Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation

Durée optimale de la bithérapie anti-agrégante plaquettaire après stent actif

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Drug-eluting stents (DES) have become the standard in percutaneous coronary revascularization. Several pivotal clinical trials have shown that, compared with a bare-metal stent (BMS), the DES is associated with significant reductions in the risk of restenosis and the need for target-lesion revascularization [1,2]. Drug-eluting stents are currently recommended as the first-choice option, especially when the risk of restenosis is high (i.e. in patients with diabetes, long lesions, chronic total occlusion, bifurcation lesions, restenotic lesions, small vessels). According to the latest guidelines on patients presenting with ST-segment elevation, if the patient has no contraindications to prolonged dual antiplatelet therapy (DAPT) (such as an indication for oral anticoagulation or estimated high long-term bleeding risk) and is likely to be compliant, DES should be preferred over BMS (class IIa, level A) [3].

The combination of aspirin and an adenosine diphosphate-receptor blocker such as clopidogrel, prasugrel or ticagrelor is mandatory after percutaneous coronary intervention (PCI). Usually, this DAPT includes aspirin 75–100 mg/day per os plus clopidogrel 75 mg/day. But, the optimal duration of DAPT after DES insertion is still debated. For example, the recommendations put forward by the American College of Cardiology/American Heart Association (AHA/ACCA) and those from the European Society of Cardiology (ESC) diverge slightly. According to the AHA/ACCA, in addition to aspirin, clopidogrel therapy should be continued for at least 12 months after DES implantation, whereas the ESC guidelines recommend continuation for 6–12 months [4,5].

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The main reason why an extended combination of DAPT therapy has been advocated is because early discontinuation of DAPT has been identified as a risk factor for late stent thrombosis in patients with a DES [6]. It was suggested that some late clinical events that occur later than 1 year after DES implantation may be due to delayed arterial healing after implantation of DES. In the absence of randomized data, two independent observational registries have largely influenced the current recommendation to prolong clopidogrel therapy for ≥12 months or for 6–12 months after DES implantation [7,8]. The BASKET-LATE trial reported a >70% increase in rates of death or myocardial infarction in DES recipients who discontinued clopidogrel at 6 months compared with patients treated with BMS [7]. Similarly, a 50% increase in rates of all-cause death or myocardial infarction was observed in the Duke Heart Center registry in patients treated with DES who discontinued clopidogrel at 6 months compared with those who continued the treatment for 24 months [8]. However, prolonged DAPT has been associated with higher severe bleeding rates compared with aspirin therapy alone: reported incidences of major bleeding ranged from 1.8% to 3.7% and from 1.7% to 5.1% for minor bleeding.

The question on the optimal duration of DAPT after DES is not only theoretical. More than 60,000 patients in France receive a DES every year. For each patient, the clinician has to make a decision. It is not surprising therefore that large clinical trials have been undertaken. Owing to the large number of DES implantations worldwide, the optimization of DAPT is important for both patient recovery and economic efficiency.

Recently, the results from four trials have suggested the possibility that a shorter duration of DAPT may be sufficient after DES implantation. The first randomized study on this issue analysed combined data from two multicentre trials: the REAL-LATE and ZEST-LATE trials [9]. This study found no significant benefit associated with continuing clopidogrel plus aspirin beyond 12 months after DES implantation. No reduction in the incidence of myocardial infarction or death from cardiac causes was found. Moreover, the rates of composite outcomes (myocardial infarction, stroke, death) were higher with clopidogrel plus aspirin than with aspirin alone, although the difference was not statistically significant.

The results from the EXCELLENT study showed that, at 12 months after DES implantation, patients treated with 12 months or 6 months of DAPT showed similar risks for target vessel failure, defined as the composite of cardiac death, myocardial infarction and ischaemia-driven target vessel revascularization [10]. However, the non-inferiority margin was wide, and the study was underpowered for death and myocardial infarction. Another study has shown that 24 months of clopidogrel therapy in patients with DES or BMS was no more effective than a 6-month clopidogrel regimen for reducing the composite endpoint of death, myocardial infarction and cerebrovascular accident [11]. In that study, 2 years of clopidogrel therapy resulted in an increase in bleeding episodes. The fourth study, the RESET trial, compared 3 months of DAPT following zotarolimus-eluting stent implantation and 12 months of DAPT following the other DES implantation. The investigators concluded that the first strategy was non-inferior to standard therapy [12].

These four studies are interesting and could provide a paradigm shift in the management of DAPT after DES implantation. Interestingly, none of these studies investigated the same course of DAPT duration: 12 months versus 24 months for LATE, 6 months versus 12 months for EXCELLENT, 6 months versus 24 months for PRODIGY, and 3 months versus 12 months for RESET. These data suggest the possibility that a shorter duration of DAPT may be sufficient after implantation of new generation DES. They do not rule out the possibility that prolonging the clopidogrel plus aspirin treatment might result in a reduction of major adverse cardiac events. As stated by the authors themselves, the studies were limited by a short follow-up and the exclusion of very high-risk patients.

Importantly, other clinical trials are currently ongoing to investigate optimal treatment duration after DES insertion. The DAPT study aims to compare the benefits and risks of 12 months versus 30 months of DAPT in patients undergoing PCI, and it has the largest number of subjects enrolled to date. Over 20,000 subjects have been enrolled at approximately 220 international clinical study sites. Most of the patients (>15,000) have received a DES. Interestingly, in that prolonged combined antiplatelet therapy, patients receive either clopidogrel or prasugrel, a new thienopyridine. Another ongoing trial (ISAR-SAFE) aims to assess whether discontinuation of clopidogrel plus aspirin at 6 months after DES implantation is non-inferior to routine 1-year treatment. Not surprisingly, French trials have also investigated this important question, including ARC-TIC, ITALIC and OPTIDUAL [13]. It would, however, probably have been wiser to perform one large trial rather than three smaller ones.

In patients at high risk of bleeding, the LEADERS FREE trial will assess the shortest course of DAPT ever used (1 month) with an active stent devoid of polymer.

Before appealing for a reduction in the duration of DAPT after DES implantation, and while awaiting the results of the ongoing trials, it has to be kept in mind that few patients with an acute coronary syndrome have been included in these four clinical trials. In patients with an acute coronary syndrome, pending the results of ongoing trials, 9–12 months of DAPT is recommended, with a strict minimum of 1 month for patients who have received a BMS and 6 months for those with a DES [1].

In conclusion, according to recent studies, a shorter course of DAPT than recommended by the guidelines may be considered, especially with new-generation everolimus and zotarolimus DES, polymer-free DES, and polymer-biodegradable DES, in the absence of ACS at the time of implantation. On the other hand, no sound evidence is available to support prolongation of DAPT beyond 12 months, although such a strategy may be considered in specific patient subsets (e.g. those with left main disease or the last remaining vessel stenting receiving DES). Lastly, it remains very important to inform patients and their physicians about the need to avoid premature discontinuation of DAPT. In the meantime, it is not unreasonable to await the results of ongoing trials before changing our practice.
Disclosure of interest

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References