Antiplatelet Therapy After Percutaneous Coronary Intervention

— Past, Current and Future Perspectives —

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Optimal antiplatelet therapy after percutaneous coronary intervention (PCI) has been changed in parallel with the improvements of coronary stent and antiplatelet therapy. Over the past 25 years, dual antiplatelet therapy (DAPT) with aspirin plus P2Y₁₂ inhibitor has been the standard of care used after coronary stent implantation. First-generation drug-eluting stent (DES) appeared to increase the risk of late stent thrombosis, and duration of DAPT was prolonged to 12 months. DAPT duration up to 12 months was the dominant strategy after DES implantation in the subsequent >10 years, although there was no dedicated randomized controlled trial supporting this recommendation. The current recommendation of DAPT duration is getting shorter due to the development of new-generation DES, use of a P2Y₁₂ inhibitor as a monotherapy, and the increasing prevalence of high-bleeding risk patients. Furthermore, an aspirin-free strategy is now emerging as one of the novel strategies of antiplatelet therapy after PCI. This review gives an overview of the history of antiplatelet therapy and provides current and future perspectives on antiplatelet therapy after PCI.

Key Words: Antiplatelet therapy; Coronary artery disease; Percutaneous coronary intervention (PCI)

Inception of Dual Antiplatelet Therapy

In 1995, 2 seminal studies presented by Colombo A, and Van Belle E, respectively, suggested the combination of aspirin and ticlopidine as a safe replacement for anticoagulant therapy after coronary stent implantation.^{1,2} In 1996, the ISAR (Intracoronary Stenting and Antithrombotic Regimen) trial demonstrated that dual antiplatelet therapy (DAPT) with ticlopidine plus aspirin, as compared with conventional anticoagulant therapy, significantly reduced the 30-day incidence of both cardiac events and hemorrhagic/vascular complications after bare-metal stent (BMS) implantation (**Figure 1**).³ In 1998, aspirin and ticlopidine treatment also demonstrated a resultant lower rate of stent thrombosis at 1-month after BMS implantation as compared with aspirin alone and a combination of aspirin and warfarin in the STARS (Stent Anticoagulation Restenosis Study) trial.⁴ FANTASTIC (Full Anticoagulation Versus Aspirin and Ticlopidine) also showed that DAPT with aspirin and ticlopidine significantly reduced rates of bleeding and subacute stent occlusion compared with conventional anticoagulation.⁵ In the MATTIS (Multicentre Aspirin and Ticlopidine Trial after Intracoronary Stenting) study, high-risk patients receiving DAPT after coronary stenting had significantly reduced bleeding and vascular complications as compared with when they were treated

with aspirin and anticoagulation.⁶ Since then, DAPT with aspirin plus thienopyridine has been the standard of care used after coronary stent implantation.

Clopidogrel emerged as a new P2Y₁₂ inhibitor in place of ticlopidine; it had greater molar potency and a better safety profile than ticlopidine. In 1997, clopidogrel was approved by the U.S. Food and Drug Administration (FDA). In 2000, the CLASSICS (Clopidogrel Aspirin Stent International Cooperative Study) trial showed that the safety/tolerability of clopidogrel was superior to that of ticlopidine, with comparable efficacy with regard to cardiac event treatment after successful stenting.⁷

First Generation DES and Long DAPT

In 2001, DAPT with clopidogrel plus aspirin for 3–12 months in patients with acute coronary syndrome (ACS) without ST-segment elevation showed significant risk reduction for cardiovascular events as compared to aspirin alone in the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial.⁸ Long-term administration of clopidogrel on top of aspirin after percutaneous coronary intervention (PCI) in ACS patients was also associated with a lower rate of cardiovascular events as compared to aspirin alone in the PC-CURE trial.⁹

In 2002, long-term (1-year) clopidogrel therapy signifi-

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cantly reduced the risk of adverse ischemic events (the combined risk of death, myocardial infarction, or stroke) in patients who were to undergo elective PCI in the CREDO trial.¹⁰

In 2003, a first-generation drug-eluting stent (DES), the sirolimus-eluting stent, was approved by the FDA. A first-generation DES resolved the problems of restenosis and repeated target-lesion revascularization (TLR) after PCI, which had been the main concerns after BMS implantation.¹¹ However, late adverse events such as very late stent thrombosis or late TLR beyond 1 year have emerged as new problems after first-generation DES implantation.¹² Inflammatory reaction, hypersensitivity, endothelial dysfunction, and neo-atherosclerosis were accused as the pathophysiologic mechanisms for late adverse events. In 2006, an expert FDA panel concluded that first-generation DES appeared to increase the risk of late stent thrombosis and recommended that the duration of DAPT should be prolonged to 12 months. There was no dedicated randomized controlled trial supporting this recommendation.¹³ Nevertheless, DAPT duration up to 12 months was the dominant strategy after DES implantation in the following >10 years. Based on previous findings from the PCI-CURE, CREDO trial, and observational studies suggesting persistent risk of stent thrombosis beyond 6 months after stent implantation,^{9,10,14-16} the 2011 American Heart Association (AHA) guideline recommended a minimum DAPT duration of at least 12 months after first-generation DES implantation.¹⁷ The European Society of Cardiology (ESC) guidelines in 2010 recommended 1 month of DAPT after BMS in stable patients, 6–12 months of DAPT after DES, and 12 months of DAPT in the case of ACS.¹⁸

Introduction of a New Generation P2Y₁₂ Inhibitor

In 2007, a novel P2Y₁₂ inhibitor, prasugrel, as compared to clopidogrel, was evaluated in TRITON-TIMI (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction) 38.¹⁹ In patients with ACS, prasugrel was associated with significantly reduced rates of ischemic events, including stent thrombosis, but with an increased risk of major bleeding, including fatal bleeding. Overall, mortality did not differ significantly between the treatment groups. In 2009, another novel P2Y₁₂ inhibitor, ticagrelor, as compared to clopidogrel, was evaluated in PLATO (Platelet Inhibition and Patient Outcomes).²⁰ In ACS patients with or without ST-segment elevation, treatment with ticagrelor, as compared to clopidogrel, significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding, but with an increase in the rate of non-coronary artery bypass grafting (CABG)-related bleeding. In 2011, AHA guidelines stated that patients receiving a stent (BMS or DES) during PCI for ACS were recommended to use a P2Y₁₂ inhibitor with clopidogrel 75mg daily, prasugrel 10mg daily, or ticagrelor 90mg twice daily for at least 12 months.¹⁷

New Generation DES and Short Duration of DAPT

In 2008, a new-generation DES, an everolimus-eluting stent, was approved by the FDA. New-generation DESs were developed to overcome adverse events, especially very late stent thrombosis, related to the first-generation DES. The risk of stent thrombosis was significantly lower after implan-

tation of a new-generation DES as compared to a first-generation DES or BMS.²¹ Several randomized trials were conducted evaluating the short- and long-term DAPT to elucidate the appropriate DAPT duration after stent implantation, which included new-generation DESs.²²⁻³⁴ In the DAPT trial, prolonged DAPT beyond 1 year after placement of DESs, as compared to aspirin therapy alone, significantly reduced the risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events, but was associated with an increased risk of bleeding.²³ In contrast, several meta-analyses did not find any increased risk of stent thrombosis with a shorter duration of DAPT.³⁵⁻³⁷ In addition, a shorter duration of DAPT resulted in fewer bleeding complications.³⁵⁻³⁷ Furthermore, there was a trend toward an excess mortality risk of prolonged DAPT duration relative to short-DAPT duration.³⁸ A shorter duration of DAPT was considered to be appropriate for patients treated with newer-generation DESs, which are associated with lower stent thrombosis and myocardial infarction rates compared to that for patients treated with first-generation DESs. A focused update on DAPT from the AHA shortened the DAPT duration for patients with stable coronary artery disease (CAD) from 12 months to 6 months after new-generation DES implantation in

2016 (Figure 2).³⁹

HBR and Short Duration of DAPT

Prolonged DAPT with aspirin plus a P2Y₁₂ inhibitor prevents ischemic events after coronary stenting, but increases bleeding.²³ Therefore, patients at high risk for bleeding who undergo PCI often received a BMS followed by 1 month of DAPT. In 2015, the LEADERS FREE (Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk) trial revealed that a polymer-free biolimus-coated stent was superior to a BMS with respect to the primary safety endpoint of a composite of cardiac death, myocardial infarction, or stent thrombosis, and an efficacy endpoint of clinically driven target-lesion revascularization when used with a 1-month course of DAPT in patients with high bleeding risks (HBR).⁴⁰ In 2017, the PRECISE-DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) score was developed using a simple 5-item risk score, which provides a standardized tool for the prediction of out-of-hospital bleeding during DAPT.⁴¹ The 2017 ECS guidelines have

Table. Clinical Studies Evaluating P2Y₁₂ Receptor Inhibitor Monotherapy vs. DAPT After PCI

Trials	Number of patients	Target patients	DAPT duration	P2Y ₁₂ i	Primary endpoint	Trial design	Result
GLOBAL LEADERS ⁵⁵	15,968	PCI	1 vs. 12	Ticagrelor	Death/MI	Superiority	Not confirmed
STOPDAPT-2 ⁵⁰	3,045	PCI	1 vs. 12	Clopidogrel	NACE	Non-inferiority	Confirmed
SMART-CHOICE ⁴⁹	2,993	PCI	3 vs. 12	Clopidogrel	NACE	Non-inferiority	Confirmed
TWILIGHT ⁵¹	9,006	HTR/HBR	3 vs. 12	Ticagrelor	Bleeding	Superiority	Confirmed
TICO ⁵⁴	3,056	ACS	3 vs. 12	Ticagrelor	NACE	Superiority	Confirmed
STOPDAPT-2 ACS ⁵⁹	4,136	ACS	1 vs. 12	Clopidogrel	NACE	Non-inferiority	Not confirmed

ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; HBR, high bleeding risk; HTR, high thrombotic risk; MI, myocardial infarction; NACE, net adverse clinical event; PCI, percutaneous coronary intervention; P2Y₁₂i, P2Y₁₂ inhibitor.

recommended to shorten the DAPT duration up to 3 months to minimize the bleeding complications in stable CAD patients with HBR (Class IIa).⁴² The CREDO-Kyoto thrombotic and bleeding risk scores were also developed to stratify the risks in Japanese patients undergoing PCI in 2018.⁴³ The CREDO-Kyoto thrombotic and bleeding risk scores demonstrated modest accuracy in stratifying thrombotic and bleeding risks; however, a large proportion of patients at high thrombotic risk also had HBR.

The Academic Research Consortium for HBR (ARC-HBR) has been proposed to standardize the definition of HBR from the literature review and by the consensus of experts in 2019.⁴⁴ In the ARC-HBR initiative, HBR was arbitrarily defined as a Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding $\geq 4\%$ at 1 year or a risk of an intracranial hemorrhage $\geq 1\%$ at 1 year. The Japanese version of the HBR (J-HBR) criteria have been

proposed by consensus of the group working on the guidelines from the Japanese Circulation Society (JCS), which included factors such as low body weight, frailty, heart failure, and peripheral vascular disease on top of the factors included in the ARC-HBR criteria.⁴⁵ Patients meeting J-HBR criteria are recommended to receive 1–3 months of DAPT after PCI regardless of the risk for thrombotic events, as advised in the JCS 2020 focused update guideline (Figure 2).⁴⁵

In 2020, the ONYX ONE (A Randomized Controlled Trial With Resolute Onyx in One Month Dual Antiplatelet Therapy (DAPT) for High-Bleeding Risk Patients) trial revealed that use of polymer-based zotarolimus-eluting stents was non-inferior to use of polymer-free drug-coated stents with regard to safety and effectiveness composite outcomes among patients with HBR who received 1 month of DAPT after PCI.⁴⁶

P2Y₁₂ Inhibitor Monotherapy After a Very Short Duration of DAPT

Aspirin has been the gold standard of single antiplatelet therapy (SAPT) after PCI. However, aspirin acting via the cyclooxygenase inhibition is associated with a higher risk for gastrointestinal bleeding as compared with a P2Y₁₂ inhibitor.⁴⁷ Furthermore, in a meta-analysis, P2Y₁₂ inhibitor monotherapy was reported to be associated with a risk reduction for myocardial infarction as compared with aspirin monotherapy in the setting of secondary prevention.⁴⁸ Considering the balance between ischemic and bleeding risks after PCI, P2Y₁₂ inhibitor monotherapy is becoming the dominant strategy for SAPT after a short duration of DAPT in clinical trials (Table). In the SMART-CHOICE (Comparison Between P2Y₁₂ Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents) trial, P2Y₁₂ inhibitor monotherapy after 3 months of DAPT compared with prolonged DAPT resulted in significant reduction of bleeding events without an increase in major adverse cardiac and cerebrovascular events.⁴⁹ In the STOPDAPT-2 (ShorT and OPTimal Duration of Dual AntiPlatelet Therapy-2) trial, clopidogrel monotherapy after 1 month of DAPT was associated with a significantly lower risk for bleeding without increasing ischemic events as compared with DAPT.⁵⁰ In TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention), ticagrelor monotherapy following 3 months of DAPT was also reported to reduce bleeding events with an equivalent ischemic risk as compared to the long duration of DAPT in high-risk patients.⁵¹ A meta-analysis of DAPT vs. monotherapy with P2Y₁₂ inhibitors in patients treated with PCI showed that use of P2Y₁₂ monotherapy was associated with 30% lower odds of major bleeding, with similar risks for ischemic and mortality outcomes.⁵² Furthermore, the HOST-EXAM (Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention) trial showed that clopidogrel monotherapy as compared with aspirin monotherapy during the chronic maintenance period after PCI significantly reduced the risk of the ischemic and bleeding events.⁵³

P2Y₁₂ Inhibitor Monotherapy After a Very Short Duration of DAPT to Treat ACS

In 2020, the TICO (Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome) trial demonstrated that ticagrelor monotherapy after 3 months of DAPT compared with ticagrelor-based DAPT for 12 months significantly reduced a composite outcome of major bleeding and cardiovascular events at 1 year among patients with ACS.⁵⁴ In post-hoc analysis of GLOBAL LEADERS (A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation), ticagrelor monotherapy was associated with a lower risk of bleeding events without increasing ischemic events as compared with DAPT between 1 month and 12 months after PCI in patients with ACS.^{55,56} In post-hoc analysis of TWILIGHT, ticagrelor monotherapy reduced clinically meaningful bleeding events without increasing ischemic risk, as compared with ticagrelor plus aspirin among patients with or without ACS who completed an initial 3-month course of DAPT following PCI.⁵⁷ Pooled analysis

of the SMART-DATE (Safety of 6-month Duration of Dual Antiplatelet Therapy after Acute Coronary Syndromes) and SMART-CHOICE trials showed that P2Y₁₂ inhibitor monotherapy after 3 months of DAPT reduced the risk of bleeding compared with conventional DAPT and aspirin monotherapy after 6 months of DAPT without increasing major adverse cardiac and cerebrovascular events in patients with ACS.⁵⁸

Recently, the STOPDAPT-2 (ShorT and OPTimal Duration of Dual AntiPlatelet Therapy-2) ACS trial findings have been presented in the ESC 2021.⁵⁹ In ACS patients, clopidogrel monotherapy after 1 month of DAPT failed to attest non-inferiority to 12 months of DAPT with aspirin and clopidogrel for the net clinical benefit, with a trend toward an increase in cardiovascular events despite substantial reduction in major bleeding events. The results of this study would be inconclusive, given the absence of a significant difference in the primary endpoint between the 2 groups. Clopidogrel monotherapy might not be the optimal antithrombotic regimen after very short duration of DAPT in patients with ACS. Therefore, further studies are warranted to define the optimal antithrombotic regimen after PCI using new generation DESs in ACS patients.

Current Recommendation of DAPT Duration in the JCS Guideline

The recommendation of DAPT duration is getting shorter due to the development of new-generation DESs, use of a P2Y₁₂ inhibitor as monotherapy, and the increasing prevalence of HBR patients.⁴⁵ In patients with stable CAD, DAPT with prasugrel 3.75 mg daily or clopidogrel 75 mg daily in addition to aspirin 81–162 mg daily is recommended for at least 1–3 months following coronary stent deployment in the JCS guideline 2020 focused update (class I) (Figure 2). Very short DAPT of 1–3 months should be considered for patients with HBR (class IIa). Monotherapy with a P2Y₁₂ receptor inhibitor should be considered in patients with high thrombotic and HBR following 1–3 months of DAPT (class IIa).

In patients with ACS, prasugrel 3.75 mg daily or clopidogrel 75 mg daily in addition to aspirin 81–162 mg daily is recommended for 3–12 months following coronary stent implantation (class I) (Figure 2). In patients with HBR, shortening of DAPT duration to 1–3 months is recommended (class I). Monotherapy with a P2Y₁₂ receptor inhibitor should be considered in patients with high thrombotic and HBR following short-term DAPT (class IIa).

Future Perspectives

An aspirin-free strategy is now emerging as the one of the novel strategies of antiplatelet therapy after PCI. In the ASET (Acetyl Salicylic Elimination Trial) pilot study, aspirin-free prasugrel monotherapy following successful everolimus-eluting stent implantation demonstrated feasibility and safety without any stent thrombosis in selected low-risk patients with stable CAD.⁶⁰ The NEO-MINDSET (Percutaneous Coronary Intervention Followed by Monotherapy Instead of Dual Antiplatelet Therapy in the SETting of Acute Coronary Syndromes) trial is now ongoing and it randomizes 3,400 patients with ACS within 96 h of hospital stay either to receive P2Y₁₂ inhibitor monotherapy or DAPT for 6 or 12 months based on the presence or absence of HBR (ClinicalTrials.gov:NCT04360720). The

STOPDAPT-3 (Short and Optimal Duration of Dual Antiplatelet Therapy-3) trial that randomizes 3,110 patients with ACS and/or HBR before PCI either to the experimental arm of reduced-dose prasugrel monotherapy or to the control arm of DAPT is also ongoing in Japan (ClinicalTrials.gov: NCT04609111) (Figure 3). These studies might pave the way toward an aspirin-free strategy after PCI using new-generation, DESs and new-generation more potent P2Y₁₂ inhibitor monotherapy.

Disclosures

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