A call for individualised medicine

Duration of dual antiplatelet therapy after coronary artery stenting

Ronald K. Binder[a], Thomas F. Lüscher[a,b]

[a] University Heart Centre, Cardiology, Schlieren Campus, University of Zurich, Switzerland
[b] University Hospital Zurich and Center for Molecular Cardiology, Schlieren Campus, University of Zurich, Switzerland

With the introduction of coronary artery stenting in the mid 1980s [1, 2] two new disease entities were born: coronary stent thrombosis (ST) [2] and coronary instent restenosis [3]. Whereas the latter was reduced by local antiproliferative drug delivery (drug eluting stents, DES) [4], the incidence of the former was decreased by administration of dual antiplatelet therapy (DAPT) [5–7] and better bicompatibility of newer generation DES [8].

After the roll-out of the first generation DES (Cypher® and Taxus®) an increased incidence of late and very late ST were observed in comparison with bare metal stents [9]. As DAPT reduces the risk of ST, guideline committees issued the arbitrary recommendation of 12 months DAPT after DES placement, without evidence from randomised controlled trials (RCTs).

In the meantime, various RCTs, which aimed at answering the question of optimal DAPT duration, have been published (fig. 1). These trials have not been uniformly designed and compared various DAPT combinations and durations (e.g., 3, 6, 12, 24, 30 months) in diverse patient populations receiving different types and generations of DES [10–13]. Some trials investigated the noninferiority of less than 12 months DAPT, while others tested the benefit of DAPT prolongation beyond a year. As RCTs with less than 12 months of DAPT did not show a significant increase in ischaemic endpoints (fig. 1) and there were signals showing an increased risk of bleeding under prolonged DAPT (fig. 2), the European Society of Cardiology reduced the recommended DAPT duration to 6 months after DES placement in patients with stable coronary artery disease [14].

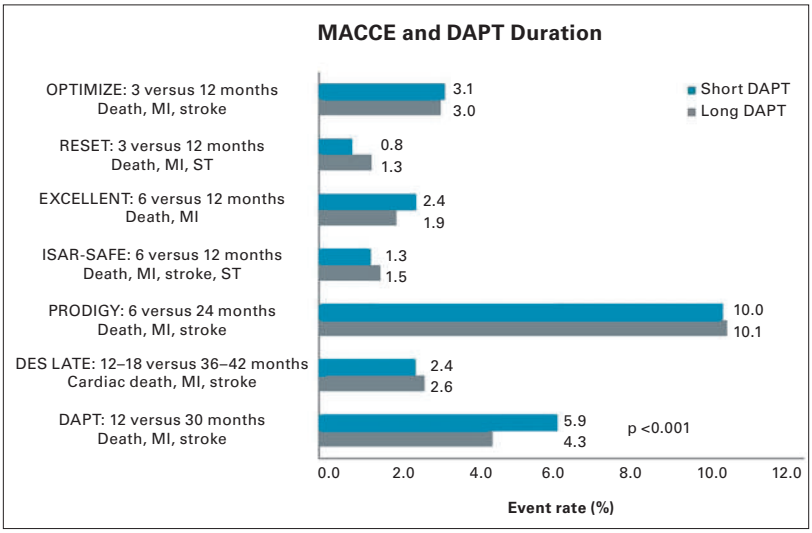

Figure 1: Most randomized controlled trials comparing different durations of dual antiplatelet therapy did not show a significant difference in the composite primary endpoint. (DAPT = dual antiplatelet therapy; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; ST = stent thrombosis)

Recently, the largest RCT in the field, the DAPT-trial, which compared 12 months versus 30 months DAPT after coronary stent placement in more than 9,000 patients, was published [15]. The prolongation of DAPT to 30 months led to a significant decrease of the combined primary endpoint of death, myocardial infarction or stroke compared with 12 months (4.3% vs 5.9%, p <0.001; fig. 1). Furthermore, the rate of ST was significantly reduced with 30 months DAPT (0.4% vs 1.4%, p <0.001). Of note, about half of the reduction in the primary endpoint could be attributed to a reduced incidence of spontaneous myocardial infarction, which was unrelated to previous coronary interventions, but rather reflected the natural history of coronary atherosclerosis. However, moderate or severe bleeding was significantly, albeit moderately increased with prolonged DAPT (2.5% vs 1.6%, p = 0.001). Surprisingly, all-cause mortality between 12 and 33 months was somewhat higher with prolonged DAPT with borderline significance (2.3% vs 1.8%, p = 0.04). Although the investigators did not provide an analysis of a combined endpoint that incorporated ischaemic as well as haemorrhagic events, extrapolation of the data suggests a marginal clinical benefit of 30 months DAPT over 12 months DAPT (ARR 1.6% vs 0.9% increased bleeding). Furthermore, there was a significant interaction between different stent types for the primary endpoint. As

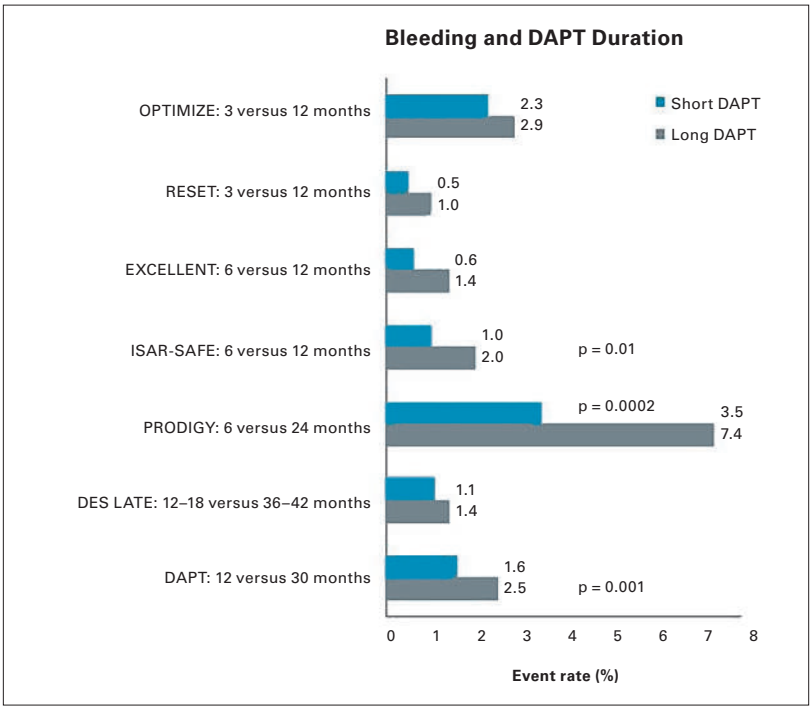

Figure 2: Bleeding events occurred more often during prolonged dual antiplatelet therapy, reaching statistical significance in some trials. (DAPT = dual antiplatelet therapy)

		Ischemic risk		
		Low	Moderate	High
Bleeding risk	Low	6 months	12–30 months	≥30 months
	Moderate	3–6 months	6–12 months	12 months
	High	≤3 months	3–6 months	6–12 months

Risk assessment may be based on clinical judgment until validated scores are established. Factors that influence the risk of bleeding or ischemia are mentioned in the main text.

Figure 3: Duration of dual antiplatelet therapy based on individual risk.

there is no levelling off in the incidence of very late ST with first generation DES, patients who received a paclitaxel-eluting stent had the highest benefit from prolonged DAPT. The increased biocompatibility of second and third generation DES leads to faster and better endothelialisation, which is reflected by a reduced incidence of late and very late ST compared with first generation DES [16]. The least benefit from 30 months of DAPT was observed in recipients of everolimus-eluting stents. These results have once again heated the debate over the optimal duration of DAPT after DES placement.

Patients have a unique and individual risk for ischaemic and haemorrhagic events. Antithrombotic therapy reduces the risk of atherothrombotic events, but increases bleeding rates. The therapeutic sweet spot between reduced ischaemia and increased bleeding markedly differs between patients. Risk factors for ST include changes in medication – most importantly the early discontinuation of DAPT – procedural issues (e.g., stent undersizing, incomplete stent expansion, incomplete apposition, inflow or outflow obstruction, persistent dissection, greater stent length, side branch stenting, overlapping stents, small vessel calibre, stent type) and patient characteristics (e.g., diabetes, acute coronary syndromes, left ventricular dysfunction, malignancy, among others).

Risk factors for bleeding include pharmacological factors (extent of platelet inhibition, combination of DAPT with oral anticoagulation, duration of DAPT, concomitant use of GP IIb/IIIa inhibitors), procedural factors (e.g., femoral approach, large sheaths, no vascular closure device) and patient characteristics (e.g., age, weight, gender, bleeding history, gastrointestinal or liver disease, renal dysfunction, history of cerebrovascular accident, malignancy). The initiation of antithrombotic therapy may unmask previously subclinical bleeding diastasis (e.g., patients with gastroduodeal erosions, diverticulosis or occult malignancies). Whereas risk scores for the assessment of ischaemic events in atrial fibrillation (e.g., CHA_2DS_2-VASc) or for the assessment of bleeding events in acute coronary syndrome patients (e.g., CRUSADE bleeding score) are well established, there are currently no validated risk scores for the long term prediction of ischaemic or haemorrhagic events in patients on antiplatelet therapy after coronary artery stent placement [17, 18].

The currently available evidence speaks for individualising the duration of DAPT, taking the patient's risk for ischaemic and haemorrhagic events into account (fig. 3). For example, a patient with a history of gastrointestinal bleeding and a short, large, newer generation DES in a simple coronary anatomy with little arteriosclerotic burden may benefit from a shortened DAPT duration of 6 months or less. A patient with a low bleeding risk, a complex coronary anatomy and DES placements in multiple arteries including long, overlapping stents in bifurcations or the left main artery should be rather treated with prolonged DAPT of more than 12 months or maybe indefinitely. As very late ST is rare for newer generation DES, the prolongation of DAPT beyond 12 months should currently be based on the risk of bleeding and the risk of new ischaemic cerebrovascular events. Further research on antiplatelet medication after DES focuses on assessment of different DAPT combinations, concomitant treatment with oral anticoagulants (e.g., PIONEER AF-PCI trial, RE-DUAL PCI trial), on comparisons of long-term single antiplatelet regimes (e.g., GLOBAL LEADERS trial) and the validation of risk scores for prediction of bleeding and ischaemic events after

DES placement. Meanwhile, clinicians need to decide on a case-by-case basis on the optimal duration of DAPT after DES placement taking all relevant patient and procedural factors that influence bleeding and thromboembolic risk into account [14]. At the same time, the changing landscape of scientific evidence and guideline recommendations should encourage anti-thrombotic management based on individualised clinical judgment.

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Correspondence:
Thomas F. Lüscher, MD, FRCP
Professor and Chairman
of Cardiology
University Heart Center
University Hospital Zurich
Raemistrasse 100
CH-8091 Zurich,
Switzerland
thomas.luescher[at]usz.ch