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Pierre Deharo, Thomas Cuisset

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# Optimal duration of dual antiplatelet therapy post percutaneous coronary intervention in acute coronary syndrome ☆,☆

Pierre Deharo [a,b,c,*], Thomas Cuisset [a,c,d]

[a] Département de Cardiologie, CHU Timone, Marseille, F-13385 France
[b] C2VN, INSERM, INRA, AMU, France
[c] Aix-Marseille Université, Faculté de Médecine, F-13385, Marseille, France
[d] Aix Marseille Univ, Inserm, Inra, C2VN, Marseille, France

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ABSTRACT

Dual antiplatelet therapy (DAPT), with aspirin plus a P2Y12 inhibitor agent, is the cornerstone treatment after percutaneous coronary intervention for acute coronary syndrome. Based on randomized clinical trial using aspirin and clopidogrel, a DAPT duration of 12 months has been recommended after an acute coronary syndrome. Despite the development of more potent antiplatelet agents (i.e. prasugrel and ticagrelor) and the reduction in ischemic recurrences after acute coronary syndrome, 12 months DAPT currently remains the gold standard. However, a significant proportion of patients experience recurrent ischemic events beyond the first 12 months after an acute coronary syndrome. Meanwhile, with more effective antiplatelet agent, bleeding has become a major safety concern on DAPT. Therefore, the ischemic and bleeding risk balance is central considering the duration of DAPT after an acute coronary syndrome. This review aims to report the evidence for an optimization and individualization of DAPT duration after an acute coronary syndrome.



## Dual antiplatelet therapy (DAPT) duration: introduction

Oral DAPT including aspirin and P2Y12 inhibitors is widely used with proven benefit for the prevention of recurrent ischemic events after acute coronary syndrome (ACS) [1,2]. Platelets play a central role in atherothrombosis during acute coronary syndrome (ACS) and adequate platelet inhibition is crucial to minimize the risk of recurrent ischemic events. An association of aspirin and a second antiplatelet agent (clopidogrel, prasugrel or ticagrelor) is the current standard antiplatelet therapy following ACS for one year and is associated with improved ischemic outcomes, mainly driven by lower recurrence of stent thrombosis [1,2].

## Dual antiplatelet therapy (DAPT) duration: initial guidelines

Current guidelines recommend the use of DAPT for 12 months since Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) results in 2001 [1–4]. CURE trial showed the superiority of DAPT with aspirin plus clopidogrel versus aspirin alone (20% of ischemic risk reduction) [1,2]. The mean duration of DAPT in this study was 9 months (from 3 to 12). Following this trial, clopidogrel has been considered the gold standard therapy after an ACS with a 1 year duration [1,2]. Since then, the European and American guidelines recommend the use of DAPT for 12 months after an acute coronary syndrome with the highest level of evidence (I A) [3,4]. However, despite those 12 months of DAPT, a significant proportion of patients did experience recurrent ischemic events within this period, and newer P12Y12 blockers have been developed [5,6]. TRITON TIMI 38 (Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes) trial proved the superiority of a DAPT with aspirin prasugrel versus aspirin clopidogrel for a mean duration of 14.5 months (from 6 to 15 months) [5]. Later, the PLATO (Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes) study showed the superiority of ticagrelor plus aspirin versus clopidogrel plus aspirin for a mean duration of 9.3 months (from 6 to 12 months) [6]. Those 2 studies consolidated the 12 months DAPT duration recommendation with newer P2Y12 blockers used in first intention. In both studies, newer P2Y12 blockers reduced the risk for ischemic recurrence but were associated with increased bleeding complications. Therefore, newer P2Y12 blockers are recommended in first intention,

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* Corresponding author at: Department of Cardiology, University Hospital la Timone, 13005 Marseille, France.
*E-mail address:* deharopierre@gmail.com (P. Deharo).

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over clopidogrel, in case of ACS [3,4,7]. They ensure an optimized protection regarding ischemic recurrence in comparison to clopidogrel. On the other arm, bleeding risk increases in line with DAPT duration regardless of the P2Y12 blocker chosen [8]. Even if 12 months remains the gold standard, a significant proportion of patients would benefit from DAPT duration adjustment and need to be identified.

## Minimal duration of DAPT after ACS: evidence supporting DAPT shorter than 12 months post ACS

After PCI for an ACS the benefit related to DAPT is double. Firstly, DAPT is essential to reduce the risk of stent thrombosis and target lesion revascularization at the coronary site of PCI. And secondarily, patients having an ACS are at high risk of other location recurrent ischemic event, which can be prevented by DAPT [9].

Regarding the risk of stent thrombosis, the development of newer device allowed over time a reduction of DAPT duration [10]. While with first generation drug eluting stent 1 year DAPT has been recommended to prevent late ST, with last generation drug eluting stent (biodegradable polymer or polymer free) DAPT duration can be significantly reduced [11].

Studies randomly compared bare metal stent versus last generation drug eluting stent with a DAPT of 1 month in patients with high bleeding risk [12–14]. All led to the same conclusions that newer drug eluting stent are superior to bare metal stent in terms of ischemic recurrence despite one month DAPT. Sub analyses were performed to assess this superiority in ACS patients, with similar results [15]. Therefore, even if a relatively low number of patients has been assessed, it seems acceptable in cases of very high bleeding risk to reduce the DAPT duration to 1 month with the use of last generation drug eluting stent even after an ACS. However, this one month duration should be reserved to very selected (and infrequent) cases [7].

Data from meta-analysis and PRECISE DAPT (predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy) study support a reduction of DAPT duration to 3 to 6 months in cases of high bleeding risk ACS patients [8,16,17]. Those trials have been designed primarily based on the fact that major bleeding on DAPT has an impact on mortality after ACS that could be even greater than recurrent MI [18,19]. Short term DAPT has shown consistent non inferiority compared to 12 months DAPT [11]. Therefore, it seems that this duration could be an acceptable compromise between ischemic and bleeding protection in high bleeding risk patients after ACS.

A growing population represents patients with a very high bleeding risk and is defined by the need for triple therapy due to long term anticoagulation indication. In this cohort, it has been shown that the association of DAPT plus OAC increases significantly the risk of bleeding [20,21]. 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 [7,22]. However, in cases of very high bleeding risk, DAPT could be omitted and replaced by the association of OAC plus clopidogrel [7,22]. Regarding the anticoagulation agent, data are in favor of the use of non-vitamin K antagonist anticoagulant [23,24]. Clopidogrel is the only P2Y12 blocker recommended as part of the DAPT in those patients [7]. Once more, according to the ischemic bleeding risk evaluation the triple therapy period could be extended if well tolerated to 3 to 6 months.

## Evidence for longer DAPT duration after ACS: evidence supporting DAPT longer than 12 Mo post ACS

There is clear evidence that some patients at high ischemic risk will benefit from prolonged treatment beyond 12 months after ACS. The data from the CHARISMA (Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events), DAPT (Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents), PEGASUS (Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction) and COMPASS (Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease) studies show that in selected patients, opting for the prolongation and/or optimization of antithrombotic strategy over 1 year (prolonged platelet anti-aggregation dual therapy or aspirin-low dose and rivaroxaban combination) is associated with a significant reduction of recurrence of ischemic events and may be associated with mortality reduction in comparison with single antiplatelet agent [25–28].

The analysis of the pilot studies (CURE, PLATO, and TRITON TIMI) and data from registries showed that the risk of recurrence of cardiovascular events becomes lower after 12 months of DAPT but still persists and affect patient's prognostic [1,5,6]. Indeed, patients with ACS presentation are by definition at high ischemic risk after PCI. As early as 2007, an analysis of the CHARISMA trial showed, in patients with a history of myocardial infarction or stroke, a signal for prolongation of DAPT duration (aspirin clopidogrel) up to 30 months [25], with lower rates of primary endpoint despite an increase in moderate bleeding. As a result, the prolongation of DAPT beyond the pre-established 12-month period was tested in randomized clinical trials. The DAPT trial tested the prolongation of aspirin plus a thienopyridine at 12 months of ACS versus thienopyridine cessation [28]. This study showed contrasting results. Indeed, DAPT prolongation leads to a persistent reduction in the risk of recurrent cardiovascular events (confirming the existence of this risk after 12 months), but this is counterbalanced by an excess of bleeding and non-cardiovascular mortality. The PEGASUS-TIMI 54 study enrolled patients with a history of myocardial infarction for more than one year, who were randomized to receive, in addition to aspirin, ticagrelor or placebo [27]. At the end of the 33-month follow-up, it appears that patients on aspirin alone are exposed to a linear risk of recurrent cardiovascular event, comparable to the first or second year post-infarction. With ticagrelor, the risk of recurrent ischemic event is decreased with a persistent benefit at 3 years. The risk reduction affected all patients, including those who did not have coronary angioplasty for ACS. Compared with placebo, the risk of bleeding was increased with ticagrelor, but the risk of fatal hemorrhage was comparable and the overall benefit / risk ratio was in favor of ticagrelor.

As a result, the current challenge remains to target the subgroups of patients who will benefit from this DAPT duration adaptations. Indeed, DAPT prolongation is associated with reduction of ischemic recurrence counterbalanced by a sure risk of bleeding. Therefore, the ischemic bleeding evaluation is central and should be reassessed during follow up to guide DAPT duration.

## De-escalation strategies after ACS

Increase of platelet reactivity during ACS is mainly observed in the early days/weeks after index event [29]; therefore de-escalation strategies with early potent antiplatelet treatment in

the acute phase followed by a less potent antiplatelet regimen has been recently investigated in clinical studies. This hypothesis is also partially supported by post hoc analysis from PLATO and TRITON-TIMI 38, showing greater ischemic benefit of more potent antiplatelet drugs in the early post ACS phase, while bleeding events occurred during the entire follow-up including the chronic phase [30,31].

Results from Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes (TROPICAL-ACS) study have been recently published [32]. 2619 patients with PCI for ACS were randomized to either standard treatment with prasugrel for 12 months (1306 patients, control group) or a stepdown regimen (1 week prasugrel followed by 1 week clopidogrel and platelet function-guided maintenance therapy with clopidogrel or prasugrel from day 14 after hospital discharge; 1304 patients, guided de-escalation group). In this de-escalation group, patients with HTPR were switched back to prasugrel (39%) and patient without HTPR were maintained on clopidogrel for 1 year. At 1 year, the combined primary endpoint (CV death, MI, stroke, bleeding BARC $\geq$2) occurred in 95 patients (7%) in the guided de-escalation group and in 118 patients (9%) in the control group (p non-inferiority = 0.0004; HR 0.81 95%CI 0.62–1.06, p superiority=0.12). The ischemic components of the primary endpoint occurred in 32 patients (3%) in the guided de-escalation group and in 42 patients (3%) in the control group (HR 0.77 95%CI 0.48–1.21; $p = 0.25$), indicating that early de-escalation did not result in an increased risk of ischemic events (p non-inferiority = 0.0115). The incidence of the key secondary endpoint of BARC 2 or higher bleedings was 5% (64 events) in the guided de-escalation group versus 6% (79 events) in the control group (HR 0.82 95%CI 0.59–1.13; $p = 0.23$). The Timing Of Platelet Inhibition after acute Coronary syndrome (TOPIC) study is a monocentric trial comparing in patients one month after ACS continuation of DAPT with aspirin and newer P2Y12 blocker, or de-escalation to aspirin plus clopidogrel [33,34]. The main study results showed that the de-escalation strategy did reduce the incidence of bleeding BARC $\geq$2 (4.0% vs. 14.9% HR 0.30 95%CI 0.18–0.50, $p < 0.01$)) while the ischemic events (9.3% vs. 11.5% HR 0.80 95%CI 0.50–1.29, $p = 0.36$)) were not different between the two groups. Overall, TROPICAL ACS and TOPIC suggested that de-escalation from newer P2Y12 blocker to clopidogrel after an ACS may reduce the risk of bleeding complications without apparent increase risk of ischemic events, and could be guided by platelet function testing. Most recent guidelines suggest that an approach of DAPT de-escalation guided by platelet function testing may be considered in ACS patients as an alternative to 12 months potent platelet inhibition, especially for patients deemed unsuitable for maintained potent platelet inhibition (Class IIb Level B) [7,35]. The key remaining challenge will be the "patient selection" to define which patient is the good candidate for de-escalation integrating both ischemic and bleeding risks and which one deserve longer potent DAPT.

## Other antithrombotic strategies after ACS

As discussed earlier, the risk of ischemic recurrences is not meaningless after the first 12 months following an ACS. We have seen that DAPT prolongation may be beneficial in this setting, despite non consistent findings. Therefore, other strategies have been developed and adding small dose of anticoagulant to antiplatelet agent has been tested in COMPASS study [26]. In a population of 27,395 patients with history of coronary artery disease or peripheral artery disease > 1 year, the combination of aspirin (<100 mg/day) and low dose rivaroxaban (2.5 twice daily) did reduce the primary endpoint of cardiovascular death, stroke and myocardial infarction in comparison to aspirin alone (HR 0.76 95%CI 0.66–0.86 $p < 0.001$) and rivaroxaban 5 mg twice daily (HR0.90 95%CI0.79 – 1.03 $p = 0.12$). Notably the association low dose anticoagulant plus aspirin did reduce the all-cause mortality versus aspirin alone. Major bleeding was increased in the combination group mostly led by non-fatal gastro intestinal bleeding. Therefore, a new strategy is now available for high risk patients 12 months after an ACS. DAPT cessation and introduction of low doses rivaroxaban may have a good efficacy safety profile for selected patients and its adoption in routine practice needs to be evaluated.

Another antithrombotic strategy consists in dropping aspirin shortly after the event to continue a single antiplatelet therapy with a P2Y12 blocker, and therefore reduce the risk of bleeding. It has been tested in the GLOBAL LEADERS trial comparing one month of aspirin plus ticagrelor followed by 23 months of ticagrelor only, versus aspirin plus ticagrelor for 12 months followed by aspirin only for the next 12 months [36]. At 2 years, ticagrelor in combination with aspirin for 1 month followed by ticagrelor alone for 23 months was not superior to 12 months of standard dual antiplatelet therapy followed by 12 months of aspirin alone in the prevention of all-cause mortality or new Q-wave myocardial infarction 2 years after percutaneous coronary intervention. Other ongoing studies are currently testing dropping aspirin and continuing P2Y12 inhibitor monotherapy and results will be available shortly [37,38].

## Individualization of DAPT duration: scores and latest guidelines

In the latest European guidelines, there is a room for DAPT duration adjustment after ACS [7]. The document allows a reduction of DAPT duration to 6 months in cases of high bleeding risk (level IIa B). On the other arm, this duration could be prolonged to 36 months in cases of high thrombotic risk if DAPT is well tolerated at 12 months (level IIb A). It has been repetitively showed that the bleeding risk associated with DAPT is increasing along with DAPT duration regardless of the type of P2Y12 blockers [39,40]. Therefore, to assess the bleeding risk of the patients Guidelines recommend to use validated scores. The PRECISE DAPT score has been designed to evaluate the risk of bleeding during the index hospitalisation for ACS [8]. It has been developed and validated retrospectively in large, randomized, patient cohorts comparing the duration of DAPT after ACS. The PRECISE DAPT score is a five-item risk score that identifies patients with a high bleeding risk after ACS, concluding that longer duration of DAPT significantly increases the bleeding risk in patients with a high PRECISE-DAPT-score. Conversely, shorter duration of DAPT in patients without a high bleeding risk increases ischaemic risk in patients with a low PRECISE DAPT-score. The defined cut off for PRECISE DAPT score is 25. In patients with a PRECISE DAPT higher than 25 the DAPT could be reduced after an ACS to 6 months instead of 12 month because the bleeding risk is continuing.

The DAPT score has been developed following the DAPT trial, to help clinicians decide whether DAPT with thienopyridine should be continued after 12 months [41]. This 9 items score could be used to predict the risk of ischemic and bleeding events from 12 months to 30 months after PCI and can be calculated online. Using this score, patients with a score $\geq$2 are predicted to benefit from prolonged DAPT since the risk of an ischemic event may outweigh the bleeding risk. On the other hand, a patient with a score <2 is predicted to be harmed by extended duration DAPT since his bleeding risk may outweigh the risk of an ischemic event.

On top of those scores, which should be calculated for all ACS patients, clinical evaluation is essential. Patients (age, weight, previous ST or bleeding…) and procedural (length and number of stents, bifurcation, left main stenting) features need to be associated to the ischemic and bleeding risk balance evaluation and therefore DAPT duration decision [42] (Fig. 1).

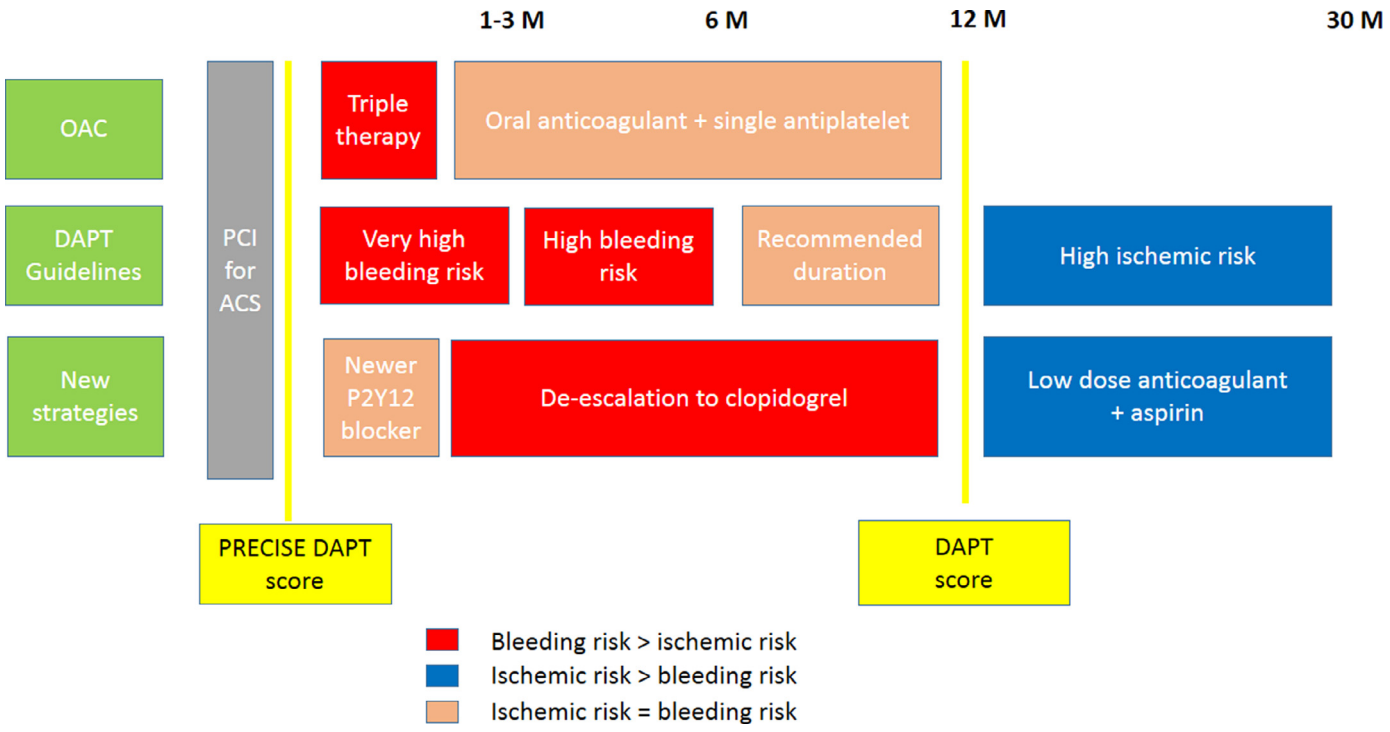


**Fig. 1.** Dual antiplatelet strategies after acute coronary syndrome.

## Conclusion and practical algorithm

In conclusion, all the strategies aiming to optimize the ischemic protection after an ACS are associated with an increase hazard of bleeding. Therefore, the selection of patients who will benefit for antithrombotic treatment optimization is essential. The ischemic and bleeding risk should be evaluated first during the index event, and then reassessed at 6 and 12 months for DAPT continuation. At 12 months in patients with high risk of ischemic recurrences and low bleeding risk the option could be to continue on DAPT, with possible de-escalation if not done before, or association of low dose rivaroxaban plus aspirin.

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