Individualization of dual antiplatelet therapy duration after drug-eluting stent implantation: paradigm and reality

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This editorial refers to ‘Should duration of dual antiplatelet therapy depend on type and/or potency of implanted stent? A pre-specified analysis from the PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia study (PRODIGY)†, by M. Valgimigli et al., on page 909

The use of drug-eluting stents (DES) results in a dramatic reduction in restenosis and represents one of the major advances in interventional cardiology. Yet, a reduction in death and myocardial infarction could not be shown with these devices; instead there were concerns about an excess of late thrombotic events compared with bare metal stents (BMS).1 The key underlying pathophysiological mechanism was suggested to be delayed arterial healing after DES implantation.2 Several non-randomized studies found controversial results regarding the duration of dual antiplatelet therapy (DAPT) and its impact on the risk of stent thrombosis.3,4 Since different stent platforms show different vessel healing5 and antiproliferative properties, it has been suggested that those with less antiproliferative properties (i.e. reduced efficacy) offer improved vascular healing (i.e. safety).6

The importance of DAPT in the early post-procedural period is well evidenced.7 However, the optimal time point when the benefit of preventing ischaemic events is outweighed by an increased bleeding risk has not been reliably defined. This controversy is also reflected in the different recommendations for DAPT duration after DES implantation by the guidelines committees on both sides of the Atlantic.8,9 Yet despite being much debated in the DES era, the problem of defining the optimal duration of DAPT for patients with coronary artery disease is not new. In the BMS era, the PCI-CURE study which enrolled patients with non-ST segment elevation acute coronary syndrome showed a significant reduction in ischaemic events with a strategy of loading and prolonging DAPT with aspirin and clopidogrel for a mean of 8 months compared with a strategy of no loading dose and a mean DAPT duration of 1 month.10 Since the trial tested dual hypotheses, i.e. loading and prolonging, without employing a factorial design, conclusions about the optimal duration of DAPT are not without concern. Moreover, there was an increase in minor bleeding with prolonged therapy. Despite the lack of solid data surrounding this topic (level of evidence C), a DAPT duration of up to 12 months is currently recommended in patients with acute coronary syndrome (regardless of whether the patient received a stent or not).11

In summary, device-specific characteristics, e.g. the type of stent implanted, and patient-specific characteristics, e.g. clinical presentation, have been suggested as potential determinants of the duration of DAPT after stent implantation. The PRODIGY trial offers answers as to whether individualization of DAPT duration according to stent or patient characteristics may improve clinical outcomes.

The main finding of the randomized PRODIGY trial was no protection from ischaemic events but even an increased bleeding risk with prolonged DAPT up to 24 months compared with 6 months.12 There was also no significant interaction between clinical presentation and treatment effect of different DAPT durations.12 Therefore, the question of whether the underlying disease should dictate the duration of therapy after stent implantation is challenged once more.

Valgimigli and colleagues now report on the pre-specified stent-based analysis of the PRODIGY trial.13 The study had a 4 × 2 factorial design, i.e. patients were randomly assigned to four different stent types [third-generation thin-strut BMS, everolimus-eluting stent (EES), paclitaxel-eluting stent (PES), or zotarolimus-eluting Endeavor Sprint stent (ZES-S)] and two regimens of DAPT (6 or 24 months duration). The analysis tested the hypothesis of whether optimal DAPT duration is stent specific and whether
there is an association between stent potency and vulnerability to short DAPT duration. Indeed the rates for target lesion revascularization in the trial of Valgimigli et al. (EES < PES < ZES-S < BMS) match with the potency differences observed in previous stent comparisons. However, the hypothesis that improved efficacy is associated with impaired safety could not be confirmed. The results are in line with those reported in the PROTECT trial.6 This randomized, open label trial aimed at comparing two different DES which represent vascular healing responses at the opposing ends of the spectrum: the sirolimus-eluting Cypher stent with strong antiproliferative properties but suggested delayed arterial healing, and the zotarolimus-eluting Endeavor stent with less antirestenotic efficacy but suggested improved healing (similar to that of a BMS). In that large, randomized study of 8709 patients, the ability of the sirolimus-eluting Cypher stent to reduce neointimal proliferation was not associated with an increased risk of definite and probable stent thrombosis at 3 years of follow-up compared with the less efficacious zotarolimus-eluting Endeavor stent.6 More evidence against that paradigm comes from the EES platform. This stent platform allies high antirestenotic efficacy14 with improved vascular healing5 and low stent thrombosis rates.15 This is also reflected by a CE Mark for newer EES platforms, recommending a minimal DAPT duration of only 3 months.

The results suggest that more complex mechanisms than intimal hyperplasia only determine vascular healing. Indeed all components of a stent platform, i.e. the stent backbone,16 the polymer,17 and the active drug,18 and their interaction with the vascular milieu have been shown to be of importance.

Although the subgroup analyses are limited by multiple testing and lack of power, two findings regarding stent-specific outcomes require special consideration.

The study of Valgimigli et al.13 showed that the primary endpoint did not differ according to DAPT duration in patients receiving a BMS, PES, or EES. However, it was significantly lower in patients randomized to ZES-S and a 6-month regimen of DAPT compared with those with ZES-S and 24 months of DAPT duration, with a significant interaction between stent type and DAPT duration regarding the primary outcome. Although pre-specified, with the small number of patients per group and the performance of multiple comparisons, this analysis does not allow any firm conclusions. At first glance, the results of increased ischaemic events with longer DAPT duration in the ZES-S group appear counterintuitive. Yet it might be worthwhile looking at the bleeding data. The main PRODIGY trial found an increase in bleeding events with prolonged DAPT. Although the mechanisms are complex and not completely understood, a strong association between bleeding and ischaemic events has been suggested.

The second interesting finding was that in PES-treated patients, the incidence of stent thrombosis (definite or probable, and definite, probable, or possible) was higher in those with the shorter DAPT duration of 6 months compared with 24 months in the 6-month landmark analysis. It should be mentioned that this was a post-hoc, subgroup, landmark analysis with a low number of patients and events. It therefore cannot be excluded that this presents a chance finding. However, the data are in line with others showing an increase in the rate of stent thrombosis with the PES when compared with the sirolimus-eluting stent.19 In one meta-analysis, the excess stent thrombosis occurred exactly at the time where clopidogrel therapy was stopped, suggesting an association between stent thrombosis rates and discontinuation of clopidogrel therapy in PES-treated patients.19 Since the PES has lost its relevance in contemporary interventional cardiology, we will probably never have the chance to validate this finding.

Different ways of individualizing duration of DAPT after stent implantation have emerged over time: adaptation according to clinical presentation and/or stent potency. Notwithstanding the limitations of the subgroup analyses, the PRODIGY trial currently offers no support for this double individualization concept.

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**References**


