Meta-Analysis of Duration of Dual Antiplatelet Therapy in Acute Coronary Syndrome Treated With Coronary Stenting

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We aimed to evaluate if a shorter course of DAPT followed by P2Y12 inhibitor monotherapy is as effective as a 12-month course with fewer bleeding events. PubMed, Scopus, and Cochrane Central were searched for randomized controlled trials of ACS patients comparing dual antiplatelet therapy (DAPT) for 1 to 3 months followed by a P2Y12 inhibitor to 12-month DAPT. Quality assessment was performed with the Cochrane Collaboration risk of bias assessment tool. Five randomized clinical trials were included, with a total of 18,046 participants. Antiplatelet strategies were aspirin and P2Y12 inhibitor for 12 months compared with aspirin and P2Y12 inhibitor for 1 to 3 months followed by P212 inhibitor alone. Patients randomized to 1 to 3 months of DAPT followed by P2Y12 inhibitor monotherapy had lower rates of major bleeding (1.42% vs 2.53%; OR 0.53; 95% CI 0.42-0.67; $p < 0.001$; $I^2 = 0\%$) and all-cause mortality (1.00% vs 1.42%; OR 0.71; 95% CI 0.53-0.95; $p = 0.02$; $I^2 = 0\%$) with similar major adverse cardiac events (MACE) (2.66% vs 3.11%; OR 0.86; 95% CI 0.71 − 1.03; $p = 0.10$; $I^2 = 0$ %) compared to 12 months of DAPT. In conclusion, shorter course of DAPT for 1 to 3 months followed by P2Y12 inhibitor monotherapy reduces major bleeding and all course mortality without increasing major adverse cardiac events compared with traditional DAPT for 12 months. **(Am J Cardiol 2021;151:25−29)**

Acute coronary syndromes (ACS) have a yearly incidence of at least 600,000 patients in the United States, the majority of whom undergo coronary angiography with percutaneous coronary intervention (PCI).[1] Dual antiplatelet therapy (DAPT) is an effective strategy to minimize the risk of recurrent thrombotic events in that population. Current ACC/AHA guidelines recommend DAPT for 12 months after ACS.[2,3] However, these guidelines are based on older studies with outdated technology and compared to aspirin monotherapy.[4] Newer-generation drug-eluting stents (DES) have lower rates stent thrombosis and stent restenosis due to more rapid endothelialization.[5,6] Recent randomized clinical trials (RCTs) comparing shorter (1 to 3 months) DAPT followed by P2Y12 inhibitor monotherapy with a traditional 1-year course of DAPT found improved outcomes in ACS patients treated with short DAPT duration undergoing PCI with newer-generation DES.[7-12] However, while these trials revealed lower major bleeding events, they were individually underpowered to detect meaningful differences in thrombotic events and mortality. Thus, we aimed to perform a systematic review and meta-analysis to assess the efficacy and safety of DAPT for 1 to 3 months followed by P2Y12 inhibitor monotherapy compared to one year of DAPT in patients undergoing PCI for ACS.

Methods

We searched PubMed, the Cochrane Library, and Scopus from inception to January 2021. We included studies that met the following criteria: (1) randomized controlled trials, (2) comparing DAPT for 12 months to a DAPT of 3 months or less in patients with ACS, (3) with continued use of a P2Y12 inhibitor monotherapy after the DAPT period; and (4) PCI performed with newer second-generation DES.

Studies were included if any of the outcomes of interest were reported. Studies were not excluded based on language. Reference lists of relevant studies were also screened. Trials that compared different DAPT regimens with the same duration were excluded. Studies that included patients with indications for full anticoagulation (e.g., atrial fibrillation, pulmonary embolism) were excluded. Search terms used included "percutaneous coronary intervention," "PCI," "stent," "dual antiplatelet therapy", "DAPT," "and "randomized." Results are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13]

Two authors (L.K. and M.F.) independently performed the search to identify relevant studies. Full articles were reviewed when the decision to include or exclude could not be performed based solely on abstract information. Disagreements regarding study inclusion were resolved with

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Data: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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the senior author. Study characteristics were extracted by the same 2 authors. Quality assessment was performed with the Cochrane Collaboration risk of bias assessment tool.[14] Authors were contacted to request further data when not all outcomes of interest were reported. This meta-analysis was not registered in PROSPERO.

Efficacy outcomes included all-cause mortality, trial-defined major adverse cardiac events (MACE), myocardial infarction (MI), and stroke (hemorrhagic and ischemic). Data were extracted at the follow-up closest to 12 months as reported in each study. The primary safety outcome was trial-defined major bleeding, and BARC definition (Bleeding Academic Research Consortium) was used preferentially, and if not available, ISTH (International Society on Thrombosis and Hemostasis) or TIMI (Thrombolysis in Myocardial Infarction) definitions were used. [15,16] Net clinical benefit was defined as the combination of MACE and major bleeding; in studies that did not report this outcome separately, MACE and major bleeding were added. A subgroup analysis with ST-segment elevation MI (STEMI) patients was planned. Odds ratio and 95% confidence intervals were used to report pooled results for dichotomous outcomes, and a 2-tailed $p < 0.05$ was considered significant. Heterogeneity was examined with the Cochran Q test and I^2 statistics. DerSimonian random effects model was used. Review Manager 5.4 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used for statistical analysis.

Results

We identified 1,978 records with the search strategy. Of these, 42 articles were reviewed in full (Figure 1). A total of 37 articles were excluded due to failure to meet the prespecified inclusion criteria in terms of the patient population (n = 22) and type of interventions (n = 15). Finally, 5 randomized studies were included in this systematic review and meta-analysis, totaling 18,046 participants.[10,12,17-19] Follow-up in all studies was 12 months. The included groups were 12-month DAPT and DAPT for 1 to 3 months followed by a P2Y12 inhibitor. Standard doses were used (ticagrelor 90mg twice daily and clopidogrel 75mg daily). Procedural characteristics and endpoint definitions are shown in Supplementary Table 1 and Supplementary Table 2, respectively.

Study characteristics are shown in Table 1. The median age was 64 years of age. Patients were predominantly male, and there was a high prevalence of diabetes. Approximately 21% of patients presented with STEMI, and ticagrelor was the most used P2Y12 inhibitor. A detailed risk of bias assessment per study can be found in Supplementary Table 3. The overall risk of bias was low to moderate. Only TWILIGHT was double-blind, but all studies had a low risk of bias in other domains. The funnel plot did not show signs of publication bias (Supplementary Figure S1). Heterogeneity was low ($I^2 = 0\%$) in all outcomes.

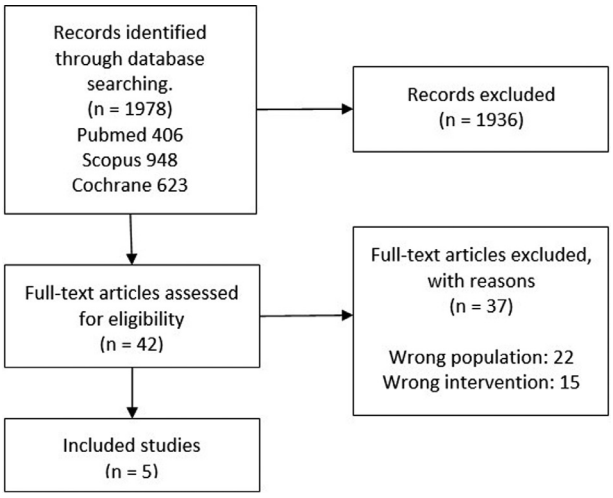

Figure 1. PRISMA flow diagram of included studies.

DAPT for 1 to 3 months followed by P2Y12 had lower major bleeding (1.42% vs 2.53%; OR 0.53; 95% CI 0.42-0.67; $p < 0.001$; $I^2 = 0\%$; Figure 2A) and all-cause mortality (1.00% vs 1.42%; OR 0.71; 95% CI 0.53-0.95; $p = 0.02$; $I^2 = 0\%$; Figure 2B) compared to DAPT for 12 months, as shown in Figures 2A and 2B. DAPT for 1 to 3 months compared to DAPT for 12 months had a similar incidence of MACE (2.66% vs 3.11%; OR 0.86; 95% CI 0.71 − 1.03; p= 0.10; $I^2 = 0\%$; Figure 2C). DAPT for 1 to 3 months decreased the incidence of a net clinical outcome of MACE plus major bleeding compared with DAPT for 12 months (5.38% vs 6.52%; 95% CI 0.72-0.91; p = 0.001; I^2=0%; Figure 2D). MI (1.68% vs 1.79%; OR 0.95; 95% CI 0.74-1.21; $p = 0.52$; $I^2 = 0\%$; Figure 2E), and stroke (0.48% vs 0.41%; OR 1.16; 95% CI 0.71-1.90; p = 0.38; $I^2 = 0\%$; Figure 2F) were similar between groups. Two trials reported data on STEMI patients (TICO and STOP-DAPT 2) on net clinical outcome, and DAPT for 1 to 3 months had numerically less events**;** however**,** this did not reach statistical significance (3.46% vs 5.07%; OR 0.67; 95% CI 0.41-1.09; $p = 0.11$; $I^2 = 0\%$; Supplementary Figure S2). No other outcomes were reported on STEMI patients.

Table 1
Study characteristics. BP = bioresorbable polymer; DAPT = dual antiplatelet therapy; DM = diabetes mellitus; DP = durable polymer; LAD = left anterior descending artery; MI = myocardial infarction; STEMI = ST elevation MI at baseline. *= The values were extracted from their main trial population.

Author/Trial name	Year	Study Population	Age	Male	Prior MI	DM	STEMI	P2Y12i used	DAPT months	Stent type	LAD
GLOBAL LEADERS[18]	2019	7,487	64	77%	18%	21%	28%	Ticagrelor	1 vs 12	BP Biolimus-A9	NA%
SMART CHOICE[10]	2019	1,741	64*	73%*	4%*	37%*	10%	Clopidogrel (77%)	3 vs 12	BP Everolimus/ sirolimus	49%*
STOP DAPT 2[12]	2019	1,148	68*	77%*	13%*	38%*	48%	Clopidogrel (62%)	1 vs 12	DP Everolimus	55%*
TICO[17]	2020	3,056	61	79%	4%	27%	36%	Ticagrelor	3 vs 12	BP Ultrathin sirolimus	48%
TWILIGHT ACS[19]	2020	4,614	64	74%	28%	35%	0%	Ticagrelor	3 vs 12	Second generation, 71% DP*	58%

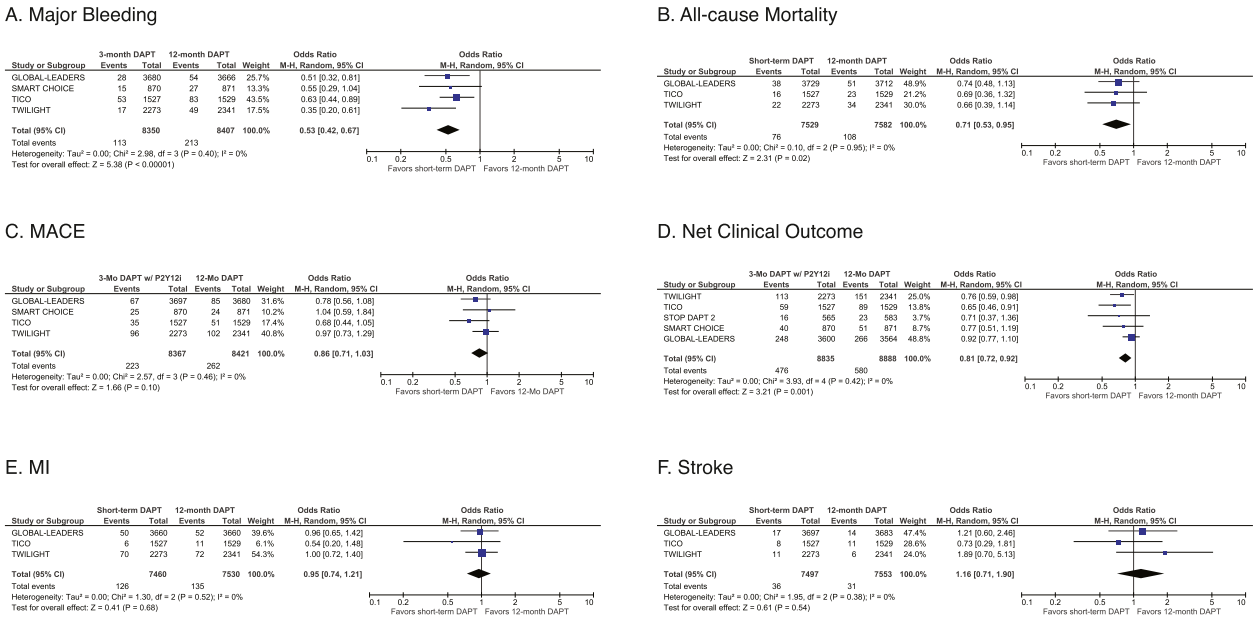

Figure 2. A: Major bleeding. B: All-cause mortality. C: Major adverse cardiovascular events. D: Net clinical outcome. E: Myocardial infarction. F: Stroke.

Discussion

The results from this systematic review and meta-analysis of 18,046 randomized patients from 5 RCTs demonstrate that 1 to 3 months of DAPT followed by P2Y12 inhibitor monotherapy reduces major bleeding complications and all-cause mortality without an increase in MACE compared with the traditional approach of 12 months of DAPT in patients undergoing PCI for ACS. These findings challenge contemporary practice guideline recommendations for 1 year of DAPT for all patients undergoing PCI for ACS.

The American College of Cardiology and American Heart Association guidelines provide a IA recommendation of DAPT for 12 months after PCI for ACS patients treated with PCI. This recommendation is, in part, based on the results of the CURE trial, published in 2001.[2,4] However, in CURE most patients were medically managed, and PCI was performed with bare-metal stents. Moreover, patients in CURE were randomized to DAPT or aspirin monotherapy and not P2Y12 inhibitor monotherapy. The recommendation for one year of DAPT after PCI for ACS was strengthened after several studies in 2006 suggested first-generation DES were associated with higher rates of late and very late stent thrombosis.[20,21] However, much has changed since the era of bare-metal stents and first-generation DES. Contemporary DES endothelialize more rapidly, reducing restenosis and stent thrombosis compared to both bare-metal stents and first-generation DES.[22,23] These improvements in stent technology have decreased the need for prolonged DAPT.

In this meta-analysis, no deleterious tradeoff in thrombotic and bleeding events was seen with 1 to 3 months of DAPT instead of 12 months. Moreover, the 1.4% absolute risk reduction found in major bleeding is particularly meaningful given the yearly number of ACS presentations (> 600,000) in the United States, thus allowing for a potential decrease in the number of major bleeding episodes in the United States by at least 6,000 patients per year. The findings are also in line with other studies suggesting omitting aspirin instead of the P2Y12 inhibitor results in a better balance in safety and efficacy. For example, in patients with atrial fibrillation undergoing PCI, RCTs have demonstrated that aspirin increases bleeding complications without any efficacy beyond the first month from PCI in patients treated with a P2Y12 inhibitor and anticoagulation.[24-26] In the 'aspirin and clopidogrel compared with clopidogrel alone after recent ischemic stroke or transient ischemic attack in high-risk patients' (MATCH) trial, 7599 stroke patients were randomized to clopidogrel or clopidogrel plus aspirin, and the addition of aspirin only contributed to bleeding complications without any reduction in MACE, stroke, or myocardial infarction.[27]

The use of P2Y12 inhibitor monotherapy instead of aspirin monotherapy after a short period of DAPT may be one of the key reasons for the better balance in efficacy and safety seen in the current analysis. Previous randomized trials have demonstrated that P2Y12 inhibitor monotherapy better balances efficacy and safety compared to aspirin monotherapy. In the CAPRIE trial, 19,185 patients with vascular disease were randomized to aspirin monotherapy or clopidogrel monotherapy, and clopidogrel monotherapy resulted in a relative 8.7% relative reduction in major adverse events without additional bleeding or adverse events compared to aspirin monotherapy.[28] These findings are in line with a substudy of the GLOBAL LEADERS trial where ticagrelor monotherapy reduced the composite of all-cause mortality, stroke, or MI (1.92% vs. 2.65%; log-rank $p = 0.01$) without any significant increase in BARC 3 or 5 bleeding complications.[29] These suggest that P2Y12 inhibitor monotherapy may result in better efficacy with similar safety compared to aspirin monotherapy. While studies like Onyx ONE suggest short DAPT followed by aspirin

monotherapy may be safe and effective, more studies evaluating this approach are warranted.[30]

The reduction in mortality in the current analysis with short-term DAPT followed by P2Y12 inhibitor therapy compared to traditional 12 months of DAPT after PCI for ACS needs to be interpreted with caution, given that data were available for only 3 studies. However, the observed decrease in mortality is a potentially important finding as it suggests guideline recommendations may be associated with decreased survival. Short-term DAPT followed by P2Y12 inhibitor monotherapy may reduce mortality by reducing bleeding without increasing MACE, creating a better-balanced safety and efficacy profile after PCI for ACS. These findings are in line with a meta-analysis of 34,880 patients from 12 randomized trials which showed that patients randomized to longer courses of DAPT have worse mortality than shorter courses of DAPT after PCI.[31]

Other meta-analyses have also been published on DAPT duration after PCI.[32,33] However, our meta-analysis is unique in focusing singularly on ACS patients. This distinction is particularly important given the important differences in prognosis and management strategies compared with chronic coronary syndrome.[2] To our knowledge, this is also the first meta-analysis to show a decrease in all-cause mortality with a DAPT duration of 1 to 3 months followed by P2Y12 inhibitor monotherapy in patients undergoing PCI for ACS.

Our study has several limitations. First, GLOBAL LEADERS' results are derived from that study's post hoc analysis. However, no heterogeneity was found in our analysis. Second, only 21% of the population in our study presented with STEMI, so the generalizability of our results to that population may be limited, although our subgroup analysis on net clinical outcome was consistent with the main analysis. Third, the included studies used newer-generation DES. Although the use of newer-generation DES is widespread, our results may not apply to first-generation DES or bare-metal stents. Fifth, the use of intravascular imaging was high in most studies and it is unknown if these results apply with lower uses of intravascular 7imaging. Sixth, only one of the included studies was double-blind. Seventh, not all studies reported data for all analyses, and there were relatively few events in each group.

In summary, a shorter DAPT duration of 1 to 3 months followed by P2Y12 inhibitor monotherapy may result in a better balance of safety and efficacy compared with the traditional 12 months of DAPT in patients undergoing PCI for ACS. Guidelines should be updated to reflect these findings.

Author Contributions

Leonardo Knijnik: Conceptualization, Methodology, Software, Validation, Visualization, Formal analysis, Investigation, Writing − Original Draft, Investigation. Marcelo Fernandes: Conceptualization, Data curation, Writing-Original draft preparation. Manuel Rivera: Writing - Review & Editing. Rhanderson Cardoso: Writing - Review & Editing. Abhinav Goyal: Writing - Reviewing and Editing. Laurence Sperling: Writing - Reviewing and Editing, Supervision. Michael McDaniel: Conceptualization, Methodology, Validation, Writing - Original Draft, Supervision.

Conflict of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.04.014.

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