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# Short-Term Dual Antiplatelet Therapy After Drug-Eluting Stenting in Patients With Acute Coronary Syndromes
## A Systematic Review and Network Meta-Analysis

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**IMPORTANCE** The optimal duration of dual antiplatelet therapy (DAPT) in patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) remains under debate.

**OBJECTIVES** To analyze the efficacy and safety of DAPT strategies in patients with ACS using a bayesian network meta-analysis.

**DATA SOURCES** MEDLINE, Embase, Cochrane, and LILACS databases were searched from inception to April 8, 2024.

**STUDY SELECTION** Randomized clinical trials (RCTs) comparing DAPT duration strategies in patients with ACS undergoing PCI were selected. Short-term strategies (1 month of DAPT followed by P2Y12 inhibitors, 3 months of DAPT followed by P2Y12 inhibitors, 3 months of DAPT followed by aspirin, and 6 months of DAPT followed by aspirin) were compared with conventional 12 months of DAPT.

**DATA EXTRACTION AND SYNTHESIS** This systematic review and network meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. The risk ratio (RR) with a 95% credible interval (CrI) was calculated within a bayesian random-effects network meta-analysis. Treatments were ranked using surface under the cumulative ranking (SUCRA).

**MAIN OUTCOMES AND MEASURES** The primary efficacy end point was major adverse cardiac and cerebrovascular events (MACCE); the primary safety end point was major bleeding.

**RESULTS** A total of 15 RCTs randomizing 35 326 patients (mean [SD] age, 63.1 [11.1] years; 26 954 male [76.3%]; 11 339 STEMI [32.1%]) with ACS were included. A total of 24 797 patients (70.2%) received potent P2Y12 inhibitors (ticagrelor or prasugrel). Compared with 12 months of DAPT, 1 month of DAPT followed by P2Y12 inhibitors reduced major bleeding (RR, 0.47; 95% CrI, 0.26-0.74) with no difference in MACCE (RR, 1.00; 95% CrI, 0.70-1.41). No significant differences were observed in MACCE incidence between strategies, although CrIs were wide. SUCRA ranked 1 month of DAPT followed by P2Y12 inhibitors as the best for reducing major bleeding and 3 months of DAPT followed by P2Y12 inhibitors as optimal for reducing MACCE (RR, 0.85; 95% CrI, 0.56-1.21).

**CONCLUSION AND RELEVANCE** Results of this systematic review and network meta-analysis reveal that, in patients with ACS undergoing PCI with DES, 1 month of DAPT followed by potent P2Y12 inhibitor monotherapy was associated with a reduction in major bleeding without increasing MACCE when compared with 12 months of DAPT. However, an increased risk of MACCE cannot be excluded, and 3 months of DAPT followed by potent P2Y12 inhibitor monotherapy was ranked as the best option to reduce MACCE. Because most patients receiving P2Y12 inhibitor monotherapy were taking ticagrelor, the safety of stopping aspirin in those taking clopidogrel remains unclear.

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Supplemental content

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Dual antiplatelet therapy (DAPT) consisting of aspirin plus a potent P2Y12 inhibitor is the current standard of care after percutaneous coronary intervention (PCI) with drug-eluting stents (DES) in patients without indication for oral anticoagulation.[1,2] DAPT reduces the risk of stent thrombosis and ischemic events, particularly early after stenting; however, DAPT is associated with an increased risk of bleeding, which is proportional to the intensity and duration of treatment.[3-6] Current guidelines advocate individual approaches to determine DAPT duration according to each patient's risk-benefit profile.[1,2,7] In patients with acute coronary syndrome (ACS), DAPT with potent P2Y12 inhibitors after PCI is recommended for at least 12 months in patients not at increased risk of bleeding.[1,2]

Recent randomized clinical trials (RCTs) have investigated short-term DAPT strategies across several patient settings. Shorter DAPT duration, achieved by either stopping the P2Y12 inhibitor or aspirin and continuing single antiplatelet therapy (SAPT) with either aspirin or P2Y12 inhibitors, respectively, may be applicable in individuals who have a reduced requirement for prolonged DAPT, such as those using newer-generation DES.[8-10] However, the optimal duration of DAPT and the agent of choice for subsequent SAPT after DES implantation are still under debate.

RCTs examining the duration of DAPT in patients with ACS undergoing PCI with DES often lack statistical power to detect differences in ischemic end points owing to the commonly applied noninferiority design. Also, prior network meta-analyses have joined diverse time frames and study designs under the same comparator, which affects transitivity between treatments, enhances inconsistency in the network, and may affect its clinical applicability in decision-making.[11-14] Therefore, we conducted an updated, comprehensive, systematic review and bayesian network meta-analysis to compare different strategies of short-term DAPT in patients with ACS.

### Key Points

**Question** What is the optimal duration of dual antiplatelet therapy (DAPT) in patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) with drug-eluting stents (DES)?

**Findings** In this systematic review and bayesian network meta-analysis including 15 randomized clinical trials and 35 326 patients, several DAPT strategies were compared for safety and efficacy in patients with ACS. Results showed that 1 month of DAPT followed by potent P2Y12 inhibitor (ticagrelor or prasugrel) monotherapy was associated with a reduction in major bleeding without increasing recurrent ischemic events; 3 months of DAPT followed by potent P2Y12 inhibitor monotherapy was ranked the best option to reduce MACCE, although statistical significance was not achieved.

**Meaning** These results may inform clinical care toward a shorter duration of DAPT after PCI in patients with ACS.

## Methods

### Study Design

This systematic review and bayesian network meta-analysis was performed and reported following the Cochrane Collaboration Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.[15,16] The prospective meta-analysis protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42023487301). PRISMA checklists are presented in eMethods 1 and 2 in Supplement 1.

### Data Source and Search Strategy

We systematically searched Cochrane Central Register of Controlled Trials (CENTRAL), PubMed/MEDLINE, Embase, and LILACS databases from inception through the final search date of April 8, 2024. We also used backward snowballing (ie, review of references and related articles sections) to identify relevant texts from articles identified in the original search. Three authors (P.C., L.M., and G.B.) performed the systematic review independently, and disagreements were resolved in a panel discussion between authors. Study selection involved screening titles and abstracts followed by a full-text evaluation of potentially eligible studies. The complete search strategy for each database is presented in eMethods 3 in Supplement 1.

### Eligibility Criteria

For inclusion, no restrictions were determined concerning the publication date, status, or language. We considered studies eligible if they (1) were RCTs, (2) enrolled patients with ACS who underwent successful PCI with DES implantation, and (3) compared different durations of short-term DAPT (<12 months). We incorporated data from published studies, and no restrictions related to race or ethnicity were applied. Only 3 studies reported these data in detail. We excluded studies that (1) did not specify a fixed DAPT duration or presented it as a wide range, (2) evaluated antithrombotic regimens in patients with atrial fibrillation undergoing PCI, (3) included patients undergoing PCI only with bare-metal stents, and (4) did not report any of the prespecified efficacy and safety end points of interest for this analysis.

### End Points

Our primary efficacy end point was major adverse cardiac and cerebrovascular events (MACCE), in most studies defined as a composite of all-cause or cardiovascular mortality, myocardial infarction, target-vessel revascularization, stent thrombosis, and stroke. Our primary safety end point was major bleeding, either Bleeding Academic Research Consortium (BARC) types 3 or 5 (applied whenever possible) or Thrombolysis in Myocardial Infarction (TIMI) major. Secondary end points included the following: all-cause mortality, myocardial infarction, stroke, target-vessel revascularization, stent thrombosis (as per-study definition in eTable 1 in Supplement 1), and any bleeding. Detailed end point definitions for each included study are provided in eTable 1 in Supplement 1.

### Quality Assessment

Quality assessment was conducted using Cochrane Risk of Bias 2 (RoB-2) tool for randomized studies. The risk of bias assessment was performed independently by 2 authors (L.M. and M.B.). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to assess the certainty of evidence in the network meta-analysis.[17] Disagreements were resolved by consensus between authors. We explored the potential for publication bias by visual inspection of the comparison-adjusted funnel plots and the Egger test.

### Statistical Analysis

A bayesian random-effects network meta-analysis model was fitted to compare multiple regimens simultaneously from November 2023 to April 2024. Inference was performed using the Markov chain Monte Carlo (MCMC) algorithm. Results are presented as risk ratios (RRs) and their respective 95% credible intervals (CrIs). We checked the convergence of MCMC for all model parameters using trace plots and Gelman-Rubin diagnostic statistics. Significance level was set at 0.05/k (k = number of comparisons) to adjust for multiple comparisons. We used the package's default setting including noninformative prior distributions with 4 parallel chains. Models were fitted with 100 000 burn-in periods and 1 000 000 iterations for inference.

We also estimated the surface under the cumulative ranking curve (SUCRA) probabilities. The SUCRA is a numerical summary that accounts for the magnitude and uncertainty of the estimated effect for each regimen. A larger SUCRA value indicates better performance for the outcome. We ranked regimens based on SUCRA for each safety and efficacy outcome.

A prespecified subgroup analysis was performed to assess the impact of the type of ACS on the primary efficacy and safety end points. Studies were grouped into 2 different ACS settings: ST-elevation myocardial infarction (STEMI), and non-ST-elevation acute coronary syndromes (NSTE-ACS). In addition, we performed a sensitivity analysis of the primary efficacy and safety end points using the following: (1) a bayesian fixed-effects model network meta-analysis, (2) a random-effects model frequentist network meta-analysis, (3) meta-regressions to analyze potential interactions with the proportion of patients using potent P2Y12 inhibitors and newer-generation DES, (4) network meta-analyses based on multivariate meta-analysis models,[18] (5) a subgroup analysis excluding the Improved Drug-Eluting Stent for All-Comers Left Main (IDEAL-LM) study, as this study based the DAPT strategy according to the stent type in the left main lesion,[19] (6) a traditional random-effects model meta-analysis to ensure the robustness of the network meta-analysis findings, and (7) a subgroup analysis including only studies with similar end point definitions. For MACCE, this subgroup analysis included any study with at least 4 of the 5 individual components of MACCE, whereas a similar definition for major bleeding was defined as BARC 3 to 5.

We used R, version 4.3.1 (R Project for Statistical Computing) and the extension packages meta, gemtc, and dmetar for all calculations and elaboration of almost all graphics. The web-application NMAstudio, version 0.1 (Cochrane Colloquium 2023) was used to create network plots.

## Results

### Study Selection and Characteristics

Our systematic search identified 6414 potential articles, of which 96 underwent full-text review (eFigure 1 in Supplement 1). Ultimately, 15 RCTs were included, totaling 35 326 patients (mean [SD] age, 63.1 [11.1] years; 8372 female [23.7%]; 26 954 male [76.3%]; 11 339 STEMI [32.1%]) .[19-35] Study design, population, antiplatelet regimens, main results, and other characteristics are available in **Table 1** and eTables 2, 3, and 4 in Supplement 1. Most patients (34 690 [98.2%]) received newer-generation DES (types of stents detailed in eTable 2 in Supplement 1). The duration of follow-up ranged from 12 to 24 months in all studies included.

### Structure of the Network Meta-Analysis

**Figure 1** depicts the network of 5 short-term DAPT regimens used in each end point analysis, including 1 month of DAPT followed by P2Y12 inhibitors, 3 months of DAPT followed by P2Y12 inhibitors, 3 months of DAPT followed by aspirin, 6 months of DAPT followed by aspirin, and 12 months of DAPT followed by aspirin. We set 12 months of DAPT followed by aspirin as the reference comparator (Figure 1).

In this network, we pooled different P2Y12 inhibitors (clopidogrel, prasugrel, and ticagrelor) together. However, the use of a potent P2Y12 inhibitor (prasugrel and ticagrelor) vs clopidogrel was different across studies. In trials that examined either 1 month of DAPT or 3 months of DAPT followed by P2Y12 inhibitors, 15 871 (88.8%) and 8065 (85.7%) patients, respectively, received a potent P2Y12 inhibitor. In trials examining other treatment comparisons, clopidogrel was more commonly used.

MACCE definitions varied across the studies. However, all studies included all-cause or cardiovascular mortality and myocardial infarction in their MACCE definitions. Eleven studies[19-21,24,26,27,30-35] included target-vessel revascularization, with 2 studies[24,34] focusing specifically on target-lesion revascularization. Nine studies[25-27,29-35] included stent thrombosis, defined as definite or probable in 6 studies[25-27,30-34] and as definite in 2 studies.[29,35] Nine studies included stroke.[22,23,25,26,28-31,33-35] All studies defined major bleeding as BARC 3 or 5, except for 1 study that used TIMI major criteria.[25] Detailed end point definitions for each included study are provided in eTable 1 in Supplement 1.

### Primary End Points

The incidence of MACCE was reported in 15 studies[19-35] in which 35 326 patients experienced 1351 events (3.8%). As illustrated in **Figure 2A-B**, no significant difference was observed in the occurrence of MACCE in all pairwise comparisons, including 1 month of DAPT followed by P2Y12 inhibitors (RR, 1.00; 95% CrI, 0.70-1.41) and 3 months of DAPT followed by P2Y12 inhibitors (RR, 0.85; 95% CrI, 0.56-1.21) compared with 12 months

Table 1. Baseline Characteristics of Included Studies

| Source (study) | Comparison | Sample size | Mean age, y | % | | | | | | P2Y12 inhibitor type | Design | Follow-up period |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Female sex | Diabetes | STEMI | NSTE-ACS | Prior PCI | Newer-generation DES | | | |
| Kedhi et al,[20] 2018 (DAPT-STEMI) | 6 mo of DAPT followed by aspirin alone vs DAPT for an additional 6 mo | 870 | 60.0 | 23.1 | 13.2 | 100 | 0.0 | 5.4 | 100 | 41.7% Clopidogrel, 29.9% prasugrel, and 28.4% ticagrelor | Open-label RCT | 24 mo |
| Gwon et al,[21] 2012 (EXCELLENT)[a] | 6 mo of DAPT followed by aspirin vs 12 mo of DAPT | 718 | 62.7 | 35.5 | 38.1 | 6.0 | 94.0 | 8.9 | 25.2 | 100% Clopidogrel | Open-label RCT | 12 mo |
| Vranckx et al,[22] 2021; Gamal et al,[23] 2021 (GLOBAL LEADERS) | 1 mo of DAPT followed by P2Y12 inhibitors alone for 23 mo vs 12 mo of DAPT followed by aspirin alone for an additional 12 mo | 7487 | 63.2 | 23.0 | 21.4 | 27.9 | 72.1 | 23.0 | 95.3 | 100% Ticagrelor | Open-label RCT | 12 mo |
| van Geuns et al,[19] 2022 (IDEAL-LM)[a] | 4 mo of DAPT followed by aspirin alone vs 12 mo of DAPT[b] | 305 | 66.4 | 20.4 | 22.0 | 33.2 | 66.8 | 33.1 | 100 | 79.3% Clopidogrel, 13.7% ticagrelor, and 7.0% prasugrel | Open-label RCT | 24 mo |
| Han et al,[24] 2016 (I-LOVE-IT)[a] | 6 mo of DAPT followed by aspirin alone vs 12 mo of DAPT | 1496 | 60.2 | 32.0 | 22.6 | 13.6 | 68.2 | 7.5 | 100 | 100% Clopidogrel | Open-label RCT | 18 mo |
| Lohaus et al,[25] 2016 (ISAR-SAFE) | 6 mo of DAPT followed by aspirin alone vs DAPT for an additional 6 mo | 1601 | 64.9 | 18.7 | 23.0 | 20.2 | 79.8 | NA | 85.4 | 100% Clopidogrel | Placebo-controlled RCT | 15 mo |
| De Luca et al,[26] 2019 (REDUCE) | 3 mo of DAPT followed by aspirin alone vs 12 mo of DAPT | 1460 | 60.5 | 20.0 | 20.5 | 47.2 | 52.8 | 10.8 | 100 | 48.9% Ticagrelor, 40.7% clopidogrel, and 10.4% prasugrel | Open-label RCT | 12 mo |

(continued)

of DAPT. Follow-up time varied across studies as depicted in Table 1.

The incidence of major bleeding was reported in 10 studies[20,22-26,29-33,35] in which 30 970 patients experienced 556 events (1.8%). As illustrated in Figure 2C-D, major bleeding was lower with 1 of month DAPT followed by P2Y12 inhibitors compared with 12 months of DAPT (RR, 0.47; 95% CrI, 0.26-0.74). No significant difference in major bleeding incidence was found in other pairwise comparisons. Follow-up time varied across studies as depicted in Table 1.

As shown in **Table 2**, the DAPT regimen strategy with the highest SUCRA (ie, best performance) for MACCE was 3 months of DAPT followed by P2Y12 inhibitors (SUCRA of 0.78), whereas 1 month of DAPT followed by P2Y12 inhibitors was ranked the best strategy to mitigate major bleeding (SUCRA of 0.87).

## Secondary End Points

No difference was observed between DAPT strategies regarding the occurrence of all-cause mortality, myocardial infarction, stroke, stent thrombosis, and target-vessel revascularization. For any bleeding, 1 month of DAPT followed by P2Y12 inhibitors (RR, 0.50; 95% CrI, 0.37-0.67) (**Figure 3**F) and 3 months of DAPT followed by P2Y12 inhibitors (RR, 0.54; 95% CrI, 0.39-0.75) (Figure 3F) were superior to 12 months of DAPT. There were no differences in other pairwise comparisons. These results are presented in Figure 3 and eFigure 2 and eTable 5 in Supplement 1.

## Subgroup Analysis

We performed prespecified subgroup analyses for patients with STEMI and NSTE-ACS. We found no difference between DAPT strategies in the relative incidences of MACCE and major bleeding end points according to the type of ACS (STEMI or NSTE-ACS). These results are presented in eTable 6 in Supplement 1.

## Sensitivity Analyses

In the sensitivity analysis using the fixed-effects model (eTable 7 in Supplement 1), there was no difference between the pairwise comparisons in the incidence of MACCE. For major bleeding, 1 month of DAPT followed by P2Y12 inhibitors was superior to 12 months of DAPT (RR, 0.50; 95% CrI, 0.39-0.63) and 6 months of DAPT (RR, 0.36; 95% CrI, 0.15-0.82). Similarly, 3 months of DAPT followed by P2Y12 inhibitors was su-

Table 1. Baseline Characteristics of Included Studies (continued)

| Source (study) | Comparison | Sample size | Mean age, y | % Female sex | % Diabetes | % STEMI | % NSTE-ACS | % Prior PCI | % Newer-generation DES | % P2Y12 inhibitor type | Design | Follow-up period |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kim et al,[27] 2012 (RESET)[a] | 3 mo of DAPT followed by aspirin alone vs 12 mo of DAPT | 601 | 62.4 | 36.4 | 29.3 | NA | NA | 3.2 | 100 | 100% Clopidogrel | Open-label RCT | 12 mo |
| Min et al,[34] 2024 (SHARE)[a] | 3 mo of DAPT followed by aspirin alone vs 12 mo of DAPT | 991 | 63.0 | 23.9 | 33.9 | 25.3 | 74.7 | 12.7 | 100 | 62,5% Clopidogrel, 37.5% ticagrelor | Open-label RCT | 12 mo |
| Hahn et al,[28] 2019 (SMART-CHOICE)[a,c] | 3 mo of DAPT followed by P2Y12 inhibitors alone vs 12 mo of DAPT | 1741 | 64.5 | 26.6 | 37.5 | 18.0 | 82.0 | NA | 100 | 77.2% Clopidogrel, 8.4% ticagrelor, and 4.4% prasugrel | Open-label RCT | 12 mo |
| Watanabe et al,[29] 2022 (STOPDAPT-2 ACS) | 1 to 2 mo of DAPT followed by P2Y12 inhibitors alone vs 12 mo of DAPT[d] | 4136 | 66.8 | 20.7 | 29.7 | 73.7 | 26.3 | 10.3 | 100 | 52.6% Clopidogrel and 47.4% of prasugrel within the first 1 to 2 mo of DAPT | Open-label RCT | 12 mo |
| Lee et al,[30] 2021; Kim et al,[31] 2020 (TICO) | 3 mo of DAPT followed by P2Y12 inhibitors alone vs DAPT for an additional 9 mo | 3056 | 61.0 | 20.6 | 27.3 | 36.1 | 63.9 | 8.6 | 100 | 100% Ticagrelor | Open-label RCT | 12 mo |
| Hong et al,[32] 2024 (T-PASS) | <1 mo of DAPT followed by P2Y12 inhibitors alone vs DAPT up to 12 mo[d] | 2850 | 61.0 | 16.7 | 29.1 | 40.4 | 59.7 | 6.5 | 100 | 100% Ticagrelor | Open-label RCT | 12 mo |
| Baber et al,[33] 2020 (TWILIGHT) | 3 mo of DAPT followed by P2Y12 inhibitors alone vs DAPT for an additional 12 mo | 4614 | 64.2 | 25.1 | 35.0 | 0.0 | 100 | 34.3 | 97.7 | 100% Ticagrelor | Open-label RCT | 12 mo |
| Ge et al,[35] 2024 (ULTIMATE DAPT) | 1 mo of DAPT followed by P2Y12 inhibitors alone vs DAPT for an additional 11 mo | 3400 | 62.0 | 25.6 | 31.6 | 27.9 | 72.1 | 10.1 | 100 | 100% Ticagrelor | Placebo-controlled RCT | 12 mo |

Abbreviations: DAPT, dual antiplatelet therapy; DAPT-STEMI, Randomized, Open Label Trial of 6 Months vs 12 Months Dual Antiplatelet Therapy After Drug-Eluting Stent in ST-Elevation Myocardial Infarction; DES, drug-eluting stent; EXCELLENT, Efficacy of Xience/Promus vs Cypher to Reduce Late Loss After Stenting; GLOBAL LEADERS, A Clinical Study Comparing 2 Forms of Antiplatelet Therapy After Stent Implantation; IDEAL-LM, Improved Drug-Eluting Stent for All-Comers Left Main; I-LOVE-IT, Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization; ISAR-SAFE, Safety and Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; NA, not applicable; NSTE-ACS, non–ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; REDUCE, Randomized Evaluation of Short-Term Dual Antiplatelet Therapy in Patients With Acute Coronary Syndrome Treated With the COMBO Dual-Therapy Stent; RESET, Real Safety and Efficacy of 3-Month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation; SHARE, Short-Term Dual Antiplatelet Therapy After Deployment of Bioabsorbable Polymer Everolimus-Eluting Stent; SMART-CHOICE, Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; STEMI, ST-elevation myocardial infarction; STOPDAPT-2 ACS, Short and Optimal Duration of Dual Antiplatelet Therapy-2 Study for the Patients With Acute Coronary Syndrome; TICO, Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome; T-PASS, Ticagrelor Monotherapy in Patients Treated With New-Generation Drug-Eluting Stents for Acute Coronary Syndrome; TWILIGHT, Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention; ULTIMATE DAPT, Comparison of 1-Month vs 12-month Dual Antiplatelet Therapy After Implantation of Drug-Eluting Stents Guided by Either Intravascular Ultrasound or Angiography in Patients With Acute Coronary Syndrome.

[a] Patient characteristics include patients with and without ACS.

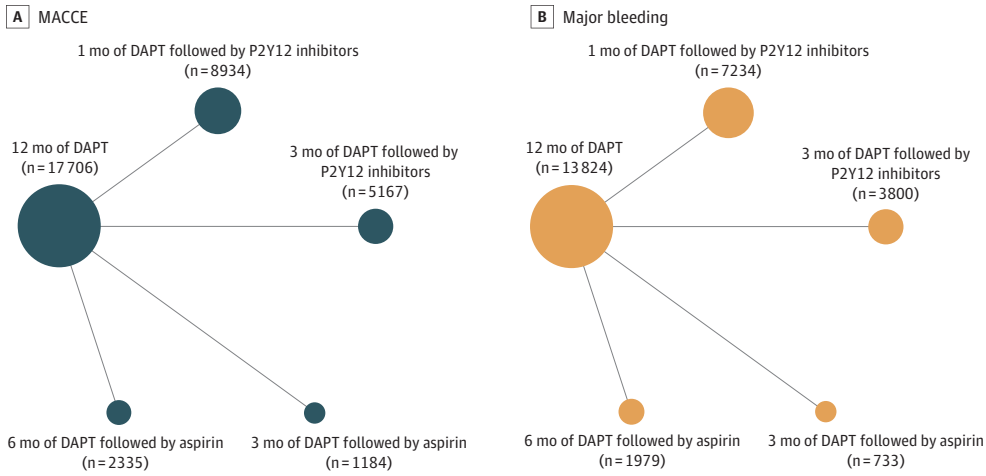
[b] This study was included in the 3 months of DAPT followed by aspirin group.

[c] In addition, random assignments were conducted at the index procedure or at a follow-up visit within 3 months after the index procedure.

[d] This study was included in the 1 month of DAPT followed by P2Y12 inhibitor group.

perior to 12 months of DAPT (RR, 0.56; 95% CrI, 0.42-0.75) and 6 months of DAPT (RR, 0.41; 95% CrI, 0.17-0.93). In a sensitivity analysis using a frequentist approach, no difference in MACCE incidence was observed. For major bleeding, 1 month of DAPT followed by P2Y12 inhibitors reduced bleeding compared with both 12 months and 6 months of

Figure 1. Primary End Points Network Plots and League Tables




Nodes represent dual antiplatelet therapy (DAPT) strategies and edges represent direct comparisons in included trials. Node size correlates with patients assigned, and edge thickness correlates with the number of direct comparisons.

DAPT, whereas 3 months of DAPT followed by P2Y12 inhibitors reduced bleeding compared with 12 months of DAPT (eTable 8 in Supplement 1). Meta-regressions were performed showing no significant interaction between MACCE and major bleeding with the covariables: (1) proportion of newer-generation DES and (2) proportion of potent P2Y12 inhibitors used (eTable 9 in Supplement 1). Network meta-analyses based on a multivariate meta-analysis model showed similar results to the primary overall analysis (eFigure 3 in Supplement 1). Similar results were seen when the IDEAL-LM trial was excluded from the analysis (eTable 10 in Supplement 1).[19] In a subgroup analysis only including studies with similar end point definitions, similar results were found compared with the overall analysis (eTable 11 in Supplement 1). A traditional random-effects meta-analysis confirmed the robustness of our findings (eFigure 4 in Supplement 1).

### Network Adequacy

All fitted models converged well, without evidence indicating inadequacy in the network meta-analysis in trace and Gelman plots. These results are presented in eFigure 5 in Supplement 1.

### Quality Assessment

No outcome presented evidence of publication bias, except by the primary safety end point of major bleeding. These results are presented in eFigures 6 and 7 in Supplement 1. In the risk of bias assessment using the RoB-2 tool, no study presented a high risk of bias (eFigure 8 in Supplement 1). The certainty of the evidence varied according to the being moderate to most comparisons. GRADE results are displayed in eTables 12, 13, and 14 in Supplement 1 for direct, indirect, and network estimates, respectively. Given the network structure with 12 months of DAPT being the common comparator to all treatment arms, the network was coherent by design.

## Discussion

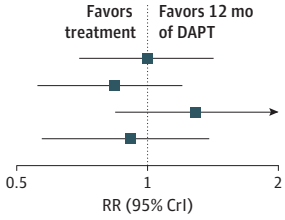
In this systematic review and network meta-analysis of 15 studies[19-35] including 35 326 patients with ACS undergoing PCI with DES, different strategies of DAPT duration were compared. The main findings from the pooled analysis were as follows: (1) there was no difference between DAPT duration strategies in the incidence of MACCE (although the CrIs were relatively wide), all-cause mortality, myocardial infarction, stroke, stent thrombosis, or target-vessel revascularization; (2) a reduction in major bleeding was associated with 1 month of DAPT followed by P2Y12 inhibitor monotherapy as compared with conventional 12 months of DAPT; (3) SUCRA analysis ranked 3 months of DAPT followed by P2Y12 inhibitors as the best for preventing MACCE and 1 month of DAPT followed by P2Y12 inhibitors as the best for preventing major bleeding; and (4) similar results were found in patients with STEMI and NSTE-ACS.

After an ACS, DAPT with aspirin and potent P2Y12 inhibitors is recommended by current guidelines for 12 months in most patients to mitigate the risk of stent thrombosis and recurrent ischemic events.[1,4] Percutaneous revascularization results in arterial injury, which is associated with an inflammatory response and, in the absence of initial reendothelialization, may facilitate the occurrence of stent thrombosis, a risk that is reduced with the use of antiplatelet therapy.[36] Compared with bare-metal stents, first-generation DES exhibited increased rates of long-term stent thrombosis, leading to the recommendation of longer DAPT schemes.[37] Newer-generation DES are more biocompatible, thinner, and sometimes devoid of polymers for drug delivery, which collectively have been shown to reduce inflammation, stent thrombosis, myocardial infarction, and target-vessel revascularization as compared with both bare-metal stents and first-generation DES.[38,39] As a result, in the era of newer-generation DES, long-term DAPT, which inherently im-

Figure 2. Primary End Points League Tables

A MACCE: 12 mo of DAPT vs short-term DAPT strategy

| Dose regimen | RR (95% CrI) |
|---|---|
| 1 mo of DAPT followed by P2Y12 inhibitors | 1.00 (0.70-1.41) |
| 3 mo of DAPT followed by P2Y12 inhibitors | 0.84 (0.56-1.20) |
| 3 mo of DAPT followed by aspirin | 1.29 (0.85-2.32) |
| 6 mo of DAPT followed by aspirin | 0.91 (0.57-1.38) |

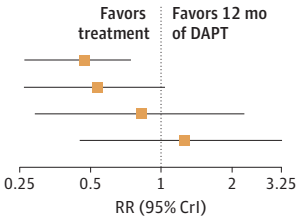



B MACCE: DAPT strategy

| | | | | |
|---|---|---|---|---|
| 1 mo of DAPT followed by P2Y12 inhibitors | | | | |
| 1.16 (0. 73-2.04) | 3 mo of DAPT followed by P2Y12 inhibitors | | | |
| 0.77 (0.38-1.28) | 0.66 (0.31-1.12) | 3 mo of DAPT followed by aspirin | | |
| 1.09 (0.65-1.95) | 0.93 (0.52-1.65) | 1.43 (0.80-3.10) | 6 mo of DAPT followed by aspirin | |
| 1.00 (0.70-1.41) | 0.85 (0.56-1.21) | 1.29 (0.85-2.32) | 0.91 (0.58-1.38) | 12 mo of DAPT |

C Major bleeding: 12 mo of DAPT vs short-term DAPT strategy

| Dose regimen | RR (95% CrI) |
|---|---|
| 1 mo of DAPT followed by P2Y12 inhibitors | 0.47 (0.26-0.74) |
| 3 mo of DAPT followed by P2Y12 inhibitors | 0.53 (0.26-1.03) |
| 3 mo of DAPT followed by aspirin | 0.82 (0.29-2.26) |
| 6 mo of DAPT followed by aspirin | 1.26 (0.45-3.26) |




D MACCE: DAPT strategy

| | | | | |
|---|---|---|---|---|
| 1 mo of DAPT followed by P2Y12 inhibitors | | | | |
| 0.88 (0.36-2.06) | 3 mo of DAPT followed by P2Y12 inhibitors | | | |
| 0.57 (0.17-1.70) | 0.65 (0.18-2.19) | 3 mo of DAPT followed by aspirin | | |
| 0.36 (0.12-1.12) | 0.42 (0.13-1.44) | 0.65 (0.17-2.80) | 6 mo of DAPT followed by aspirin | |
| 0.47 (0.26-0. 7 4)[a] | 0.53 (0.26-1.03) | 0.82 (0.29-2.26) | 1.26 (0.45-3.26) | 12 mo of DAPT |

A and C, Risk ratios (RRs) and 95% credible intervals (CrIs) were plotted comparing 12 months of dual antiplatelet therapy (DAPT), the reference treatment, with each short-term DAPT strategy. B and D, DAPT strategies are listed alphabetically. Data are RRs with 95% CrI. Comparisons should be read from left to right comparing column-defining treatment with row-defining treatment. RRs lower than 1 favor the column-defining treatment compared with the row-defining treatment. MACCE indicates major adverse cardiac and cerebrovascular events; RR, risk ratio.

[a]Indicates significant results.

poses an ongoing risk of bleeding, may not be required to further reduce already low rates of stent thrombosis and ischemic MACCE. In our analysis, 98.2% of patients received newer-generation DES in the pooled sample, reinforcing that our results apply to these contemporary devices.

Most of the studies included in this meta-analysis had noninferiority designs for MACCE and many were underpowered to analyze clinical end points in patients with ACS. Also, many of the available trials enrolled a large number of patients with stable coronary artery disease, a subgroup inherently at lower ischemic risk compared with patients with ACS. Thus, the significant reduction in MACCE with prolonged DAPT schemes was more pronounced among individuals who presented with ACS than among those with stable coronary disease.[4] However, it is also noteworthy that the classic recommendation of 12 months of DAPT was originally based on studies using clopidogrel, but more recent studies tested ticagrelor or prasugrel instead, and showed superior efficacy with more potent P2Y12 inhibitors in this population.[40,41] In addition, monotherapy with P2Y12 inhibitors is superior to monotherapy with aspirin in preventing ischemic outcomes across different scenarios, including after PCI and initial treatment with DAPT,

Table 2. Surface Under the Cumulative Ranking (SUCRA) Analysis for Each Antiplatelet Strategy

| | SUCRA | |
|---|---|---|
| DAPT strategy | MACCE | Major bleeding |
| 1 mo of DAPT followed by P2Y12 inhibitor monotherapy | 0.4863 | 0.8728[a] |
| 3 mo of DAPT followed by P2Y12 inhibitor monotherapy | 0.7833[a] | 0.7626 |
| 3 mo of DAPT followed by aspirin monotherapy | 0.1144 | 0.4381 |
| 6 mo of DAPT followed by aspirin monotherapy | 0.6496 | 0.1614 |
| 12 mo of DAPT | 0.4665 | 0.2590 |

Abbreviations: DAPT, dual antiplatelet therapy; MACCE, major adverse cardiac and cerebrovascular events.

[a] The regimens with the highest SUCRA.

without significantly increasing rates of major bleeding.[42-44] Our study expands on these findings by showing that short-term DAPT for 1 month followed by potent P2Y12 inhibitor monotherapy was equally effective as the conventional 12 months of DAPT in suppressing the risk of ischemic MACCE while resulting in the lowest risk of major hemorrhagic events.

Compared with prior meta-analyses in this patient population, our study has several advantages. After short-term DAPT, we separately analyzed P2Y12 inhibitor monotherapy with aspirin monotherapy, with currently available evidence favoring P2Y12 inhibitor monotherapy for long-term secondary prevention.[44] Our analysis focused on short-term DAPT strategies and excluded long-term DAPT studies (beyond 12 months, mostly using bare-metal stents or first-generation DES) to increase the homogeneity and avoid type I errors. Prior meta-analyses have included a wide range of DAPT durations instead of a fixed time point across various clinical scenarios, which may interfere with the network assumptions, especially indirect comparisons and their transitivity.[11,12,45-49] Furthermore, the focus on homogeneous nodes (DAPT time frames) increases the reliability of the findings, making the conclusions more practical to guide clinical practice with a specific and fixed-duration regimen instead of a range of approaches. To date and to our knowledge, this was the most comprehensive network meta-analysis focused on patients with ACS undergoing PCI with contemporary DES.

Our results suggest that the use of a short-term DAPT regimen lasting 1 month, incorporating potent P2Y12 inhibitors followed by the cessation of aspirin and continuation of P2Y12 inhibitors as monotherapy, may be the preferred strategy in ACS. Based on these pooled data together with the totality of current evidence, ticagrelor or prasugrel are preferred compared with clopidogrel, whenever possible, due to their greater efficacy and avoidance of variability in response.[50,51] Results of the present study suggest that, among patients with ACS who are stable after PCI and receiving 1 month of DAPT, the routine use of potent P2Y12 inhibitors without aspirin for the next 11 months was associated with a reduction in major and minor bleeding without increasing the risk for ischemic MACCE. A traditional random-effects meta-analysis was performed and confirmed our findings. Of note, the Short and Optimal Duration of Dual Antiplatelet Therapy 2 Study for the Patients With Acute Coronary Syndrome (STOPDAPT-2 ACS) study increased the heterogeneity in the MACCE overall analysis due to increased incidence of MACCE in the subgroup receiving 1 month of DAPT (eFigure 4 in the Supplement). The STOPDAPT-2 ACS study mostly used clopidogrel, and the exclusion of this study reduced the heterogeneity and reinforced the use of potent P2Y12 inhibitors when a short-term DAPT is used. Of note, the impact of initiating SAPT immediately after PCI in patients with ACS has not been examined. The Percutaneous Coronary Intervention Followed by Monotherapy Instead of Dual Antiplatelet Therapy in the Setting of Acute Coronary Syndromes (NEOMINSET) trial is further exploring whether P2Y12 inhibitor monotherapy using ticagrelor or prasugrel is noninferior to 12 months of DAPT for MACE and is also investigating its superiority for bleeding events.[52]

Our meta-analysis of 15 RCTs suggests that in patients with ACS undergoing PCI, particularly with new-generation DES, long-term DAPT may be associated with increased bleeding risk without reducing recurrent ischemic events. However, these results cannot be generalized to all patients with ACS. The available data do not permit stratification by specific patient subgroups, such as those with varying risks for thrombotic vs bleeding events, which is essential for tailoring DAPT duration more precisely. In addition, the incidence of recurrent ischemic events was low, leading to relatively wide CrIs (eTable 4 in Supplement 1). Therefore, individualized decisions based on clinical and procedural factors are necessary. Nonetheless, this meta-analysis supports the safety of short-term DAPT for patients in most typical clinical scenarios.

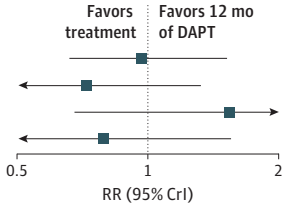
## Limitations

Our study has limitations. First, most studies had a noninferiority design for MACCE, and null results may be due to lack of power. However, examination of the 95% CrIs around the point estimates suggests that any absolute increase in the risk of MACCE is likely to be small. Second, different subsets of ACS were plotted together. Although outcomes were consistent in subgroups with STEMI and NSTE-ACS, sample size and statistical power were reduced in these cohorts compared with the main prespecified analysis. Third, despite the evidence of DAPT superiority over aspirin, to date and to our knowledge, there is no RCT directly comparing DAPT with P2Y12 inhibitors as a monotherapy immediately after the index ACS or PCI in the long term (beyond 12 months), limiting this extrapolation of our findings.[53-55] Fourth, the use of potent P2Y12 inhibitors was different across studies of different DAPT durations, with most patients in the treatment arms of 1 month and 3 months of DAPT followed by P2Y12 inhibitors receiving ticagrelor, whereas other subgroups received mainly clopidogrel, further limiting a head-to-head comparison. Similarly, we can make no direct comparisons of long-term treatment with prasugrel alone compared with ticagrelor alone. Ticagrelor monotherapy was more commonly used in the included studies whereas prasugrel monotherapy is less explored. Fifth, each treatment is compared with 12 months of DAPT but not directly compared with one another. Consequently, compari-

Figure 3. Secondary End Points

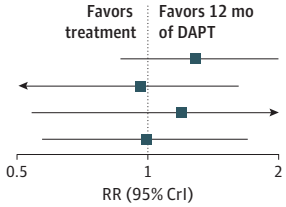
A All-cause mortality

| Dose regimen | RR (95% CrI) |
|---|---|
| 1 mo of DAPT followed by P2Y12 inhibitors | 0.97 (0.66-1.51) |
| 3 mo of DAPT followed by P2Y12 inhibitors | 0.72 (0.39-1.31) |
| 3 mo of DAPT followed by aspirin | 1.54 (0.68-3.83) |
| 6 mo of DAPT followed by aspirin | 0.79 (0.39-1.55) |



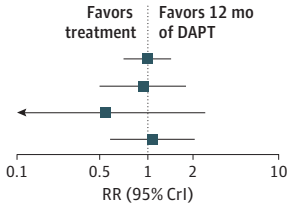

B Myocardial infarction

| Dose regimen | RR (95% CrI) |
|---|---|
| 1 mo of DAPT followed by P2Y12 inhibitors | 1.28 (0.87-1.98) |
| 3 mo of DAPT followed by P2Y12 inhibitors | 0.96 (0.50-1.61) |
| 3 mo of DAPT followed by aspirin | 1.19 (0.54-2.64) |
| 6 mo of DAPT followed by aspirin | 0.99 (0.57-1.68) |



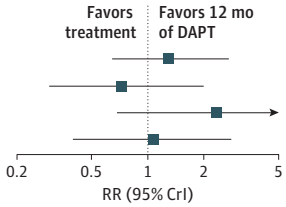

C Stroke

| Dose regimen | RR (95% CrI) |
|---|---|
| 1 mo of DAPT followed by P2Y12 inhibitors | 0.99 (0.65-1.49) |
| 3 mo of DAPT followed by P2Y12 inhibitors | 0.92 (0.43-1.93) |
| 3 mo of DAPT followed by aspirin | 0.47 (0.06-2.70) |
| 6 mo of DAPT followed by aspirin | 1.07 (0.52-2.25) |



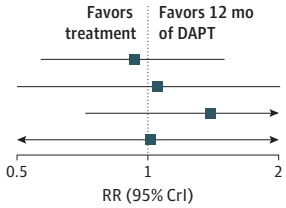

D Stent thrombosis

| Dose regimen | RR (95% CrI) |
|---|---|
| 1 mo of DAPT followed by P2Y12 inhibitors | 1.28 (0.65-2.67) |
| 3 mo of DAPT followed by P2Y12 inhibitors | 0.72 (0.30-1.96) |
| 3 mo of DAPT followed by aspirin | 2.32 (0.69-9.45) |
| 6 mo of DAPT followed by aspirin | 1.06 (0.40-2.76) |



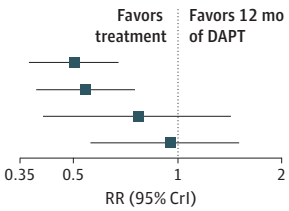

E Target-vessel revascularization

| Dose regimen | RR (95% CrI) |
|---|---|
| 1 mo of DAPT followed by P2Y12 inhibitors | 0.93 (0.57-1.50) |
| 3 mo of DAPT followed by P2Y12 inhibitors | 1.05 (0.49-2.06) |
| 3 mo of DAPT followed by aspirin | 1.40 (0.72-3.72) |
| 6 mo of DAPT followed by aspirin | 1.02 (0.47-2.22) |




F Any bleeding

| Dose regimen | RR (95% CrI) |
|---|---|
| 1 mo of DAPT followed by P2Y12 inhibitors | 0.50 (0.37-0.67) |
| 3 mo of DAPT followed by P2Y12 inhibitors | 0.54 (0.39-0.75) |
| 3 mo of DAPT followed by aspirin | 0.77 (0.41-1.42) |
| 6 mo of DAPT followed by aspirin | 0.95 (0.56-1.50) |




Risk ratios (RRs) and 95% credible intervals (CrIs) compared with 12 months of dual antiplatelet therapy (DAPT), the reference, were plotted for all secondary outcomes.

sons involving nonreference treatments are driven by indirect evidence, and the consistency assumption could not be verified. Nonetheless, the greatest efficacy of a regimen of 1 month of DAPT in decreasing major bleeding is biologically plausible. Sixth, different types of DES were pooled together; however, 98.2% of patients received newer-generation DES

with most platforms showing similar comparative outcomes. Seventh, the major bleeding outcome has signs of potential publication bias. Eighth, these results do not apply to patients with a high risk of bleeding, as such patients were generally excluded from the analyzed trials. Ninth, ranking results should be interpreted along the relative treatment effects and the 95% CrI, as they are primarily influenced by the estimated effect size.[56,57]

Lastly, as shown in eTable 1 in Supplement 1, different definitions of bleeding and MACCE end points were used across studies, which may have affected our results. We applied the BARC 3 or 5 definitions for major bleeding wherever possible to increase homogeneity, and only 1 study[25] used TIMI major criteria. A sensitivity analysis excluding this study showed results similar to the overall analysis. Additionally, a subgroup analysis including only studies with similar MACCE definitions produced comparable results, although with reduced statistical power.

## Conclusions

Results of this systematic review and network meta-analysis suggest that, in patients with ACS undergoing PCI with newer-generation DES, 1 month of DAPT followed by P2Y12 inhibitor monotherapy (especially with potent P2Y12 inhibitors), was associated with a significant reduction in the risk of major bleeding without increasing the risk of ischemic MACCE when compared with 12 months of DAPT. Three months of DAPT followed by potent P2Y12 inhibitors monotherapy was ranked as the best option to reduce MACCE. Most patients receiving P2Y12 inhibitor monotherapy were taking ticagrelor, the safety of stopping aspirin in those taking clopidogrel remains unclear, and an increased risk of MACCE cannot be excluded. The present comprehensive bayesian network meta-analysis provides contemporary insights to inform clinical practice on the optimal duration of DAPT after PCI in patients with ACS.

ARTICLE INFORMATION

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**Author Contributions:** Dr Lopes had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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