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Dual Antiplatelet Therapy after ACS: Time to Reconsider the 12 Months for All

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ABSTRACT

After percutaneous coronary intervention for acute coronary syndrome (ACS), dual antiplatelet therapy (DAPT) with aspirin plus a P2Y12 inhibitor agent is a cornerstone treatment. Despite the emergence of new generation of antiplatelet agents (i.e. prasugrel and ticagrelor) with a reduction in ischemic recurrences, 12 months DAPT is still the gold standard. However, neither the role of ischemic risk persisting after 12 months nor the importance of bleeding risk with these more effective platelet agents cannot be overlooked. Therefore, DAPT after ACS should now be individualized according to ischemic and bleeding risk balance.

Keywords: Antiplatelet therapy; Aspirin; Bleeding

DESCRIPTION

Dual Antiplatelet Therapy (Dapt) Duration: What did the Guidelines Originally Say?

Current European and American guidelines recommend the use of DAPT for 12 months after acute coronary syndrome (ACS) with the highest level of evidence (IA) [1,2]. The first trial (CURE) show the superiority of DAPT with aspirin plus clopidogrel over aspirin alone [3,4]. However, during the 12 months of DAPT, a significant proportion of patients have recurrent ischemic events on Clopidogrel, which is why the new P12Y12 blockers have been developed. The TRITON TIMI 38 trial demonstrated the superiority of DAPT with aspirin plus prasugrel over aspirin plus clopidogrel for a mean duration of 14.5 months (6 to 15 months) and the PLATO trial demonstrated the superiority of ticagrelor plus aspirin versus clopidogrel plus aspirin for a mean duration of 9.3 months (6 to 12 months) [5,6]. In both studies, the new P2Y12 blockers reduced the risk of ischemic recurrence but increases the bleeding complications. Therefore, the newer P2Y12 blockers in combination with aspirin are recommended in first-line therapy for ACS compared to clopidogrel [1,2] However, regardless of P2Y12 inhibition, the risk of bleeding increases with the duration of DAPT [7]. Even if, duration of 1 year remains the rule, patients can benefit of an individualization of the DAPT duration according to their ischemic and bleeding risk.

Can we Make it Shorter than 12 Months after ACS?

After percutaneous coronary intervention (PCI), DAPT is essential to reduce the risk of stent thrombosis and revascularization of the target lesion, but also to limit the risk of ischemic events at other sites [8]. Thanks to the development of the latest generation of stents, which limits the risk of stent thrombosis, the duration of this DAPT can be reduced, particularly for patients at high risk of bleeding [9,10].

This is shown by randomized studies that have compared, in patients at high bleeding risk, bare metal stent versus last generation drug eluting stent with a DAPT of one month [11-13]. In fact, drug eluting stents were superior to bar metal stents in terms of ischemic recurrence. This is why it seems acceptable today, in very high bleeding risk, to reduce the duration of DAPT to one month with the use of a drug eluting stent, even if

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this strategy is reserved for much selected cases [14].

Similarly, data from meta-analysis and the PRECISE DAPT study have shown that the reduction of DAPT to 3/6 months in patients at high bleeding risk is non-inferior to a 12-month DAPT [15-17]. Therefore, it appears that this duration may be an acceptable compromise between ischemic prevention and limiting bleeding risk in patients at high bleeding risk.

If curative anticoagulation is indicated, the combination with DAPT significantly increases the risk of bleeding [18,19]. Therefore, this association should be as short as possible and the general consensus is to stop the DAPT at one month after an ACS to maintain a single antiplatelet agent in addition to oral anticoagulation [20]. However, in cases of very high bleeding risk, DAPT could be omitted and replaced by the association of oral anti-coagulant (OAC) plus clopidogrel. Currently the anticoagulation of choice is the new generation of oral anticoagulants [21,22]. The only P2Y12 that can be recommended for DAPT in those patients is clopidogrel [14]. If the ischemic risk is major without risk of bleeding, the triple therapy could be extended to 3 or 6 months in case of good tolerance.

Can we Make it Longer than 12 Months after ACS?

Some patients at high ischemic risk may benefit from prolonged treatment beyond 12 months after ACS. In fact, analysis of pilot studies (CURE, PLATO and TRITON TIMI) and registry data have shown that the risk of recurrence of cardiovascular events decreases after 12 months of DAPT but persists and affects prognosis particularly in patients with ACS [4-6]. The DAPT trial evaluated the prolongation of aspirin plus thienopyridine at 12 months after ACS versus discontinuation of thienopyridine [23]. Prolongation of DAPT reduced risk of recurrent cardiovascular events, but with excess bleeding and non-cardiovascular mortality. Similarly, the PEGASUS-TIMI 54 is a randomized study, including patients with a history of ACS for more than one year, comparing a DAPT with ticagrelor or placebo in addition to aspirin [24]. The risk of ischemic events is decreased in patients receiving aspirin plus ticagrelor. However, ticagrelor increases the bleeding risk but not the risk of fatal hemorrhage resulting in a risk-benefit balance in favor of ticagrelor in these patients. Therefore, the current challenge is to identify patients who may benefit from this strategy because it is both associated with a reduction in ischaemic recurrence but offset by an increased risk of bleeding. Therefore, assessment of ischemic bleeding is central and should be reassessed at follow-up to adjust the duration of DAPT.

De-Escalation Strategies after ACS: What to do?

The critical thrombotic period after ACS is observed in the first days/weeks following the cardiovascular event, therefore de-escalation strategies with early potent antiplatelet therapy during the acute phase followed by less potent antiplatelet therapy have recently been studied [25-27].

The TROPICAL-ACS study included 2619 patients with PCI for ACS who were randomized to either standard therapy with prasugrel for 12 months or tapering therapy (prasugrel followed by one week of platelet-function-guided maintenance therapy with clopidogrel or prasugrel starting on day 14 after hospital discharge) [28]. After 1 year, the ischemic components of the primary endpoint were similar between the 2 groups but without benefit on bleeding risk.

The TOPIC study is a monocentric trial comparing, in patients at one month after ACS, continuation of a more recent DAPT aspirin plus P2Y12 blocker, or de-escalation to aspirin plus clopidogrel [29,30]. De-escalation strategy reduced the incidence of BARC ≥ 2 bleeding while ischemic events were not different between the two groups.

These studies suggest that this de-escalation strategy may reduce the risk of bleeding complications without increasing the risk of ischemic events. This is proposed in the latest guidelines as an alternative to 12 months of potent platelet inhibition, particularly in patients with disease who are judged to be unable to maintain potent platelet inhibition (class IIb level B) [14,31].

Is there any other Strategy?

The addition of a low dose anticoagulant to the antiplatelet agent at 12 months of ACS was studied in the COMPASS study [32]. In a population of 27,395 patients with a history of coronary or peripheral arterial disease >1 year, the combination of aspirin and low-dose rivaroxaban reduced the primary endpoint (cardiovascular death, stroke and myocardial infarction) and all-cause mortality compared to aspirin alone. Major hemorrhage increased in the rivaroxaban group, primarily due to non-fatal gastrointestinal hemorrhage. Therefore, a new strategy is now available for high-risk patients 12 months after ACS with the introduction of low doses of rivaroxaban in addition to aspirin.

Another strategy is to rapidly stop aspirin after the event and continue a P2Y12 blocker alone to reduce the risk of bleeding. The GLOBAL LEADERS trial compared a new strategy with one month of aspirin plus ticagrelor followed by 23 months of ticagrelor alone, versus a standard therapy with aspirin plus ticagrelor for 12 months followed by aspirin alone for the next 12 months [33]. At 2 years, the new strategy was finally no superior to a standard strategy in the prevention of all-cause mortality or new myocardial infarction.

Individualization of DAPT Duration: What did the Latest Guidelines Say?

The latest European guidelines, recommend the individualization of the DAPT duration, in particular by reducing it to 6 months in cases of high risk of bleeding (level IIa B) or, conversely, by extending it to 36 months in cases of high thrombotic risk and if DAPT is well tolerated (level IIb A) [14].

The guidelines also introduce 2 scores from large studies that allow the individualization of DAPT duration. The PRECISE DAPT score helps to identify patients at high risk of bleeding after ACS [7]. In patients with a high PRECISE DAPT score (>25), DAPT could be reduced to 6 months instead of 12 months because of a predominant bleeding risk. The DAPT score was developed to help clinicians decide whether DAPT with thienopyridine should be continued after 12 months using ischemic and bleeding risk criteria [34]. Patients with a score ≥ 2 are predicted to benefit from prolonged DAPT since the risk of an ischemic event may outweigh the bleeding risk.

On top of those scores, patient (age, weight, ST or previous bleeding, etc.) and procedural (length and number of stents, bifurcation, common core) features need to be associated to the ischemic and bleeding risk balance evaluation and there-

fore DAPT duration decision [35].

CONCLUSION AND PRACTICAL ALGORITHM

The selection of patients who will benefit from optimized antithrombotic therapy is essential. The ischemic and bleeding risk should be assessed initially after the event, particularly to identify patients with a high bleeding risk who should receive a short DAPT. Then, at 12 months, a reassessment is required. This will allow to identify patients with a high ischemic risk and a low risk of bleeding, in order to prolong the DAPT, with possible de-escalation if this has not been done before, or replacement of the P2Y12 blocker with low dose rivaroxaban in addition of aspirin.

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CONFLICT OF INTEREST

Authors declare no conflict of interest

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