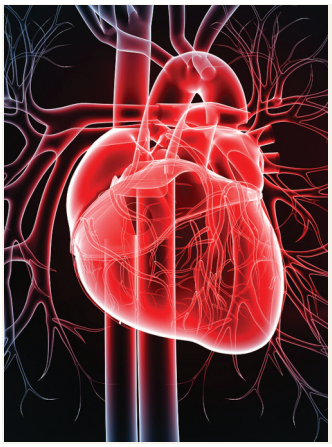

LOURDES CARDIOLOGY

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HEARTBEAT

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Update: Prolonged Duration of DAPT

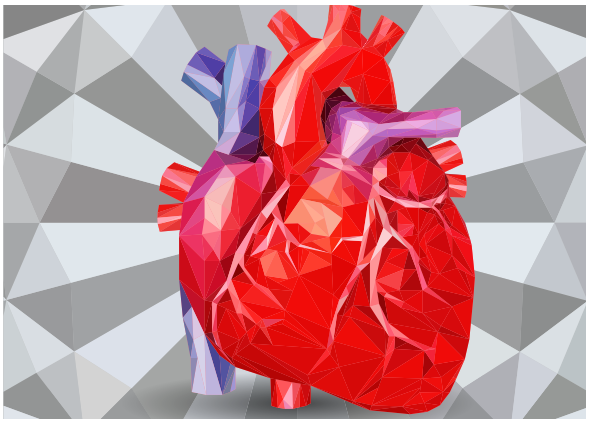
Last year, 2017, was the 21st anniversary of the publication of the first randomized clinical trial to establish the superiority of dual antiplatelet therapy (DAPT) over anticoagulant therapy among patients undergoing percutaneous coronary intervention (PCI).[1] Based on over 35 randomized clinical trials, including more than 225,000 patients, DAPT is among the most intensively investigated treatment options in the field of cardiovascular (CV) medicine. Along with progressive refinement of $P2Y_{12}$ inhibition strategies—embracing firstly safer (from ticlopidine to clopidogrel) and then more potent and predictable (from clopidogrel [Plavix] to ticagrelor [Brilinta] or prasugrel Effient]) drugs—research has concomitantly focused on optimal treatment duration.

The need to investigate longer DAPT regimens first arose from concerns over late and very-late stent thrombosis (ST) occurring after first-generation drug-eluting stent (DES) implantation.[2] Yet, the advent of safer, newer-generation DESs and the results of the most recent randomized controlled trials (RCTs) have established a major paradigm shift in the way DAPT should be conceived and used in clinical practice. DAPT remains a highly effective preventive treatment for ST across the board, even as the duration of DAPT has shortened from a year to as short as three months. However, the risks of late and (even more) very-late ST have declined considerably since the advent of newer-generation DESs. Hence, the risk of bleeding associated with DAPT prolongation beyond one year does not seem to be justified by the small absolute benefit observed in terms of very-late ST prevention.

On the other hand, there is emerging evidence that DAPT reduces the long-term risk of non-stent-related myocardial infarction (MI) as well as stroke. Hence, after 21 years of research, DAPT has moved from a local (i.e. stent-related) to a systemic treatment strategy (i.e. capable of preventing thrombotic arterial vessel occlusion), conveying global patient protection.

There is, however, confusion in the community around the optimal type and duration of DAPT in patients with established coronary artery disease (CAD), undergoing coronary revascularization or not.[3] This derives from apparently conflicting results arising from the available studies and limited evidence on various patient subsets (e.g. elderly patients, with comorbidities or at greater bleeding risk) in whom the trade-off between the benefits and risks of DAPT may differ from those observed in more selected patient cohorts included in trials.

Current evidence suggests that DAPT mitigates the risk of ST across the whole spectrum, from acute to very-late events. However, treatment with DAPT beyond one year after MI, or after PCI, exerts the majority of its benefit by reducing the rate of spontaneous MI, which is associated with mortality rates of 15%.[4] Nonetheless, because



continued antiplatelet therapy is also associated with increased bleeding risk, it is necessary to weigh this risk against the potential benefit. Current evidence suggests that the risk of bleeding in patients on DAPT is proportionally related to its duration both within and beyond one year of treatment duration. Since the benefits of prolonged DAPT, especially for mortality endpoints, appear highly dependent on prior CV history [such as prior acute coronary syndrome (ACS)/MI vs. stable CAD], and prediction models to estimate on-DAPT bleeding risk have been developed, an individualized approach based on ischemic vs. bleeding risk assessment is warranted.

Summary of the Clinical Problem

The combination of aspirin and platelet $P2Y_{12}$ receptor inhibitor therapy—DAPT—reduces the risk of recurrent ischemia following ACS and reduces risk of ST following PCI regardless of clinical presentation, yet it increases the risk of bleeding. Until recently, there have been few RCTs assessing the duration of treatment beyond one year.

Benefits and Harms

Decisions regarding the duration of DAPT inherently involve balancing a reduction in the risk of ischemia with an increase in the risk of bleeding. Overall, continued DAPT is associated with lower risks of MI and ST and a higher risk of nonfatal bleeding.[5,6,7]

Discussion

Individualization of therapy based on balancing the expected benefits and harms is central to deciding the duration of DAPT. A recent focused update[8] included a summary of factors associated with ischemic risk (i.e., extensive coronary atherosclerosis, or treatment of bifurcations or stent restenosis) or bleeding risk (oral anticoagulant therapy, low body weight or anemia), as well as a new decision tool—the DAPT Score (Table 1), that may help predict the expected benefit or risk of continued DAPT.[9] For patients receiving DAPT for one year without significant bleeding or ischemic events, a score of 2 or higher indicates a favorable benefit-to-risk ratio for continuing DAPT beyond one year. A score of less than 2 indicates an unfavorable benefit-to-risk ratio. The focused update does not recommend routine use of platelet function testing or genotyping to guide clinical decisions.

Table 1. DAPT Score (After 12 Months of Uneventful DAPT)

DAPT SCORE CALCULATION	
Variable	**Points**
Age ≥ 75 Years	-2
Age 65 ≤ 75 Years	-1
Age < 65 Years	0
Current Cigarette Smoker	1
Diabetes Mellitus	1
MI at Presentation	1
Prior PCI or Prior MI	1
Stent Diameter < 3 mm	1
Paclitaxel-eluting Stent	1
CHF or LVEF < 30%	2
Saphenous Vein Graft PCI	2

Risk Score as a numerical value between -2 and +10, where a higher DAPT score suggests that the benefit-risk ratio with prolonged DAPT may be favorable. Conversely, lower DAPT scores suggest that the benefit-risk ratio with prolonged DAPT is NOT favorable.

A free app for your phone provides a DAPT score.

Prolonged DAPT resulted in harm in patients with low DAPT scores undergoing PCI, but reduced risk for ischemic events in patients with high scores receiving paclitaxel-eluting stents. Whether prolonged DAPT benefits patients with high scores treated with contemporary drug-eluting stents requires further study.[10]

Update: More Perspective

In the May 2017 issue of *JAMA Cardiology*, Secemsky et al present findings that lend further support to end the one-size-fits-all era regarding the potency and duration of antithrombotic agents.[11] The DAPT Study does not unconditionally support the extension of DAPT beyond one year in all patients after coronary stenting.

Key Points

Continuing DAPT beyond 12 months based on theoretical concerns about very-late ST is unjustified. Even in the setting of the study by Secemsky et al, in which 32.4% of patients received paclitaxel-eluting stents (which were confirmed to be independently associated with higher ischemic risk), ST was rare (22.5% of ischemic events), while most ischemic events were MI not related to ST

(61.0% of ischemic events). Therefore, DAPT, after one year, should be continued with the chief aim of preventing spontaneous MI rather than protecting the few previously stented millimeters of coronary arteries. Treatment should be directed at secondary prevention with aspirin, statins, diet and exercise… *We are no longer treating the stents.*

Current evidence does not support a clear-cut survival advantage of extending DAPT beyond one year in patients with prior MI. The primary analysis from the PEGASUS-TIMI 54 trial showed that extended DAPT in patients with prior MI reduced CV events and increased bleeding but provided no mortality advantage.[12]

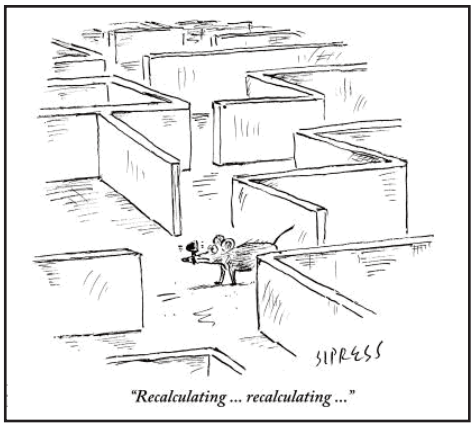
Rather, a survival advantage is more likely to result from established guideline-directed therapies—optimal medical therapy (OMT), including smoking cessation and the use of regular exercise, aspirin, statins, angiotensin-converting enzyme inhibitors and β-blockers.[13]

DAPT is not indicated in purely medically managed patients (i.e. without prior PCI) with stable CAD and no history of prior MI. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study included patients with stable vascular disease or at risk of atherothrombotic events, and showed that clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of MI, stroke or death from CV causes.[14]

Although longer DAPT reduces the risk for ischemic events compared with shorter DAPT, longer DAPT is also associated with greater mortality due to an increase in bleeding-related deaths.[15] Thus, in the large population of patients enrolled in these studies, prolonging DAPT increased the risk of bleeding and non-cardiac mortality in large part because of bleeding-related deaths—an association that became more evident when DAPT was prolonged for more than 18 months. Nonetheless, patients at high risk for ischemic events may still benefit from prolonged DAPT. The optimal DAPT duration for individual patients should be determined by considering the specific demographic and anatomic factors that determine their absolute and relative risks of ischemic versus bleeding events.

In another recent study from the October 2017 *JACC*, the authors conclude: "Complex target-lesion anatomy is associated with increased ischemic events, particularly within the first year after PCI. Among those without events in the first 12 months, the benefits of extending DAPT were similar in subjects with and without complex lesions (further supporting *'we are no longer treating the stent'*). A high DAPT score identified those experiencing the most benefit from extended treatment among patients with and without complex anatomy. (The Dual Antiplatelet Therapy Study [DAPT Study)."[16]

In summary, choosing between two evils occurring at similar frequencies and carrying comparable prognostic implications is still evil. Personalized treatment algorithms (DAPT score ≥ 2) maximizing benefits over risks represent the only sensible way forward. **OMT is key**, but we would consider continuing DAPT in high–risk post-MI patients with low bleeding risk along with aggressive secondary prevention treatment and a proton pump inhibitor after appropriate discussion with the patient.



"Recalculating ... recalculating ..."

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