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Extended Clopidogrel Monotherapy vs DAPT in Patients With Acute Coronary Syndromes at High Ischemic and Bleeding Risk
The OPT-BIRISK Randomized Clinical Trial

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IMPORTANCE Purinergic receptor P2Y12 (P2Y12) inhibitor monotherapy after a certain period of dual antiplatelet therapy (DAPT) may be an attractive option of maintenance antiplatelet treatment for patients undergoing percutaneous coronary intervention (PCI) who are at both high bleeding and ischemic risk (birisk).

OBJECTIVE To determine if extended P2Y12 inhibitor monotherapy with clopidogrel is superior to ongoing DAPT with aspirin and clopidogrel after 9 to 12 months of DAPT after PCI in birisk patients with acute coronary syndromes (ACS).

DESIGN, SETTING, AND PARTICIPANTS This was a multicenter, double-blind, placebo-controlled, randomized clinical trial including birisk patients with ACS who had completed 9 to 12 months of DAPT after drug-eluting stent implantation and were free from adverse events for at least 6 months at 101 China centers between February 2018 and December 2020. Study data were analyzed from April 2023 to May 2023.

INTERVENTIONS Patients were randomized either to clopidogrel plus placebo or clopidogrel plus aspirin for an additional 9 months.

MAIN OUTCOMES AND MEASURES The primary end point was Bleeding Academic Research Consortium (BARC) types 2, 3, or 5 bleeding 9 months after randomization. The key secondary end point was major adverse cardiac and cerebral events (MACCE; the composite of all-cause death, myocardial infarction, stroke or clinically driven revascularization). The primary end point was tested for superiority, and the MACCE end point was tested for sequential noninferiority and superiority.

RESULTS A total of 7758 patients (mean [SD] age, 64.8 [9.0] years; 4575 male [59.0%]) were included in this study. The primary end point of BARC types 2, 3, or 5 bleeding occurred in 95 of 3873 patients (2.5%) assigned to clopidogrel plus placebo and 127 of 3885 patients (3.3%) assigned to clopidogrel plus aspirin (hazard ratio [HR], 0.75; 95% CI, 0.57-0.97; difference, −0.8%; 95% CI, −1.6% to −0.1%; $P = .03$). The incidence of MACCE was 2.6% (101 of 3873 patients) in the clopidogrel plus placebo group and 3.5% (136 of 3885 patients) in the clopidogrel plus aspirin group (HR, 0.74; 95% CI, 0.57-0.96; difference, −0.9%; 95% CI, −1.7% to −0.1%; $P < .001$ for noninferiority; $P = .02$ for superiority).

CONCLUSIONS AND RELEVANCE Among birisk patients with ACS who completed 9 to 12 months of DAPT after drug-eluting stent implantation and were free from adverse events for at least 6 months before randomization, an extended 9-month clopidogrel monotherapy regimen was superior to continuing DAPT with clopidogrel in reducing clinically relevant bleeding without increasing ischemic events.

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Visual Abstract

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Supplemental content

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Group Information: The members of the OPT-BIRISK Investigators appear in Supplement 4.

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Antiplatelet therapy is the cornerstone of treatment to reduce thrombotic events in patients with acute coronary syndromes (ACS) and in those undergoing percutaneous coronary intervention (PCI).[1-4] However, antiplatelet therapy also increases the risk of bleeding. Accordingly, assessing ischemic and bleeding risks in individual patients receiving antiplatelet therapy is crucial to balance the potential benefits and harm of treatment.[5] Randomized clinical trials have demonstrated that adverse outcomes such as myocardial infarction (MI) and stent thrombosis are reduced with a prolonged (>1 year) course of dual antiplatelet therapy (DAPT) in patients at increased ischemic risk, such as those with ACS.[1-5] Conversely, patients at increased bleeding risk (eg, patients older than 75 years) warrant less intensive therapy.[1-5] In real-world practice, many patients are at increased risk for both ischemic and bleeding events; the optimal antithrombotic treatment regimen in such patients is unknown.[6]

In recent years, the use of purinergic receptor P2Y12 (P2Y12) inhibitor monotherapy after a brief (ie, 1-3 month) period of DAPT has emerged as an effective antiplatelet strategy to reduce bleeding in patients undergoing PCI, irrespective of PCI complexity.[7-9] However, increased ischemic event rates have been reported in patients with ACS after PCI who are treated with DAPT for only 1 to 2 months followed by clopidogrel monotherapy[10] or with DAPT for only 6 months followed by aspirin monotherapy.[11] These observations underscore the importance of maintaining DAPT for guideline-recommended durations (eg, 12 months) in high ischemic-risk settings, particularly when using a P2Y12 inhibitor with modest platelet inhibitory effects such as clopidogrel.[1-4] Following this time frame, although a strategy of clopidogrel monotherapy is an attractive option, particularly for patients at both high ischemic and bleeding risk, this has never been tested.[12]

We, therefore, conducted the Optimal Antiplatelet Therapy for High Bleeding and Ischemic Risk Patients (OPT-BIRISK) trial to determine whether, in patients with ACS and both high bleeding- and ischemic-risk characteristics (birisk) who remained event-free after a standard course of DAPT after PCI, an extended course of clopidogrel monotherapy would be superior to ongoing DAPT treatment with aspirin and clopidogrel.

Key Points

Question What is the optimal antiplatelet regimen in patients with acute coronary syndromes (ACS) undergoing percutaneous coronary interventions (PCIs) who are at both high bleeding and ischemic risks (birisk)?

Findings In this double-blind, randomized clinical trial including 7758 PCI-treated birisk patients with ACS who completed 9 to 12 months of dual antiplatelet therapy (DAPT) after PCI, clopidogrel monotherapy for an additional 9 months resulted in a 25% reduction in the risk of Bleeding Academic Research Consortium types 2, 3, or 5 bleeding compared with clopidogrel plus aspirin.

Meaning Among birisk patients with ACS who completed 9 to 12 months of DAPT after PCI, subsequent treatment with clopidogrel was superior to continuing DAPT with aspirin and clopidogrel in reducing clinically relevant bleeding.

Methods

Trial Design and Organization

The OPT-BIRISK trial was an investigator-initiated, multicenter, double-blind, placebo-controlled, randomized clinical trial. The study rationale and design have been previously published (Supplement 1 and Supplement 2).[13] The trial organization and participating centers are listed in the eAppendix in Supplement 3. The study protocol was approved by the ethics committee of the General Hospital of Northern Theater Command and was conducted in accordance with the Declaration of Helsinki. The study was approved by the ethics committee at each participating center and written informed consent was provided by all patients before randomization. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Patients

Patients who completed at least 9 months and no more than 12 months of DAPT (aspirin plus either clopidogrel or ticagrelor) after drug-eluting stent (DES) implantation for the treatment of ACS (unstable angina, non–ST-segment–elevation MI [NSTEMI] or ST-segment–elevation MI [STEMI]), who were free from major adverse clinical events during the prior 6 months, were eligible for enrollment. Study entry criteria and definitions of bleeding and ischemic risks at the time of index PCI are listed in the eAppendix in Supplement 3. In brief, patients with ACS were qualified as meeting criteria for both high ischemic and bleeding risk if 1 of the following 3 conditions were met: (1) any patient 75 years or older (ischemic risk criteria met by ACS; bleeding risk criteria met by advanced age), (2) patients aged 65 to 75 years who also met at least 1 additional criterion of ischemic or bleeding risk, or (3) patients 65 years or younger who met at least additional 1 criterion of ischemic risk and at least 1 additional criterion of bleeding risk. The standard DAPT course was allowed to range as short as 9 months and as long as 12 months before randomization because of the presence of criteria for both high bleeding as well as ischemic risk. Participant race and ethnicity data were not gathered as this study was conducted in domestic Chinese centers, where the vast majority of patients were East Asians.

Randomization and Treatments

Patients were randomly assigned in a 1:1 ratio using an interactive web response system with block size of 4, stratified by center. After randomization, patients were treated with repackaged aspirin, 100 mg per day (Bayer), or matching placebo (Boji Pharmacy) plus open-label clopidogrel, 75 mg per day (Sanofi Winthrop), in both groups for 9 months. Antiplatelet therapy was then used per physician discretion, although aspirin (100 mg per day) was recommended for at least 3 months after the randomization period to minimize the risk of a rebound in ischemic events. Follow-up was performed at 3, 6, 9, and 12 months after randomization.

End Points and Definitions

The primary end point was the rate of clinically relevant bleeding 9 months after randomization (during the double-blind, placebo-controlled phase), defined as Bleeding Academic

Research Consortium (BARC) types 2, 3, or 5 bleeding. The key secondary end point was the rate of major adverse cardiac and cerebral events (MACCE), defined as the composite of all-cause death, MI, stroke, or clinically driven revascularization, 9 months after randomization. Other end points included the 9-month postrandomization rates of the individual components of MACCE, any bleeding, and stent thrombosis. Bleeding was defined according to the BARC definition.[14] Stent thrombosis was defined as definite or probable according to the ARC criteria.[15] Detailed end point definitions and study processes appear in the eAppendix in Supplement 3. All end point events were adjudicated by an independent clinical events committee blinded to randomization assignment. An independent data safety monitoring board monitored study data periodically during the trial.

Statistical Analysis

The trial was powered to demonstrate a reduction in clinically relevant (BARC types 2, 3, or 5) bleeding. Assuming a 6.0% incidence of the primary end point in the DAPT group during the randomization period and allowing for 10% loss to follow-up,[16] 7700 total patients (3850 per group) would provide 80% power to detect a reduction in bleeding to 4.5% with 9 months of clopidogrel monotherapy compared with extended DAPT (a 25% relative reduction) tested with a log-rank test at a 2-sided α of .05. For the key secondary end point, we assumed MACCE would occur in 8.0% of patients in the DAPT group during the 9-month randomization period. With a noninferiority margin of 1.6% (20% relative difference), tested at a 1-sided α of .025, 7700 total patients would provide 73% power to conclude that clopidogrel monotherapy would be noninferior to DAPT in anti-ischemic efficacy during this period. If noninferiority was achieved, superiority would be tested.

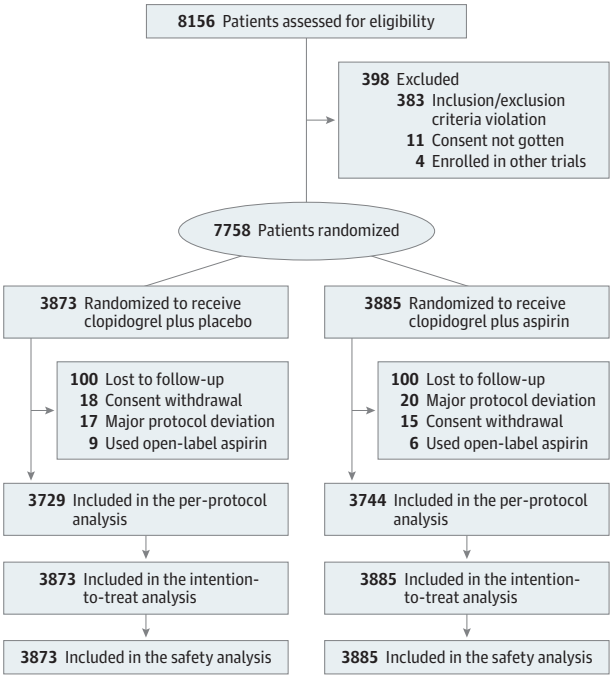
All primary analyses were by intention to treat (ITT). Sensitivity analyses were performed in the per-protocol population, defined as patients assigned per ITT who did not have major protocol violations, did not use open-label aspirin during follow-up, and who completed 9-month follow-up after randomization or died. Categorical variables were compared using the χ^2 or Fisher exact test. Continuous data are presented as means with SD or medians with IQR and were compared using *t* tests if normally distributed or the Wilcoxon rank sum test if nonnormally distributed. Time to first event rates were estimated by the Kaplan-Meier method and were compared with the log-rank test. Hazard ratios (HRs) and 95% CIs were determined from a Cox model. Consistency of the treatment effect for the primary end point was examined by interaction testing in 14 prespecified subgroups. A 2-sided *P* value <.05 was considered significant for all superiority tests. All statistical analyses were performed with SAS, version 9.4 (SAS Institute). Study data were analyzed from April 2023 to May 2023.

Results

Patient Characteristics

A total of 7758 patients (mean [SD] age, 64.8 [9.0] years; 3183 female [41.0%]; 4575 male [59.0%]) who had presented with ACS, underwent PCI with newer-generation DES, completed 9 to 12 months of DAPT, and were free from adverse events for at least the prior 6 months were randomized at 101 Chinese centers between February 12, 2018, and December 4, 2020. A total of 3873 patients (49.9%) were randomly assigned to receive clopidogrel plus placebo, and 3885 patients (50.1%) were randomly assigned to receive clopidogrel plus aspirin (**Figure 1**). Demographic, clinical, and procedural characteristic were well matched between the 2 groups (**Table 1** and **Table 2**). A total of 4072 patients (52.5%) had diabetes, 1418 (18.3%) had a history of MI, and 1171 (15.1%) had a history of ischemic stroke. A total of 4191 patients (54.0%) underwent index PCI for unstable angina, 1958 (25.2%) for NSTEMI, and 1609 (20.7%) for STEMI. The qualifying high ischemic- and bleeding-risk criteria are listed in eTable 1 in Supplement 3. Patients had a mean (SD) of 3.2 (1.6) high ischemic-risk criteria and a mean (SD) of 1.4 (0.9) high bleeding-risk criteria (eFigure 1 in Supplement 3). The median (IQR) time interval between the index PCI and randomization was 340 (307-358) days. Study medication adherence was high (eTable 2 in Supplement 3).

Figure 1. Study Flowchart



Safety Outcomes

Complete clinical follow-up at 12 months after randomization was completed in 7558 of 7758 randomized patients (97.4%), and vital status was obtained in 7712 of 7758 patients (99.4%). The key outcomes are shown in **Table 3**, eTable 4 in Supplement 3, and **Figure 2**. The primary end point of BARC types 2, 3, or 5 bleeding at 9 months after randomization occurred in 95 of 3873 patients (2.5%) assigned to clopidogrel plus placebo and in 127 of 3885 patients (3.3%) assigned to clopidogrel plus aspirin (HR, 0.75; 95% CI, 0.57-0.97; difference, −0.8%; 95% CI, −1.6% to −0.1%; *P* = .03). The number needed to treat to prevent 1 BARC type 2, 3, or 5 bleed was 122. The

Table 1. Baseline Characteristics of the Study Groups

Characteristic	Clopidogrel plus placebo (n = 3873)	Clopidogrel plus aspirin (n = 3885)
Age, mean (SD), y	64.9 (8.9)	64.7 (9.1)
Aged ≥75 y, No. (%)	510 (13.2)	529 (13.6)
Sex, No. (%)		
Female	1584 (40.9)	1599 (41.2)
Male	2289 (59.1)	2286 (58.8)
Body mass index, mean (SD)[a]	25.3 (3.4)	25.2 (3.3)
Medical history, No. (%)		
Hypertension	2661 (68.7)	2607 (67.1)
Diabetes mellitus	2035 (52.5)	2037 (52.4)
Medically treated	1965 (50.7)	1970 (50.7)
Insulin treated	715 (18.5)	709 (18.3)
Hyperlipidemia	1177 (30.4)	1198 (30.8)
Smoking		
Active	1011 (26.1)	953 (24.5)
Former	671 (17.3)	700 (18.0)
Never	2191 (56.6)	2232 (57.5)
Previous myocardial infarction	702 (18.1)	716 (18.4)
Previous PCI	929 (24.0)	941 (24.2)
Previous stroke		
Ischemic	581 (15.0)	590 (15.2)
Hemorrhagic	50 (1.3)	55 (1.4)
Peripheral artery disease	233 (6.0)	212 (5.5)
Previous heart failure	308(8.0)	345(8.9)
Previous bleeding events	180 (4.6)	189 (4.9)
Presentation		
Unstable angina	2064 (53.3)	2127 (54.7)
NSTEMI	1016 (26.2)	942 (24.3)
STEMI	793 (20.5)	816 (21.0)
Hemoglobin, mean (SD), g/L	136.6 (16.0)	136.4 (16.0)
Anemia, No./total No. (%)[b]	248/3808 (6.5)	242/3815 (6.3)
eGFR, mean (SD)[c]	98.7 (50.8)	99.0 (38.0)
eGFR<60, No./total No. (%)	244/3806 (6.4)	260/3819 (6.8)
GRACE score		
Mean (SD)	89.9 (24.0)	89.5 (23.7)
Median (IQR)	88 (75-103)	88 (75-104)
CRUSADE score		
Mean (SD)	26.7 (11.8)	26.6 (11.8)
Median (IQR)	26 (18-34)	26 (18-34)
PRECISE-DAPT score		
Mean (SD)	16.5 (10.4)	16.6 (10.2)
Median (IQR)	15 (9-22)	15 (9-22)
ARC-HBR, No./total No. (%)	986/3793 (26.0%)	1003/3789 (26.5%)
DAPT score, No./total No. (%)		
<2	2322/3752 (61.9)	2344/3759 (62.4)
≥2	1430/3752 (38.1)	1415/3759 (37.6)
Time interval between index PCI and randomization, median (IQR), d	339 (308-358)	340 (307-358)
Medications between the index PCI and randomization, No./total No. (%)		
Aspirin	3857/3872 (99.6)	3866/3878 (99.7)
P2Y12 inhibitors		
Clopidogrel	2872/3871 (74.2)	2849/3878 (73.5)
Ticagrelor	952/3871 (24.6)	996/3878 (25.7)
Switch	42/3871 (1.1)	30/3878 (0.8)
None	5/3871 (0.1)	3/3878 (0.1)
Statins	3792/3870 (98.0)	3793/3879 (97.8)
ACEI/ARB	2258/3870 (58.3)	2219/3879 (57.2)
β-Blockers	2711/3870 (70.1)	2761/3879 (71.2)
Proton pump inhibitor	1203/3870 (31.1)	1290/3879 (33.3)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARC-HBR, Academic Research Consortium High Bleeding Risk; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association guidelines; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; PRECISE-DAPT, Predicting Bleeding Complications in Patients Undergoing Stent Implantation And Subsequent Dual Antiplatelet Therapy; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; P2Y12, purinergic receptor P2Y12; STEMI, ST-segment–elevation myocardial infarction.

SI conversion factor: To convert hemoglobin to grams per deciliter, divide by 10.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Anemia was defined as hemoglobin less than 130 g/L for male patients and less than 120 g/L for female patients.

[c] Calculated as milliliters per minute per 1.73 meters squared.

treatment effect for the primary end point was consistent across prespecified subgroups except for patients with anemia (eFigure 2 in Supplement 3).

Efficacy Outcomes

MACCE occurred in 101 of 3873 patients (2.6%) in the clopidogrel plus placebo group and in 136 of 3885 patients (3.5%) in the clopidogrel plus aspirin group (HR, 0.74; 95% CI, 0.57-0.96; difference, −0.9%; 95% CI, −1.7% to −0.1%; *P* for noninferiority <.001; P for superiority = .02). The number needed to treat to prevent 1 MACCE was 112. The incidences of all-cause death (13 of 3873 [0.3%] vs 18 of 3885 [0.5%]), MI (16 of 3873 [0.4%] vs 27 of 3885 [0.7%]), stroke (26 of 3873 [0.7%] vs 33 of 3885 [0.8%]), and clinically driven revascularization (53 of 3873 [1.4%] vs 71 of 3885 [1.8%]) were not significantly different between patients treated with clopidogrel plus placebo and clopidogrel plus aspirin respectively (Table 3). Three patients had stent thrombosis during the 9-month randomization period: 2 (0.05%) in the clopidogrel plus placebo group and 1 (0.03%) in the clopidogrel plus aspirin group. The effects of clopidogrel monotherapy on MACCE were consistent across prespecified subgroups (eFigure 3 in Supplement 3).

Table 2. Characteristics of the Index Percutaneous Coronary Intervention Procedure

Characteristic	Clopidogrel plus placebo (n = 3873)	Clopidogrel plus aspirin (n = 3885)
Arterial access, No./total No. (%)		
Transradial	3584 /3834 (93.5)	3631/3842 (94.5)
Transfemoral	233/3834 (6.1)	203/3842 (5.3)
Other	17/3834 (0.4)	8/3842 (0.2)
Target vessels per patient, No./total No. (%)		
1	2812/3741 (75.2)	2860/3769 (75.9)
2	771/3741 (20.6)	739/3769 (19.6)
≥3	158/3741 (4.2)	170/3769 (4.5)
Target vessel, No./total No. (%)		
Left main	251/4841 (5.2)	225/4861 (4.6)
Left anterior descending	2157/4841 (44.6)	2112/4861 (43.4)
Left circumflex	1014/4841 (20.9)	1009/4861 (20.8)
Right coronary artery	1419/4841 (29.3)	1515/4861 (31.2)
No. of target lesions per patient, mean (SD)	1.4 (0.7)	1.4 (0.7)
Target lesion morphology, No./total No. (%)[a]		
Chronic total occlusion	242/3763 (6.4)	261/3768 (6.9)
Bifurcation	244/3763 (6.5)	247/3768 (6. 6)
Moderate or severe calcification	220/3763 (5.8)	203/3768 (5.4)
Diffuse disease	3142/3763 (83.5)	3117/3768 (82.7)
Small vessel	929/3763 (24.7)	952/3768 (25.3)
No. of stents per patient, mean (SD)	1.8 (1.0)	1.8 (1.0)
Drug-eluting stent type, No./total No. (%)[b]		
Biodegradable polymer or polymer-free	2321/3739 (62.1)	2301/3776 (60.9)
Durable polymer	1711/3739 (45.8)	1793/3776 (47.5)
Total length of stents, mean (SD), mm	47.2 (31.0)	47.1 (30.1)

[a] Multiple lesion morphologies were present in 2342 of 7531 patients (31.1%).

[b] Stents of more than one type were implanted in 611 of 7582 patients (8.1%).

Additional Analyses

Safety and efficacy results in the per-protocol population (eTable 3 and eFigure 4 in Supplement 3) were consistent with those in the ITT population. The incidences of BARC types 2, 3, or 5 bleeding and MACCE were similar between groups during the 3-month open-label aspirin-only period after randomization, without evidence of rebound (eFigure 5 in Supplement 3). The risks of bleeding and ischemic events during the 9-month randomized period were also consistent between nonprespecified subgroups including the type of ACS, proton pump inhibitor use, and specific prerandomization P2Y12 inhibitor agent used (eTable 5 in Supplement 3). The incidence of net adverse clinical events (defined as a composite of BARC types 2, 3, 5 bleeding or MACCE) was also reduced with clopidogrel plus placebo compared with clopidogrel plus aspirin (191 of 3873 [4.9%] vs 256 of 3885 [6.6%]; HR, 0.74; 95% CI, 0.62-0.90; P = .002) (eFigure 6 in Supplement 3).

Discussion

Patients with enriched ischemic or bleeding risk features have been studied in previous trials of optimal antiplatelet therapy after PCI.[17,18] However, OPT-BIRISK is the first, to our knowledge, dedicated large-scale, double-blind, placebo-controlled randomized clinical trial to examine the optimal long-term duration of DAPT in a common, difficult-to-treat patient cohort including birisk patients with ACS successfully treated with PCI who remain event free after an initial mandatory duration of DAPT. In this trial, among patients with ACS and high-risk criteria for both ischemic and bleeding treated with contemporary DES and who had completed 9 to 12 months of DAPT and were free from adverse events for at least 6 months, we evaluated the safety and efficacy of extending antiplatelet treatment for an additional 9 months with either clopidogrel monotherapy vs continuing DAPT with aspirin plus clopidogrel. The principal finding of the present trial is that clopidogrel monotherapy resulted in a 25% reduction in the risk of BARC types 2, 3, or 5 bleeding during the 9-month randomization period compared with ongoing DAPT. During this interval, clopidogrel monotherapy was also superior in reducing MACCE.

Aspirin monotherapy after a certain duration of DAPT after PCI has been the standard of care for decades. In recent years, DAPT followed by P2Y12 inhibitor monotherapy has emerged as a strategy to reduce bleeding after PCI,[7,8,19-21] although ischemic events have been reduced only with ticagrelor monotherapy. Conversely, in other studies, DAPT followed by clopidogrel or aspirin monotherapy was associated with an increase in ischemic events,[10,11] underscoring the importance of maintaining DAPT for guideline-recommended durations (eg, 12 months) in most high ischemic-risk patients unless ticagrelor monotherapy is used.

The present trial enrolled a unique difficult-to-treat patient population with criteria for not only increased ischemic risk but also increased bleeding risk who were maintained on standard DAPT by their treating physicians for at least 9 months and not more than 12 months before randomization without major adverse events. This time point was considered ideal to test our study hypothesis given the time-dependent risk of ischemia and bleeding after PCI in ACS,[22] and the relatively high rate of DAPT discontinuation in patients with ACS at 9 to 12 months after PCI in older adult patients in China.[23] Moreover, although contemporary guidelines recommend potent P2Y12 inhibition with ticagrelor or prasugrel as the first-line choice for patients with ACS undergoing PCI,[1-4] clopidogrel remains the most commonly used P2Y12 inhibitor and represents the agent of choice for most East Asian patients, especially in those with features predisposing to bleeding.[24-27] In this regard, real-world studies have demonstrated that the benefits of ticagrelor compared with clopidogrel are principally observed in patients at low bleeding risk and are diminished in patients at high bleeding risk.[27]

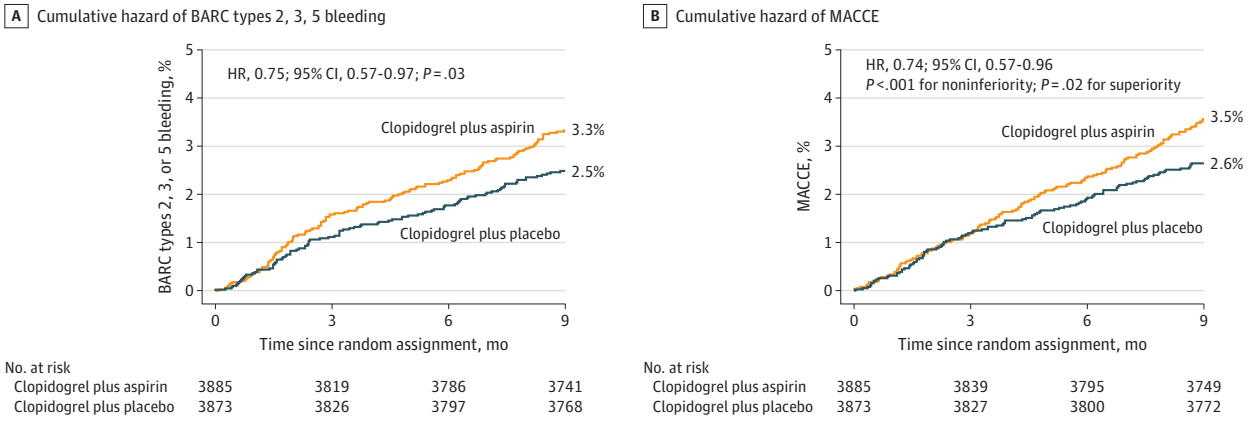
Table 3. Clinical Outcomes at 9 Months After Randomization

Outcome	No. (%)		Hazard ratio (95% CI)	*P* value
	Clopidogrel plus placebo (n = 3873)	Clopidogrel plus aspirin (n = 3885)		
Primary end point: BARC types 2, 3, or 5 bleeding	95 (2.5)	127 (3.3)	0.75 (0.57-0.97)	.03
BARC types 1, 2, 3, or 5 bleeding	560 (14.5)	704 (18.1)	0.78 (0.70-0.88)	<.001
BARC types 3 or 5 bleeding	22 (0.6)	26 (0. 7)	0.85 (0.48-1.50)	.57
Key secondary end point: major adverse cardiac and cerebral events[a]	101 (2.6)	136 (3.5)	0.74 (0.57-0.96)	.02
Death from any cause	13 (0.3)	18 (0.5)	0.72 (0.35-1.48)	.38
Cardiovascular	11 (0.3)	9 (0.2)	1.23 (0.51-2.96)	.65
Myocardial infarction	16 (0.4)	27 (0.7)	0.59 (0.32-1.10)	.10
Ischemic stroke	26 (0.7)	33 (0.8)	0.79 (0.47-1.32)	.37
Clinically driven revascularization	53 (1.4)	71 (1.8)	0.75 (0.52-1.07)	.11
Target lesion	18 (0.5)	21 (0.5)	0.86 (0.46-1.61)	.64
Nontarget lesion	35 (0.9)	50 (1.3)	0.70 (0.46-1.08)	.11
Stent thrombosis, definite or probable	2 (0.05)	1 (0.03)	2.01 (0.18-22.11)	.57

Abbreviation: BARC, Bleeding Academic Research Consortium.

[a] The upper limit of the 95% CI for the difference indicated noninferiority (*P* < .001).

Figure 2. Kaplan-Meier Curves for the Principal 9-Month Study Outcomes



A, Cumulative hazard of Bleeding Academic Research Consortium (BARC) types 2, 3, 5 bleeding. B, Cumulative hazard of major adverse cardiac and cerebral events (MACCE). HR indicates hazard ratio.

All patients are at an ongoing risk of major adverse cardiovascular events (2% to 3% per year) beyond the first year after stent implantation, a period when aspirin monotherapy is typically used.[28] Based on existing evidence,[16,29,30] current guidelines recommend considering extending DAPT beyond 1 year after PCI in patients at high ischemic risk to minimize the long-term rate of thrombotic events.[1-4] However, extended DAPT is associated with increased bleeding compared with aspirin alone[30,31] and is especially harmful in patients at high bleeding risk. Accordingly, guidelines do not recommend extending DAPT beyond 12 months in patients at increased bleeding risk, irrespective of ischemic risk.[4] These observations underscore the need to better define alternative antiplatelet approaches for patients at both high ischemic and bleeding risk, representing the rationale for the present trial.

Emerging data suggest that long-term clopidogrel (or in some patients, more potent P2Y12 inhibitor therapy) is a superior monotherapy regimen to aspirin alone. In the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial clopidogrel monotherapy was marginally superior to aspirin in preventing thrombotic events in patients with established atherosclerotic vascular disease.[32] The Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-Extended Antiplatelet Monotherapy (HOST-EXAM) trial compared clopidogrel vs aspirin for chronic antiplatelet monotherapy up to a median of 5.8 years in 5530 South Korean patients (72.1% ACS) who remained event free after a 6- to 18-month course of DAPT after PCI. Significant reductions in both thrombotic and bleeding events were noted in the clopidogrel monotherapy group.[33,34] However, the optimal antiplatelet regimen for extended treatment has not been defined in patients with ACS who are at increased bleeding risk as well as ongoing risk for recurrent ischemia. In the OPT-BIRISK trial, we therefore tested the safety and efficacy of extended clopidogrel monotherapy vs DAPT for 9 months after the successful completion of at least 9 months and not more than 12 months of DAPT in birisk patients with ACS who were treated with PCI. Our study

demonstrated a significant reduction in clinically relevant bleeding with clopidogrel monotherapy, as well as a reduction in MACCE. These results extend the findings from previous studies that have shown that P2Y12 inhibitor monotherapy is associated with a lower risk of gastrointestinal mucosal injury compared with DAPT while providing effective platelet inhibition.[35-38] The outcomes from the present study, in concert with the findings from the HOST-EXAM trial and a prior meta-analysis,[33,39] suggest that chronic clopidogrel monotherapy should be a preferred treatment option after 9 to 12 months of DAPT in appropriate patients with ACS.

The incidence of the primary bleeding end point was lower than that estimated from the DAPT trial,[16] which may be explained by ethnic differences between the studies and interval improvements in bleeding avoidance strategies. Nevertheless, the incidence of bleeding in the present study in the randomization period was similar to that observed between 1 to 2 years after PCI in other trials involving East Asian populations.[34,40] The treatment effect of withholding aspirin in reducing bleeding risk in this trial (25%) was smaller than that observed in previous trials (approximately 50%)[17,21] and was mainly derived from the reduction of BARC type 2 bleeding. This lower reduction may be explained by the study protocol requiring that patients had survived after 9 to 12 months of DAPT and were free from major ischemic and bleeding events for at least 6 months before randomization. Similarly, the observed MACCE rates were also less than anticipated, perhaps in part due to improvements in stent design and technique, making noninferiority for this key secondary end point easier to be achieved. Nevertheless, MACCE rates with clopidogrel monotherapy were significantly lower than with continued DAPT, demonstrating that this strategy may even provide benefit in reducing ischemic events. Neither MACCE nor other secondary end points were powered for superiority and their findings were not adjusted for multiplicity; these outcomes should thus be considered hypothesis generating. However, it is well-established that bleeding is correlated with ischemic events and is likely causative in some cases because of direct effects (hypotension, hypoxia), adverse consequences of blood transfusions or other invasive therapies to treat bleeding, and discontinuation of life-saving therapies as a response to bleeding or hypotension.[41-43] With this perspective and considering the large size of the present trial, the observed reduction in MACCE is plausible. Moreover, a borderline significant interaction for MACCE between study medications and different DAPT score stratifications was observed (eFigure 3 in Supplement 3), indicating that clopidogrel monotherapy may outperform DAPT in patients with a DAPT score less than 2 but not in those with a higher score. Further studies are warranted to determine patient cohorts who most benefit more from DAPT de-escalation.

Limitations

Study limitations include the fact that the mean number of high-risk bleeding criteria was relatively low. If a higher bleeding risk population had been enrolled, the impact of clopidogrel monotherapy on bleeding compared with DAPT may have potentially been even more pronounced. As recommended in the guidelines,[1-4] bleeding and ischemic risk were assessed at the time of the index PCI; all patients were at high ischemic risk given their presentation with ACS, and all met additional risk criteria for increased ischemia or bleeding. However, enrolled patients were event free for at least 6 months after a 9- to 12-month course of DAPT, selecting for a relatively lower-risk subset of birisk patients. Nonetheless, these patients represent a large cohort commonly encountered in clinical practice in whom the question of continuing DAPT vs de-escalating to clopidogrel monotherapy at this time has not previously been addressed. Our trial results apply to this cohort. Methodologically, this is also the proper time to recruit and randomize this group. The OPT-BIRISK study was designed before publication of what are currently the most widely used high bleeding-risk criteria, the Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) and Academic Research Consortium High Bleeding Risk (ARC-HBR) scores.[44,45] Not all patients enrolled in the present study met high bleeding-risk criteria according to these risk instruments. However, the birisk criteria we selected were chosen from elements from previously published risk scores for ischemia and bleeding (eTable 6 in Supplement 3), and performed well in discriminating birisk patients with ACS in a real-world registry.[46] Confirmatory studies are warranted to determine whether our findings apply to birisk populations defined by other ischemic and bleeding risk criteria. The present trial was conducted solely in a Chinese population. In this regard, the higher incidence of loss-of-function alleles adversely affecting clopidogrel metabolism and antiplatelet efficacy in East Asian patients may have increased ischemic event rates in the clopidogrel monotherapy arm.[47] The fact that MACCE rates were lower in this arm than when compared with ongoing DAPT thus supports use of this regimen in a population without these concerns. Finally, the ratio of unstable angina to NSTEMI was higher than in other studies from the US and elsewhere due to the infrequent use of high-sensitivity troponin tests in China. Also, prasugrel is not available in China; as such, the present results are applicable to P2Y12 inhibitor treatment with clopidogrel or ticagrelor only. Additional randomized clinical trials are warranted to examine whether clopidogrel monotherapy after a mandatory DAPT period in patients with ACS with high-risk bleeding characteristics is safe and effective in a Western population.

Conclusions

In conclusion, in the present large-scale, double-blind, placebo-controlled randomized clinical trial, among PCI-treated patients with ACS who are at high risk for both ischemic and bleeding events and who had completed 9 to 12 months of DAPT and were free from adverse events for at least 6 months, subsequent treatment with clopidogrel alone was superior to continuing DAPT with aspirin and clopidogrel in reducing clinically relevant bleeding and MACCE for an additional 9 months.

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REFERENCES

1. Collet JP, Thiele H, Barbato E, et al; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42(14):1289-1367. doi:10.1093/eurheartj/ehaa575

2. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: executive summary: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2022;145(3):e4-e17. doi:10.1161/CIR.0000000000001039

3. Neumann FJ, Sousa-Uva M, Ahlsson A, et al; ESC Scientific Document Group. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40(2):87-165. doi:10.1093/eurheartj/ehy394

4. Valgimigli M, Bueno H, Byrne RA, et al; ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 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(3):213-260. doi:10.1093/eurheartj/ehx419

5. Angiolillo DJ, Galli M, Collet JP, Kastrati A, O'Donoghue ML. Antiplatelet therapy after percutaneous coronary intervention. *EuroIntervention*. 2022;17(17):e1371-e1396. doi:10.4244/EIJ-D-21-00904

6. Capodanno D, Angiolillo DJ. Timing, selection, modulation, and duration of P2Y12 inhibitors for patients with acute coronary syndromes undergoing PCI. *JACC Cardiovasc Interv*. 2023;16(1):1-18. doi:10.1016/j.jcin.2022.10.023

7. Capodanno D, Baber U, Bhatt DL, et al. P2Y12 inhibitor monotherapy in patients undergoing percutaneous coronary intervention. *Nat Rev Cardiol*. 2022;19(12):829-844. doi:10.1038/s41569-022-00725-6

8. Capodanno D, Bhatt DL, Gibson CM, et al. Bleeding avoidance strategies in percutaneous coronary intervention. *Nat Rev Cardiol*. 2022;19(2):117-132. doi:10.1038/s41569-021-00598-1

9. Gragnano F, Mehran R, Branca M, et al; Single vs Dual Antiplatelet Therapy (Sidney-2) Collaboration. P2Y12 inhibitor monotherapy or dual antiplatelet therapy after complex percutaneous coronary interventions. *J Am Coll Cardiol*. 2023;81(6):537-552. doi:10.1016/j.jacc.2022.11.041

10. Watanabe H, Morimoto T, Natsuaki M, et al; STOPDAPT-2 ACS Investigators. Comparison of clopidogrel monotherapy after 1 to 2 months of dual antiplatelet therapy with 12 months of dual antiplatelet therapy in patients with acute coronary syndrome: the STOPDAPT-2 ACS randomized clinical trial. *JAMA Cardiol*. 2022;7(4):407-417. doi:10.1001/jamacardio.2021.5244

11. Hahn JY, Song YB, Oh JH, et al; SMART-DATE investigators. 6-Month vs 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomized, open-label, noninferiority trial. *Lancet*. 2018;391(10127):1274-1284. doi:10.1016/S0140-6736(18)30493-8

12. Capodanno D, Angiolillo DJ. Long-term P2Y12 inhibitor or aspirin as single antiplatelet therapy in patients with previous percutaneous coronary

intervention. *Circulation*. 2023;147(2):118-121. doi:10.1161/CIRCULATIONAHA.122.063004

13. Li Y, Jing Q, Wang B, et al. Extended antiplatelet therapy with clopidogrel alone vs clopidogrel plus aspirin after completion of 9- to 12-month dual antiplatelet therapy for acute coronary syndrome patients with both high bleeding and ischemic risk—rationale and design of the OPT-BIRISK double-blinded, placebo-controlled randomized trial. *Am Heart J*. 2020;228:1-7. doi:10.1016/j.ahj.2020.07.005

14. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123(23):2736-2747. doi:10.1161/CIRCULATIONAHA.110.009449

15. Garcia-Garcia HM, McFadden EP, Farb A, et al; Academic Research Consortium. Standardized end point definitions for coronary intervention trials: the Academic Research Consortium 2 consensus document. *Eur Heart J*. 2018;39(23):2192-2207. doi:10.1093/eurheartj/ehy223

16. Mauri L, Kereiakes DJ, Yeh RW, et al; DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*. 2014;371(23):2155-2166. doi:10.1056/NEJMoa1409312

17. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med*. 2019;381(21):2032-2042. doi:10.1056/NEJMoa1908419

18. Valgimigli M, Frigoli E, Heg D, et al; MASTER DAPT Investigators. Dual Antiplatelet Therapy after PCI in patients at high bleeding risk. *N Engl J Med*. 2021;385(18):1643-1655. doi:10.1056/NEJMoa2108749

19. Giacoppo D, Matsuda Y, Fovino LN, et al. Short dual antiplatelet therapy followed by P2Y12 inhibitor monotherapy vs. prolonged dual antiplatelet therapy after percutaneous coronary intervention with second-generation drug-eluting stents: a systematic review and meta-analysis of randomized clinical trials. *Eur Heart J*. 2021;42(4):308-319. doi:10.1093/eurheartj/ehaa739

20. Ullah W, Zahid S, Sandhyavenu H, et al. Extended, standard, or de-escalation antiplatelet therapy for patients with coronary artery disease undergoing percutaneous coronary intervention: a trial-sequential, bivariate, influential, and network meta-analysis. *Eur Heart J Cardiovasc Pharmacother*. 2022;8(7):717-727. doi:10.1093/ehjcvp/pvac020

21. Valgimigli M, Gragnano F, Branca M, et al. P2Y12 inhibitor monotherapy or dual antiplatelet therapy after coronary revascularization: individual patient level meta-analysis of randomised controlled trials. *BMJ*. 2021;373(1332):n1332. doi:10.1136/bmj.n1332

22. D'Ascenzo F, Biolè C, Raposeiras-Roubin S, et al. Average daily ischemic versus bleeding risk in patients with ACS undergoing PCI: insights from the BleeMACS and RENAMI registries. *Am Heart J*. 2020;220:108-115. doi:10.1016/j.ahj.2019.10.001

23. Li J, Li Y, Qiu M, et al. Impact of dual antiplatelet therapy duration on 1-year clinical outcomes in diabetic patients with acute coronary syndrome undergoing percutaneous coronary intervention: Insights from the real-world OPT-CAD study. *Catheter Cardiovasc Interv*. 2020;95(suppl 1):579-586. doi:10.1002/ccd.28653

24. Huo Y, Jeong YH, Gong Y, et al. 2018 update of expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. *Sci Bull (Beijing)*. 2019;64(3):166-179. doi:10.1016/j.scib.2018.12.020

25. Ahn JH, Ahn Y, Jeong MH, et al; other KAMIR-NIH Registry Investigators. Ticagrelor vs clopidogrel in acute myocardial infarction patients with multivessel disease; from Korea Acute Myocardial Infarction Registry—National Institute of Health. *J Cardiol*. 2020;75(5):478-484. doi:10.1016/j.jjcc.2019.11.003

26. Xi Z, Qiu Z, Li J, et al. Clopidogrel vs ticagrelor in East Asian patients aged 75 years or older with acute coronary syndrome: observations from the GF-APT registry. *Platelets*. 2022;33(8):1270-1278. doi:10.1080/09537104.2022.2118250

27. Wang HY, Li Y, Xu XM, Li J, Han YL. Impact of baseline bleeding risk on efficacy and safety of ticagrelor vs clopidogrel in chinese patients with acute coronary syndrome undergoing percutaneous coronary intervention. *Chin Med J (Engl)*. 2018;131(17):2017-2024. doi:10.4103/0366-6999.239306

28. Madhavan MV, Stone GW. Adverse events beyond 1 year after percutaneous coronary intervention. *Curr Opin Cardiol*. 2020;35(6):687-696. doi:10.1097/HCO.0000000000000792

29. Bonaca MP, Bhatt DL, Cohen M, et al; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372(19):1791-1800. doi:10.1056/NEJMoa1500857

30. Khan SU, Singh M, Valavoor S, et al. Dual Antiplatelet therapy after percutaneous coronary intervention and drug-eluting stents: a systematic review and network meta-analysis. *Circulation*. 2020;142(15):1425-1436. doi:10.1161/CIRCULATIONAHA.120.046308

31. Yin SH, Xu P, Wang B, et al. Duration of dual antiplatelet therapy after percutaneous coronary intervention with drug-eluting stent: systematic review and network meta-analysis. *BMJ*. 2019;365:l2222. doi:10.1136/bmj.l2222

32. CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel vs aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348(9038):1329-1339. doi:10.1016/S0140-6736(96)09457-3

33. Koo BK, Kang J, Park KW, et al; HOST-EXAM investigators. Aspirin vs clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicenter trial. *Lancet*. 2021;397(10293):2487-2496. doi:10.1016/S0140-6736(21)01063-1

34. Kang J, Park KW, Lee H, et al. Aspirin vs clopidogrel for long-term maintenance monotherapy after percutaneous coronary intervention: the HOST-EXAM extended study. *Circulation*. 2023;147(2):108-117. doi:10.1161/CIRCULATIONAHA.122.062770

35. Johnson TW, Baos S, Collett L, et al. Pharmacodynamic comparison of ticagrelor monotherapy vs ticagrelor and aspirin in patients after percutaneous coronary intervention: the TEMPLATE (Ticagrelor Monotherapy and Platelet Reactivity) randomized controlled trial. *J Am Heart Assoc*. 2020;9(24):e016495. doi:10.1161/JAHA.120.016495

36. Baber U, Zafar MU, Dangas G, et al. Ticagrelor with or without aspirin after PCI: the TWILIGHT platelet substudy. *J Am Coll Cardiol*. 2020;75(6):578-586. doi:10.1016/j.jacc.2019.11.056

37. Han Y, Liao Z, Li Y, et al. Magnetically controlled capsule endoscopy for assessment of antiplatelet therapy-induced gastrointestinal injury. *J Am Coll Cardiol*. 2022;79(2):116-128. doi:10.1016/j.jacc.2021.10.028

38. Tang C, Zhu Y, Yang X, et al. Upper gastrointestinal mucosal injury associated with ticagrelor plus aspirin, ticagrelor alone, or aspirin alone at 1-year after coronary artery bypass grafting. *J Gastroenterol Hepatol*. 2020;35(10):1720-1730. doi:10.1111/jgh.15030

39. Gragnano F, Cao D, Pirondini L, et al; PANTHER Collaboration. P2Y12 inhibitor or aspirin monotherapy for secondary prevention of coronary events. *J Am Coll Cardiol*. 2023;82(2):89-105. doi:10.1016/j.jacc.2023.04.051

40. Choi KH, Park YH, Song YB, et al; SMART-CHOICE Investigators. Long-term effects of P2Y12 inhibitor monotherapy after percutaneous coronary intervention: 3-year follow-up of the SMART-CHOICE randomized clinical trial. *JAMA Cardiol*. 2022;7(11):1100-1108. doi:10.1001/jamacardio.2022.3203

41. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation*. 2006;114(8):774-782. doi:10.1161/CIRCULATIONAHA.106.612812

42. Redfors B, Kirtane AJ, Liu M, et al. Dual antiplatelet therapy discontinuation, platelet reactivity, and adverse outcomes after successful percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2022;15(8):797-806. doi:10.1016/j.jcin.2022.01.300

43. Palmerini T, Bacchi Reggiani L, Della Riva D, et al. Bleeding-Related Deaths in Relation to the Duration of Dual-Antiplatelet Therapy After Coronary Stenting. *J Am Coll Cardiol*. 2017;69(16):2011-2022. doi:10.1016/j.jacc.2017.02.029

44. Costa F, van Klaveren D, James S, et al; PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet*. 2017;389(10073):1025-1034. doi:10.1016/S0140-6736(17)30397-5

45. Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Eur Heart J*. 2019;40(31):2632-2653. doi:10.1093/eurheartj/ehz372

46. Na K, Qiu M, Wei N, et al. Effect of dual antiplatelet therapy prolongation in acute coronary syndrome patients with both high ischemic and bleeding risk: insight from the OPT-CAD study. *Front Cardiovasc Med*. 2023;10:1201091. doi:10.3389/fcvm.2023.1201091

47. Stone GW, Camaj A. Platelet reactivity testing: East meets West. *JACC Cardiovasc Interv*. 2022;15(22):2266-2269. doi:10.1016/j.jcin.2022.09.046