Extended Duration of Dual-Antiplatelet Therapy After Percutaneous Coronary Intervention: How Long Is Too Long?

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The most recent American College of Cardiology/American Heart Association guidelines on duration of dual-antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) with drug-eluting stents (DESs) give a class I recommendation to continue DAPT for at least 12 months after an acute coronary syndrome (ACS) and at least 6 months after revascularization in the setting of stable ischemic heart disease.[1] These guidelines also give a class IIb recommendation for continuation of DAPT beyond 6 and 12 months in patients with stable ischemic heart disease and ACS, respectively, if these patients have tolerated DAPT without a bleeding event and are at low risk for bleeding in the future.[1] However, they do not provide any guidance with respect to how long DAPT should be continued and leave it to the clinician to discuss the risks versus benefits with the patient and individualize antiplatelet therapy. Therefore, in clinical practice, we often see patients on DAPT several years after a PCI as they are instructed by their providers to never discontinue them. In fact, given how much the importance of taking DAPT in the early period after PCI is emphasized, patients at times are uncomfortable stopping the second antiplatelet agent at any time. The lack of a clear recommendation is not surprising, despite multiple recent randomized controlled trials[2–5] evaluating differing durations of extended DAPT given several evolving factors and the overall risk/benefits of DAPT.

Guidelines commenting on DAPT duration have largely included trials using clopidogrel and early-generation stents. The advent of more potent $P2Y_{12}$ inhibitors, such as prasugrel and ticagrelor, has reduced major adverse cardiovascular events, but at the cost of increased bleeding.[6,7] On the other hand, the newer-generation DESs, with their thinner stent struts, a more biocompatible polymer, and favorable drug-eluting characteristics, have considerably decreased the risk of stent thrombosis, particularly late stent thrombosis.[8] Although extended DAPT duration has been associated with reduction in recurrent myocardial infarction (MI) and cardiovascular death, there are statistically significant increases in major bleeding events.[2,5] With the increased recognition of bleeding events and advancements in DES technology, it has been hypothesized that shorter durations of DAPT may be more appropriate. The European and American College of Cardiology/American Heart Association guidelines have already reduced the minimum absolutely required duration of DAPT by incorporating short DAPT into their recommendations.[1,9] However, the question about the value of extended DAPT duration in selected patients still remains to be answered.

To our knowledge, there are 4 randomized controlled trials that have compared the efficacy and bleeding outcomes of standard 12-month therapy versus extended-duration DAPT (>24 months), which are listed below:

1. PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54) trial.[2]
2. DAPT (Dual Antiplatelet Therapy) trial.[5]
3. DES LATE (Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Event) trial.[4]
4. OPTIDUAL (Optimal Dual Antiplatelet Therapy) trial.[3]

The summary of these trials can be seen in Table 1. Two of these trials, comparing >24 months of DAPT with 12 months of DAPT, showed no difference in their primary efficacy end points of cardiovascular death/MI/stroke and death/MI/stroke/major bleeding (DES-LATE and OPTIDUAL trials), respectively.[3,4] Unlike the other 3 trials, the OPTIDUAL trial included major bleeding as part of the primary efficacy end points,

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Table 1. Randomized Controlled Trials Examining Extended Duration of Dual-Antiplatelet Therapy

Trial and Year	Duration Comparison, mo	No. of Participants	Primary Efficacy End Point	Primary Efficacy End Point Result	Bleeding Definition	Bleeding End Point Result	$P2Y_{12}$ Inhibitor	Stent Type	Patients With ACS, %
DAPT 2014[5]	12 vs 30	9961	1. Composite of death, MI, and stroke 2. Stent thrombosis.	Decrease with extended DAPT for both the composite end point (4.3% vs 5.9%) and stent thrombosis (0.4% vs 1.4%)	GUSTO severe or moderate bleeding*	Statistically significant increase in extended DAPT (2.5% vs 1.6%), driven by moderate GUSTO bleeding	Clopidogrel (65%) or prasugrel (35%)	Sirolimus or paclitaxel in ≈40%, zotarolimus or everolimus in ≈60%	≈40
DES-LATE 2014[4]	12 vs 36	5045	Composite of cardiovascular death, MI, and stroke	No difference	TIMI major†	No statistical difference but trend t oward increase in extended DAPT	Clopidogrel	Sirolimus or paclitaxel in ≈65%, zotarolimus or everolimus in ≈30%	≈60
PEGASUS 2015[2]	12 vs 33	21 162	Composite of cardiovascular death, MI, and stroke	Decreased with extended DAPT (7.85% vs 9.04%), primarily driven by MI and stroke.	TIMI major†	Statistically significant increase in extended DAPT (2.6% vs 1.1%)	Ticagrelor	No stenting in 20%, BMS in 41%, DES in 39%	100% with ACS 1–3 y prior
OPTIDUAL 2015[3]	12 vs 33	1385	Composite of death, MI, stroke, and major bleeding	No difference	International Society on Thrombosis and Hemostasis‡	No difference	Clopidogrel	Sirolimus or paclitaxel in ≈35%, zotarolimus or everolimus in ≈60%	≈35

ACS indicates acute coronary syndrome; BMS, bare metal stent; DAPT, Dual Antiplatelet Therapy; DES, drug-eluting stent; DES-LATE, Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Event; MI, myocardial infarction; OPTIDUAL, Optimal Dual Antiplatelet Therapy; PEGASUS, Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin; TIMI, Thrombolysis in Myocardial Infarction.

*GUSTO (Global Utilization of Streptokinase and Tpa for Occluded Arteries) severe indicates intracerebral hemorrhage or bleed, resulting in substantial hemodynamic compromise requiring treatment. GUSTO moderate indicates requiring blood transfusion but not resulting in hemodynamic compromise.

†TIMI major: any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo magnetic resonance imaging) or clinically overt signs of hemorrhage associated with a decrease in hemoglobin of ≥5 g/dL.

‡International Society on Thrombosis and Hemostasis: fatal bleeding and/or symptomatic bleeding in a critical area or organ and/or bleeding causing a decrease in hemoglobin level of ≥20 g/L or leading to transfusion of ≥2 units of whole blood or red cells.

which could be a reason for no statistical difference.[5] The other 2 trials showed an absolute risk reduction in their primary efficacy end points by 1.6% (DAPT trial: death/MI/stroke), 1% (DAPT trial: stent thrombosis), and 1.3% (PEGASUS trial: cardiovascular death/MI/stroke) with prolonged DAPT,[2,5] although this was accompanied by a statistically significant increase in bleeding events (absolute increase in bleeding by 0.9% and 1.54% for DAPT and PEGASUS trials, respectively). However, there was no statistically significant difference in severe GUSTO or fatal bleeding.[2,5]

As noted above, 2 of these 4 trials showed an improved primary efficacy end point of >24 months DAPT compared with standard 12-month DAPT, whereas the other 2 showed no difference. The 2 studies showing a decrease in the primary end point were both larger trials, and both were driven primarily by a decrease in MI.[2,5] These 2 trials that showed a decrease in the primary efficacy end point also showed an increase in the bleeding risk. Given these differing findings, it is important to highlight some of the key differences between the trials. First, the PEGASUS trial, the largest of the randomized controlled trials, was the only extended DAPT trial to use ticagrelor.[2] The 2 smaller trials, DES-LATE and OPTIDUAL trials, used solely clopidogrel as the $P2Y_{12}$ inhibitor, whereas the DAPT trial used either clopidogrel or prasugrel.[3–5] In patients with ACS, both ticagrelor and prasugrel provide better cardiovascular outcomes compared with clopidogrel[6,7]; hence, it is possible that the differing results may be, in part, because of the particular $P2Y_{12}$ inhibitor used.

Certain high-risk conditions, such as ACS presentation, complex coronary anatomical features, diabetes mellitus, or renal failure, can influence the rate of future events. The PEGASUS trial involved only patients who experienced a prior ACS event 1 to 3 years before enrollment and had an additional high-risk feature (aged >65 years, diabetes mellitus, a second MI, multivessel disease, or chronic renal dysfunction). This key difference, along with its larger enrollment and power, could potentially explain the more significant decrease in primary efficacy end point compared with other trials with patients at a lower risk for ischemic events. Hence, it is not surprising that the event rates in the PEGASUS trial are much higher than those in other 3 trials,[2–5] as seen in Table 1. The other 3 trials[3–5] have a few key similar limitations. Notably, only patients who were adherent to medications and event free in the prior 12 months, without major bleeding or major adverse cardiovascular or cerebrovascular events, were eligible to continue into the extended DAPT arm, a study design that likely selects for those at lower risk for late adverse events and for bleeding. In addition, as detailed in Table 1, these trials included a variable proportion of patients receiving PCI for an ACS event to those receiving PCI without ACS.[2–5]

Patients receiving first-generation DESs are at higher risk for in-stent thrombosis because of delayed endothelialization, incomplete healing, and hypersensitivity.[10] Although DAPT reduces this risk, first-generation DESs had late and very late stent thrombosis, leading to development of improved second-generation DESs, which have been safer than the first-generation DESs.[11] This is important as ≈65% of stents in the DES-LATE trial, ≈40% in the DAPT trial, and ≈35% in the OPTIDUAL trial were older-generation (sirolimus and paclitaxel) stents,[3–5] which may, in part, contribute to some differences in the results of these trials. Of note, in the PEGASUS trial, ≈20% of participants did not receive a stent and still derived significant benefit from extended DAPT.[2]

So, what does the future hold for extended-duration DAPT? It is likely that adverse thrombotic and cardiac events will continue to decrease with the continuously improving polymer and stent technology, including development of ultrathin struts. Indeed, current trials, such as HOST-IDEA (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis - Coronary Intervention With Next Generation Drug-Eluting Stent Platforms and Abbreviated Dual Antiplatelet Therapy Trial) (ClinicalTrials.gov identifier NCT02601157), are recruiting patients to compare 2 ultrathin biodegradable and polymer-free stents with varying DAPT durations.[12] Even in ACS, the pendulum is swinging toward shorter DAPT durations. A recent randomized trial assessing safety of interruption of DAPT before 12 months in patients with ST-segment–elevation MI treated with DES reported the noninferiority of a shorter 6-month DAPT regimen compared with the standard treatment.[13]

A meta-analysis by Udell et al showed that extended DAPT beyond 1 year among stabilized high-risk patients with previous MI decreased the risk of major adverse

Table 2. Clinical Characteristics Benefiting From Extended-Duration DAPT

Clinical Characteristics Benefiting From Extended-Duration DAPT
ACS presentation/prior ACS event
Peripheral arterial disease
Diabetes mellitus
Renal dysfunction
Current cigarette use
Left ventricular ejection fraction <30%
Congestive heart failure
Increased procedure complexity
Stent diameter <3 mm
Vein graft PCI
High CAD burden
Older-generation stents

ACS indicates acute coronary syndrome; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

cardiovascular events but at the cost of an increased risk of major bleeding.[14] Given patients at increased risk of cardiovascular events are often also at higher risk of fatal bleeding events, determining which patients will benefit from extended DAPT can be challenging. Several clinical scores have been devised to aid clinicians in decision making of whether to continue or discontinue DAPT.[15,16] Although not perfect, the DAPT score is a validated risk score designed to identify patients for whom anticipated reduction in ischemia with continued DAPT outweighs the anticipated bleeding risk and vice versa.[15] Factors that contribute to a high DAPT score include diabetes mellitus, current cigarette use, prior PCI or prior MI, congestive heart failure or left ventricular ejection fraction <30%, MI at presentation, vein graft PCI, and stent diameter <3 mm; older age contributes to a lower DAPT score. In addition to the DAPT score, procedural complexity, burden of coronary artery disease, and stent type should also be taken into consideration while deciding on the optimal DAPT duration as extended DAPT reduces events progressively in those with greater procedural complexity.[17] Likewise, several subgroups from the PEGASUS trial, including those with peripheral arterial disease, diabetes mellitus, and renal dysfunction, had a particularly robust absolute risk reduction in major adverse cardiovascular events with extended DAPT.[18–20] Table 2 lists clinical characteristics that may benefit from more extended durations of DAPT.

In summary, prolonged DAPT appears more beneficial in patients with ACS treated with ticagrelor or prasugrel, with risk factors for recurrent ischemia at a cost of increased bleeding. However, any clinician will also recognize that not all bleeding or ACS events carry the same risk. Indeed, a clinician-patient shared decision making seems apt when discussing the optimal duration of DAPT. On the other hand, the clinician must also remember that trials evaluating DAPT over 5 years are currently lacking. Therefore, although possibly beneficial, any DAPT beyond this time period has no strong clinical evidence. With the continuous medication and stent advances, the optimal DAPT duration will likely be altered, but until then the current guidelines supporting DAPT duration of 12 months in ACS with further tailoring of therapy based on an individual risk of further ischemic or bleeding events provide an excellent framework to begin. Evolving research will help us further understand the risks and benefits of extended-duration DAPT, especially with the newer-generation stents.

Disclosures

None.

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