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The stent in the high-bleeding risk patient: antiplatelet monotherapy?

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Dual antiplatelet therapy (DAPT) is the recommended treatment after percutaneous coronary intervention (PCI). The introduction into clinical practice of new drug-eluting stents (DESs) with significantly improved safety profiles has made it possible to shorten the DAPT. Randomized studies have established the superiority of DES over bare metal stents in high-bleeding risk (HBR) patients treated with antiplatelet monotherapy after 1 month of DAPT from PCI. This regimen has been adopted in randomized trials comparing different DES in patients with HBR. Furthermore, antiplatelet monotherapy after 1 month of DAPT from PCI has been shown to reduce bleeding risk without increasing ischaemic events compared with a conventional DAPT regimen (3–12 months) in a recent randomized study that included HBR patients treated with DES. Parallel to the trend of shortening DAPT, there is growing debate about which antiplatelet monotherapy is optimal after discontinuation of DAPT, with some recent studies exploring the paradigm shift from aspirin monotherapy to $P2Y_{12}$ inhibitor monotherapy. Finally, future studies are underway to evaluate the clinical effect of monotherapy with ticagrelor or prasugrel directly after implantation of DES thus eliminating DAPT.

Dual antiplatelet therapy (DAPT) is currently the recommended treatment after percutaneous coronary intervention (PCI) with or without stent implantation. Current guidelines recommend in Class I a standard regimen of DAPT lasting 6 months after PCI performed for chronic coronary syndrome and 12 months after acute coronary syndrome (ACS) regardless of treatment strategy, with PCI or medical therapy. However, the duration of DAPT after PCI and/or ACS may be shortened or prolonged from the standard recommended periods in the presence of high-bleeding risk (HBR) or thrombotic risk, respectively. In fact, although the benefits of DAPT have been demonstrated, bleeding complications remain high with this therapy, especially with a prolonged duration and in patients with HBR, where the risk could outweigh the benefit associated with DAPT. Growing evidence has shown that bleeding is associated with an increase in mortality, thus giving a strong impetus to the search for strategies aimed at reducing bleeding, of which shortening the DAPT by a duration that can minimize the bleeding risk while preserving the efficacy on ischaemic events, is among the most studied.

The shortening of DAPT was made possible by the introduction in clinical practice of new generation drug-eluting stents (DESs) with significantly improved safety profiles, such as to make this device the treatment of choice compared with bare metal stents (BMSs) even with a short duration DAPT regimen. Indeed, randomized trials have established the superiority of DES over BMS in patients with HBR treated with antiplatelet monotherapy after 1 month of DAPT from PCI.[1] Subsequently, in the context of patients with HBR, randomized studies were designed to compare different DES platforms by adopting a 1-month DAPT regimen. One such trial has been completed, demonstrating a similar safety profile

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of a permanent polymer DES (Resolute™) and polymer-free DES (BioFreedom™) in HBR patients treated with single antiplatelet therapy after 1 month of DAPT.[2] However, those studies focused on HBR patients in whom they tested different types of DES using a very short duration of DAPT of only 1 month, but they did not evaluate the efficacy and safety of different periods of DAPT by comparing monotherapy and conventional DAPT, thus leaving the question on the optimal antithrombotic strategy in patients with HBR.

Several registries compared a shortened (1–3 months) vs. traditional DAPT regimen in HBR patients treated with specific types of DES, showing that prolonged DAPT was associated with an increased risk of bleeding with no additional benefit on ischaemic events.[3,4] However, such single-arm registries compared the different periods of DAPT after implantation of some DES platforms using historical cohorts as a conventional DAPT control group or using a performance goal. These latter are non-randomized methodologies with inherent limits and residual confounding factors that do not allow to provide accurate and conclusive answers on the optimal duration of DAPT after DES implantation. In the MASTER DAPT trial (The Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated vs. Standard DAPT Regimen), patients with HBR treated with a DES consisting of a biodegradable polymer (Ultimaster™) were randomized 1 month after PCI to discontinue the DAPT, continuing with single antiplatelet therapy, or to continue DAPT for a further 3 months in patients who had a concomitant indication for oral anticoagulation and at least 5 months and up to 11 months after randomization in patients without indication for oral anticoagulation.[5]

The results showed that, in the per protocol population ($n = 4434$ patients), 1 month after PCI, antiplatelet monotherapy was non-inferior to DAPT in terms of the net clinical endpoint (composite of death from all causes, myocardial infarction, stroke, or major bleeding) and major adverse cerebrovascular and cardiac events (defined as the composite of all-cause death, myocardial infarction, stroke). Furthermore, in the intention-to-treat population ($n = 4579$ patients), DAPT discontinued at 1 month after PCI with DES compared with prolonged PCI was superior in reducing the primary safety endpoint which included major or non-major but clinically relevant bleeding. These results observed in the overall trial population were consistent across the analysed subgroups including those stratified by clinical presentation with or without ACS, which was present in 48.3% of patients. It is important to emphasize that in the MASTER DAPT study, 36.4% of the included patients also received concomitant oral anticoagulation, since this feature was present among the criteria for defining the HBR status. A subanalysis of the trial showed that the incidences of the net clinical endpoint and major cerebrovascular and cardiac adverse events were similar between the two regimens of abbreviated and traditional DAPT in patients with and without concomitant indication for oral anticoagulation, while the regimen of shortened DAPT was associated with a reduction in bleeding, which however reached the statistical significance only in the group without indication for oral anticoagulation.[6]

Parallel to the scientific interest in a DAPT of shorter duration after DES implantation, a debate has recently emerged about which is the optimal antiplatelet monotherapy, aspirin or a $P2Y_{12}$ inhibitor, after the discontinuation of the DAPT, especially if the latter is given for a very short period after the PCI procedure. Several considerations, including the fact that aspirin has been associated with a risk of gastrointestinal bleeding complications and the hypothesis that aspirin in addition to more effective $P2Y_{12}$ inhibitors may not add relevant benefit, have prompted the design of several studies evaluating an aspirin-free antithrombotic approach in patients undergoing PCI with and without concomitant indication of anticoagulation. In particular, randomized trials that included only patients undergoing PCI without concomitant indication for oral anticoagulation compared the monotherapy with a $P2Y_{12}$ inhibitor after a short period of DAPT (1–3 months) vs. a traditional DAPT regimen maintained for 12 months after PCI.[7–11] These studies have generally shown that monotherapy with a $P2Y_{12}$ inhibitor vs. DAPT was associated with a reduction in bleeding without increasing ischaemic risk. Ticagrelor and clopidogrel are the most studied $P2Y_{12}$ inhibitors in monotherapy compared with DAPT, raising the question of what might be the optimal agent in monotherapy after PCI. Probably, the choice between different $P2Y_{12}$ inhibitors depends upon risk stratification. This observation was suggested by the STOPDAPT-2 ACS study in which, in a population of ACS patients undergoing PCI ($n = 4136$, of which 56% had ST-segment elevation myocardial infarction), clopidogrel monotherapy after a shortened period of DAPT (1–2 months), failed to prove to be not inferior than the standard 12-month DAPT regimen in terms of net clinical benefit, since, despite a reduction in bleeding, it was associated with an increase in ischaemic events.[12] Therefore, this study suggested that clopidogrel monotherapy after a very short period of DAPT is an inappropriate antiplatelet treatment for unselected patients with ACS at high thrombotic risk and in the absence of a very high-bleeding risk. While the results of studies comparing $P2Y_{12}$ inhibitor monotherapy vs. the standard DAPT are promising, it should be noted that patients included in those trial were generally at low risk, and most studies did not focus on patients with HBR (although the latter was not an exclusion criterion), thus remaining doubts on the ideal candidates for $P2Y_{12}$ inhibitor monotherapy after a short period of DAPT after PCI, and on whether this antithrombotic strategy is applicable in patients with high thrombotic risk and low haemorrhagic risk as alternative to prolonged DAPT.

At present, monotherapy with a $P2Y_{12}$ inhibitor should probably be considered in patients with HBR, especially if at high thrombotic risk.[13] However, the clinical effect of monotherapy with a $P2Y_{12}$ inhibitor compared with that of aspirin monotherapy after discontinuation of DAPT, especially if the latter occurs early after PCI, remains still undetermined and controversial. A recent randomized study demonstrated a better net clinical benefit with clopidogrel vs. aspirin alone in patients undergoing PC treated with

DAPT lasting 6–18 months and who had no clinical events during the DAPT period. However, these latest data do not allow to draw conclusions on a clear superiority of one monotherapy over another for secondary cardiovascular prevention, and several studies are underway to answer the question whether $P2Y_{12}$ inhibitor monotherapy is preferable to aspirin monotherapy after discontinuation of DAPT in patients undergoing PCI.

The tendency of the scientific community to test an ever-shorter DAPT after DES implantation has led to assess the strategy of performing $P2Y_{12}$ monotherapy directly after PCI without a period of DAPT and therefore with aspirin given before PCI but suspended on the day of the procedure. This strategy was preliminarily evaluated in the ASET study in which prasugrel monotherapy after DES implantation in patients with stable low-risk coronary heart disease ($n = 201$) was found to be feasible and safe.[14] Indeed, no thrombotic events were observed with single prasugrel therapy during 3-month follow up. A larger clinical study is underway, the NEOMINDSET randomized trial (PercutaNEOus Coronary Intervention Followed by Monotherapy INstead of Dual Antiplatelet Therapy in the SETting of Acute Coronary Syndromes), which is comparing the efficacy and safety of a monotherapy with prasugrel or ticagrelor vs. conventional 12-month DAPT in patients with ACS treated with PCI.

In conclusion, growing evidence supports the benefit of an antithrombotic strategy consisting of antiplatelet monotherapy after a shortened DAPT vs. conventional DAPT in patients with HBR undergoing DES implantation. Currently available data suggest that 1 month of DAPT followed by antiplatelet monotherapy represents a safe antithrombotic option for patients with HBR. The ongoing TARGET-SAFE study is comparing the net clinical benefit of 1-month DAPT followed by aspirin monotherapy vs. that of a conventional 6-month DAPT in HBR patients undergoing PCI with a DES based on a resorbable polymer (Firehawk™). Further data are needed to define whether to prefer aspirin or the P2Y12 inhibitor as a single antiplatelet therapy, especially after early discontinuation of DAPT in patients with HBR. In addition, future studies are underway to evaluate the clinical effect of monotherapy with ticagrelor or prasugrel directly after DES implantation by completely eliminating DAPT.

Conflict of interest: None declared.

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