG)

A. New, significant Q waves in at least two contiguous leads of an electrocardiogram that were not present with the presenting ischemic event;

B. Patients whose most recent cardiac markers measured before reinfarction, which were normal, required an increase in CK-MB or troponin that was above the 99th percentile upper limit of normal and at least ≥20% above the most recent value.

2) Within 48 hours after CABG

A CABG-related myocardial infarction was defined by elevation of cardiac biomarker values >10 times the 99th percentile upper reference limit in patients with normal baseline cardiac troponin values (≤99th percentile upper reference limit) plus either new pathological Q waves; new left bundle-branch block, angiographically documented new graft, or native coronary artery occlusion; or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Stroke was confirmed by a neurologist on the basis of imaging studies and symptoms and was defined as follows:

1) A focal neurologic deficit of central origin lasting >72 hours, or

2) A focal neurologic deficit of central origin lasting >24 hours, with imaging evidence of cerebral infarction or intracerebral hemorrhage, or

3) A non-focal encephalopathy lasting >24 hours with imaging evidence of cerebral infarction or hemorrhage adequate to account for the clinical state, or

4) Transient ischemic attack, defined as the presence of acute focal neurological deficit thought to be of vascular origin with signs and symptoms lasting less than 24 hours.

Retinal arterial ischemia or hemorrhage was included in the definition of stroke.

Repeat revascularization was defined as any ischemia-driven repeat percutaneous coronary intervention or bypass surgery.

Major bleeding was defined as a combination of in-hospital reoperation due to bleeding and hospitalization for bleeding after discharge.

1) Reoperation due to bleeding: reoperation after the closure of sternotomy for the purpose of controlling bleeding.

2) Hospitalization for bleeding: any clinically overt bleeding events resulting in hemodynamic compromise requiring hospitalization for specific treatment, defined as a healthcare professional-guided medical treatment with intravenous inotropic agents or transfusion, or percutaneous or surgical intervention to stop or treat bleeding. Prolonged hospitalization or transfer to a hospital unit capable of providing a higher level of care were also included.

Statistical Methods

Summary statistics were presented as frequencies and proportions for categorical variables, and means with standard deviations or medians with interquartile ranges for continuous variables depending on data distribution. We compared baseline characteristics between DAPT and aspirin monotherapy using Student's t-tests or Wilcoxon rank sum-tests for continuous variables and chi-square tests for categorical variables, as appropriate.

Because of the nonrandomized nature of the study and the anticipated significant differences between study groups, we used inverse probability of treatment weighting (IPTW) based on propensity scores to construct a weighted cohort of patients who differed with respect to postoperative antiplatelet strategy but were similar with respect to other measured characteristics to control for potential confounders of the treatment-outcome relationship. A propensity score for the predicted probability of receipt of DAPT in each patient was calculated with the use of a nonparsimonious multivariable logistic regression model fit with patient characteristics selected on the basis of their a priori possibility of confounding the relationship between antiplatelet strategy and clinical outcomes. Patient-level covariates in the propensity model included age, sex, body mass index, smoking status, diabetes (no diabetes, non-insulin-treated diabetes, insulin-treated diabetes), hypertension, hyperlipidemia, chronic lung disease, peripheral artery disease, previous percutaneous coronary intervention, previous myocardial infarction, previous cerebrovascular accident, clinical presentation (stable angina, unstable angina, non-ST-elevation myocardial infarction, ST-elevation myocardial infarction), number of diseased vessels, left ventricular ejection fraction, EuroSCORE (0-2, 3-5, $\geqslant$6), hemoglobin, platelet count, serum creatinine, preoperative aspirin, preoperative $P2Y_{12}$ inhibitors, preoperative statins, preoperative beta-blockers, preoperative angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), emergency surgery, cardiopulmonary bypass use (on-pump or off-pump), left internal mammary artery to left anterior descending artery graft, number of arterial grafts, number of venous grafts, duration of surgery, cardiopulmonary bypass time, cross-clamp time, and year of surgery. There were missing data for several baseline variables (1.3% for preoperative hemoglobin and platelet count; <0.3% for height, weight, and preoperative creatinine). To account for these missing data, a single mean imputation stratified by study groups was used.

We weighted each patient in the DAPT group by the patient's inverse propensity score, and we weighted those in the aspirin monotherapy group by the inverse of 1 minus the propensity score to estimate the average treatment effect (ATE), that is, the effect of treatment on the entire population eligible for isolated CABG. We truncated the scores at the 1st and 99th percentiles to limit the influence of extreme weights. Stabilized weights were also used to reduce the variability in the inverse probability of treatment-weighted models. Balance among covariates was assessed using standardized differences, and a difference of 10% or

less was considered the ideal balance. Comparisons of individual propensity score distributions showed sufficient overlap and suggested that application of the weights of the inverse probability of treatment resulted in a cohort in which the distribution of variables was comparable between treatment groups; hence, comparisons between treatment groups were feasible.

Time-to-event analyses for MACCE and all-cause mortality were performed using weighted Cox proportional hazards models. Cardiovascular death, myocardial infarction, stroke, repeat revascularization, and major bleeding were analyzed in the weighted population, accounting for death (or non-cardiovascular death) as a competing risk using the Fine and Gray method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with a robust variance estimator to account for the weighted nature of the population. The proportional hazards assumption was confirmed with visual inspection and statistical tests based on the scaled Schoenfeld residuals. However, even if the proportional hazards assumption was not met for the treatment group variable, the HR may be interpreted as an "average" over the observed event times. IPTW-adjusted Kaplan-Meier curves were constructed for patients who received DAPT and those who received aspirin alone. To test for equality of outcome in the two groups, an IPTW-adjusted log-rank test was used. For each outcome analyzed, the follow-up period began upon initiation of DAPT or aspirin monotherapy (time 0). Patients were censored on first occurrence of the event, death, loss to follow-up, or reaching 180 days of follow-up.

Subgroup analyses

Prespecified subgroup analyses for the primary outcome and major secondary outcomes were performed using weighted survival models stratified by key clinical variables, including sex, age (older or younger than 65 years), clinical presentations (stable angina or acute coronary syndrome), presence or absence of diabetes, presence or absence of hyperlipidemia, on-pump or off-pump bypass, surgery risk (EuroSCORE I $\leq$2 or $\geq$3), and number of venous grafts ($\leq$2 or $\geq$3). A post-hoc analysis stratified by year of surgery (2013-2015 or 2016-2017) was also conducted. For each subgroup, a separate propensity score and stabilized weight were derived. Tests for interaction were performed to assess heterogeneity of treatment effect among subgroups by the incorporation of formal interaction terms in the weighted models.

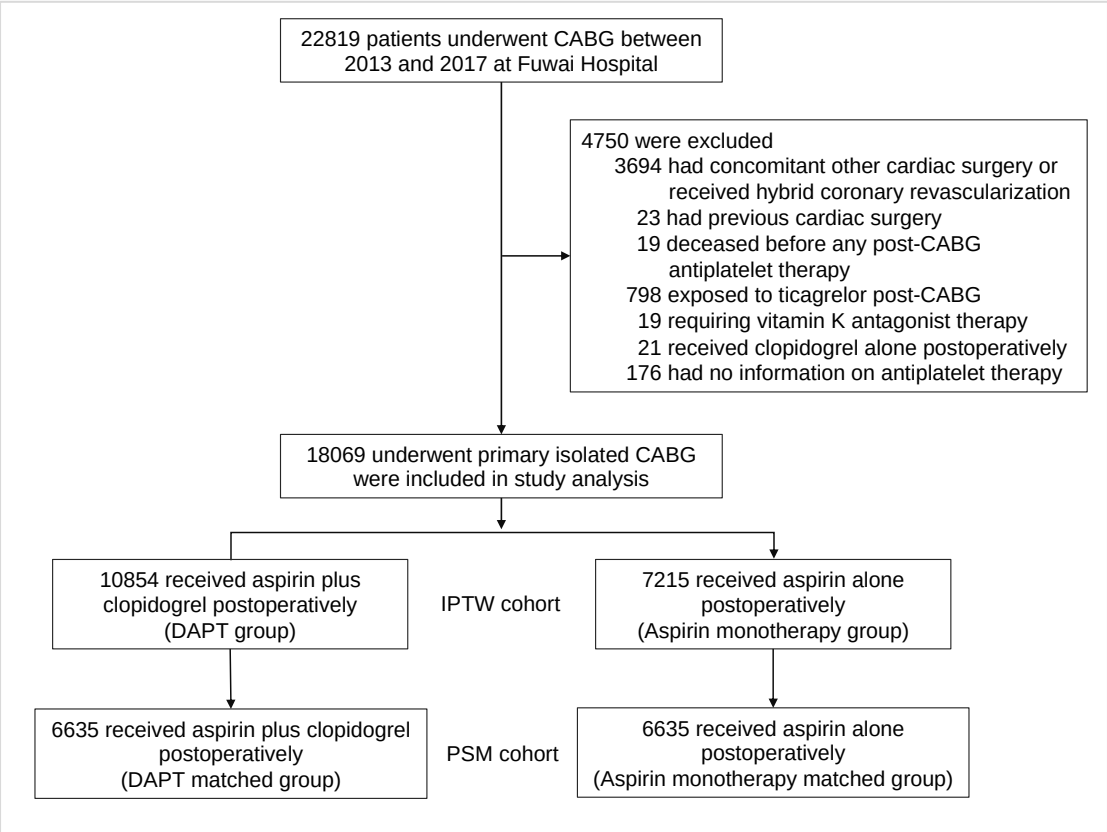
Sensitivity analyses

We performed several sensitivity analyses to assess the robustness of the primary analysis. First, DAPT and aspirin monotherapy were compared in a propensity score-matched cohort in which patients treated with DAPT were randomly selected and matched with those who received aspirin alone using the 1:1 nearest-neighbor matching method (caliper width equal to 0.2 of the standard deviation of the logit of the propensity score) without replacement. The

matched cohort was used to estimate the average treatment effect for the treated (ATT), and the outcomes were compared using a robust sandwich variance estimator to account for the matched design. Second, HRs and 95% CIs for the main study outcomes were re-estimated using multivariable Cox proportional hazard models without propensity scores. Covariates for each model were identical to those used for calculating propensity scores. Third, to eliminate the potential risk for insufficient covariate balance and model misspecification, we repeated the analyses using the method of doubly robust estimation to combine the propensity score and outcome regression by further adjust for baseline covariates in the weighted Cox regression model. Fourth, to ensure that treatment-related outcome differences were not confounded by differential use of other secondary prevention medications, the survival models were refitted with postoperative treatment as a covariate (statin, beta blocker, ACEI/ARB). Fifth, separate analyses of the weighted population were adjusted by including principal surgeon as a random effect in the survival models. Sixth, because a proportion of patients in the DAPT group started clopidogrel a few days after the initiation of aspirin rather than starting the two medications simultaneously, we repeated the primary analysis after exclusion of patients from the DAPT group who did not start clopidogrel and aspirin on the same day to minimize possible immortal time bias. Seventh, analyses of the primary and secondary outcomes were performed in a separate IPTW cohort of patients after excluding those who received any $P2Y_{12}$ inhibitors within 5 days before CABG. Finally, because the study database did not include any falsification endpoint (i.e., an endpoint that is known to be unrelated to the treatment under study such as death from injury), we alternatively calculated the E value to quantify the potential for unmeasured confounders to explain the effect of DAPT on estimated HRs. The E-value evaluates how strongly an unmeasured confounder would have to be associated with both the use of DAPT and aspirin monotherapy and the outcomes of interest to reduce the observed effect to the null, conditional on the measured covariates.

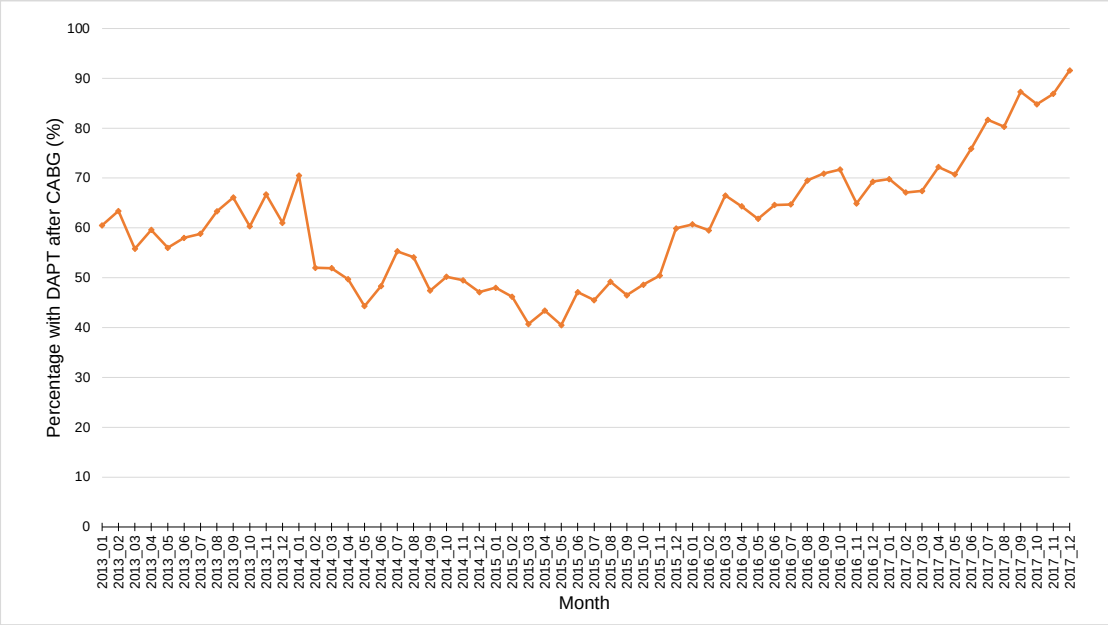
All tests were two-tailed, with P values less than 0.05 indicating statistical significance. Because all analyses were considered exploratory, no correction for multiple comparisons was performed. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and began in March 2020.

Figure S1. Study Population.



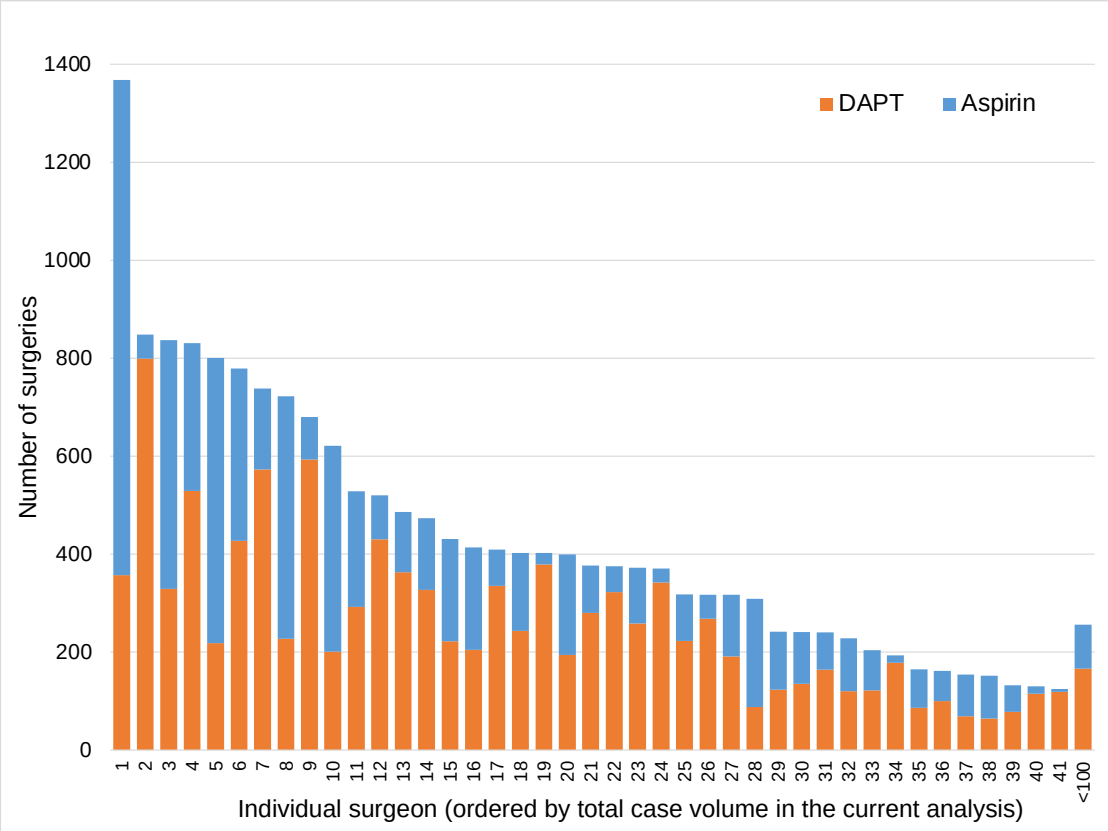
CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; IPTW, inverse probability of treatment weighting; PSM, propensity score matching.

Figure S2. Percentage of Patients Treated with DAPT After CABG per Month Between January 2013 and December 2017.



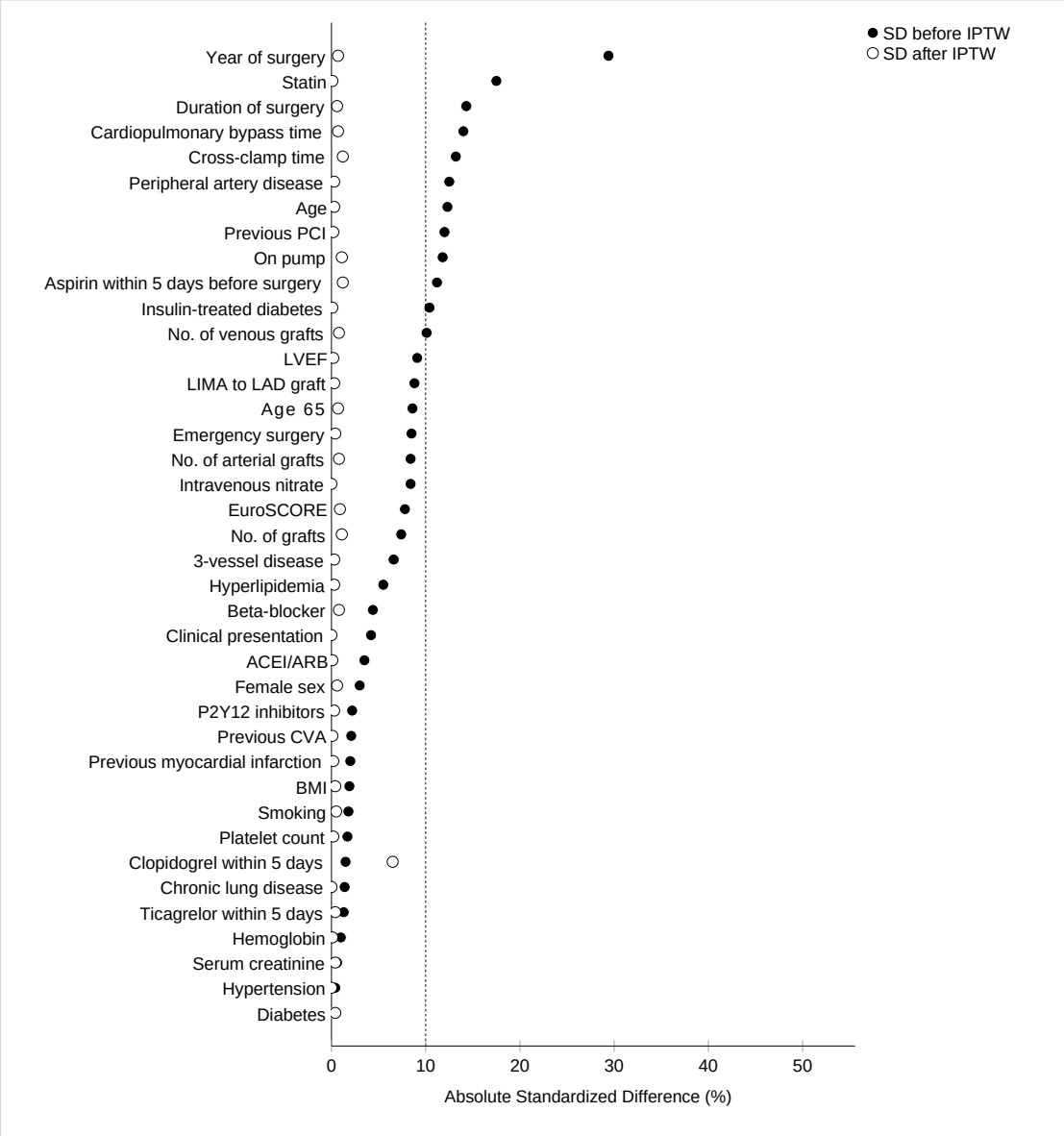
CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy.

Figure S3. Proportion of DAPT Prescription Among Different Surgeons in the Current Study.



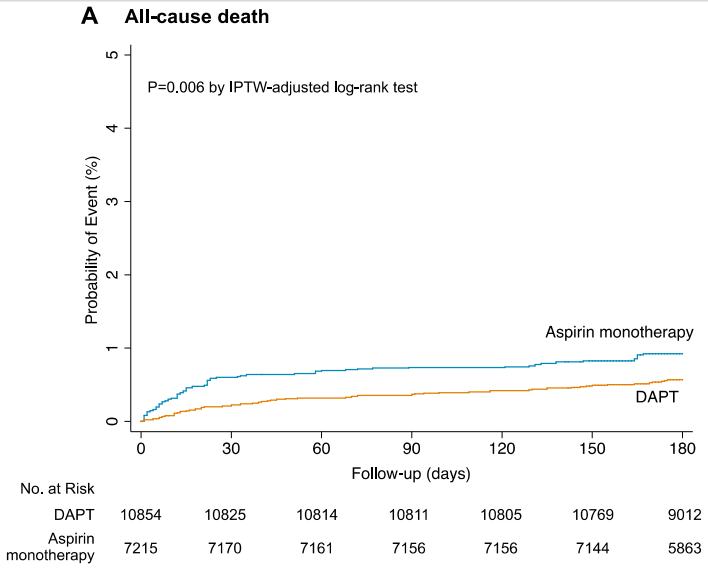
Each number from 1 to 41 on the x-axis represents an individual surgeon. Surgeons with less than 100 cases in the current study were combined (labeled as <100). Abbreviations: DAPT, dual antiplatelet therapy.

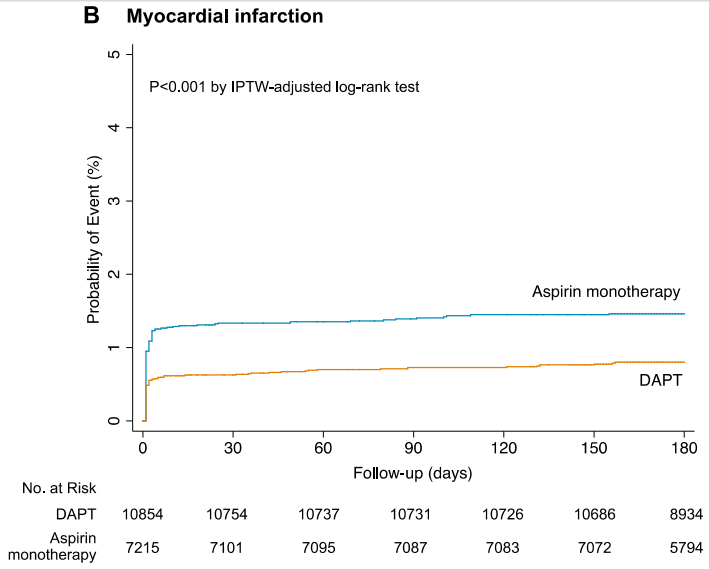
Figure S4. Absolute Standardized Differences Between DAPT and Aspirin Monotherapy Group Before and After Inverse Probability of Treatment Weighting in the Primary Analysis.

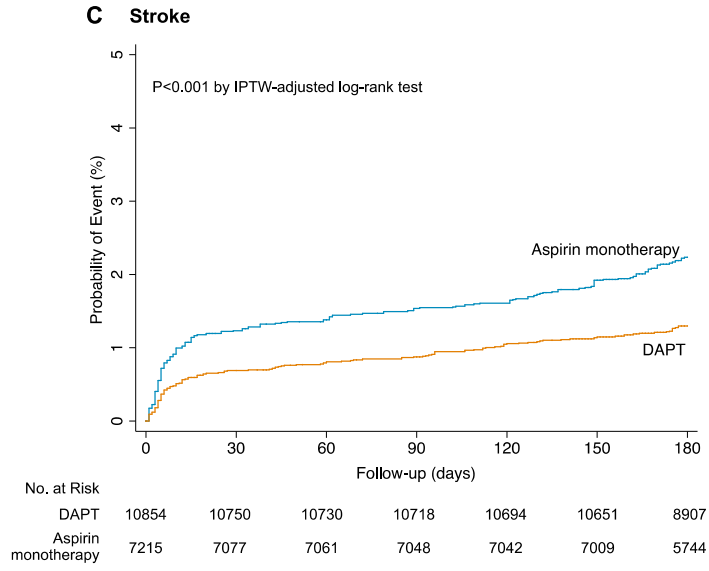


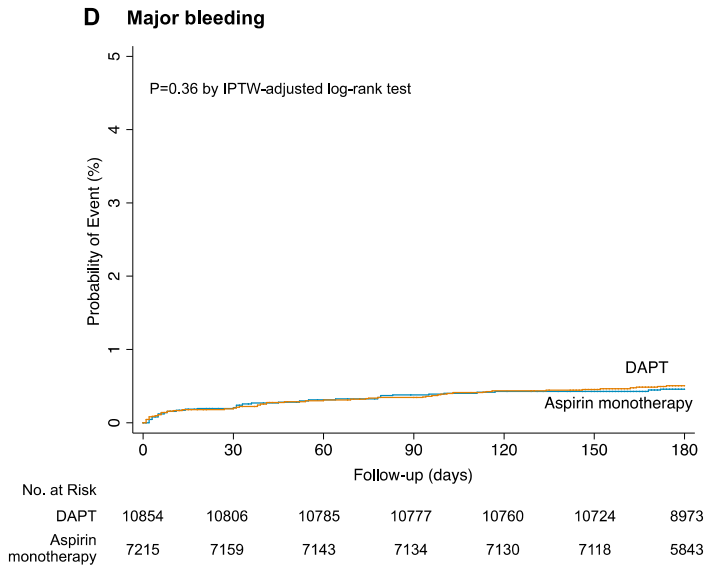
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CVA, cerebrovascular accident; EuroSCORE, European System for Cardiac Operative Risk Evaluation I; IPTW, inverse probability of treatment weighting; LAD, left anterior descending artery; LIMA, left internal mammary artery; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

Figure S5. Inverse Probability of Treatment Weighting-Adjusted Kaplan-Meier Analyses for Secondary Clinical Outcomes.









A, all-cause death. **B,** myocardial infarction. **C,** Stroke. **D,** Major bleeding. Definitions of the individual outcomes are provided in the Supplemental Methods. The outcome was evaluated with follow-up starting from date of DAPT or aspirin monotherapy initiation until the date of each specific outcome, death, loss to follow-up, or reaching 180 days of follow-up. The at-risk table shows the actual number of patients at risk. DAPT, dual antiplatelet therapy; IPTW, inverse probability of treatment weighting.

Table S1. Patient Characteristics Before Inverse Probability Weighting in the Primary Analysis.

Characteristics	DAPT (N=10854)	Aspirin Monotherapy (N=7215)	Absolute Standardized Difference (%)
Age, years, mean (SD)	60.8 (8.6)	61.9 (8.5)	12.3
Age ≥65, No. (%)	3542 (32.6)	2651 (36.7)	8.6
Female sex, No. (%)	2441 (22.5)	1715 (23.8)	3.0
BMI*, kg/m^2, mean (SD)	25.7 (3.0)	25.7 (3.0)	1.9
Year of surgery, No. (%)			29.4
2013	2051 (18.9)	1338 (18.5)	
2014	1932 (17.8)	1828 (25.3)	
2015	1834 (16.9)	2054 (28.5)	
2016	2351 (21.7)	1226 (17.0)	
2017	2686 (24.7)	769 (10.7)	
Medical history, No. (%)			
Smoking	6029 (55.5)	3944 (54.7)	1.8
Diabetes	4201 (38.7)	2782 (38.6)	0.3
Insulin-treated diabetes	903 (8.3)	409 (5.7)	10.4
Hypertension	7091 (65.3)	4700 (65.1)	0.4
Hyperlipidemia	7134 (65.7)	4553 (63.1)	5.5
Peripheral artery disease	1051 (9.7)	454 (6.3)	12.5
Chronic lung disease	395 (3.6)	282 (3.9)	1.4
Previous myocardial infarction	2880 (26.5)	1852 (25.7)	2.0
Previous PCI	1485 (13.7)	708 (9.8)	12.0
Previous CVA	1248 (11.5)	781 (10.8)	2.1
Clinical presentation, No. (%)			4.2
Stable angina	4810 (44.3)	3051 (42.3)	
Unstable angina	5341 (49.2)	3683 (51.0)	
NSTEMI	310 (2.9)	215 (3.0)	
STEMI	393 (3.6)	266 (3.7)	
3-vessel disease, No. (%)	9511 (87.6)	6472 (89.7)	6.6
LVEF, No. (%)			9.1
≥50%	10183 (93.8)	6713 (93.0)	
40-49%	528 (4.9)	379 (5.3)	
30-39%	135 (1.2)	115 (1.6)	
<30%	8 (0.1)	8 (0.1)	
EuroSCORE†, No. (%)			7.8
0-2	7000 (64.5)	4453 (61.7)	
3-5	3135 (28.9)	2194 (30.4)	
≥6	719 (6.6)	568 (7.9)	

Preoperative lab tests			
Hemoglobin, g/L, mean (SD)	136.2 (14.8)	136.4 (15.1)	1.0
Platelet count, 10^9/L, mean (SD)	211 (57)	210 (56)	1.7
Serum creatinine, μmol/L, mean (SD)	81.2 (19.6)	81.1 (19.5)	0.6
Medication use before surgery, No. (%)			
Aspirin within 5 days before surgery	1045 (9.6)	952 (13.2)	11.2
$P2Y_{12}$ inhibitors	4012 (37.0)	2589 (35.9)	2.2
Clopidogrel within 5 days	770 (7.1)	540 (7.5)	1.5
Ticagrelor within 5 days	38 (0.4)	20 (0.3)	1.3
Intravenous nitrate	1533 (14.1)	817 (11.3)	8.4
Beta-blocker	9699 (89.4)	6346 (88.0)	4.4
Statin	9194 (84.7)	5622 (77.9)	17.5
ACEI/ARB	4362 (40.2)	3022 (41.9)	3.5
Surgical procedure characteristics			
Emergency surgery‡, No. (%)	330 (3.0)	126 (1.7)	8.5
On pump, No. (%)	5561 (51.2)	3272 (45.3)	11.8
LIMA to LAD graft, No. (%)	10067 (92.7)	6844 (94.9)	8.8
No. of grafts, mean (SD)	3.3 (0.9)	3.4 (0.9)	7.4
No. of arterial grafts	1.0 (0.4)	1.0 (0.2)	8.4
No. of venous grafts	2.3 (0.9)	2.4 (0.9)	10.1
Cardiopulmonary bypass time, min, median (IQR)	101 (83, 116)	98 (81, 110)	14.0
Cross-clamp time, min, median (IQR)	69 (55, 80)	68 (54, 77)	13.2
Duration of surgery, min, median (IQR)	245 (214, 285)	240 (208, 275)	14.3
Concomitant medical treatment at discharge, No. (%)			
Statin	9226 (85.0)	5156 (71.5)	33.3
Beta-blocker	10177 (93.8)	6731 (93.3)	1.9
ACEI/ARB	567 (5.2)	389 (5.4)	0.8

*Calculated as weight in kilograms divided by height in meters squared.

†The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is a risk model for predicting the risk of death after cardiac surgery; scores range from 0 to 100%, with higher scores indicating greater risk.

‡Operation before the beginning of the next working day after decision to operate.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CVA, cerebrovascular accident; DAPT, dual antiplatelet therapy; EuroSCORE, European System for Cardiac Operative Risk Evaluation I; IQR, interquartile range; LAD, left anterior descending artery; LIMA, left internal mammary artery; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-elevation myocardial infarction.

Table S2. Administration of Antiplatelet Regimens.

	DAPT (N=10854)	Aspirin Monotherapy (N=7215)
Day of Aspirin initiation after CABG, No. (%)		
Day 0/1	10735 (98.9)	7158 (99.2)
Day 2	95 (0.9)	45 (0.6)
Day 3	9 (0.1)	5 (0.1)
Day >3	15 (0.1)	7 (0.1)
Day of DAPT initiation after CABG, No. (%)		
Day 0/1	5387 (49.6)	–
Day 2	2134 (19.7)	–
Day 3	950 (8.8)	–
Day >3	2383 (22.0)	–
Days between Aspirin and DAPT initiation, No. (%)		
0	5370 (49.5)	–
1	2165 (19.9)	–
2	952 (8.8)	–
3	726 (6.7)	–
>3	1641 (15.1)	–

CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy.

Table S3. Patient Characteristics in the Propensity Score-Matched Cohort*.

Characteristics	DAPT (N=6635)	Aspirin Monotherapy (N=6635)	Absolute Standardized Difference (%)
Age, years, mean (SD)	61.6 (8.4)	61.6 (8.5)	0.5
Age ≥65, No. (%)	2375 (35.8)	2346 (35.4)	0.9
Female sex, No. (%)	1578 (23.8)	1557 (23.5)	0.8
BMI†, kg/m^2, mean (SD)	25.7 (3.0)	25.7 (3.1)	0.5
Year of surgery, No. (%)			0.6
2013	1643 (24.8)	1069 (16.1)	
2014	1387 (20.9)	1649 (24.9)	
2015	1167 (17.6)	1942 (29.3)	
2016	1302 (19.6)	1208 (18.2)	
2017	1136 (17.1)	767 (11.6)	
Medical history, No. (%)			
Smoking	3601 (54.3)	3627 (54.7)	0.8
Diabetes	2524 (38.0)	2530 (38.1)	0.2
Insulin-treated diabetes	411 (6.2)	402 (6.1)	0.6
Hypertension	4345 (65.5)	4317 (65.1)	0.9
Hyperlipidemia	4265 (64.3)	4239 (63.9)	0.8
Peripheral artery disease	447 (6.7)	447 (6.7)	0
Chronic lung disease	256 (3.9)	250 (3.8)	0.5
Previous myocardial infarction	1689 (25.5)	1700 (25.6)	0.4
Previous PCI	704 (10.6)	693 (10.4)	0.5
Previous CVA	735 (11.1)	722 (10.9)	0.6
Clinical presentation, No. (%)			2.1
Stable angina	2804 (42.3)	2848 (42.9)	
Unstable angina	3396 (51.2)	3347 (50.4)	
NSTEMI	198 (3.0)	197 (3.0)	
STEMI	237 (3.6)	243 (3.7)	
3-vessel disease, No. (%)	5905 (89.0)	5911 (89.1)	0.3
LVEF, No. (%)			1.2
≥50%	6168 (93.0)	6208 (93.6)	
40-49%	359 (5.4)	324 (4.9)	
30-39%	100 (1.5)	97 (1.5)	
<30%	8 (0.1)	6 (0.1)	
EuroSCORE‡, No. (%)			1.1
0-2	4136 (62.3)	4162 (62.7)	
3-5	2002 (30.2)	1982 (29.9)	
≥6	497 (7.5)	491 (7.4)	
Preoperative lab tests			

Hemoglobin, g/L, mean (SD)	136.2 (14.8)	136.4 (15.1)	0.9
Platelet count, 10^9/L, mean (SD)	210 (58)	210 (56)	0.1
Serum creatinine, μmol/L, mean (SD)	81.0 (19.7)	81.0 (19.4)	0
Medication use before surgery, No. (%)			
Aspirin within 5 days before surgery	768 (11.6)	765 (11.5)	0.1
$P2Y_{12}$ inhibitors	2426 (36.6)	2412 (36.4)	0.4
Clopidogrel within 5 days	564 (8.5)	446 (6.7)	6.7
Ticagrelor within 5 days	20 (0.3)	20 (0.3)	0
Intravenous nitrate	814 (12.3)	785 (11.8)	1.3
Beta-blocker	5849 (88.2)	5859 (88.3)	0.5
Statin	5320 (80.2)	5323 (80.2)	0.1
ACEI/ARB	2803 (42.2)	2780 (41.9)	0.7
Surgical procedure characteristics			
Emergency surgery§, No. (%)	128 (1.9)	125 (1.9)	0.3
On pump, No. (%)	3186 (48.0)	3149 (47.5)	1.1
LIMA to LAD graft, No. (%)	6253 (94.2)	6273 (94.5)	1.3
No. of grafts, mean (SD)	3.3 (0.9)	3.3 (0.9)	0.4
No. of arterial grafts	1.0 (0.3)	1.0 (0.2)	1.4
No. of venous grafts	2.4 (0.9)	2.4 (0.9)	0
Cardiopulmonary bypass time, min, median (IQR)	101 (82, 113)	99 (81, 110)	1.9
Cross-clamp time, min, median (IQR)	69 (54, 79)	68 (54, 78)	1.6
Duration of surgery, min, median (IQR)	240 (210, 277)	240 (210, 278)	2.4

*A total of 6635/10854 (61.1%) patients in the DAPT group were randomly selected and matched because of the larger sample size in this group as compared with the aspirin monotherapy group. The results should be interpreted in the specific matched population, which represents a different target population than the original sample.

†Calculated as weight in kilograms divided by height in meters squared.

‡The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is a risk model for predicting the risk of death after cardiac surgery; scores range from 0 to 100%, with higher scores indicating greater risk.

§Operation before the beginning of the next working day after decision to operate.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CVA, cerebrovascular accident; DAPT, dual antiplatelet therapy; EuroSCORE, European System for Cardiac Operative Risk Evaluation I; IQR, interquartile range; LAD, left anterior descending artery; LIMA, left internal mammary artery; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-elevation myocardial infarction.

Table S4. Association of DAPT Versus Aspirin Monotherapy with Outcomes in the Propensity Score-Matched Cohort.

	DAPT (N=6635)	Aspirin Monotherapy (N=6635)	HR (95% CI)*	P Value
Primary outcome, No. (%)				
MACCE†	193 (2.9)	282 (4.3)	0.68 (0.57, 0.82)	<0.001
Secondary outcomes, No. (%)				
All-cause death	37 (0.6)	58 (0.9)	0.64 (0.42, 0.96)	0.033
Cardiovascular death	27 (0.4)	44 (0.7)	0.61 (0.38, 0.99)	0.046
MI	56 (0.8)	88 (1.3)	0.64 (0.46, 0.88)	0.007
Stroke	91 (1.4)	154 (2.3)	0.59 (0.45, 0.76)	<0.001
Repeat revascularization	23 (0.3)	20 (0.3)	1.15 (0.63, 2.10)	0.65
Cardiovascular death, MI, or ischemic stroke	163 (2.5)	263 (4.0)	0.62 (0.51, 0.75)	<0.001
Cardiovascular death or MI	78 (1.2)	115 (1.7)	0.68 (0.51, 0.90)	0.007
Major bleeding	32 (0.5)	28 (0.4)	1.14 (0.69, 1.90)	0.60
In-hospital reoperation for bleeding	9 (0.1)	9 (0.1)	1.28 (0.50, 3.27)	0.60
Hospitalization for bleeding	23 (0.3)	19 (0.3)	1.21 (0.66, 2.23)	0.54
Net clinical benefit outcome, No. (%)				
MACCE, major bleeding	219 (3.3)	305 (4.6)	0.71 (0.60, 0.85)	<0.001

*Estimated using Cox regression or Fine and Gray model in the propensity score-matched population.

†A composite of all-cause mortality, myocardial infarction, stroke, and repeat revascularization.

CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.

Table S5. Association of DAPT Versus Aspirin Monotherapy with Outcomes Estimated by Multivariable Cox Proportional Hazards Regression Analysis and Doubly Robust Analysis with Augmented Inverse Probability of Treatment Weighting.

	Adjusted HR (95% CI)*	P Value	Adjusted HR (95% CI)†	P Value
Primary outcome, No. (%)				
MACCE‡	0.66 (0.56, 0.78)	<0.001	0.62 (0.52, 0.73)	<0.001
Secondary outcomes, No. (%)				
All-cause death	0.66 (0.46, 0.95)	0.027	0.60 (0.41, 0.88)	0.009
Cardiovascular death	0.65 (0.42, 1.00)	0.049	0.56 (0.36, 0.89)	0.015
MI	0.58 (0.43, 0.78)	<0.001	0.51 (0.37, 0.68)	<0.001
Stroke	0.58 (0.46, 0.73)	<0.001	0.59 (0.46, 0.75)	<0.001
Repeat revascularization	1.00 (0.57, 1.76)	0.99	0.97 (0.55, 1.71)	0.91
Cardiovascular death, MI, or ischemic stroke	0.60 (0.50, 0.71)	<0.001	0.56 (0.47, 0.67)	<0.001
Cardiovascular death or MI	0.67 (0.52, 0.87)	0.002	0.58 (0.45, 0.76)	<0.001
Major bleeding	1.12 (0.70, 1.78)	0.63	1.15 (0.70, 1.89)	0.59
In-hospital reoperation for bleeding	1.51 (0.63, 3.65)	0.36	1.52 (0.62, 3.71)	0.36
Hospitalization for bleeding	1.12 (0.64, 1.95)	0.70	1.21 (0.66, 2.24)	0.54
Net clinical benefit outcome, No. (%)				
MACCE, major bleeding	0.69 (0.59, 0.81)	<0.001	0.65 (0.56, 0.77)	<0.001

*Estimated using multivariable Cox regression model without propensity scores. Covariates for the model were identical to those used for calculating propensity scores. †Estimated using doubly robust estimation by further adjusting for baseline covariates in the IPTW-adjusted Cox regression model (augmented inverse probability of treatment weighting) to eliminate the potential risk for insufficient covariate balance and model misspecification.
‡A composite of all-cause mortality, myocardial infarction, stroke, and repeat revascularization.
CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.

Table S6. Association of DAPT Versus Aspirin Monotherapy with Outcomes in Primary Weighted Cohort After Exclusion of Patients Who Received $P2Y_{12}$ Inhibitors Within 5 Days Before CABG.

	DAPT (N=10046)	Aspirin Monotherapy (N=6655)	Adjusted HR (CI)*	P Value
Primary outcome, No. (%)				
MACCE†	286 (2.8)	279 (4.2)	0.67 (0.56, 0.79)	<0.001
Secondary outcomes, No. (%)				
All-cause death	53 (0.5)	60 (0.9)	0.62 (0.41, 0.93)	0.021
Cardiovascular death	39 (0.4)	44 (0.7)	0.59 (0.37, 0.96)	0.034
MI	85 (0.8)	88 (1.3)	0.59 (0.43, 0.81)	0.001
Stroke	131 (1.3)	149 (2.2)	0.58 (0.46, 0.75)	<0.001
Repeat revascularization	31 (0.3)	20 (0.3)	1.09 (0.61, 1.95)	0.78
Cardiovascular death, MI, or ischemic stroke	241 (2.4)	257 (3.9)	0.61 (0.50, 0.73)	<0.001
Cardiovascular death or MI	120 (1.2)	113 (1.7)	0.67 (0.51, 0.88)	0.004
Major bleeding	50 (0.5)	26 (0.4)	1.21 (0.73, 2.00)	0.46
In-hospital reoperation for bleeding	14 (0.1)	8 (0.1)	1.34 (0.55, 3.24)	0.52
Hospitalization for bleeding	36 (0.4)	18 (0.3)	1.31 (0.71, 2.42)	0.39
Net clinical benefit outcome, No. (%)				
MACCE, major bleeding	327 (3.3)	302 (4.5)	0.70 (0.59, 0.83)	<0.001

*Estimated with the use of inverse probability of treatment-weighted Cox regression or Fine and Gray model.

†A composite of all-cause mortality, myocardial infarction, stroke, and repeat revascularization.

CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.