Journal of the American Heart Association

ORIGINAL RESEARCH

$P2Y_{12}$ Inhibitor-Based Single Antiplatelet Therapy Versus Conventional Dual Antiplatelet Therapy After Newer-Generation Drug-Eluting Stent Implantation in Chronic and Acute Coronary Syndromes: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

Juan F. Iglesias, MD; Benjamin Assouline, MD; Quentin Chatelain, MD; Yazan Musayeb, MD; Sophie Degrauwe, MD*; Marco Roffi, MD*

BACKGROUND: $P2Y_{12}$ inhibitor-based single antiplatelet therapy (SAPT) after drug-eluting stent implantation reduces major bleeding without increasing the risk of major adverse cardiovascular and cerebral events compared with 12-month dual antiplatelet therapy (DAPT). The differential effects of $P2Y_{12}$ inhibitor monotherapy compared with conventional DAPT in patients with chronic coronary syndromes versus acute coronary syndromes (ACS) remain uncertain.

METHODS AND RESULTS: PubMed, Embase, and Cochrane Central Register of Controlled Trials were searched for randomized controlled trials comparing oral $P2Y_{12}$ inhibitor-based SAPT after ≤3 months DAPT versus 12-month DAPT after newer-generation drug-eluting stent implantation. Patients were categorized based on baseline presentation (chronic coronary syndromes versus ACS). The co-primary end points were major bleeding and major adverse cardiovascular and cerebral events, a composite of all-cause death, myocardial infarction, or ischemic stroke.

A total of 43 945 (ACS, 28 360, 65%) patients from 7 randomized controlled trials were included. At a median follow-up of 12 months, $P2Y_{12}$ inhibitor-based SAPT was associated with a lower risk of major bleeding (risk ratio [RR], 0.63 [95% CI, 0.48–0.82]; $P<0.001$) compared with 12-month DAPT. The risk of major bleeding was significantly lower among patients with ACS (RR, 0.55 [95% CI, 0.40–0.75]; $P<0.001$). Compared with standard DAPT, $P2Y_{12}$ inhibitor-based SAPT was associated with a similar risk of major adverse cardiovascular and cerebral events (RR, 0.98 [95%CI, 0.87–1.11]; $P=0.74$) among patients with chronic coronary syndromes and ACS. There was no significant interaction between treatment effect and baseline presentation.

CONCLUSIONS: Compared with 12-month DAPT, $P2Y_{12}$ inhibitor-based SAPT after newer-generation drug-eluting stent implantation is associated with a lower risk of major bleeding without increasing the risk of major adverse cardiovascular and cerebral events, a difference primarily driven by patients with ACS.

REGISTRATION: URL: https://www.crd.york.ac.uk/prospero/; Unique identifier: CRD42023239341.

Correspondence to: Juan F. Iglesias, MD, Department of Cardiology, Geneva University Hospitals, Rue Gabrielle-Perret-Gentil 4, Geneva 1205, Switzerland. Email: juanfernando.iglesias@hug.ch

*S. Degrauwe and M. Roffi contributed equally.

This article was sent to Saket Girotra, MD, SM, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.036642

For Sources of Funding and Disclosures, see page 10.

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

Key Words: acute coronary syndrome ■ drug-eluting stent ■ P2Y$_{12}$ receptor inhibitor ■ percutaneous coronary intervention

CLINICAL PERSPECTIVE

What Is New?

- P2Y$_{12}$ inhibitor-based single antiplatelet therapy following ≤3 months dual antiplatelet therapy after percutaneous coronary intervention with newer-generation drug-eluting stents is associated with a lower risk of major bleeding while preserving ischemic protection compared with conventional 12 months of dual antiplatelet therapy.
- The clinical benefits of P2Y$_{12}$ inhibitor-based single antiplatelet therapy in reducing the risk of major bleeding after newer-generation drug-eluting stent implantation compared with conventional 12-month dual antiplatelet therapy is primarily driven by patients with acute coronary syndrome.

What Are the Clinical Implications?

- Transition to P2Y$_{12}$ inhibitor-based single antiplatelet therapy after a short dual antiplatelet therapy regimen following newer-generation drug-eluting stent implantation represents a safe and effective antiplatelet treatment strategy for patients with acute coronary syndrome and potentially for those with chronic coronary syndrome who are at low risk for ischemic events.

Nonstandard Abbreviations and Acronyms

BARC	bleeding academic research consortium
CCS	chronic coronary syndrome
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
MACCE	major adverse cardiovascular and cerebral events
NACE	net adverse clinical events
SAPT	single antiplatelet therapy

Dual antiplatelet therapy (DAPT) with aspirin and P2Y$_{12}$ receptor inhibitors represents the cornerstone of antithrombotic pharmacotherapy for patients undergoing percutaneous coronary intervention (PCI) with drug-eluting stents (DES) to prevent stent-related thrombotic complications.[1,2] After DES implantation, current guidelines recommend DAPT for 6 and 12 months in patients presenting with chronic (CCS) and acute (ACS) coronary syndromes, respectively.[1,2] However, DAPT is associated with an increased risk of major bleeding[3] that, in turn, has been shown to increase all-cause mortality after PCI.[4]

Modern iterations of DES designs with reduced thrombogenicity have prompted the introduction of novel antiplatelet strategies aimed at mitigating the risk of major bleeding while maintaining antithrombotic efficacy.[5] Initially, the common approach to reduce DAPT intensity was to shorten duration of DAPT by discontinuing the P2Y$_{12}$ receptor inhibitor and transitioning to aspirin monotherapy.[5] Recently, P2Y$_{12}$ inhibitor-based single antiplatelet therapy (SAPT) has emerged as an attractive alternative strategy to limit the need for DAPT after DES implantation.[5] Recent evidence from several randomized controlled trials (RCTs) indicates that aspirin discontinuation at the time of transition from a short DAPT regimen to P2Y$_{12}$ inhibitor-based SAPT reduces major bleeding without increasing the risk of major adverse ischemic outcomes compared with prolonged DAPT after newer-generation DES implantation.[6,7]

Short-term DAPT following PCI among patients at high ischemic risk remains a matter of concern. Compared with those with CCS, patients with ACS have an increased risk for ischemic[8] and major bleeding[9] complications due to an enhanced prothrombotic and proinflammatory milieu that prompts the use of potent antithrombotic strategies and longer DAPT durations following PCI. Due to insufficient statistical power of individual studies to assess treatment effects with respect to low-incidence adverse ischemic events, concerns remain that P2Y$_{12}$ inhibitor-based SAPT after DES implantation may not offer a safe tradeoff between major bleeding avoidance and protection against major ischemic outcomes compared with conventional DAPT among patients with ACS. We therefore performed a study-level meta-analysis of RCTs to investigate the differential effects of P2Y$_{12}$ inhibitor-based SAPT after a short DAPT course compared with conventional DAPT in patients with CCS versus ACS undergoing PCI with newer-generation DES.

METHODS

This meta-analysis of RCTs was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[10] and Cochrane Collaboration[11] recommendations (Table S1). The protocol was registered with International Prospective Register of Systematic Reviews, number CRD42023239341. As the present research was

a study-level meta-analysis of published randomized trials, the requirement for ethics committee approval was waived. The data that support the findings of this meta-analysis are available from the corresponding author upon reasonable request.

Data Sources and Search Strategy

We performed a systematic literature search of PubMed, Embase, and Cochrane Central Register of Controlled Trials databases as of January 4, 2024. Details of the *Medical Subject Headings* terms used for literature search are shown in Table S2. Reference lists of studies, review articles, meta-analyses, and editorials identified were screened for additional eligible studies. No language or sample size restrictions were considered.

Study Selection

In this meta-analysis, we included peer-reviewed publications of RCTs with the following prespecified eligibility criteria (Table S3): (1) patients who underwent PCI with newer-generation DES, (2) studies with random allocation of different antiplatelet regimens, (3) studies comparing 2 antiplatelet strategies: P2Y$_{12}$ inhibitor SAPT following a short course (≤3 months) of DAPT versus conventional (6–12 months) DAPT, (4) studies reporting on patient baseline clinical presentation, and (5) studies reporting clinical outcomes. We excluded individual reports of the same trial providing outcome data at different follow-up periods, as well as observational and unpublished studies due to the inherent risk of bias. For the STOPDAPT-2 (Short and Optimal Duration of Dual Antiplatelet Therapy 2) trial, we used the results from the prespecified pooled analysis[12] that combined individual patient data from STOPDAPT-2[13] and STOPDAPT-2 ACS trials,[14] thus providing a direct comparison between patients with CCS and ACS included in both studies. Two authors (S.D., Q.C.) independently performed the literature search, reviewed the identified titles and abstracts, and selected studies for inclusion based on the predefined criteria. Disagreements were resolved by consensus and arbitration by a third author (J.F.I.).

Data Extraction and Risk of Bias Assessment

Two independent investigators (S.D., Q.C.) individually performed data extraction, which was verified by a third investigator (J.F.I.). The following information was extracted for each individual study: study characteristics (including authors, publication year, journal, study design, recruitment period, follow-up duration, and number of patients randomized and analyzed for each outcome), patient characteristics (including age, sex, comorbidities, and baseline clinical presentation), experimental and comparator treatment groups (randomized antiplatelet regimen and antiplatelet treatment duration), and outcome data (including reported outcome definitions). The risk of bias in each individual study was assessed by 2 investigators (S.D., Q.C.) using the Cochrane Collaboration criteria,[11] which includes the following items: allocation sequence generation, allocation concealment, participant, personnel and outcome assessors blinding, completeness of outcome data, and selective outcome reporting. Blinding was considered complete when outcome assessors were blinded. Studies with high or unclear risk for bias were considered at high risk of bias, whereas the remaining studies were considered at low risk for bias.

Study End Points

The study co-primary end points were (1) major bleeding according to the Bleeding Academic Research Consortium classification, and (2) major adverse cardiovascular and cerebrovascular events (MACCE). Major bleeding was defined as BARC type 3 or 5 (Bleeding Academic Research Consortium type 3 or 5) major bleeding in all studies included, with the exception of the SMART-CHOICE (Comparison Between P2Y12 Antagonist Monotherapy and Dual Antiplatelet Therapy After DES) trial[15] (BARC type 2 to 5 major bleeding). MACCE was defined as the composite of all-cause death, myocardial infarction, or ischemic stroke, with the exception of the STOPDAPT-3[16] trial (cardiac death, myocardial infarction, ischemic stroke, or definite stent thrombosis). Secondary end points included net adverse clinical events (NACE), defined as the composite of Bleeding Academic Research Consortium major bleeding, all-cause death, myocardial infarction, or ischemic stroke; all-cause death; myocardial infarction; any revascularization; any stroke; and definite or probable stent thrombosis according to the Academic Research Consortium definition.[17]

Statistical Analysis

Meta-analyses were performed if data from at least 3 trials or 100 patients could be combined. For dichotomous outcomes, risk ratios (RRs) with 95% CI were computed to compare intervention and control groups at the study level. Due to a priori moderate-to-high level of heterogeneity between studies, we used random-effects models[18] with inverse-variance weighting (Der Simonian and Laird's approach). Heterogeneity between studies was assessed using Higgins and Thompson's I^2 statistic with values ≤25%, between 25% and 75%, and ≥75% considered low, moderate, and high heterogeneity, respectively. Results were displayed by using forest plots illustrating the relative

contribution to the summary estimate of each individual trial. We performed subgroup analyses according to baseline clinical presentation (CCS versus ACS) and the antiplatelet treatment strategy investigated ($P2Y_{12}$ inhibitor-based SAPT versus conventional DAPT). Due to significant differences between studies concerning duration of DAPT (≤1 month versus 1–3 months) in the experimental $P2Y_{12}$ inhibitor-based SAPT group, we performed sensitivity analyses by leave-one-out to determine the influence of each individual trial on the overall effect-size estimate for major bleeding, MACCE, and NACE. Finally, because of important differences in the definition of MACCE across studies included, we also performed a sensitivity analysis according to definitions used in each individual study. A *P* value <0.05 was considered statistically significant for interaction. Statistical analyses were performed using RevMan 5.4 (Cochrane Collaboration, Oxford, United Kingdom).

RESULTS

Overall, 43 949 patients from 7 RCTs (GLOBAL LEADERS subanalysis,[19] SMART CHOICE,[15] STOPDAPT-2 total cohort,[12] TWILIGHT [Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention]-ACS subanalysis,[20] TICO [Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome],[21] STOPDAPT-3,[16] and T-PASS [Ticagrelor Monotherapy in Patients Treated With New-Generation Drug-Eluting Stents for Acute Coronary Syndrome][22]) comparing $P2Y_{12}$ inhibitor SAPT following a short (≤3 months) DAPT regimen (21 960 patients) versus conventional (6–12 months) DAPT (21 989 patients) after PCI with newer-generation DES qualified for inclusion (Figure 1, Table 1). Newer-generation DES included second-generation or later DES (permanent polymer DES, biodegradable polymer DES, polymer-free DES, and bioresorbable vascular scaffolds). The full list of DES used in individual studies included is detailed in Table 1. In the experimental group, ticagrelor-based SAPT was investigated in 4 trials (14 488 patients, 66%),[19–22] whereas non–ticagrelor-based SAPT regimens were evaluated in the remaining 3 studies (7472 patients, 34%) using mainly clopidogrel in 2 trials (4488 patients)[12,15] and (low-dose) prasugrel in 1 trial (2984 patients)[16] (Table 1). Due to missing information, 4 patients from 2 studies[15,20] were excluded, and a total of 43 945 patients were finally included in the present analysis. Among those, 15 585 patients presented with CCS (35%), whereas 28 360 patients were treated for ACS (65%; ST-segment–elevation myocardial infarction, 26%). The duration of DAPT in the $P2Y_{12}$ inhibitor-based SAPT arm was <1 month in 1 study,[22] 1 month in 2 studies,[12,19] and 3 months in 3 studies.[15,20,21] In addition, $P2Y_{12}$ inhibitor-based SAPT was initiated before PCI without aspirin (no DAPT course) in 1 study[16] (Table 1). The median follow-up duration was 12 months (interquartile range, 12–12 months). The bias risk assessment of trials included in the present meta-analysis is detailed in Table S4. Concerns about a high risk of bias were found in 6 studies related to the open-label treatment allocation. Overall, 6 studies were rated as having a low risk of bias with regard to the primary outcome measure assessment. Baseline clinical characteristics of patients enrolled in the individual trials included in this meta-analysis are reported in Table 1.

Total Population

In the total population (n=43 945), the risk of major bleeding was lower among patients treated with $P2Y_{12}$ inhibitor-based SAPT versus conventional DAPT after DES implantation (RR, 0.63 [95% CI, 0.48–0.82]; *P*<0.001; I^2=75%). The risk of MACCE did not significantly differ between patients treated with $P2Y_{12}$ inhibitor-based SAPT and those receiving conventional DAPT (RR, 0.98 [95% CI, 0.87–1.11]; *P*=0.74; I^2=26%). Accordingly, treatment with $P2Y_{12}$ inhibitor-based SAPT was associated with a lower risk for NACE compared with conventional DAPT (RR, 0.85 [95% CI, 0.76–0.97]; *P*=0.01; I^2=60%) (Figure 2). Individual adverse ischemic outcomes, including all-cause death, any myocardial infarction, ischemic stroke, and any stent thrombosis, did not significantly differ between patients receiving $P2Y_{12}$ inhibitor-based SAPT and those treated with conventional DAPT (Figure 2). In a sensitivity analysis by leave-one-out, the results for major bleeding, MACCE and NACE remained consistent after exclusion of the STOPDAPT-3[16] and T-PASS trials[22] (Table S5).

Chronic Coronary Syndrome

Among patients undergoing PCI for CCS, the risk of major bleeding did not differ between patients treated with $P2Y_{12}$ inhibitor-based SAPT and conventional DAPT (RR, 0.81 [95% CI, 0.52–1.28]; *P*=0.37; I^2=66%). There were no differences in the risks for MACCE (RR, 0.95 [95% CI, 0.83–1.10]; *P*=0.53; I^2=0%) and NACE (RR, 0.96 [95% CI, 0.85–1.08]; *P*=0.46; I^2=0%) between CCS patients treated with $P2Y_{12}$ inhibitor-based SAPT and those receiving conventional DAPT (Figure 3). In addition, there were no significant differences between $P2Y_{12}$ inhibitor-based SAPT and conventional DAPT with respect to any of the following ischemic end points: all-cause death, any myocardial infarction, ischemic stroke, any stroke, any revascularization, and any stent thrombosis (Figure S1). In a leave-one-out sensitivity analysis, the results for major bleeding, MACCE and NACE were consistent after excluding the STOPDAPT-3[16] and T-PASS[22] trials (Table S6).

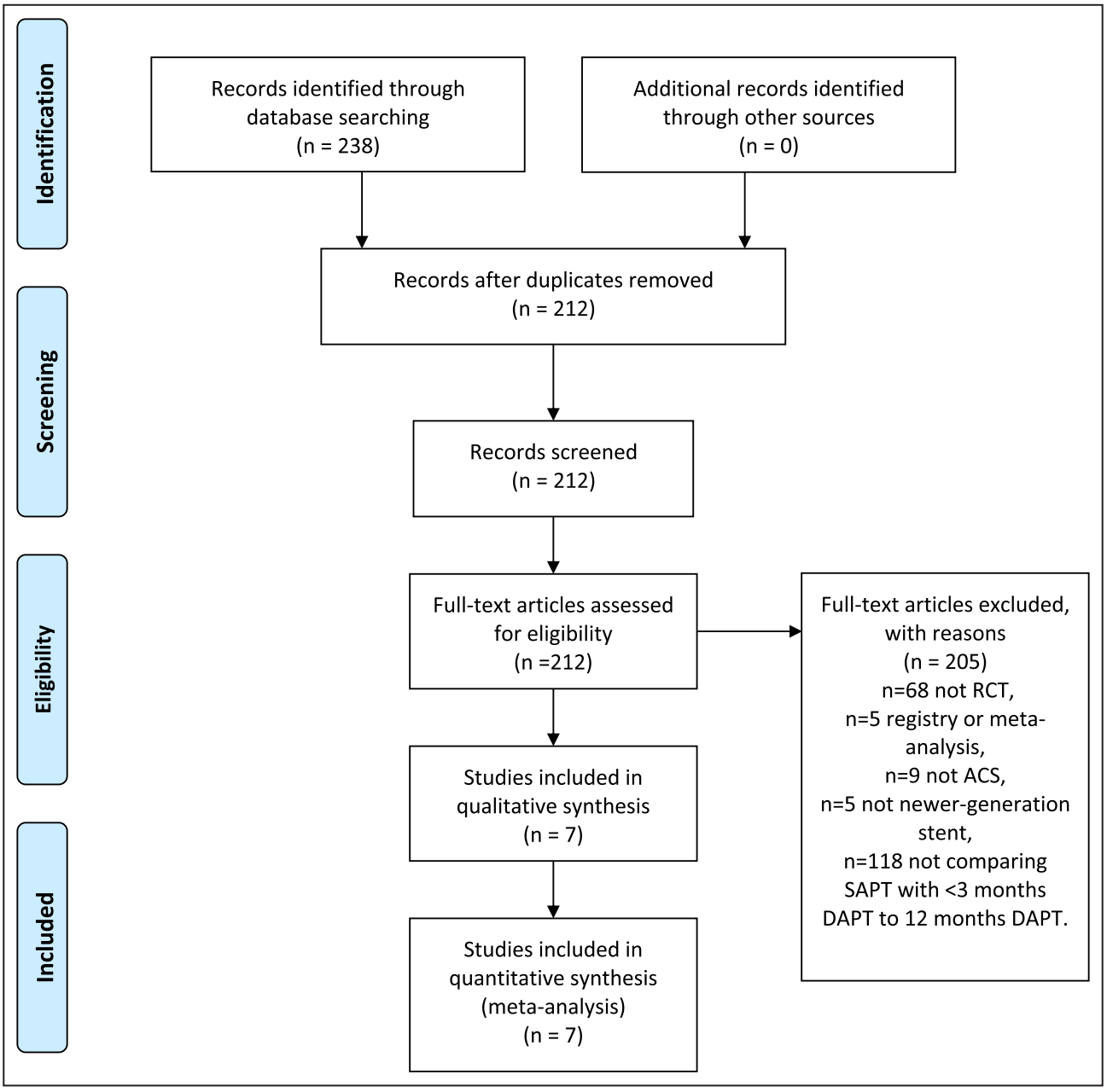


Figure 1. Study selection (PRISMA flow diagram).
ACS indicates acute coronary syndrome; DAPT, dual antiplatelet therapy; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; and SAPT, single antiplatelet therapy.

Acute Coronary Syndrome

The risk for major bleeding was lower among patients with ACS treated with P2Y$_{12}$ inhibitor SAPT as compared with those receiving conventional DAPT (RR, 0.55 [95% CI, 0.40–0.75]; P<0.001; I^2=74%). The risk of MACCE did not differ between ACS patients treated with P2Y$_{12}$ inhibitor SAPT or conventional DAPT (RR, 0.98 [95% CI, 0.80–1.21]; P=0.88; I^2=54%). Treatment with P2Y$_{12}$ inhibitor-based SAPT was associated with a lower risk for NACE compared with conventional DAPT (RR, 0.82 [95% CI, 0.68–0.98]; P=0.03; I^2=74%) (Figure 3). There were no significant differences between ACS patients treated with P2Y$_{12}$ inhibitor SAPT and conventional DAPT with respect to any individual adverse ischemic outcome, including all-cause death, cardiac and noncardiac death, any myocardial infarction, ischemic stroke, any stroke, any revascularization, and any stent thrombosis (Figure S2). Leave-one-out sensitivity analyses demonstrated consistent results with regards to major bleeding, MACCE, and NACE after exclusion of the STOPDAPT-3[16] and T-PASS[22] trials (Table S7). Overall, there was no significant

Table 1. Baseline Clinical and Procedural Characteristics of Randomized Clinical Trials Included

Trials	Patients, N	Experimental group			Reference group			Drug-eluting stents	MACCE, study definition	Primary end point assessment, mo	Mean age, y	Men, %	Diabetes, %	CCS, n/%	ACS, n/%	Unstable angina, %	STEMI, %	Non–STEMI, %
		Patients, N	SAPT regimen	DAPT duration, mo	Patients, N	DAPT regimen	DAPT duration, mo											
GLOBAL LEADERS subanalysis[19]	15 968	7980	Ticagrelor	1	7988	Aspirin+ ticagrelor	12	BP biolimus-eluting stents	All-cause death, or new MI	24	64.5	76.7	25.3	8481 (53.1%)	7487 (46.9%)	12.7	13.1	21.1
SMART-CHOICE[15]	2993	1495	Clopidogrel 77%; ticagrelor 19%; prasugrel 4%	3	1498	Aspirin+ clopidogrel (78%)/ ticagrelor (18%)/ prasugrel (4%)	12	DP cobalt-chromium everolimus-eluting (35%); BP platinum-chromium everolimus-eluting (32%); BP sirolimus-eluting stents (32%); DP-zotarolimus-eluting stents (<1%); paclitaxel-cilostazol coated-stents (<1%)	All-cause death, MI, or stroke	12	64.6	73.4	37.5	1250 (41.8%)	1741 (58.2%)	32.0	10.5	15.7
STOPDAPT-2 (total cohort)[12]	5997	2993	Clopidogrel 57%; prasugrel 43%	1	3004	Aspirin+ clopidogrel (58%)/ prasugrel (42%)	12	DP cobalt-chromium everolimus-eluting stents	Cardiac death, MI, definite stent thrombosis, or stroke	12	67.0	78.7	29.5	1861 (31.0%)	4136 (69.0%)	16.4	55.8	19.8
TWILIGHT-ACS subanalysis[20]	7119	3555	Ticagrelor	3	3564	Aspirin+ ticagrelor	12	DP cobalt chromium everolimus-eluting stents; DP everolimus-eluting stents; DP zotarolimus-eluting stents; DP cobalt chromium sirolimus eluting stents; BP drug-eluting stents; polymer free drug-eluting stents; bioresorbable vascular scaffold; sirolimus-eluting self-apposing stents; tacrolimus-eluting carbostents	All-cause death, MI, or stroke	12	65.6	76.1	33.3	2503 (35.2%)	4614 (64.8%)	35.0	0	29.8
TICO[21]	3056	1527	Ticagrelor	3	1529	Aspirin+ ticagrelor	12	BP sirolimus-eluting stents	All-cause death, MI, stroke, stent thrombosis, or TVR	12	61.0	79.5	27.3	0 (0%)	3056 (100%)	30.3	36.1	33.6

Table 1. Continued

Trials	Patients, N	Experimental group			Reference group			Drug-eluting stents	MACCE, study definition	Primary end point assessment, mo	Mean age, y	Men, %	Diabetes, %	CCS, n/%	ACS, n/%	Unstable angina, %	STEMI, %	Non–STEMI, %
		Patients, N	SAPT regimen	DAPT duration, mo	Patients, N	DAPT regimen	DAPT duration, mo											
STOPDAPT-3[16]	5966	2984	Prasugrel (low-dose)	0	2982	Aspirin+ prasugrel (low-dose)	1	DP cobalt-chromium everolimus-eluting stents	Cardiac death, MI, definite stent thrombosis, or ischemic stroke	11	71.6	76.6	40.7	1490 (25.0%)	4476 (75.0%)	13.9	18.3	42.8
T-PASS[22]	2850	1426	Ticagrelor	<1	1424	Aspirin+ ticagrelor	12	BP sirolimus-eluting stents	Cardiac death, MI, stroke, or ischemia driven TVR	12	61.0	83.3	29.1	0 (0%)	2850 (100%)	24.8	34.8	40.4

ACS indicates acute coronary syndrome; BP, biodegradable polymer; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; DP, durable polymer; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; SAPT, single antiplatelet therapy; STEMI, ST-segment–elevation myocardial infarction; and TVR, target vessel revascularization.

interaction between treatment effect (P2Y$_{12}$ inhibitor-based SAPT versus conventional DAPT) and clinical presentation (CCS versus ACS) with respect to major bleeding, MACCE, NACE, all-cause death, any myocardial infarction, ischemic stroke, or any stent thrombosis (Figure 3, Figure S3).

DISCUSSION

The main findings of this updated systematic review and meta-analysis including >40 000 patients from 7 RCTs who underwent PCI with newer-generation DES and comparing clinical effects between P2Y$_{12}$ inhibitor-based SAPT after ≤3 months of DAPT and conventional 12-month DAPT can be summarized as follows: (1) P2Y$_{12}$ inhibitor-based SAPT following a short DAPT course was associated with a lower risk of major bleeding compared with 12-month DAPT, a difference mainly driven by patients with ACS; (2) aspirin discontinuation within 3 months of DAPT and transition to P2Y$_{12}$ inhibitor-based SAPT was associated with a similar risk for ischemic and thrombotic events compared with conventional 12-month DAPT, thus contributing to a favorable net clinical benefit primarily driven by ACS patients; and (3) overall, treatment effects between P2Y$_{12}$ inhibitor-based SAPT and standard DAPT with respect to major bleeding and MACCE were consistent among patients with or without ACS.

DAPT combining aspirin and a P2Y$_{12}$ inhibitor remains the standard of care after PCI with newer-generation DES.[1,2] Recent developments in DES technology have significantly reduced the incidence of stent-related thrombotic complications after PCI,[23] thus facilitating the emergence of novel antiplatelet strategies to reduce the dependence on prolonged DAPT after DES implantation with its inherent risk of major bleeding.[3] Different antiplatelet therapy modulation strategies have recently been proposed to improve safety without compromising efficacy after PCI with DES, including (1) deescalation by P2Y$_{12}$ inhibitor switching, P2Y$_{12}$ inhibitor (prasugrel) dose-reduction, and aspirin or P2Y$_{12}$ inhibitor discontinuation; or (2) abbreviation of DAPT duration by discontinuing the P2Y$_{12}$ inhibitor and transitioning to aspirin monotherapy.[24] Our meta-analysis demonstrates that P2Y$_{12}$ inhibitor-based SAPT after a short DAPT course following contemporary DES implantation is associated with a ~40% reduction in the risk of major bleeding events and a similar risk for major adverse ischemic outcomes compared with conventional 12-month DAPT. These findings confirm those from previous study[6]- and patient[7]-level meta-analyses and support most recent international guidelines[25,26] that endorse P2Y$_{12}$ inhibitor SAPT after a short DAPT regimen as an alternative strategy to reduce major bleeding among

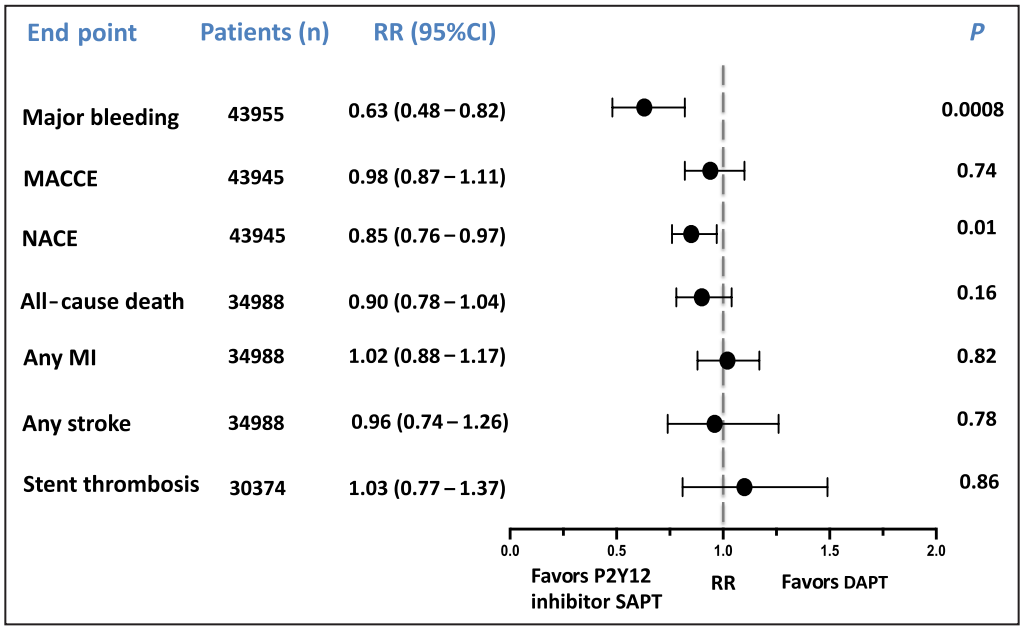


Figure 2. Clinical outcomes with P2Y$_{12}$ inhibitor-based SAPT following ≤3 months of DAPT versus 12-month DAPT after DES implantation in the total population.
DAPT indicates dual antiplatelet therapy; MACCE, major adverse cardiovascular and cerebral events; MI, myocardial infarction; NACE, net adverse clinical events; RR, risk ratio; and SAPT, single antiplatelet therapy.

patients undergoing PCI with newer-generation DES. The present meta-analysis adds on existing knowledge by including a larger number of studies and patients, particularly patients with ACS, thus increasing statistical power to detect potential treatment effects related to individual low-incidence adverse ischemic events in higher ischemic patients subgroups. In addition, our study included, for the first time to our knowledge, 2 recent randomized trials comparing P2Y$_{12}$ inhibitor-based SAPT following a very short (≤1 month)[22] or no DAPT[16] course versus conventional DAPT after DES implantation and found consistent results with regards to major bleeding and MACCE, regardless of DAPT duration adopted before transitioning to P2Y$_{12}$ inhibitor-based SAPT (≤1 versus 1–3 months).

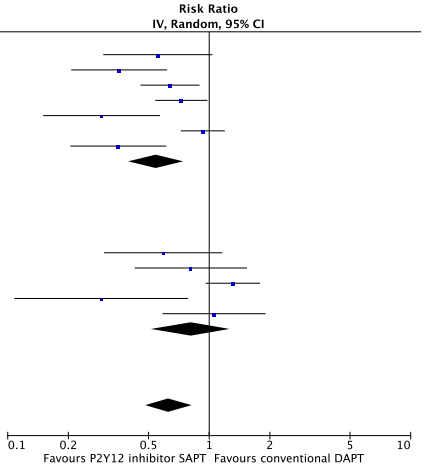
The early discontinuation of aspirin after a short DAPT course following DES implantation in patients at high ischemic risk, as those with ACS, might raise some concerns about a potential increased risk for major ischemic and thrombotic events. In this meta-analysis, we found that the clinical benefits of P2Y$_{12}$ inhibitor-based SAPT compared with standard DAPT in reducing major bleeding without compromising protection against MACCE were consistent among patients with and without ACS. Despite the lack of significant treatment interaction, P2Y$_{12}$ inhibitor-based SAPT was associated with significant reductions in major bleeding compared with 12-month DAPT in patients with ACS but not CCS. In addition, P2Y$_{12}$ inhibitor-based SAPT did not significantly increase the risk of MACCE compared with conventional DAPT among patients with ACS, thus translating into a significant net clinical benefit from P2Y$_{12}$ inhibitor-based SAPT compared with conventional DAPT after PCI with newer-generation DES in patients with ACS but not CCS.

The absence of ischemic trade-off with P2Y$_{12}$ inhibitor-based SAPT in ACS patients supports the hypothesis that potent P2Y$_{12}$ receptor inhibitors may provide sufficient ischemic protection compared with conventional DAPT while mitigating the risk of major

Figure 3. Clinical outcomes with P2Y$_{12}$ inhibitor-based SAPT following ≤3 months of DAPT versus 12-month DAPT after DES implantation in patients with chronic and acute coronary syndromes.
ACS indicates acute coronary syndrome; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; MACCE, major adverse cardiovascular and cerebral events; MH, Mantel–Haenszel; NACE, net adverse clinical events; SAPT, single antiplatelet therapy; SMART-CHOICE, Comparison Between P2Y12 Antagonist Monotherapy and Dual Antiplatelet Therapy After DES; STOPDAPT-2, Short and Optimal Duration of Dual Antiplatelet Therapy 2; TICO, Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome; T-PASS, Ticagrelor Monotherapy in Patients Treated With New-Generation Drug-Eluting Stents for Acute Coronary Syndrome; and TWILIGHT, Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention.

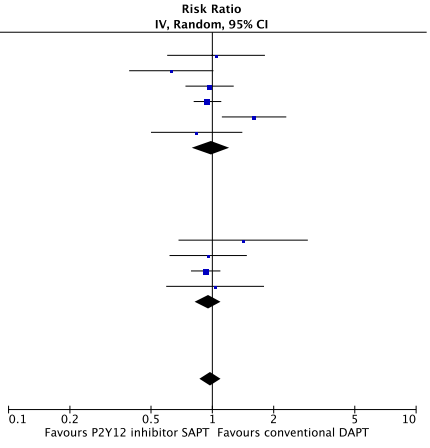
Major bleeding

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI	Year
2.1.1 ACS							
SMART-CHOICE (15)	15	870	27	871	7.4%	0.56 [0.30, 1.04]	2019
TWILIGHT (20)	17	2273	49	2341	8.1%	0.36 [0.21, 0.62]	2020
TICO (21)	53	1527	83	1529	10.3%	0.64 [0.46, 0.90]	2020
GLOBAL LEADERS (19)	73	3750	100	3737	10.7%	0.73 [0.54, 0.98]	2021
STOPDAPT-2 (12)	11	2058	38	2078	7.0%	0.29 [0.15, 0.57]	2022
STOPDAPT-3 (16)	111	2242	119	2234	11.1%	0.93 [0.72, 1.20]	2023
T-PASS (22)	17	1426	48	1424	8.2%	0.35 [0.20, 0.61]	2023
Subtotal (95% CI)		**14146**		**14214**	**62.9%**	**0.55 [0.40, 0.75]**	
Total events	297		464				
Heterogeneity: Tau² = 0.12; Chi² = 23.31, df = 6 (P = 0.0007); I² = 74%							
Test for overall effect: Z = 3.79 (P = 0.0001)							
2.1.2 CSS							
SMART-CHOICE (15)	13	625	22	625	6.9%	0.59 [0.30, 1.16]	2019
TWILIGHT (20)	17	1281	20	1222	7.2%	0.81 [0.43, 1.54]	2020
GLOBAL LEADERS (19)	90	4230	69	4251	10.6%	1.31 [0.96, 1.79]	2021
STOPDAPT-2 (12)	5	935	17	926	4.6%	0.29 [0.11, 0.79]	2022
T-PASS (22)	22	742	21	748	7.7%	1.06 [0.59, 1.90]	2023
Subtotal (95% CI)		**7813**		**7772**	**37.1%**	**0.81 [0.52, 1.28]**	
Total events	147		149				
Heterogeneity: Tau² = 0.16; Chi² = 11.61, df = 4 (P = 0.02); I² = 66%							
Test for overall effect: Z = 0.90 (P = 0.37)							
Total (95% CI)		**21959**		**21986**	**100.0%**	**0.63 [0.48, 0.82]**	
Total events	444		613				
Heterogeneity: Tau² = 0.15; Chi² = 44.13, df = 11 (P < 0.00001); I² = 75%							
Test for overall effect: Z = 3.37 (P = 0.0007)							
Test for subgroup differences: Chi² = 2.00, df = 1 (P = 0.16), I² = 50.1%							



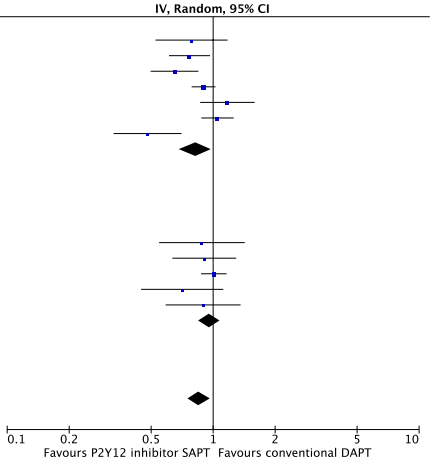
MACCE

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI	Year
2.2.1 ACS							
SMART-CHOICE (15)	25	870	24	871	4.4%	1.04 [0.60, 1.81]	2019
TICO (21)	27	1527	43	1529	5.7%	0.63 [0.39, 1.01]	2020
TWILIGHT (20)	96	2273	102	2341	13.6%	0.97 [0.74, 1.27]	2020
GLOBAL LEADERS (19)	284	3750	299	3737	24.9%	0.95 [0.81, 1.11]	2021
STOPDAPT-2 (12)	73	2058	46	2078	8.9%	1.60 [1.11, 2.31]	2022
T-PASS (22)	26	1426	31	1424	5.0%	0.84 [0.50, 1.40]	2023
Subtotal (95% CI)		**11904**		**11980**	**62.7%**	**0.98 [0.80, 1.21]**	
Total events	531		545				
Heterogeneity: Tau² = 0.03; Chi² = 10.95, df = 5 (P = 0.05); I² = 54%							
Test for overall effect: Z = 0.15 (P = 0.88)							
2.2.2 CSS							
SMART-CHOICE (15)	17	625	12	625	2.6%	1.42 [0.68, 2.94]	2019
TWILIGHT (20)	39	1281	39	1222	6.6%	0.95 [0.62, 1.48]	2020
GLOBAL LEADERS (19)	251	4230	272	4251	23.7%	0.93 [0.79, 1.10]	2021
STOPDAPT-2 (12)	25	935	24	926	4.4%	1.03 [0.59, 1.79]	2022
Subtotal (95% CI)		**7071**		**7024**	**37.3%**	**0.95 [0.82, 1.10]**	
Total events	332		347				
Heterogeneity: Tau² = 0.00; Chi² = 1.31, df = 3 (P = 0.73); I² = 0%							
Test for overall effect: Z = 0.64 (P = 0.52)							
Total (95% CI)		**18975**		**19004**	**100.0%**	**0.98 [0.87, 1.11]**	
Total events	863		892				
Heterogeneity: Tau² = 0.01; Chi² = 12.33, df = 9 (P = 0.20); I² = 27%							
Test for overall effect: Z = 0.32 (P = 0.75)							
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%							



NACE

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI	Year
2.3.1 ACS							
SMART-CHOICE (15)	40	870	51	871	5.8%	0.79 [0.52, 1.18]	2019
TWILIGHT (20)	120	2273	161	2341	10.3%	0.77 [0.61, 0.97]	2020
TICO (21)	83	1527	128	1529	9.1%	0.65 [0.50, 0.85]	2020
GLOBAL LEADERS (19)	366	3750	406	3737	13.5%	0.90 [0.79, 1.03]	2021
STOPDAPT-2 (12)	86	2058	74	2078	8.0%	1.17 [0.87, 1.59]	2022
STOPDAPT-3 (16)	217	2242	206	2234	11.9%	1.05 [0.88, 1.26]	2023
T-PASS (22)	38	1426	79	1424	6.3%	0.48 [0.33, 0.70]	2023
Subtotal (95% CI)		**14146**		**14214**	**64.9%**	**0.82 [0.68, 0.98]**	
Total events	950		1105				
Heterogeneity: Tau² = 0.04; Chi² = 23.43, df = 6 (P = 0.0007); I² = 74%							
Test for overall effect: Z = 2.14 (P = 0.03)							
2.3.2 CSS							
SMART-CHOICE (15)	30	625	34	625	4.6%	0.88 [0.55, 1.42]	2019
TWILIGHT (20)	56	1281	59	1222	6.8%	0.91 [0.63, 1.29]	2020
GLOBAL LEADERS (19)	349	4230	348	4251	13.2%	1.01 [0.87, 1.16]	2021
STOPDAPT-2 (12)	30	935	42	926	4.9%	0.71 [0.45, 1.12]	2022
T-PASS (22)	39	742	44	748	5.6%	0.89 [0.59, 1.36]	2023
Subtotal (95% CI)		**7813**		**7772**	**35.1%**	**0.96 [0.85, 1.08]**	
Total events	504		527				
Heterogeneity: Tau² = 0.00; Chi² = 2.48, df = 4 (P = 0.65); I² = 0%							
Test for overall effect: Z = 0.74 (P = 0.46)							
Total (95% CI)		**21959**		**21986**	**100.0%**	**0.85 [0.76, 0.97]**	
Total events	1454		1632				
Heterogeneity: Tau² = 0.02; Chi² = 27.68, df = 11 (P = 0.004); I² = 60%							
Test for overall effect: Z = 2.53 (P = 0.01)							
Test for subgroup differences: Chi² = 1.94, df = 1 (P = 0.16), I² = 48.4%							



bleeding associated with the use of aspirin.[5] Pivotal secondary prevention studies investigating the role of aspirin for ischemic protection were performed at a time when other effective strategies decreasing the individual risk for adverse ischemic events (eg, advent of newer-generation DES, potent $P2Y_{12}$ receptor inhibitors, and intense lipid- or glucose-lowering therapies) were either not available or widely adopted.[5] The relative clinical benefits of aspirin may therefore translate into smaller absolute effects, thus challenging its current use for secondary prevention. In addition, the safety and efficacy of aspirin SAPT versus placebo or an aspirin-free control group for the prevention of thrombotic or ischemic complications have not been investigated to date. Overall, our results challenge the pivotal role of DAPT in all-comer patients undergoing contemporary DES implantation and provide rationale for a practice shift toward early initiation of $P2Y_{12}$ inhibitor-based SAPT after a short DAPT course regardless of baseline clinical presentation. The routine use of $P2Y_{12}$ inhibitor-based SAPT in unselected patients with CCS may, however, require caution considering that patients with CCS were underrepresented in studies included in the present meta-analysis and may represent a potentially low ischemic risk patient population. A recent pooled patient-level data analysis that included 4685 patients (CCS, 40%) undergoing complex PCI with newer-generation DES demonstrated a lower risk of major bleeding and similar risks for major adverse ischemic events with $P2Y_{12}$ inhibitor-based SAPT after a short DAPT compared with standard DAPT in patients with higher ischemic risk.[27] Future dedicated randomized evidence including higher-risk patients is, however, needed to better identify which subgroups of patients with CCS may benefit from $P2Y_{12}$ inhibitor SAPT based on their individual bleeding and ischemic risks.

The present analysis must be interpreted in view of several limitations. First, as with any meta-analysis, our study shares the limitations of studies included. Second, we did not have access to individual patient data from the trials included and a study-level meta-analysis precludes therefore multivariable and subgroup analyses to account for differences in baseline characteristics between antiplatelet regimens and DAPT durations in the control group. We were also unable to stratify clinical outcomes according to ACS presentation. In addition, CYP2C19 genotyping among patients treated with clopidogrel was not performed or reported in studies included and the potential impact of CYP2C19 loss-of-function and clopidogrel poor metabolizers on the observed treatment effects can therefore not be determined. Third, there was moderate-to-high heterogeneity between included studies. Fourth, we conducted multiple testing, which may increase the risk of type 1 error. However, the statistical significance of our results with respect to co-primary outcomes was robust and persisted after adjustment with the Bonferroni method. Publication bias was not addressed with the use of funnel plots as <10 trials were included.[28] However, we conducted a detailed search in different databases and did not find additional unpublished studies in clinical trials registers. In addition, we performed a detailed assessment of selective nonreporting or underreporting of results in studies identified, and we did not observe missing results for the main outcomes assessed in this meta-analysis. Fifth, individual definitions of MACCE varied considerably across included studies (Table 1) and may have differed from MACCE definition used in this study. However, in a sensitivity analysis accounting for individual definitions of MACCE used in included studies (Figure S4), we found consistent results with respect to MACCE, regardless of the definition used. The findings that the risk of MACCE may not be affected by antiplatelet regimen among patients with ACS need to be cautiously interpreted due to the current lack of dedicated randomized trials adequately powered for primary ischemic end points and comparing $P2Y_{12}$ inhibitor-based SAPT versus conventional DAPT after newer-generation DES implantation. Sixth, the median follow-up period was limited to 12 months. Similar studies with longer-term follow-up are needed to confirm these findings and determine the long-term term clinical benefits of a $P2Y_{12}$ inhibitor-based SAPT strategy compared with conventional DAPT after PCI with contemporary DES, particularly among patients at high ischemic risk, such as those with ACS. Finally, the type of $P2Y_{12}$ inhibitor used in $P2Y_{12}$ inhibitor-based SAPT regimens and the duration of DAPT before aspirin discontinuation differ across studies included in the present meta-analysis, and caution is therefore warranted before extrapolating the study results to all $P2Y_{12}$ inhibitor-based SAPT strategies. The majority of trials included have investigated ticagrelor-based SAPT versus conventional DAPT, which may represent a potential source of bias when interpreting the overall treatment effects. In addition, clopidogrel-based SAPT was investigated only in Asian patients and the number of studies evaluating prasugrel-based SAPT is limited.

CONCLUSIONS

In a meta-analysis of randomized controlled trials including >40 000 patients who underwent PCI with newer-generation DES, $P2Y_{12}$ inhibitor-based SAPT following ≤3 months of DAPT is associated with a lower risk of major bleeding and a similar risk of MACCE compared with conventional 12 months of DAPT, a benefit that is primarily driven by patients with ACS.

ARTICLE INFORMATION

Received May 17, 2024; accepted January 17, 2025.

Affiliations

Department of Cardiology (J.F.I., Q.C., Y.M., S.D., M.R.) and Intensive Care Unit (B.A.), Geneva University Hospitals, Geneva, Switzerland.

Sources of Funding

None.

Disclosures

Juan F. Iglesias reports research grants to the institution from Abbott Vascular, Astra Zeneca, Biotronik, Concept Medical, Philips, SMT, and Terumo Corp., outside the submitted work; speaker fees from Astra Zeneca, Biosensors, Biotronik, Biosensors, Bristol Myers Squibb, Cordis, Concept Medical, Medtronic, Novartis, Terumo Corp., Penumbra, Pfizer, Philips, and ReCor Medical outside the submitted work. Marco Roffi reports research grants to the institution from Biotronik, Boston Scientific, Cordis, Medtronic, and Terumo Corp., outside the submitted work. Sophie Degrauwe reports research grants to the institution from Biotronik and Abbott Vascular, outside the submitted work; speaker fees from Biotronik, outside the submitted work. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S7
Figures S1–S4

REFERENCES

1. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, 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. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, Bittl JA, Cohen MG, DiMaio JM, Don CW, 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:e4–e17. doi: 10.1161/CIR.0000000000001039
3. Gargiulo G, Valgimigli M, Capodanno D, Bittl JA. State of the art: duration of dual antiplatelet therapy after percutaneous coronary intervention and coronary stent implantation—past, present and future perspectives. *EuroIntervention*. 2017;13:717–733. doi: 10.4244/EIJ-D-17-00468
4. Palmerini T, Bacchi Reggiani L, Della Riva D, Romanello M, Feres F, Abizaid A, Gilard M, Morice MC, Valgimigli M, Hong MK, et al. Bleeding-related deaths in relation to the duration of dual-antiplatelet therapy after coronary stenting. *J Am Coll Cardiol*. 2017;69:2011–2022. doi: 10.1016/j.jacc.2017.02.029
5. Capodanno D, Bhatt DL, Gibson CM, James S, Kimura T, Mehran R, Rao SV, Steg PG, Urban P, Valgimigli M, et al. Bleeding avoidance strategies in percutaneous coronary intervention. *Nat Rev Cardiol*. 2022;19:117–132. doi: 10.1038/s41569-021-00598-1
6. Giacoppo D, Matsuda Y, Fovino LN, D'Amico G, Gargiulo G, Byrne RA, Capodanno D, Valgimigli M, Mehran R, Tarantini G. 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;42:308–319. doi: 10.1093/eurheartj/ehaa739
7. Valgimigli M, Gragnano F, Branca M, Franzone A, Baber U, Jang Y, Kimura T, Hahn JY, Zhao Q, Windecker S, et al. P2Y12 inhibitor monotherapy or dual antiplatelet therapy after coronary revascularisation: individual patient level meta-analysis of randomised controlled trials. *BMJ*. 2021;373:n1332. doi: 10.1136/bmj.n1332
8. Costa F, Van Klaveren D, Feres F, James S, Räber L, Pilgrim T, Hong MK, Kim HS, Colombo A, Steg PG, et al. Dual antiplatelet therapy duration based on ischemic and bleeding risks after coronary stenting. *J Am Coll Cardiol*. 2019;73:741–754. doi: 10.1016/j.jacc.2018.11.048
9. Gragnano F, Spirito A, Corpataux N, Vaisnora L, Galea R, Gargiulo G, Siontis GCM, Praz F, Lanz J, Billinger M, et al. Impact of clinical presentation on bleeding risk after percutaneous coronary intervention and implications for the ARC-HBR definition. *EuroIntervention*. 2021;17:e898–e909. doi: 10.4244/EIJ-D-21-00181
10. Moher D, Liberati A, Tetzlaff J, Altman DG; Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
11. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi: 10.1136/bmj.l4898
12. Obayashi Y, Watanabe H, Morimoto T, Yamamoto K, Natsuaki M, Domei T, Yamaji K, Suwa S, Isawa T, Watanabe H, et al. Clopidogrel monotherapy after 1-month dual antiplatelet therapy in percutaneous coronary intervention: from the STOPDAPT-2 Total cohort. *Circ Cardiovasc Interv*. 2022;15:e012004. doi: 10.1161/CIRCINTERVENTIONS.122.012004
13. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, Ohya M, Suwa S, Takagi K, Nanasato M, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA*. 2019;321:2414–2427. doi: 10.1001/jama.2019.8145
14. Watanabe H, Morimoto T, Natsuaki M, Yamamoto K, Obayashi Y, Ogita M, Suwa S, Isawa T, Domei T, Yamaji K, et al. 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;7:407–417. doi: 10.1001/jamacardio.2021.5244
15. Hahn JY, Song YB, Oh JH, Chun WJ, Park YH, Jang WJ, Im ES, Jeong JO, Cho BR, Oh SK, et al. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. *JAMA*. 2019;321:2428–2437. doi: 10.1001/jama.2019.8146
16. Natsuaki M, Watanabe H, Morimoto T, Yamamoto K, Obayashi Y, Nishikawa R, Ando K, Domei T, Suwa S, Ogita M, et al. An aspirin-free versus dual antiplatelet strategy for coronary stenting: STOPDAPT-3 randomized trial. *Circulation*. 2024;149:585–600. doi: 10.1161/CIRCULATIONAHA.123.066720
17. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, Onuma Y, Morel MA, van Es GA, Zuckerman B, et al. Standardized end point definitions for coronary intervention trials: the academic research Consortium-2 consensus document. *Circulation*. 2018;137:2635–2650. doi: 10.1161/CIRCULATIONAHA.117.029289
18. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed effect and random-effects models for meta-analysis. *Res Synth Methods*. 2010;1:97–111. doi: 10.1002/jrsm.12
19. Vranckx P, Valgimigli M, Odutayo A, Serruys PW, Hamm C, Steg PG, Heg D, Mc Fadden EP, Onuma Y, Benit E, et al. Efficacy and safety of ticagrelor monotherapy by clinical presentation: pre-specified analysis of the GLOBAL LEADERS trial. *J Am Heart Assoc*. 2021;10:e015560. doi: 10.1161/JAHA.119.015560
20. Baber U, Dangas G, Angiolillo DJ, Cohen DJ, Sharma SK, Nicolas J, Briguori C, Cha JY, Collier T, Dudek D, et al. Ticagrelor alone vs. ticagrelor plus aspirin following percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes: TWILIGHT-ACS. *Eur Heart J*. 2020;41:3533–3545. doi: 10.1093/eurheartj/ehaa670
21. Kim BK, Hong SJ, Cho YH, Yun KH, Kim YH, Suh Y, Cho JY, Her AY, Cho S, Jeon DW, et al. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. *JAMA*. 2020;323:2407–2416. doi: 10.1001/jama.2020.7580
22. Hong SJ, Lee SJ, Suh Y, Yun KH, Kang TS, Shin S, Kwon SW, Lee JW, Cho DK, Park JK, et al. Stopping aspirin within 1 month after stenting for ticagrelor monotherapy in acute coronary syndrome: the T-PASS randomized noninferiority trial. *Circulation*. 2024;149:562–573. doi: 10.1161/CIRCULATIONAHA.123.066943
23. Palmerini T, Biondi-Zoccai G, Della Riva D, Mariani A, Genereux P, Branzi A, Stone GW. Stent thrombosis with drug-eluting stents: is the paradigm shifting? *J Am Coll Cardiol*. 2013;62:1915–1921. doi: 10.1016/j.jacc.2013.08.725
24. Capodanno D, Mehran R, Krucoff MW, Baber U, Bhatt DL, Capranzano P, Collet JP, Cuisset T, De Luca G, De Luca L, et al. Defining strategies of modulation of antiplatelet therapy in patients with coronary artery disease: a consensus document from the academic research consortium. *Circulation*. 2023;147:1933–1944. doi: 10.1161/CIRCULATIONAHA.123.064473

25. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, Claeys MJ, Dan GA, Dweck MR, Galbraith M, et al. 2023 ESC guidelines for the management of acute coronary syndromes. *Eur Heart J*. 2023;44:3720–3826. doi: 10.1093/eurheartj/ehad191
26. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, Banning AP, Budaj A, Buechel RR, Chiariello GA, et al. 2024 ESC guidelines for the management of chronic coronary syndromes. *Eur Heart J*. 2024;45:3415–3537. doi: 10.1093/eurheartj/ehae177
27. Gragnano F, Mehran R, Branca M, Franzone A, Baber U, Jang Y, Kimura T, Hahn JY, Zhao Q, Windecker S, et al. P2Y12 inhibitor monotherapy or dual antiplatelet therapy after complex percutaneous coronary interventions. *J Am Coll Cardiol*. 2023;81:537–552. doi: 10.1016/j.jacc.2022.11.041
28. Dalton JE, Bolen SD, Mascha EJ. Publication bias: the elephant in the review. *Anesth Analg*. 2016;123:812–813. doi: 10.1213/ANE.0000000000001596