Editorial

The optimal duration of dual antiplatelet therapy after implantation of drug-eluting coronary stents: an unanswered question

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The efficacy and safety of percutaneous coronary interventions have been improved by the advent of drug-eluting stents (DES) in conjunction with adjunctive medical treatment (1). Although previous studies have demonstrated the efficacy of DES in reducing neointimal hyperplasia and clinical restenosis compared to bare-metal stents (2,3), the increased incidence of late or very late stent thrombosis after DES implantation remains an important concern due to its clinical consequences, including myocardial infarction and death in up to 80% (4-6). Early stent thrombosis is largely independent of stent type and mainly related to procedural variables, such as major edge dissections and stent underexpansion (7). In contrast, the mechanisms underlying late or very late stent thrombosis are still poorly defined, but premature of dual antiplatelet therapy (DAPT) discontinuation may play a major role (8). Nevertheless, prolonged DAPT has a clinical impact since it increases both bleeding risk (9,10). Furthermore, a series of interventions like endoscopic, dental, and surgical procedures are often delayed because of prolonged DAPT, thus affecting the patient's quality of life (11). On the bases of all these considerations, determining the optimal (or minimal necessary) duration of DAPT is very important.

The results of previous studies investigating DAPT duration, even after the introduction of new-generation DES, are conflicting. Indeed, trials have shown that a shorter therapy may be sufficient to prevent cardiovascular events after DES implantation, but their data are inconsistent in terms of the stent types and are underpowered for low frequency endpoints such as stent thrombosis (12-15). To date, the largest amount of data about DAPT duration after DES implantation is provided by the DAPT trial (16). According to DAPT trial, major adverse cardiovascular events, including stent thrombosis, were reduced in patients with DAPT further 18 months (4.3% *vs*. 5.9%, HR, 0.71; 95% CI: 0.59 to 0.85 for major cardiovascular events; 0.4% *vs*. 1.4%, HR, 0.29; 95% CI: 0.17 to 0.48 for stent thrombosis), but risk for bleeding was increased (2.5% *vs*. 1.6%, P=0.001). However, the characteristics of enrolled population, patients without an ischemic or bleeding event during the first 12 months after DES implantation and with fully DAPT compliance, limit the trial findings impact in clinical practice. Recently, the double-blind PEGASUS-TIMI 54 study has also demonstrated that in patients with a myocardial infarction more than 1 year previously, a longer treatment with ticagrelor significantly reduced the risk of cardiovascular death, myocardial infarction, or stroke (HR for 90 mg of ticagrelor *vs*. placebo, 0.85; 95% CI: 0.75 to 0.96; HR for 60 mg of ticagrelor *vs*. placebo, 0.84; 95% CI: 0.74 to 0.95) and increased the risk of major bleeding (2.60% with 90 mg and 2.30% with 60 mg, 1.06% with placebo, P<0.001 for each dose *vs*. placebo) with similar rates of intracranial haemorrhage or fatal bleeding (0.63% with 90 mg, 0.71% with 60 mg and 0.60% with placebo) (17). Subsequently, full evaluation of data has demonstrated that high-risk ischaemic subgroups, such as patients with renal dysfunction, have a significant net clinical benefit by a longer DAPT duration, because of the greater absolute risk

in this subgroup (18).

According to these conflicting data recommendations about DAPT duration following DES are inconsistent. The American College of Cardiology and American Heart Association guidelines recommend DAPT for ≥12 months after DES implantation (19), whereas in the European Society of Cardiology guidelines 6-month DAPT is permitted for new generation DES treatment in stable coronary disease (20).

In the context of this intense debate Hong *et al*. have investigated clinical outcomes in 1,400 patients undergone long length (total stent length >45 mm) everolimus eluting stent implantation randomized to receive 6- or 12-month DAPT (21). Their data are extrapolated by the IVUS-XPL and, as mentioned by the authors, the sample size estimation was not performed on the basis of testing the different DAPT durations and the 6-month arm was open label and not placebo controlled. At 1 year follow up the incidence of the primary endpoint (composite of cardiac death, myocardial infarction, stroke or TIMI major bleeding) and define or probable stent thrombosis were similar in the two groups (2.2% in 6-month group *vs*. 2.1% in 12-month DAPT group for the primary endpoint and 0.3% in both groups for define or probable stent thrombosis). According to these data a short DAPT duration, balancing between stent thrombosis prevention and reduction of bleeding risk, is safe also for patients with complex and length lesions treated with new generation everolimus-eluting stents.

In previous randomized studies investigating optimal DAPT duration the use of different types of second-generation DES may concur explain the observed results. Indeed, a significant interaction between DES type and DAPT duration for cardiovascular events was demonstrated in DAPT trial (16). Similar to Hong study, the ITALIC trial, investigating the optimal DAPT duration in everolimus eluting stents, has reported the safety of shorter therapy duration (22). The favourable strut coverage of everolimus eluting stent, as demonstrated by optical coherence tomographic study (23), could be explained the low rate of cardiovascular events in short duration of DAPT after this stent type implantation.

Hong *et al*. have also shown no significant differences in the clinical outcomes of diabetic patients. This finding disagreed with the EXCELLENT pre-specified subgroup analysis of diabetic patients, in which target vessel failure occurred more frequently in the 6-month DAPT group than in the 12-month group (HR, 3.16; 95% CI: 1.42–7.03) (12). Instead in a recent meta-analysis of 15 studies, a prolonged DAPT following PCI was associated with similar adverse clinical outcomes (OR: 1.03; 95% CI: 0.65–1.64) but with a significantly increased BARC defined bleeding (OR: 1.92, 95% CI: 1.58–2.34) compared to a short term DAPT use in diabetic patients (24).

Furthermore a post hoc subgroup analyses of IVUS-XPL had also revealed that a prolonged DAPT tended to have better clinical outcomes in patients with angiographic guidance compared to IVUS guidance (HR, 0.33; 95% CI: 0.09–1.21). This finding is the most important data in term of clinical application. Procedural variables, such as major edge dissections and stent underexpansion have always considered predictors of early stent thrombosis, indeed their role has remain poorly defined in late and very late thrombosis. Recently Taniwaki *et al*. have demonstrated that malapposition and stent underexpansion, without differences between patients treated with early- and new-generation DES, are the leading associated findings to late and very late stent thrombosis (25). Therefore the use of imaging technique in PCI optimization to reduce malapposition, underexpansion and edge dissection, should be considered above all in high risk bleeding patients to reduce DAPT duration.

Recent data suggest that the new-generation DES with biodegradable polymer might be associated with a less incidence of late stent thrombosis compared with durable polymer DES. The absorbable polymer might promote vascular healing, permitting a shortened duration of DAPT. A post hoc analysis of the multicenter registry of the Multi-Center Registry of EXCEL Biodegradable Polymer Drug Eluting Stents (CREATE) study demonstrated that prolonged DAPT (greater than 6 months) after biodegradable polymer-coated DES increases the risk of bleeding (OR: 1.814; 95% CI: 1.064–3.091), and is associated with adverse cardiac events at 1-year follow-up (P<0.001) (26). The limitations of non-randomized trial of this post hoc analysis are resolved in the Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization (I-LOVE-IT 2) trial. Indeed this prospective, multicentre, randomized study has demonstrated that 6-month DAPT seemed non inferior to 12-month DAPT in 1,829 patients who underwent PCI with a new-generation biodegradable polymer sirolimus-eluting stent implantation (27).

Although data on the safety of short DAPT duration after long length everolimus eluting stent and biodegradable polymer stent implantation are promising, all-comer randomized trials with long clinical follow-up

are required to confirm these findings. Furthermore an optimal management of DAPT should be an individualized management in which a prolonged DAPT is used in high risk ischaemic patients with a significant net clinical benefit by prolonged therapy, and conversely, a shorter DAPT is adopted in clinical setting of unnecessary or deleterious prolonged therapy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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