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**Cardiology**

# Duration of DAPT After Stent Implantation, How Low Can We Go?

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**Abstract** **Original Research Article**

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is the main actor in secondary prevention of recurrent coronary ischemic events and stent thrombosis. For this exact purpose the combination of two antiplatelet molecules have proven efficacy and superiority compared to monotherapy, aspirin alone, but this comes with an increased risk of major and potentially fatal bleedings, making the choice of the molecules and especially the duration of treatment a true challenge for every cardiologist. We are going to discuss some of the main factors that play a role in the decision, and the most important trials that studied the subject.

**Keywords**: Dual antiplatelet therapy, aspirin, P2Y12 inhibitor, short DAPT, De-escalation.



## INTRODUCTION

Dual antiplatelet therapy (DAPT), is a very common treatment, frequently used in today's medicine, with an estimated yearly prescription in more than 2 million patients with myocardial infarction (MI) or after treatment with percutaneous coronary intervention (PCI) [1], added to those, 7 million patients being treated for thrombotic stroke, peripheral vascular disorders and transient ischemic attack [2].

DAPT efficiently reduces platelet aggregation, limiting the risk for stent thrombosis or vascular thrombosis at sites distant from the initially stented lesion [3]. Yet, by the same mechanism, after interfering with the first line of coagulation, DAPT increases the risk for major bleeding, which is linked directly to an increased morbidity and mortality [4, 5].

So, initiating DAPT as a treatment will have to answer to two main questions: bleeding risk and the ischemic risk, the first one can be estimates using many scores available, ARC HBR being the most adapted, but the appreciation of the clinician will remain the most important.

As for the thrombotic risk, related to reinfarction, stent thrombosis and other recurrent coronary ischemic events, it will depend mainly on the patient risk factors and procedural aspects.

Subsequently, the optimal duration of treatment, that can decrease both the ischemic and bleeding risks, have been widely studied for the past 20 years [6, 7], and still the subject of great debate because of many factors. The current guidelines point out that it is a class one recommendation to continue DAPT for a minimum of 12 months after revascularization and ischemic heart disease. Surprisingly, the European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines regarding the duration of DAPT after stent implantation are different, ESC suggest six to 12 months, and the AHA recommends at least 12 months in the stable patient. The extension or the shortening of DAPT in special population with high bleeding or ischemic risk is also a possibility that figures in the latest update of ESC guidelines, and it is based on many trials, that we will try to discuss further in this document.

**Available Data on reducing the duration of DAPT after coronary stenting:**

The reduction of DAPT duration from the initial standard proposed of 12 months has been evaluated in many RCTs, in general these studies tested the primary hypothesis that a shorter DAPT regimen was non-inferior to the standard of care in terms of ischemic events or net adverse clinical events (MACE).

The possibility to reduce safely treatment duration has been often tested in conjunction to specific

stent designs, in order to demonstrate their safety in the context of a shorter treatment duration [8, 9].

The first study published in 2012, was the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) trial. It included patients treated with drug-eluting stent (DES) and randomized to 6 *vs.* 12 months DAPT after the implantation. Most patients were treated with everolimus-eluting stents and about half presented with acute coronary syndrome (ACS). The trial results showed non-inferiority of 6 *vs.* 12 months of DAPT with respect to the primary end point (composite of cardiac death, MI, or ischemia-driven target vessel revascularization). The major and minor bleeding, was higher in the 12-month group, but the difference was not statistically significant. However, the study was considered to be underpowered, and it needed to be confirmed on a larger scale [10].

The Second-Generation Drug-Eluting Stent Implantation Followed by Six-Versus Twelve-Month Dual Antiplatelet Therapy (SECURITY) [11] and the Intracoronary Stenting and Antithrombotic Regimen: Safety and Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) [12], both tested among patients treated with DES, the non-inferiority of 6 *vs.* 12 months DAPT for a composite primary endpoint including ischemic and major bleeding. Both studies were stopped early due to slow enrollment but ultimately reached the pre-specified goal, the non-inferiority hypothesis.

The Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization (I-LOVE-IT 2) trial randomized 1,829 patients to 6 *vs.* 12 months of DAPT. All patients were treated with DES, but the type of stent was also randomized, with a balanced mixture of durable-polymer *vs.* bioresorbable-polymer cobalt-chromium sirolimus eluting stents. The study indicated noninferiority in safety and efficacity of 6-months versus 12-month DAPT after implantation of bioresorbable-polymer stent, although it was not specifically powered for it [13].

The Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions (IVUS-XPL) study, was conducted in 2016, and it was founded on double randomization, the first one based on the use of intravascular ultrasound guidance to complete the PCI, while the second randomization was for DAPT duration (6 *vs.* 12 months). At 12-months follow-up the composite of Cardiac death, MI, stroke and TIMI major bleeding was similar between patients treated for 6- or 12-month. Interestingly, at the subgroup analysis for the primary endpoint, patients treated with intravascular ultrasound guided stent implantation benefitted more from a shorter DAPT treatment as compared to those treated with angiographic guidance alone [14].

More recently a randomized trial tested a shorter DAPT duration of 6 months in patients with ACS. SMART-DATE enrolled a total of 2,712 patients undergoing PCI for an ACS. As stated by the study protocol, patients were randomized to a treatment with DAPT for 6 or 12 months. One third of patients were diagnosed with STEMI, the others were equally divided between unstable angina and NSTEMI. The primary endpoint was a composite of all-cause death, MI, or stroke, it occurred equally in the two study arms meeting the non-inferiority criteria. Yet, the increased risk of myocardial infarction and the wide non-inferiority margin prevent us from concluding that short term DAPT is safe in patients with ACS.

In line with this study, the more recent DAPT-STEMI trial, presented in 2017, included 870 patients with STEMI treated with primary PCI and second-generation DES that after 6 months of DAPT with no events, were randomized to continue treatment up to 12 months or to stop P2Y12 inhibitor and continue with aspirin only. The primary study endpoint was a composite of death, MI, revascularization, stroke and major bleeding at 24 months after primary PCI. Once again, DAPT to 06 months was not inferior to DAPT for 12 months in patients with event-free STEMI at 06 months after primary PCI. Still, due to the small sample size, the low event rate and the wide non-inferiority margin these results should be interpreted with caution.

Six months of treatment were compared to a more than 12 months treatment duration in two non-inferiority studies: ITALIC and NIPPON trial, in which patients were randomly allocated to 6 *vs.* 24 months of DAPT and 6 *vs.* 18 months of DAPT respectively. Both studies met the prespecified non-inferiority, yet the results from these studies should be interpreted with caution due to the study early termination and the wide non-inferiority margin selected, which exceeded the event rate of the experimental arm [15, 16].

More recently, the REDUCE trial, presented in 2017, selected a population with a higher baseline ischemic risk to test the non-inferiority of 3 *vs.* 12 months of DAPT in patients with ACS treated at the index procedure exclusively with a bioabsorbable polymer DES (COMBO stent). The primary endpoint was a composite of all cause death, MI, stent thrombosis, stroke, target vessel revascularization or bleeding. The study ultimately reached non-inferiority with an event rate of 8.2% in the short DAPT arm and 8.4% in the long DAPT arm.

We have also the DETECT-OCT trial, explored the alluring relation between stent strut coverage evaluated by optical coherence tomography (OCT) and the duration of DAPT 18. This study was not randomized for DAPT duration, but instead we assigned treatment duration (3 *vs.* 12 months) based on OCT findings, longer DAPT (12 months) if >6% of uncovered stent

strut were observed at the 3 months invasive follow-up, or a shorter DAPT (3 months) in case of sufficient stent strut coverage. The composite endpoint of cardiac death, MI, stent thrombosis, and major bleeding was rare and similar in both study arms at 12 months follow-up. Even though this analysis was the result of a small sample size in a non-randomized study, it deserves to be further explored.

Another important trial is MASTER-DAPT published in 2021, conducted by Valgimigli and his team, on high bleeding risk patients, where 4579 patients were randomized into 02 groups after PCI using an Ultimaster stent, the first one received a standard duration of DAPT, the second one beneficiated of only one month of DAPT, at the end of 12 months the decision of whether to continue DAPT or stop it was upon cardiologists.

The study not only showed the non-inferiority of the abbreviated antiplatelet therapy, but also its superiority in bleeding events compared to the standard regimen [19].

Another trial, T-PASS trial, proved that in patients undergoing PCI with bioresorbable polymer sirolimus- eluting stents in the context of ACS, Ticagrelor alone after 1 month of DAPT was both noninferior and superior for the primary ischemic plus bleeding endpoint at 12 months of DAPT, driven once again, primarily by a reduction in significant bleeding events in the monotherapy group [20].

Last but not least the STOPDAPT 3 trial that randomized 5966 patients undergoing PCI using an everolimus-eluting stent (Xcience series) with a documented high bleeding risk or after un acute coronary syndrome, to either DAPT with aspirin and Prasugrelor or Prasugrel monotherapy, The results of this trial indicate that monotherapy was not superior to DAPT for bleeding events among patients undergoing PCI with Xience DES either for ACS or among those considered to be at high bleeding risk. In addition, although cardiovascular events met criteria for noninferiority, they were higher in the monotherapy group at 30 days, including a 3.4-fold higher risk of subacute stent thrombosis. These results indicate that a strategy of de-escalation immediately post-PCI is not beneficial and could in fact be harmful, especially among ACS patients. DAPT should remain the standard strategy 1 month after coronary stent implantation [18].

## DISCUSSION

All these studies discussing a short DAPT following a stent implantation in the context of an ACS or CCS, were of medium to small size and the relatively low period of divergence between the two treatments arms (9 months in 3 vs 12 months and 6 in 6 vs 12 months), made these trials underpowered to detect differences in treatment effect for rare clinical events, in addition to that the moderate dissimilarity in the inclusion criteria, type of events, individual bleeding risks and the type of stent used, make it a very heterogenous group and difficult to set up a definitive conclusion regarding the duration of DAPT.

## CONCLUSION

Despite the numerous trials and studies that discussed the duration of DAPT after stenting and whether it was in the light of an acute coronary syndrome or a high bleeding risk, the results are still conflicting and needs to be widely confirmed, but a 01-month strategy is a potential light at the end of the tunnel.

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