

## Novel directions for the management of dual antiplatelet therapy in patients with coronary artery disease

Francesco Costa<sup>a</sup>, Marco Valgimigli<sup>b</sup>

<sup>a</sup> Department of Clinical and Experimental Medicine, Policlinic "G. Martino", University of Messina, Italy

<sup>b</sup> Swiss Cardiovascular Centre Bern, Bern University Hospital, Switzerland

### Summary

Dual antiplatelet therapy has been extensively studied in the last two decades, giving opportunities for thorough evidence-based recommendations. The ESC/EACTS guidelines on DAPT in CAD provide guidance for DAPT type and duration, maintaining a patient-centred focus. Patient-specific and dynamic evaluation of the ischaemic and bleeding risks is key for optimal treatment decisions.

**Keywords:** DAPT, clopidogrel, prasugrel, ticagrelor, PRECISE-DAPT, ESC, guidelines, PCI, anticoagulant

### Introduction

Dual antiplatelet therapy (DAPT), the combination of aspirin and a P2Y<sub>12</sub> inhibitor, was first tested more than 20 years ago in patients undergoing percutaneous coronary intervention (PCI) and showed superiority compared with oral anticoagulation [1]. DAPT is now one of the most widely used treatments for secondary prevention in patients with coronary artery disease (CAD) suffering an acute coronary syndrome or undergoing coronary stent implantation [2]. In the last two decades, the introduction of novel and more potent P2Y<sub>12</sub> inhibitors [3, 4] and prolongation of their administration [5, 6] was found to progressively reduce the risk of recurrent ischaemic coronary events [7, 8]. At the same time, longer or more potent treatments were associated with an increased risk of bleeding complications, which are associated with a higher morbidity and mortality [9]. The need for informed decision-making and the huge amount of high-quality scientific data that has accumulated in the recent years prompted the creation of a dedicated document that summarises the evidence and provides a pragmatic guide for everyday clinical practice (fig. 1) [2, 10, 11].

### Novel directions for DAPT duration in patients with coronary artery disease

The focused update on DAPT duration was drafted in a joint effort of the European Society of Cardiology (ESC) and the European Association of Cardio-Thoracic Surgery (EACTS) task forces. It aimed to provide a novel approach

to decision-making about DAPT type and duration, based on a four-layer scheme focusing on treatment individualisation (fig. 2). This is hierarchically based on the *type of intervention* (PCI, coronary artery bypass graft or medical treatment alone without revascularisation), on the *treatment indication* (stable coronary artery disease or ACS), on the *type of device* used in the case of PCI (drug-eluting stent [DES], bare-metal stent [BMS], bioresorbable vascular scaffold [BVS], drug-eluting balloon [DEB]) and finally on the estimated *bleeding risk*. Treatment indication has been widely demonstrated to be one of the major drivers for DAPT duration [12, 13]. Patients presenting with ACS are at higher ischaemic risk, and remain at higher ischaemic risk for a longer period of time after the index event, hence justifying more potent and prolonged antiplatelet treatment [13–15]. Unlike in the past, the choice between a BMS and DES is no longer a driver for differences in treatment duration [2, 16, 17]. In fact, a DES is recommended as the default treatment strategy, and no specific preference for a BMS is based on anticipated DAPT duration. Novel recommendations have now been provided for BVSs, which are recognised as more thrombogenic devices requiring longer treatment [18]. Bleeding risk is formally included in the treatment algorithm as the final de-

**Figure 1:** Novel recommendations and treatment paradigms from the ESC/EACTS DAPT in CAD guidelines.

#### ESC/EACTS FOCUSED UPDATE ON DAPT IN CAD: NOVEL CONCEPTS

- Dual antiplatelet therapy duration should be reevaluated overtime and the approach to decision-making should be individualized and dynamic.
- The main (but not the only) factors to be considered for DAPT duration decision-making are clinical presentation, type of procedure and device used and bleeding risk.
- Dedicated risk scores are now available and can support decision-making for dual antiplatelet therapy duration.
- In selected patients, dual antiplatelet therapy may be extended beyond 12 months, and a preference may be given to Ticagrelor 60mg b.i.d. on top of aspirin.
- Patients with a concurrent indication for chronic oral anticoagulant carry an elevated bleeding risk, and a personalized approach based on the ischemic and bleeding risk should drive treatment decision.
- Proton pump inhibitors are indicated as long as a treatment with dual antiplatelet therapy is on-board.
- Elective surgery should be delayed for at least 1 month after percutaneous coronary intervention.

**Correspondence:**  
Marco Valgimigli, MD,  
PhD, FESC, Swiss Cardiovascular Center Bern, Bern University Hospital,  
CH-3010, Bern, marco.valgimigli[at]insel.ch

cision-making point for treatment duration, based on the assumption that patients considered at higher bleeding risk should receive a shorter treatment.

Finally, the document discusses for the first time indications for DAPT extension beyond 12 months, based on the evidence provided by the DAPT and the PEGASUS studies [5, 6]. The document's conclusion is that for patients who are not at high bleeding risk, who have tolerated treatment during the first 12 months without bleeding, and who have an elevated ischaemic risk, an extension of DAPT beyond 12 months may be reasonable. Among those with a prior myocardial infarction (MI) in whom treatment extension is considered, ticagrelor 60 mg b.i.d. may be preferred to clopidogrel or prasugrel, given its better efficacy/safety profile observed in DAPT extension studies [6, 19, 20].

### Current evidence for individualisation of DAPT duration

The ESC/EACTS guidelines on DAPT have a specific focus on treatment individualisation. Multiple studies have explored the effect of DAPT duration in several subgroups and may potentially be used to inform treatment individualisation based on single-patient characteristics. Factors explored in these studies were the clinical presentation at the time of the index event, the complexity of the PCI performed, the bleeding risk at baseline codified according to specific scores, and others.

### Clinical presentation

The clinical presentation at the time of the coronary event represents the first major determinant of the baseline ischaemic risk [21]. This is lower among patients presenting with stable CAD, increases in patients presenting with unstable angina and is highest among those presenting with MI. In a prespecified analysis of the PRODIGY trial that evaluated patients presenting with ACS or stable CAD, a significant heterogeneity of the treatment effect of long vs short DAPT duration was found for net adverse clinical

events (NACE) ( $p_{int} = 0.024$ ) [12]. This suggests a differential impact of DAPT duration depending on clinical presentation, with net harm from longer DAPT in stable CAD patients (hazard ratio [HR] 2.50, 95% confidence interval [CI] 1.35–4.69,  $p = 0.004$ ), and a substantial equipoise of a longer treatment duration in the ACS subgroup (HR 1.15, 95% CI 0.88–1.50;  $p = 0.29$ ) [12].

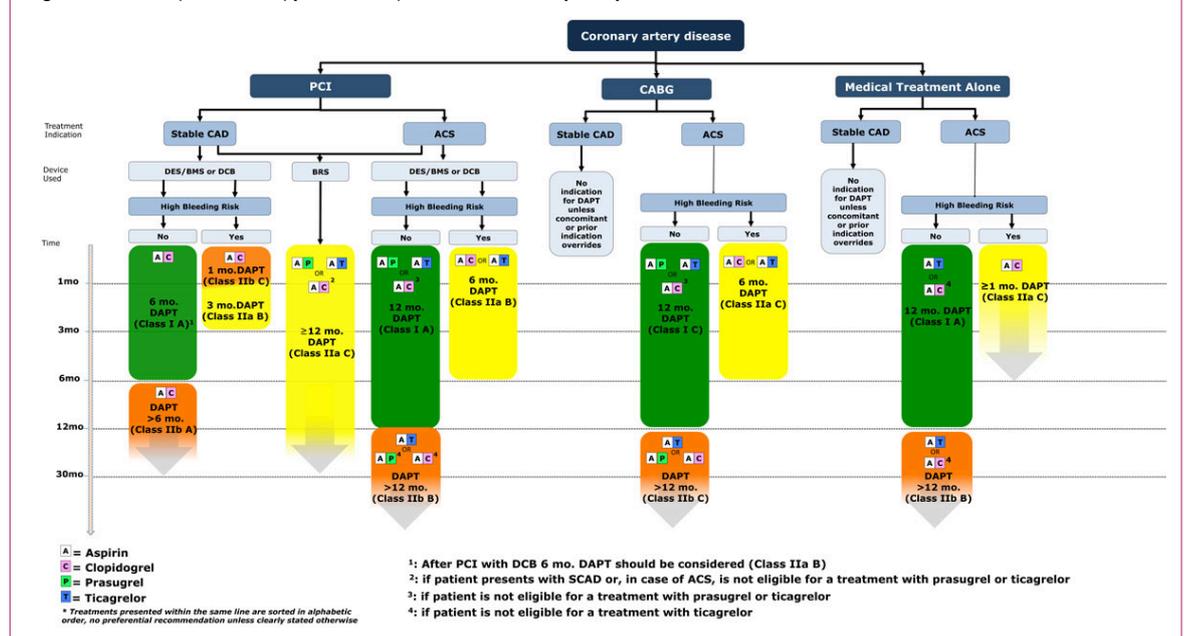
In a subgroup analysis of the DAPT trial focused on patients with or without MI at presentation, longer DAPT duration of up to 30 months significantly reduced major adverse cardiovascular and cerebrovascular events (MACCE) in patients with MI at presentation (3.9 vs 6.8%;  $p < 0.001$ ) but not in those without MI at presentation, with a positive interaction testing ( $p_{int} = 0.03$ ) [13].

The higher efficacy of prolonged DAPT in patients with MI at presentation is further supported by a meta-analysis of six randomised controlled trials including 33,435 patients, which found a significant reduction of cardiovascular death, MI or stroke (6.4 vs 7.5%; ARD = 1.1%;  $p = 0.001$ ) after a longer treatment with DAPT [22]. Based on these considerations, guidelines now provide different recommendations for DAPT duration based on clinical presentation (6 months of DAPT after PCI in patients with stable CAD and 12 months in patients with ACS).

### Complex PCI

PCI complexity has always been considered a major determinant for DAPT duration, but a lack of a standard definition limited consistent treatment selection [23]. A novel definition of PCI complexity has been endorsed in the document and includes six procedural factors: three-vessel PCI, implantation of three or more stents, three or more coronary lesions, bifurcation stenting, total stent length >60 mm, treatment of a chronic total occlusion. The presence of at least one of these elements indicating complex PCI was explored in a patient-level analysis of more than 9000 patients, which showed that long-term DAPT ( $\geq 12$  months) significantly reduced MACE (HR 0.56, 95% CI 0.350.89) compared with a shorter term DAPT ( $\leq 6$

Figure 2: Dual antiplatelet therapy duration in patients with coronary artery disease.



months) in patients undergoing complex PCI [24]. Similar results were also observed in the PRODIGY trial, in which patients with angiographic evidence of CAD in the left main or proximal left anterior descending coronary artery obtained a larger benefit from longer (24-month) as compared with shorter (6-month) DAPT duration [25]. Patients suffering stent thrombosis should also be considered for prolonged DAPT, given their higher risk of further stent-related adverse events [26]. Counselling patients regarding the importance of treatment adherence, especially those treated with complex PCI or with prior stent thrombosis is of paramount importance [27, 28].

### Risk scores

Use of a risk score to guide decision-making on DAPT duration was first explored in the PRODIGY trial, where patients were stratified according to the CRUSADE bleeding risk score into *high* (CRUSADE >40) vs *non-high* (CRUSADE ≤40) bleeding risk at baseline [29, 30]. In this analysis patients deemed at high bleeding risk had a significant increase in major bleeding and red blood cell transfusion when treated with 24- vs 6-month DAPT, whereas those not deemed at high bleeding risk did not suffer significant excess of bleeding with longer DAPT duration ( $p_{\text{int}} = 0.05$ ) [29].

In the following years specific tools generated from randomly allocated DAPT populations have been validated.

The DAPT score was generated from a population of 11,648 patients in the DAPT trial [31]. It includes nine clinical and procedural variables driving a score that ranges from -2 to +10 points. This tool has been validated for predicting the difference between the anticipated reduction in ischaemic events and the anticipated increase in bleeding events with extended DAPT. Patients with a score of 2 points or more appeared to derive a net benefit from 30 months of DAPT; in turn patients with a score of less than 2 points did not derive any benefit from treatment extension, and were better managed with a 12 months DAPT [31].

The PREdicting bleeding Complications In patients undergoing Stent implantation and subsequent Dual Anti Platelet Therapy (PRECISE-DAPT) score was generated from a pooled dataset of eight randomised controlled trials including a total of 14,963 patients treated with PCI and subsequent DAPT [32]. It includes five clinical and laboratory variables driving a score that ranges from 0 to 100 points. This tool has been validated for evaluation of the benefit and risk of 3–6 months vs 12–24 months of DAPT. Patients with a score of 25 points or more did not derive any benefit from longer DAPT and had a significant increase in major bleeding; patients with a score of less than 25 points did not experience a significant excess of bleeding but had a reduction of ischaemic events from longer treatment with DAPT [32].

### Other subgroups

Multiple characteristics and comorbidities that have been traditionally considered for DAPT duration decision-making [23] failed to show a significant treatment by subgroup heterogeneity in specific analyses. Hence there is no compelling evidence to support a different type and duration

of treatment for gender [33], diabetes mellitus [34–36], chronic kidney disease [37–40] or smoking status [41].

### Concomitant need for long-term oral anticoagulation

Patients with a need for long-term oral anticoagulation (OAC) represent a higher bleeding risk population that has invariably been excluded from randomised clinical trials of DAPT duration [42]. In the WOEST and PIONEER-AF PCI study, a total of 573 and 2124 patients on OAC undergoing PCI were enrolled respectively. Both studies found a significant reduction of the primary endpoint of bleeding events with a strategy of dual therapy (OAC + P2Y<sub>12</sub> inhibitor) vs triple therapy (OAC + P2Y<sub>12</sub> inhibitor + aspirin) with no apparent increase in coronary or cerebrovascular ischaemic events. However, neither study was powered to detect differences in ischaemic events.

For this reason, and in line with the philosophy of the ESC DAPT guideline document, a focused approach on treatment individualisation is suggested for patients on OAC based on the baseline ischaemic risk and bleeding risk. Three different treatment paths are suggested (fig. 3) [2]. Treatment with potent P2Y<sub>12</sub> inhibitors is contraindicated during OAC treatment, and non-vitamin K oral anticoagulant (NOACs) should be preferred over vitamin-K antagonists (VKAs) to improve safety [2].

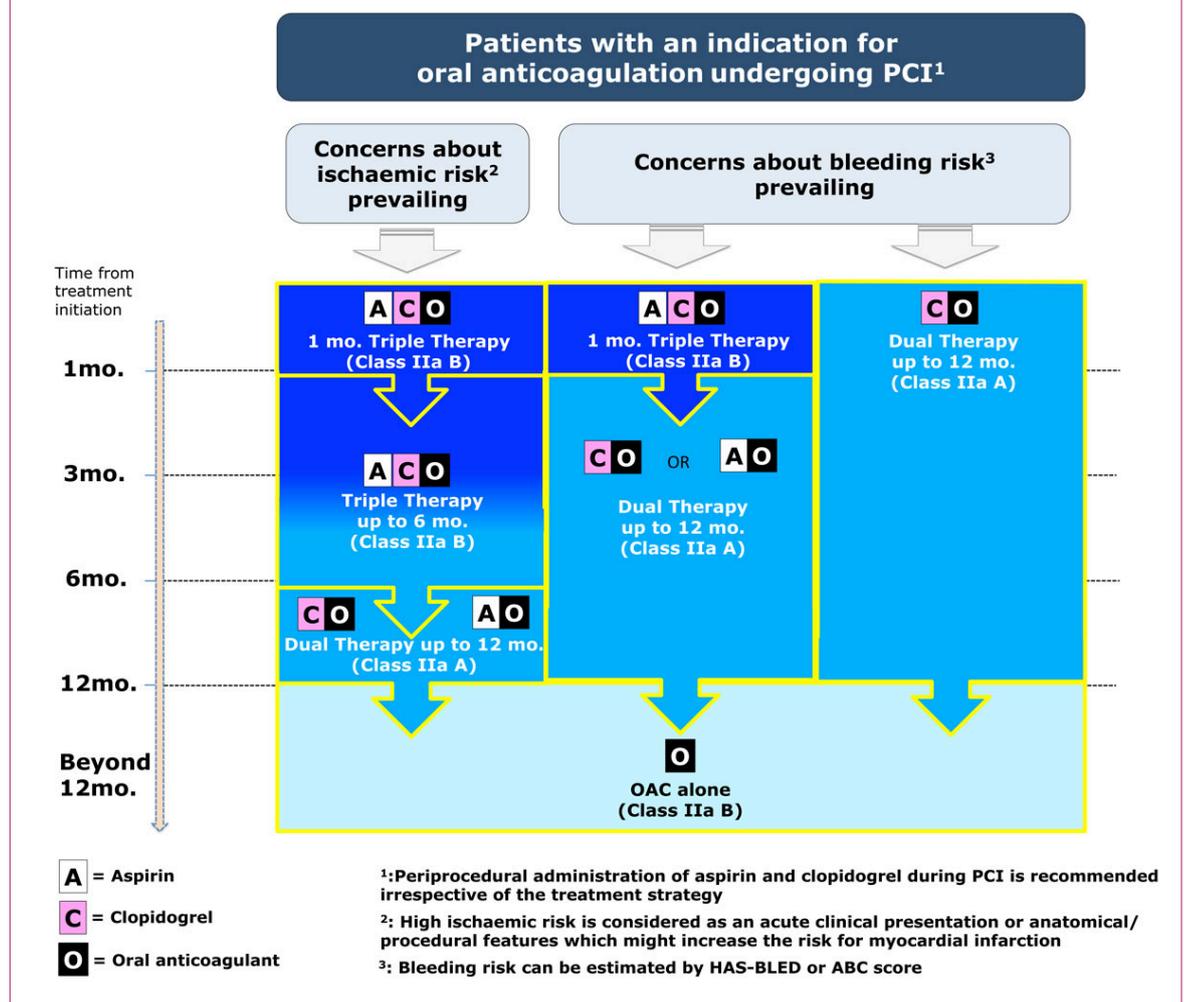
More recently, and after publication of the ESC DAPT guidelines, the RE-DUAL PCI trial and a large patient-level meta-analysis found a similar reduction of bleeding events with dual vs triple therapy, with no difference in the rate of trial-defined major adverse cardiac events, thus further supporting the safety of the dual therapy strategy. Nonetheless, it has to be highlighted that in most of the randomised patients, dual therapy was associated with NOAC administration, whereas triple therapy included VKAs. Hence, with the current data it is difficult to fully understand the risk/benefit profile of a triple vs a dual therapy strategy including NOACs. Future study results will be soon available and will help to clarify this issue (AUGUSTUS [NCT02415400], ENTRUST-AF-PCI [NCT02866175]).

### DAPT and proton pump inhibitors

As compared with aspirin alone, DAPT increases the risk of bleeding, and this is most commonly related to gastrointestinal bleeding events [43]. The association of a proton pump inhibitor (PPI) could reduce this risk by preventing upper and lower gastrointestinal bleeding [44]. The COGENT trial, which randomised patients treated with DAPT to omeprazole or placebo, found no difference in the rate of ischaemic events and a 50% reduction of major bleeding events among patients treated with a PPI [14]. For this reason, during DAPT, PPI use (preferentially pantoprazole or rabeprazole, which appeared to have the lowest propensity for clinically relevant drug-drug interactions) is recommended to reduce the risk of major gastrointestinal bleeding.

### DAPT and surgery

A novel set of recommendations now supports specific decision-making for the timing of elective surgery and the

**Figure 3:** Treatment decisions for patients with concomitant indications for chronic oral anticoagulation and dual antiplatelet therapy.

time of withdrawal of the P2Y<sub>12</sub> inhibitor [2]. It is recommended to maintain treatment with aspirin perioperatively in most of the situations when surgical bleeding risk allows [45], the need to interrupt the P2Y<sub>12</sub> inhibitor represents in most cases the limiting step for early elective surgery after PCI. Elective, non-emergency surgery requiring P2Y<sub>12</sub> inhibitor interruption should be delayed for at least 1 month after stenting [46], and a delay of 6 months is recommended whenever possible to reduce the risk for recurrent ischaemic events. When a 6-month delay is not feasible, early surgery (1–6 months after PCI) should be considered in patients initially treated for stable CAD, and may be considered in those treated for an ACS. In order to reduce intra-operative bleeding, ticagrelor should be interrupted at least 3 days before surgery, clopidogrel at least 5 days before surgery and prasugrel at least 7 days before surgery [2]. The P2Y<sub>12</sub> inhibitor, when still indicated, should be restarted as soon as deemed safe and when the operative bleeding risk is controlled.

### Take-home messages

1. The overall duration and type of dual antiplatelet therapy should be individualised based on single-patient characteristics.
2. Patients with a concomitant indication for chronic oral anticoagulation should be considered at higher bleed-

ing risk and careful treatment decisions should be prompted by ischemic vs. bleeding risk evaluation.

3. A proton-pump inhibitor should be administered while DAPT is on-board to reduce the risk of gastrointestinal bleeding.
4. Elective, non-emergency surgery should be delayed for at least 1 month after PCI and preferably for 6 months. If the surgery cannot be performed while the patient is on P2Y<sub>12</sub> inhibitor therapy, aspirin should be maintained if the bleeding risk allows; ticagrelor, clopidogrel and prasugrel should be interrupted at least 3, 5 and 7 days before surgery, respectively.

### Disclosure statement

No financial support and no other potential conflict of interest relevant to this article was reported.

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