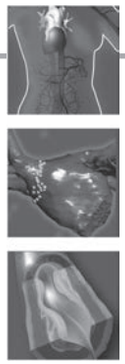

How do we decide the optimal duration of dual antiplatelet therapy after percutaneous coronary intervention?

"*To determine the optimal duration of dual antiplatelet therapy and the risk–benefit ratio for long-term dual antiplatelet therapy after drug-eluting stents, several clinical studies have been performed, but study findings are still equivocal.*"

KEYWORDS: antiplatelet therapy ■ clopidogrel ■ coronary disease ■ drug-eluting stents

Seung-Jung Park

Author for correspondence: Department of Cardiology, University of Ulsan College of Medicine, Asan Medical Center, 388-1 Poongnap-dong, Songpa-gu, Seoul 138-736, Korea
Tel.: +82 2 3010 4812
Fax: +82 2 475 6898
sjpark@amc.seoul.kr

Duk-Woo Park

Department of Cardiology, University of Ulsan College of Medicine, Asan Medical Center, 388-1 Poongnap-dong, Songpa-gu, Seoul 138-736, Korea

On the basis of previous trials performed in the era of balloon angioplasty or bare-metal stents [1,2], over the past decade, dual antiplatelet therapy (DAPT) with aspirin and platelet P2Y12 inhibitor has been the mainstay of short- and mid-term pharmacologic management in patients with acute coronary syndrome or who are undergoing percutaneous coronary intervention (PCI).

One of the remarkable changes over the past decade in PCI practice was that drug-eluting stents (DES) have been used in the majority of patients receiving intracoronary stents regardless of patient and lesion characteristics. However, due to delayed or incomplete endothelialization of stent strut, an increased propensity for late stent thrombosis was reported and early discontinuation of DAPT regimen was a most important risk factor for these events [3]. Such observations led to recommendations for prolonged courses of DAPT after DES placement. However, the extended duration of DAPT was accordingly associated with substantial increases in bleeding risk [4] and therefore careful balancing of ischemic benefit and bleeding risk is required for patients receiving DES placement.

Current clinical evidence: from real-world registry to randomized trials

To determine the optimal duration of DAPT and the risk–benefit ratio for long-term DAPT after DES, several clinical studies have been performed, but study findings are still equivocal. In the real-world of PCI practice, several small-to-large observational studies showed conflicting results concerning the need for prolonged DAPT after DES placement. Some studies suggested that long-term use of DAPT beyond 1 or 2 years after DES was associated with a significant reduction of ischemic events [5–7], but others showed that prolonged courses of therapy with clopidogrel were not related to a reduction of ischemic events and otherwise associated with increased risk of bleeding [8,9]. This inconsistency among observational studies may be due to a profound selection bias, unmeasured confounding factors, or chance effect by small number of events and limited number of patients.

To overcome these inherent limitations in observational studies, several randomized trials were conducted. The first randomized trial, ZEST-LATE/REAL-LATE, showed that longer-term use of DAPT for more than 12 months was not significantly more effective than aspirin monotherapy in reducing the rate of myocardial infarction or cardiovascular death [10]. In the extended study DES-LATE, these findings were confirmed again [11]. Similar findings were also observed and repeated in other randomized clinical trials including more current generation DES [12–15]. The PRODIGY trial comparing 6 and 24 months of DAPT showed that there was no difference in primary and secondary ischemic events, but an excess of bleeding was found in 24-month group [12]. The EXCELLENT trial comparing 6- and 12-month DAPT showed that he risks of target vessel failure and any efficacy and safety outcomes were similar among the two groups [13]. Short-term DAPT of less than 6 months was also tested. The RESET trial comparing 3- and 12-month DAPT showed that 3-month therapy was noninferior to 12-month therapy with respect to the occurrence of net clinical events (cardiovascular death, myocardial infarction, stent thrombosis, target vessel revascularization or bleeding) [14]. This finding was also consistent in the recent OPTIMIZE trial comparing 3- and 12-month DAPT [15]. Meta-analysis including available randomized trials showed that extended courses of clopidogrel exceeding 12 months do not contribute favorably

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to patient outcomes for reducing death, myocardial infarction, stent thrombosis or stroke, and may in fact be detrimental with increased bleeding risk [16,17].

Unmet evidence & unresolved issues

Although important findings from randomized trials have been reported, they were still criticized for being underpowered to predict outcome due to a relatively small number of patients and low rate of events, and as to adopt open-label designs that might cause a potential and considerable bias. In addition, neither trials have been designed to distinguish outcomes according to clinical, angiographic, or procedural complexity, which might cause heterogeneity of future ischemic and bleeding risk. Therefore, current available evidence should be confirmed or refuted through larger randomized, clinical trials with long-term follow-up. The DAPT study aims to compare the benefits and risks of 12 versus 30 months of DAPT duration in more than 20,000 patients undergoing coronary stents; therapy was blinded and allocation was also masked. In addition, this trial included first- and second-generation DES and clopidogrel, prasugrel, or a new thienopyridine, unlike the preceding clinical trials [18]. Thus, in the upcoming years, it would make more reliable and confirmative sense to establish a firm policy regarding optimal duration of DAPT among patients who are receiving DES in clinical practice. Another ongoing trial (ISAR-SAFE) was also designed to assess whether discontinuation of clopidogrel plus aspirin at 6 months after DES implantation is noninferior to 1-year treatment [19] and diverse duration of DAPT is currently under investigation via several clinical trials (OPTIMIZE, ARCTIC and EDUCATE trial). The ISAR-CAUTION study will address another important issue regarding whether clopidogrel should be discontinued abruptly or with dose-tapering.

> *"If more confirmative data were available in the near future, a shorter course of dual antiplatelet therapy ... may be considered..."*

Several other issues should be also resolved via future clinical studies. First, there is histopathologic and clinical evidence that newer generation DES, at least, lead to a more favorable healing profile with improved safety outcomes. From theoretical and practical viewpoints, shorter duration of DAPT might be enough, or beneficial, for patients receiving newer-generation everolimus- or zotarolimus-eluting stents or bio-absorbable/polymer-free DES. For ensuring whether the optimal duration of DAPT may be stent specific, more DES-specific studies are eagerly required. Second, neither previous clinical studies nor randomized trial, thus far have been designed to distinguish outcomes according to several clinical, lesion and procedural features that suggest higher risk of ischemic complications (i.e., acute coronary syndrome, diabetes mellitus, renal failure, low ejection fraction, multiple stents, long stents, left main stents or bifurcation stents) and those whose baseline risk is low. Since the risk/benefit balance with prolonged DAPT use according to clinical and angiographic complexity might be heterogenous, further, larger trials with sufficient statistical power to address this specific issue in several subtypes may be required. Third, in the future, an increasing number of patients will receive newer-generation P2Y12 antagonists (prasugrel or ticagrelor), which have greater platelet inhibition than clopidogrel. Although current guidelines recommend prasugrel and ticagrelor on equal terms with clopidogrel for more than at least 12 months for patients with acute coronary syndrome and DES implantation [20], the balance between ischemic and bleeding risk may significantly differ between short- and long-term therapies with newer-generation P2Y12 antagonists. Finally, noncardiac surgery after DES implantation is not uncommon in clinical practice and is associated with increased risk of adverse cardiovascular events after cessation of DAPT. Further clinical trials would be needed to determine optimal bridging antiplatelet therapy for patients undergoing major noncardiac surgery within the first year after DES placement.

Conclusion & future perspective

Owing to the relative risk and benefit associated with use of DES and DAPT, defining optimal duration of DAPT after DES implantation is crucial in routine clinical practice. Available evidence from randomized clinical trials suggested that a prolonged course of clopidogrel exceeding 12 months does not contribute favorably for reducing ischemic cardiovascular events and may, in fact, be detrimental with an increased risk of bleeding. However, owing to a relatively small number of patients, events and limitations of study designs, more confirmative and larger clinical trials, such as the DAPT trial, will guide the physician in making informed decisions on the optimal duration of DAPT for such patients.

Given the present level of evidence, our current practice is as follows for patients receiving DES placement; we recommend routine use of

DAPT for at least 12 months irrespective of DES type. For patients with stable coronary disease or receiving a simple procedure (one or two stents for simple lesions), 12-month use of DAPT has been mostly recommended. However, for high-risk patients (diabetes, low ejection fraction, renal failure, or index complex angioplasty, e.g., left main or bifurcation stenting, or multivessel/multiple stenting more than at least three stents, among others), longer-term duration of DAPT (2 years or sometimes up to 3–5 years) has been prescribed based on patients' conditions and/or physician's preference. If more confirmative data were available in the near future, a shorter course of DAPT (i.e., 3 or 6 months) may be considered, especially with new-generation DES (everolimus and zotarolimus DES, polymer-free or polymer-biodegradable DES and bioabsorbable DES) or with simple clinical and lesion characteristics.

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