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Risk of Early Adverse Events After Clopidogrel Discontinuation in Patients Undergoing Short-Term Dual Antiplatelet Therapy

An Individual Participant Data Analysis

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ABSTRACT

OBJECTIVES The study sought to evaluate the presence of a clinically relevant rebound phenomenon after dual antiplatelet therapy (DAPT) discontinuation in randomized trials.

BACKGROUND It is currently unknown whether clopidogrel discontinuation after short-term DAPT is associated with an early hazard of ischemic events.

METHODS The authors performed an individual participant data analysis and aggregate meta-analysis. The primary outcome was major adverse cardiac and cerebrovascular events (MACCE), defined as the composite of cardiac death, myocardial infarction (MI), or stroke.

RESULTS The study included 11,473 PCI patients with individual participant data from 6 randomized trials comparing short-term DAPT (3 or 6 months) versus long-term DAPT (12 months or more). During the first 90 days following clopidogrel discontinuation, there was no significant increase in the risk of MACCE between patients randomized to short-term DAPT compared with long-term DAPT (hazard ratio [HR]: 1.18; 95% confidence interval [CI]: 0.71 to 1.98; $p = 0.52$; absolute risk difference 0.10%; 95% CI: −0.16% to 0.36%). The risk of MI or stent thrombosis was similar among patients randomized to short-term DAPT versus long-term DAPT (HR: 0.93; 95% CI: 0.46 to 1.90; $p = 0.85$). In the aggregate data meta-analysis of 11 trials including 38,919 patients, a higher risk of early MACCE was observed after long-term (≥12 months) DAPT duration (HR: 2.28; 95% CI: 1.69 to 3.09; $p < 0.001$) but not short-term (<12 months) DAPT duration (HR: 1.08; 95% CI: 0.67 to 1.74; p for interaction = 0.036).

CONCLUSIONS Among patients undergoing PCI with predominantly new-generation DES, discontinuation of clopidogrel after 3 or 6 months DAPT duration was not associated with an early increase in adverse clinical events. An early increase in MACCE was observed after long-term (≥12 months) DAPT exposure. (J Am Coll Cardiol Intv 2017;10:1621–30)

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

HR = hazard ratio

IPD = individual participant data

MACCE = major adverse cardiovascular and cerebrovascular event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

ST = stent thrombosis

Dual antiplatelet therapy (DAPT), with aspirin and a $P2Y_{12}$ receptor inhibitor, is an evidence-based, guideline-recommended standard of care among patients undergoing percutaneous coronary intervention (PCI) (1–4). Randomized trials demonstrated that DAPT is effective at preventing atherothrombosis in the treated coronary segments as well as in the surrounding coronary vasculature (3,5,6). However, it remains unclear if a clustering of adverse events ensues in the aftermath of $P2Y_{12}$ inhibitor withdrawal. This alleged phenomenon, termed the *rebound effect*, has been initially investigated in the past decade and recently 2 trials provided additional evidence that a gathering of ischemic events may occur shortly after DAPT discontinuation. In the DAPT trial, which compared 30-month DAPT with 12-month DAPT among patients undergoing PCI, a higher risk of ischemic events occurred 3 months following $P2Y_{12}$ inhibitor discontinuation (7). Patients randomized to discontinue DAPT at 12 months incurred a higher risk of myocardial infarction (MI) and stent thrombosis (ST) between 12 and 15 months compared with those randomized to 30-month DAPT (7). A similar cluster of ischemic coronary events was noted 3 months following $P2Y_{12}$ inhibitor discontinuation after 30-month therapy. More recently, the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) trial, compared DAPT with aspirin and ticagrelor versus aspirin alone for the long-term secondary prevention in patients with prior MI, and found that the benefit of DAPT was more pronounced among patients who continued or recommenced DAPT after a brief (i.e., ≤30 days) interruption of $P2Y_{12}$ inhibitor (8). These findings suggest that discontinuing $P2Y_{12}$ inhibitor after 1 year or more exposure to DAPT might trigger newer atherothrombotic manifestations, which might have remained otherwise clinically silent.

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As of yet, it remains undetermined whether a consistent clustering of ischemic events also occurs after discontinuation of a shorter (i.e., <12 months) DAPT regimen.

We sought to investigate the early time course of adverse events following clopidogrel discontinuation after 3- or 6-month DAPT versus uninterrupted treatment duration by pooling data from 6 randomized trials that compared short-term DAPT versus long-term DAPT after drug-eluting stent (DES) implantation among patients with predominantly stable coronary artery disease or low-risk acute coronary syndrome. Moreover, we performed a systematic review of randomized trials to evaluate whether duration of DAPT before $P2Y_{12}$ inhibitor discontinuation affects the risk of adverse ischemic events following discontinuation.

METHODS

STUDY DESIGN AND PATIENT POPULATION OF THE POOLED ANALYSIS. Patient-level data from 6 randomized clinical trials comparing short (3 or 6 months) versus long duration of DAPT (≥1 year) were

has served on the data monitoring committee of the Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and Population Health Research Institute; has received honoraria from American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (Secretary/Treasurer), and WebMD (CME steering committees); has served as the Deputy Editor of *Clinical Cardiology*; has served as the Chair of the NCDR-ACTION Registry Steering Committee and VA CART Research and Publications Committee; has received research funding from Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi, and The Medicines Company; has received royalties from Elsevier (Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); has served as the site co-investigator for Biotronik, Boston Scientific, and St. Jude Medical; has served as a trustee of the American College of Cardiology; and has performed unfunded research for FlowCo, PLx Pharma, and Takeda. Dr. Palmerini has received a speaker fee from Abbott Vascular; and a research grant from Eli Lilly. Dr. Windecker has received institutional research grants from Abbott Vascular, Biotronik, Boston Scientific, Medtronic, Edwards Lifesciences, and St. Jude Medical. Dr. Valgimigli has served on the advisory board for AstraZeneca and St. Jude Vascular; has received lecture fees from AstraZeneca, Terumo Medical, Alvimedica, St. Jude Medical, Abbott Vascular, The Medicines Company, and Correvio; has received travel support from The Medicines Company; and has received institutional grant support from AstraZeneca. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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pooled in an anonymized electronic dataset, as previously described (9). Included were the RESET (Real Safety and Efficacy of 3-Month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation) (10), EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) (11), PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) (12), OPTIMIZE (Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice) (13), SECURITY (Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy) (14), and ITALIC (Is There a Life for DES After Discontinuation of Clopidogrel) trials (Online Tables 1 and 2) (15). Patients who were randomized to bare-metal stents in the PRODIGY trial were excluded (12). The study was conducted according to the PRISMA-IPD (Preferred Reporting Items for Systematic Review and Meta-analyses-Individual participant data) Statement (16).

DEFINITIONS AND MAIN OUTCOMES MEASURES. The principal outcome of this study was major adverse cardiovascular and cerebrovascular events (MACCE), defined as the composite of cardiac death, MI, or stroke. Additional outcomes included the composite of MI or definite or probable ST, all-cause death, cardiac death, stroke, MI, ST, and any bleeding (minor or major). For consistency purposes, outcomes were assessed through 90 days after DAPT discontinuation in the short-term arms of included studies and contrasted to those observed in patients who continued treatment (7,8,17). The endpoint definitions as applied in each trial were used for all analyses. ST was consistently defined according to the Academic Research Consortium criteria throughout all 6 studies (18). In 4 trials bleeding was defined according to the Thrombolysis In Myocardial Infarction criteria (10–12,15), in 1 trial the Bleeding Academic Research Consortium criteria were used (14), whereas the REPLACE (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events) study criteria were applied in the remainder study (13).

SYSTEMATIC REVIEW OF RANDOMIZED TRIALS. The objective of the systematic review was to evaluate the early (i.e., within 90 days) risk of MACCE after DAPT discontinuation by including randomized trials for which individual participant-level data were not available. Moreover, we aimed at evaluating whether the risk of MACCE was affected by the time of DAPT discontinuation and therefore included randomized trials directly comparing different long-term (≥12 months) DAPT duration regimens. Randomized trials allowing recruitment of non-PCI patients were included as long as PCI was performed at least in 80% of participants.

Randomized controlled trials were identified by 2 investigators (R.P., M.V.) through a comprehensive, systematic search in PubMed, EMBASE, and 3 websites (www.tctmd.com, www.escardio.org, www.acc.org). The search was last updated on December 9, 2016. The detailed search algorithm is provided in the Online Appendix.

RISK OF BIAS ASSESSMENT. Two investigators (R.P., M.V.) independently assessed the risk of bias by using the Cochrane Collaboration's tool on the following items: sequence generation, allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), completeness of outcome data (attrition bias), and selective outcome reporting (reporting bias).

STATISTICAL ANALYSIS. The intention-to-treat population was used for the main analyses, including all patients according to randomized treatment arm regardless of actual treatment. Categorical variables are reported as count and percentages and compared with Cochran-Mantel-Haenszel test using trial identifier as stratification variable. Continuous variables are reported as mean ± SD and compared with 2-way analysis of variance using trial identifier as stratification variable. Cox regression analyses stratified by trial, using trial identifiers as random effects, were used to evaluate the clinical outcomes between the short- and long-term DAPT groups. Clinical events are reported as counts, with rates computed according to the Kaplan-Meier method. Risk estimates are expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). In each trial contributing to the individual participant data (IPD) analysis, time to event was expressed in days with time 0 corresponding to the time of DAPT discontinuation in the short-term DAPT arm according to the randomization scheme (i.e., 3 months for the RESET and OPTIMIZE trials and 6 months for all other trials). Sequential landmark analyses were undertaken at 4 landmark points (−90, 0, 90, and 180 days), with HRs calculated separately for the following 3 periods: from −90 to −1 days (corresponding to the time when both short- and long-term DAPT arms were on DAPT), from 0 to 90 days (corresponding to the period when the 2 randomized DAPT began to differ), and from 91 to 180 days (corresponding to the additional 3 months after the period of observation of possible

rebound effect). For each type of event, patients were censored at the time of the first event: a patient who experienced an event contributing to the primary composite outcome during the first 90 days, for example, was censored at the time of the event and excluded from the analysis after the landmark point (from 91 to 180 days). A p value for trend for interaction between treatment effect (short-term DAPT vs. long-term DAPT) and time window (−90 to −1 days vs. 0 to 90 days vs. 91 to 180 days) was calculated. The hazard function throughout the follow-up was plotted by using an Epanechnikov kernel function using the estimated hazard contributions. From 0 to 90 days, the risk of the primary efficacy outcome between short- and long-term DAPT was evaluated in the following subgroups of interest: sex, age, clinical presentation, diabetes, previous MI, type of DES, and timing of withdrawal (3 or 6 months). As sensitivity analysis, we excluded patients that prematurely discontinued DAPT (defined by DAPT interruption occurring at least 1 month before the period scheduled by randomization, unless caused by an adverse event, such as bleeding). A per-protocol analysis was additionally conducted to compare short-term DAPT versus long-term DAPT in patients who effectively discontinued or continued DAPT if randomized to short or prolonged DAPT, respectively.

For the systematic review, we performed a random effects meta-analysis by combining the risk of HR for MACCE across trials. The risk of MACCE from 0 to 90 days after DAPT discontinuation was retrieved from published data for the DAPT and PEGASUS-TIMI 54 trials (7,8). When unavailable (ISAR-SAFE [Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting], ARCTIC-I [Assessment by a double Randomisation of a Conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and, of Treatment Interruption versus Continuation 1 year after stenting-Interruption], DES-LATE [Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Event] trials) (19–21), estimates were derived from reconstructed time-to-event data of individual trials using Cox regression analysis. Kaplan-Meier curves were digitized by using Engauge Digitizer 9.5 (Mark Mitchell, Torrance, California) and then time-to-event data were reconstructed by using the algorithm specified by Guyot et al. (22). We visually assessed the concordance between original and reconstructed time-to-event curves in terms of shape and cumulative incidence curve. We used meta-regression for calculating the interaction in the risk of MACCE between trials of short-term (<12 months) versus long-term (≥12 months) DAPT exposure. Heterogeneity between trials was determined by using the I^2 statistic, with estimates near 25% indicating a small, near 50% a moderate, and near 75% a large extent of heterogeneity. All p values are 2 sided and statistical significance was assumed for $p < 0.05$. All analyses were carried out with Stata Statistical Software, release 13 (StataCorp, College Station, Texas).

RESULTS

Of 11,473 patients undergoing PCI across 6 trials, 5,730 (49.9%) were randomized to short-term DAPT (i.e., 3- or 6-month therapy duration) and 5,743 (50.1%) were randomized to long-term DAPT (i.e., 12 months or more). The main characteristics of the pooled studies are described in the Online Appendix (Online Tables 1 to 3). A 3-month versus 12-month DAPT regimen was investigated in the RESET and OPTIMIZE trials (10,13), whereas the EXCELLENT, PRODIGY, SECURITY, and ITALIC trials mandated 6-month versus 12- or 24-month DAPT durations (11,14,15,23).

DAPT consisted of aspirin and clopidogrel in all cases. Baseline characteristics were well balanced between patients randomized to short- or long-term DAPT (Online Table 4). Overall, patients' mean age was 63.1 ± 10.6 years, 69.9% of patients were men, and 32.3% of patients were diabetic. Among 11,473 randomized patients, 4,758 (41.5%) presented with acute coronary syndrome and 6,714 (58.5%) had stable coronary artery disease. The majority of acute coronary syndromes (67.0%) were classified as unstable angina. In 1 patient the clinical presentation was not defined. New-generation DES was implanted in 88.5% of the pooled population.

IPD ANALYSIS. Clinical outcomes from 0 to 90 days after DAPT discontinuation. MACCE occurred in 0.59% of the patients randomized to short-term DAPT compared with 0.49% of the patients randomized to long-term DAPT during the first 90 days after DAPT discontinuation (HR: 1.18; 95% CI: 0.71 to 1.98; p = 0.52; absolute risk difference 0.10%; 95% CI: −0.16% to 0.36%) (**Table 1**). The composite of MI or ST occurred in 0.27% of patients randomized to short-term DAPT compared with 0.29% of patients randomized to long-term DAPT (HR: 0.93; 95% CI: 0.46 to 1.90; p = 0.85). Definite or probable ST occurred in 6 (0.11%) patients randomized to short-term DAPT and in 3 (0.05%) patients randomized to long-term DAPT (HR: 1.98; 95% CI: 0.50 to 7.92;

p = 0.33). There were no between-group differences for any of the other endpoints.

Clinical outcomes throughout the follow-up. The results of landmark analyses throughout the 3 periods of observation (−90 to −1 days, 0 to 90 days, and 91 to 180 days) are summarized in Figures 1 and 2. There was no significant interaction between randomized DAPT durations and the 3 time intervals for MACCE (p for trend for interaction = 0.41), MI or ST (p for trend for interaction =0.62), death or MI (p for trend for interaction = 0.62), and MI (p for trend for interaction = 0.99). In contrast, there was a significant interaction for any bleeding (p for trend for interaction = 0.022) due to a reduction of bleeding risk over time among patients randomized to short-term DAPT ($HR_{-90\ to\ -1days}$: 1.12; 95% CI: 0.69 to 1.82; $HR_{0\ to\ 90\ days}$: 0.62; 95% CI: 0.28 to 1.36; and $HR_{91\ to\ 180\ days}$: 0.33; 95% CI: 0.12 to 0.91). Online Figure 1 shows the instantaneous risk of MACCE.

SUBGROUP AND SENSITIVITY ANALYSES. During 0 to 90 days after clopidogrel discontinuation, there was no significant interaction in the risk of MACCE among pre-specified subgroups (Figure 3). There was no significant treatment heterogeneity for MACCE (p = 0.54) between the patients who discontinued DAPT at 3 months versus 6 months. Similarly, there was no interaction (p = 0.97) between patients with stable coronary artery disease and those with predominantly low-risk acute coronary syndrome (Figure 3).

Data on premature DAPT discontinuation were available in 4 trials (n = 8,180). After excluding 279 patients (3.41%) who prematurely discontinued DAPT, results remained consistent with the main analyses (Online Table 5).

A total of 6,424 patients were receiving the randomly allocated therapy from 0 to 90 days (6,424 of 7,375, or 87.11%). Results of per-protocol analysis were consistent with the intention-to-treat analysis (Online Table 6).

AGGREGATE DATA META-ANALYSIS. A total of 11 trials with 38,919 patients were included in the systematic review (Online Figure 2). Seven studies, including the 6 trials that were pooled at IPD level and the ISAR-SAFE trial (N = 15,473) (19), compared a DAPT duration of shorter than 1 year versus at least 1 year, whereas 4 trials (N = 23,446) compared a DAPT duration of longer than 1 year versus 1 year (7,8,20,21).

As reported in Figure 4, the MACCE risk within 90 days after DAPT discontinuation versus continuation was not increased (HR: 1.08; 95% CI: 0.67 to 1.74; p = 0.74; I^2 = 0%) in trials mandating <12-month DAPT duration in the short-term arm. Conversely, in trials that randomized DAPT at or after 12 months, the risk of MACCE through 90 days after DAPT discontinuation was 2-fold higher (HR: 2.28; 95% CI: 1.69 to 3.09; p < 0.001; I^2=0%), with positive interaction testing (p = 0.036).

TABLE 1 Individual Participant Data Analysis: Clinical Events From 0 to 90 Days After DAPT Discontinuation in Patients Randomized to Short-Term DAPT

Endpoint	Short DAPT (≤6 months) (n = 5,730)	Long DAPT (12 months) (n = 5,743)	HR (95% CI)	p Value
MACCE	32 (0.59)	27 (0.49)	1.18 (0.71–1.98)	0.52
MI or ST	15 (0.27)	16 (0.29)	0.93 (0.46–1.90)	0.85
Death	20 (0.36)	23 (0.42)	0.86 (0.47–1.57)	0.62
Cardiac death	15 (0.27)	13 (0.24)	1.14 (0.54–2.40)	0.73
Noncardiac death	5 (0.09)	10 (0.18)	0.49 (0.17–1.45)	0.20
MI	14 (0.26)	15 (0.27)	0.93 (0.45–1.93)	0.85
Definite ST	5 (0.09)	2 (0.04)	2.48 (0.48–12.74)	0.28
Definite or probable ST	6 (0.11)	3 (0.05)	1.98 (0.50–7.92)	0.33
Stroke	7 (0.13)	6 (0.11)	1.18 (0.39–3.55)	0.77
Death, MI, or stroke	33 (0.60)	32 (0.58)	1.03 (0.63–1.67)	0.91
Death or MI	27 (0.49)	30 (0.55)	0.89 (0.53–1.50)	0.67
Cardiac death or MI	26 (0.48)	23 (0.42)	1.12 (0.64–1.97)	0.68
Cardiac death, MI, or definite/probable ST	27 (0.49)	23 (0.42)	1.17 (0.67–2.04)	0.59
Any bleeding	10 (0.18)	16 (0.29)	0.62 (0.28–1.36)	0.23
Major bleeding	5 (0.09)	11 (0.20)	0.45 (0.16–1.31)	0.14
Minor bleeding	7 (0.13)	6 (0.11)	1.15 (0.39–3.40)	0.81

Values are first event (% from Kaplan-Meier estimate) unless otherwise indicated. Major adverse cardiovascular and cerebrovascular event(s) (MACCE) included the composite of cardiac death, myocardial infarction (MI), or stroke.

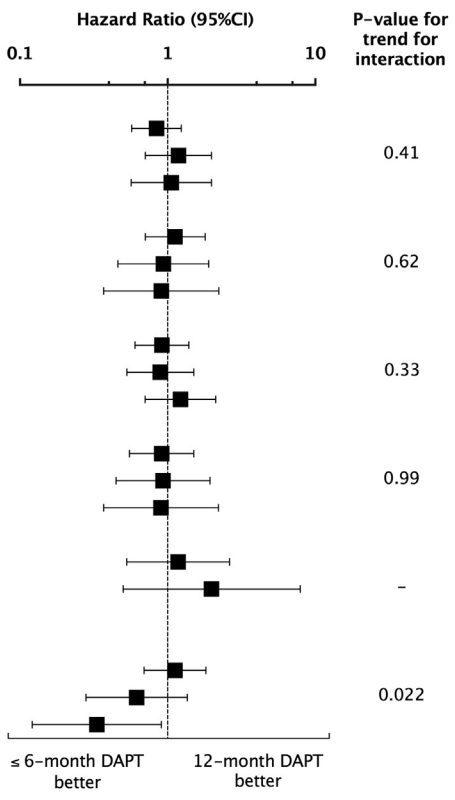
CI = confidence interval; DAPT = dual antiplatelet therapy; HR = hazard ratio; ST = stent thrombosis.

RISK OF BIAS. All trials were judged at low risk of bias for all items with the exception of performance bias, which was high risk for 8 trials because of open-label design (10-14,20,21) (Online Table 7).

DISCUSSION

In this study, we performed an IPD analysis of 6 trials comparing a shortened versus a more prolonged (i.e., ≥12 months) DAPT duration among >11,000 patients undergoing PCI with predominantly new-generation DES. We found no evidence for an increased risk of early adverse events following DAPT discontinuation at 3 or 6 months after PCI. In the systematic review, including 11 trials in nearly 35,000 patients, there was a significant interaction between DAPT duration before discontinuation and outcomes after therapy withdrawal, with a higher risk of MACCE in the first 90 days after DAPT cessation in trials where DAPT was stopped at or after 1 year but not in those mandating shorter treatment duration.

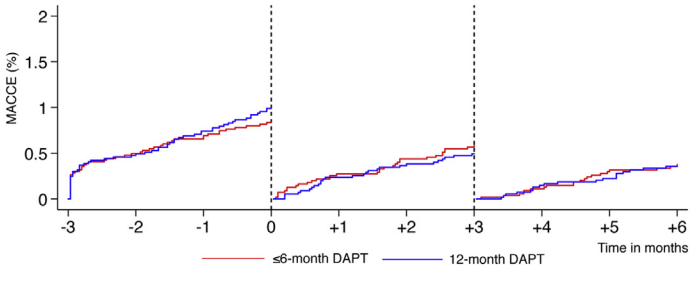
FIGURE 1 Clinical Outcomes Throughout Follow-Up in the Individual Participant Data Analysis



Adverse events are shown before (−90 to −1 days), during (0 to 90 days), and after (91 to 180 days) the period of dual antiplatelet therapy (DAPT) discontinuation in patients randomized to short-term DAPT. CI = confidence interval; MACCE = major adverse cardiovascular and cerebrovascular event(s); MI = myocardial infarction; ST = stent thrombosis.

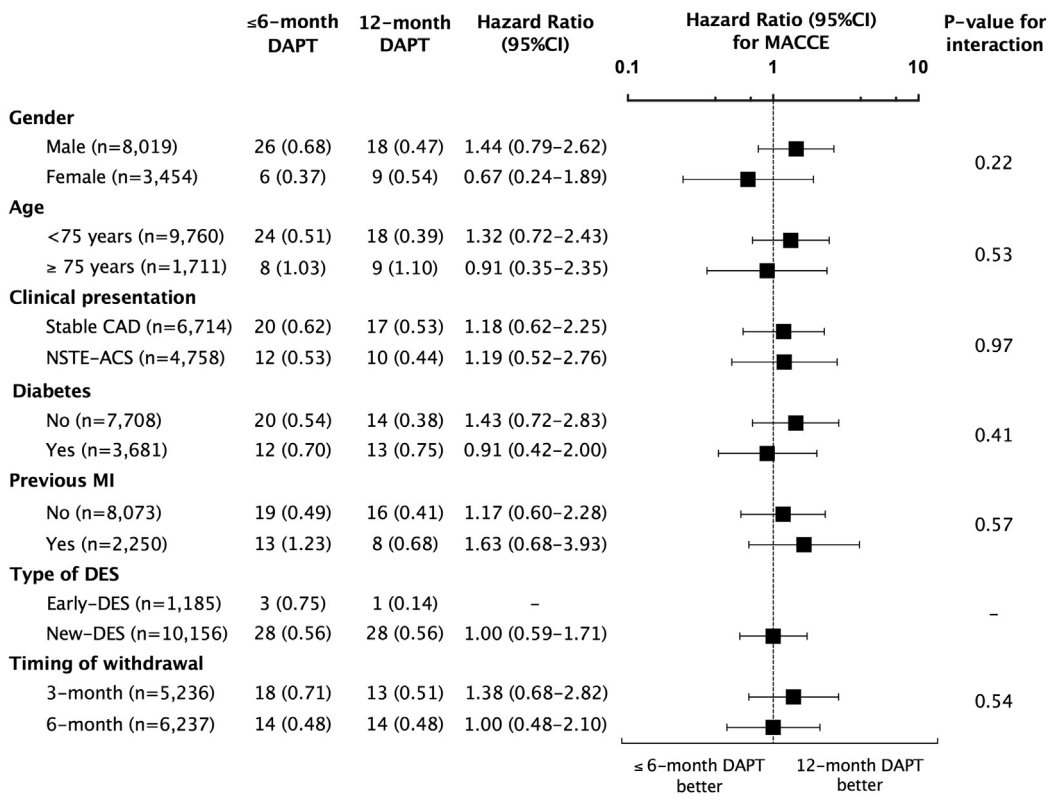
The pathobiological hypothesis of a rebound in platelet reactivity is that chronic inhibition of $P2Y_{12}$ receptor may result in a biological adaptation of pathways involved in the signal transduction on platelets and megakaryocytes, conferring enhanced sensitivity to physiological levels of adenosine diphosphate and other stimuli upon DAPT withdrawal (24,25). The presence of a clinically relevant rebound effect after discontinuation of DAPT was first suggested by Ho et al. (17), who reported a clustering of death or MI events among patients with acute coronary syndrome in the initial 90-day period after clopidogrel withdrawal in an observational study. More recently, the DAPT trial also observed an apparent rebound phenomenon consisting of a clustering of ischemic events both in the 12-month as well the 30-month DAPT arms in the first 3 months following DAPT cessation (7). Similarly, the PEGASUS-TIMI 54 trial indirectly supported the existence of a rebound effect after DAPT discontinuation because patients in the placebo arm who had discontinued the $P2Y_{12}$ inhibitor within the past 30 days had a higher risk of cardiovascular death, MI, or stroke when compared with those who had discontinued 30 days to 1 year before and those who stopped more than

FIGURE 2 Kaplan-Meier Time-to-Event Curves for MACCE in the Individual Participant Data Analysis



Landmark analyses at -90, 0, and 91 days for MACCE in patients randomized to short-term DAPT versus long-term DAPT. Abbreviations as in Figure 1.

FIGURE 3 Subgroup Analysis for MACCE



Subgroup analysis for MACCE during the first 90 days after DAPT discontinuation among patients included in the individual participant data analysis. CAD = coronary artery disease; DES = drug-eluting stent(s); NSTE-ACS = non-ST-segment elevation acute coronary syndrome; other abbreviations as in Figure 1.

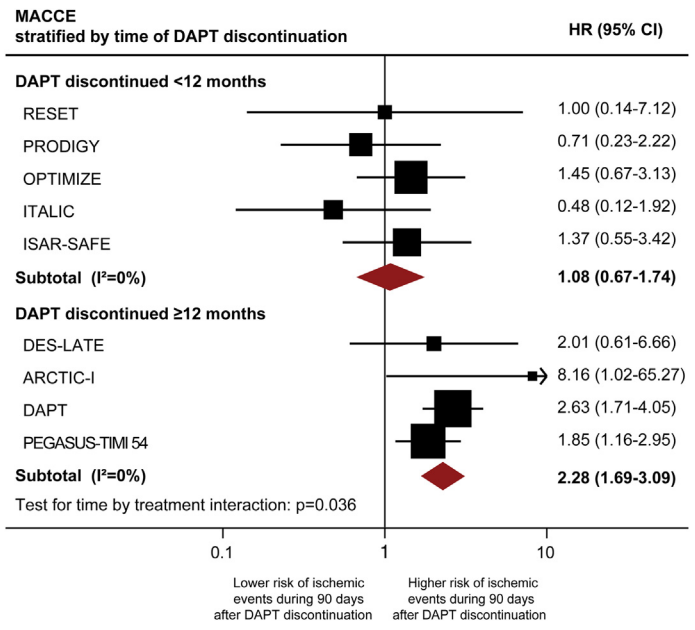
1 year before randomization (p for trend = 0.0097). Examining the cumulative event curves over time, this relative excess was particularly pronounced early, within the first 90 days from randomization, with event rates in terms of cardiovascular death, MI, or stroke of 1.46%, 0.55%, and 0.60%, respectively, in the 3 groups (8).

When taken separately, multiple single- and medium-sized randomized trials testing ≤6-month DAPT duration as compared with ≥12-month DAPT duration failed to observe the existence of a clear rebound of ischemic events shortly after DAPT cessation. To rule out the possibility that this null finding reflects a type II error, we pooled 6 trials and included in the present analysis a similar number of patients as those included in the DAPT trial. Our results are consistent with the PARIS (patterns of non-adherence to anti-platelet regimens in stented patients) registry, which analyzed the impact of different modalities of DAPT cessation among 5,018 PCI patients and found that physician-guided DAPT discontinuation did not result in an excess of ischemic events after 3- or 6-month therapy (26).

According to our systematic review, the duration of DAPT before therapy cessation may explain the seemingly diverging observations on the rebound effect. When analyzing the risk of MACCE accumulating from DAPT discontinuation to 90 days, we found evidence for a significant interaction between trials that stopped DAPT after long-term exposure compared with trials discontinuing DAPT after short-term exposure.

Several mechanistic studies evaluated the platelet reactivity status after $P2Y_{12}$ inhibition cessation and results were different according to the duration of clopidogrel exposure. Among 32 patients with stable coronary artery disease, Mylotte et al. (27) showed an increase in platelet reactivity 1 month after discontinuation of long-term DAPT (>1 year) and a significant reduction in platelet aggregation to

FIGURE 4 Random Effects Meta-Analysis of HRs of MACCE During the First 90 Days After DAPT Discontinuation Stratified by Type of Trial



(Top) Trials with DAPT discontinuation before 12 months; **(bottom)** trials with DAPT discontinuation at 12 months or more. MACCE were the composite of cardiac death, MI, or stroke in the RESET (REal Safety and Efficacy of a 3-month dual antiplatelet Therapy following E-ZES implantation), PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study), OPTIMIZE (Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice), ITALIC (Is There A LIfe for DES After Discontinuation of Clopidogrel), DES-LATE (Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Event), and PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54) trials; the composite of death, MI, ST, or stroke in the ISAR-SAFE (Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting) trial; the composite of death, MI, stroke, ST, or urgent revascularization in the ARCTIC-I (Assessment by a double Randomisation of a Conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and, of Treatment Interruption versus Continuation 1 year after stenting-Interruption) trial; and the composite of death, MI, or stroke in the DAPT trial. For trials without availability of individual participant-level data, hazard ratios (HRs) were derived from the original publications for the DAPT and PEGASUS-TIMI 54 trials and from digitized Kaplan-Meier curves for ISAR-SAFE, DES-LATE, and ARCTIC-I trials. For the PEGASUS-TIMI 54 trial, HR refers to patients withdrawn from $P2Y_{12}$ inhibition ≤30 days from randomization by treatment (placebo vs. ticagrelor doses pooled). HR were not calculated for the EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) and SECURITY (Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy) trials due to arms with 0 event. Abbreviations as in Figure 1.

adenosine diphosphate and epinephrine from 1 to 3 months after clopidogrel discontinuation. Likewise, 4 other studies found a transient increase in platelet reactivity at 4 to 6 weeks after clopidogrel discontinuation among patients who received DAPT for more than 1 year (28-31). On the other hand, Ford et al. (32) showed no evidence of rebound effect after discontinuation of short-term DAPT (1 month) in a randomized study including 171 patients with stable coronary artery disease or peripheral artery disease. Similarly, in a small randomized study, no rebound of platelet reactivity was observed after short-term DAPT with multiple assays and agonists against a baseline evaluation (33). Overall, pharmacodynamic studies seem to confirm the existence of a platelet hyper-reactivity status after $P2Y_{12}$ inhibition cessation in patients discontinuing treatment after 1 year or more of therapy, but not in those discontinuing clopidogrel therapy at an earlier time point.

By adding complementary clinical data to available evidence, the present study provides a nuanced interpretation of the rebound effect. At variance with the DAPT and PEGASUS-TIMI 54 trials as well as the observational study by Ho et al. (7,8,17), patients randomized to short-term DAPT in pooled trials received clopidogrel for either 3 or 6 months. Thus, in keeping with pharmacodynamic data, clinical findings seem to corroborate the paradigm that long rather than short term exposure to $P2Y_{12}$ inhibitors may be associated with a rebound effect on DAPT withdrawal.

However, it is important to acknowledge that this may also simply reflect differences in the level of risk of the patients included across different trials. Stable coronary artery disease represented the indication to PCI in approximately 60% of patients included in the IPD meta-analysis. Conversely, the PEGASUS-TIMI 54 trial (8) and Ho et al. (17) included exclusively patients with prior MI or acute coronary syndrome, respectively, which typically feature a higher risk profile and increased risk of recurrent ischemic events. Furthermore, even though the DAPT trial included patients with stable coronary artery disease, the exclusion of those experiencing treatment failure before randomization (i.e., any ischemic event while on DAPT) might have selected a cohort at high likelihood of ischemic events soon after DAPT cessation. Nevertheless, the MACCE rate in the experimental arm during the first 90 days after DAPT withdrawal amounted to 0.6% and 0.8% in the DAPT and PEGASUS-TIMI 54 trial, respectively, which is similar to 0.5% observed in IPD meta-analysis.

New-generation DES were implanted in nearly 90% of patients analyzed in the IPD meta-analysis. Because vessel healing is more complete and occurs at an earlier time point with new-generation compared with early-generation DES, the

predominant use of newer devices may have favorably attenuated the impact of DAPT discontinuation on stent-related outcomes.

STUDY LIMITATIONS. First, the study has limitations inherent in patient-level, pooled analyses reflecting the shortcomings of the original studies. Second, the majority of patients presented with stable coronary artery disease at the time of the index PCI and acute MI was reported in <15% of patients. Therefore, the results of our study are not generalizable to patients with acute coronary syndrome, particularly to those with high-risk features, even though no significant heterogeneity was observed at subgroup analysis between acute coronary syndrome and stable patients (**Figure 3**). Along this line, it is noteworthy that we already described a higher risk of MI or ST with 3-month instead of 12-month DAPT among patients with acute coronary syndrome (9). Arguably, these findings suggest that DAPT during the first year after acute coronary syndrome is protective against newer ischemic events through mechanisms unrelated to the rebound phenomenon. Third, all randomized trials included in the IPD meta-analysis were open label and this obviously represents an additional limitation, potentially introducing bias. Fourth, the endpoint definitions as well as the inclusion and exclusion criteria differed across trials and this might have introduced heterogeneity. Nonetheless, to reduce this heterogeneity, we included trial as random effect in our analyses. Finally, all 6 randomized trials were not designed to evaluate the presence of a rebound effect after DAPT discontinuation and therefore the results of this study should be carefully interpreted in view of its post hoc nature.

CONCLUSIONS

In this IPD analysis of 6 randomized trials, including 11,473 patients predominantly undergoing treatment with new-generation DES for stable coronary artery disease, there was no evidence for a clinically relevant rebound effect following DAPT discontinuation at 3 or 6 months. Our systematic review and aggregate data meta-analysis corroborated such findings and generated the hypothesis of the existence of a heightened risk of MACCE after cessation of long-term (i.e., ≥12 months) DAPT but not short-term DAPT. This latter finding remains however speculative and requires further investigation.

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PERSPECTIVES

WHAT IS KNOWN? DAPT is mandatory for patients undergoing PCI, although its optimal duration is still debated.

WHAT IS NEW? There is no increased risk of MACCE during the first 90 days after DAPT discontinuation in trials that administered aspirin and clopidogrel for 3 or 6 months.

WHAT IS NEXT? It is important to determine whether the cumulative exposure to DAPT is a risk factor for a clinically relevant rebound phenomenon as well as to evaluate patient or lesion subsets at higher risk of adverse events upon thienopyridine withdrawal.

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KEY WORDS clopidogrel, dual antiplatelet therapy, percutaneous coronary intervention

APPENDIX For an expanded methods section as well as supplemental tables and figures, please see the online version of this article.