Optimal Duration of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention

Arjun Majithia, MD[a], Deepak L. Bhatt, MD, MPH[b,*]

KEYWORDS

• Dual antiplatelet therapy • Percutaneous coronary intervention • Coronary artery disease

KEY POINTS

- Dual antiplatelet therapy (DAPT) remains an essential component of treatment in patients with coronary artery disease, treated with and without percutaneous coronary intervention (PCI).
- Recommendations for duration of DAPT after PCI should consider patient-specific risk, clinical presentation, stent characteristics, and technical and procedural factors.
- Overall, primary studies and meta-analyses of prolonged DAPT longer than 12 months after PCI demonstrate reduction in rates of stent thrombosis (ST) and myocardial infarction (MI), at the cost of increased bleeding.
- Studies of shorter-duration DAPT after PCI in non–acute coronary syndrome populations treated with a second-generation drug-eluting stent, suggest similar mortality, MI, ST, and lower bleeding when compared with longer DAPT duration.

INTRODUCTION

Antiplatelet therapy is a cornerstone in the management of patients with coronary artery disease (CAD) after percutaneous coronary intervention (PCI).[1] Historically, dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is administered for a period of at least 1 month to 1 year after implantation of a bare-metal stent (BMS) or drug-eluting stent (DES), respectively, to mitigate stent thrombosis (ST) and future myocardial infarctions (MIs). This standard was supported by studies of patients presenting with acute coronary syndromes (ACS), and electively, treated with PCI.[2,3] However, the optimal duration of antiplatelet therapy after PCI remains uncertain. Longer DAPT exposure decreases ischemic events, but leads to an increase in clinically meaningful bleeding. Strategies for both prolonged DAPT of longer than 1 year, and abbreviated DAPT for 3 to 6 months have been proposed.

Here, we review current evidence for strategies of prolonged DAPT and abbreviated DAPT following PCI.

PROLONGED DUAL ANTIPLATELET THERAPY OF LONGER THAN 12 MONTHS FOLLOWING PERCUTANEOUS CORONARY INTERVENTION

Rationale for Studies of Prolonged Dual Antiplatelet Therapy (Longer than 12 Months)

First-generation DESs were developed to address the high restenosis rates associated

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[a] Landsman Heart and Vascular Center, Lahey Hospital and Medical Center, 41 Burlington Mall Road, Burlington, MA 01805, USA; [b] Heart & Vascular Center, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA

* Corresponding author.

E-mail address: dlbhattmd@post.harvard.edu

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with BMS, but were limited by higher rates of late ST. The BASKET-LATE (Basel Stent Kosten Effektivitäts Trial-Late Thrombotic Events) trial followed 746 patients treated with DES or BMS for 1 year after discontinuation of clopidogrel, and demonstrated no difference in overall 18-month cardiovascular death or MI.[4] However, the study demonstrated higher rates of death and MI in the DES group after discontinuation of clopidogrel (between months 7–18), with twice as frequent late ST (2.6% vs 1.3%). These results suggested that despite an initial benefit of reducing target vessel revascularization (TVR) compared with BMS, the benefit of first-generation DES may be attenuated by late ST, leading to increased cardiac death and MI.

Several factors affect the likelihood of ST. First-generation, polymer-based, drug-coated stents elute sirolimus or paclitaxel to attenuate aggressive neointimal hyperplasia and subsequent restenosis within the stent lumen. However, autopsy studies of patients treated with first-generation DES who have died from late ST demonstrate delayed arterial healing, characterized by persistent fibrin deposition, and poor stent endothelialization.[5,6] Clinical presentation at the time of index PCI also affects the likelihood of ST. The use of DES in patients with acute MI (AMI) is associated with greater incidence of late ST when compared with those with stable plaques.[6] Procedural factors, such as stent underexpansion, malapposition, and stent edge dissection also influence the likelihood of ST, although these factors tend to promote early ST, and affect both BMS and DES similarly, as evidenced by the similar rate of early ST with BMS and DES.[5] A strategy of prolonged DAPT was proposed to mitigate ST and ischemic events involving and unrelated to the index lesion. However, the safety of long-term DAPT exposure is uncertain.

Recent studies have identified potential safety concerns with prolonged antiplatelet therapy. The CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial randomized 15,603 with cardiovascular disease or multiple risk factors to clopidogrel and aspirin versus aspirin alone.[7] At a median of 28 months, the primary efficacy endpoint of MI, stroke, or death from cardiovascular causes was not significantly different between groups. In the subgroup of patients with multiple risk factors (but without clinically evident atherosclerotic disease), the incidence of death was higher in the group treated with clopidogrel. In the subgroup of patients with clinically evident atherothrombotic disease, there was a suggestion of benefit in the clopidogrel group. The subgroup with prior ischemic events such as MI seemed to derive particular benefit from prolonged dual antiplatelet therapy with aspirin plus clopidogrel.[8] Among the entire population of patients, those treated with clopidogrel plus aspirin demonstrated a significant increase in moderate bleeding, and a trend toward an increase in severe bleeding.

Studies Evaluating Prolonged Dual Antiplatelet Therapy (of Longer than 12 Months)

Studies of prolonged DAPT exposure and PCI have reported conflicting results with regard to the efficacy of extending therapy beyond 1 year. The DES-LATE (Optimal Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation) trial, randomized 5045 patients who received DES and were event free at 12 months to aspirin or aspirin and clopidogrel.[9] The study demonstrated no difference in a composite endpoint of death, MI, or stroke at 24 months, and similar bleeding rates between groups. Similarly, the ARCTIC-Interruption (Assessment by a double Randomisation of a Conventional antiplatelet strategy vs a monitoring-guided strategy for DES implantation and, of Treatment Interruption vs Continuation 1 year after stenting-Interruption) trial, an extension of the ARCTIC-Monitoring trial, demonstrated no clinical benefit with prolonged DAPT, but a significant increase in major or minor bleeding with prolonged therapy.[10]

Other studies have demonstrated results in favor of prolonged DAPT. The DAPT (Dual Antiplatelet Therapy) study, a large, multicenter, blinded, placebo-controlled trial addressed several limitations of previous studies.[11] A total of 9961 patients who had undergone DES were randomly assigned to continued thienopyridine (clopidogrel or prasugrel) plus aspirin versus aspirin plus placebo for a period of 18 months after completing 12 months of DAPT after PCI. Prolonged DAPT resulted in a reduced rate of ST and major adverse cardiovascular or cerebrovascular events (MACCE), a composite of death, MI, or stroke, driven by a reduction in the rate of MI (including nonstent thrombosis–related MI). The study also demonstrated an increase in moderate or severe bleeding, and a signal for increased noncardiovascular death with prolonged therapy. An analysis of ST and MI in the period surrounding discontinuation revealed elevated risk during the 3 months after discontinuation of thienopyridines in both groups. Most recently, the OPTIDUAL (OPTImal DUAL Antiplatelet Therapy Trial) study