The Janus Face of the Dual Anti-Platelet Therapy (DAPT) after Myocardial Infarction. What can be done to overcome the Risk by the Beneficial Potential of its use?

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Editorial

Cardiovascular disease is the leading cause of death worldwide. Acute Myocardial Infarction (AMI) substantially contributes to this mortality, accounting for almost 1.8 million annual deaths [1]. Patients who had a myocardial infarction are at heightened risk for a recurrence of the ischemic event over the long term [2-4]. Thus, extensive research efforts were made to improve the management of available therapeutic tools that can limit the side effects and implement them in clinical practice. Based on over 35 randomized clinical trials enrolling more than 225,000 patients, dual anti-platelet therapy, DAPT, is among the most intensively investigated treatment options in the field of cardiovascular medicine and it is shown to reduce the risk of recurrent infarction in patients with ST-Elevation Myocardial Infarction (STEMI) [5-9], by decreasing the mortality rate of 12% [10].

DAPT consists of the combination of aspirin and an oral inhibitor of platelet P2Y12 receptor for Adenosine 5’-Diphosphate (ADP) that includes safer first-generation drugs such as ticlopidine and clopidogrel, as well as more potent and predictable drugs such as prasugrel or ticagrelor. DAPT is recommended for up to 12 months in STEMI patients who underwent primary Percutaneous Coronary Intervention (PCI) as well as for patients undergoing fibrinolysis with subsequent PCI [11,12].

Because continued DAPT beyond 12 months is associated with an increased risk of bleeding, research has more recently focused on the optimal treatment duration. Multiple studies have shown that shortening the treatment from 12 months (or longer) to 6 months reduces the event of bleeding, with no apparent trade-off in ischemic event [13,14]. For example, the PROLonging Dual Antiplatelet Treatment After Grading stent-induced Intimal hyperplasia study (PRODIGY) showed that individuals with high bleeding risk (bleeding score > 40 as defined by the CRUSADE) treated with DAPT for 24 months had bleeding complications or needed transfusion with no additional ischemic benefits compared to patients treated for 6 months; whereas, patients with a CRUSADE bleeding score < 40 did not show such bleeding liability [14,15].

Why is it necessary to investigate on the optimal DAPT duration? In 2004, a study by McFadden et al reported 4 cases of late and very late stent thrombosis occurring after first-generation Drug-Eluting Stent (DES) implantation [16], that resulted in myocardial infarction. All these cases occurred soon after the interruption of the antiplatelet therapy. Despite DAPT remains the mostly effective preventive treatment for stent thrombosis across the board, the risk of bleeding associated with DAPT beyond 1 year is higher compared to the small benefits observed in terms of stent thrombosis prevention [17] and along with the advent of safer newer-generation DESs, prolonged DAPT appears unnecessary. On the other hand, there is emerging evidence that DAPT reduces the long-term risk of non-stent-related MI as well as stroke.

According to the data collected from the 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 (PEGASUS-TIMI 54) trial, extension of DAPT up to 3 years can be beneficial [18]. More specifically, PEGASUS-TIMI 54 trial analyze a total of 21,162 patients on aspirin treatment plus ticagrelor (90 or 60 mg b.i.d.) or placebo and show a reduction of Major Adverse Cardiovascular Events (MACE) with ticagrelor at both doses compared to placebo (hazard ratio, HR 0.85, 95% Confidence Interval [CI] 0.75-0.96, P=0.008 for 90 mg vs. placebo; HR 0.84, 95% CI 0.74-0.95; P=0.004 for 60 mg vs. placebo). Despite the fact that the incidence of bleeding in both ticagrelor groups was significantly augmented compared to the aspirin monotherapy (HR 2.32, 95% CI 1.68 to
Despite DAPT has increased overtime in clinical practice, its “Janus-faced” nature requires an effort to mitigate the risk of bleeding complications while the patient is on DAPT. It highly reduces the risk of MI recurrence (12%), but on the other hand it increases the risk of bleeding especially when it extended up to 1 year or more. In order to control such undesirable effect, different approaches can be considered. First, it is important to control modifiable risk factors for bleeding, such as hypertension or concomitant use of another anticoagulant. Second, it can be managed the dose of the oral anticoagulant and use low dose of aspirin, low dose of P2Y12 inhibitor as appropriate. Of note, the progressive refinement of P2Y12 inhibition strategies increases the possibility to select the appropriate anticoagulant per each patient if drug-specific contraindications exist. Furthermore, it is fundamental to associate PPI as routine therapy to prevent gastric bleeding. Finally, the benefits of prolonged DAPT, especially for mortality endpoints, appear highly dependent on each patient cardiovascular history [such as prior ACS/MI vs. stable CAD], and prediction rules to estimate on-DAPT beneficial (reduction of ischemic > bleeding)/risk (reduction of ischemic < bleeding) potential have been developed, thus an individualized approach based on ischemic vs. bleeding risk assessment is warranted.

References


