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Review

Antiplatelet therapy after drug-eluting stent implantation

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ABSTRACT

Dual antiplatelet therapy (DAPT), which is the combination of aspirin and a platelet $P2Y_{12}$ inhibitor, is the cornerstone of secondary prevention in ischemic heart disease requiring intracoronary stenting. Although the efficacy of DAPT in the reduction of ischemic events has been well validated, the optimal duration, and indeed combination, of therapy is yet to be established. This area continues to attract debate with new developments in stent design and antiplatelet agents, as well as evolving clinical skill levels.

Presently, clinical guidelines advocate the use of DAPT for 6–12 months following drug-eluting stent (DES) implantation, but this can vary according to clinical indication, bleeding risk, and country of practice. Concerns have arisen that unnecessary prolongation of DAPT may be associated with increased bleeding events, as well as cost. Whether these guidelines effectively cater to current stenting techniques, devices, and antiplatelet agents remains to be determined. This review analyzes contemporary issues surrounding DAPT following DES implantation, as researchers continue to seek to strike the optimal balance between bleeding and thrombotic risk.

Although reduced DAPT durations continue to show promising results in preventing ischemic events while also mitigating bleeding risk, ultimately the consideration of clinical presentation as well as medical and social history is paramount to guiding the optimal duration and cessation of DAPT.

Contents

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Introduction

Dual antiplatelet therapy (DAPT), defined as the combination of aspirin and a platelet $P2Y_{12}$ inhibitor, is initiated following intracoronary stent implantation to prevent stent thrombosis and subsequent ischemic complications [1]. DAPT is the foundation of secondary prevention in ischemic heart disease requiring stenting, but the optimal combination and duration of therapy continue to attract debate with the development of new stent designs and antiplatelet agents, as well as evolving clinical skill levels. Drug-eluting stents (DES) were first introduced over a decade ago with the aim of preventing in-stent restenosis through the delivery of anti-proliferative agents to inhibit early vascular endothelialization [2]. Their superiority to traditional bare metal stents (BMS) has been established in the prevention of in-stent restenosis [3,4]; this advantage came with a paradoxical risk of late stent thrombosis, more common in the earlier generation DES and sometimes associated with premature DAPT cessation. This resulted in a conservative extension of DAPT to mitigate these risks. Subsequently, second-generation DES were developed to provide earlier and more comprehensive endothelial coverage, which has resulted in reduced late stent thrombotic events, as well as myocardial infarction (MI) and stroke [5,6]. More recently, polymer-free DES have been developed to eliminate other potential causes of late stent thrombosis, although conclusive data on these newer designs are yet to be established.

Presently, clinical guidelines advocate the use of DAPT for 6–12 months following DES implantation, but this can vary according to clinical indication, bleeding risk, and country of practice [1,7,8]. Concerns have arisen that unnecessary prolongation of DAPT may be associated with increased bleeding events, as well as cost. Whether these guidelines effectively cater to current stenting techniques, devices, and antiplatelet agents remains to be determined. This review will analyze contemporary issues surrounding DAPT following DES implantation, as researchers continue to seek to strike the optimal balance between bleeding and thrombotic risk.

Drug-eluting stents: development and risks

The two major complications associated with stent implantation are stent thrombosis and in-stent restenosis. Stent thrombosis, although uncommon, refers to the potentially fatal acute occlusion of the treated vessel, commonly presenting as death or MI. The risk is maximal early after stent implantation and attenuates as endothelialization occurs [9]. As DES are designed to delay endothelialization, there is a risk of late (12 months) and very late (>12 months) stent thrombosis, more commonly seen in the first-generation DES which were very potent inhibitors of re-endothelialization. This risk is further compounded by other mechanisms that are less well understood, such as polymer hypersensitivity [10]. It is the risk of stent thrombosis that is the driving argument behind prolonged DAPT. In-stent restenosis is the gradual re-occlusion of the stented segment, generally occurring 3–12 months after stent implantation due to arterial damage and excessive neointimal tissue proliferation [11]. In contrast to stent thrombosis, in-stent restenosis usually presents with less acute manifestations rendering this complication less morbid [12]. Although the incidence of in-stent restenosis has been greatly reduced by DES [13], the risk is not negligible, which must be considered as DES become more and more widely used.

The first-generation DES, which contained either sirolimus or paclitaxel, first received approval by the US Food and Drug Administration over the years 2003–4. These antiproliferative agents prevent in-stent restenosis and associated target lesion revascularization by preventing neointimal hyperplasia. The recommended minimum duration of DAPT was set at 3 and 6 months for sirolimus- and paclitaxel-eluting stents respectively based on randomized controlled trial data [10]. However, the initial enthusiasm heralding the release of the first-generation DES was tempered considerably by the unexpectedly high rates of late and very late stent thrombosis seen in these patients [14]. Subsequently, the extension of therapy to a minimum of 12 months was mandated [14], which remained the recommended standard of care with the introduction of second-generation DES five years later. However, the data informing the use of 12-month DAPT originated from trials using first-generation DES and therefore may overestimate the risk of adverse events in newer stent platforms, which have demonstrable superiority in terms of safety and efficacy [15]. Indeed, besides the added cost associated with prolongation of DAPT, there is also concern regarding the increased risk of major bleeding, which correlates with length of therapy [16,17].

Dual antiplatelet therapy: antiplatelet selection

The role of aspirin in the secondary prevention of thrombotic events following DES implantation has been well established [18,19]. Although most of the large-scale trials are based on data using clopidogrel as the adjunctive antiplatelet agent, newer and more potent agents such as ticagrelor and prasugrel are generating increasing attention as they continue to display promising antithrombotic potential. Both ticagrelor and prasugrel have been integrated into the current American College of Cardiology Foundation/American Heart Association/Society of Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI) clinical guidelines for use following acute coronary syndromes (ACS).

The efficacy of clopidogrel, an irreversible $P2Y_{12}$ inhibitor, is also well recognized [20,21]. However, the variability in patient responsiveness [22], as well as its low bioavailability and relative slow onset of action, has led to the call for development of alternative adjuncts.

Prasugrel is also a thienopyridine that inhibits platelet aggregation, but does so with less variability. In terms of antithrombotic potential, it was shown in the TRITON-TIMI 38 trial [23] to be superior to clopidogrel in reducing stent thrombosis. Although the reduction was realized at the cost of increased bleeding risk, it did not translate to mortality differences. Increased risk of bleeding was most marked in patients $\geq$75 years, <60 kg, and those with a history of stroke or transient ischemic attack (TIA), resulting in its contraindication in this patient subset [1]. Regardless, post hoc analysis demonstrated a net clinical benefit, and a sub-analysis indicated that benefit was most significant in the diabetic population [24].

Ticagrelor is a reversible inhibitor of platelet aggregation, which also demonstrated superiority for reducing composite thrombotic end-points compared to clopidogrel in the PLATO trial [25]. Significantly, ticagrelor did not increase bleeding, a finding which persisted regardless of stent selection. Landmark analysis showed an early benefit from ticagrelor over the first 30 days following stent implantation, which indicates that it may be a viable substitute for clopidogrel over shorter durations.

Guidelines indicate that ticagrelor and prasugrel are viable alternatives to clopidogrel in the setting of ACS for the duration of one year. However, there are currently no published randomized studies comparing durations of DAPT following DES that integrate the newer thienopyridine agents.

Duration of dual antiplatelet therapy: determining optimal length of therapy

One of the major questions surrounding antiplatelet therapy following DES implantation is the optimal duration of DAPT. At