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Short- Versus Long-Term Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation

An Individual Patient Data Pairwise and Network Meta-Analysis

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ABSTRACT

BACKGROUND Randomized controlled trials comparing short- (≤6 months) with long-term (≥1 year) dual antiplatelet therapy (DAPT) after drug-eluting stent(s) (DES) placement have been insufficiently powered to detect significant differences in the risk of major adverse cardiac events (MACE).

OBJECTIVES This study sought to compare clinical outcomes between short- (≤6 months) and long-term (1 year) DAPT and among 3 months, 6 months, and 1 year of DAPT post-DES placement by performing an individual patient data pairwise and network meta-analysis.

METHODS Randomized controlled trials comparing DAPT durations after DES placement were searched through the MEDLINE, EMBASE, and Cochrane databases and in international meeting proceedings. The primary study outcome was 1-year risk of MACE (cardiac death, myocardial infarction, or definite/probable stent thrombosis).

RESULTS Four trials including 8,180 randomized patients were identified. At 1-year follow-up, short-term DAPT was associated with similar rates of MACE (hazard ratio [HR]: 1.11; 95% confidence interval [CI]: 0.86 to 1.43; p = 0.44), but significantly lower rates of bleeding (HR: 0.66; 95% CI: 0.46 to 0.94; p = 0.03) versus prolonged DAPT. Comparable results were apparent in the landmark period between DAPT discontinuation and 1-year follow-up (for MACE: HR: 1.20; 95% CI: 0.77 to 1.89; p = 0.42) (for bleeding: HR: 0.44; 95% CI: 0.21 to 0.91; p = 0.03). There were no significant differences in 1-year rates of MACE among 3-month versus 1-year DAPT, 6-month versus 1-year DAPT, or 3-month versus 6-month DAPT.

CONCLUSIONS Compared with prolonged DAPT, short-term DAPT is associated with similar rates of MACE but lower rates of bleeding after DES placement. (J Am Coll Cardiol 2015;65:1092–102) © 2015 by the American College of Cardiology Foundation.

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The optimal duration of dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor after drug-eluting stent(s) (DES) implantation remains a matter of debate. Despite demonstration of improved efficacy, first-generation sirolimus-eluting stents and paclitaxel-eluting stent(s) (PES) result in greater rates of very late stent thrombosis (ST) and adverse cardiac events compared with bare-metal stents (1,2). Based on pathological findings showing delayed arterial endothelialization after sirolimus-eluting stents and PES implantation (3,4), as well as clinical retrospective studies suggesting higher rates of ST with first-generation DES versus bare-metal stents at time of DAPT discontinuation (5,6), the American College of Cardiology/American Heart Association guidelines extended the duration of DAPT from 3 months after sirolimus-eluting stents and 6 months after PES placement (per randomized clinical trials [RCT]) to at least 1 year (7). Thus, 1 year of DAPT has become the standard of care worldwide for patients receiving DES, irrespective of DES type and despite the absence of evidence-based RCT results.

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Because prolonged DAPT is associated with increased bleeding and health care costs (8), establishing optimal DAPT duration is of paramount importance. Yet observational studies have been inconsistent; some reports suggest increased rates of adverse events in patients with premature DAPT discontinuation (5,9), whereas others refute this association (10,11). Recently, several RCTs failed to show any benefit of prolonging DAPT (≥1 year) versus a shorter course, challenging the notion that 1 year of DAPT is necessary after DES implantation (12–16). However, given the low frequency of adverse events after DAPT discontinuation, all of these studies were insufficiently powered to detect modest but clinically meaningful differences in ischemic outcomes. For this reason, we performed an individual patient data meta-analysis of RCTs investigating the safety and efficacy of shortening DAPT to <1 year post-DES implantation.

METHODS

Eligible studies for this meta-analysis were RCTs comparing short-duration (3 or 6 months) with longer-duration DAPT (≥1 year). Randomized trials comparing 1 year with >1 year DAPT were excluded. Relevant RCTs were searched through MEDLINE, the Cochrane database, the EMBASE database, www.tctmd.com, www.clinicaltrials.gov, www.clinicaltrialresults.org, www.cardiosource.com, and abstracts and presentations from major cardiovascular meetings, using the keywords "randomized clinical trial," "drug-eluting stent," "dual antiplatelet therapy," "clopidogrel," "aspirin," and "thienopyridines." Two investigators (T.P. and A.M.) independently reviewed the titles, abstracts, and studies to determine whether they met the inclusion criteria. Reviewer conflicts were resolved by consensus. No language, publication date, or publication status restrictions were imposed. The most updated or inclusive data for a given study were abstracted. Internal validity of RCTs was assessed by evaluating concealment of allocation, blind adjudication of events, and inclusion of all randomized patients in the analysis.

The primary endpoint was the 1-year rate of major adverse cardiac events (MACE), including the composite of cardiac death, myocardial infarction (MI), or definite/probable ST. Secondary pre-specified

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)
CI = confidence interval
CrI = credible interval
DAPT = dual antiplatelet therapy
DES = drug-eluting stent(s)
HR = hazard ratio
MACE = major adverse cardiac event(s)
MI = myocardial infarction
OR = odds ratio
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
RCT = randomized clinical trials
ST = stent thrombosis

received speaker fees from Abbott and Cardiovascular System Inc. Dr. Bhatt is on the advisory board of Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; is on the Board of Directors of Boston VA Research Institute and the Society of Cardiovascular Patient Care; is Chair of the American Heart Association Get With The Guidelines Steering Committee; is on the Data Monitoring Committees at Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and Population Health Research Institute; has received honoraria from the American College of Cardiology (Editor, *Clinical Trials*, *Cardiosource*), Belvoir Publications (Editor-in-Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor-in-Chief, *Journal of Invasive Cardiology*), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), and WebMD (CME steering committees); is the Deputy Editor of *Clinical Cardiology*; is the Section Editor for pharmacology for the *Journal of the American College of Cardiology*; has received research grants from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Roche, Sanofi, and The Medicines Company; and has received unfunded research from FlowCo, PLx Pharma, and Takeda. Dr. Stone has served as a consultant for Boston Scientific, Eli Lilly, Daiichi-Sankyo, and AstraZeneca. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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