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STATE-OF-THE-ART REVIEW

Timing, Selection, Modulation, and Duration of $P2Y_{12}$ Inhibitors for Patients With Acute Coronary Syndromes Undergoing PCI

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ABSTRACT

Dual antiplatelet therapy with aspirin and the oral $P2Y_{12}$ inhibitor clopidogrel as the cornerstone of treatment for patients with an acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) was firstly established in 2001. Soon thereafter, the newer-generation $P2Y_{12}$ inhibitors prasugrel and ticagrelor became commercially available. The clinical management of ACS patients undergoing PCI has evolved significantly in the last 2 decades, with a shift toward more rapid invasive management, broader use of drug-eluting stents, and the increasing recognition that major bleeding due to antiplatelet therapy is detrimental. In this ever-changing scenario, numerous studies have addressed 4 main questions regarding $P2Y_{12}$ inhibition in ACS patients undergoing PCI: timing, selection, modulation, and duration. This paper reviews the latest evidence surrounding these topical questions, with a focus on efficacy and safety data, practice guidelines, and residual areas of uncertainty. (J Am Coll Cardiol Intv 2023;16:1–18) © 2023 by the American College of Cardiology Foundation.

The platelet $P2Y_{12}$ receptor plays a central role in amplification of platelet activation, aggregation, secretion, and procoagulant activity.[1] Such a central role is supported by the undisputed efficacy on reducing thrombotic events achieved by selective inhibition of the $P2Y_{12}$ receptor, with over 2 decades of trials aimed at optimizing what currently represents the cornerstone of treatment of high-risk patients with coronary atherosclerotic disease. In 2001, the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial established the benefit of the oral $P2Y_{12}$ inhibitor clopidogrel, given for 12 months in addition to aspirin, for patients presenting with an acute coronary syndrome (ACS).[2] In the CURE trial, patients who were treated with percutaneous coronary intervention (PCI) had better outcomes if clopidogrel was given early (ie, before coronary angiography),[3] although this effect was observed in the context of a prolonged interval between clinical presentation and PCI (ie, median 10 days). Following these results, the 2007 American guidelines for non-ST-segment elevation acute coronary syndrome (NSTE-ACS) started to recommend dual antiplatelet therapy (DAPT) with aspirin and clopidogrel initiated before diagnostic angiography and continued for 12 months.[4] Soon thereafter, the newer-generation oral $P2Y_{12}$ inhibitors prasugrel and ticagrelor—characterized by more prompt and potent

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

DAPT = dual antiplatelet therapy

HPR = high on-treatment platelet reactivity

MACE = major adverse cardiac event(s)

NACE = net adverse cardiac event(s)

NSTE-ACS = non-ST-segment elevation acute coronary syndrome

PCI = percutaneous coronary intervention

STE-ACS = ST-segment elevation acute coronary syndrome

platelet inhibitory effects as well as superior efficacy compared with clopidogrel—became commercially available after the results of the TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) and PLATO (Platelet Inhibition and Patient Outcomes) trials.[5,6] The intravenous $P2Y_{12}$ inhibitor cangrelor became commercially available in 2015 based on the results of the CHAMPION (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition)-PHOENIX trial.[7] The oral vicagrel[8] and the subcutaneous selatogrel[9] are 2 more $P2Y_{12}$ inhibitors under clinical development. **Table 1** summarizes the pharmacological characteristics of clopidogrel, prasugrel, ticagrelor, cangrelor, vicagrel, and selatogrel.

The clinical management of ACS patients undergoing PCI has evolved significantly since the publication of the CURE trial, with a shift toward more rapid invasive management, broader use of drug-eluting stents with very low rates of thrombotic complications, and the increasing recognition that major bleeding due to DAPT is detrimental.[10-12] In this ever-changing scenario, numerous studies have addressed 4 main questions regarding $P2Y_{12}$ inhibition in ACS patients undergoing PCI: timing, selection, modulation, and duration. This paper reviews the latest evidence surrounding these topical questions, with a focus on efficacy and safety data, practice guidelines, and residual areas of uncertainty. Because the topic of antithrombotic therapy for PCI patients on oral anticoagulation has been covered extensively in recent guidelines and consensus documents,[12,13] we focus on studies of patients in sinus rhythm and/or without a baseline indication to oral anticoagulation.

HIGHLIGHTS

- The rationale for pretreatment with $P2Y_{12}$ inhibitors in patients with ACS is weak in the era of quick access to early invasive coronary angiography.
- Prasugrel and ticagrelor are first-line options for DAPT combinations with aspirin, but clopidogrel reduces the risk of bleeding, which may be useful in some patients at risk.
- The duration of $P2Y_{12}$ inhibition on a background of aspirin must be tailored to the individual risks of thrombotic/ischemic and bleeding complications.
- Strategies of $P2Y_{12}$ inhibitor monotherapy with no aspirin or de-escalation from a more potent to a less potent $P2Y_{12}$ inhibitor intensity are emerging.

TIMING OF ORAL $P2Y_{12}$ INHIBITORS

EFFICACY AND SAFETY OF PRETREATMENT. In interventional pharmacology, the word *pretreatment* refers to the practice of administering an oral $P2Y_{12}$ inhibitor before the coronary anatomy has been defined.[14] The rationale for pretreatment and its theoretical advantages and disadvantages are schematized in **Figure 1**. The time interval between a diagnosis of ACS and invasive coronary angiography has decreased significantly since the publication of the PCI substudy of the CURE trial.[2] Guidelines from the United States[15] and Europe[12] currently recommend a quick invasive management for the vast majority of patients with NSTE-ACS, and patients with ST-segment elevation acute coronary syndrome (STE-ACS) must also receive PCI as soon as possible.[15,16] Therefore, the window of opportunity for pretreatment is narrow, and its actual need must also be contextualized to the relative proportions of PCI, coronary artery bypass grafting, and conservative treatment in contemporary ACS practice. In fact, while patients with STE-ACS are typically referred to primary PCI with few exceptions,[15,17] the proportion of those with NSTE-ACS who ultimately require surgical revascularization is not trivial (~11%).[11]

Table 2 summarizes the characteristics and results of the 3 largest randomized trials of pretreatment for patients with ACS. Overall, the evidence supporting pretreatment is modest or null. In fact, the ACCOAST (Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction) trial did not find a significant benefit in reducing major adverse cardiac events (MACE) with prasugrel pretreatment in NSTE-ACS, and the risk of major bleeding was increased.[18] These effects were observed across a broad spectrum of subgroups, including patients who underwent PCI.[19] Similarly, the ATLANTIC (Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery) trial did not find a higher degree of reperfusion with prehospital vs in-hospital initiation of ticagrelor in patients with STE-ACS.[20] Stent thrombosis was significantly reduced with pretreatment, especially when ticagrelor was given within

TABLE 1 Pharmacologic Characteristics of $P2Y_{12}$ Inhibitors

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor	Vicagrel	Selatogrel
Class	Thienopyridine	Thienopyridine	Cyclopentyl-triazolo-pyrimidine	Adenosine triphosphate analog	Thienopyridine	2-phenyl-pyrimidine-4-carboxamide analog
Reversible	No	No	Yes	Yes	No	Yes
Metabolic conversion	Yes	Yes	No	No	Yes	No
Route	Oral	Oral	Oral	Intravenous	Oral	Subcutaneous
Dose in ACS	600 mg LD, 75 mg daily MD	60 mg LD, 10 mg daily MD	180 mg LD, 90 mg twice daily MD	30-μg/kg bolus, 4-μg/kg/min infusion (2-4 h) for PCI	20 mg LD, 5 mg daily MD	16 mg
Onset of action	2-6 h	0.5-4 h	0.5-2 h	2 min	4 h	15-30 min
Offset of action	7-10 d	7-10 d	3-5 d	1-1.5 h	5-10 d	8 h
Half-life	AM: 30 min; parent: 6 h	AM: 7 h	AM: 9-12 h; parent: 8 h	3-5 min	AM: 45 min	4-7 h
Approved for clinical use	Yes	Yes	Yes	Yes	No	No

ACS = acute coronary syndrome; AM = active metabolite; CKD = chronic kidney disease; LD = loading dose; MD = maintenance dose; PCI = percutaneous coronary intervention.

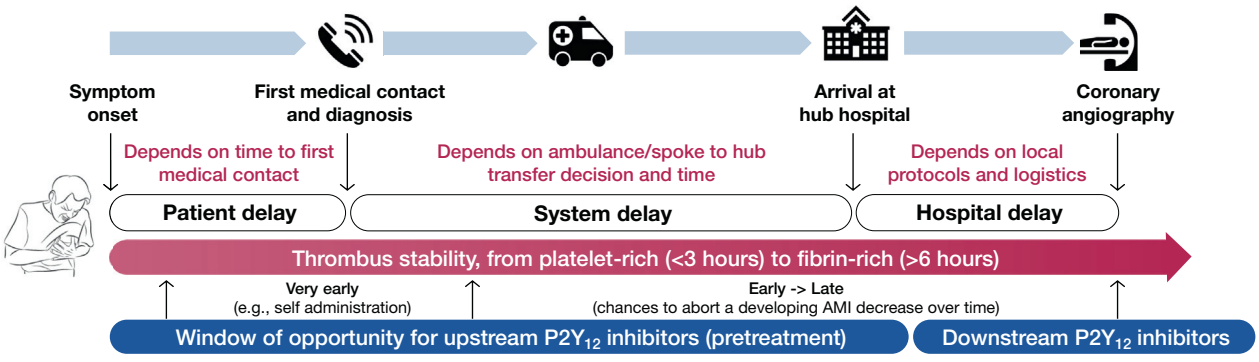
3 hours of symptom onset,[20,21] and major bleeding was not increased. As such, some guideline task forces have interpreted these results as neutral or possibly beneficial.[22] More recently, the ISAR-REACT 5 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5) trial compared ticagrelor (given before coronary angiography) with prasugrel (given before or after coronary angiography in patients with STE-ACS and NSTE-ACS, respectively).[23] This study cannot be considered a pure study of pretreatment because ticagrelor and prasugrel were given based on their respective instructions for use.[24] However, in the two-thirds of patients with NSTE-ACS, the trial compared not only the 2 $P2Y_{12}$ inhibitors, but also different times of administration; therefore, the results in this subgroup, which pointed at better outcomes with prasugrel given at the time of PCI (consistently with the main trial results) are informative on the subject of pretreatment.[25] Finally, in 2020, the DUBIUS (Downstream Versus Upstream Strategy for the Administration of $P2Y_{12}$ Receptor Blockers In Non-ST Elevated Acute Coronary Syndromes With Initial Invasive Indication) trial included patients undergoing invasive management for NSTE-ACS and was stopped early for futility.[26] A downstream strategy of oral $P2Y_{12}$ inhibitors administration did not differ significantly compared with a pretreatment strategy for a composite of net adverse cardiac events (NACE). This result was confirmed among patients undergoing PCI (72% of the population) and was irrespective of the timing of coronary angiography (eg, within or after 24 hours from enrollment).

Dawson et al[27] conducted a meta-analysis of 13,226 patients (93% with a diagnosis of NSTE-ACS, 83% undergoing PCI) from 7 randomized trials of pretreatment, including those discussed previously.[28] Overall, pretreatment was not associated with a significant reduction in MACE at 30 days; in contrast, the risk of major bleeding was increased. Another meta-analysis compared early vs delayed $P2Y_{12}$ inhibition in 9,648 patients from 7 trials of PCI for STE-ACS.[29] Early treatment resulted into a 27% significant relative reduction in MACE, and major bleeding was not increased.

Large-scale observational data are also available. A real-world investigation from Dworeck et al[30] investigated pretreatment with ticagrelor or clopidogrel using prospective data of 64,857 PCI patients with NSTE-ACS from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry) nationwide cohort. All-cause death at 30 days did not differ between the 92.4% of patients who were pretreated and those who were not, and in-hospital bleeding was increased. In another study also using data from the SCAAR registry, Redfors et al[31] investigated pretreatment (mostly with clopidogrel or ticagrelor) in 44,804 STE-ACS patients undergoing PCI. Death at 30 days and in-hospital bleeding did not differ with pretreatment.

GUIDELINE RECOMMENDATIONS. In 2020, the European guidelines for NSTE-ACS issued a Class III recommendation (ie, harm) for "routine pretreatment with a $P2Y_{12}$ receptor inhibitor in patients in whom coronary anatomy is not known and an early invasive management is planned."[12] However, a Class IIb recommendation also indicated that "pre-treatment with a $P2Y_{12}$ receptor inhibitor may be considered in patients with NSTE-ACS who are not planned to undergo an early invasive strategy and do not have

FIGURE 1 **Window of Opportunity, Rationale, Advantages, and Disadvantages of Pretreatment With Oral P2Y$_{12}$ Inhibitors in Patients With ACS**



	Pre-treatment	No pre-treatment
PROs	• More time to achieve the full effect of oral drugs • Thrombotic protection while waiting ICA • Less risk of peri-procedural thrombotic complications • Less need for bailout GPIs	• Avoid unnecessary antiplatelet therapy in patients without CAD, or need for wash-out before CABG • More time for personalized decisions based on angiographic and procedural considerations
CONs	• Higher risk of bleeding • Harmful for patients who need immediate CABG and useless for those without CAD • Prolonged hospitalization if washout required for CABG	• Little time for oral drugs to achieve their effect • Increased risk of peri-procedural thrombotic or ischemic complications • More need for bailout GPIs

After the onset of symptoms, patients with acute coronary syndrome (ACS) normally ask for medical care, with patient delay varying from minutes to hours or days. After the first medical contact, treatment decisions and, ultimately, the time to invasive coronary angiography depend on several factors. Each phase before the coronary anatomy is part of a window of opportunity for pretreatment. The longer the time from the beginning of the ACS is, the more the thrombus becomes organized (ie, fibrin-rich) and unlikely to spontaneously dissolve with P2Y$_{12}$ inhibitors. AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; CAD = coronary artery disease; GPI = glycoprotein IIb/IIIa inhibitors; ICA = invasive coronary angiography.

a high bleeding risk." Conversely, current European guidelines for STE-ACS indicate that "a potent P2Y$_{12}$ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI [...] unless there are contraindications such as excessive risk of bleeding."[17] The 2021 American guidelines for coronary revascularization indicate that "in patients with ACS undergoing PCI, a loading dose of P2Y$_{12}$ inhibitor, followed by daily dosing, is recommended to reduce ischemic events" (Class I).[15] This recommendation implies that patients with NSTE-ACS, who were previously recommended pretreatment with ticagrelor or clopidogrel, are no longer recommended to receive a P2Y$_{12}$ inhibitor until a decision for PCI is taken.

AREAS OF UNCERTAINTY. In the ACCOAST trial, the neutral effect and harm of pretreatment were consistent irrespective of the interval between prasugrel administration and invasive coronary angiography, but there were relatively few patients with an interval longer than 24 hours.[32] Therefore, the impact of pretreatment for patients with time to coronary angiography longer than 24 hours, which is still frequently observed in the real world,[33] remains uncertain. Also, whether the negative results of prasugrel in the ACCOAST trial also apply to ticagrelor is unknown. In the PLATO trial, ticagrelor was allowed before invasive coronary angiography in both patients with and without ST-segment elevation: because no significant treatment interaction was observed between patients with and without invasive management,[34] some guidelines task forces have interpreted this finding as supportive of pretreatment with ticagrelor in NSTE-ACS[22]; however, only a dedicated trial of ticagrelor pretreatment would conclusively support this strategy. Similarly, there are no trials of pretreatment with prasugrel in STE-ACS, and even ATLANTIC cannot be considered definitive for ticagrelor because the trial was not powered for clinical endpoints.

Although prasugrel and ticagrelor feature pharmacologic characteristics that may have theoretical advantages over clopidogrel for pretreatment

TABLE 2 Key Randomized Trials of Pretreatment in Patients With ACS

	ACCOAST	ATLANTIC	DUBIUS
Year	2013	2014	2020
Sample size	4,033	1,862	1,449
Blinded	Yes	Yes	No
Population	NSTEMI (PCI 69%)	STEMI (PCI 88%)	ACS (NSTEMI 79%, UA 21%; PCI 72%)
Time from LD to randomization	Not reported	Not reported	Not reported
Time from LD to ICA/PCI	4.3 h	0.8 h	23.3 h
Intervention	Prasugrel 30 mg LD before ICA, followed by 30 mg at the time of PCI	Ticagrelor 180 mg LD in ambulance	Ticagrelor before ICA
Control	Prasugrel 60 mg LD given at the time of PCI	Ticagrelor 180 mg LD in the catheterization laboratory	Ticagrelor or prasugrel after ICA and before PCI
Primary endpoint(s)	MACE	Absence of ST-segment resolution, absence of TIMI flow grade 3	NACE
Follow-up	7 d	After ICA and before PCI	30 d
Result	HR: 1.02; 95% CI: 0.84 to 1.25; $P = 0.81$	OR for absence of ST-segment resolution: 0.93; 95% CI: 0.69 to 1.25; $P = 0.63$; OR for absence of TIMI flow grade 3: 0.97; 95% CI: 0.75 to 1.25; $P = 0.82$	ARD: −0.46%; 95% CI: −2.90 to 1.90

ACCOAST = Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction; ARD = absolute risk difference; ATLANTIC = Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery; DUBIUS = Downstream Versus Upstream Strategy for the Administration of $P2Y_{12}$ Receptor Blockers In Non-ST Elevated Acute Coronary Syndromes With Initial Invasive Indication: ICA = invasive coronary angiography; MACE = major adverse cardiac events; NACE = net adverse cardiac events; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction; UA = unstable angina; other abbreviations as in Table 1.

(Table 1),[35] their onset of action is delayed in ACS,[36] due to slower absorption and to the potential use of morphine.[37] With the rapid door-to-balloon times desired in STE-ACS, any oral $P2Y_{12}$ inhibitor administered at time of clinical presentation is unlikely to exert meaningful antithrombotic effects (eg, impact on Thrombolysis In Myocardial Infarction flow grade 3 or ST-segment resolution). Administering higher loading doses does not circumvent this limitation,[38,39] while some more platelet inhibition is noted with crushed tablets[40-42] or orodispersible compounds.[43] Vicagrel has a more efficient metabolic conversion than clopidogrel but has currently limited data and no indication for use in clinical practice.[8] Cangrelor is given intravenously and is active within minutes, thereby representing a quick option to achieve prompt and potent $P2Y_{12}$ inhibitory effects in patients who are not pretreated.[44] Indeed, the availability of cangrelor has made pretreatment with oral drugs less relevant if their purpose is to inhibit platelets at the time of PCI. However, cangrelor has never been compared with prasugrel or ticagrelor on a clinical scale and has not been tested before arrival in the catheterization laboratory (eg, in ambulance or in the emergency department). A trial of pretreatment with cangrelor would be of interest because the drug has pharmacologic properties that may provide a better safety profile compared with other intravenous antiplatelet agents, such as glycoprotein IIb/IIIa inhibitors, which have failed to show benefit when administered upstream.

Finally, the impact of $P2Y_{12}$ inhibition earlier than the first medical contact is unknown. Selatogrel is given subcutaneously and therefore might be interesting for the purpose of pretreatment,[9] as patients can theoretically self-administer it earlier in time, before or at the time of seeking medical attention. The SOS-AMI trial (NCT04957719) is an ongoing investigation of selatogrel vs placebo for subjects discharged with a confirmed diagnosis of acute myocardial infarction. The trial plans to enroll ~14,000 patients with a primary endpoint of MACE at 7 days. Inherent challenges of this trial include its probabilistic approach, with treatment administered before the diagnosis, and the active role of patients as decision makers for timely self-injections.

SUMMARY. Based on the available evidence and clinical guidelines, pretreatment with oral $P2Y_{12}$ inhibitors is not indicated in patients with NSTE-ACS, with the possible exception of those with a long delay to coronary angiography. The evidence supporting routine pretreatment in patients with STE-ACS is scarce.

TABLE 3 Key Randomized Trials Comparing P2Y$_{12}$ Inhibitors in Patients With ACS

	TRITON	PLATO	PRASFIT-ACS	PHILO	PRAGUE-18
Year	2007	2009	2014	2015	2016
Sample size	13,608	18,624	1,363	801	1,230
Blinded	Yes	Yes	No	Yes	No
Population	ACS-PCI (STE-ACS 26%)	ACS (STE-ACS, PCI 84%)	ACS-PCI (STE-ACS 50%)	ACS (STE-ACS 52%, PCI 85%)	ACS (STE-ACS, PCI 99%)
Intervention	Prasugrel 10 mg once daily	Ticagrelor 90 mg twice daily	Prasugrel 3.75 mg once daily	Ticagrelor 90 mg twice daily	Prasugrel 5-10 mg once daily
Control	Clopidogrel 75 mg/d	Clopidogrel 75 mg/d	Clopidogrel 75 mg/d	Clopidogrel 75 mg/d	Ticagrelor 90 mg twice daily
Follow-up	Median 14.5 mo	Median 9 mo	6 mo	12 mo	7 d
Primary endpoint(s)	MACE	MACE	MACE	PLATO major bleeding, MACE	NACE
Result	HR: 0.81; 95% CI: 0.73 to 0.90; $P < 0.001$	HR: 0.84; 95% CI: 0.77 to 0.92; $P < 0.001$	HR: 0.77; 95% CI: 0.56 to 1.07	HR: 1.54; 95% CI: 0.94 to 2.53 (bleeding); HR: 1.47; 95% CI: 0.88 to 2.44 (MACE)	OR: 0.98; 95% CI: 0.55 to 1.73; $P = 0.94$
Primary bleeding outcome	TIMI major bleeding	PLATO major bleeding	Any TIMI bleeding	Same as first co-primary endpoint	Trial-defined bleeding
Result	HR: 1.32; 95% CI: 1.03 to 1.68	HR: 1.04; 95% CI: 0.95 to 1.13	HR: 1.48; 95% CI: 1.25 to 1.74	See first co-primary endpoint	OR: 1.07; 95% CI: 0.39 to 2.96

TABLE 3 Continued

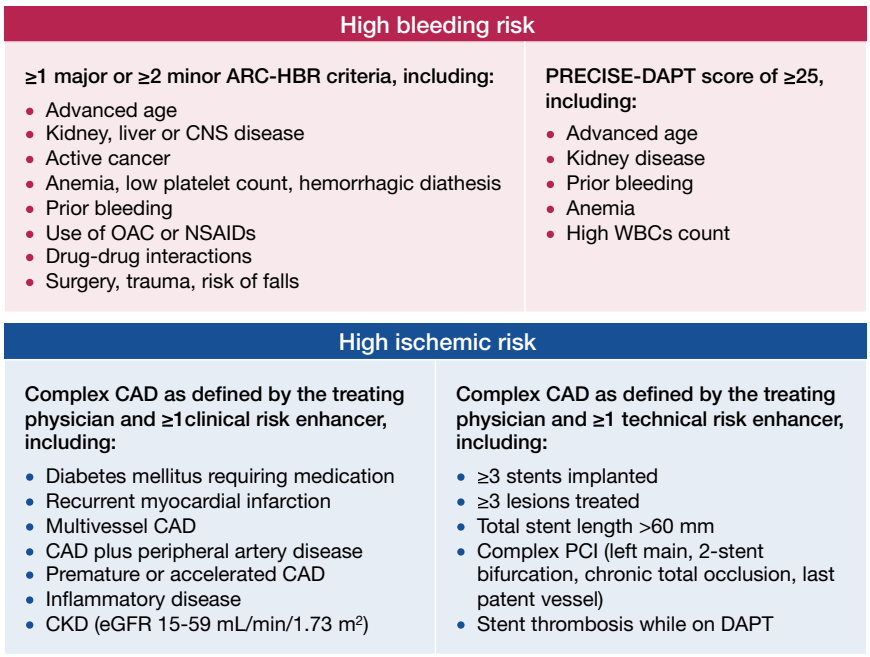
	Elderly ACS 2	TIKAKOREA	ISAR-REACT 5	POPular Age
Year	2018	2019	2019	2020
Sample size	1,443	800	4,018	1,002
Blinded	No	No	No	No
Population	ACS-PCI (STE-ACS 42%)	ACS (STE-ACS, PCI 84%)	ACS (STE-ACS 41%, PCI 84%)	UA/NSTEMI (PCI 46%)
Intervention	Prasugrel 5 mg once daily	Ticagrelor 90 mg twice daily	Ticagrelor 90 mg twice daily	Clopidogrel 75 mg/d
Control	Clopidogrel 75 mg/d	Clopidogrel 75 mg/d	Prasugrel 5-10 mg once daily	Ticagrelor 90 mg twice daily or prasugrel 5-10 mg once daily
Follow-up	Median 12 mo	12 mo	12 mo	12 mo
Primary endpoint(s)	MACE	PLATO major or minor bleeding	MACE	PLATO major or minor bleeding, NACE
Result	HR: 1.01; 95% CI: 0.78 to 1.30; $P = 0.96$	HR: 2.26; 95% CI: 1.34 to 3.79; $P = 0.002$	HR: 1.36; 95% CI: 1.09 to 1.70; $P = 0.006$	HR: 0.71; 95% CI: 0.54 to 0.94; $P = 0.02$ (bleeding); ARD: -4%, 95% CI: -10% to 1.4%; $P = 0.03$ for noninferiority (NACE)
Primary bleeding outcome	BARC ≥2 bleeding	Same as primary endpoint	BARC ≥3 bleeding	Same as first co-primary endpoint
Result	OR: 1.52; 95% CI: 0.85 to 3.16	See primary endpoint	HR: 1.12; 95% CI: 0.83 to 1.51	See first co-primary endpoint

BARC = Bleeding Academic Research Consortium; Elderly ACS 2 = A Comparison of Reduced-dose Prasugrel and Clopidogrel in Elderly Patients With Acute Coronary Syndrome Undergoing Early Percutaneous Coronary Intervention 2; ISAR-REACT 5 = Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5; PHILO = Study to Assess Safety and Efficacy of Ticagrelor Versus Clopidogrel in Asian/Japanese Patients With Non-ST or ST Elevation ACS; PLATO = Platelet Inhibition and Patient Outcomes; POPular Age = Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome; PRAGUE-18 = Comparison of prasugrel and ticagrelor in the treatment of acute myocardial infarction; PRASFIT-ACS = Prasugrel compared with clopidogrel for Japanese patients with ACS undergoing PCI; STE-ACS = ST-segment elevation acute coronary syndrome; TIKAKOREA = Ticagrelor Versus Clopidogrel in Asian/Korean Patients with ACS Intended for Invasive Management; TRITON = Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel; other abbreviations as in Tables 1 and 2.

CHOICE OF ORAL P2Y$_{12}$ INHIBITORS

COMPARATIVE EFFICACY AND SAFETY OF ORAL P2Y$_{12}$ INHIBITORS. The risk of recurrent ischemic and bleeding events after PCI for ACS decreases over time but not uniformly. In STE-ACS, for example, the daily risk of bleeding exceeds the risk of ischemia within 30 days, and the daily risk of ischemia significantly exceeds the daily risk of bleeding beyond 30 days.[45] This observation generally supports the use of intensified platelet inhibition with prasugrel or ticagrelor during the first year after an ACS. However, early bleeding is strongly associated with mortality,[46] which raises a note of caution over the unselected use

FIGURE 2 Characteristics of High Bleeding and Ischemic Risk in Patients With ACS



Criteria of high bleeding and ischemic risk are displayed. Criteria of high ischemic risk are reported as defined by the European Society of Cardiology.[12] ARC-HBR = Academic Research Consortium for High Bleeding Risk; CKD = chronic kidney disease; CNS = central nervous system; DAPT = dual antiplatelet therapy; eGFR = estimated glomerular filtration rate; NSAID = nonsteroidal anti-inflammatory drug; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; PRECISE-DAPT = Predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy; WBC = white blood cell; other abbreviations as in Figure 1.

of potent $P2Y_{12}$ inhibitors in patients at high risk of bleeding (eg, elderly, concomitant use of oral anticoagulation, presence of chronic kidney disease).[47,48]

Table 3 summarizes the characteristics and results of 9 randomized trials comparing oral $P2Y_{12}$ inhibitors in ACS. More than a decade ago, prasugrel and ticagrelor were compared with clopidogrel in the landmark TRITON and PLATO trials: 1) in the TRITON trial, prasugrel reduced the risk of MACE by 19% in patients undergoing PCI; and 2) in the PLATO trial, which included ACS patients invasively and noninvasively managed, ticagrelor decreased the risk of MACE by 16%.[5,6] On the downside, both prasugrel and ticagrelor increased the risk of bleeding not related to coronary artery bypass grafting compared with clopidogrel. A reduced dose of prasugrel showed similar bleeding rates than clopidogrel in Japanese patients in the PRASFIT-ACS (Prasugrel compared with clopidogrel for Japanese patients with ACS undergoing PCI) trial[49] and Italian patients in the ELDERLY ACS 2 (A Comparison of Reduced-dose Prasugrel and Clopidogrel in Elderly Patients With Acute Coronary Syndrome Undergoing Early Percutaneous Coronary Intervention 2) trial[50]; however, both studies were much smaller than the TRITON trial. Conversely, an increased risk of bleeding with ticagrelor was consistently observed in East Asian patients from the small PHILO (Study to Assess Safety and Efficacy of Ticagrelor Versus Clopidogrel in Asian/Japanese Patients With Non-ST or ST Elevation ACS) and TIKA-KOREA (Ticagrelor Versus Clopidogrel in Asian/Korean Patients with ACS Intended for Invasive Management) trials.[51,52] The POPular Age (Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome) trial, which included elderly patients with or without PCI, found a 29% relative risk reduction in bleeding with clopidogrel compared with ticagrelor or prasugrel, and noninferiority was established for NACE at 12 months.[53] PRAGUE-18 (Comparison of prasugrel and ticagrelor in the treatment of acute myocardial infarction), the first randomized head-to-head comparison of prasugrel and ticagrelor in STE-ACS, was stopped for futility at a time when none of the drugs showed to be more effective or safer than the other.[54] Ticagrelor and prasugrel were also

TABLE 4 Key Randomized Trials of De-Escalation or Down-Adjustment in Patients With ACS

	ANTARCTIC	TOPIC	TROPICAL ACS	POPular Genetics	HOST-REDUCE	TALOS-AMI
Year	2016	2017	2017	2019	2020	2021
Sample size	877	646	2,610	2,488	2,338	2,697
Blinded	No	No	No	No	No	No
Population	ACS-PCI (elderly only)	ACS-PCI, event-free on standard DAPT for 1 mo	ACS-PCI	ACS-PCI (STEMI only)	ACS-PCI	ACS-PCI, event-free on standard DAPT for 1 mo
Intervention	De-escalation and/or up- or down-adjustment (guided by PFT)	De-escalation (unguided)	De-escalation (guided by PFT)	De-escalation (guided by genotyping)	Down-adjustment (unguided)	De-escalation (unguided)
Control	DAPT with halved prasugrel	Standard DAPT	Standard DAPT	Standard DAPT	Standard DAPT	Standard DAPT
Follow-up	12 mo	11 mo	12 mo	12 mo	12 mo	11 mo
Primary endpoint(s)	NACE	NACE	NACE	NACE, PLATO major or minor bleeding	NACE	NACE
Result	HR: 1.00; 95% CI: 0.78 to 1.29; $P = 0.98$	HR: 0.48; 95% CI: 0.34 to 0.68; $P < 0.01$	HR: 0.81; 95% CI: 0.62 to 1.06; $P = 0.0004$ for noninferiority; $P = 0.12$ for superiority	ARD: -0.7%; 95% CI: −2.0 to 0.7; $P < 0.001$ for noninferiority (NACE); HR: 0.78; 95% CI: 0.61 to 0.98; $P = 0.04$ (bleeding)	HR: 0.70; 95% CI: 0.52 to 0.92; $P < 0.0001$ for noninferiority; $P = 0.012$ for equivalence	HR: 0.55; 95% CI: 0.40 to 0.76; P <0.001 for noninferiority; $P = 0.0001$ for superiority
Primary bleeding outcome	BARC ≥2 bleeding	BARC ≥2 bleeding	BARC ≥2 bleeding	Same as second co-primary endpoint	BARC ≥2 bleeding	BARC ≥2 bleeding
Result	HR: 1.04; 95% CI: 0.78 to 1.40	HR: 0.30; 95% CI: 0.18 to 0.50	HR: 0.82; 95% CI: 0.59 to 1.13	See second co-primary endpoint	HR: 0.48; 95% CI: 0.32 to 0.73	HR: 0.52; 95% CI: 0.35 to 0.77

ANTARCTIC = Tailored Antiplatelet Therapy Versus Recommended Dose of Prasugrel; DAPT = dual antiplatelet therapy; HOST-REDUCE = Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases Trial - Comparison of REDUCTION of PrasugrEl Dose in ACS Patients; PFT = platelet function testing; POPular Genetics = CYP2C19 Genotype-Guided Antiplatelet Therapy in ST-Segment Elevation Myocardial Infarction Patients — Patient Outcome after Primary PCI; TALOS-AMI = TicAgrelor Versus CLOpidogrel in Stabilized Patients With Acute Myocardial Infarction; TOPIC = Timing of platelet inhibition after acute coronary syndrome; TROPICAL ACS = Testing Responsiveness To Platelet Inhibition On Chronic Antiplatelet Treatment For Acute Coronary Syndromes; other abbreviations as in Tables 1 to 3.

compared head to head in the previously mentioned ISAR-REACT 5 trial, in which ticagrelor was associated with a 36% increased risk in MACE with no difference in bleeding.[23]

In an updated network meta-analysis of 52,816 ACS patients from 12 randomized trials, ticagrelor was found to significantly reduce the risk of death compared with clopidogrel, while the risk reduction with prasugrel was not statistically significant.[55] Both ticagrelor and prasugrel reduced the risk of stent thrombosis and increased the risk of bleeding, and prasugrel reduced the risk of myocardial infarction. There were no significant differences in mortality and other clinical outcomes, including bleeding, between ticagrelor and prasugrel.

Additional large-scale real-world evidence on the subject came from a retrospective cohort study using propensity score to match 31,290 pairs of patients with ACS and PCI who received ticagrelor or clopidogrel in the United States and South Korea; the study did not find a significant difference in NACE between the 2 drugs, while the risk of bleeding was significantly higher with ticagrelor.[56]

GUIDELINE RECOMMENDATIONS. The 2020 European guidelines for NSTE-ACS indicate prasugrel for "$P2Y_{12}$ receptor inhibitor-naïve patients proceeding to PCI," ticagrelor "irrespective of the planned treatment strategy (invasive or conservative)," and clopidogrel "only when prasugrel or ticagrelor are not available, cannot be tolerated, or are contraindicated" with a Class I recommendation.[12] For patients undergoing PCI, prasugrel "should be considered in preference to ticagrelor" (Class IIa) and cangrelor "may be considered in $P2Y_{12}$ receptor inhibitor-naïve patients" (Class IIb). The European guidelines for STE-ACS share the same recommendations but do not indicate a preference for prasugrel, likely because they were published before the results of the ISAR-REACT 5 trial became available.[17] The 2021 American guidelines for coronary revascularization also do not mention the results of the ISAR-REACT 5 trial and indicate that "in patients with ACS undergoing PCI, it is reasonable to use ticagrelor or prasugrel in preference to clopidogrel" (Class IIa), without establishing a preference for one or the other.[15]

AREAS OF UNCERTAINTY. Despite that the PLATO trial enrolled more than 18,000 to demonstrate the benefit of ticagrelor over clopidogrel, smaller randomized studies have recently casted concerns over its preferential use, for example, in older and East

TABLE 5 Key Contemporary Randomized Trials of Short $P2Y_{12}$ Inhibition in Patients With ACS

	DAPT-STEMI	SMART-DATE	REDUCE-ACS	TICO	STOPDAPT-2 ACS
Year	2018	2018	2019	2020	2022
Sample size	1,100	2,712	1,496	3,056	4,169
Blinded	No	No	No	No	No
Population	ACS (STE-ACS 100%) on DAPT and event-free at 6 mo	ACS (STE-ACS 38%)	ACS (STE-ACS 47%)	ACS (STE-ACS 36%)	ACS (STE-ACS 56%)
Intervention	Aspirin only	6-mo DAPT followed by aspirin monotherapy	3-mo DAPT followed by aspirin monotherapy	3-mo DAPT followed by ticagrelor monotherapy	1- to 2-mo DAPT followed by clopidogrel monotherapy
Control	6-mo DAPT	12-mo DAPT	12-mo DAPT	12-mo DAPT	12-mo DAPT
Follow-up	18 mo	18 mo	12 mo	12 mo	12 mo
Primary endpoint(s)	NACE	MACE	NACE	NACE	NACE
Result	HR: 0.73, 95% CI: 0.41-1.27; $P = 0.004$ for noninferiority; $P = 0.26$ for superiority	ARD: 0.5%; upper limit of 1-sided 95% CI: 1.8%; $P = 0.03$ for noninferiority	ARD: -0.2%; upper limit of 1-sided 95% CI: 2.7%; $P < 0.001$ for noninferiority	HR: 0.66, 95% CI: 0.48-0.92; $P = 0.01$	ARD: 0.37%; upper limit of 1-sided 95% CI: 1.42%; $P = 0.06$ for noninferiority
Primary bleeding outcome	TIMI major bleeding	BARC ≥2 bleeding	BARC ≥2 bleeding	TIMI major bleeding	TIMI major or minor bleeding
Result	HR: 0.51; 95% CI: 0.05-5.57	HR: 0.69; 95% CI: 0.45-1.05	HR: 0.82; 95% CI: 0.48-1.41	HR: 0.56; 95% CI: 0.34-0.91	HR: 0.46; 95% CI: 0.23-0.94

DAPT-STEMI = Randomized, Open Label Trial of 6 Months Versus 12 Months DAPT After Drug-Eluting Stent in STEMI; REDUCE-ACS = Short-term Dual Anti Platelet Therapy in Patients With ACS Treated With the COMBO Dual-therapy Stent; SMART-DATE = Safety of 6-month Duration of Dual Antiplatelet Therapy After Acute Coronary Syndromes; STOPDAPT-2 ACS = ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study for the Patients With ACS; TICO = Trial of Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome; other abbreviations as in Tables 1 to 3.

Asians patients with ACS. Still, these trials are largely unpowered to detect the treatment efficacy noted in the PLATO trial, and the increase of bleeding compared with clopidogrel is not surprising. The question of the comparative efficacy of prasugrel and ticagrelor is more relevant and intriguing. On this subject, concerns have been raised on the findings of the ISAR-REACT 5 trial due to its sample size, open-label design, and adherence to treatment in patients assigned to ticagrelor.[24] The SWITCH SWEDEHEART trial is an open label, stepped wedge cluster randomized clinical study in which administrative regions in Sweden will switch from ticagrelor to prasugrel every 9 months in a random order.[57] The investigators plan to enroll 16,000 participants and power the study for the composite of death, myocardial infarction, or stroke; the study completion is expected by the end of 2025.

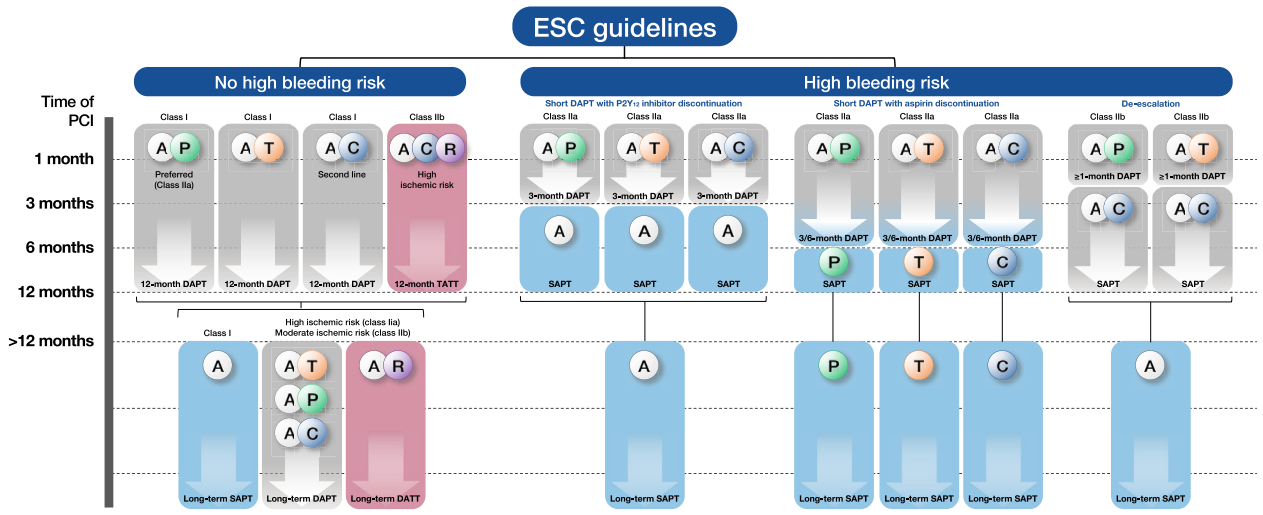
SUMMARY. Two large, randomized trials support prasugrel and ticagrelor as first-line options for patients with ACS, but clopidogrel remains a plausible choice for patients at high risk of bleeding. The comparative safety and efficacy of prasugrel and ticagrelor is a topic of ongoing research.

MODULATION OF ORAL $P2Y_{12}$ INHIBITION

EFFICACY AND SAFETY OF DE-ESCALATION AND DOWN-ADJUSTMENT OF $P2Y_{12}$ INHIBITORS. The switch from the more potent prasugrel or ticagrelor to clopidogrel, at some time from PCI and after an initial period with another $P2Y_{12}$ inhibitor, is known as "de-escalation."[59] The goal of de-escalation is to reduce the risk of bleeding at a time from the index event when the daily ischemic risk attenuates and clopidogrel may suffice for thrombotic or ischemic protection. Details on the rationale and mode of switching $P2Y_{12}$ inhibitors (eg, with or without a loading dose) is elaborated in an international expert consensus document.[58] Of note, a strategy based on a $P2Y_{12}$ inhibitor implies not only selecting the drug, but also defining its dose. Down-adjustment (ie, reducing the dose of prasugrel or ticagrelor) has also been proposed to decrease the risk of bleeding over time. De-escalation and down-adjustment can be offered unselectively (ie, to all patients) or selectively to patients who have adequate clopidogrel-induced platelet inhibition. Clopidogrel in fact is characterized by variability in interindividual response with up to 30% of subjects who persist with high on-treatment platelet reactivity (HPR), a marker of thrombotic risk. Hence, a guided approach is based on excluding clopidogrel-treated patients with HPR by means of platelet function testing, or those at risk of having HPR by means of genetic testing.[59]

Table 4 summarizes the characteristics and results of 6 randomized trials of de-escalation or down-adjustment of $P2Y_{12}$ inhibition after an initial period of DAPT with prasugrel or ticagrelor. The ANTARCTIC (Tailored Antiplatelet Therapy Versus Recommended

FIGURE 3 European Guidelines on Choices and Duration of Antithrombotic Therapy After PCI in Patients With ACS



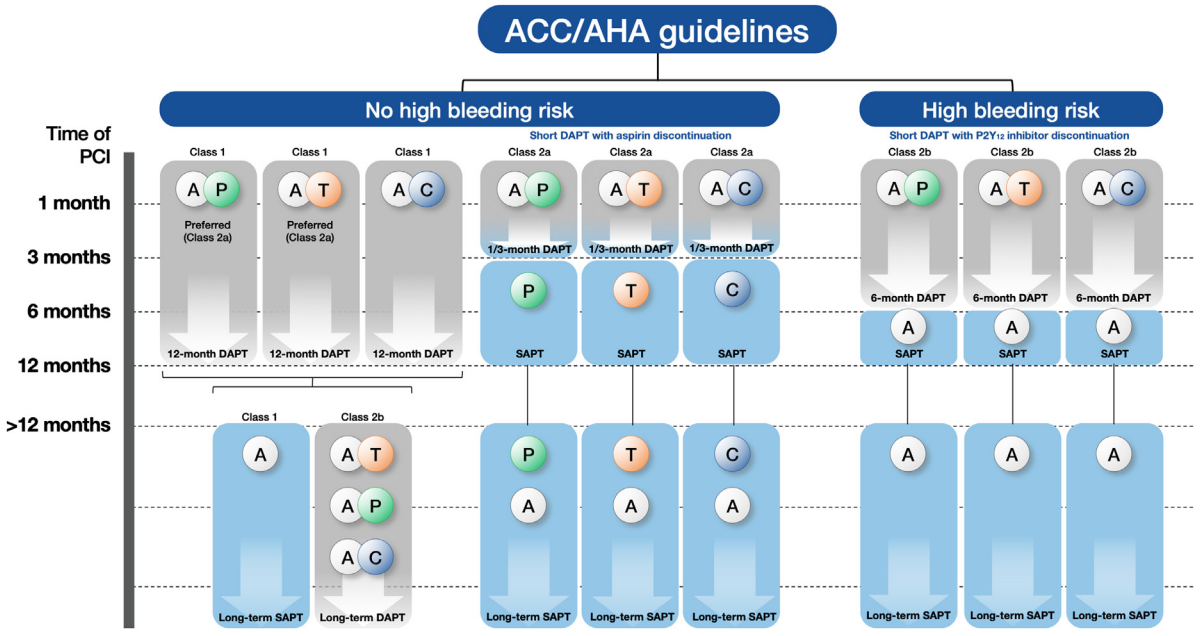
The figure reflects current recommendations for patients with acute coronary syndromes from the European Society of Cardiology.[12] A = aspirin; C = clopidogrel; DATT = dual antithrombotic therapy; ESC = European Society of Cardiology; P = prasugrel; R = rivaroxaban; SAPT = single antiplatelet therapy; TATT = triple antithrombotic therapy; T = ticagrelor; other abbreviations as in Figures 1 and 2.

Dose of Prasugrel) trial, which included elderly patients on a 5-mg dose of prasugrel, did not demonstrate a net benefit of DAPT modulation (mostly de-escalation) based on the results of platelet function testing.[60] In contrast, the other 5 trials were positive: 1) the TOPIC (Timing of platelet inhibition after acute coronary syndrome) trial concluded for a reduction in NACE driven by less bleeding with unguided switch to clopidogrel[61]; 2) in TROPICAL-ACS (Testing Responsiveness To Platelet Inhibition On Chronic Antiplatelet Treatment For Acute Coronary Syndromes), de-escalation from prasugrel to clopidogrel was tested in patients who did not have clopidogrel HPR using platelet function testing and was found noninferior to standard DAPT with prasugrel[62]; 3) POPular Genetics (CYP2C19 Genotype-Guided Antiplatelet Therapy in ST-Segment Elevation Myocardial Infarction Patients-Patient Outcome after Primary PCI) included only patients with STE-ACS and found noninferiority for NACE and superiority for bleeding when patients received clopidogrel or a more potent $P2Y_{12}$ inhibitor based on the rapid results of genotype testing for CYP2C19 loss-of-function alleles indicating an increased risk of clopidogrel HPR[63]; 4) the HOST-REDUCE (Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases Trial-Comparison of REDUCTION of PrasugrEl Dose in ACS Patients) trial demonstrated the equivalence of unguided down-adjustment to a halved dose of prasugrel, driven by a reduction in bleeding[64]; and finally, 5) the TALOS-AMI (TicAgrelor Versus CLOpidogrel in Stabilized Patients With Acute Myocardial Infarction) trial showed a significant reduction in NACE with unguided de-escalation to clopidogrel.[65]

Several meta-analyses of de-escalation have been conducted, with mixed conclusions. A study of 55,798 patients from 15 randomized trials of ACS patients concluded that compared with other established uses of DAPT, de-escalation (unguided or guided) is the strategy with the largest net benefit.[66] In another meta-analysis of 61,898 ACS patients from 5 trials, the approach based on guided selection of the $P2Y_{12}$ inhibitor was associated with the best trade-off between efficacy and safety compared with routine selection of prasugrel or ticagrelor.[67] While this study advocated for a broader use of platelet function or genotype testing in ACS, another recent meta-analysis of 69,746 patients from 19 trials compared the guided selection of DAPT vs an approach of uniform and unguided de-escalation and concluded that the second is preferable due to larger reduction in bleeding with no increase in ischemic events.[68]

GUIDELINE RECOMMENDATIONS. The 2020 European guidelines for NSTE-ACS issued for the first time a Class IIb recommendation (ie, selective use) for "de-escalation of $P2Y_{12}$ receptor inhibitor treatment (eg, with a switch from prasugrel or ticagrelor to clopidogrel) as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition." Based on these guidelines, "de-

FIGURE 4 American Guidelines on Choices and Duration of Antithrombotic Therapy After PCI in Patients With ACS



The figure reflects current recommendations for patients with coronary revascularization from the American College of Cardiology and the American Heart Association.[15] ACC = American College of Cardiology; AHA = American Heart Association; other abbreviations as in Figures 1 to 3.

escalation may be done unguided based on clinical judgment or guided by platelet function testing or CYP2C19 genotyping, depending on patient's risk profile and availability of respective assays." The 2021 American guidelines for coronary revascularization did not include a recommendation supporting the de-escalation approach.[15]

AREAS OF UNCERTAINTY. There are many unsolved questions surrounding the emerging concepts of de-escalation or down-adjustment of DAPT. First, there at least 4 ways to achieve de-escalation or down-adjustment: unguided uniform de-escalation, unguided selective de-escalation (ie, de-escalation in selected patients deemed at high bleeding risk or with active bleeding), de-escalation guided by platelet function testing, and de-escalation guided by genotyping. The comparative effectiveness and safety of these strategies can be addressed only by head-to-head comparisons in adequately powered randomized trials. Notably, the practicality of guided selection of DAPT is hampered by the ability to perform platelet function testing and genotyping, although rapid assays have become available. Second, there are legitimate questions regarding the comparative value of de-escalation or down-adjustment. Third, whether down-adjustment should imply the use of a halved dose (eg, from prasugrel 10 mg to prasugrel 5 mg) or a reduced dose (eg, from ticagrelor 90 mg to ticagrelor 60 mg) is also uncertain. Fourth, the optimal timing for de-escalation is unknown; for example, some trials of unguided modulation (eg, TOPIC, TALOS-AMI, HOST-REDUCE) switched or down-adjusted the participants at 1 month, while others did so at 2 weeks (eg, TROPICAL ACS) or even at a median of 1 day from the index event (eg, POPular Genetics). While these questions emerge, at least 4 more trials of DAPT modulation are ongoing in ACS: 1) EASTYLE (Ticagrelor De-escalation Strategy in East Asian Patients With AMI; NCT04755387) will test a strategy of unguided dose reduction from ticagrelor 90 mg to ticagrelor 60 mg or 45 mg after discharge; 2) ELECTRA-SIRIO (Evaluation of Safety and Efficacy of Two Ticagrelor-based De-escalation Antiplatelet Strategies in Acute Coronary Syndrome; NCT04718025) will test a strategy of unguided dose reduction from ticagrelor 90 mg to 60 mg at 1 month; 3) MATE (Sequential MonotherApy of TicagrElor and Clopidogrel After Coronary Intervention; NCT04937699) will test the unguided switch from DAPT with ticagrelor and aspirin at 1 month after PCI to ticagrelor monotherapy for 5 months followed by clopidogrel for 6 months; and 4) Dan-DAPT (Reduced Antithrombotic Strategy for High Bleeding Risk

TABLE 6 Ongoing Randomized Trials of P2Y$_{12}$ Inhibitor Monotherapy After PCI in Patients With ACS

Trial	Sample Size	Population	Intervention	Control	Primary Outcomes
BULK-STEMI (NCT04570345)	1,002	Patients with ACS undergoing PCI, receiving DAPT with ticagrelor plus aspirin for 3 mo	Ticagrelor (SAPT)	Ticagrelor plus aspirin (DAPT)	NACE, MACE, and BARC type 3 or 5 bleeding at 12 mo after PCI
COMPARE STEMI ONE (NCT05491200)	1,608	Patients with STE-ACS receiving DAPT with prasugrel plus aspirin for 30-45 d	Prasugrel (SAPT)	Prasugrel plus aspirin (DAPT)	NACE at 12 mo after PCI
TARGET FIRST (NCT04753749)	2,246	Patients with ACS undergoing PCI, receiving DAPT with clopidogrel, prasugrel, or ticagrelor plus aspirin for 1 mo after PCI	Clopidogrel, prasugrel, or ticagrelor (SAPT)	Clopidogrel, prasugrel, or ticagrelor plus aspirin (DAPT)	NACE and BARC type ≥2 bleeding between 1 and 12 mo after PCI
T-PASS (NCT03797651)	2,850	Patients with ACS undergoing PCI, on DAPT for <1 mo after PCI	Ticagrelor monotherapy (SAPT)	Ticagrelor plus aspirin (DAPT)	NACE at 12 mo after PCI
MATE (NCT04937699)	2,856	Patients with ACS undergoing PCI, receiving DAPT with ticagrelor plus aspirin for 1 mo after PCI	Low-dose ticagrelor followed by clopidogrel (SAPT)	Ticagrelor plus aspirin (DAPT)	NACE at 12 mo after PCI
STOPDAPT-3 (NCT04609111)	3,110	Patients undergoing PCI with ACS or at high risk of bleeding, receiving DAPT with prasugrel plus aspirin for 1 mo	Prasugrel (SAPT)	Prasugrel plus aspirin (DAPT)	BARC type 3 or 5 bleeding at 1 mo after PCI, and MACE at 12 mo after PCI
NEO-MINDSET (NCT04360720)	3,400	Patients with ACS undergoing PCI	Ticagrelor or prasugrel (SAPT)	Ticagrelor or prasugrel plus aspirin (DAPT)	MACE and BARC type ≥2 bleeding at 12 mo after PCI
ULTIMATE-DAPT (NCT03971500)	3,486	Patients with ACS undergoing PCI who are free from MACCE or bleeding at 30 d after PCI, receiving DAPT with ticagrelor plus aspirin	Ticagrelor plus matching placebo (SAPT)	Ticagrelor plus aspirin (DAPT)	MACE and BARC type ≥2 bleeding between 1 and 12 mo after PCI

BULK-STEMI = 3 Months Versus 12 Months Dual Antiplatelet Therapy After Drug-eluting Stent Implantation in STEMI; COMPARE STEMI ONE = Comparison Of Reduced DAPT Followed by P2Y$_{12}$ Inhibitor Monotherapy With Prasugrel vs stAndard Regimen in STEMI Patients; ISTH = International Society of Thrombosis and Haemostasis; MACCE, major adverse cardiac or cerebrovascular events; MATE = Sequential MonotherApy of TicagrElor and Clopidogrel After Coronary Intervention; NEO-MINDSET = PercutaNEOus Coronary Intervention Followed by Monotherapy INstead of Dual Antiplatelet Therapy in the SETting of Acute Coronary Syndromes; OAC = oral anticoagulation; SAPT = single antiplatelet therapy; STOPDAPT-3 = ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-3 Study; T-PASS = Ticagrelor Monotherapy in PAtients Treated With New-generation Drug-eluting Stents for Acute Coronary Syndrome; TARGET FIRST = Evaluation of a Modified Anti-Platelet Therapy Associated With Low-dose DES Firehawk in Acute Myocardial Infarction Patients Treated With Complete Revascularization Strategy; ULTIMATE-DAPT = 1-month vs 12-month DAPT for ACS Patients Who Underwent PCI Stratified by IVUS; other abbreviations as in Tables 1 to 3.

Patients With Myocardial Infarction; NCT05262803) will investigate genotype-guided DAPT (ticagrelor or prasugrel in carriers of CYP2C19*2 or CYP2C19*3 loss-of-function alleles, clopidogrel in noncarriers) for 3 or 6 months, followed by aspirin monotherapy. The results of these trials are expected between 2024 and 2026.

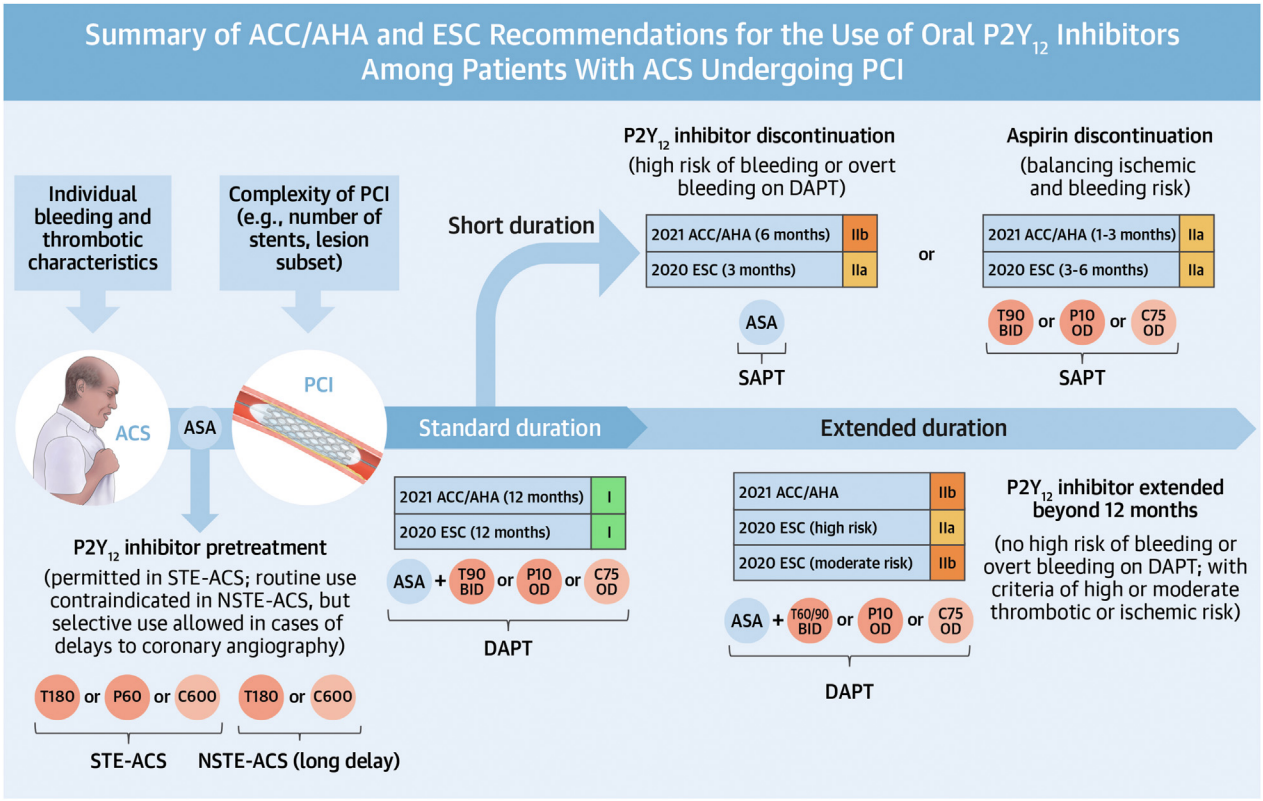
SUMMARY. The intensity of DAPT can be modulated by a switch from more potent P2Y$_{12}$ inhibitors to clopidogrel, or to their dose reduction. This strategy is selectively recommended only by the European guidelines, with an option for guidance by platelet function testing or genotyping.

DURATION OF ORAL P2Y$_{12}$ INHIBITION IN ACS

EFFICACY AND SAFETY OF DIFFERENT DURATIONS OF P2Y$_{12}$ INHIBITION. In ACS patients, the default duration of DAPT is 12 months, which can be shortened or extended according to the thrombotic/ischemic and bleeding risks of the individual patient. Several tools are available to identify patients at high bleeding risk who are potential candidate to short DAPT, such as those with a PRECISE-DAPT (Predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy) score ≥25, or those with fulfillment of criteria from the Academic Research Consortium for high bleeding risk.[47,69-72] Similarly, groups of patients at high risk of thrombotic or ischemic complications who may be good candidates to extended P2Y$_{12}$ inhibition have been proposed (Figure 2).

Short DAPT duration and P2Y$_{12}$ inhibitor monotherapy. For years, shortening the duration of DAPT has been achieved by discontinuation of the P2Y$_{12}$ inhibitor and continuation of aspirin monotherapy. However, there has now been a paradigm shift toward studies assessing discontinuation of aspirin after a brief period (eg, 1-3 months) of DAPT and continuation of P2Y$_{12}$ inhibitor monotherapy. The rationale and evidence for discontinuing aspirin rather than the P2Y$_{12}$ inhibitor is summarized in detail elsewhere.[73,74] Several studies of short DAPT have included patients with and without ACS, and subgroup analyses

CENTRAL ILLUSTRATION **Summary of Recommendations on Timing and Duration of Oral $P2Y_{12}$ Inhibition in ACS**



Capodanno D, et al. J Am Coll Cardiol Intv. 2023;16(1):1-18.

Management of antiplatelet therapy in patients with acute coronary syndromes based on current ACC/AHA and ESC guidelines. Antiplatelet de-escalation is an option only for the ESC guidelines and is therefore not depicted here. ACC = American College of Cardiology; ACS = acute coronary syndrome; AHA = American Heart Association; ASA = acetylsalicylic acid; BID = bis in die; DAPT = dual antiplatelet therapy; ESC = European Society of Cardiology; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; OD = once daily; PCI = percutaneous coronary intervention; SAPT = single antiplatelet therapy; STE-ACS = ST-segment elevation acute coronary syndrome.

of large trials of $P2Y_{12}$ inhibitor monotherapy have shown more pronounced treatment effects in patients with ACS.[75-78] For example, in the TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial, the relative benefit of $P2Y_{12}$ inhibitor monotherapy in reducing bleeding complications compared with standard DAPT was 53% in patients with NSTE-ACS and 24% in stable patients ($P = 0.03$ for interaction).[76] Some trials have included only patients with ACS and are therefore especially informative for the purpose of this review.

Table 5 summarizes the characteristics and results of 3 dedicated trials of short $P2Y_{12}$ inhibition and 2 trials of $P2Y_{12}$ inhibitor monotherapy in ACS. Among trials of $P2Y_{12}$ inhibitor discontinuation, DAPT-STEMI (Randomized, Open Label Trial of 6 Months Versus 12 Months DAPT After Drug-Eluting Stent in STEMI) compared aspirin vs 6-month of DAPT in patients with STE-ACS who were event-free at 6 months from primary PCI.[79] The risk of NACE did not differ between the 2 strategies and the noninferiority of $P2Y_{12}$ inhibitor discontinuation was demonstrated; however, the prespecified margin of noninferiority was large. The SMART-DATE (Safety of 6-month Duration of Dual Antiplatelet Therapy After Acute Coronary Syndromes) trial compared 6- and 12-month durations of DAPT[80]; although 6-month DAPT was noninferior for MACE, the risk of myocardial infarction was increased. The REDUCE-ACS (Short-term Dual Anti Platelet Therapy in Patients With ACS Treated With the COMBO Dual-therapy Stent) trial compared 3- and 12-month durations[81]; the shortest duration was noninferior for NACE, but the rate of stent thrombosis was doubled. Among trials of aspirin

discontinuation and P2Y$_{12}$ inhibitor monotherapy continuation, TICO (Trial of Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome) showed the superiority for NACE of ticagrelor monotherapy started at 3 months,[82] while STOPDAPT-2 ACS (ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study for the Patients With ACS) failed to show the noninferiority for NACE of clopidogrel monotherapy started at 1 or 2 months, due to a significant increase in myocardial infarction.[83]

An individual patient data pairwise and network meta-analysis of 11,473 patients from 6 trials of DAPT duration (41.5% with ACS) compared short-term (≤6-months) vs long-term (12-month) DAPT and 3-month vs 6-month vs 12-month DAPT.[84] In ACS patients from this meta-analysis, 3-month DAPT was associated with increased ischemic risk. In another network meta-analysis comparing standard DAPT with alternative strategies in 50,602 ACS patients, discontinuation of aspirin reduced the risk of major bleeding, while discontinuation of the P2Y$_{12}$ inhibitor did not.[85] Both strategies were not associated with increased thrombotic or ischemic complications. Compared with standard DAPT, short DAPT was the best strategy in reducing major bleeding, while de-escalation was the best strategy in reducing NACE.

Extended duration. Most data on DAPT extension in ACS can be inferred by large-scale trials. The DAPT trial compared aspirin vs 18-month DAPT with clopidogrel or prasugrel in patients who were event-free at 12 months from PCI, showing significant reductions in thrombotic and ischemic events with extended DAPT, in both patients with and without a prior myocardial infarction, which came at the price of increased bleeding.[86,87] The results were applicable to both patients with and without a prior myocardial infarction. The PEGASUS (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin) trial included patients with prior (ie, 1-3 years) myocardial infarction and enrichment factors (eg, age of 65 years or older, diabetes mellitus requiring medication, a second prior spontaneous myocardial infarction, multivessel coronary artery disease, or chronic renal dysfunction), and compared DAPT with 2 doses of ticagrelor (90 and 60 mg twice daily) vs aspirin.[88] The DAPT regimen reduced the primary efficacy endpoint (but increased the risk of bleeding), with an effect that was more pronounced in patients with shorter time since DAPT discontinuation. The 60-mg dose of ticagrelor was then approved by regulatory authorities for patients with prior myocardial infarction.

In a meta-analysis of 33,425 patients with prior myocardial infarction from Udell et al,[89] also including patients from the DAPT and PEGASUS trials, DAPT beyond 1 year was associated with less thrombotic or ischemic events compared with aspirin alone and significantly increased the risk of major bleeding.

GUIDELINE RECOMMENDATIONS. A summary of guidelines recommendations on the duration of antithrombotic therapy for ACS patients undergoing PCI is provided in **Figures 3 and 4**. The 2020 European guidelines for NSTE-ACS recommend as a Class I that "a P2Y$_{12}$ receptor inhibitor on top of aspirin is given for 12 months unless there are contraindications such as excessive risk of bleeding."[12] However, in patients with a high risk of bleeding, discontinuation of the P2Y$_{12}$ inhibitor should be considered after 3 months (Class IIa), or discontinuation of aspirin should be considered at 3 to 6 months (Class IIa). Adding a P2Y$_{12}$ receptor inhibitor to aspirin for extended long-term secondary prevention should be considered (Class IIa) in patients with a high risk of ischemic events (**Figure 2**) and may be considered (Class IIb) in those at moderate risk (those with noncomplex coronary artery disease but presenting with diabetes mellitus, history of recurrent myocardial infarction, polyvascular disease, and/or chronic kidney disease) if they have no increased risk of major or life-threatening bleeding. For these patients, dual-pathway inhibition with aspirin and a low-dose of the factor Xa inhibitor rivaroxaban is also an option, following the results of a large trial of patients with stable atherosclerosis.[90] Discussing the dual-pathway inhibition strategy goes beyond the scope of this review, but relevant information can be found elsewhere.[91] Similarly to the European guidelines, the 2021 American guidelines also indicate a standard 12-month duration of DAPT (Class I) and recommend the discontinuation of aspirin at 1 to 3 months in all patients (Class IIa) or the discontinuation of the P2Y$_{12}$ inhibitor at 6 months in selected patients with "high risk of bleeding or overt bleeding on DAPT" (Class IIb), and the continuation beyond 12 months in those without (Class IIb).[15]

AREAS OF UNCERTAINTY. The evidence supporting short DAPT in ACS is weak; 3 trials have met their noninferiority objective for durations shorter than 12 months but using large noninferiority margins and with some evidence of withdrawal of protection in the SMART-DATE, REDUCE-ACS, and STOPDAPT-2 ACS studies if aspirin or clopidogrel remain as single antiplatelet agents. Differently, a strategy of short

DAPT followed by potent $P2Y_{12}$ inhibitor monotherapy was effective in TICO. COMPARE STEMI ONE (Comparison Of Reduced DAPT Followed by $P2Y_{12}$ Inhibitor Monotherapy With Prasugrel vs stAndard Regimen in STEMI Patients; NCT05491200) and STOPDAPT-3 (ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-3 Study; NCT04609111), 2 trials of short DAPT with prasugrel followed by prasugrel monotherapy, are ongoing. Other ongoing trials of ticagrelor monotherapy after short DAPT with aspirin and ticagrelor are BULK-STEMI (3 Months Versus 12 Months Dual Antiplatelet Therapy After Drug-eluting Stent Implantation in STEMI; NCT04570345), T-PASS (Ticagrelor Monotherapy in PAtients Treated With New-generation Drug-eluting Stents for Acute Coronary Syndrome; NCT03797651), and ULTIMATE-DAPT (1-month vs 12-month DAPT for ACS Patients Who Underwent PCI Stratified by IVUS; NCT03971500). In the NEO-MINDSET (PercutaNEOus Coronary Intervention Followed by Monotherapy INstead of Dual Antiplatelet Therapy in the SETting of Acute Coronary Syndromes; NCT04360720), prasugrel or ticagrelor monotherapy will be started from the very beginning, with virtually no DAPT. The designs of these and other trials of $P2Y_{12}$ inhibitor monotherapy after PCI in patients with ACS are listed in **Table 6**.

After 12 months from an ACS, DAPT with ticagrelor was compared vs placebo in PEGASUS, but no comparisons exist vs DAPT with prasugrel or clopidogrel, or vs dual-pathway inhibition. Given the trade-off between benefits and risks with extended DAPT, the duration of DAPT should be individualized based on ischemic vs bleeding risks (**Central Illustration**). The DAPT score is a standardized tool to identify patients who derive benefit or lack of benefit from a prolonged course of DAPT. PARTHENOPE (Personalized Vs. Standard Duration of Dual Antiplatelet Therapy and New-generation Polymer-Free vs- Biodegradable-Polymer DES; NCT04135989) is an ongoing randomized trial testing whether personalized duration of DAPT based on the DAPT score provides net clinical benefit compared with standard DAPT.

SUMMARY. Twelve months of DAPT is the standard of care for patients with ACS, but physicians should be sensitive to identify those at high risk of bleeding and/or thrombotic complications who are candidate to shorter or extended periods of DAPT.

CONCLUSIONS

The rationale for pretreatment with $P2Y_{12}$ inhibitors in patients with ACS is weak in the era of quick access to early invasive coronary angiography. Current guidelines recommend against routine pretreatment in patients with NSTE-ACS, and allow pretreatment in those with STE-ACS. Pretreatment maintains a sound rationale for NSTE-ACS who are not planned to undergo an early invasive strategy and do not have a high risk of bleeding. Prasugrel and ticagrelor are first-line options for DAPT combinations with aspirin, but clopidogrel reduces the risk of bleeding, which may be a desirable option in selected patients at higher bleeding risk. The duration of $P2Y_{12}$ inhibition in patients who are on aspirin must be tailored to the individual risks of thrombotic/ischemic and bleeding complications. Strategies of $P2Y_{12}$ inhibitor monotherapy with no aspirin or de-escalation from a more potent to a less potent $P2Y_{12}$ inhibitor intensity are emerging and already represent guideline recommended treatment alternatives.

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APPENDIX For a supplemental video, please see the online version of this paper.

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