Circulation

ORIGINAL RESEARCH ARTICLE

Dual Antiplatelet Therapy After Percutaneous Coronary Intervention and Drug-Eluting Stents

A Systematic Review and Network Meta-Analysis

BACKGROUND: The optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention with drug-eluting stents remains uncertain. We compared short-term (<6-month) DAPT followed by aspirin or P2Y12 inhibitor monotherapy; midterm (6-month) DAPT; 12-month DAPT; and extended-term (>12-month) DAPT after percutaneous coronary intervention with drug-eluting stents.

METHODS: Twenty-four randomized, controlled trials were selected using Medline, Embase, Cochrane library, and online databases through September 2019. The coprimary end points were myocardial infarction and major bleeding, which constituted the net clinical benefit. A frequentist network meta-analysis was conducted with a random-effects model.

RESULTS: In 79 073 patients, at a median follow-up of 18 months, extended-term DAPT was associated with a reduced risk of myocardial infarction in comparison with 12-month DAPT (absolute risk difference, –3.8 incident cases per 1000 person-years; relative risk, 0.68 [95% CI, 0.54–0.87]), midterm DAPT (absolute risk difference, –4.6 incident cases per 1000 person-years; relative risk, 0.61 [0.45–0.83]), and short-term DAPT followed by aspirin monotherapy (absolute risk difference, –6.1 incident cases per 1000 person-years; relative risk, 0.55 [0.37–0.83]), or P2Y12 inhibitor monotherapy (absolute risk difference, –3.7 incident cases per 1000 person-years; relative risk, 0.69 [0.51–0.95]). Conversely, extended-term DAPT was associated with a higher risk of major bleeding than all other DAPT groups. In comparison with 12-month DAPT, no significant differences in the risks of ischemic end points or major bleeding were observed with midterm or short-term DAPT followed by aspirin monotherapy, with the exception that short-term DAPT followed by P2Y12 inhibitor monotherapy was associated with a reduced risk of major bleeding. There were no significant differences with respect to mortality between the different DAPT strategies. In acute coronary syndrome, extended-term in comparison with 12-month DAPT was associated with a reduced risk of myocardial infarction without a significant increase in the risk of major bleeding.

CONCLUSIONS: The present network meta-analysis suggests that, in comparison with 12-month DAPT, short-term DAPT followed by P2Y12 inhibitor monotherapy reduces major bleeding after percutaneous coronary intervention with drug-eluting stents, whereas extended-term DAPT reduces myocardial infarction at the expense of more bleeding events.

Safi U. Khan, MD
Maninder Singh, MBBS
Shahul Valavoor, MD
Muhammad U. Khan, MD
Ahmad N. Lone, MD
Muhammad Zia Khan, MD
Muhammad Shahzeb Khan, MD
Preethi Mani, MD
Samir R. Kapadia, MD
Erin D. Michos, MD, MHS
Gregg W. Stone, MD
Ankur Kalra, MD*
Deepak L. Bhatt, MD, MPH*

*Drs Kalra and Bhatt contributed equally.

Key Words: drug-eluting stents ■ dual anti-platelet therapy ■ network meta-analysis ■ percutaneous coronary intervention

Sources of Funding, see page 1434

https://www.ahajournals.org/journal/circ

ORIGINAL RESEARCH ARTICLE

Clinical Perspective

What Is New?

- Extended-term (>12-month) dual antiplatelet therapy (DAPT) was associated with less myocardial infarction in comparison with 12-month DAPT or short-term to midterm (≤6-month) DAPT followed by aspirin monotherapy or P2Y12 inhibitor monotherapy after percutaneous coronary intervention with drug-eluting stents or acute coronary syndrome.
- Overall, extended-term DAPT was associated with a higher risk of major bleeding than all other DAPT groups, with the exception of patients with acute coronary syndrome.

What Are the Clinical Implications?

- In comparison with 12-month DAPT, the net clinical benefit appears to favor short-term DAPT followed by P2Y12 inhibitor monotherapy instead of aspirin in select patients, although extended-term DAPT has a role for patients who have low bleeding risk but with higher ischemic risk such as acute coronary syndrome.
- A personalized approach considering each patient's relative and absolute risk of ischemia and bleeding should be considered when deciding on the optimal intensity and duration of DAPT after percutaneous coronary intervention.

The optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) remains unsettled.[1] In patients with chronic coronary syndrome, the 2016 American College of Cardiology/American Heart Association update recommended DAPT (aspirin and a P2Y12 inhibitor) for 6 months after PCI with drug-eluting stent (DES), with the potential to extend DAPT for a longer duration in those who remain free of a bleeding complication during this period and do not carry high bleeding risk.[2] Conversely, patients at high bleeding risk may discontinue DAPT at 3 months. Similarly, the 2017 European Society of Cardiology update recommends 6-month DAPT in chronic coronary syndrome irrespective of stent type, with further prolongation of DAPT reserved for patients with low bleeding risk but high thrombotic risk, and 1 to 3 months of DAPT for patients with high bleeding risk.[3] In patients with acute coronary syndromes (ACS), both the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines recommend at least 12 months of DAPT, with consideration that the duration could be extended beyond 12 months in patients with lower risk of bleeding, and 6 months of DAPT in patients with high risk of bleeding.[2,3] Both guidelines recommend indefinite continuation of aspirin monotherapy after discontinuation of DAPT.[2,3]

These recommendations were based on the evidence derived from 15 randomized, controlled trials conducted in patients with predominantly chronic coronary syndrome.[4] More recent clinical trials have been performed, including several conducted in ACS and those studying ≤3-month DAPT followed by discontinuation of aspirin rather than the P2Y12 inhibitor.[5–8] We therefore performed an updated trial-level network meta-analysis to compare different durations of DAPT and strategies focused on different types of antiplatelet monotherapy (aspirin versus P2Y12 inhibitor) after DAPT discontinuation in patients undergoing PCI with DES either in the acute or chronic setting.

METHODS

Data Availability Statement

The authors declare that all supporting data are available within the article (and in its Data Supplement).

Data Sources and Searches

This study was exempt from institutional review board approval given the deidentified nature of the patients included in the component trials of this network meta-analysis and publicly available data. The present study was performed following the Cochrane Collaboration guidelines, American Heart Association scientific report on systematic reviews and meta-analyses, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[9–11] Two independent investigators (M.U.K. and S.V.) performed the literature search by using Medline, Embase, and the Cochrane Library though September 2019. Additional online resources included TCTMD, ClinicalTrials.gov, Clinical Trial Results (http://www.clinicaltrialresults.org), and the proceedings of major cardiovascular conferences. The search strategy was devised using relevant search terms: "dual antiplatelet therapy," "drug-eluting stent," "percutaneous coronary intervention," "cardiovascular outcomes," and "mortality" (Tables I through III in the Data Supplement). After the removal of duplicates, 2 investigators (M.U.K. and S.V.) screened the remaining articles at the title and abstract level, and then at full-text on the basis of the prespecified selection criteria.

Study Selection

The predefined selection criteria were: (1) randomized, controlled trials comparing different durations of DAPT in patients undergoing PCI with DES; (2) sample size ≥500 patients and follow-up duration of at least 6 months; and (3) reporting on cardiovascular and bleeding outcomes of interest. We excluded pharmacokinetic and pharmacodynamic studies, those with crossover design, or if a minority of patients included in the study received PCI or DES.

Quality Assessment and Data Extraction

Two authors (M.U.K. and A.N.L.) independently extracted data, adjudicated the data, and resolved any conflicts related

to data with discussion or opinion of a third author (S.U.K.). We abstracted data on the characteristics of the trials, procedural characteristics of the participants and trials, medical therapy, crude point estimates, number of events, and sample sizes (Tables IV through XV in the Data Supplement). We also examined patient-level meta-analyses of clinical trials, subgroup analyses, or post hoc analyses of clinical trials for additional information.[12,13] The data extraction was performed according to the intention-to-treat principle. We preferred to abstract outcome data at maximum follow-up duration from each trial. The trial level risk of bias assessment was performed using the Cochrane Risk of Bias Tool (Table XVI in the Data Supplement).

Interventions were stratified into the following groups: short-term (<6-month) DAPT followed by aspirin monotherapy or P2Y12 inhibitor monotherapy; midterm (6-month) DAPT followed by aspirin monotherapy; 12-month DAPT; and extended-term (>12-month) DAPT. Figure 1 illustrates the network of DAPT groups.

Outcome

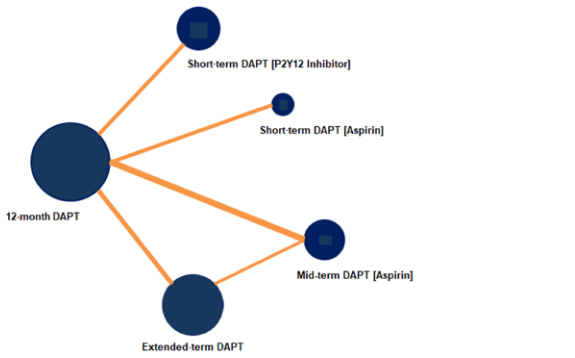
The coprimary end points were myocardial infarction (MI) and major bleeding, which constituted the net clinical benefit.[14] The secondary end points were: major adverse cardiovascular events (MACE, a composite of MI, cerebrovascular accident, cardiovascular mortality), cerebrovascular accident, cardiovascular mortality, all-cause mortality, definite or probable stent thrombosis, repeat revascularization, any bleeding events, and net adverse clinical events (NACE, a composite of major bleeding and ischemic end points such as MI, stent thrombosis, revascularization, or mortality). The outcomes are defined in Tables IV through IX in the Data Supplement.

Statistical Analysis

We performed frequentist network meta-analysis using a random-effects model. Outcomes were reported as risk ratios (RRs) and absolute risk differences (ARDs) with 95% CIs, which were derived from an analysis with adjusted models by person-years to account for potential differences in follow-up durations across trials. The *P* score metric was used to compare the hierarchy of effectiveness and safety of the treatments. The *P* score was derived from the point estimates and corresponding standard errors. The *P* scores measure the extent of certainty that an intervention is better than the others, averaged over all competing interventions. *P*-score values vary between 0% and 100%, that is, the higher the value, the higher the likelihood that a therapy is in the top rank or highly effective. The consistency between direct and indirect sources of evidence was examined by the node-splitting method (Table XVII in the Data Supplement), and heterogeneity was interpreted by the τ^2 and I^2 statistic (values of <25%, 25%–50%, and >50% representing low, moderate, and high degrees of heterogeneity; Table XVIII in the Data Supplement).

Subgroup analyses were performed in patients who had ACS. Sensitivity analyses were conducted in patients who received newer-generation stents (recipients of DES other than first-generation stents that used paclitaxel and sirolimus), patients with high risk for combined bleeding and recurrent MACE, exclusion of data reported in abstracts (because of the lack of confirmation in a subsequent publication), trials with high risk of bias, type of P2Y12 inhibitor, stratification of short-term DAPT versus 12-month DAPT, and pairwise meta-analyses using the DerSimonian and Laird random-effects model reporting direct estimates (Tables XIX through XXI in the Data Supplement). Small-study bias was evaluated at the outcome level by using the Egger regression test, which was adequately powered for detecting bias given ≥10 trials for each end point (Table XXII in the Data Supplemental).

Additional details of statistical analyses are reported in the Data Supplement. Ninety-five percent confidence intervals that do not cross 1 were considered statistically significant. All analyses were performed using R Project for Statistical Computing using the *netmeta and meta* packages.



Comparison	No. of Trials (Patients)
Extended-term vs 12-month	5 (20,351)
Mid-term [Aspirin] vs 12-month	8 (15,020)
Mid-term [Aspirin] vs Extended term	3 (7,099)
Short-term [Aspirin] vs 12-month	4 (7,514)
Short-term [P2Y12 inhibitor] vs 12-month	4 (29,089)

Figure 1. Network of DAPT interventions.
The area of the circles is based on the total number of patients for each treatment among all trials. The thickness of the lines is based on the total number of studies comparing the 2 treatments. DAPT indicates dual antiplatelet therapy.

RESULTS

Study Search and Study Characteristic

Of 11 805 articles, 6203 were screened after duplicates were removed; 6091 articles were excluded at the title and abstract level, and an additional 88 full-text articles were removed based on a priori selection criteria. Twenty-four trials encompassing 79 073 patients (112 387 patient-years of follow-up) were ultimately included in the network meta-analysis (Figure I in the Data Supplemental). For direct comparisons, 5 trials[15–19] compared extended-term DAPT with 12-month DAPT, 3 trials[20–22] compared midterm DAPT followed by aspirin monotherapy with extended-term DAPT, 8 trials[23–30] compared midterm DAPT followed by aspirin monotherapy with 12-month DAPT, 4 trials[31–34] compared short-term DAPT followed by aspirin monotherapy with 12-month DAPT, and 4 trials[5–8] compared short-term DAPT followed by P2Y12 inhibitor monotherapy with 12-month DAPT. Among these 24 trials, 14 trials

reported outcomes in patients with ACS. The median follow-up duration across all trials was 18 months (interquartile range, 12–24). The baseline characteristics of trials and participants are reported in the Table and Tables X through XIII in the Data Supplement.

Risk of Bias and Publication Bias

Of 24 included trials, 95% had low risk of bias for sequence generation and 75% had low risk of bias for allocation concealment; 33% had high risk of bias for blinding and 21% had high risk of detection bias. Small-study bias was evident for repeat revascularization (Egger test, $P<0.001$; Table XXII in the Data Supplemental).

Primary Outcomes

Myocardial Infarction

In comparison with 12-month DAPT, extended-term DAPT was associated with a reduced risk of MI (ARD, –3.8 incident cases per 1000 person-years; RR, 0.68 [0.54–0.87]), whereas, midterm DAPT (ARD, 1.2 incident cases per 1000 person-years; RR, 1.11 [0.86–1.45]), short-term DAPT followed by aspirin monotherapy (ARD, 2.2 incident cases per 1000 person-years; RR, 1.24 [0.89–1.72]) or P2Y12 inhibitor monotherapy (ARD, –0.3 incident cases per 1000 person-years; RR, 0.97 [0.78–1.22]) showed no significant differences (Figure 2). In comparison with extended-term DAPT, 12-month DAPT, midterm DAPT, and short-term DAPT followed by aspirin monotherapy or P2Y12 inhibitor monotherapy were associated with significantly higher risk of MI (Table XIX in the Data Supplement).

Major Bleeding

In comparison with 12-month DAPT, extended-term DAPT was associated with a higher risk of major bleeding (ARD, 4.9 incident cases per 1000 person-years; RR, 1.63 [1.15–2.30]), and short-term DAPT followed by P2Y12 inhibitor monotherapy was associated with a lower risk of major bleeding (ARD, –3.7 incident cases per 1000 person-years; RR, 0.69 [0.50–0.96]; Figure 2). Both midterm DAPT and short-term DAPT followed by aspirin monotherapy showed no significant differences versus 12-month DAPT. In comparison with extended-term DAPT, 12-month DAPT, midterm DAPT, and short-term DAPT followed by aspirin or P2Y12 inhibitor monotherapy were associated with a reduced risk of major bleeding (Table XIX in the Data Supplement).

Net Clinical Benefit

Figure 3 illustrates the risk of major bleeding versus MI of different DAPT strategies in comparison with 12-month DAPT. The net clinical benefit favored short-term DAPT followed by P2Y12 inhibitor monotherapy for comparable effectiveness (MI) with better safety (fewer major bleeding events) in the entire cohort. In patients with ACS, the net benefit favored extended-term DAPT, given reduced risk of MI and nonsignificant risk of major bleeding in comparson with 12-month DAPT.

Secondary Outcomes

MACE and Definite or Probable Stent Thrombosis

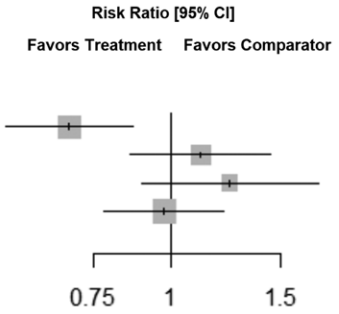
Compared with 12-month DAPT, extended-term DAPT was associated with a reduced risk of MACE (ARD, –1.8 incident cases per 1000 person-years; RR, 0.83 [0.70–1.00]), whereas, midterm DAPT, short-term DAPT followed by aspirin monotherapy, and P2Y12 inhibitor

Table. Baseline Characteristics of Trials and Participants

Characteristics	Extended-Term Versus 12-Month	Midterm [Aspirin] Versus 12-Month	Midterm [Aspirin] Versus Extended-Term	Short-Term [Aspirin] Versus 12-Month	Short-Term [P2Y12 Inhibitor] Versus 12-Month
No. of trials (patients)	5 (20351)	8 (15020)	3 (7099)	4 (7514)	4 (29089)
Age, y, mean (SD)	62.8 (1.13)	62.7 (2.63)	65.4 (2.7)	62.7 (2.8)	65.6 (1.9)
Women, %	23.1	27.5	23.1	43.1	23.9
Type of P2Y12 inhibitor, %					
Clopidogrel	90.9	84.3	99.3	80.3	46.3
Ticagrelor	14.2	9.9	0.1	16.0	72.6
Prasugrel	10.9	9.4	0.6	3.3	14.2
Oral anticoagulant	0.0	0.0	1.6	0.7	0.0
Drug-eluting stent, %					
Sirolimus-eluting stent	32.6	9.9	0.0	14.3	0.0
Paclitaxel-eluting stent	21.7	0.4	8.3	0.0	0.2
Everolimus-eluting stent	36.1	39.7	41.6	43.3	74.5
Zotarolimus-eluting stent	14.9	29.1	8.3	85.0	0.25
Biolimus-eluting stent	0.0	26.7	50.0	0.0	42.4

Myocardial infarction

Treatment	Comparator	Absolute RD [95% CI]	RR [95% CI]
Extended-term	vs 12-month	-3.8 [-6.1, -1.4]	0.68 [0.54, 0.87]
Mid-term [Aspirin]		1.2 [-1.5, 3.7]	1.11 [0.86, 1.45]
Short-term [Aspirin]		2.2 [-1.1, 5.4]	1.24 [0.89, 1.72]
Short-term [P2Y12 Inhibitor]		-0.3 [-2.5, 2.0]	0.97 [0.78, 1.22]



Major bleeding

Treatment	Comparator	Absolute RD [95% CI]	RR [95% CI]
Extended-term	vs 12-month	4.9 [1.4, 8.3]	1.63 [1.15, 2.30]
Mid-term [Aspirin]		-1.6 [-5.7, 2.5]	0.85 [0.56, 1.28]
Short-term [Aspirin]		-4.1 [-8.5, 0.4]	0.67 [0.43, 1.04]
Short-term [P2Y12 Inhibitor]		-3.7 [-7.0, -0.4]	0.69 [0.50, 0.96]

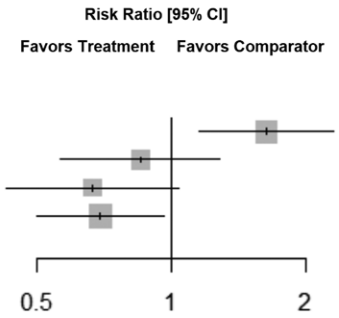


Figure 2. Network meta-analyses for myocardial infarction and major bleeding.
Midterm [aspirin] represents discontinuation of DAPT at midterm followed by continuation of aspirin. Short-term [aspirin] represents discontinuation of DAPT at short term followed by continuation of aspirin. Short-term [P2Y12 inhibitor] represents discontinuation of DAPT at short term followed by continuation of P2Y12 inhibitor. Absolute risk differences are reported as incident cases per 1000 person-years. DAPT indicates dual antiplatelet therapy; RD, risk difference; and RR, risk ratio.

monotherapy showed no significant differences (Figure 4). In comparison with extended-term DAPT, midterm DAPT, and short-term DAPT followed by aspirin or P2Y12 inhibitor monotherapy were not associated with higher risk of MACE (Table XIX in the Data Supplement). In terms of definite or probable stent thrombosis, in comparison with 12-month DAPT, extended-term DAPT reduced the risk of definite or probable stent thrombosis (ARD, –5.9 incident cases per 1000 person-years; RR, 0.55 [0.35–0.87]); whereas, midterm or short-term DAPT followed by aspirin or P2Y12 inhibitor monotherapy showed no significant differences (Figure 4). In comparison with extended-term DAPT, 12-month DAPT, midterm DAPT, and short-term DAPT followed by aspirin were associated with higher risks of definite or probable stent thrombosis. However, this effect was not observed with the use of short-term DAPT followed by P2Y12 inhibitor monotherapy.

Cardiovascular or All-Cause Mortality

Cardiovascular and all-cause mortality were similar in extended-term DAPT, 12-month DAPT, midterm DAPT, or short-term DAPT followed by aspirin or P2Y12 inhibitor monotherapy (Figure 4).

Cerebrovascular Accident and Repeat Revascularization

Cerebrovascular events (Figure 4) or repeat revascularization (Figure II in the Data Supplement) were similar in extended-term DAPT, 12-month DAPT, midterm DAPT, or short-term DAPT followed by aspirin therapy or P2Y12 inhibitor monotherapy.

Net Adverse Clinical Events

In comparison with 12-month DAPT, extended-term DAPT, midterm DAPT, and short-term DAPT followed by aspirin monotherapy showed no significant differences (Figure 4). Conversely, short-term DAPT followed by P2Y12 inhibitor monotherapy had a lower risk of NACE than 12-month DAPT (ARD, –3.1 incident cases per 1000 person-years; RR, 0.74 [0.57–0.96]).

Outcomes in Patients With ACS

In comparison with 12-month DAPT, extended-term DAPT was associated with a reduced risk of MI (ARD, –8.7 incident cases per 1000 person-years; RR, 0.42 [0.27–0.65]), whereas, midterm to short-term DAPT followed by aspirin monotherapy or short-term DAPT followed by P2Y12 inhibitor monotherapy showed no significant differences (Figure III and Table XX in the Data Supplement). For major bleeding, in comparison with 12-month DAPT, extended-term DAPT, midterm DAPT, and short-term DAPT followed by aspirin monotherapy showed no significant differences. However, short-term DAPT followed by P2Y12 inhibitor monotherapy versus 12-month DAPT was associated with a lower risk of major bleeding (ARD, –4.4 incident cases per 1000 person-years; RR, 0.64 [0.46–0.90]). There were no significant

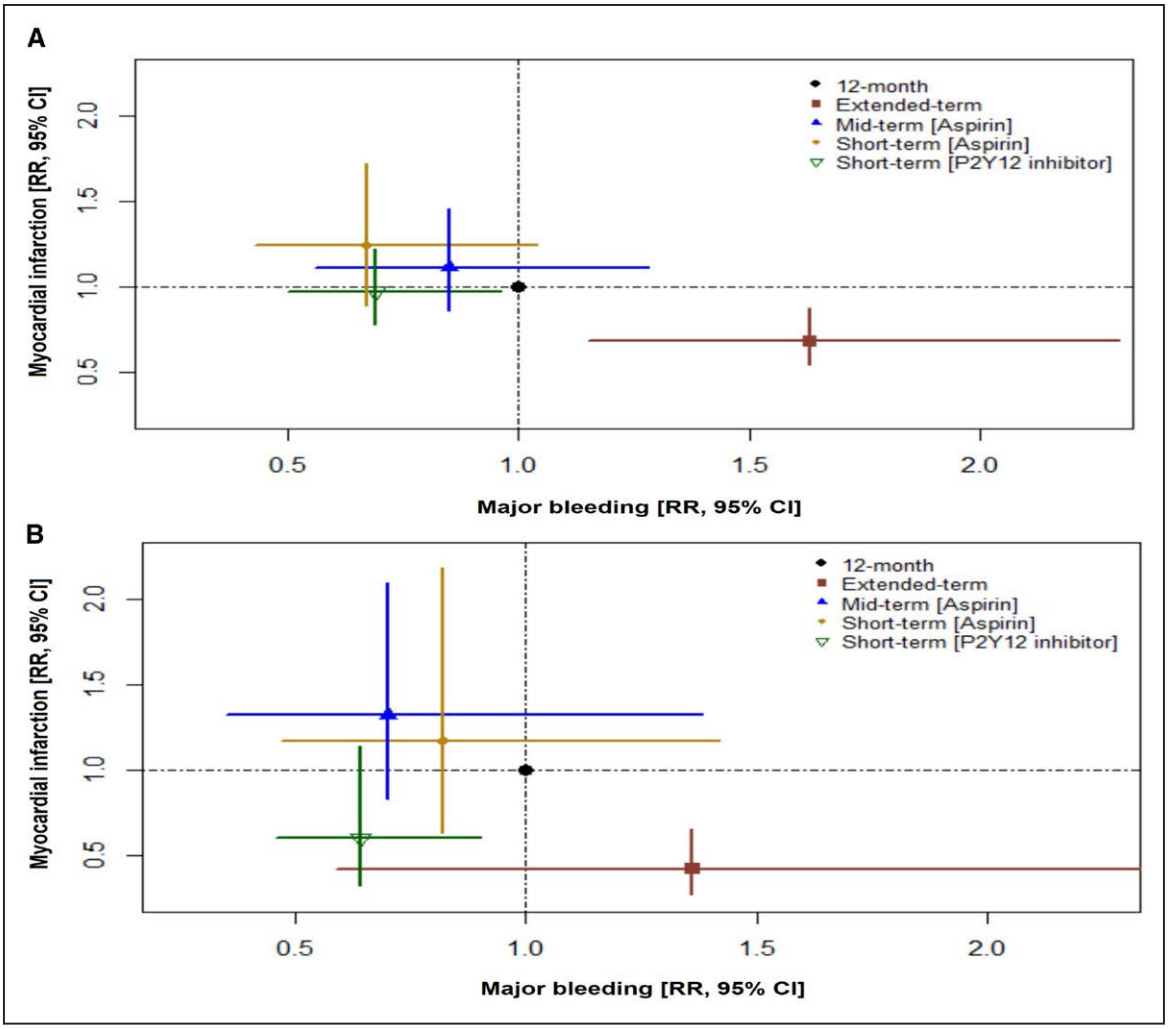


Figure 3. Net clinical benefit.
Risk ratios of different DAPT strategies in comparison with 12-month DAPT (reference) and associated 95% confidence intervals are plotted. Major bleeding is on the *x* axis and myocardial infarction is on the *y* axis. **A** and **B** represent comparison in total cohort and acute coronary syndrome cohort, respectively. DAPT indicates dual antiplatelet therapy; and RR, risk ratio.

differences with respect to cardiovascular or all-cause mortality between the different DAPT strategies.

Ranking of Treatment Strategies

Extended-term DAPT was ranked the best strategy for reducing MI (*P* score, 0.98; Figure 5), MACE (*P* score, 0.90), and definite or probable stent thrombosis (*P* score, 0.98), but least effective for limiting major bleeding (*P* score, 0.01). Short-term DAPT followed by aspirin (*P* score, 0.82), and P2Y12 inhibitor monotherapy (*P* score, 0.80) were ranked the best strategies for reducing major bleeding. Short-term DAPT followed by P2Y12 inhibitor monotherapy was ranked the best strategy for reducing NACE (*P* score, 0.97), and second best for reducing MI (*P* score, 0.54) and MACE (*P* score, 0.80). Rankograms for the remaining outcomes are reported in Figure IV in the Data Supplement. Sensitivity analysis showed that, in the short-term DAPT followed by P2Y12 inhibitor group, clopidogrel was ranked the best strategy for limiting major bleeding (*P* score, 0.87) and NACE (*P* score, 0.88), whereas ticagrelor was ranked best strategy for reducing MI (*P* score, 0.68) and MACE (*P* score, 0.73). In patients with ACS, extended-term DAPT was the best strategy for reducing MI (*P* score, 0.91), whereas short-term DAPT followed by P2Y12 inhibitor monotherapy was ranked the best strategy for limiting major bleeding (*P* score, 0.82; Table XXIII in the Data Supplemental).

Sensitivity Analyses

Sensitivity analyses did not affect the estimates in terms of MI or major bleeding with short-term DAPT followed by P2Y12 inhibitor monotherapy in comparison with 12-month DAPT (Table XXI in the Data Supplement). One-month DAPT followed by P2Y12 inhibitor monotherapy was associated with a lower risk of any bleeding events than 12-month DAPT (RR, 0.28 [0.12–0.67]), or 3-month DAPT followed by aspirin monotherapy

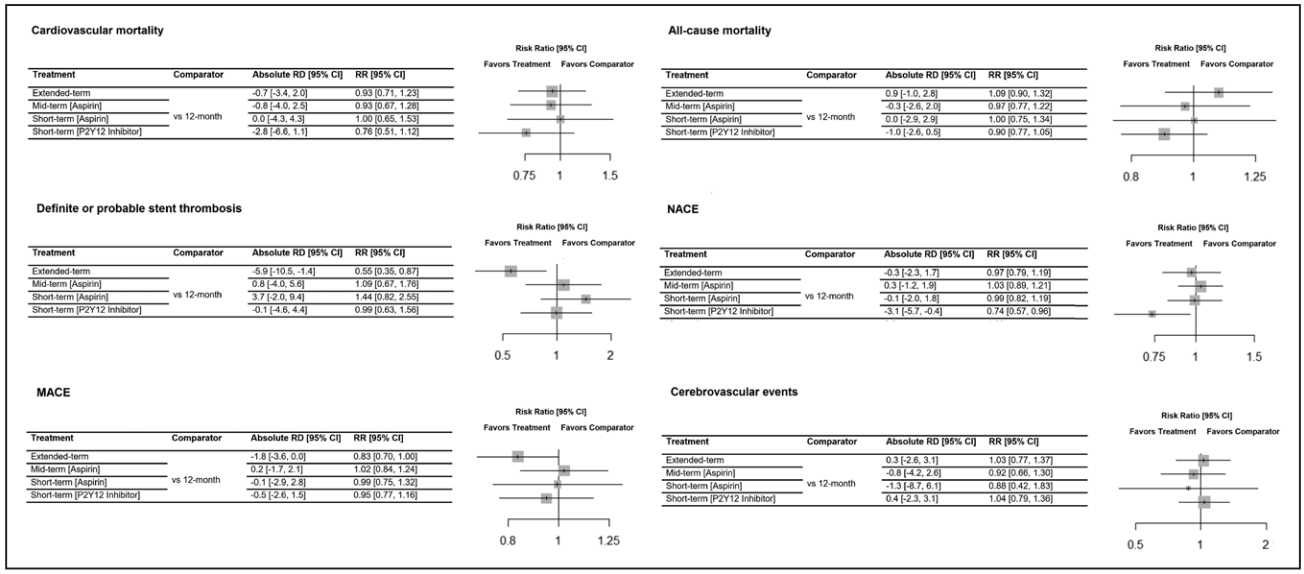


Figure 4. Network meta-analyses for secondary end points.
Midterm [aspirin] represents discontinuation of DAPT at midterm followed by continuation of aspirin. Short-term [aspirin] represents discontinuation of DAPT at short term followed by continuation of aspirin. Short-term [P2Y12 inhibitor] represents discontinuation of DAPT at short term followed by continuation of P2Y12 inhibitor. Absolute risk differences are reported as incident cases per 1000 person-years. DAPT indicates dual antiplatelet therapy; MACE, major adverse cardiovascular events; NACE, net adverse clinical events; RD, risk difference; and RR, risk ratio.

(RR, 0.37 [0.14–0.95]). Three-month DAPT followed by P2Y12 inhibitor monotherapy was also associated with a lower risk of any bleeding events than 12-month DAPT (RR, 0.57 [0.47–0.69]). However, this effect was not consistent between 3-month DAPT followed by aspirin monotherapy versus 12-month DAPT. For ischemic end points, there were no significant differences between 1 and 3 months of DAPT followed by P2Y12 inhibitor monotherapy, 3-month DAPT followed by aspirin monotherapy, and 12-month DAPT. Extended-term DAPT remained superior in terms of MI in comparison with 12-month DAPT in all sensitivity analyses, with the exception of patients with high risk for bleeding and recurrent MACE.

Network Consistency and Heterogeneity

For the total population, heterogeneity was low for most of the primary and secondary outcomes (I^2 ≤25%). In patients with ACS, heterogeneity varied from low to moderate (0%–40%). Network analyses showed consistency between direct and indirect evidence for all outcomes except all-cause mortality (P=0.02).

DISCUSSION

The principal results of the present network meta-analysis of 24 trials with 79 073 patients and 112 387 patient-years of follow-up are that among patients who underwent PCI with DES, short-term DAPT followed by P2Y12 inhibitor monotherapy was noninferior for MI, MACE, and mortality, and superior for major bleeding and NACE, in comparison with 12-month DAPT. In the short-term DAPT followed by P2Y12 inhibitor monotherapy group, ticagrelor influenced the ischemic end points, whereas the reduction in bleeding was predominantly driven by clopidogrel. Both midterm and short-term DAPT followed by aspirin monotherapy had similar safety and effectiveness in comparison with 12-month DAPT, and better safety than extended-term DAPT; however, these strategies had a higher risk of MI and stent thrombosis than extended-term DAPT. Extended-term DAPT reduced ischemic end points but at the cost of more frequent major bleeding events, with the exception of the ACS subgroup. None of the DAPT durations and strategies were associated with differences in either cardiovascular or all-cause mortality. These findings were consistent across various sensitivity analyses.

Sensitivity analysis favored 1 to 3 months of DAPT followed by P2Y12 inhibitor monotherapy for reducing bleeding and having comparable cardiovascular outcomes in comparison with 12 months of DAPT. Deescalation of DAPT to P2Y12 inhibitor monotherapy within 1 to 3 months after PCI with DES is a relatively new approach that has been tested in 4 recent trials.[5–8] The STOPDAPT-2 trial (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent) and SMART-CHOICE trial (Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy versus Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents) tested a noninferiority hypothesis of deescalation of short-term DAPT (aspirin plus clopidogrel for 1 month and 3 months, respectively) to clopidogrel monotherapy in comparison with 12-month

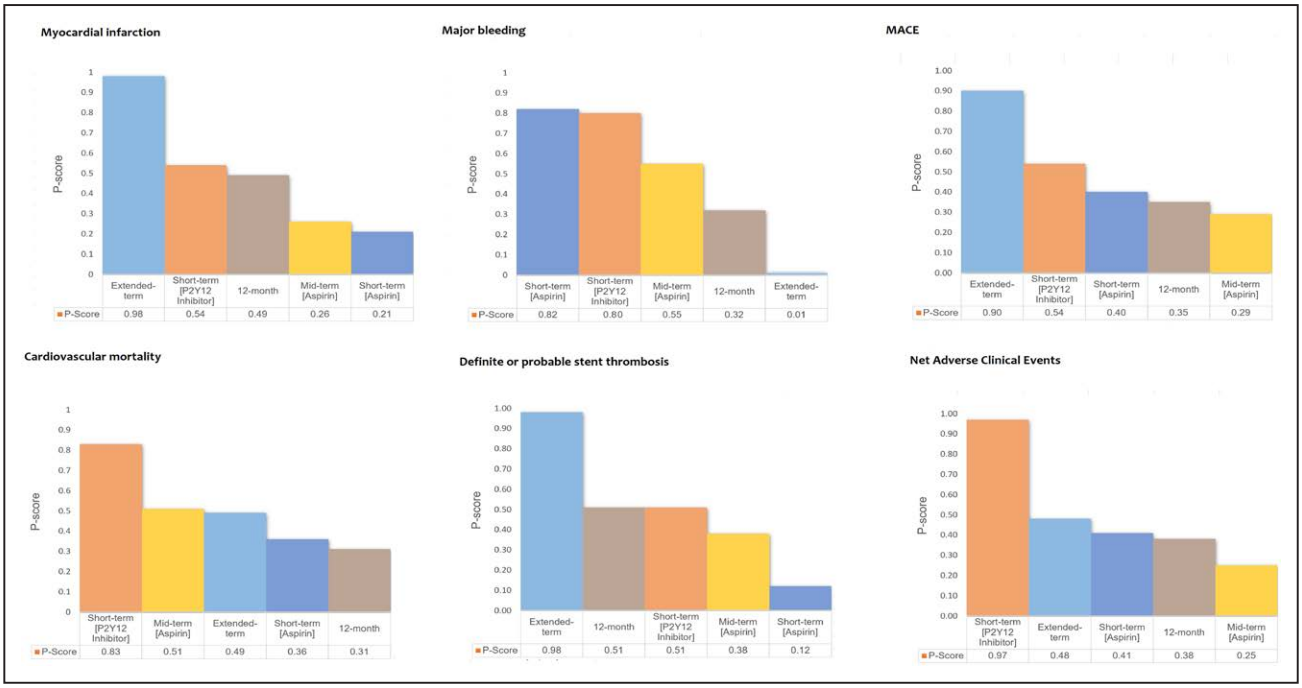


Figure 5. Rankograms for clinical outcomes.
Mid-term [aspirin] represents discontinuation of dual antiplatelet therapy at midterm followed by continuation of aspirin. Short-term [aspirin] represents discontinuation of dual antiplatelet therapy at short term followed by continuation of aspirin. Short-term [P2Y12 inhibitor] represents discontinuation of dual antiplatelet therapy at short term followed by continuation of P2Y12 inhibitor. MACE indicates major adverse cardiovascular events; and NACE, net adverse clinical events.

DAPT for major ischemic end points.[5,7] GLOBAL LEADERS (open label, randomized, controlled, multicentered superiority trial exploring 2 treatment strategies of short-term DAPT [1-month] followed by ticagrelor monotherapy versus standard DAPT [12-month] followed by aspirin monotherapy in patients undergoing PCI with DES) tested a superiority hypothesis of deescalation of short-term DAPT (aspirin plus ticagrelor for 1 month followed by ticagrelor monotherapy) for ischemic end points.[6] TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) tested a superiority hypothesis of deescalation of short-term DAPT (aspirin plus ticagrelor for 3 months followed by ticagrelor monotherapy) for major bleeding events.[8] The STOPDAPT-2, SMART-CHOICE, and TWILIGHT trials all demonstrated significant reductions in bleeding, with similar rates of ischemic end points with short-term DAPT followed by P2Y12 inhibitor monotherapy.[5,6,8] Conversely, GLOBAL LEADERS failed to demonstrate the superiority of the short-term DAPT strategy in comparison with 12-month DAPT duration.[6] Possible explanations for this discordance include differences in follow-up duration after randomization (2 years in GLOBAL LEADERS versus 1 year in the others), lack of adjudication of clinical events in GLOBAL LEADERS, and nonadherence to ticagrelor monotherapy in ≈20% of patients in GLOBAL LEADERS in the short-term DAPT arm.[6] Later, the centrally adjudicated data were reported in GLASSY (GLOBAL LEADERS Adjudication Sub-Study) which showed that 1-month DAPT was noninferior to 12-month DAPT at preventing the composite end point of all-cause death, MI, stroke, or urgent target vessel revascularization.[35]

Our results showed that 1-month DAPT followed by P2Y12 monotherapy was superior to 3-month DAPT followed by aspirin monotherapy in limiting the bleeding risk. Previous data have favored P2Y12 inhibitor monotherapy over aspirin for its superior safety and efficacy profile.[36] In the CAPRIE trial (Clopidogrel versus Aspirin in Patients at risk of Ischemic Events), clopidogrel reduced MACE and hospitalization for gastrointestinal bleeding in comparison with 325 mg aspirin in patients with history of cardiovascular disease.[36,37] With the advancement in stent technology and improved pharmacological therapies, early deescalation of DAPT to P2Y12 inhibitor monotherapy might be an optimal strategy after PCI with DES in selected patients, especially those at higher bleeding risk but lower ischemic risk.

Our results extend the findings from previous meta-analyses.[1,13,38] A recent network meta-analysis by Yin et al[38] showed a similar risk of ischemic events between short-term (≤6-month) and 12-month DAPT, with a higher risk of bleeding events in the 12-month DAPT group. In the ACS subgroup in that meta-analysis,[38] short-term DAPT showed similar effectiveness and safety versus 12-month DAPT, whereas extended-term (>12-month) DAPT was associated with increased mortality in comparison with short-term DAPT in newer-generation stents. That meta-analysis varied from the

current meta-analysis based on the stratification of DAPT into different groups and fewer trials (17 trials). Another meta-analysis by Navarese and colleagues[1] showed a similar risk of ischemic events with a lower risk of bleeding complications with shorter DAPT duration in comparison with 12 months of DAPT; however, the definition of short-term (<12-month) DAPT was different than in our study. A more recent aggregate level meta-analysis of 6 trials was in keeping with our report, demonstrating better ischemic profile with >1-year DAPT at the price of higher bleeding events.[13]

The strength of the current network meta-analysis is the incorporation of the most recent clinical trials. These findings can be reassuring for physicians, considering that short DAPT duration followed by P2Y12 inhibitor monotherapy appeared to be safe with no excess risk of ischemia for carefully selected patients without ACS. Preliminary data have also signaled adequate antiplatelet efficacy with the use of a lower dose of ticagrelor 1 month after acute MI.[39] However, in the absence of clinical data, cautious interpretation is still required before applying this dose of ticagrelor to high-risk patients, including those with ACS and complex chronic coronary syndrome (eg, left main disease or multiple stents).[40] A multidimensional approach encompassing aggressive risk factor management, use of potent P2Y12 inhibitors, contemporary stents, and optimal procedural techniques might further enable the benefits of short-term DAPT to be realized while ensuring low adverse ischemic complications.[8] The current study also provided evidence favoring extended-term therapy for ischemic events, which may be appropriate for certain patients who are at a higher risk of cardiovascular events after PCI and low risk of bleeding, such as those presenting with ACS or with diabetes mellitus or at high ischemic risk in whom several trials support the concept of extended-duration dual antithrombotic therapy.[41–48] Nonetheless, we advocate a personalized approach considering each patient's relative and absolute risks of ischemia and bleeding when deciding on the optimal duration of DAPT after PCI.[49]

Limitations

The present study has several limitations. This network meta-analysis generated evidence from study-level data only. Only 8 of the 24 trials were designed to test the superiority of different DAPT strategies; the remainder were powered for noninferiority. Time of randomization varied substantially across the trials. Many trials did not randomly assign patients at the time of DAPT versus single-agent allocation, with randomization occurring either months before or at the time of PCI, thereby including the period when all patients were on DAPT.[13] This may bias the results toward the null. In general, lower rates of ischemic events were observed than anticipated in most of the trials, resulting in limited statistical power for ischemic and mortality outcomes. Moreover, the baseline health status, indications for PCI, definitions of clinical end points, and duration of follow-up were heterogeneous across the trials, adding imprecision. There was a paucity of data for the ACS cohort, and we had to rely on subgroup analyses, patient-level meta-analyses, or post hoc analyses to generate evidence. Therefore, all these analyses must be considered exploratory in view of limited statistical power. In conformity, given limited data, we could not perform analyses for patients with stable CAD, or some important end points such as noncardiovascular mortality or definite stent thrombosis. Noncardiovascular mortality can influence cardiovascular mortality and all-cause mortality. Certain aspects limit the generalizability of the results. In most of the trials, DAPT discontinuation was followed by aspirin monotherapy and only 4 trials were designed for continuing P2Y12 inhibitor monotherapy, and all of these compared short-term (1- or 3-month) DAPT with 12-month DAPT. Most trials used clopidogrel, whereas the overall prevalence of ticagrelor and prasugrel use was only ≈8.5% and 5.2%, respectively, although a recent meta-analysis suggested that only ticagrelor reduced mortality in ACS.[50] The proportion of women varied from as low as 17.1% to 37.1%. Few studies included patients with first-generation DES, in which any benefits of extended-term DAPT might be greater than with present-generation DES. Patients with ACS enrolled in most trials were at low risk. Last, network meta-analysis in part uses indirect evidence between multiple treatments, allowing comparisons to be made when direct trial evidence is limited. This approach respects randomization but does not represent randomized evidence.

Conclusions

Among patients undergoing PCI with DES, extended-term DAPT was effective in reducing MI at the expense of more major bleeding events. Short-term DAPT followed by P2Y12 inhibitor monotherapy was associated with reduced bleeding rates and was noninferior for ischemic outcomes compared with 12-month but not extended-term DAPT. In comparison with 12-month DAPT, the net clinical benefit appears to favor short-term DAPT followed by P2Y12 inhibitor monotherapy in patients similar to the ones included in these trials. However, extended-term DAPT in patients with ACS or at a higher risk of recurrent ischemic MACE is still warranted in patients selected to be at low bleeding risk.

ARTICLE INFORMATION

Received February 12, 2020; accepted July 17, 2020.

ORIGINAL RESEARCH ARTICLE

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.120.046308.

Correspondence

Deepak L. Bhatt, MD, MPH, Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, 75 Francis St, Boston, MA 02115. Email DLBhattMD@post.Harvard.edu

Affiliations

Department of Medicine, West Virginia University, Morgantown (S.U.K., S.V., M.U.K., A.N.L., M.Z.K.). Department of Cardiovascular Medicine, Guthrie Health System/Robert Packer Hospital, Sayre, PA (M.S.). Department of Medicine, John H. Stroger Jr. Hospital of Cook County, Chicago, IL (M.S.K.). Department of Cardiovascular Medicine, Heart, Vascular, and Thoracic Institute, Cleveland Clinic, OH (P.M., S.R.K., A.K.). Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins School of Medicine, Baltimore, MD (E.D.M.). The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, NY, and the Cardiovascular Research Foundation (G.W.S.). Section of Cardiovascular Research, Heart, Vascular, and Thoracic Department, Cleveland Clinic Akron General, OH (A.K.). Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, Boston, MA (D.L.B.).

Acknowledgments

Conception and design: Drs S.U. Khan, Kalra, and Bhatt. Analysis and interpretation of the data: Drs S.U. Khan, Valavoor, and M.U. Khan. Drafting of the article: Drs S.U. Khan, Singh, Mani, Kapadia, Michos, Stone,. Kalra, and Bhatt. Critical revision of the article for important intellectual content: Drs S.U. Khan, Singh, M.S. Khan, Mani, Kapadia, Michos, Stone, Kalra, and Bhatt. Final approval of the article: Drs S.U. Khan, Valavoor, M.U. Khan, Lone, M.Z. Khan, M.S. Khan, Mani, Kapadia, Michos, Stone, Kalra, and Bhatt. Provision of study materials or patients: Drs S.U. Khan, M.U. Khan, Valavoor, and Lone. Statistical expertise: Drs S.U. Khan, Valavoor, and M.Z.Khan. Collection and assembly of data: Drs S.U. Khan, M.U. Khan, Valavoor, and Lone. Dr Khan is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Sources of Funding

None.

Disclosures

Dr Bhatt discloses the following relationships: Advisory Board: Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Level Ex, Medscape Cardiology, PhaseBio, PLx Pharma, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial [Portopulmonary Hypertension Treatment With Macitantan: a Randomized Clinical Trial], funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial [CENTERA THV System in Intermediate Risk Patients Who Have Symptomatic, Severe, Calcific, Aortic Stenosis Requiring Aortic Valve Replacement], funded by Edwards), Contego Medical (Chair, PERFORMANCE 2 [Protection Against Emboli During Carotid Artery Stenting Using the Neuroguard IEP System]), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial [Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation], funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; REDUAL PCI clinical trial (Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting) steering committee funded by Boehringer Ingelheim; AEGIS-II (Study to Investigate CSL112 in Subjects With Acute Coronary Syndrome) executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial [A Trial Comparing Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Advanced Prostate Cancer and Cardiovascular Disease], funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (continuing medical education steering committees), MJH Life Sciences, Population Health Research Institute (for the COMPASS [Cardiovascular Outcomes for People Using Anticoagulation Strategies] operations committee, publications committee, steering committee, and USA national coleader, funded by Bayer), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (continuing medical education steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); Site Co-Investigator: Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, Takeda. Dr Stone discloses the following relationships: speaker or other honoraria from Cook, Terumo, QOOL Therapeutics and Orchestra Biomed; has served as a consultant to Valfix, TherOx, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, Matrizyme; and has equity/options from Ancora, Qool Therapeutics, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, MedFocus family of funds, Valfix. Dr Singh discloses the following relationships: Minor-Reimbursement from C3 Interventional Academy, Abiomed and Siemens for attending a conference and workshop. The other authors report no conflicts.

Supplemental Material

Expanded Methods
Data Supplement Tables I–XXIII
Data Supplement Figures I–IV

REFERENCES

1. Navarese EP, Andreotti F, Schulze V, Kołodziejczak M, Buffon A, Brouwer M, Costa F, Kowalewski M, Parati G, Lip GY, et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials. *BMJ.* 2015;350:h1618. doi: 10.1136/bmj.h1618
2. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation.* 2016;134:e123–e155. doi: 10.1161/CIR.0000000000000404
3. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, 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;39:213–260. doi: 10.1093/eurheartj/ehx419
4. Udell JA, Bonaca MP, Collet JP, Lincoff AM, Kereiakes DJ, Costa F, Lee CW, Mauri L, Valgimigli M, Park SJ, et al DL. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. *Eur Heart J.* 2016;37:390–399. doi: 10.1093/eurheartj/ehv443

5. Hahn JY, Song YB, Oh JH, Chun WJ, Park YH, Jang WJ, Im ES, Jeong JO, Cho BR, Oh SK, et al; SMART-CHOICE Investigators. 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
6. Vranckx P, Valgimigli M, Jüni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C, et al; GLOBAL LEADERS Investigators. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet.* 2018;392:940–949. doi: 10.1016/S0140-6736(18)31858-0
7. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, Ohya M, Suwa S, Takagi K, Nanasato M, et al; STOPDAPT-2 Investigators. 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
8. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, Cha JY, Collier T, Dangas G, Dudek D, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med.* 2019;381:2032–2042. doi: 10.1056/NEJMoa1908419
9. Rao G, Lopez-Jimenez F, Boyd J, D'Amico F, Durant NH, Hlatky MA, Howard G, Kirley K, Masi C, Powell-Wiley TM, et al; American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; and Stroke Council. Methodological standards for meta-analyses and qualitative systematic reviews of cardiac prevention and treatment studies: a scientific statement from the American Heart Association. *Circulation.* 2017;136:e172–e194. doi: 10.1161/CIR.0000000000000523
10. van Tulder M, Furlan A, Bombardier C, Bouter L; Editorial Board of the Cochrane Collaboration Back Review Group. Updated method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group. *Spine (Phila Pa 1976).* 2003;28:1290–1299. doi: 10.1097/01.BRS.0000065484.95996.AF
11. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med.* 2015;162:777–784. doi: 10.7326/M14-2385
12. Jang JY, Shin DH, Kim JS, Hong SJ, Ahn CM, Kim BK, Ko YG, Choi D, Hong MK, Park KW, et al. Optimal duration of DAPT after second-generation drug-eluting stent in acute coronary syndrome. *PLoS One.* 2018;13:e0207386. doi: 10.1371/journal.pone.0207386
13. Palmerini T, Bruno AG, Gilard M, Morice MC, Valgimigli M, Montalescot G, Collet JP, Della Riva D, Bacchi-Reggiani ML, Steg PG, et al. Risk-benefit profile of longer-than-1-year dual-antiplatelet therapy duration after drug-eluting stent implantation in relation to clinical presentation. *Circ Cardiovasc Interv.* 2019;12:e007541. doi: 10.1161/CIRCINTERVENTIONS.118.007541
14. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation.* 2011;123:2736–2747. doi: 10.1161/CIRCULATIONAHA.110.009449
15. Park SJ, Park DW, Kim YH, Kang SJ, Lee SW, Lee CW, Han KH, Park SW, Yun SC, Lee SG, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. *N Engl J Med.* 2010;362:1374–1382. doi: 10.1056/NEJMoa1001266
16. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, et al; DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med.* 2014;371:2155–2166. doi: 10.1056/NEJMoa1409312
17. Lee CW, Ahn JM, Park DW, Kang SJ, Lee SW, Kim YH, Park SW, Han S, Lee SG, Seong IW, et al. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: a randomized, controlled trial. *Circulation.* 2014;129:304–312. doi: 10.1161/CIRCULATIONAHA.113.003303
18. Collet JP, Silvain J, Barthélémy O, Rangé G, Cayla G, Van Belle E, Cuisset T, Elhadad S, Schiele F, Lhoest N, et al; ARCTIC investigators. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. *Lancet.* 2014;384:1577–1585. doi: 10.1016/S0140-6736(14)60612-7
19. Helft G, Steg PG, Le Feuvre C, Georges JL, Carrie D, Dreyfus X, Furber A, Leclercq F, Eltchaninoff H, Falquier JF, et al; Optimal Dual Antiplatelet Therapy Trial Investigators. Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: the OPTIDUAL randomized trial. *Eur Heart J.* 2016;37:365–374. doi: 10.1093/eurheartj/ehv481
20. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fucà G, et al; Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) Investigators. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation.* 2012;125:2015–2026. doi: 10.1161/CIRCULATIONAHA.111.071589
21. Nakamura M, Iijima R, Ako J, Shinke T, Okada H, Ito Y, Ando K, Anzai H, Tanaka H, Ueda Y, et al; NIPPON Investigators. Dual antiplatelet therapy for 6 versus 18 months after biodegradable polymer drug-eluting stent implantation. *JACC Cardiovasc Interv.* 2017;10:1189–1198. doi: 10.1016/j.jcin.2017.04.019
22. Gilard M, Barragan P, Noryani AAL, Noor HA, Majwal T, Hovasse T, Castellant P, Schneeberger M, Maillard L, Bressolette E, et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multicenter ITALIC trial. *J Am Coll Cardiol.* 2015;65:777–786. doi: 10.1016/j.jacc.2014.11.008
23. Gwon HC, Hahn JY, Park KW, Song YB, Chae IH, Lim DS, Han KR, Choi JH, Choi SH, Kang HJ, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation.* 2012;125:505–513. doi: 10.1161/CIRCULATIONAHA.111.059022
24. Colombo A, Chieffo A, Frasheri A, Garbo R, Masotti-Centol M, Salvatella N, Oteo Dominguez JF, Steffanon L, Tarantini G, Presbitero P, et al. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. *J Am Coll Cardiol.* 2014;64:2086–2097. doi: 10.1016/j.jacc.2014.09.008
25. Schulz-Schüpke S, Byrne RA, Ten Berg JM, Neumann FJ, Han Y, Adriaenssens T, Tölg R, Seyfarth M, Maeng M, Zrenner B, et al; Intracoronary Stenting and Antithrombotic Regimen: Safety And Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) Trial Investigators. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. *Eur Heart J.* 2015;36:1252–1263. doi: 10.1093/eurheartj/ehu523
26. Hong SJ, Shin DH, Kim JS, Kim BK, Ko YG, Choi D, Her AY, Kim YH, Jang Y, Hong MK; IVUS-XPL Investigators. 6-month versus 12-month dual-antiplatelet therapy following long everolimus-eluting stent implantation: the IVUS-XPL randomized clinical trial. *JACC Cardiovasc Interv.* 2016;9:1438–1446. doi: 10.1016/j.jcin.2016.04.036
27. Han Y, Xu B, Xu K, Guan C, Jing Q, Zheng Q, Li X, Zhao X, Wang H, Zhao X, et al. Six versus 12 months of dual antiplatelet therapy after implantation of biodegradable polymer sirolimus-eluting stent: randomized substudy of the I-LOVE-IT 2 trial. *Circ Cardiovasc Interv.* 2016;9:e003145. doi: 10.1161/CIRCINTERVENTIONS.115.003145
28. Kedhi E, Fabris E, van der Ent M, Buszman P, von Birgelen C, Roolvink V, Zurakowski A, Schotborgh CE, Hoorntje JCA, Eek CH, et al. Six months versus 12 months dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction (DAPT-STEMI): randomised, multicentre, non-inferiority trial. *BMJ.* 2018;363:k3793. doi: 10.1136/bmj.k3793
29. Lee BK, Kim JS, Lee OH, Min PK, Yoon YW, Hong BK, Shin DH, Kang TS, Kim BO, Cho DK, et al. Safety of six-month dual antiplatelet therapy after second-generation drug-eluting stent implantation: OPTIMA-C randomised clinical trial and OCT Substudy. *EuroIntervention.* 2018;13:1923–1930. doi: 10.4244/EIJ-D-17-00792
30. Hahn JY, Song YB, Oh JH, Cho DK, Lee JB, Doh JH, Kim SH, Jeong JO, Bae JH, Kim BO, et al; SMART-DATE investigators. 6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. *Lancet.* 2018;391:1274–1284. doi: 10.1016/S0140-6736(18)30493-8
31. Kim BK, Hong MK, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Kang TS, Park BE, Kang WC, et al; RESET Investigators. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol.* 2012;60:1340–1348. doi: 10.1016/j.jacc.2012.06.043

32. Feres F, Costa RA, Abizaid A, Leon MB, Marin-Neto JA, Botelho RV, King SB 3rd, Negoita M, Liu M, de Paula JE, et al; OPTIMIZE Trial Investigators. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA.* 2013;310:2510–2522. doi: 10.1001/jama.2013.282183
33. De Luca G, Damen SA, Camaro C, Benit E, Verdoia M, Rasoul S, Liew HB, Polad J, Ahmad WA, Zambahari R, et al; Collaborators. Final results of the randomised evaluation of short-term dual antiplatelet therapy in patients with acute coronary syndrome treated with a new-generation stent (REDUCE trial). *EuroIntervention.* 2019;15:e990–e998. doi: 10.4244/EIJ-D-19-00539
34. Van Geuns RJ. IDEAL-LM: A Randomized Trial of a Bioabsorbable Polymer DES With 4-Month DAPT vs. a Durable Polymer DES With 12-Month DAPT in Patients With Left Main Coronary Artery Disease. Paper presented at: Transcatheter Cardiovascular Therapeutics meeting (TCT 2019); 2019; San Francisco, CA.
35. Franzone A, McFadden E, Leonardi S, Piccolo R, Vranckx P, Serruys PW, Benit E, Liebetrau C, Janssens L, Ferrario M, et al; GLASSY Investigators. Ticagrelor alone versus dual antiplatelet therapy from 1 month after drug-eluting coronary stenting. *J Am Coll Cardiol.* 2019;74:2223–2234. doi: 10.1016/j.jacc.2019.08.1038
36. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet.* 1996;348:1329–1339.
37. Bhatt DL, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Reduction in the need for hospitalization for recurrent ischemic events and bleeding with clopidogrel instead of aspirin. CAPRIE investigators. *Am Heart J.* 2000;140:67–73. doi: 10.1067/mhj.2000.108239
38. Yin SH, Xu P, Wang B, Lu Y, Wu QY, Zhou ML, Wu JR, Cai JJ, Sun X, Yuan H. 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
39. Kubica J, Adamski P, Buszko K, Barańska M, Sikora J, Marszałł MP, Sobczak P, Sikora A, Kuliczkowski W, Fabiszak T, et al. Platelet inhibition with standard vs. lower maintenance dose of ticagrelor early after myocardial infarction (ELECTRA): a randomized, open-label, active-controlled pharmacodynamic and pharmacokinetic study. *Eur Heart J Cardiovasc Pharmacother.* 2019;5:139–148. doi: 10.1093/ehjcvp/pvz004
40. Eisen A, Bhatt DL. Antiplatelet therapy: defining the optimal duration of DAPT after PCI with DES. *Nat Rev Cardiol.* 2015;12:445–446. doi: 10.1038/nrcardio.2015.87
41. Steg PG, Bhatt DL, Simon T, Fox K, Mehta SR, Harrington RA, Held C, Andersson M, Himmelmann A, Ridderstråle W, et al; THEMIS Steering Committee and Investigators. Ticagrelor in patients with stable coronary disease and diabetes. *N Engl J Med.* 2019;381:1309–1320. doi: 10.1056/NEJMoa1908077
42. Bhatt DL, Steg PG, Mehta SR, Leiter LA, Simon T, Fox K, Held C, Andersson M, Himmelmann A, Ridderstråle W, et al; THEMIS Steering Committee and Investigators. Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial. *Lancet.* 2019;394:1169–1180. doi: 10.1016/S0140-6736(19)31887-2
43. Connolly SJ, Eikelboom JW, Bosch J, Dagenais G, Dyal L, Lanas F, Metsarinne K, O'Donnell M, Dans AL, Ha JW, et al; COMPASS investigators. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet.* 2018;391:205–218. doi: 10.1016/S0140-6736(17)32458-3
44. Bhatt DL, Eikelboom JW, Connolly SJ, Steg PG, Anand SS, Verma S, Branch KRH, Probstfield J, Bosch J, Shestakovska O, et al; COMPASS Steering Committee and Investigators. Role of combination antiplatelet and anticoagulation therapy in diabetes mellitus and cardiovascular disease: insights from the COMPASS trial. *Circulation.* 2020;141:1841–1854. doi: 10.1161/CIRCULATIONAHA.120.046448
45. Bainey KR, Welsh RC, Connolly SJ, Marsden T, Bosch J, Fox KAA, Steg PG, Vinereanu D, Connolly DL, Berkowitz SD, et al; COMPASS Investigators. Rivaroxaban Plus Aspirin Versus Aspirin Alone in Patients With Prior Percutaneous Coronary Intervention (COMPASS-PCI). *Circulation.* 2020;141:1141–1151. doi: 10.1161/CIRCULATIONAHA.119.044598
46. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, et al; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med.* 2006;354:1706–1717. doi: 10.1056/NEJMoa060989
47. Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, et al; CHARISMA Investigators. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol.* 2007;49:1982–1988. doi: 10.1016/j.jacc.2007.03.025
48. Bhatt DL, Steg PG. THEMIS and THEMIS-PCI: new option for antiplatelet therapy in patients with stable atherosclerosis and diabetes: key findings from THEMIS and THEMIS-PCI. *Eur Heart J.* 2019;40:3378–3381.
49. Steg PG, Bhatt DL. Is there really a benefit to net clinical benefit in testing antithrombotics? *Circulation.* 2018;137:1429–1431. doi: 10.1161/CIRCULATIONAHA.117.033442
50. Navarese EP, Khan SU, Kołodziejczak M, Kubica J, Buccheri S, Cannon CP, Gurbel PA, De Servi S, Budaj A, Bartorelli A, et al. Comparative Efficacy and Safety of Oral P2Y12 Inhibitors in Acute Coronary Syndrome: Network Meta-Analysis of 52 816 Patients From 12 Randomized Trials. *Circulation.* 2020;142:150–160. doi: 10.1161/CIRCULATIONAHA.120.046786