Optimizing the Duration of Dual Antiplatelet Therapy After Implantation of Drug-eluting Coronary Stents

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Percutaneous coronary intervention (PCI) with implantation of drug-eluting stents (DESs) has become the standard of care for coronary artery disease and gives a great impetus to device industry.[1,2] In 2013, approximately half million patients with coronary artery disease underwent PCI in China, with a penetration rate of DES reaching beyond 95%.[3] The use of DES including domestic ones is highly effective in preventing coronary restenosis, but there is a collateral cost to be borne in terms of delayed healing or re-endothelialization of the stented arterial segment and risk of stent thrombosis.[4] Therefore, dual antiplatelet therapy (DAPT) with aspirin and P2Y12 receptor antagonist for at least 12 months after DES implantation is strongly recommended by Chinese guidelines on PCI.[5] Since prolonged DAPT may increase major bleeding and subsequent mortality, balancing ischemia (or thrombotic events) and bleeding with DAPT is always important for improving overall clinical outcome after DES-based PCI.[6]

Premature discontinuation of DAPT has been proved to be a major determinant of stent thrombosis,[7] but trials with the newer generation DES have suggested low thrombotic event rates despite a relatively short DAPT duration.[8-10] Currently, two kinds of imported second-generation DES (zotarolimus- and everolimus-eluting stents) and more than 10 different types of home-made sirolimus-eluting stents with or without biodegradable polymer coating are used in daily clinical practice.[3] The PROTACT trial demonstrated that adherence to DAPT modifies the outcome of stent thrombosis to a great extent after sirolimus-eluting stent deployment than after zotarolimus-eluting stent deployment, most likely due to different healing characteristics.[11] Likewise, Silber *et al*.[12] found a lack of association between DAPT use and stent thrombosis between 1 and 12 months in a pooled population of patients receiving resolute zotarolimus-eluting stent implantation. The EXCELLENT trial indicated that 6-month DAPT did not increase the risk of target vessel failure defined as the composite of cardiac death, myocardial infarction, or ischemia-driven target vessel revascularization at 12 months after everolimus-eluting stent placement compared with 12-month DAPT.[13] In this issue of *Chinese Medical Journal*, Zhang *et al*.[14] investigated the relationship between DAPT use and clinical safety in Chinese patients undergoing everolimus-eluting stent implantation (the SEEDS study). The major strength of this elegant study was that it included a large cohort of high-risk patients with small vessel disease, long lesions, or multi-vessel disease and assessed outcomes during long-term follow-up. Discontinuation of DAPT defined as any interruption of aspirin and/or clopidogrel more than 14 days was found in 2.28% of patients at 6 months, 30.50% at 12 months, and 64.60% at 2 years. However, the overall incidence of all-cause death (0.90%), stroke (1.10%), and definite/probable stent thrombosis (0.70%) was low. Interestingly, among 73 patients who had discontinuation of clopidogrel within 1 year, none had stent thrombotic events at 12 months, and only one patient experienced stent thrombosis between 1 and 2 years. Multivariate analysis revealed that DAPT was not an independent predictor for net adverse cardio-cerebral events. In contrast, the incidence of major bleeding was increased in patients receiving prolonged DAPT.

In China, the motivation behind the development of newer DES has been the attainment of optimal anti-restenotic efficacy at a minimum of stent thrombosis. Unfortunately, few studies have addressed the issue of DAPT use after implantation of a domestic DES. In a multicenter, prospective CREATE registry involving 2077 "real-world" patients who were treated exclusively with Excel biodegradable polymer-coated DES, the rate of stent thrombosis was 0.87%

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and 1.10% at 18-month and 5-year follow-up, respectively, despite 80.50% of patients discontinuing clopidogrel at 6 months.[15-17] In contrast, the risk of bleeding was increased with longer use of DAPT (>6 months).[18] The FIREHAWK sirolimus-eluting stent with biodegradable polymer-coated cobalt-chromium and abluminal groove enables drug release to the vessel wall in a uni-directional manner, with the goal of minimizing long-term inflammation and decreasing stent thrombosis while maintaining anti-restenotic effect. The multicenter randomized TARGET I trial demonstrated similar rates of major adverse cardiac events and definite or probable stent thrombosis at 1-year follow-up in comparison with everolimus-eluting stents,[19,20] and the TARGET II registry further confirmed the long-term safety and efficacy of this home-made DES in real-world practice. Previous studies have shown that fully biodegradable DES would be attractive and promising because of its potential advantages with regard to reduction of stent thrombosis.[21] Since drug elution and vessel scaffolding are only provided by the stent until the vessel had healed, no triggers for stent thrombosis (polymer and struts) exist long-term, which may reduce the need of DAPT. Taken together, these observations suggested that an overall decreased risk of recurrent ischemic events with the newer generation DES potentially limits the benefits of long-term DAPT.[22]

Nevertheless, the duration of DAPT may be also tailored in individual patients with high-risk clinical and angiographic profiles. A highly significant interaction between the presence of diabetes or chronic kidney disease and stent type on target lesion failure has been reported.[23-27] In a prespecified subgroup analysis, Gwon *et al*.[13] found that the treatment effect of DAPT varied depending on the presence of diabetes mellitus. Target vessel failure occurred more frequently in the 6-month DAPT group than in the 12-month DAPT group among diabetic patients, whereas it occurred less frequently in the 6-month DAPT group than in the 12-month group among those without diabetes mellitus. Among diabetic patients, rates of myocardial infarction, target vessel revascularization and stent thrombosis were higher in the 6-month DAPT group than in the 12-month DAPT group. In an observational study of diabetes mellitus, longer use of clopidogrel was associated with a lower incidence of death or myocardial infarction after implantation of DES, suggesting that the minimum necessary duration of DAPT may be longer in diabetic than in nondiabetic patients.[23] Similarly, patients with chronic kidney disease often have poor clinical outcomes after DES-based PCI even at mild renal insufficiency.[25] Renal dysfunction is also an independent risk factor for late or very late stent thrombosis and bleeding after PCI with DES implantation.[26,27] Both diabetes mellitus and chronic kidney disease are regarded as proinflammatory and prothrombotic conditions.[26-28] Further studies are needed to elucidate the mechanistic pathways underlying the poor prognosis of patients with diabetes or chronic kidney disease, with a focus toward development of novel DES and DAPT regimen to improve outcomes. DAPT is a cornerstone in the treatment of acute coronary syndrome.[29,30] In a contemporary, real-life acute coronary syndrome population, Varenhorst *et al*.[31] found that DAPT for more than 3 months compared with a shorter duration was associated with a lower risk of death, stroke, or re-infarction. The optimal duration of DAPT for patients with left main disease and bifurcation stenting requires further investigations.[32]

In summary, the optimal duration of DAPT after DES placement is determined by multiple clinical and procedural characteristics as well device-specific factors. Based on recent evidence on DAPT use after implantation of newer generation DES and the results of SEEDS and CREATE registries, I suggest that the recommendation of DAPT use in the current Chinese guidelines on PCI (at least >12 months) needs to be revised. Because each patient is an individual and one size does not fit all, patient-specific therapy still requires clinical judgment, which is based on several factors, so that the duration of DAPT after implantation of DES could be maximally optimized and long-term safety and efficacy of DES could be further improved.

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