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REVIEW

Potent P2Y12 Inhibitor Monotherapy for Acute Coronary Syndrome

Sung-Jin Hong, MD, PhD; Byeong-Keuk Kim, MD, PhD

Dual antiplatelet therapy (DAPT), consisting of aspirin and a P2Y12 inhibitor, has been the principal antiplatelet therapy after drug-eluting stent (DES) implantation in patients with acute coronary syndrome (ACS) and chronic coronary disease. Particularly in patients with ACS, which presents a higher ischemic risk than chronic coronary artery disease, DAPT for up to 12 months is the recommended standard treatment. However, to decrease bleeding events related to the potency of P2Y12 inhibitors and a prolonged duration of DAPT, recent studies have suggested P2Y12 inhibitor monotherapy after short-term DAPT (1–3 months), which decreased the bleeding risk without an increased ischemic risk. In this article, we discuss the evidence related to the efficacy of a P2Y12 inhibitor as single-antiplatelet therapy after short-term DAPT compared with standard DAPT, with a focus on patients with ACS treated with DES.

Key Words: Acute coronary syndrome; Antiplatelet therapy; Drug-eluting stent; Percutaneous coronary intervention

Antiplatelet Treatment for Acute Coronary Syndrome (ACS): Past

Aspirin has been a cornerstone of antiplatelet therapy for ACS,[1] and dual antiplatelet therapy (DAPT), consisting of aspirin and P2Y12 inhibitors, is the initial main antiplatelet therapy in patients with ACS.[1–4] An early study by Lewis et al investigated the use of aspirin for the treatment of ACS.[5] In that study, aspirin (324 mg/day) was compared to placebo in 1,266 men with unstable angina for 3 months. The authors found that the primary endpoint of death and acute myocardial infarction (MI) was significantly lower in the aspirin than placebo group.[5] In the Second International Study of Infarct Survival (ISIS-2), which enrolled 17,187 patients with suspected MI, treatment with aspirin (160 mg/day) demonstrated decreased total vascular mortality over 35 days.[6] Similarly, a meta-analysis of 287 studies including 135,000 patients with acute or previous vascular diseases or other risk factors showed that aspirin use was associated with a 23% reduction in major cardiovascular events and a 33% reduction in non-fatal MI.[7] However, the number of randomized studies evaluating the role of aspirin was relatively small and they were conducted at the fibrinolysis stage with a short follow-up duration.

Regarding the use of P2Y12 inhibitors, several randomized trials have evaluated their safety and efficacy in ACS subsets with a longer follow-up duration than that of aspirin using the following designs: (1) P2Y12 inhibitor single-antiplatelet therapy (SAPT) vs. placebo; (2) P2Y12 inhibitor SAPT vs. aspirin SAPT; and (3) P2Y12 inhibitor plus aspirin as DAPT vs. aspirin SAPT.[8–13] Notably, in the Clopidogrel in Unstable Angina to Prevent Recurrent Events trial,[8] clopidogrel SAPT was superior to the placebo regarding the composite outcome of non-fatal MI, stroke, and cardiovascular death at 9 months. Similarly, in the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, long-term administration of clopidogrel was more effective than aspirin in reducing the combined risk of ischemic stroke, MI, or vascular death.[9] With the advent of potent P2Y12 inhibitors (ticagrelor or prasugrel), 2 landmark randomized trials were conducted to compare potent P2Y12 inhibitor-based DAPT and clopidogrel-based DAPT.[12,13] In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI 38), which compared prasugrel-based DAPT and clopidogrel-based DAPT, the primary outcome of cardiovascular mortality, non-fatal MI, or stroke was significantly lower in those treated with prasugrel than in those treated with clopidogrel.[12] Furthermore, the Study of Platelet Inhibition and Patient Outcomes (PLATO) trial showed ticagrelor's superiority with regard to the composite outcome of cardiovascular mortality, stroke, or MI at 12 months.[13] Ticagrelor was also associated with a significant reduction in all-cause mortality. Therefore, the US and European guidelines recommend at least 12 months of DAPT for patients with ACS, which is longer than that recommended for patients with chronic coronary disease (CCD).[2,3]

Aspirin-Free Strategy as a De-Escalation of Antiplatelet Therapy: Present

Although DAPT with a potent P2Y12 inhibitor is a standard treatment for patients with ACS undergoing percutaneous coronary intervention (PCI),[14] prolonged DAPT

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Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
Mailing address: Byeong-Keuk Kim, MD, PhD, Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Yonsei-ro 50-1, Seodaemun-gu, 3722, Seoul, Republic of Korea. email: kimbk@yuhs.ac

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Table 1. Evidence for Ticagrelor Monotherapy After Short-Term DAPT From Randomized Trials and Their ACS Subset Analyses

	GLOBAL-LEADERS[29]	GLOBAL-LEADERS ACS subset[30,31]	TWILIGHT[32]	TWILIGHT ACS subset[33]	TICO[34]
No. patients	15,986	7,487	7,119	4,614	3,056
Key inclusion criteria	CCD or ACS	ACS subset	High-risk patients	ACS subset	ACS
% Patients with ACS	47	100	65	100	100
% Patients with STEMI	13	28	Not included	Not included	36[A]
Experimental vs. control group	1-month ticagrelor-based DAPT followed by ticagrelor SAPT vs. 12-month DAPT followed by aspirin SAPT	1-month ticagrelor-based DAPT followed by ticagrelor SAPT vs. 12-month ticagrelor-based DAPT	3-month ticagrelor-based DAPT followed by ticagrelor SAPT vs. 15-month ticagrelor-based DAPT	3-month ticagrelor-based DAPT followed by ticagrelor SAPT vs. 5-month ticagrelor-based DAPT	3-month ticagrelor-based DAPT followed by ticagrelor SAPT vs. 2-month ticagrelor-based DAPT
Primary endpoint (hypothesis)	All-cause mortality or new Q-wave MI at 24 months (superiority)	All-cause mortality or new Q-wave MI between 31 and 365 days after randomization	BARC Type 2, 3, or 5 bleeding at 15 months (superiority)	BARC Type 2, 3, or 5 bleeding at 15 months	Death, MI, ST, stroke, TVR, or major bleeding at 12 months (superiority)
Primary endpoint results	3.8% vs. 4.4% (RR 0.87; 95% CI 0.75–1.01)	1.5% vs. 2.0% (HR 0.73; 95% CI 0.51–1.03)	4.0% vs. 7.1% (HR 0.56; 95% CI 0.45–0.68)	3.6% vs. 7.6% (HR 0.47; 95% CI 0.36–0.61): interaction with CCD (P=0.03)	3.9% vs. 5.9% (HR 0.66; 95% CI 0.48–0.92)
Other key endpoints	BARC Type 3 or 5 bleeding: 2.0% vs. 2.1% (RR 0.97; 95% CI 0.78–1.20)	BARC Type 3 or 5 bleeding: 0.8% vs. 1.5% (HR 0.52; 95% CI 0.33–0.80)	Death, MI, stroke: 3.9% vs. 3.9% (HR 0.99; 95% CI 0.78–1.25)	Death, MI, stroke: 4.3% vs. 4.4% (HR 0.97; 95% CI 0.74–1.28)	TIMI major bleeding: 1.7% vs. 3.0% (HR 0.56; 95% CI 0.34–0.91)

[A]Stratified randomization according to STEMI vs. non-ST-elevation ACS. ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; CCD, chronic coronary disease; CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; MI, myocardial infarction; RR, risk ratio; TIMI, Thrombolysis in Myocardial Infarction; SAPT, single antiplatelet therapy; ST, stent thrombosis; STEMI, ST-elevation myocardial infarction; TVR, target-vessel revascularization.

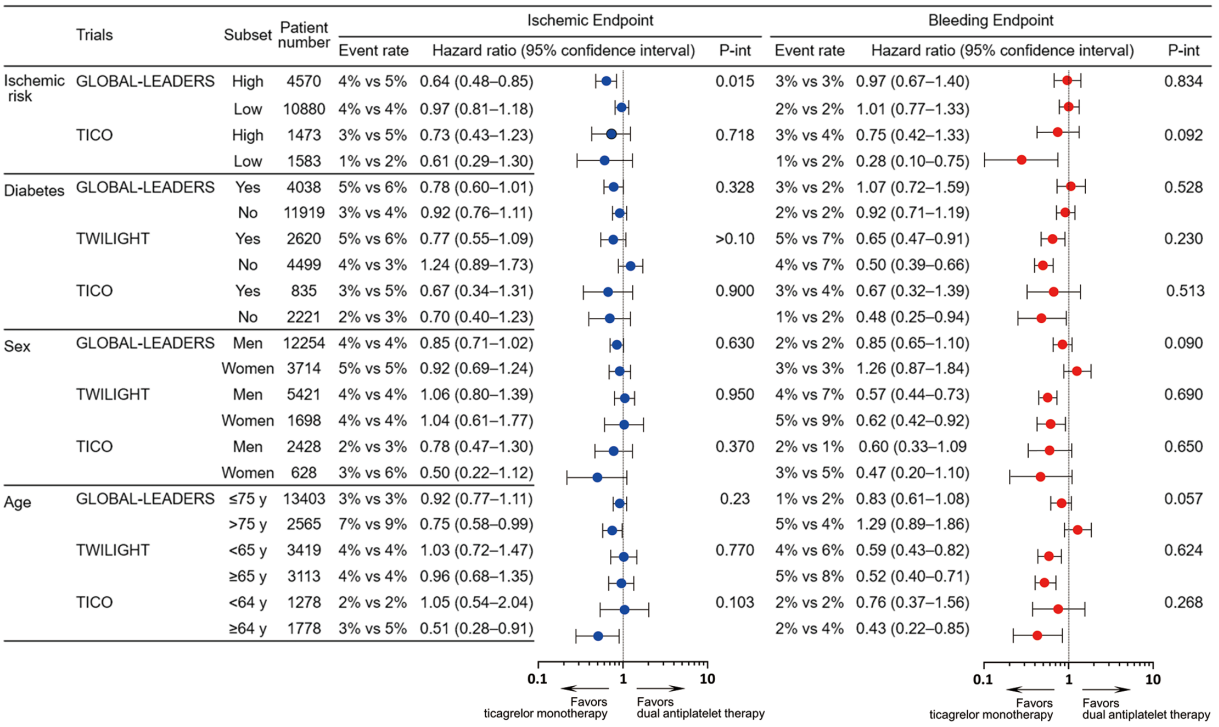
with a potent P2Y12 inhibitor may be associated with an increased bleeding risk. East Asian populations in particular are considered to be more susceptible to bleeding risks than White patients due to the so-called East Asian paradox.[15,16] In the Study to Assess Safety and Efficacy of Ticagrelor Versus Clopidogrel in Asian/Japanese Patients with Non-ST or ST-elevation ACS (PHILO), which was primarily conducted in Japan, ticagrelor, compared with clopidogrel, was associated with a higher incidence of major and minor bleeding events at 12 months (23.8% vs. 14.7%; hazard ratio [HR] 1.72; 95% confidence interval [CI] 1.23–2.40) and a numerically higher risk of the composite outcome of cardiovascular death, MI, and stroke.[17] Similarly, in the Ticagrelor vs. Clopidogrel in Asian/Korean Patients with ACS Intended for Invasive Management (TICAKOREA) trial conducted in Republic of Korea, the incidence of clinically significant bleeding was higher in the ticagrelor group (11.7%) than in the clopidogrel group (5.3%; HR 2.26; 95% CI 1.34–3.79; P=0.002).[18] No statistically significant differences were found in the P2Y12 reaction unit values between low-dose (60 mg twice daily) and standard-dose (90 mg twice daily) ticagrelor when added to aspirin, which may suggest that a strategy of ticagrelor-based DAPT may be relatively potent in East Asian populations.[19]

Notably, patients undergoing PCI for ACS represent high bleeding and ischemic risks due to the more frequent use of strong antiplatelet or anticoagulant therapy, such as heparin or glycoprotein IIb/IIIa inhibitors, even after successful revascularization.[20–22] The increased bleeding risks of these patients are also closely associated with mortality and morbidity.[23] Therefore, several strategies have been evaluated for the de-escalation of antiplatelet therapy: discontinuation, switching, and dose reduction.[24] Discontinuation refers to stopping 1 of the 2 antiplatelet agents and transitioning to SAPT (aspirin or a P2Y12 inhibitor), switching refers to changing from a P2Y12 inhibitor with more potent platelet inhibition (prasugrel or ticagrelor) to a less potent P2Y12 antagonist (clopidogrel), and dose reduction refers to reducing the dose of prasugrel or ticagrelor in DAPT.[24] As a discontinuation strategy, stopping aspirin has been investigated in several pharmacodynamic studies, where aspirin failed to substantially add to platelet inhibition in the presence of strong P2Y12 receptor inhibition.[25–27]

In the Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) platelet substudy, ticagrelor monotherapy and DAPT were compared. Both thrombus size and platelet reactivity in response to ADP and thrombin were similar with and without aspirin, whereas platelet reactivity in response to markers sensitive to cyclooxygenase-1 blockade was higher in patients undergoing ticagrelor monotherapy.[28] These results suggest that strong P2Y12 inhibition provides sufficient inhibition of the key pathways of thrombus formation. Therefore, the choice of a more potent P2Y12 inhibitor may be better when a P2Y12 inhibitor monotherapy strategy is considered after short-term DAPT, especially during the vulnerable period or in high-risk ischemic patients, such as those with ACS.[25,28]

Evidence for Ticagrelor Monotherapy vs. DAPT From Randomized Trials

Several randomized clinical trials have evaluated the efficacy and safety of P2Y12 inhibitor monotherapy after short-term DAPT (1–3 months) compared with DAPT.[29–45]



	Trials	Subset	Patient number	Ischemic Endpoint: Event rate	Ischemic Endpoint: Hazard ratio (95% confidence interval)	Ischemic Endpoint: P-int	Bleeding Endpoint: Event rate	Bleeding Endpoint: Hazard ratio (95% confidence interval)	Bleeding Endpoint: P-int
Ischemic risk	GLOBAL-LEADERS	High	4570	4% vs 5%	0.64 (0.48–0.85)	0.015	3% vs 3%	0.97 (0.67–1.40)	0.834
		Low	10880	4% vs 4%	0.97 (0.81–1.18)		2% vs 2%	1.01 (0.77–1.33)	
	TICO	High	1473	3% vs 5%	0.73 (0.43–1.23)	0.718	3% vs 4%	0.75 (0.42–1.33)	0.092
		Low	1583	1% vs 2%	0.61 (0.29–1.30)		1% vs 2%	0.28 (0.10–0.75)	
Diabetes	GLOBAL-LEADERS	Yes	4038	5% vs 6%	0.78 (0.60–1.01)	0.328	3% vs 2%	1.07 (0.72–1.59)	0.528
		No	11919	3% vs 4%	0.92 (0.76–1.11)		2% vs 2%	0.92 (0.71–1.19)	
	TWILIGHT	Yes	2620	5% vs 6%	0.77 (0.55–1.09)	>0.10	5% vs 7%	0.65 (0.47–0.91)	0.230
		No	4499	4% vs 3%	1.24 (0.89–1.73)		4% vs 7%	0.50 (0.39–0.66)	
	TICO	Yes	835	3% vs 5%	0.67 (0.34–1.31)	0.900	3% vs 4%	0.67 (0.32–1.39)	0.513
		No	2221	2% vs 3%	0.70 (0.40–1.23)		1% vs 2%	0.48 (0.25–0.94)	
Sex	GLOBAL-LEADERS	Men	12254	4% vs 4%	0.85 (0.71–1.02)	0.630	2% vs 2%	0.85 (0.65–1.10)	0.090
		Women	3714	5% vs 5%	0.92 (0.69–1.24)		3% vs 3%	1.26 (0.87–1.84)	
	TWILIGHT	Men	5421	4% vs 4%	1.06 (0.80–1.39)	0.950	4% vs 7%	0.57 (0.44–0.73)	0.690
		Women	1698	4% vs 4%	1.04 (0.61–1.77)		5% vs 9%	0.62 (0.42–0.92)	
	TICO	Men	2428	2% vs 3%	0.78 (0.47–1.30)	0.370	2% vs 1%	0.60 (0.33–1.09	0.650
		Women	628	3% vs 6%	0.50 (0.22–1.12)		3% vs 5%	0.47 (0.20–1.10)	
Age	GLOBAL-LEADERS	≤75 y	13403	3% vs 3%	0.92 (0.77–1.11)	0.23	1% vs 2%	0.83 (0.61–1.08)	0.057
		>75 y	2565	7% vs 9%	0.75 (0.58–0.99)		5% vs 4%	1.29 (0.89–1.86)	
	TWILIGHT	<65 y	3419	4% vs 4%	1.03 (0.72–1.47)	0.770	4% vs 6%	0.59 (0.43–0.82)	0.624
		≥65 y	3113	4% vs 4%	0.96 (0.68–1.35)		5% vs 8%	0.52 (0.40–0.71)	
	TICO	<64 y	1278	2% vs 2%	1.05 (0.54–2.04)	0.103	2% vs 2%	0.76 (0.37–1.56)	0.268
		≥64 y	1778	3% vs 5%	0.51 (0.28–0.91)		2% vs 4%	0.43 (0.22–0.85)	

Figure 1. Evidence for ticagrelor monotherapy vs. dual antiplatelet therapy in various subsets. A composite of all-cause death or new Q-wave myocardial infarction (MI) in the GLOBAL-LEADERS trial, a composite of all-cause death, MI, or stroke in the TWILIGHT trial, and a composite of death, MI, stent thrombosis, stroke, or target-vessel revascularization are used for the ischemic endpoint according to each trial. Bleeding Academic Research Consortium (BARC) Type 3 or 5 bleeding in the GLOBAL LEADERS trial, BARC Type 2, 3, or 5 bleeding in the TWILIGHT trial, and Thrombolysis in Myocardial Infarction (TIMI) major bleeding are used for the bleeding endpoint.[29–45] P-int, P for interaction.

The Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation (GLOBAL-LEADERS), TWILIGHT, and the Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome (TICO) trial used ticagrelor as a P2Y12 inhibitor.[29–45] In the GLOBAL-LEADERS trial, all-cause mortality and Q-wave MI at 24 months were compared between groups undergoing 1-month ticagrelor-based DAPT followed by ticagrelor SAPT and 12-month DAPT followed by aspirin SAPT using a superiority design in 15,968 patients with CCD or ACS (ACS: 47%).[29] Notably, the experimental regimen did not demonstrate superiority when compared with control (**Table 1**).[29] In contrast, in an ACS subset, Bleeding Academic Research Consortium (BARC) Type 3 or 5 bleeding was lower in the group undergoing ticagrelor-based 1-month DAPT followed by ticagrelor monotherapy than in the group undergoing ticagrelor-based 12-month DAPT (**Table 1**); however, the primary outcome did not differ.[30] When testing the interaction between ticagrelor monotherapy after 1-month DAPT and conventional DAPT based on clinical presentation (with or without ACS),[31] there was a significant treatment-by-subgroup interaction for the composite of the co-primary efficacy endpoint (composite of death, MI, stroke, urgent target vessel revascularization, or BARC Type 3 or 5 bleeding; P for interaction=0.005) and BARC Type 3 or 5 bleeding (P for interaction=0.039). This suggests a net clinical benefit of ticagrelor monotherapy among patients with ACS but not among those with CCD.[31]

In the TWILIGHT trial of 9,006 clinically or angiographically high-risk patients with DES (ACS, 65%; ST-elevation MI [STEMI], exclusion; **Table 1**), the primary endpoint (BARC Type 2, 3, or 5 bleeding) was compared between ticagrelor monotherapy after 3-month DAPT and ticagrelor plus aspirin.[32] In all, 7,119 patients underwent randomization, and the incidence of the primary endpoint was significantly lower in patients receiving ticagrelor alone than in those receiving ticagrelor and aspirin.[32] The incidence of death, non-fatal MI, or non-fatal stroke also met the non-inferiority criterion. These findings were consistent in the ACS subset, where ticagrelor monotherapy reduced BARC Type 2, 3, or 5 bleeding by 53% (3.6% vs. 7.6%; HR 0.47; 95% CI 0.36–0.61; P<0.001) in the ACS subset and by 24% in the CCD subset (4.8% vs. 6.2%; HR 0.76; 95% CI 0.54–1.06; P=0.11), with a significant interaction (P for interaction=0.03).[33]

In the TICO trial, which enrolled 3,056 patients with ACS, the net adverse clinical events of 3-month ticagrelor-based DAPT followed by ticagrelor SAPT was compared with 12-month ticagrelor-based DAPT.[34] The proportion of STEMI in this population was 36% (n=1,103; **Table 1**). The primary outcome, a net adverse clinical event (a composite of major bleeding and major adverse cardiac and cerebrovascular events), was higher and major bleeding was lower in patients who received ticagrelor monotherapy

Table 2. Evidence for P2Y12 Inhibitor Other Than Ticagrelor as SAPT From Randomized Trials and Their ACS Subset Analyses

	SMART-CHOICE[49]	SMART-CHOICE ACS subset[49]	STOPDAPT-2[50]	STOPDAPT-2 ACS[51]	STOPDAPT-3[53]
No. patients	2,993	1,741	3,045	4,169	5,966
Key inclusion criteria	CCD or ACS	ACS subset	CCD or ACS	ACS	ACS or high bleeding risk
% Patients with ACS	59	100	38	100	75
% Patients with STEMI	11	18	18	56	43
Experimental vs. control group	3-month DAPT followed by any P2Y12 inhibitor SAPT vs. 12-month DAPT	3-month DAPT followed by any P2Y12 inhibitor SAPT vs. 12-month DAPT	1-month DAPT followed by clopidogrel SAPT vs. 12-month clopidogrel-based DAPT	1- to 2-month DAPT followed by clopidogrel SAPT vs. 12-month clopidogrel-based DAPT	Prasugrel monotherapy vs. prasugrel-based DAPT
Primary endpoint (hypothesis)	Death, MI, or stroke at 12 months (non-inferiority)	Death, MI, or stroke at 12 months	CV death, MI, stroke, ST, or major or minor bleeding at 12 months (non-inferiority)	CV death, MI, stroke, or ST or major or minor bleeding at 12 months (non-inferiority)	BARC Type 3 or 5 bleeding at 1 month (superiority)
Primary endpoint results	2.9% vs. 2.5% (difference: 0.4%; 95% 1-sided CI 1.3%; non-inferiority P=0.007)	3.0% vs. 2.9% (HR 1.06; 95% CI 0.61–1.85)	2.4% vs. 3.7% (HR 0.64; 95% CI 0.42–0.98)	3.2% vs. 2.8% (HR 1.14; 95% CI 0.80–1.62; non-inferiority P=0.06)	4.5% vs. 4.7% (HR 0.95; 95% CI 0.75–1.20)
Other key endpoints	BARC Type 2 or 5 bleeding: 2.0% vs. 3.4% (HR 0.58; 95% CI 0.36–0.92)	BARC Type 2 or 5 bleeding: 1.8% vs. 3.2% (HR 0.56; 95% CI 0.30–1.05)	Major or minor bleeding: 0.4% vs. 1.5% (HR 0.26; 95% CI 0.11–0.64)	Major or minor bleeding: 0.5% vs. 1.2% (HR 0.46; 95% CI 0.23–0.94)	CV death, MI, stent thrombosis or stroke: 4.1% vs. 3.7% (HR 1.12; 95% CI 0.87–1.45; non-inferiority P=0.01)

CV, cardiovascular. Other abbreviations as in Table 1.

after 3-month DAPT.[34]

The role of ticagrelor monotherapy in patients with ST-segment elevation has not been thoroughly investigated in randomized studies. The TICO trial was randomized with a stratification of clinical presentation (STEMI vs. non-ST-elevation ACS), and there were no interactions according to the clinical presentations.[35] Aspirin-free strategies may raise concerns for patients with high ischemic risk. Notably, the results from both the GLOBAL-LEADERS and TICO trials were consistent in patients who underwent complex PCI and in those with high-ischemic features, respectively (**Figure 1**).[36,37] These findings were consistent regardless of the presence of diabetes, sex, or age (**Figure 1**).[38–45] Various other subgroup analyses from the TICO trial also revealed consistent findings regardless of the presence of high bleeding risk, preprocedural coronary blood flow, or body mass index.[46–48]

Evidence for P2Y12 Inhibitors Other Than Ticagrelor in SAPT vs. DAPT

In the Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs. Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents (SMART-CHOICE) trial, 2,993 patients undergoing PCI with DES (ACS, 59%) were randomized to receive aspirin and P2Y12 inhibitors for 3 months followed by P2Y12 inhibitor alone (clopidogrel, 77%; prasugrel or ticagrelor, 23%) or DAPT for 12 months (**Table 2**).[49] At 12 months, the primary endpoint (composite of death, MI, or stroke) met a non-inferiority criterion. Moreover, the rate of BARC Type 2–5 bleeding was significantly lower with P2Y12 inhibitor monotherapy than with DAPT, and subgroup analyses according to the clinical presentation showed consistent effects (**Table 2**).

In the Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent (STOP-DAPT-2) trial (n=3,045; ACS, 38%), 1-month DAPT followed by clopidogrel monotherapy was compared with 12-month DAPT with regard to the 1-year composite of cardiovascular death, MI, stroke, definite stent thrombosis, and major bleeding.[50] As a result, 1-month DAPT was both non-inferior and superior to 12-month DAPT with regard to the primary endpoint, meeting the criteria for both non-inferiority (P<0.001) and superiority (P=0.04). Moreover, the incidence of major secondary bleeding endpoints was significantly lower in the 1-month DAPT group than in the 12-month DAPT group. However, in the STOPDAPT-2 ACS trial targeting patients with ACS, when 1–2 months of DAPT followed by clopidogrel monotherapy and 12 months of DAPT were compared, 1–2 months of DAPT failed to meet the non-inferiority margin of 50% on the HR scale for the composite of cardiovascular or bleeding events.[51] These findings may explain why clopidogrel could have the limitation of high interindividual variability. Therefore, potent P2Y12 inhibitors, which can provide more potent platelet inhibition than clopidogrel, may be a better choice for patients with ACS if de-escalation by discontinuation is considered after very-short-term DAPT.[52]

The STOPDAPT-3 trial, which enrolled 6,002 patients at a high bleeding risk (~55%) or with ACS (~75%), compared a group undergoing prasugrel monotherapy

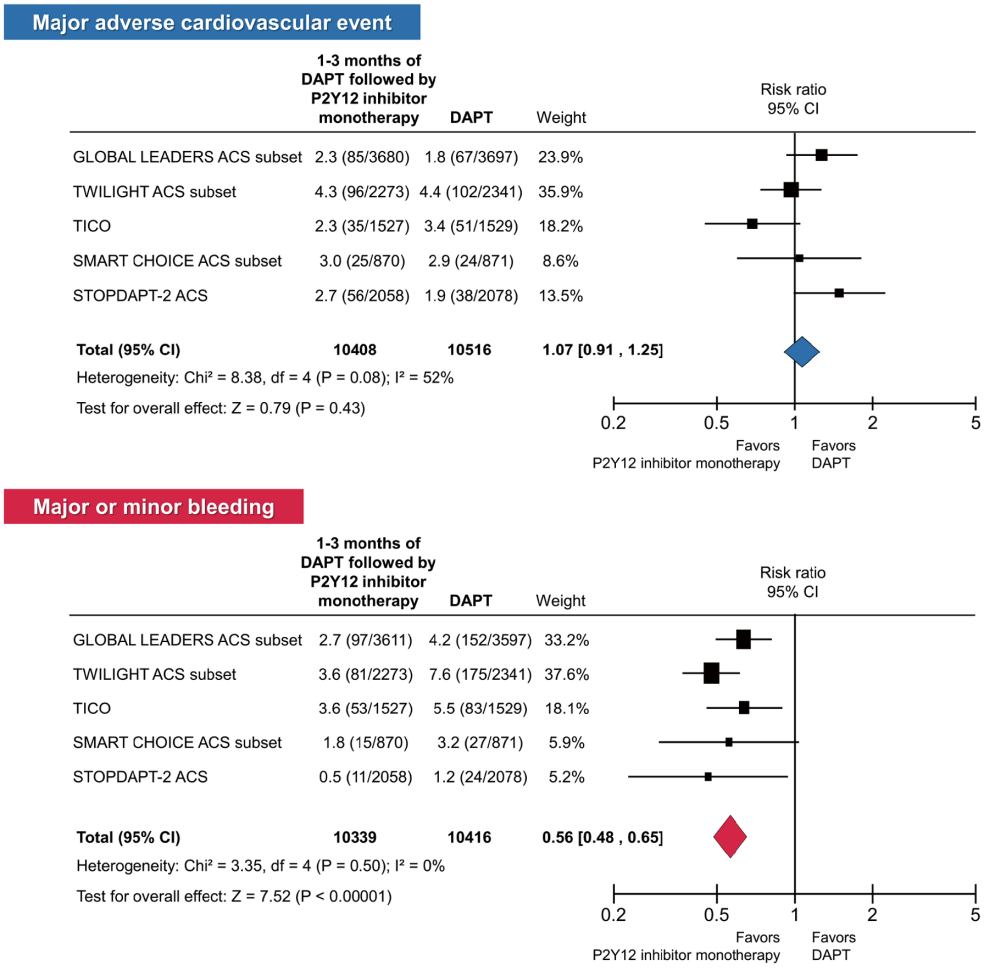


Figure 2. Evidence for P2Y12 inhibitor monotherapy from randomized trials and their acute coronary syndrome (ACS) subset analyses. The primary bleeding and major adverse cardiovascular event outcomes are the prespecified definitions in each trial. CI, confidence interval; DAPT, dual antiplatelet therapy.

(3.75 mg/day) before index PCI with a change to clopidogrel monotherapy at 1 month after PCI with a group undergoing DAPT comprising of aspirin and prasugrel before the index PCI with a change to aspirin monotherapy at 1 month after PCI.[53] The primary endpoint of BARC Type 3–5 bleeding at 1 month was not superior in the prasugrel monotherapy group compared to the DAPT group (4.47% vs. 4.71%; HR 0.95; 95% CI 0.75–1.20; P=0.66), whereas a composite outcome of cardiovascular death, MI, ischemic stroke, or definite stent thrombosis at 1 month met non-inferiority criteria. In addition, the incidence of any unplanned coronary revascularization (1.05% vs. 0.57%; HR 1.83; 95% CI 1.01–3.30; P<0.05) or subacute definite or probable stent thrombosis (0.58% vs. 0.17%; HR 3.40; 95% CI 1.26–9.23; P<0.05) was significantly higher in the prasugrel monotherapy group than in the other group.[53] These results suggest that treatment with aspirin during the periprocedural period may be required if prasugrel at a dose of 3.75 mg/day is administered. Further trials are required to confirm whether potent P2Y12 inhibitor monotherapy at full dose after decreasing aspirin administration may lead to different results.

Recent Evidence of P2Y12 Inhibitor Monotherapy vs. DAPT From Meta-Analyses

Several meta-analyses have been performed regarding the randomized trials investigating P2Y12 inhibitor monotherapy.[54–56] From 5 randomized trials (GLOBAL-LEADERS, SMART-CHOICE, STOPDAPT-2, TWILIGHT, and TICO) including 32,145 patients (18,046 [56.1%] with ACS), the discontinuation of aspirin 1–3 months after PCI with continued P2Y12 inhibitor monotherapy was compared with traditional DAPT.[54] In the experimental arm, use of a P2Y12 inhibitor included clopidogrel in 16.5% of patients and prasugrel or ticagrelor in 83.5% of patients. Discontinuation of aspirin therapy 1–3 months after PCI significantly reduced the risk of major bleeding by 40% (2.0% vs. 3.1%; HR 0.60; 95% CI 0.45–0.79), with no observed increase in the risk of major adverse cardiovascular events (2.7% vs. 3.1%; HR 0.88; 95% CI 0.77–1.02), MI (1.1% vs. 1.3%; HR 0.85; 95% CI 0.69–1.06), or all-cause death (1.3% vs. 1.5%; HR 0.85; 95% CI 0.70–1.03). These findings were consistent among patients who underwent PCI for ACS.[54] Similarly, of the 5 randomized trials,

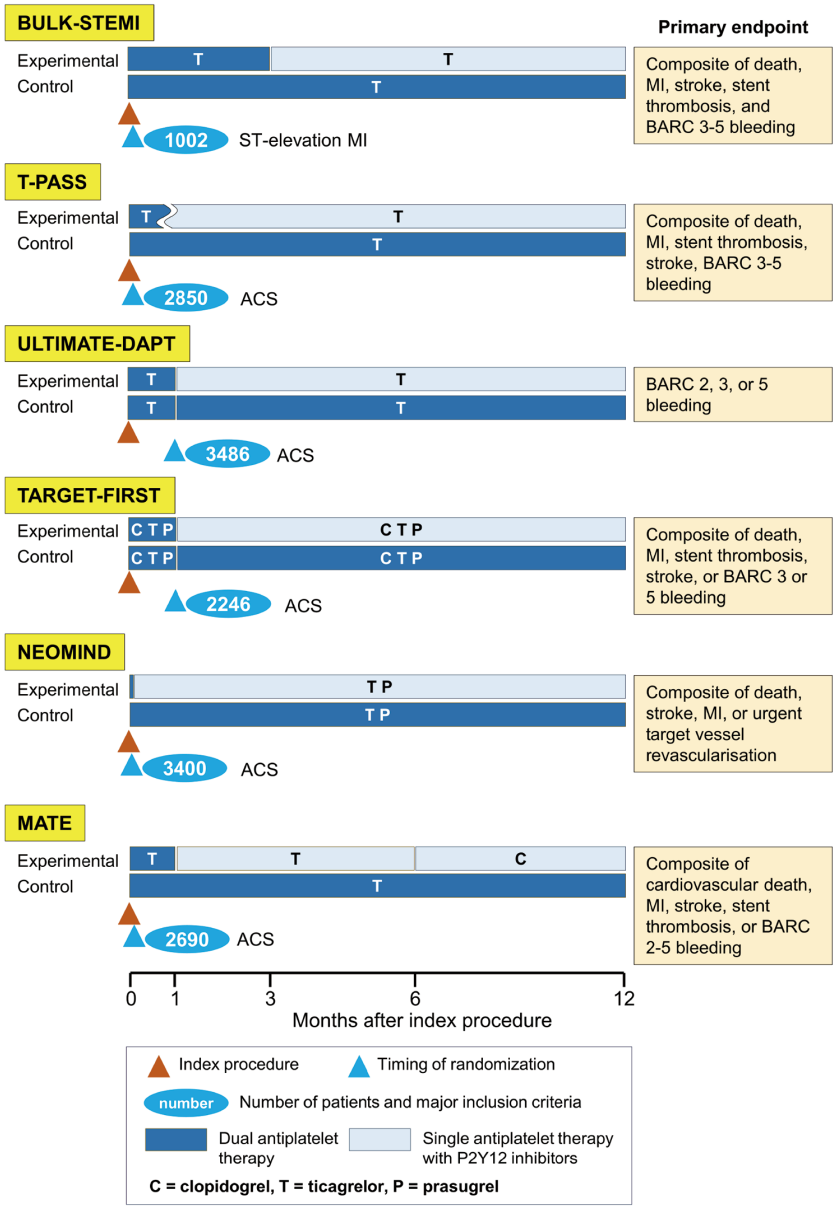


Figure 3. Ongoing randomized clinical trials evaluating $P2Y_{12}$ inhibitor monotherapy after short-term dual antiplatelet therapy (DAPT) in patients with acute coronary syndrome (ACS). For each trial, the upper panel is the experimental group and the lower panel is the control group. Dark blue represents DAPT and light blue represents single antiplatelet therapy. BARC, Bleeding Academic Research Consortium; MI, myocardial infarction.

Giacoppo et al found that 1–3 months of DAPT followed by $P2Y_{12}$ inhibitor SAPT was associated with a lower risk of major bleeding, similar stent thrombosis, all-cause death, MI, and stroke compared with prolonged DAPT.[55] These trials only included the STOPDAPT-2 trial, not the STOPDAPT-2 ACS trial, which was the most recent trial. Notably, the analyses of ACS only showed similar findings: a significant 44% relative reduction in major or minor bleeding without a difference in major adverse cardiac and cerebrovascular events (**Figure 2**). Meta-analyses of the 3 randomized trials with ticagrelor as SAPT (26,143 patients) showed that ticagrelor monotherapy after short-term DAPT of 1–3 months was associated with decreased all-cause mortality (risk ratio 0.80; 95% CI 0.65−0.98; P=0.03) and BARC Type 3 or 5 bleeding, which was not offset by an increased risk of cardiac death, ischemic stroke, acute MI, and stent thrombosis.[52]

A recent individual patient-level meta-analysis of randomized clinical trials, not aggregate data meta-analyses, showed similar findings, and this study could provide additional information on the subgroups of interest.[56] $P2Y_{12}$ inhibitor monotherapy was associated with a similar risk of death, MI, or stroke, with evidence that this association may be modified by sex (P for interaction=0.02).[56] This suggests that $P2Y_{12}$ inhibitor monotherapy lowers the risk of the primary ischemic endpoint in women, but not in men.[56] Moreover, the risk of bleeding was lower with $P2Y_{12}$ inhibitor monotherapy than with DAPT, which was consistent across subgroups, with the exception of the type of $P2Y_{12}$ inhibitor used (P for interaction=0.02), suggesting greater benefit when a newer $P2Y_{12}$ inhibitor rather than clopidogrel was part of the DAPT regimen.[56]

Guidelines and Consensus Documents

The 2021 American College of Cardiology/American Heart Association Joint Committee Guidelines have newly recommended the discontinuation of aspirin after 1–3 months with continued P2Y12 inhibitor monotherapy in selected patients undergoing PCI (both CCD and ACS; Class 2a; level of evidence A).[57] The European guidelines recommend stopping aspirin after 3–6 months, depending on the balance between the ischemic and bleeding risk after stent implantation in patients undergoing a strategy of DAPT, according to the 2020 guidelines for the management of ACS in patients presenting without persistent ST-segment elevation (Class 2a; level of evidence A).[58]

The Japanese Circulation Society 2020 guideline on antithrombotic therapy in patients with coronary artery disease also includes a statement on P2Y12 inhibitor monotherapy as follows: monotherapy with a P2Y12 receptor inhibitor should be considered in patients with high thrombotic and bleeding risks following short-term DAPT (Class 2a; level of evidence A).[59]

The 2020 Korean Society of MI Expert Consensus Document recommends that the use of standard-dose potent P2Y12 inhibitors requires caution regarding the increased risk of bleeding, especially in Korean patients with bleeding risk factors. The use of 3-month DAPT and P2Y12 receptor inhibitor monotherapy is recommended in patients with a high bleeding risk and low ischemic risk.[60]

Ongoing Randomized Clinical Trials: Future

Although the optimal timing of whether the duration of DAPT could be further reduced or the choice of SAPT, such as the type of P2Y12 inhibitor or comparison of aspirin and P2Y12 inhibitors, remains undetermined, ongoing randomized clinical trials may answer these questions (**Figure 3**). The 3 Months Versus 12 Months Dual Antiplatelet Therapy After Drug-eluting Stent Implantation in STEMI (BULK-STEMI) trial (NCT04570345) is enrolling 1,002 patients with STEMI to compare net adverse clinical events at 12 months between 3-month ticagrelor-based DAPT followed by ticagrelor SAPT and ticagrelor-based 12-month DAPT.

Furthermore, the Ticagrelor Monotherapy in PAtients Treated With New-generation Drug-eluting Stents for Acute Coronary Syndrome (T-PASS) (NCT03797651), 1-month vs 12-month DAPT for ACS Patients Who Underwent PCI Stratified by IVUS (ULTIMATE-DAPT) (NCT03971500), Evaluation of a Modified Anti-Platelet Therapy Associated With Low-dose DES Firehawk in Acute Myocardial Infarction Patients Treated With Complete Revascularization Strategy (TARGET-FIRST) (NCT04753749), PercutaNEOus Coronary Intervention Followed by Monotherapy INstead of Dual Antiplatelet Therapy in the SETting of Acute Coronary Syndromes (NEO-MINDSET) (NCT04360720), and Sequential MonotherApy of TicagrElor and Clopidogrel After Coronary Intervention (MATE) (NCT04937699) trials will compare 1-month or <1-month DAPT followed by P2Y12 inhibitor monotherapy with prolonged DAPT. These trials may indicate the feasibility of further reducing the duration of DAPT to <1 month, particularly in patients with ACS (**Figure 3**). The T-PASS trial (NCT03797651) will compare DAPT with a duration of <1 month followed by ticagrelor SAPT and 12-month ticagrelor-based DAPT to evaluate the net clinical benefit at 12 months. Similarly, the ULTIMATE-DAPT trial (NCT03971500) will compare ticagrelor SAPT and ticagrelor-based DAPT with regard to major adverse cardiac events or BARC Type 2–5 bleeding between 1 and 12 months after PCI. The TARGET-FIRST trial (NCT04753749) will compare 1-month post-procedural DAPT followed by P2Y12 inhibitor monotherapy and 12-month DAPT for the next 11 months to evaluate the net adverse clinical events and BARC Type 2–5 bleeding between 1 and 12 months after PCI. This trial is using clopidogrel, prasugrel, and ticagrelor as the P2Y12 inhibitors. The NEO-MINDSET trial (NCT04360720) will compare ticagrelor or prasugrel SAPT and ticagrelor or prasugrel-based DAPT with regard to major adverse cardiac and cerebrovascular events and BARC Type 2–5 bleeding at 12 months. In this trial, patients with ACS treated with successful PCI will be enrolled and aspirin will be discontinued immediately after randomization. In the MATE trial (NCT04937699), the experimental group will receive sequential monotherapy with ticagrelor and clopidogrel (ticagrelor 90 mg twice daily DAPT for 1 month, followed by ticagrelor 90 mg twice daily SAPT for 5 months, followed by clopidogrel 75 mg once daily SAPT for another 6 months), whereas the control group will receive ticagrelor 90 mg twice daily DAPT for 12 months.

Conclusions

Recent evidence from randomized clinical trials and meta-analyses suggests that P2Y12 inhibitor monotherapy after short-term DAPT (1–3 months), as a de-escalation by discontinuation of aspirin, decreases the bleeding risk without increasing the risk of ischemia. Although the timing of whether the duration of DAPT could be further reduced or the choice of type of SAPT, such as the type of P2Y12 inhibitor or comparison between aspirin and P2Y12 inhibitors, remains to be determined, potent P2Y12 inhibitors as SAPT after short-term DAPT may be optimal, especially for patients with ACS.

Disclosures

The authors have no conflicts of interest to declare.

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