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SCIENTIFIC EDITORIAL

The saga of the duration of dual antiplatelet therapy after drug-eluting stent placement

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Clinicians have widely adopted drug-eluting stents (DES) over bare-metal stents (BMS) for percutaneous revascularization (PCI) in patients with coronary artery disease, because DES decrease the risk for in-stent coronary restenosis and repeated revascularization [1,2]. Moreover, a landmark trial has shown that second-generation DES reduce the rates of stent thrombosis compared with first-generation DES [3]. Research is being conducted to further improve the new stents, the bioabsorbable stents being the latest proof of this continuing process. Barragan et al. were the pioneers in the field of dual antiplatelet therapy (DAPT) after BMS placement [4]; they were convinced that aspirin plus the only thienopyridine available at the end of the last century — namely, ticlopidine — were together the best therapy after DES placement. Indeed, we have to keep in mind that stent thrombosis was at this time not only dramatic, as it is nowadays, but also much more frequent. After the first publication suggesting the efficacy of DAPT, Schömig et al. clearly demonstrated the benefit of such therapy in reducing the risk of stent thrombosis [5]. Interestingly, in the first publications leading to the approval of DES, involving the sirolimus-eluting stent and the paclitaxel-eluting stent, the duration of DAPT was rather short, 3 and 6 months, respectively. Then, findings from observational studies suggested that in patients who had undergone DES placement, discontinuation of DAPT resulted in an elevated risk of acute stent thrombosis. In 2006, the so-called ''firestorm'' at the European Society of Cardiology (ESC) Congress, held in Barcelona, reached the cardiology world. The possible increase in the rate of late stent thrombosis with DES compared with BMS became a real nightmare for cardiologists. The advent of a sudden unexpected late stent thrombosis was a major concern. Imagine a young, stable patient with a significant stenosis in a lateral artery in whom a DES was successfully implanted. This patient, now angina free, dies suddenly

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2 months after stopping treatment with clopidogrel. The fact that this patient could have died due to a stent thrombosis related to clopidogrel discontinuation leads comprehensively to many questions, including the duration of DAPT. The old question about a possible rebound after cessation of antithrombotic drugs emerges with clopidogrel. A clustering of adverse events in the initial 3 months after stopping clopidogrel among both medically treated and PCI-treated patients with acute coronary syndromes was observed [6]. Therefore, because stent thrombosis was frequently associated with myocardial infarction, and sometimes with death, many clinicians responded to these events by suggesting indefinite treatment with DAPT, despite the fear of bleeding. Among these clinicians were recognized experts in the field. Therefore, in everyday clinical practice, about half of the patients who received a DES also received DAPT for much more than 1 year. The optimal duration of DAPT after DES implantation was highly controversial. Even the recommendations laid out in guidelines from Europe and North America diverged slightly [7,8], DAPT is currently recommended for at least 6—12 months after implantation of a DES.

The question on the optimal duration of DAPT after DES placement is not only a theoretical question. For each patient, the clinician has to make a decision. Therefore, it is not surprising that many clinical trials have been undertaken to try to evaluate this issue. In 2012, the first meta-analysis of four randomized trials comparing the clinical effect of extended DAPT after PCI in the DES era was published [9]. Four trials have indeed compared extended DAPT (12 to 24 months) versus shorter durations (3 to 12 months). A total of 8158 patients were available for this analysis. The authors concluded that extension of DAPT duration after PCI may increase the risk of bleeding without reducing the risk of ischaemic events. They acknowledged that these results would need corroboration in ongoing large trials. These results were favorably accepted, particularly in Europe, and by interventional cardiologists. It is understandable that if DES would need very long-term treatment with DAPT, implantation of these stents would be more problematic. Then, other studies have shown no significant differences in net clinical outcome between 6 and 12 months or 24 months of clopidogrel therapy after DES implantation. The new turning point was the publication of the DAPT study, the largest study on this topic, powered to detect differences in-stent thrombosis and major cardiac adverse cardiovascular and cerebrovascular events (MACCE) with or without extended DAPT [10]. A total of 9961 patients free from myocardial infarction, stroke, repeat coronary revascularization, stent thrombosis, and moderate or severe bleeding and compliant after 12 months of treatment with clopidogrel or prasugrel and aspirin following a DES implantation, were randomly assigned to continue thienopyridine treatment or to receive placebo. In this important study, DAPT therapy beyond 1 year after placement of a DES, versus aspirin therapy alone, significantly reduced the risk of stent thrombosis and MACCE but was associated with an increased risk of bleeding. The rate of stent thrombosis decreased from 1.4% to 0.4% with DAPT, and the rate of myocardial infarction decreased from 4.1% to 2.4%. Surprisingly, the rate of death from any cause increased from 1.5% to 2.0% with DAPT ($P = 0.05$). Counter to what has been reported, in the DAPT study, the use of thienopyridine beyond 1 year reduced the risks of both outcomes across all stent types. A few months later, the findings from the PEGASUS trial were released. The PEGASUS trial was designed to evaluate the potential benefit of DAPT (ticagrelor and aspirin) beyond 1 year after a myocardial infarction, with or without stent implantation [11]. More than 21,000 patients were randomized between ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily or placebo, on a background of aspirin. Treatment with ticagrelor significantly reduced the risk of cardiovascular death, myocardial infarction or stroke. However, once again, the rates of TIMI major bleeding were higher with ticagrelor than with placebo. Both the DAPT trial and the PEGASUS trial have shown that prolonged $P2Y_{12}$-receptor blockade reduced the rate of ischaemic events and increased the rate of bleeding events among patients with coronary disease. Then, several meta-analyses were performed trying to combine evidence regarding the optimum duration of DAPT. The authors of one such analysis concluded that extended DAPT is associated with approximately eight fewer myocardial infarctions per 1000 treated patients per year, but with six more major bleeding events, compared with a shorter duration of DAPT [12].

With regards to this controversial question, the recently published OPTIDUAL trial aimed to demonstrate the superiority of extended DAPT up to 48 months compared with 12 months of DAPT in reducing the rate of net adverse clinical events, a composite of death, myocardial infarction, stroke and major ISTH bleeding [13]. At 12 ± 3 months after DES implantation, patients who were receiving DAPT (clopidogrel plus aspirin) and who had remained free of major cardiovascular and cerebrovascular events or major bleeding were randomly assigned (1:1) to receive clopidogrel 75 mg daily (extended DAPT group) for a further 36 additional months (total treatment duration with DAPT: 48 ± 3 months) or to discontinue clopidogrel (aspirin group). While the trial did not demonstrate the superiority of extended DAPT, there was a borderline but non-statistically significant reduction in the post-hoc ischaemic outcomes (a composite of death, myocardial infarction and stroke) with extended DAPT. With extended DAPT up to 48 months after DES placement, there was a lower rate of ischaemic outcomes that appeared related to consistently lower rates of all ischaemic components (risk reduction > 30%). Interestingly, there was no apparent increase in all-cause mortality and major bleeding. The rates of major ISTH bleeding were identical in both groups (2.0%). Therefore, the OPTIDUAL results are consistent with the findings from the DAPT trial regarding the value of prolonging DAPT after DES placement. It appears that OPTIDUAL selected a population at low risk of bleeding, particularly as DAPT is associated with a greater risk of bleeding in the first year after initiating therapy.

In everyday clinical practice, the decision on the optimum duration of DAPT for a given patient remains difficult to determine. The physician has to identify who will benefit from prolonged DAPT for protection against ischaemic complications, with the least hazard of bleeding. Undoubtedly, better risk stratification strategies — to balance the risk of ischaemic events against those of bleeding — are needed to assess the need for long-term treatment with antiplatelet agents. The other perspectives for finding a better outcome with extended DAPT after DES placement could be new antiplatelet agents, such as the protease-activated

receptor 1 inhibitors (e.g. vorapaxar or others), or perhaps a single antiplatelet agent without aspirin, which could improve the safety while preserving ischaemic outcomes benefit. What is clear: the saga of antiplatelet therapy after DES is not yet finished.

Disclosure of interest

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