

[ REVIEW ARTICLE ]

## Update on Antithrombotic Therapy after Percutaneous Coronary Intervention

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### Abstract:

Percutaneous coronary intervention (PCI) has become a standard-of-care procedure in the setting of angina or acute coronary syndrome. Antithrombotic therapy is the cornerstone of pharmacological treatment aimed at preventing ischemic events following PCI. Dual antiplatelet therapy as the combination of aspirin and P2Y<sub>12</sub> inhibitor has been proven to decrease stent-related thrombotic risks. However, the optimal duration of dual antiplatelet therapy, an appropriate P2Y<sub>12</sub> inhibitor, and the choice of aspirin versus P2Y<sub>12</sub> inhibitor as single antiplatelet therapy remain controversial. Furthermore, the combined use of oral anticoagulation in addition to antiplatelet therapy is a complex issue in clinical practice, such as in patients with atrial fibrillation. The key challenge concerning the optimal antithrombotic regimen is ensuring a balance between protection against thrombotic events and against excessive increases in bleeding risk. In this review article, we summarize the current evidence concerning antithrombotic therapy in patients with coronary artery disease undergoing PCI.

**Key words:** antithrombotic therapy, dual antiplatelet therapy, percutaneous coronary intervention

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### Introduction

Percutaneous coronary intervention (PCI) with coronary stent has become a standard-of-care procedure in the setting of angina or acute coronary syndrome (ACS) worldwide. There are several sources of thrombotic risk after coronary stenting, such as prothrombotic conditions related to the underlying patient characteristics, activation of local thrombotic risk by stent and PCI results, and chronic atherosclerotic disease manifestations remote from the procedure.

The introduction of P2Y<sub>12</sub> receptor inhibitors in addition to aspirin, termed dual antiplatelet therapy (DAPT), has led to a substantial reduction in post-PCI thrombotic events (1, 2). At present, DAPT is the guideline-recommended cornerstone of antithrombotic therapy for patients undergoing PCI (3-6). However, adjunctive antithrombotic therapy used to mitigate thrombotic risks should be balanced against bleeding events, as both are associated with fatal events. In this article, we aim to provide an in-depth review of antithrombotic therapy after PCI in patients with coronary artery disease (CAD), mainly discussing the dura-

tion of DAPT, choice of P2Y<sub>12</sub> inhibitors, utility of aspirin versus P2Y<sub>12</sub> inhibitor as single antiplatelet therapy (SAPT), and the optimal regimen for patients indicated for oral anticoagulation (OAC), from a Japanese perspective.

### Duration of DAPT

#### Short- Versus Long-Term DAPT

Since the ISAR trial in 1996 and STARS in 1998 demonstrated the superiority of DAPT over aspirin alone or OAC (warfarin) plus aspirin, DAPT with aspirin plus a P2Y<sub>12</sub> inhibitor has been the cornerstone of antithrombotic management among patients undergoing PCI with stenting. In these randomized control trials (RCTs), DAPT with aspirin plus ticlopidine dramatically reduced thrombotic events [death, myocardial infarction (MI) and revascularization] by 75% to 85% compared to aspirin alone or warfarin plus aspirin therapy within 1 month after PCI (1, 2). Because of some side effects of ticlopidine (e.g., agranulocytosis), the second-generation thienopyridine clopidogrel became the first broadly administered P2Y<sub>12</sub> inhibitor as a part of DAPT.

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Thereafter, based on some RCT results indicating that 12-month DAPT was beneficial in reducing major cardiovascular events (7, 8), and concerns regarding stent thrombosis following first-generation drug-eluting stent (DES) implantation (9), guidelines have recommended 6- to 12-month DAPT. However, the supporting evidence for this duration has been limited.

To provide further data for minimizing the risk of ischemic and bleeding complications, extensive research has been focused on investigating the optimal duration of DAPT [i.e., short-term ( $\leq 1$  year) or long-term ( $> 1$  year)]. The first data from RCTs were published in 2010, in which DAPT for longer than 12 months was not more effective than aspirin monotherapy in reducing MI or death in patients treated with DES (10), while the largest RCT comparing short- versus long-term DAPT, called the DAPT study, showed a different result (11). In the DAPT study, 9,961 participants were randomized to receive either P2Y<sub>12</sub> inhibitor or placebo after 12 months with DAPT following the index PCI. Patients treated with P2Y<sub>12</sub> inhibitor had significantly lower rates of MI (2.1% vs. 4.1%,  $p < 0.001$ ) and stent thrombosis (0.4% vs. 1.4%,  $p < 0.001$ ) than those treated with placebo during the 18-month follow-up, whereas the incidences of severe bleeding (2.5% vs. 1.6%,  $p = 0.001$ ) and all-cause mortality (2.0% vs. 1.5%,  $p = 0.05$ ) were higher in the continued DAPT group than in the other group (11). The DAPT study is the only large-scale placebo-control RCT that has been conducted thus far, but the results should be interpreted cautiously, as patients were randomized after 12-month DAPT. Based on the findings of subsequent RCTs, numerous meta-analyses have been reported, consistently indicating that 1) long-term DAPT reduces the rates of MI and stent thrombosis but is associated with an increased risk of bleeding compared to short-term DAPT, and 2) mortality may be higher in patients with long-term DAPT than in those with short-term DAPT, mainly driven by an increased rate of non-cardiovascular death (not counterbalanced by a reduction in cardiac mortality) (12-14).

Bleeding is known to be significantly associated with non-cardiovascular mortality, although a meta-analysis indicated that the incidence of stent thrombosis may not be necessarily related to cardiovascular and all-cause mortality in a study-level analysis among RCTs comparing the DAPT duration in the new-generation DES era (15). These findings suggest that the impact of bleeding on mortality is greater than that of stent thrombosis. Therefore, in patients with a high bleeding risk (HBR) and/or low ischemic risk, short-term DAPT should be considered.

Recently, the STOPDAPT-2 trial randomized 3,045 patients in Japan to receive 1 month of DAPT followed by clopidogrel monotherapy versus 12 months of DAPT and showed that the 1-month DAPT regimen resulted in a lower rate of a composite of cardiovascular and bleeding events (cardiovascular death, MI, definite stent thrombosis, ischemic and hemorrhagic stroke, or Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding) at 1 year

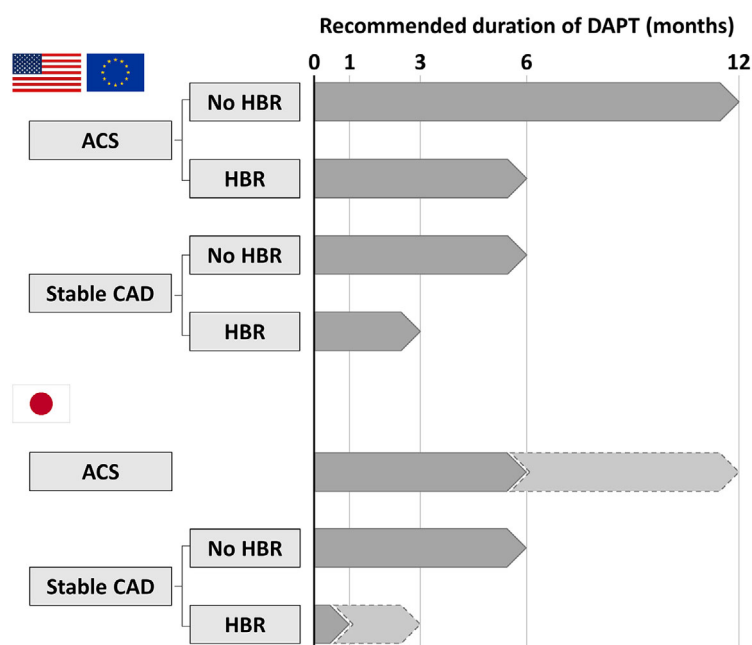
than the longer regimen (2.4% vs. 3.7%,  $p = 0.04$ ) (16). Therefore, in the contemporary era with appropriate secondary prevention (e.g. low-density lipoprotein cholesterol-lowering therapy) and PCI optimization with new-generation DESs and intravascular imaging, the DAPT duration can be shortened to as little as 1 month (5). However, the eligible patients who were not included had higher-risk features than the patients included in the STOPDAPT-2 trial (16). The external generalizability of the trial, especially in patients at high ischemic risk, therefore remains unclear, and there may be some subsets of patients who would benefit from long-term DAPT. The current guideline recommendations are shown in Fig. 1. In fact, patients who present with ACS are candidates for long-term DAPT, according to the guidelines (3, 4, 6, 17).

The recently published SMART-DATE trial randomly assigned 2,712 ACS patients either to 6- or 12-month DAPT and showed that short-term DAPT was non-inferior with respect to the primary endpoint (a composite of all-cause death, MI, or stroke) at 18 months after the index procedure (4.7% vs. 4.2%,  $p$  for non-inferiority 0.03) (18). Of note, although the incidence of bleedings was not significantly different [hazard ratio (HR) 0.57, 95% confidence interval (CI) 0.29-1.12,  $p = 0.10$ ], the rate of MI was significantly higher in the 6-month DAPT group than in the 12-month group beyond 6 months (HR 5.06, 95% CI 1.46-17.47,  $p = 0.01$ ), suggesting that long-term DAPT may be beneficial for ACS patients. However, another recent RCT comparing 6- versus 12-months DAPT in patients with ST-elevation MI (DAPT-STEMI trial) showed no marked differences between the two regimens (19). A meta-analysis that studied 10 RCTs, including the SMART-DATE and DAPT-STEMI trials, showed that short-term DAPT ( $\leq 6$  months) tended to be associated with increased risks of MI [odds ratio (OR) 1.21, 95% CI 0.94-1.57,  $p = 0.14$ ], stent thrombosis (OR 1.54, 95% CI 1.0-2.38,  $p = 0.052$ ), and reduced bleeding (OR 0.74, 95% CI 0.49-1.11,  $p = 0.14$ ) compared to long-term DAPT ( $\geq 12$  months), despite a lack of significance (20). Therefore, although ACS presentation is an important determinant for guiding antithrombotic therapy after PCI, whether or not ACS patients should uniformly undergo long-term DAPT remains unclear.

The guidelines also indicate HBR as a factor to consider when determining the duration of DAPT (Fig. 1). Therefore, short-term DAPT should be considered for most patients after PCI, but the optimal duration of DAPT depends on the ischemic and bleeding risk profiles, which should be comprehensively assessed.

### Risk Assessments

Risk characterization for ischemic or bleeding complications is recommended in guidelines, although it is recognized that many patients are at a high risk for both types of events. The identification of candidates for long-term DAPT is often based on clinical judgement in daily practice (e.g., age, extension of CAD, or clinical presentation). Some risk



**Figure 1.** Basic recommendations concerning the DAPT duration in patients not indicated for oral anticoagulation undergoing percutaneous coronary intervention. The American and European guidelines in 2016 and 2017 recommend DAPT for 3 to 12 months (Class I or IIa) depending on the patient characteristics. The Japanese guidelines in 2018 recommend 6- to 12-month DAPT for ACS and 1- to 3-month DAPT for stable CAD patients with HBR (3-6). ACS: acute coronary syndrome, CAD: coronary artery disease, DAPT: dual antiplatelet therapy, HBR: high bleeding risk

**Table 1.** Risk Scores for Dual Antiplatelet Therapy Decision-Making.

	PRECISE-DAPT score	DAPT score	PARIS score
First published	2017	2016	2016
Applicability	In-hospital	DAPT beyond 1 year (no bleedings during the 1st year)	In-hospital
DAPT duration strategies assessed	Short DAPT (3-6 months) vs. Standard/long DAPT (12-24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)	N/A
Number of items	5	8	6 for ischemic plus 6 for bleeding events
Components	Age; CCr; hemoglobin; WBC count; previous spontaneous bleeding	Age; Smoking within 1 year; DM; MI at presentation; Prior PCI or MI; Paclitaxel-eluting stent; Stent diameter <3 mm; CHF or LVEF <30%; Vein graft stent	For ischemic events: DM; ACS; Current smoking; CCr; Prior PCI; Prior CABG For bleedings: Age; BMI; Current smoking; Anemia; CCr; TT on discharge
Cut-off value (range)	25 for high risk (0 to 100)	2 (-2 to 10)	5 for high thrombotic risk (0 to 10) 8 for high bleeding risk (0 to 14)
Outcomes	Bleeding risk	Net ischemic/bleeding risk	Ischemic and bleeding risks

ACS: acute coronary syndrome, BMI: body mass index, CABG: coronary artery bypass grafting, CCr: creatinine clearance, CHF: congestive heart failure; DAPT: dual antiplatelet therapy, DM: diabetes mellitus, LVEF: left ventricular ejection fraction, MI: myocardial infarction, N/A: not applicable, PCI: percutaneous coronary intervention, TT: triple therapy, WBC: white blood cell

scores and decision-making tools may aid in tailoring the DAPT duration after PCI in order to maximize ischemic protection and minimize bleeding risk for each individual case. Table 1 lists the representative risk scores, with the PRECISE-DAPT and DAPT score as guideline-recommended risk assessment tools for determining the DAPT duration after PCI (3-5). The PRECISE-DAPT score consists of only five items that can be measured at the bedside, while the score only intrinsically predicts bleeding

events (21). A Korean registry that included 904 patients with DAPT who underwent stent implantation confirmed the predictivity of the PRECISE-DAPT score for 1-year bleeding (22). Although the DAPT score was also developed to differentiate between ischemic and bleeding risks, it is useful when considering prolonged DAPT after follow-up if no bleeding events were encountered (23). The DAPT score successfully stratified ischemic and bleeding risks in a pooled cohort of three large studies in Japan, but the

ischemic event rate was remarkably low, even in patients with high DAPT scores (24). In contrast, nationwide data in Sweden indicated that the DAPT score did not adequately discriminate ischemic and bleeding risk (25). The PARIS score is another risk-assessing tool for predicting both ischemic and bleeding events following PCI with similar discrimination properties to the others, but it has not been investigated when using an alternative DAPT regimen (26). The CREDO Kyoto thrombotic and bleeding risk scores were newly developed to predict thrombotic and bleeding events in a Japanese population (27). However, whether or not these risk scores are useful for determining the duration of DAPT is uncertain. Several other risk stratification models have been proposed in the TRA 2°P-TIMI 50, ADAPT-DES, HORIZON AMI, and CRUSADE trials (28-31), and some risk scores are reportedly associated with surrogates of coronary atherosclerosis or other adverse events (32, 33). Of note, however: none of the risk-predicting models has been tested in a prospective RCT to guide antithrombotic regimen.

In addition to risk assessment scores, PCI complexity can also be a determinant for DAPT duration. The real-world data in Japan showed that coronary calcification had a significant impact on the clinical outcomes in the new-generation DES era (34). A post hoc patient-level pooled analysis of 6 RCTs showed that complex PCI, defined by angiographic characteristics (e.g., bifurcation with 2 stents implanted and chronic total occlusion), was significantly associated with increased risks of major adverse cardiac events (5.4% vs. 2.9%,  $p < 0.001$ ) during a median follow-up of 392 days (35). In that analysis, compared with short-term DAPT (3 or 6 months), long-term DAPT ( $\geq 12$  months) yielded significant reductions in these events in the complex PCI group (adjusted HR: 0.56, 95% CI 0.35-0.89) versus the noncomplex PCI group (adjusted HR: 1.01, 95% CI 0.75-1.35,  $p$  for interaction 0.01). In the DAPT study, although a complex target-lesion anatomy was related to worse clinical outcomes, the benefits of extending DAPT were similar between subjects with and without complex lesions (36). These results may be dependent on the different criteria for PCI complexity among the studies (37).

The guideline-endorsed high-risk features of stent-driven recurrent ischemic events were as follows: prior stent thrombosis on adequate antiplatelet therapy, stenting of the last remaining patent coronary artery, diffuse multivessel disease (especially in diabetic patients), chronic kidney disease, at least 3 stents implanted, at least 3 lesions treated, bifurcation with 2 stents implanted, total stent length  $> 60$  mm, and treatment of a chronic total occlusion (4). Among these features, bifurcation treatment with two stents is most likely to influence the DAPT duration (38, 39). However, the bleeding risk should also be assessed beyond risk models. Recently, the Academic Research Consortium defined the criteria for HBR, which include the age, renal or liver disease, medications, and others factors (40). Indeed, it was reported that long-term DAPT for patients with end-stage renal dis-

ease was associated with an increased risk of bleeding (41).

In summary, the DAPT duration can be shortened in most patients following PCI in the current era. However, long-term DAPT may be beneficial in some specific populations, such as patients with ACS and/or complex PCI. Clinicians should comprehensively assess patients' ischemic and bleeding risks, taking into account risk scores and other factors.

### Minimizing Ischemic and Bleeding Complications

Antithrombotic therapy is one of the most important factors for improving the clinical outcomes following PCI. However, every effort should be made to minimize ischemic and bleeding events beyond choosing the optimal antithrombotic regimen. Individualization of therapy includes the choice of stent, PCI optimization, and use of proton pump inhibitors (PPIs).

While the introduction of bare metal stents (BMS) improved the procedural success and acute outcomes compared to balloon angioplasty (42), the rate of in-stent restenosis remained high. New-generation DESs have been shown to have superior safety and efficacy concerning reducing the rates of MI, stent thrombosis, and revascularization compared to BMSs and so are recommended for all patient and lesion subsets in PCI (17, 43), except for lesions in a saphenous vein graft (44). Favorable findings concerning new-generation DESs have been shown in real-world settings, including high-risk patient populations with long-term follow-up (45-47). A meta-analysis of 10 RCTs with 32,135 patients showed that short-term DAPT was associated with a higher rate of stent thrombosis than long-term DAPT (OR 1.71, 95% CI 1.26-2.32,  $p = 0.001$ ); however, the effect of short-term DAPT on stent thrombosis was attenuated with the use of new-generation DESs (OR 1.54, 95% CI 0.96-2.47) compared to that with first-generation DESs (OR 3.94, 95% CI 2.20-7.05,  $p$  for interaction 0.008) (13). The recently published optical coherence tomography (OCT) study showed good vascular responses to a new-generation DES (cobalt-chromium everolimus-eluting stent) even at two weeks after acute MI (48), at least partially supporting the feasibility of short-term DAPT in patients with new-generation DESs. Although very-short-term DAPT (e.g., 1 month) is reported to result in equivalent outcomes to a longer DAPT duration in the BMS setting (49), new-generation DESs should be used in most cases to reduce ischemic risks, enabling the shortening of the DAPT duration.

PCI optimization has also contributed to improved clinical outcomes. A recent RCT, the ULTIMATE trial, reported that intravascular ultrasound (IVUS)-guided PCI significantly reduced the rate of target vessel failure, a composite of cardiac death, target vessel MI, and clinically driven target vessel revascularization, compared with angiography-guided PCI at 1-year follow-up in an all-comers population (2.9% vs. 5.4%,  $p = 0.02$ ) (50). In addition, a meta-analysis including 10 RCTs with 5,060 patients showed that IVUS guidance was associated with a reduced incidence of cardiovas-

**Table 2. A Comparison of Oral P2Y<sub>12</sub> Inhibitor.**

	Clopidogrel	Prasugrel	Ticagrelor
Drug class	Thienopyridine	Thienopyridine	Cyclopentyltriazolopyrimidine
Prodrug	Yes	Yes	No (active drug)
Reversibility	No	No	Yes
Metabolism	Hepatic (CYP2C19)	Hepatic (CYP3A4 and CYP2B6)	Hepatic (CYP3A4)
Half-life	-6 hours	-7 hours	-7 hours
Loading dose	300-600 mg (W)/300 mg (J)	60 mg (W)/20 mg (J)	180 mg
Maintenance dose (/day)	75 mg	10 mg (W)/3.75 mg (J)	180 mg following ACS 120 mg for OMI (J)
Onset of effect	2-4 hours	0.5 hours	0.5 hours
Duration of effect	3-10 days	5-10 days	3-4 days
Administration (/day)	once	once	Twice

W represents Western countries (America and Europe) and J represents Japan. ACS: acute coronary syndrome, OMI: old myocardial infarction

cular death (OR 0.44, 95% CI 0.26-0.75) and MI (OR 0.55, 95% CI 0.32-0.94) compared with angiography guidance (51). OCT is an alternative intracoronary imaging modality to IVUS (52). Although a meta-analysis indicated that OCT guidance was not related to reduced risks of cardiovascular events compared to angiography guidance in PCI (53), a head-to-head comparison of IVUS-guided with OCT-guided PCI demonstrated the non-inferiority of OCT guidance in a randomized setting (54). Thus, intracoronary image guidance should be considered in most PCI cases in order to reduce ischemic events (55).

The application of coronary physiology, such as the fractional flow reserve and instantaneous wave-free ratio, can also be a driver of improved outcomes following PCI, reducing the number of treated lesions and stents (56, 57). In fact, state-of-the-art PCI with a new-generation DES and intracoronary imaging as well as the consideration of the coronary physiology in the SYNTAX II trial resulted in a lower ischemic event rate (a composite of all-cause death, cerebrovascular event, any MI, and any revascularization) at 1 year compared to PCI a decade ago (10.6% vs. 17.4%,  $p=0.006$ ) (58). Therefore, PCI results should be optimized with these technologies to reduce patient ischemic risk, allowing for short-term DAPT to be applied.

Measures to diminish bleeding complications after PCI include the use of a PPI. Utilizing a PPI prevents upper gastrointestinal (GI) bleeding (59), which is the most common type of bleeding (>60%) after PCI (60). A Danish nationwide dataset showed that, among patients receiving DAPT after MI, the use of a PPI was associated with a lower risk of upper GI bleeding than with no PPI use (risk ratio 0.62, 95% CI 0.48-0.77) (61). Although whether or not the routine use of a PPI can improve the clinical outcomes in patients with SAPT or single OAC remains unknown, routine PPI use in patients on DAPT after PCI is recommended as a standard strategy in the current guidelines (4).

### Choice of P2Y<sub>12</sub> Inhibitors

Clopidogrel has been the basic P2Y<sub>12</sub> inhibitor of choice for DAPT for two decades, and prasugrel and ticagrelor are

presently available as novel and potent P2Y<sub>12</sub> inhibitors. Table 2 compares these three P2Y<sub>12</sub> inhibitors (62).

Previous studies using platelet function testing showed the rapid onset of the effect and potency of prasugrel and ticagrelor compared to clopidogrel (63-65). In clinical trials, prasugrel therapy was associated with significantly reduced rates of ischemic events (9.9% vs. 12.1%,  $p<0.001$ ) but with an increased risk of major bleeding (2.4% vs. 1.8%,  $p=0.03$ ) at 15 months compared to clopidogrel therapy in patients with ACS in the TRITON-TIMI 38 study (66). Similarly, in the PLATO trial, treatment with ticagrelor significantly reduced the rate of ischemic events compared to clopidogrel (9.8% vs. 11.7%,  $p<0.001$ ) but with an increase in the rate of bleeding unrelated to coronary artery bypass grafting (4.5% vs. 3.8%,  $p=0.03$ ) at 12 months (67). These results reflect the notion that potent antithrombotic therapy reduces ischemic events but increases the bleeding rate.

Given their characteristics, prasugrel and ticagrelor in addition to aspirin are recommended in patients with ACS in Western countries (4). However, an increasing body of data suggests that East Asian patients have differing risk profiles for both ischemic and bleeding events compared to white patients (68). Despite having a higher degree of platelet reactivity during treatment with aspirin and clopidogrel, East Asian patients have a rate of ischemic events after PCI similar to or even lower than white patients, although their bleeding risk is higher (68). In Japan, a lower dose of prasugrel is approved and used (Table 2) (69), but similar findings are observed even at the low dose (63, 65, 70). In contrast, ticagrelor is approved at the same dosage in Japan and Western countries, and the PHILO randomized study showed that ticagrelor-based regimens tended to be associated with increased risks of ischemic (9.0% vs. 6.3%, HR 1.47, 95% CI 0.88-2.44) and bleeding events (10.3% vs. 6.8%, HR 1.54, 95% CI 0.94-2.53) at 12 months compared to clopidogrel-based regimens among 801 East Asian patients with ACS. Japanese guidelines recommend both clopidogrel and prasugrel in DAPT for ACS, but ticagrelor is indicated only when a patient is intolerant to clopidogrel and prasugrel (6). For patients with stable CAD undergoing PCI, DAPT with aspirin plus clopidogrel is recommended as an

initial antithrombotic strategy in European and American guidelines (3, 43), while Japanese guidelines do not specify the P2Y<sub>12</sub> inhibitor (5).

Switching from prasugrel or ticagrelor back to clopidogrel is another clinical challenge and is observed in more than 10% of cases with ACS, due to bleeding or other side-effects (71). Switching back to clopidogrel did not seem to lead to more ischemic events than continuation of the potent P2Y<sub>12</sub> inhibitor in the TRANSLATE-ACS trial (71). The recent TROPICAL-ACS randomized trial demonstrated that the outcomes in the patients receiving platelet function testing-guided de-escalation of antiplatelet therapy from prasugrel to clopidogrel was non-inferior to those in the control group among patients with ACS following successful PCI, with a non-significant reduction in the bleeding event rate at 12 months (8.7% vs. 10.5%,  $p=0.14$ ) (72). The potential benefit of switching DAPT drugs may be a reduction in medical cost and improvement of adherence due to fewer side-effects (e.g., bleeding and dyspnea). An improved adherence to antiplatelet therapy is important because the PARIS registry clearly showed that DAPT disruption was associated with worse clinical outcomes (73).

### Aspirin Versus P2Y<sub>12</sub> Inhibitors as SAPT

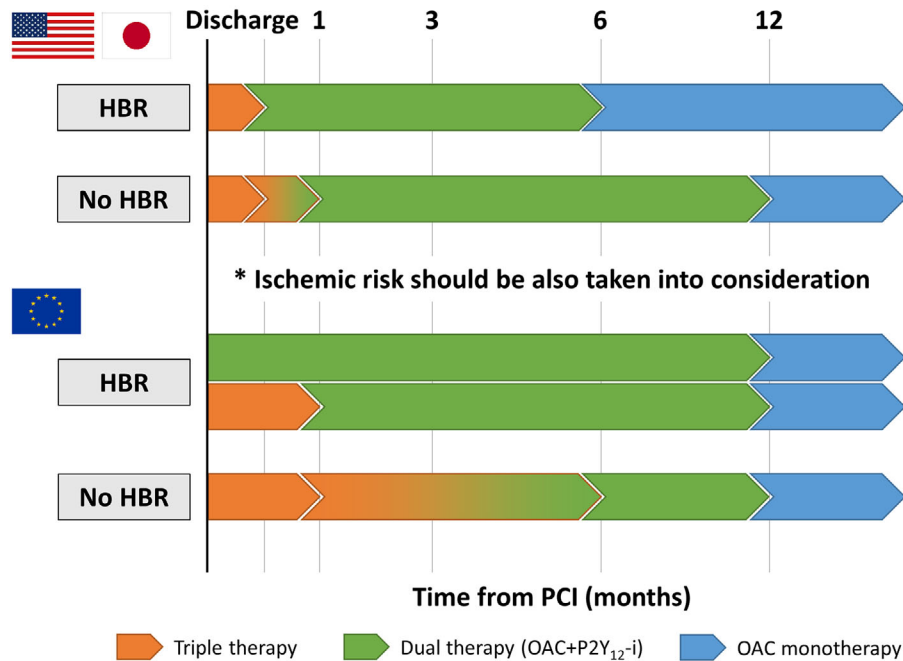
After DAPT has concluded, lifelong SAPT is indicated for patients with CAD who have undergone PCI. Aspirin is affordable and historically used worldwide and so has been a basic choice of SAPT. However, several RCTs have addressed the potential superiority of P2Y<sub>12</sub> inhibitors over aspirin. The CAPRIE study, in which 19,185 patients with prior ischemic stroke, MI, or peripheral artery disease were randomized to either clopidogrel or aspirin treatment, was the first large-scale RCT comparing aspirin with a P2Y<sub>12</sub> inhibitor (74). At 3 years, patients treated with clopidogrel had a 5.32% annual rate of ischemic stroke, MI, or vascular death compared to 5.83% in those treated with aspirin ( $p=0.04$ ), while the incidence of bleeding was not markedly different (rate of GI bleeding was less in the clopidogrel group). These findings suggest the superiority of clopidogrel over aspirin; however, they should be interpreted with caution for several reasons. First, the study patients were enrolled from 1992 to 1995, when PCI was not widely performed and secondary prevention was not established; second, only one-third of the patients had prior MI, and no significant difference of the study endpoint was observed between clopidogrel and aspirin treatment in this specific population (5.03% vs. 4.84% per year,  $p=0.66$ ); third, the absolute risk reduction was tiny (0.5% per year); and fourth, the dosage of aspirin used in this study was 325 mg/day (74). A Korean observational study suggested that clopidogrel monotherapy after 12-month DAPT following DES implantation was associated with a reduction in risk for a composite of cardiac death, MI, or stroke compared to aspirin monotherapy (HR 0.54, 95% CI 0.32-0.92,  $p=0.02$ ), while the rate of major bleeding was similar (HR 1.03, 95%

CI 0.46-2.32  $p=0.95$ ) (75). The GLOBAL LEADERS is an RCT for evaluating the efficacy of ticagrelor, with 15,968 patients randomized to receive aspirin 75-100 mg/day plus 90 mg ticagrelor twice daily for 1 month, followed by 23 months of ticagrelor monotherapy, or standard DAPT with aspirin 75-100 mg/day plus clopidogrel 75 mg/day (for patients with stable CAD) or 90 mg ticagrelor twice daily (for patients with ACS) for 12 months, followed by aspirin monotherapy for 12 months (76). Beyond 12 months, ticagrelor monotherapy was compared to aspirin monotherapy in this RCT, although there were no marked differences noted between the experimental group and control group in terms of the primary endpoint of all-cause death and new Q-wave MI through 2 years (3.81% vs. 4.37%,  $p=0.07$ ) and from 1 to 2 years (1.89% vs. 1.95%,  $p=0.79$ ). In the recent STOPDAPT-2 and SMART-CHOICE trials (16, 77), the non-inferiority of short-term DAPT (1 or 3 months) followed by clopidogrel monotherapy was evaluated compared with 12-month DAPT. Although these RCTs did not compare P2Y<sub>12</sub> inhibitor monotherapy with aspirin alone, the feasibility of clopidogrel monotherapy after DAPT in patients with DES implantation was shown. At present, whether or not P2Y<sub>12</sub> inhibitors are superior to aspirin as SAPT remains unclear. Ongoing studies (STOPDAPT-2 and TWILIGHT) will address this issue (16, 78). Aspirin is still a basic choice of SAPT globally because of its affordability and is widely used even in low-income countries (79).

### Patients Indicated for OACs

Long-term treatment with OACs is indicated for patients with mechanical heart valves and in most with atrial fibrillation (AF), of whom 20% to 30% have concomitant CAD that needs PCI (80). In such cases, triple therapy (combination of an OAC and DAPT) has been used to prevent ischemic stroke and stent thrombosis. However, such treatment is known to be associated with an increased risk of serious bleeding (81).

Based on recent RCT results, the consensus recommendations have been updated to suggested a shortened duration of triple therapy (Fig. 2) (5, 82-85). The WOEST trial is the first RCT to compare triple therapy to dual therapy with a vitamin-K antagonist (VKA) plus clopidogrel. This study clearly showed that triple therapy is associated with an increased risk of any bleeding compared to dual therapy at 1 year (44.4% vs. 19.4%,  $p<0.001$ ) (80). Although this study lacked sufficient power to detect differences in ischemic events, the rate of a composite of death, MI, stroke, systemic embolism, target vessel revascularization, and stent thrombosis was also higher in patients receiving triple therapy than in those with dual therapy (17.6% vs. 11.1%,  $p=0.025$ ). Subsequently, the PIONEER AF-PCI and RE-DUAL PCI trials showed the superior safety of dual therapy with a direct oral anticoagulant (DOAC) plus P2Y<sub>12</sub> inhibitor over triple therapy including a VKA (e.g., warfarin) in patients with AF undergoing PCI (86, 87). Most recently, the



**Figure 2.** Basic recommendations concerning antithrombotic therapy for patients indicated for oral anticoagulation after PCI. In the North American consensus document (82), the default approach is triple therapy, a combination of aspirin, clopidogrel, and an OAC for patients indicated for life-long anticoagulation treatment after PCI only during index hospitalization, followed by dual therapy with clopidogrel plus an OAC after hospital discharge. If a patient has HBR, dual therapy for up to six months is recommended. For patients with high ischemic and low bleeding risks, triple therapy for up to one month is acceptable. The Japanese guidelines' recommendation is similar to the North American recommendation (5). The European consensus document recommends one-month triple therapy or dual therapy with an OAC plus clopidogrel as the initial strategy for HBR patients, while triple therapy for up to six months may be considered in patients with a high ischemic risk (83). A DOAC is preferred to a VKA, and clopidogrel is the basic choice of P2Y<sub>12</sub> inhibitor for triple or dual therapy. However, the North American perspective and European consensus document indicate ticagrelor as a potential alternative in patients with high ischemic and low bleeding risks. The Japanese guidelines allow prasugrel to be selected as the P2Y<sub>12</sub> inhibitor in addition to clopidogrel. HBR: high bleeding risk, OAC: oral anticoagulant, P2Y<sub>12</sub>-i: P2Y<sub>12</sub> inhibitor, PCI: percutaneous coronary intervention

AUGUSTUS trial, a large RCT with a 2×2 factorial design comparing apixaban with a VKA in an open-label manner and aspirin with placebo, showed that apixaban was associated with a lower risk of bleeding events than a VKA (10.5% vs. 14.5%,  $p < 0.001$ ), and additional aspirin led to a higher risk of bleeding than placebo in the double-blind study (16.1% vs. 9.0%,  $p < 0.001$ ) at 6 months (88). It should be noted, however, that the median time from the index event to randomization was 6 days (up to 14 days) in the AUGUSTUS trial. Therefore, whether or not aspirin can be safely omitted during the very early period from PCI or ACS remains uncertain.

Based on these RCT results, consensus documents recommend that the duration of triple therapy be as short as possible (during index hospitalization or up to one month), and dual therapy with an OAC and P2Y<sub>12</sub> inhibitor is an alternative initial antithrombotic regimen, depending on the ischemic and bleeding risks in patients indicated for life-

long OAC treatment undergoing PCI (Fig. 2). Clopidogrel is preferred to aspirin or other P2Y<sub>12</sub> inhibitors in dual therapy, as most studies have used clopidogrel for testing. Real-world data suggest the possible association of aspirin use with GI bleeding in patients with AF undergoing PCI (89). In Japanese guidelines, prasugrel is also allowed in dual therapy with an OAC in addition to clopidogrel because of its low dosage (5). DOACs are preferred as OACs instead of a VKA in this specific setting. Although data are scarce, the present guideline-recommended antithrombotic therapy beyond one year after coronary stenting is OAC monotherapy. The recent OAC-ALONE study assessed OAC monotherapy versus OAC plus SAPT beyond one year after PCI, but the findings were inconclusive due to a lack of statistical power (90). The upcoming AFIRE trial will address this issue (91).

## Conclusions

In patients with CAD undergoing PCI, DAPT is the standardized initial strategy for antithrombotic therapy. Short-term DAPT for 1 to 3 months is feasible in most cases in the contemporary PCI era, but patients at a high ischemic risk, such as those with ACS presentation and complex PCI, may benefit from long-term DAPT. Ischemic and bleeding risks should be comprehensively assessed using risk stratification models. Every effort should be also made to minimize ischemic risk through PCI optimization using new-generation DESs, intracoronary imaging, and evaluations of the coronary physiology, and the bleeding risk should be reduced using a PPI during the DAPT period. Among the three currently available P2Y<sub>12</sub> inhibitors, clopidogrel is the basic choice for treatment of stable CAD, while prasugrel and ticagrelor are more potent. Whether or not a P2Y<sub>12</sub> inhibitor is superior to aspirin in SAPT remains unclear. In patients indicated for life-long OAC administration, triple antithrombotic therapy should be kept as short as possible (during index hospitalization or for up to 1 month). DOACs are preferred to VKAs for OAC in this specific population. Ongoing clinical trials will help clarify the optimal antithrombotic strategy for patients with CAD undergoing PCI.

### Author's disclosure of potential Conflicts of Interest (COI).

Yoshio Kobayashi: Honoraria, Amgen Astellas BioPharma, Sanofi, Daiichi Sankyo, Bristol-Myers Squibb and Boehringer Ingelheim.

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