

Dual Antiplatelet Therapy in Cardiology: Novel Guidelines

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• Introduction

In 1996, in coronary patients who had been treated with percutaneous coronary interventions (PCI) dual antiplatelet therapy (DAPT) with the COX1/2 inhibitor aspirin and the P₂Y₁₂ inhibitor clopidogrel was found to be more effective than oral anticoagulation (OAC) in reducing the risk of recurring ischemic coronary events [1]. DAPT became a standard therapy in cardiac patients with acute coronary syndrome (ACS) and in those treated with PCI. In the last years, prasugrel [2] and ticagrelor [3], more potent P₂Y₁₂ inhibitors than clopidogrel, were marketed and the DAPT duration was prolonged [4,5]. The more potent and longer DAPT further reduced the risk of ischemic coronary events [6,7] but was associated with an increased risk of bleeding complications and a consequent higher morbidity and mortality [8].

Because of a huge amount of new scientific data on DAPT the European Society of Cardiology (ESC) and the European Association of Cardio-Thoracic Surgery (EACTS) recently updated the guidelines on DAPT [9-12]. It is remarkable that some authors, e.g. Costa (in 23 papers), Valgimigli (in 15 papers), and Ariotti (in 11 papers) are extremely active in the presentation of data on DAPT. Thus, this short review derives the majority of data from the same highly active group of investigators.

• Presentation of cardiac ischemic event and DAPT

The PRODIGY trial evaluated patients presenting with either stable angina pectoris (AP) or ACS and found that the impact of DAPT duration differs according to the clinical presentation of myocardial ischemia [14-16]. The net side effects of a longer DAPT duration are greater among patients with stable AP and smaller among patients with ACS.

Considering these data, actual guidelines [9-12] offer different recommendation for DAPT duration after PCI according to clinical presentation of myocardial ischemia. *Patients with stable AP at presentation should be treated with DAPT for 6 months. Conversely, patients treated for ACS require a potent and 12 months DAPT because are and remain at higher risk for a longer period of time after the initial event [13,14].* Also, in the subgroup analysis on patients with or without

myocardial infarction (**MI**) at presentation, the PRODIGY trial found that a longer DAPT duration of up to 30 months significantly reduced major adverse cardiovascular and cerebrovascular events (**MACCE**) among patients with MI at presentation, but not among those without MI [17].

The higher efficacy of prolonged DAPT in patients presenting with MI is also supported by the PEGASUS studies [4,18,19]. A meta-analysis of 6 randomized trials including 33,435 patients show that *in patients presenting with MI, cardiovascular death or MACCE are significantly reduced by a longer DAPT duration* [20].

In conclusion, *the clinical presentation of the cardiac ischemic event at baseline is the first major determinant of the recurring ischemic risk, but the bleeding risk is formally included in the decision of type and duration of DAPT and patients at high bleeding risk should receive a shorter DAPT treatment* [9-13]. Patients who have been treated with DAPT during the first 12 months without bleeding, who are at high ischemic coronary risk and are not at high bleeding risk a DAPT duration beyond 12 months may be reasonable. Ticagrelor has been proven to have a better efficacy and safety than prasugrel and clopidogrel, and *in patients with a prior MI* who are considered for a DAPT treatment beyond 12 months, ticagrelor 60 mg bid may be a better choice [4,20,21].

• **PCI complexity and DAPT**

PCI complexity was always considered important for DAPT duration, but the interpretation was complicated by lacking standardized definitions for PCI complexity [22]. In more than 9,000 patients the PCI complexity was judged according to 6 interventional factors: • 3-vessel PCI, • implantation of 3 or more stents, • 3 or more complex coronary lesions, • bifurcation stenting, total stent length >60 mm, and • treatment of a chronic total coronary occlusion [23]. Considering the presence of at least one of the above factors, it was found that a >12 months DAPT duration significantly reduced MACCE compared to a ≤6 months DAPT duration.

Lastly, the PRODIGY trial [24] found that in coronary patients with occlusion in the left main or proximal left anterior descending artery a 24 months DAPT duration had larger benefits as compared with 6 months DAPT duration.

• **DAPT in bare metal stents, drug eluting stents and in-stent thrombosis**

Bare metal stents (**BMS**) are more thrombogenic than drug eluting stents (**DES**) [25]. However, the distinction between BMS or DES is no longer important for choosing the duration of DAPT and the therapy is based on the above described arguments [2,3,26,27].

Patients with an in-stent thrombosis should be treated with a prolonged DAPT duration because they have a higher risk of recurring stent-related ischemic effects [28]. Of note, patients who need a prolonged DAPT, e.g. those with complex PCI or with in-stent thrombosis, must be informed in order to adhere to treatment [29,30].

• DAPT risk scores

The PRODIGY trial [30,31] used the CRUSADE bleeding score to stratify patients treated with DAPT. At baseline patients were classified into *high* (CRUSADE score >40) and *non-high* (CRUSADE score ≤40) bleeding risk. When treated with 24- versus 6-month DAPT *patients at high bleeding risk had a significant increase in major bleeding and need for erythrocyte transfusion. Conversely, patients at non high bleeding risk did not suffer significant excess of bleeding with longer DAPT duration.*

Yeh et al. [33] generated a DAPT score in 11,648 patients. This score includes 9 clinical and procedural variables and ranges from -2 to +10 points. This score has been useful for predicting the difference between the desired reduction in ischemic events and the anticipated increased in bleeding events with extended DAPT duration. *Patients with a score of ≥ 2 points appear to get a net benefit from 30 months of DAPT duration. Conversely, patients with a score <2 points did not benefit for this long DAPT duration and were better treated with a 12-months DAPT duration.*

The PREdicting bleeding Complications In patients undergoing Stent Implantation and subsequent Dual AntiPlatelet Therapy trial (PRECISE-DAPT) [34] pooled data of 8 randomized trials including 14,963 patients treated with PCI and subsequent DAPT and generated a score (ranging from 0 to 100 points) from 5 clinical and laboratory variables. This score was used to evaluate benefit and risk of a 3-6-month DAPT duration versus a 12-24 month DAPT duration. *Patients with a ≥25 points score did not benefit from longer DAPT duration and had a significant increase in major bleeding. Conversely, patients with a <25 points score had a significant reduction of ischemic events without excess bleeding.*

In conclusion, the coronary re-ischemic risk is: • lower among patients presenting with stable AP; • higher among patients presenting with unstable AP; and • even higher among patients presenting with acute MI.

• DAPT, co-morbidities and gender

In the past co-morbidities and gender were considered for deciding DAPT duration [22]. However, it has been shown that these considerations are useless in decision making. Also, there is no compelling evidence to support a different type and duration of DAPT considering gender (35), chronic kidney disease (36-38), diabetes mellitus [39-41] and smoking status [42].

- **DAPT and surgery**

The Canadian Cardiovascular Society, the AHA/ ACC (43) and the ESC/EACTS guidelines on DAPT [11] have given recommendations on the timing of elective surgery in patients on DAPT. *The indication for DAPT is based on the medical indication but the bleeding risks must be considered.* The bleeding risk derives from the surgical intervention, where neurosurgical interventions induce the highest bleeding risk [43]. When P₂Y₁₂ inhibition is used, elective surgery should be delayed for at least 1 month [44] but, If the bleeding risk allows, aspirin should be maintained [45]. On the other hand, whenever possible, elective surgery should be delayed for 6 months to reduce the coronary ischemic risk related to a less intensive antiplatelet therapy. Surgery after 1-6 months may be feasible in patients with stable AP, and may be considered in those with ACS [11]. To reduce the bleeding risk, prasugrel ought to be interrupted at least 7 days before surgery, clopidogrel at least 5 days before, and ticagrelor at least 3 days before [11]. If still indicated, the P₂Y₁₂ inhibition should be restarted as soon as possible when the surgical bleeding is controlled.

- **DAPT and proton pump inhibitors**

DAPT carries a greater bleeding risk than aspirin alone, mostly manifested as a gastrointestinal bleeding [46]. In patients treated with DAPT the use of a proton pump inhibitor (**PPI**) could reduce the risk of gastric bleeding. Indeed, the COGENT trial [47] found a 50% reduction of major bleeding in patients treated with clopidogrel when omeprazole was added to the therapy, without a change in the ischemic coronary risk. At present, pantoprazole or rabeprazole, which have less propensity for drug-drug interactions, are often used in patients on DAPT. However, it should be considered that PPI should reduce the gastric bleeding risk without reducing the jejunal bleeding risk. *Therefore, an increased risk for intestinal bleeding remains present in patients treated with DAPT.*

- **DAPT and oral anticoagulation.**

Most patients with atrial fibrillation (**AF**) are treated with oral anticoagulants (**OAC**). Approximately 20–45% of patients with AF have evidence of CAD and, depending on the presentation of the myocardial ischemia, may require coronary revascularization with either PCI or coronary artery bypass grafting [13,48-51]. Patients with AF and coronary artery disease were usually excluded from randomized trials of DAPT duration [51]. However, these patients represent a very high bleeding risk population with increased morbidity and mortality [48,51].

The WOEST trial [48] enrolled 573 patients and the PIONEER-AF PCI study [49] studied 2,124 patients on OAC who underwent PCI. Both studies found a significant reduction of the primary endpoints of bleeding event with dual therapy (DT), OAC + P₂Y₁₂ inhibitor, vs a triple therapy (TT), OAC + DAPT, without an apparent increase in coronary or cerebral ischemic events. Of note, neither study was powered to detect difference in ischemic events.

Based on the available data the ESC DAPT guidelines [9,12] suggest a focused individualized approach, considering the ischemic and bleeding risks. Treatment with potent P₂Y₁₂ inhibitors is contraindicated during OAC therapy, and non-vitamin oral anticoagulants (NAOC) should be preferred over vitamin-K antagonists (VKA). However, after publication of the ECS DAPT guidelines, the RE-Dual PCI trial [52] and a recent meta-analysis [53] found a similar reduction of bleeding events with DT vs TT, with no differences in the rate of trial-defined MACCE. These recent data seem to support the safety of TT, but is it of note that that in most randomized patients DT was used with NOAC, whereas the TT included VKA.

Interestingly, the New Real-World Study with Xarelto® [54] found that, against current contraindications, many patients treated with rivaroxaban were also receiving either ticagrelor or prasugrel. Fortunately the bleeding risk was not increased. Therefore, with the available data is it difficult to evaluate appropriately the risk/benefit profile of a TT vs DT with NOAC and running studies are evaluating the problem [54,55].

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