Editorial

Time for science to catch up with clinical practice?

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Siddiqi *et al.* performed a retrospective analysis of the large Veterans database to explore the effect of clopidogrel prolongation beyond 12 months compared with 12 months or less after coronary stenting (1). Patients treated between 2002 and 2006 were divided in two groups: normal renal function (n=18,162) or chronic kidney disease (CKD, n=4,880) based on an estimated glomerular filtration rate (eGFR) cut-off of ≥ or <60 mL/min, respectively. A further stratification was made to compare patients treated with bare metal stents (BMS) and those treated with drug-eluting stents (DES). Outcomes were evaluated in patients free from ischemic or bleeding events within the first 12 months after percutaneous coronary intervention (PCI), at a follow-up ranging from 1 to 4 years after PCI. The primary endpoint was the combined outcome of death or acute myocardial infarction (MI), which was significantly increased in patients with CKD in both DES and BMS subgroups. However, CKD was also associated with an increased risk of disabling or life-threatening bleeding after DES and BMS implantation.

The authors reported that clopidogrel use of more than 12 months after PCI in patients with CKD receiving DES was associated with lower risk of death or MI (18% *vs.* 24%, HR=0.74; 95% CI, 0.58 to 0.95), and death (15% *vs.* 23%, HR=0.61; 95% CI, 0.47 to 0.80). At multivariate and propensity-score adjusted analyses, however, results were confirmed for death but not for the composite of death or MI. Furthermore, the potential benefits of prolonged dual antiplatelet therapy (DAPT) on the primary endpoint did not apply to patients treated with BMS. No significant increase of life-threatening bleeding was observed by prolonging DAPT administration after both DES or BMS implantation in patients with CKD at multivariate or propensity analyses, however: (I) a trend of increased risk was present (significant at univariate analysis in DES subgroup); (II) the rates of major bleeding were not reported and (III) the number of life-threatening bleeding events was probably too low to detect a significant difference between subgroups.

Finally, in patients with normal renal function, the authors observed consistent findings but the magnitude of ischemic risk reduction was lower than that observed in CKD patients treated with DES.

Although affected by some inherent critical limitations, this large retrospective study is well conducted and of interest to the community because it deals with a specific patient population (i.e., patients affected by CKD) in whom few data from randomized trials are available.

DAPT administration aims to reduce the risk of stent thrombosis (ST) after coronary stent implantation and prevent coronary atherothrombotic events at sites outside of the stented segment. However, the optimal duration of DAPT after stent implantation in general, and following DES implantation in particular, is matter of ongoing debate (2,3).

Does this study help in identifying the target population in which DAPT should be prolonged well beyond 12 months? We believe the reader should apply caution while interpreting study results. Beyond the obvious limitations carried by a retrospective and non-randomized analysis, these findings should be critically contrasted with the results of randomized controlled studies, which showed a clear effect of DAPT prolongation on non-fatal ischemic endpoints, i.e., MI and very late ST, in the absence of a mortality benefit. How can we reconcile those with the observed reduction in mortality but not mortality or MI risk in the current analysis? A plausible interpretation is that in clinical practice clinicians are able to identify patients

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who benefit from prolonged DAPT duration and using sophisticated statistical tools, no adjustment can be made for baseline or updated covariates that are not routinely captured, and perhaps not even capturable, in registries.

Drug eluting stents have consistently reduced in-stent restenosis as compared with BMS but at the expense of safety concerns duo to an increase in late and very late ST. In particular, first-generation DES were associated with a four- to five-fold higher risk of very late ST as compared with BMS, which fueled "the longer the better" recommendation for DAPT duration in patients treated with DES (4). Conversely, second-generation devices were shown to be safer in terms of ST as compared with both first-generation DES and BMS (5).

Recent trials, reviews and meta-analyses (2,6-12) compared efficacy and safety of short (<12 months) and long term (≥12 months) DAPT after first- and second-generation DES implantation with respect to the currently recommended 12-month therapy (13,14). A short course of DAPT was associated with a significant reduction in major bleeding without significant differences in ischemic or thrombotic outcomes. Moreover, patients associated with high risk of bleeding events were recently evaluated in two different trials (15,16) in which DAPT was stopped very early (1 month) after second-generation DES implantation without safety concerns in terms of ischemic events. In particular, the ZEUS trial (15) compared Zotarolimus-eluting Endeavor sprint stent followed by 30-day DAPT with BMS followed by the same DAPT regimen, while the LEADERS FREE trial (16) compared a polymer-free Biolimus-eluting stent with a very similar BMS platform followed by 1-month DAPT. Both studies demonstrated that a treatment strategy consisting of second-generation DES implantation followed by a shorter than currently recommended DAPT regimen (30 days) resulted in a lower risk of MACE as compared with BMS in high-bleeding risk patients.

Conversely, prolonging DAPT over 12 months yielded a significant reduction in terms of MI and ST, in particular in trials including first-generation DES use (10,17), but at the price of a substantial increasing in major bleeding. Moreover, all-cause mortality was also significantly increased in the long-term DAPT population (10,11,18). Actually, bleeding and ST may have a different impact on mortality as highlighted in a recent meta-analysis reporting a significant association between bleeding and non-cardiovascular death but not between ST and cardiovascular death (19).

As a result, a personalized DAPT duration based on patient's bleeding and ischemic risk seems to be a more logical strategy in order to reach maximum benefits with limited side effects.

Patients with CKD represent a sizable proportion of patients (between 33% and 50%) with myocardial ischemia undergoing percutaneous coronary stent implantation (20), although frequently excluded or marginally represented in major randomized trials evaluating clopidogrel duration after coronary stenting. Siddiqi *et al.* included a high number of patients with eGFR <60 mL/min in whom primary and secondary outcomes were evaluated with multivariate and propensity analyses (1). The sensitivity analyses using the CKD-Epi equation, which seems to be more precise in estimating renal function, supported the consistency of their results. Unfortunately, due to the small number of subjects with eGFR <30 mL/min, the differences across different degrees of CKD have not been evaluated in this study (1).

In early-stage CKD population the risk for premature cardiovascular disease is increased by 25% to 30% while in end-stage CKD patients it is more than 30- to 50-fold higher. On the other hand, also the bleeding risk is increased in patients with renal dysfunction (1,20). Indeed, renal disease was identified to be commonly used in the clinical practice to weigh the bleeding risk after DES implantation in a recent survey (3), and it is also included in the most relevant available bleeding risk scores (i.e., CRUSADE and HAS-BLEED).

Siddiqi *et al.* concluded that: "in patients with CKD, prolonging clopidogrel beyond 12 months after PCI may decrease the risk of death or MI only in patients receiving first-generation DES as compared with BMS". Key questions remains with respect to whether and how much these results may be applicable to patients with more severely reduced renal function (i.e., eGFR <30 mL/min) or to patients treated with contemporary devices, such as newer generation DES.

The observation that prolonged DAPT did not increase bleeding risk, a finding which has been remarkably consistent across all randomized controlled studies and meta-analyses, further raising concerns on the adequacy of adjustment for biases in the current analysis.

Conclusions

Prolongation of DAPT still remains highly debated, irrespective of specific subgroups of patients, because it

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is associated with ischemic benefits, but also with a time-dependent risk of major and clinically relevant bleeding complications, which in turn significantly affect morbidity and mortality.

The present study offers data for additional debate as it focuses on a large sub-population of patients with high ischemic and bleeding risks, who are frequently under-represented in randomized trials on DAPT duration and/or stent types. The key lesson here is that perhaps clinicians seem to be able to select the ideal CKD population in whom DAPT may and should be prolonged, better than conventional inclusion or exclusion criteria so far employed in clinical trials. Hence, once more trialists and device or drug manufacturing companies need to learn from clinicians more than vice versa.

Randomized trials of new generation DES and reliable $P2Y_{12}$ inhibitors (ticagrelor or prasugrel) are needed to help clinicians to perform even better.

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Footnote

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