Commentary

Dual antiplatelet therapy duration after drug-eluting stents: how long?

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The implantation of drug-eluting stents (DES) has become a standard treatment for the management of patients with coronary artery disease (1). Millions of patients worldwide undergo coronary stenting each year. The use of dual antiplatelet therapy is critically important for the prevention of coronary stent thrombosis (2). Current clinical guidelines recommend at least 6- to 12-month treatment after DES implantation, but a longer duration of dual antiplatelet therapy (DAPT) may be beneficial. Interestingly, there is a slight but significant difference between the European and American guidelines, the European recommending 6 to 12 months, the American recommending at least 12 months after DES (3,4). Indeed, the recent guidelines of the European Society of Cardiology have suggested that 6-month DAPT is reasonable after second generation DES implantation in patients with stable CAD (3). The question of stopping DAPT is an important everyday problem for many clinicians. In everyday clinical practice, the decision on the optimum duration of DAPT for a given patient has to be determined. Several randomized trials comparing different durations of DAPT have been performed, and several meta-analyses have already been published demonstrating the importance of this topic in cardiology (5-9).

In this context, the report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines on Duration of Dual Antiplatelet Therapy in patients with Coronary Artery Disease is important and is asking three crucial questions about the optimal duration of DAPT after implantation of newer-generation DES (10). The first is the minimum duration of DAPT required after DES implantation, the second is about the clinical benefit of prolonging DAPT up to 18 to 48 months, the third is the clinical effect on DAPT in stable patients who are >1 year past a myocardial infarction.

About the minimum duration of DAPT required after DES implantation, the report has shown that DAPT of 12 months' duration, as compared with therapy of 3 to 6 months' duration was associated with no differences in death, major hemorrhage and stent thrombosis. It should be noted however that only two of the trials dealing with this question have compared a very short duration of 3 months compared to a longer duration (11,12). Moreover, in these two trials, patients were at low risk of thrombotic events. In the first one, the RESET Trial, 85% of the patients included had stable angina or unstable angina, in the second one, the OPTIMIZE trial, only 32% of the patients had a recent low-risk ACS. Therefore, there is still an uncertainty about safety of a very short duration (3 months) of DAPT after DES. Importantly, the context in which the stent is implanted is crucial.

Although the optimal DAPT duration in patients with ACS is controversial, there is general consensus that in patients having an ACS, DAPT should be recommended for at least 1 year. Therefore it appears premature to recommend very short term duration of DAPT in patients with ACS and in patients with high thrombotic risk. It is however true that the evidence supporting the recommendation on DAPT duration after an ACS relies on a single randomized trial (the CURE trial) performed when ACS patients were treated conservatively, and with either balloon angioplasty or bare metal stents (13).

The second controversial point in the report is the

possible clinical benefit effect of prolonging DAPT up to 18 to 48 months. In fact, only four randomized trial have prospectively compared 12 months of DAPT with a longer duration after DES placement (14-17). The DAPT trial has included the largest number of patients. The analysis has shown that prolonged DAPT significantly reduces the risks of myocardial infarction and stent thrombosis but increases the risk of major hemorrhage. There is indeed a difficult balance between the reduction in thrombotic events and the increase of bleedings. The authors of the present report performed a risk-benefit analysis and found with a longer DAPT duration no significant difference in the incidence of all-cause death, three fewer stent thrombosis (95% CI: 2–5) and six fewer myocardial infarctions (95% CI: 2–11) but five more major bleeds (95% CI: 3–9) per 1,000 patients per year. Therefore, it is not surprising that efforts have been done in identifying factors predicting whether the expected benefits of prolonging DAPT outweigh the feared increase in bleeding. Recently, Yeh *et al.* have developed a clinical decision tool to identify such patients (18). Using the large DAPT study, a prediction rule was derived stratifying patients according to their ischemic and bleeding risks. The validation was both internal and external. Because the DAPT study has randomized patients without thrombotic or bleeding events the first year after stenting, the DAPT score they derived applies only to these relatively low risk patients. Also, the authors acknowledged that their prediction rule assessing risks about DAPT continuation showed only modest accuracy. Nevertheless, it is interesting to note that among the different variables of the DAPT score, age is an important factor, and particularly an age >75 years is affected by a coefficient of –2. In other words, the older your patient is, the more cautious you have to be if you think to prolong DAPT. It seems that a prolonged duration of DAPT may be possible in patients at low bleeding risk who have tolerated DAPT the first year after stenting.

The third question is related to the clinical effect of DAPT in stable patients, more than 1 year after an acute myocardial infarction. The authors of the review conclude that the use of DAPT more than 1 year after a myocardial infarction reduces the composite risk of cardiovascular death, myocardial infarction or stroke but increases the risk of major bleeding. Once again, the equipoise is difficult but in the DAPT trial, the benefit of prolonged DAPT was accentuated in patients with MI at presentation (19). This is also reflected by the DAPT score in which myocardial at presentation at the time of PCI and prior myocardial infarction are taken into account. But in this situation also, the use of extended DAPT requires caution given the increased bleeding risk.

It has to be noted that the different trials analyzed in the report of Bittl *et al.* have included patients with implantation of predominantly newer-generation DES. The rationale for a prolonged duration of DAPT is only partially the prevention of stent thrombosis that is remarkably rare with the latest-generation stent, but also the prevention of ischemic events unrelated to the index coronary lesion (17). Newer-generation DES are associated with a risk of stent thrombosis approximately one half that of the first-generation DES, as it is reported by Bittl *et al.* (10).

In conclusion, the decision to continue or discontinue DAPT is still difficult. It depends on the bleeding and ischemic risks that are also evolving during time. The duration of DAPT has not always to be recommended at the time of the stent implantation. The rule of 1 year DAPT treatment after stenting does no more apply to each patient. In patients treated with new-generation DES for stable coronary disease, 6 months (and perhaps 3) of DAPT is an option. On the other hand, in patients at low bleeding risk, after 1 year without a cardiovascular event after DES, extension of DAPT beyond 12 months to prevent myocardial infarction may be optimal. However, there is room for better risk stratification strategies.

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Footnote

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