Journal of the Society for Cardiovascular Angiography & Interventions 2 (2023) 100607

JSCAI

The official journal of the Society for Cardiovascular Angiography & Interventions

Comprehensive Review

Antiplatelet Strategies Following PCI: A Review of Trials Informing Current and Future Therapies

Alexander Thomas, MD [a,†], Mauro Gitto, MD [a,b,c,†], Samit Shah, MD, PhD [a,d], Yuichi Saito, MD, PhD [a,e], Daniela Tirziu, PhD [a], Alaide Chieffo, MD [f], Giulio G. Stefanini, MD, PhD, MSc [b,c], Alexandra J. Lansky, MD [a,*]

[a] *Section of Cardiovascular Medicine, Yale School of Medicine, New Haven, Connecticut;* [b] *Department of Biomedical Sciences, Humanitas University, Pieve Emanuele-Milan, Italy;* [c] *Humanitas Research Hospital IRCCS, Rozzano-Milan, Italy;* [d] *Department of Medicine, VA Connecticut Healthcare System, West Haven, Connecticut;* [e] *Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine, Chiba, Japan;* [f] *Interventional Cardiology Unit, San Raffaele Scientific Institute, Milan, Italy*

ABSTRACT

Dual antiplatelet therapy (DAPT) has been paramount in preventing thrombosis following percutaneous coronary intervention for nearly 3 decades. However, over the years, DAPT has seen significant changes in the agents utilized and duration of therapy as trials have raced to keep up with advancements made in stent technology and our understanding of bleeding and ischemic risk. Recently, there have been a number of trials demonstrating significant reductions in bleeding events with shorter DAPT durations, which are not yet reflected in practice guidelines. Further, there has been a shift toward more individualized antiplatelet regimens to meet patient-specific risk profiles. This review provides a comprehensive summary of the major trials that have informed current DAPT strategies, puts into context recent trials driving a shift toward more tailored antiplatelet regimens, and highlights gaps in knowledge that remain and the ongoing trials designed to address them.

Goals of antiplatelet therapy

The utility of antiplatelet agents in acute coronary syndromes (ACS) was first described by Paul Gibson in his letter "Salicylic acid for coronary thrombosis?" from 1948.[1] As plaque rupture and subsequent platelet aggregation were better understood as the pathophysiologic mechanisms behind ACS, aspirin became mainstay therapy, with large trials subsequently confirming its therapeutic benefit.[2] With the placement of the first coronary stents in the late 1980s, a new concern for stent thrombosis and its 5% to 45% mortality rate arose.[3] Anticoagulation was first attempted to prevent this devastating complication with regimens comprising aspirin, dipyridamole, heparin, and eventually warfarin for 1 to 3 months after stent placement.[4] In 1995, Colombo et al[5] reported an initial experience of 359 patients who underwent Palmaz-Schatz stent placement with intravascular ultrasound optimization using only ticlopidine and/or aspirin antiplatelet therapy, pioneering both the use of intravascular ultrasound for stent dilation as well as antiplatelet therapy without anticoagulation after stent placement. Subsequently, ticlopidine, the first P2Y purinoceptor 12 inhibitors ($P2Y_{12}i$), demonstrated superior outcomes in the ISAR trial (1996) by reducing the rates of both stent thrombosis and hemorrhagic complications in comparison to anticoagulation, thereby ushering in the era of dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}i$.[6] Ticlopidine, however, was poorly tolerated and had multiple undesirable gastrointestinal and hematologic side effects leading to its replacement with clopidogrel and then additional and more potent $P2Y_{12}i$, prasugrel, and ticagrelor.[7] Since then, there has been an intense devotion to the refinement of antiplatelet therapies. Early post-percutaneous coronary intervention (PCI) DAPT strategies focused on minimizing ischemic and thrombotic complications through DAPT intensification, following an increased risk of early and late stent thrombosis with first-generation drug-eluting stents (DESs).[8] There subsequently has been a shift toward shorter and/or less intense DAPT therapy as advancements in DES technology have minimized thrombotic complications, and awareness

Abbreviations: ACS, acute coronary syndromes; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulation; MACE, major adverse cardiovascular events; NACE, net adverse clinical events; NSTE, non-ST segment elevation; OAC, oral anticoagulants; $P2Y_{12}i$, P2Y purinoceptor 12 inhibitors; PFT, platelet function testing; SIHD, stable ischemic heart disease.

Keywords: dual antiplatelet therapy; percutaneous coronary intervention; pharmacotherapy.

* Corresponding author: alexandra.lansky@yale.edu (A.J. Lansky).

† Co-first authors.

https://doi.org/10.1016/j.jscai.2023.100607

Received 9 December 2022; Received in revised form 10 February 2023; Accepted 13 February 2023

Available online 6 March 2023

has grown regarding the high mortality and poor outcomes associated with bleeding post-PCI.[9] As a result, in recent years, numerous trials have been completed or are in progress to optimize the duration of DAPT, leaving many guidelines struggling to keep up. Thus, we will describe the evidence behind current guidelines and practices and contextualize the abundance of data that has recently emerged regarding shorter and more tailored DAPT therapies with the aim of serving as an up-to-date resource for clinicians to facilitate optimizing their patients' antiplatelet regimens after PCI.

Current antiplatelet agents and evidence from the trials

Aspirin is an irreversible inhibitor of cyclooxygenase, a key enzyme for synthesizing the potent platelet aggregator thromboxane A2. It became the first antiplatelet agent to demonstrate therapeutic benefit in ACS in 1988 when the ISIS-2 trial found 1 month of 160 mg aspirin started within 24 hours of a suspected acute myocardial infarction (AMI) resulted in a 23% relative reduction in vascular mortality and a 50% relative reduction in nonfatal reinfarction.[2] This led to the adoption of aspirin as the foundational therapy in the treatment of ACS, and it has remained as such in current practice guidelines. The optimal dosing of aspirin, with a 300 to 325 mg load followed by 75 to 100 mg/d, was subsequently defined in the ACS population undergoing invasive evaluation in the CURRENT-OASIS 7 trial (2010) after a maintenance dose of 75 to 100 mg/d demonstrated no difference in ischemic outcomes compared with 300 to 325 mg/d (Table 1).[10]

Clopidogrel is an oral, second-generation thienopyridine prodrug that requires 2-step hepatic activation by cytochrome P450 and then irreversibly inhibits the $P2Y_{12}$ ADP receptor. It was first used to prevent ischemic events in at-risk populations after showing superior ischemic and bleeding outcomes compared with daily aspirin 325 mg in the CAPRIE trial.[11] Shortly thereafter, clopidogrel demonstrated similar effectiveness to ticlopidine in preventing stent thrombosis and ischemic events 30 days post-PCI but had a superior safety profile.[12,13] Clopidogrel's short-term efficacy was further confirmed by 2 randomized trials of 2316 patients undergoing PCI for ACS and stable ischemic heart disease (SIHD).[14,15] The CURE trial (2001) then showed patients with non-ST-elevation (NSTE)-ACS, including those who underwent PCI and those who were medically managed, benefited from a longer duration of DAPT with clopidogrel for 3 to 12 months (mean 9 months) by demonstrating a 20% relative reduction in the composite of cardiovascular death, nonfatal myocardial infarction (MI), or stroke (9.3% vs 11.4%) at 12 months.[16] Although this came at the expense of increased major bleeding (3.7% vs 2.7%), those who underwent PCI derived a more pronounced ischemic benefit.[17] The CREDO trial (2002) then demonstrated a similar ischemic benefit with up to 12 months of clopidogrel following elective PCI.[18] Following these results, clopidogrel, in conjunction with aspirin, became the preferred regimen for DAPT post-PCI. The optimal dose of clopidogrel, however, was not critically evaluated until nearly a decade later when the CURRENT-OASIS 7 trial demonstrated increased major bleeding without further ischemic benefit in over 25,000 patients with ACS undergoing invasive evaluation with double- versus single-dose clopidogrel (600 mg load followed by 150 mg/d for 6 days and 75 mg/d maintenance vs 300 mg load followed by 75 mg/d, respectively).[10] Among the over 17,000 who had PCI, however, double-dose clopidogrel did show a significant reduction in stent thrombosis (1.6% vs 2.3%), contributing to current guidelines recommending a load of 600 mg in clopidogrel-naive patients followed by 75 mg/d maintenance.[19,20]

Prasugrel is an oral, third-generation thienopyridine prodrug that undergoes rapid activation by cytochrome P450 enzymes (compared with clopidogrel) and then irreversibly binds to the $P2Y_{12}$ ADP receptor.[7,21] Due to concerns over variability in clopidogrel's pharmacologic response coupled with the more rapid and potent effects of prasugrel, clopidogrel was compared head-to-head with prasugrel in the TRITON-TIMI 38 trial (2007).[22] Compared with clopidogrel, prasugrel demonstrated fewer ischemic events (9.9% vs 12.1%; $P < .001$), with slightly more bleeding (2.4% vs 1.8%; $P = .03$) at 14 months among >13,000 patients with ACS undergoing PCI. PRINCIPLE-TIMI 44, a drug effect trial, then demonstrated that prasugrel (60 mg load, 10 mg/d maintenance) had superior platelet inhibition and antiplatelet effects compared with clopidogrel (600 mg load and 75 mg/d maintenance) in 201 patients post-PCI.[23] As a result, prasugrel became preferred over clopidogrel in the ACS population only when undergoing PCI and has remained as such in current guidelines,[24,25] whereas clopidogrel is the preferred agent for those with SIHD, largely due to a paucity of data for the other $P2Y_{12}$i.[19,20] In addition, it should be noted that prasugrel is contraindicated for patients with a history of transient ischemic attack or stroke due to an increased rate of stroke (6.5% with prasugrel vs 1.2% with clopidogrel) in TRITON-TIMI 38.

Ticagrelor is an oral cyclopentyl-triazolopyrimidine class, active, competitive inhibitor of the $P2Y_{12}$ ADP receptor with rapid onset and offset of platelet inhibition requiring twice daily dosing. Similar to prasugrel, ticagrelor was directly compared with clopidogrel in the PLATO trial among patients with ACS treated medically or with revascularization.[26] Compared with clopidogrel, ticagrelor demonstrated a significant reduction in the composite of vascular death, MI, or stroke at 1 year (9.8% vs 11.7%; $P < .001$) without an increase in major bleeding (11.6% vs 11.2%; $P = .43$) and a reduction in vascular and all-cause mortality (vascular: 4.0% vs 5.1%, $P = .001$; all-cause: 4.5% vs 5.9%, $P < .001$). Following this result, ticagrelor became a guideline-preferred $P2Y_{12}$i in the ACS population undergoing PCI.[19,20] Ticagrelor was subsequently directly compared with prasugrel in an open-label, large ACS population undergoing invasive evaluation in the ISAR-REACT 5 trial (2019). In this trial, ticagrelor was associated with significantly higher ischemic events compared with prasugrel (9.3% vs 6.9%; hazard ratio [HR], 1.36; $P = .006$) without a significant difference in major bleeding (5.4% with ticagrelor and 4.8% with prasugrel; $P = 0.46$).[27] Ticagrelor was further associated with higher discontinuation rates due to side effects. A subsequent randomized trial of 90 subjects undergoing PCI for ACS found prasugrel, compared with clopidogrel and ticagrelor, had improved endothelial function, stronger platelet inhibition, and reduced IL-6 levels,[28] which may, in part, explain the physiology behind the lower ischemic event rates seen in ISAR-REACT 5. These findings have led to a change in the European Society of Cardiology (ESC) guidelines, which now prefer prasugrel over ticagrelor for patients with NSTE-ACS who proceed to PCI,[24] whereas American College of Cardiology (ACC)/American Heart Association (AHA)/SCAI guidelines continue to recommend both ticagrelor and prasugrel in ACS, including the most recent 2021 *Guidelines for Coronary Artery Revascularization*.[25] Currently, the ongoing SWITCH SWEDEHEART trial is comparing ticagrelor to prasugrel among a planned population of 16,000 patients with ACS (NCT05183178) and should provide further insight as to the preferred $P2Y_{12}$i in the ACS population.

Cangrelor is an intravenous, nonthienopyridine, active, high affinity, reversible inhibitor of the $P2Y_{12}$ ADP receptor with an immediate onset and very short half-life of approximately 5 minutes.[29] It is uniquely suited for the peri-PCI period, as it allows for immediate platelet inhibition, is given intravenously, and is quickly reversible compared with other $P2Y_{12}$i and glycoprotein IIb/IIIa inhibitors (GPIs).[30] The CHAMPION PCI and CHAMPION PLATFORM trials (2009) first evaluated cangrelor with subsequent clopidogrel monotherapy in the peri-PCI period when it was compared with clopidogrel load given either immediately before or immediately following PCI among patients with ACS and SIHD. Both trials were terminated prematurely for futility to meet the composite primary end point of death, MI, or ischemia-driven revascularization at 48 hours, driven heavily by nonfatal MI.[31,32] Among those enrolled, however, stent thrombosis was noted to be significantly lower in the cangrelor groups. A subsequent post hoc pooled analysis

Table 1. Landmark efficacy trials on antiplatelet therapies.

Study drug	Trial	Year	Population (N)	Groups	Load: maintenance doses (duration)	Primary outcome (timepoint)	Primary outcome result	*P* value	Bleeding outcome	Bleeding outcome result	*P* value
Aspirin	ISIS-2[2]	1988	ACS (17,187)	1. S		Vascular death (5 wk)	9.2%	<.001	Bleed	0.54%	<.001
				2. A	A = 160 mg/d		9.4%	<.001	requiring	0.36%	
				3. S + A	A = 160 mg/d		8.0%	<.001	transfusion	0.56%	<.001
				4. Placebo			13.2%			0.26%	
Clopidogrel	CURE[16]	2001	ACS (12,562)	1. C + A	C = 300 mg: 75 mg/d (3-12 mo)	CV death, MI,	9.30%	<.001	Major	3.70%	.001
				2. Placebo + A	A = 162-325 mg: 81-162 mg/d	stroke (12 m)	11.40%		bleeding	2.70%	
	CREDO[18]	2002	Elective PCI (2116)	1. C + A	C = 300 mg: 75 mg/d (12 mo); A = 162-325 mg: 81-162 mg/d	Death, MI, stroke (12 m)	8.50%	.02	Major bleeding	8.80%	.07
				2. Placebo (C 28d) + A	C = 75 mg/d (28 d); A = 162-325 mg: 81-162 mg/d		11.50%			6.70%	
	CURRENT-OASIS 7[10]	2010	ACS (25,086)	1. C (High) + A	C = 600 mg: 150 mg/d (6 d): 75 mg/d	CV death, MI, stroke (30 d)	4.20%	.3	Major bleeding	2.50%	.01
				2. C (Low) + A	C = 300 mg: 75 mg/d		4.40%			2.00%	
				3. A (High) + C	A = 300-325 mg: 300-325 mg/d		4.20%	.61		2.30%	.9
				4. A (Low) + C	A = 300-325 mg: 75-100 mg/d		4.40%			2.30%	
Prasugrel	TRITON -TIMI 38[22]	2007	ACS (13,608)	1. P + A	P = 60 mg: 10 mg/d (6-15 mo)	CV death, MI, stroke (15 m)	9.90%	<.001	Major	2.40%	.03
				2. C + A	C = 300 mg: 75 mg/d (6-15 mo)		12.10%		bleeding	1.80%	
Ticagrelor	PLATO[26]	2009	ACS (18,624)	1. T + A	T = 180 mg: 90 mg twice daily	Vascular death, MI, stroke	9.80%	<.001	Major	11.60%	.43
				2. C + A	C = 300-600 mg: 75 mg/d	(12 m)	11.70%		bleeding	11.20%	
Ticagrelor vs prasugrel	ISAR-REACT 5[27]	2019	ACS (4018)	1. T + A	T = 180 mg: 90 mg twice daily	Death, MI, stroke (12 m)	9.30%	.006	BARC major	5.40%	.46
				2. P + A	P = 60 mg: 10 mg/d		6.90%		bleeding	4.80%	
Cangrelor	CHAMPION PCI[32]	2009	SIHD or ACS (8667)	1. Cg + C+ A	Cg = 30 μg/kg: 4 μg/kg (2-4 h); C = 600 mg: 75 mg/d	Death, MI, IDR (48 h)	7.50%	.59	Major bleeding	3.60%	.06
				2. C + A	C = 600 mg: 75 mg/d		7.10%			2.90%	
	CHAMPION PLATFORM[31]	2009	SIHD or ACS (5301)	1. Cg + C+ A	Cg = 30 μg/kg: 4 μg/kg (2-4 h); C = 600 mg: 75 mg/d	Death, MI, IDR (48 h)	7.00%	.17	Major bleeding	5.50%	<.001
				2. C + A	C = 600 mg: 75 mg/d		8.00%			3.50%	
	CHAMPION PHOENIX[30]	2013	ACS (10,942)	1. Cg + C+ A	Cg = 30 μg/kg: 4 μg/kg (2-4 h); C = 600 mg/300 mg: 75 mg/d	Death, MI, IDR, ST (48 h)	4.70%	.005	Severe bleeding	0.16%	.44
				2. C + A	C = 600 mg: 75 mg/d		5.90%			0.11%	

A, aspirin; ACS, acute coronary syndromes; BARC, Bleeding Academic Research Consortium; C, clopidogrel; Cg, cangrelor; CV, cardiovascular; IDR, ischemia-driven revascularization; MI, myocardial infarction; P, prasugrel; PCI, percutaneous coronary intervention; S, streptokinase; SIHD, stable ischemic heart disease; ST, stent thrombosis; T, ticagrelor.

using the Third Universal Definition of MI compared with the protocol MI definition demonstrated a significant reduction in the primary end point.[33] The CHAMPION PHOENIX trial, which included 11,000 patients undergoing urgent or elective PCI, found cangrelor at the time of PCI followed by infusion for 2 to 4 hours followed by clopidogrel was superior to clopidogrel alone, with a significant reduction in ischemic events (4.7% vs 5.9%; $P = .005$), including stent thrombosis, without a significant increase in severe bleeding.[30] As a result, cangrelor was approved in patients undergoing PCI if not pretreated with a $P2Y_{12}$i to reduce the risk of periprocedural MI, repeat coronary revascularization, and stent thrombosis.[25,34,35]

Abciximab, Eptifibatide, and Tirofiban are intravenous direct-acting GPIs and the only alternative parenteral antiplatelet agents to cangrelor, though abciximab is no longer available in many countries (including the US). Their initial trials predated the use of $P2Y_{12}$i and did not improve ischemic outcomes but increased bleeding complications.[36–38] A 2011 meta-analysis of randomized controlled trials evaluating GPIs, once the utilization of clopidogrel and ticlopidine became routine, found an association with fewer MIs, no improvement in mortality, but an increase in minor bleeding.[39] Though no head-to-head trials comparing cangrelor and GPIs in the immediate peri-PCI period exist, an exploratory analysis of the CHAMPION trials demonstrated no difference in ischemic outcomes between the 2 agents, with significantly higher rates of bleeding for those receiving GPIs,[40] which was also observed in a real-world patient sample undergoing PCI.[41] GPI agents have, however, demonstrated the ability to decrease thrombus burden[42]; therefore, they remain a therapeutic consideration in ACS patients undergoing PCI when a large thrombus burden exists, or there is slow flow, or no-reflow believed to be a result of distal clot embolization.[25,35]

Finally, vorapaxar, an oral protease-activated–receptor 1 antagonist that inhibits thrombin-induced platelet activation, was evaluated as an added antiplatelet agent to patients already on DAPT following PCI to reduce ischemic events further. It was evaluated in the TRACER study (2012) and demonstrated no difference in the primary composite outcome of cardiovascular death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization among nearly 13,000 patients with NSTE-ACS.[43] Though there was a significant reduction in the composite of cardiovascular death, MI, or stroke (HR, 0.89; 95% CI, 0.81-0.98; $P = .02$), this came at the cost of increased moderate to severe bleeding (7.2% vs 5.2%; $P < .001$) and significantly higher rates of intracranial hemorrhage (1.1% vs 0.2%; $P < .001$).

Pretreatment

Pretreatment, or the administration of a $P2Y_{12}$i, often as a loading dose, prior to defining coronary anatomy has been a topic of debate since $P2Y_{12}$i came into use. Pretreatment provides a theoretical advantage by allowing the $P2Y_{12}$i time to achieve the full antiplatelet effect, thereby decreasing ischemic and periprocedural thrombotic complications at the cost of increased risk for periprocedural bleeding and operative delays when coronary artery bypass graft surgery is recommended.[44]

The subanalyses of the early clopidogrel trials (CREDO, CURE, and PCI-CLARITY) demonstrated mixed results for ischemic and bleeding outcomes following pretreatment among SIHD and ACS populations.[17,18,45] The PRAGUE-8 (2008) and ARMYDA-5 PRELOAD (2010) trials evaluated clopidogrel pretreatment ~6 hours prior to angiography versus clopidogrel given in the laboratory at the time of PCI after anatomy was defined in a predominantly SIHD population; neither demonstrated an improvement in ischemic outcomes, with significantly higher rates of bleeding with preloading in PRAGUE-8 (3.5% vs 1.4%; $P = .025$) and a trend toward the same in ARMYDA-5 PRELOAD.[46,47] Following these trials and subsequent meta-analyses,[48] preloading has generally not been recommended in the SIHD population until coronary anatomy is defined.[25] The CIPAMI trial (2012) subsequently compared in-lab to out-of-hospital clopidogrel loading, which occurred on average 47 minutes prior to angiography among 337 patients with ST-segment elevation myocardial infarction (STEMI). Although pretreatment did not improve the primary outcome of Thrombolysis in Myocardial Infarction (TIMI) 2/3 patency before PCI, post hoc analysis found a significant reduction in composite death, reinfarction, or revascularization at 7 days or hospital discharge (2.5% vs 7.5%; $P < .05$) with out-of-hospital clopidogrel administration.[49] This result subsequently led to pretreatment trials for the more potent $P2Y_{12}$i.

The ACCOAST trial (2013) evaluated pretreatment with 30 mg prasugrel and found no improvement in the composite of cardiovascular death, MI, stroke, urgent revascularization, or GPI rescue therapy at 7 and 30 days and significantly more bleeding (2.6% vs 1.4%; $P = .006$) among over 4000 patients with NSTE-ACS undergoing coronary angiography.[50] There was no significant difference among the cohort who ultimately underwent PCI (68.7%). The ATLANTIC trial compared out-of-hospital to in-laboratory ticagrelor loading (mean difference 31 minutes) in nearly 2000 patients with STEMI undergoing PCI. Here, there was no difference in the coprimary end points of ST-segment resolution before PCI or TIMI 3 flow but found significantly lower rates of stent thrombosis in the out-of-hospital group (0% vs 0.8% at 24 hours; 0.2% vs 1.2% at 30 days) without an increase in major bleeding.[51] The DUBIUS trial (2020) recently readdressed pretreatment in the NSTE-ACS population with ticagrelor (average 23 hours prior to coronary angiogram) and was stopped prematurely due to futility after enrolling 1446 patients with NSTE undergoing an invasive evaluation; no difference was found in the composite primary outcome of vascular death, MI, stroke, or BARC (Bleeding Academic Research Consortium) 3, 4, and 5 bleeding (3.3% vs 2.9%).[52]

Current American and European pretreatment guidelines are listed in Table 2. Both documents recommend preloading (latest at the time of PCI) of a $P2Y_{12}$i in the setting of STEMI with a Class 1 indication unless otherwise contraindicated due to excessive bleeding risk or if there is uncertainty regarding the diagnosis.[53,54] In SIHD, both documents state that there is no significant evidence to support pretreatment unless anatomy is already known and PCI is planned.[25,35] In the setting of NSTE myocardial infarction (NSTEMI), there has been significant evolution in the European guideline recommendations,[55] which currently recommend against routine pretreatment with unknown anatomy when an early invasive strategy is planned,[24] whereas the American guidelines highlight the conflicting data and state that current practice is largely to load at the time of PCI.[25]

Current guidelines on DAPT duration following percutaneous coronary intervention

DAPT primarily serves to prevent thrombotic complications in the period of vascular healing and strut endothelization after stent placement.[56] The sharp rise in early and late stent thrombosis seen with first-generation DES from delayed arterial healing resulted in a significant intensification of DAPT therapies during the mid-2000s and early 2010s. In addition, advancements in DES technology have now drastically improved the safety profile of contemporary DES, with complete endothelization now achieved as early as 1 month and up to 6 months after implantation.[57] Current guidelines for DAPT duration following PCI largely come from the 2016 AHA/ACC and 2017 ESC-focused updates on DAPT, which are based on the duration of treatment used in the early large-scale DAPT trials that predominantly predate the contemporary DES era. In addition, the most recent 2021 AHA/ACC revascularization and 2020 ESC NSTEMI guidelines largely reiterate prior DAPT duration recommendations, with the addition of recommendations for patients at high bleeding risk (HBR) and considerations for earlier transition to $P2Y_{12}$i monotherapy. In general, both European

Table 2. Societal guidelines on P2Y purinoceptor 12 inhibitors pretreatment.

Population	Society	Year	Recommendation class	Recommendation
STEMI	ESC	2017/2018	Class 1	Recommend potent $P2Y_{12}i$ (prasugrel or ticagrelor) or clopidogrel (if prasugrel and ticagrelor are not available or contraindicated) before (or at latest at the time of) PCI unless there are contraindications such as bleeding or if STEMI diagnosis is not clear
	ACC/AHA	2013	Class 1	A loading dose of $P2Y_{12}i$ should be given as early as possible or at the time of primary PCI to patients with STEMI
NSTEMI	ESC	2020	Class 3	Recommends against routine pretreatment with $P2Y_{12}i$ when anatomy is unknown and early (<24 h) invasive management is planned
			Class 2b	Pretreatment with $P2Y_{12}i$ can be considered when the early invasive strategy is not planned AND the patient does not have a high risk of bleeding
	ACC/AHA	2014	Class 1	A loading dose of a $P2Y_{12}i$ should be given before the procedure in patients undergoing PCI with stenting
		2021	No recommendation	There are conflicting data on the benefits of pretreatment with a $P2Y_{12}i$ before the anatomy is known. Currently, most undergo an early invasive angiogram with loading after anatomy is defined, which appears to offer a similar benefit to preloading
SIHD	ESC	2018	Class 1	Clopidogrel 600 mg is recommended in elective PCI once coronary anatomy is known and the decision is made to proceed with PCI
			Class 2b	Pretreatment with clopidogrel may be considered if the probability of PCI is high
	ACC/AHA	2021	No recommendation	There is no compelling evidence to support routine pretreatment with a $P2Y_{12}i$ before coronary angiography when the coronary anatomy is not known

ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; NSTEMI, non-ST-segment elevation myocardial infarction; $P2Y_{12}i$, P2Y purinoceptor 12 inhibitors; PCI, percutaneous coronary intervention; SIHD, stable ischemic heart disease; STEMI, ST-segment elevation myocardial infarction.

and American guidelines have Class 1 recommendations for 6 months of DAPT with aspirin and clopidogrel for patients with SIHD and 12 months of DAPT with aspirin and $P2Y_{12}i$, ticagrelor or prasugrel (AHA/ACC) or prasugrel (ESC) as the preferred $P2Y_{12}i$ for those with all forms of ACS. See Figure 1 for a complete summary of current guidelines regarding DAPT duration.

Patients with ACS complicated by cardiogenic shock or out-of-hospital cardiac arrest represent a unique population with challenges requiring additional considerations for antiplatelet selection. Because these patients have altered $P2Y_{12}i$ absorption, either due to inadequate intestinal perfusion or opiate administration or from a physical lack of oral access, delays in the onset of $P2Y_{12}i$ effects can occur and lead to adverse thrombotic events in patients already at a very high risk of thrombosis. Currently, there are no large-scale randomized trials to guide $P2Y_{12}i$ selection in this population, and thus we are predominantly reliant on pharmacology studies which have found lower levels of platelet inhibition with the use of clopidogrel compared to ticagrelor or prasugrel.[58] The use of intravascular cangrelor has demonstrated the ability to further accelerate platelet inhibition compared to oral $P2Y_{12}i$ agents based on nonrandomized data.[59,60] Currently, recommendations for antiplatelet

Figure 1.

Major societal guidelines for dual antiplatelet therapy following drug-eluting stent placement.

A, aspirin; ACC, American College of Cardiology; ACS, acute coronary syndromes; AHA, American Heart Association; C, clopidogrel; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulants; ESC, European Society of Cardiology; HBR, high bleeding risk; P, prasugrel; $P2Y_{12}i$, P2Y purinoceptor 12 inhibitors; PCI, percutaneous coronary intervention; T, Ticagrelor; VKA, vitamin K antagonist; SAPT, single antiplatelet therapy; SIHD, stable ischemic heart disease; LM, left main; *taking into account bleeding and ischemic risk; †, Very high bleeding risk (bleeding in the past month and/or non-deferrable surgery); ‡, Suggests cut-off of PRECISE-DAPT >25 to define high bleeding risk; **, Recommendation from 2020 ACC Expert Consensus decision pathway for anticoagulant and antiplatelet therapy in patients with atrial fibrillation or venous thromboembolism undergoing percutaneous coronary interventionor with atherosclerotic cardiovascular disease.[89]

Green = Class 1, Yellow = Class 2a, Orange = Class 2b.

therapies in cardiogenic shock and out-of-hospital cardiac arrest are based on the ESC joint position paper, [61] which recommends prasugrel or ticagrelor over clopidogrel when there is no excess risk of bleeding and recommends intravascular antithrombotic therapy to bridge the delayed onset of oral $P2Y_{12}i$ agents, with a preference for cangrelor given lower rates of bleeding compared to GPI agents.

Extended DAPT duration

Late (>1 year) stent thrombosis associated with first-generation DES led to the exploration of extended (>12 months) DAPT.[8] The first major trial was the DAPT trial (2014) among 9961 patients (43% ACS), which found that extended DAPT (clopidogrel 65%, prasugrel 35%) between 12 and 30 months post-PCI significantly lowered rates of stent thrombosis and major adverse cardiac events (MACE) at the cost of significantly higher bleeding rates (2.5% vs 1.6%; $P = .001$).[8] Subsequently, the PEGASUS-TIMI 54 trial (2015) evaluated extended DAPT with ticagrelor at 2 different doses (90 mg and 60 mg) among 21,162 patients with post-MI (83% with PCI) with 1 or more risk factors for ischemia and excluding some HBR groups.[62] Extended DAPT with ticagrelor reduced MACE (7.85% vs 7.77% vs 9.04%; $P = .008$) but increased major bleeding 3 years post-MI (2.6% vs 2.3% vs 1.1%; $P = .004$), with the incidence of any bleeding or dyspnea being numerically lower with 60 mg compared with 90 mg. The COMPASS trial (2017) randomized almost 25,000 patients with SIHD in a 1:1:1 fashion at 12 months post-PCI to rivaroxaban at a dose of 2.5 mg twice daily with aspirin, rivaroxaban 5 mg twice daily without aspirin, and aspirin alone.[63] The use of rivaroxaban with aspirin was associated with reduced MACE events compared to aspirin alone at a 2-year follow-up (4% vs 6%; $P < .001$) but at the cost of increased bleeding (3% vs 2%; $P < .001$). Rivaroxaban alone did not decrease MACE compared to aspirin and had higher bleeding rates (3% vs 2%; $P < .001$).

On the basis of these trials, ESC guidelines recommend that patients without HBR and moderate (2b) or high (2a) ischemic risk (defined in Supplemental Table S1) be considered for prolonged DAPT beyond 12 months.[24] Similarly, the ACC/AHA made a 2b recommendation to consider prolonged DAPT beyond 12 months for patients with high ischemic risk.[25] For patients with SIHD at high ischemic and low bleeding risk, prolonged DAPT beyond 6 months is a 2b recommendation for both societies.[20,25]

More recently, the HOST-EXAM trial (2021) challenged the paradigm of aspirin monotherapy following a standard duration of DAPT. Their clopidogrel demonstrated superiority compared to aspirin with fewer net adverse clinical events NACE (5.7% vs 7.7%; $P = .003$) and fewer individual thrombotic and bleeding events at 24 months when used following an uneventful 6 to 18 months of DAPT in a predominantly ACS population (5438 patients with post-PCI; 72% ACS).[64] A recently published extension to the HOST-EXAM trial, the HOST-EXAM Extended Study (2022), found this reduction in NACE persisted beyond 5 years (12.8% vs 16.9%; $P < .001$), as did the reduction in thrombotic and bleeding events within the clopidogrel treatment group.[65] Currently, the A-CLOSE trial compares clopidogrel monotherapy beyond 12 months to extended DAPT (NCT03947229).

Short DAPT in HBR

With the improved thrombotic risk profile of the newest generation of stents, derived from the use of inert fluoropolymers and reduced strut thickness, along with heightened awareness of the poor outcomes associated with bleeding after PCI,[66] the contemporary emphasis has been on minimizing bleeding events. Historically, patients with HBR were treated with bare metal stents (BMS) with 1 month of DAPT for adequate thrombotic protection. With improvements in DES, this paradigm was challenged by 3 randomized controlled trials comparing BMS versus DES with 1 month of DAPT in patients with HBR.[67–69] The LEADERS FREE trial (2015) compared the BioFreedom biolimus-coated stent (Biosensors) to a BMS in 2466 patients with HBR after PCI (42% ACS) randomized to 1-month DAPT (aspirin and clopidogrel) followed by aspirin alone or 12 months continued DAPT.[67] At 1 year, the BioFreedom stent outperformed BMS with regard to the primary end point of composite cardiac death, MI, or stent thrombosis (9.4% vs 12.9%; $P = .005$ for superiority). A prespecified subgroup analysis of 828 patients with HBR (63% ACS) from the ZEUS trial (2015) demonstrated similar findings, with the zotarolimus-eluting Endeavor Sprint stent (Medtronic) having significantly lower rates of MACE (22.6% vs 29.0%; $P = .03$) and stent thrombosis (6.2% vs 2.6%; $P = .02$) at 1 year after 30 days of DAPT compared with BMS.[68] Finally, the SENIOR trial (2018) found among 1200 elderly patients (≥75 years), half with ACS, that the Synergy bioabsorbable polymer DES (Boston Scientific) after 30 days of DAPT had significantly lower rates of MACE (12% vs 16%; $P = 0.02$) at 1 year compared with BMS (Figure 2).[69]

Numerous studies have since set out to evaluate very short (1 month) duration DAPT in the HBR population (Table 3). To date, 6 trials have been published, all demonstrating noninferiority and/or superiority with regard to ischemic and bleeding outcomes with 1-month DAPT.[70–75] It should be noted, however, that there exists significant variability in the design of these studies, including the use of a blanking period, evaluation for noninferiority versus superiority, and choice of a comparator arm which has included randomized and historical controls as well as performance goals. Further, although the ACS population was well captured in these trials, patients with STEMI were poorly represented, making up 0% to 7% of total participants in all but the MASTER DAPT trial, in which patients with STEMI made up 12%. Finally, although the HBR study populations did not have particularly complex coronary disease, a recent subanalysis of the MASTER DAPT trial found those with complex coronary disease and HBR had no difference in NACE nor MACE, with significantly lower bleeding after the discontinuation of either aspirin or $P2Y_{12}i$ at 1 month.[76] There are at least 7 ongoing trials to further evaluate 1-month DAPT therapy among the HBR populations, including the COMPARE STEMI ONE trial, which plans to enroll 1608 patients with STEMI and compare 30 to 45 days of DAPT followed by prasugrel monotherapy to the currently recommended 12 months of DAPT (NCT05491200) (Table 3).

Given many of these trials were published since 2020, after the publication of most DAPT guidelines, they have not been incorporated into current recommendations, and much of the data for HBR populations comes from earlier trials that included HBR cohorts and predominantly evaluated a more conservative 3-month DAPT duration. Regardless, for the HBR population, current AHA/ACC guidelines do provide 2b recommendations to consider discontinuation of DAPT at 3 months and 6 months following PCI in SIHD and ACS populations, respectively.[25] The ESC guidelines similarly give 2a recommendations to discontinue DAPT at 3 months in both SIHD and ACS settings in patients with HBR and a 2a recommendation to consider stopping DAPT after 1 month when bleeding risk is considered very high (Figure 1).[20,24] Currently, XIENCE (Abbott Vascular) and Resolute Onyx (Medtronic) stents have FDA labeling for 1-month DAPT in patients with HBR.

It is critically important to emphasize the significant overlap of patients with high bleeding and high ischemic risk, making clinical decisions regarding DAPT duration complex and requiring an individualized approach tailored to specific patient risk factors (Central Illustration). This has led to the development of multiple risk-stratifying tools to aid in decision-making, including the DAPT, PARIS (Patterns of nonadherence to antiplatelet regimen in stented patients), PARIS-DAPT, and Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) scores, with the PRECISE-DAPT score recommended within the ESC guidelines.[20] Due to limitations and lack of agreement

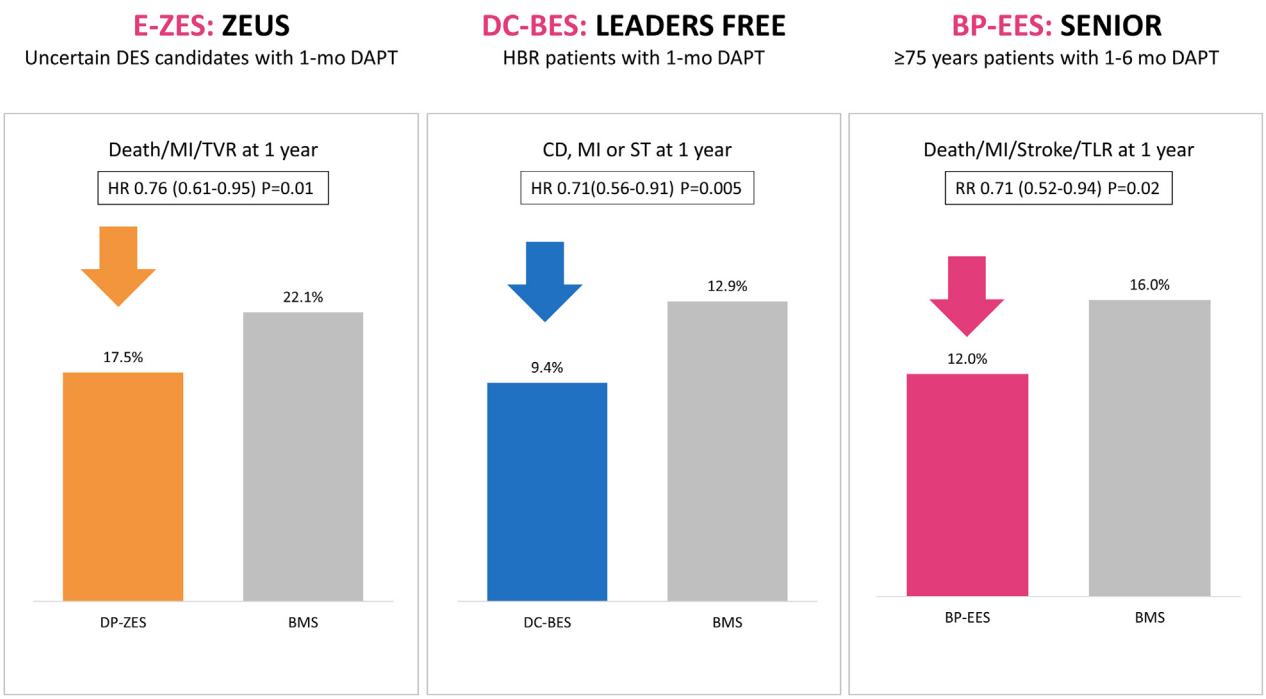


Figure 2.
Trials of drug-eluting stents versus BMS with 1-month DAPT.
BMS, bare metal stent; BP-EES, biodegradable polymer everolimus-eluting stent; CD, cardiac death; DAPT, dual antiplatelet therapy; DC-BES, drug coated balloon expandable stent; DES, drug-eluting stents; E-ZES, Endeavour zotarolimus-eluting stent; HBR, high bleeding risk; HR, hazard ratio; MI, myocardial infarction; RR, rate ratio; ST, stent thrombosis; TLR, target lesion revascularization; TVR, target vessel revascularization.

between these risk scores, the Academic Research Consortium for HBR developed a consensus document to better identify and classify the factors associated with HBR among patients undergoing PCI.[77] This comprehensive list of clinical features is further classified into major and minor criteria and was validated in a population of nearly 10,000 patients with post-PCI, where being classified as HBR (at least 1 major or 2 minor criteria) corresponded to nearly 3-fold increased risk of bleeding compared to patients without HBR, and was associated with an increased rate of 1-year mortality (4.7% vs 0.6%) and MI (4.2% vs 2.0%).[78] It further demonstrated a stepwise increased risk of bleeding based on the number of times the Academic Research Consortium for HBR definition was met, with patients meeting criteria 1 time being associated with a 2-fold increased risk of bleeding and those meeting criteria 4 times having a 12-fold increased risk. With most current risk stratification tools focusing predominantly on bleeding, recent data does suggest bleeding may take precedence over ischemic risk, outside of extremes, when patients display both moderate-to-high bleeding and ischemic risk factors.[79]

DAPT in atrial fibrillation

Patients requiring concomitant oral anticoagulation (OAC) and antiplatelet therapy after PCI are a unique HBR subpopulation. Initially, both OAC and DAPT were believed necessary to prevent the devastating complications of stroke, thromboembolism, and stent thrombosis in these patients who were treated with triple therapy. Triple therapy, however, is associated with a major bleeding risk of up to 16% per year.[80] With the high prevalence of atrial fibrillation in 5% to 8% of the PCI population, there was an urgent need to mitigate the excess bleeding complications.[81]

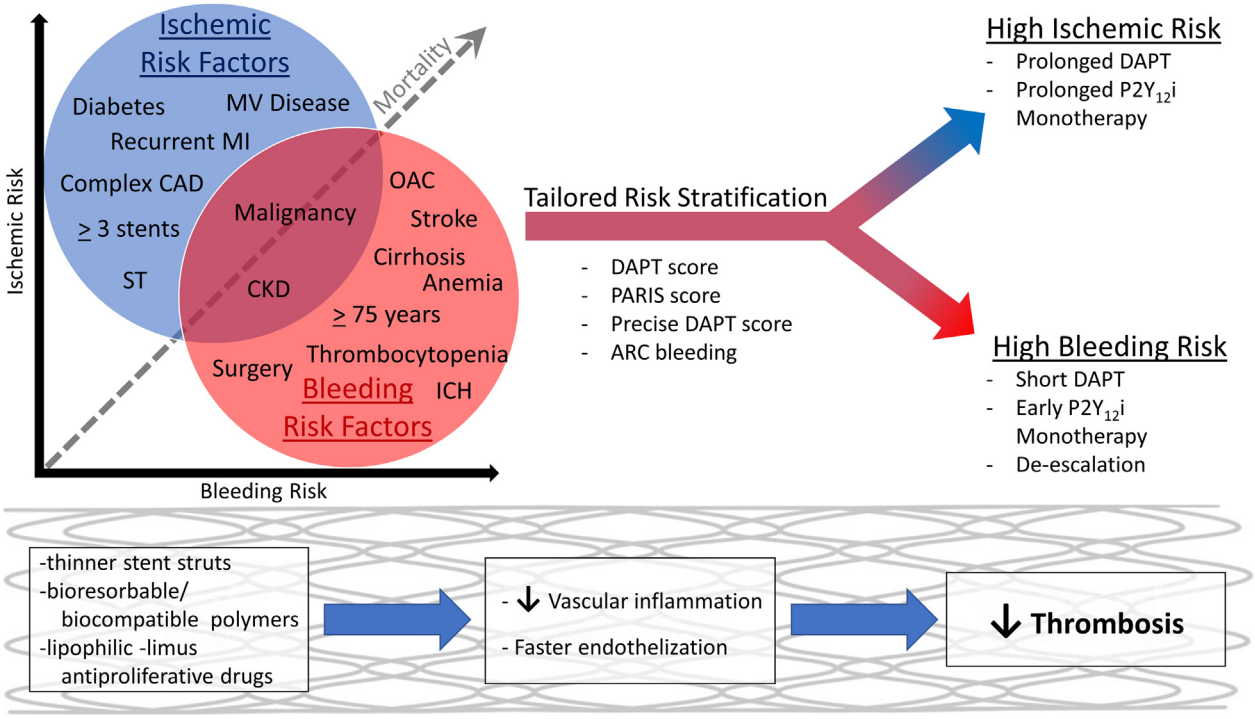
To date, 5 randomized controlled trials have evaluated antiplatelet therapies in the atrial fibrillation population requiring OAC. The first was the WOEST trial (2013), where 573 patients on warfarin undergoing PCI (27% of ACS) were randomized to either clopidogrel (dual therapy) or aspirin and clopidogrel (triple therapy). At 1 year, dual therapy significantly reduced bleeding (19.4% vs 44.4%; $P < .0001$) and MACE (11% vs 18%; $P = .025$) and numerically reduced stent thrombosis (1.4% vs 3.2%).[82] With the transition to primarily direct OAC (DOAC), PIONEER-AF (2016) evaluated 2124 patients with atrial fibrillation requiring PCI (51% ACS) randomized in a 1:1:1 fashion to either: (1) Rivaroxaban (15 mg/d) plus a $P2Y_{12}i$ for 12 months, (2) very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months, or (3) standard therapy with a dose-adjusted vitamin K antagonist (once daily) plus DAPT for 1, 6, or 12 months with clopidogrel used as the primary $P2Y_{12}i$ in 93% to 96%.[81] Rivaroxaban significantly outperformed warfarin in both the primary outcome of clinically significant bleeding (17% vs 18% vs 27% for groups 1, 2, and 3, respectively) with no significant differences in MACE or stent thrombosis. The RE-DUAL PCI (2017) trial found dual therapy with dabigatran and clopidogrel or ticagrelor had lower rates of bleeding and no difference in MACE or stent thrombosis compared with triple therapy (warfarin, a $P2Y_{12}i$, and 1-3 months of aspirin) in 2725 patients (50% ACS).[83] The ENTRUST-AF PCI (edoxaban; 2019) and the AUGUSTUS (apixaban; 2019) trials demonstrated noninferior and superior bleeding outcomes, respectively, with DOACs compared to warfarin with dual rather than triple therapy without a difference in ischemic outcomes among 1506 (52% ACS) and 4614 patients (61% ACS, 37% with and 24% without PCI), respectively (Figure 3).[84,85] A large-scale meta-analysis of 10,234 patients evaluating the safety and efficacy of double versus triple antithrombotic therapy (>90% with clopidogrel), including the 4 aforementioned DOACs trials, demonstrated significantly lower rates of major and clinically relevant nonmajor bleeding (rate ratio [RR], 0.66; 95% CI, 0.56-0.78; $P < .0001$) without significant differences in all-cause death, cardiovascular death, or trial-defined MACE among those treated with dual therapy.[86] Notably, however, those receiving dual therapy had a borderline significantly higher rate of MI (3.6% vs 3.0%; $P = .07$) driven by the RE-DUAL PCI population and a significantly

Table 3. Summary of recent and ongoing 1-month DAPT trials in patients at HBR.

Trial (y)[a]	N[b]	ACS % (STEMI %) of total population	Comparison	DES	Design	DAPT duration study (control)	$P2Y_{12}i$	Monotherapy	Primary outcome	Timepoint	Primary outcome	*P* value
LEADERS FREE II (2020)[75]	1148	44% (3%)	DCS vs BMS[c]	BioFreedom	Superiority	1 m (1 m)	C preferred	A preferred	CV death, MI TLR	1 y	9.3% vs 12.4% 7.2% vs 9.2%	$P = .015$ $P = .034$
Onyx ONE Global (2020)[71]	1996	51% (5% to 6%)	ZES vs DCS	Resolute Onyx vs BioFreedom	Noninferiority	1 m (1 m)	87% C, 11% T, <1% P	51% A, 41% $P2Y_{12}i$	MACE	1 y	17.1% vs 16.9%	$P = .01$
Onyx ONE Clear (2020)[70]	1506	49% (4%)	ZES vs OPC	Resolute Onyx	Noninferiority	1 m (12 m)	C preferred	A or $P2Y_{12}i$	CV Death, MI	1 y	7.0% vs OPC 9.7%	$P < .001$
XIENCE 28 (2021)[72]	1605	34% (0%)	EES vs EES[c]	XIENCE	Noninferiority	1 m (6 m)	86% C, 13% T, 1% P	91% A, 6% $P2Y_{12}i$	All-cause death, MI	6 mo or 12 mo	3.5% vs 4.3%	$P = .0005$
MASTER DAPT (2021)[73]	4434	59% (12%)	SES vs SES	Ultimaster	Noninferiority Noninferiority Superiority	1 m (>3 m)	80% C, 17% T, 3% P	31% A, 71% $P2Y_{12}i$ (56% C)	NACE MACCE Bleeding	1 y 1 y 1 y	7.5% vs 7.7% 6.1% vs 5.9% 6.5% vs 9.4%	$P < .001$ $P = .001$ $P < .001$
POEM (2022)[74]	443	41% (7%)	EES vs OPC	Synergy	Noninferiority	1 m (1 m)	88% C, 10% T, <1% P	A preferred	MACE	1 y	4.82% vs OPC 9.4%	$P < .001$
EluNIR HBR (2021) (NCT03877848)	316	SIHD + ACS	RES vs OPC	EluNIR	Noninferiority	1 m SIHD, 3 m ACS	—	—	MACE	1 y	—	
Bioflow-DAPT (2023) (NCT04137510)	1949	SIHD + ACS	SES vs ZES	Orsiro vs Resolute Onyx	Noninferiority	1 m	—	—	MACE	1 y		
COMPARE 60/80 HBR (2023) (NCT04500912)	736	SIHD + ACS	SES vs SES	Supraflex Cruz vs Ultimaster Tansei	—	1 m	—	—	NACE	1 y		
TARGET SAFE (2023) (NCT03287167)	1720	SIHD + ACS	SES vs SES	Firehawk	Noninferiority	1 m (6 m)	—	—	NACE	1 y		
ZEVS-HBR (2025) (NCT05240781)	280	SIHD + ACS	SES vs ZES	Ultimaster vs Resolute Onyx	Noninferiority	1 m or 3 m (high ischemic risk)	—	$P2Y_{12}i$ preferred	TLF	1 y		
C-MODE (2025) (NCT05320926)	3744	SIHD only	ZES vs ZES	Resolute Onyx	Superiority	1 m (HBR arm)	C	A or C	NACE	1 y		
COMPARE STEMI ONE (2026) (NCT05491200)	1608	STEMI only	—	—	Noninferiority	30-45 d (12 m)	P	$P2Y_{12}i$ preferred	NACE	1 y		

A, aspirin; ACS, acute coronary syndromes; BMS, bare metal stent; C, clopidogrel; CV, cardiovascular; DAPT, dual antiplatelet therapy; DCS, drug coated stent; DES, drug-eluting stent; EES, everolimus-eluting stent; HBR, high bleeding risk; MACCE, major adverse cardiac or cerebral events (a composite of death from any cause; myocardial infarction; or stroke); MACE, major adverse cardiac events; MI, myocardial infarction; NACE, net adverse clinical events (a composite of death from any cause; myocardial infarction; stroke; or major bleeding); OPC, objective performance criteria; P, prasugrel; $P2Y_{12}i$, P2Y purinoceptor 12 inhibitor; RES, ridaforolimus eluting stent; SES, sirolimus-eluting stent; SIHD, stable ischemic heart disease; STEMI, ST-segment elevation myocardial infarction; T, ticagrelor; TLF, target lesion failure; TLR, target lesion revascularization; ZES, zotarolimus-eluting stent.

[a] For ongoing trials, the year represents the planned completion date. [b] For ongoing trials, N represents planned enrollment. [c] Historical cohort.



Central Illustration.
Tailored antiplatelet strategies in the contemporary drug-eluting stents era. ARC, Academic Research Consortium; CAD, coronary artery disease; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; ICH, intracranial hemorrhage; MI, myocardial infarction; MV, multivessel; OAC, oral anticoagulation; $P2Y_{12}i$, P2Y purinoceptor 12 inhibitors; PARIS, Patterns of nonadherence to antiplatelet regimen in stented patients; ST, stent thrombosis.

higher rate of stent thrombosis (1.0% vs 0.6%; $P = .04$) driven by RE-DUAL PCI and AUGUSTUS populations. The signal for harm with dual therapy in this meta-analysis, however, was largely confined to those at otherwise very low and low bleed risk with predominantly high ischemic risk. As a result, there remains ongoing debate as to the need and duration for a brief period of triple therapy in high ischemic, low bleed risk populations for which there are actively planned and ongoing trials evaluating 7 and 30 days of triple therapy (NCT04436978) and the use of more potent $P2Y_{12}i$ (NCT04695106).

Currently, ACC/AHA guidelines for patients on OAC undergoing PCI recommend discontinuation of aspirin at 1 to 4 weeks following PCI (Class 1)[25] with a 2021 North American Consensus update recommendation for ≤1-week aspirin, except with high thrombotic risk in which case aspirin should be extended to 1 month if bleeding risk is acceptable.[87] Clopidogrel is specifically identified as the preferred $P2Y_{12}i$ in this setting, with ticagrelor being an alternative and stating prasugrel should be avoided. Similarly, the ESC guidelines recommend aspirin be discontinued in ≤1 week in SIHD and patients with ACS undergoing

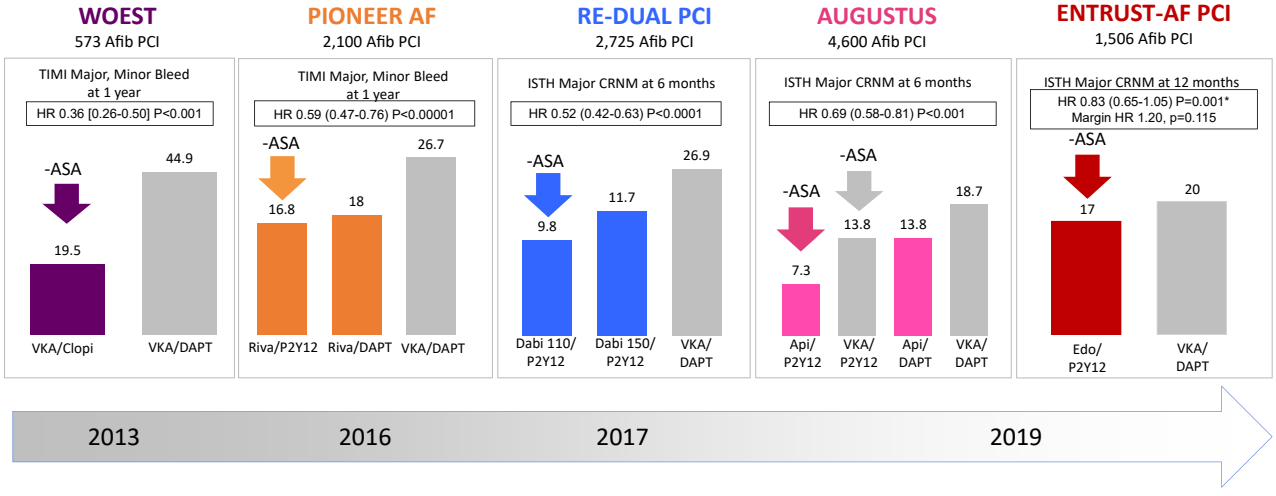


Figure 3.
Major trials of dual vs triple therapy in atrial fibrillation following percutaneous coronary intervention.
Afib, atrial fibrillation; Api, apixaban; ASA, aspirin; clopi, clopidogrel; CRNM, clinically relevant nonmajor bleeding; dabi, dabigatran; DAPT, dual antiplatelet therapy; Edo, edoxaban; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; $P2Y_{12}i$, P2Y purinoceptor 12 inhibitors; PCI, percutaneous coronary intervention; riva, rivaroxaban; TIMI, thrombolysis in myocardial infarction; VKA, vitamin K antagonist. *noninferiority

uncomplicated PCI (Class 1) and between 1 and 4 weeks if the risk of stent thrombosis outweighs bleeding risk (2a) with clopidogrel as the preferred $P2Y_{12}i$ agent.[88] Beyond 12 months, ESC guidelines, a 2020 ACC Expert Consensus document, and the 2021 North American Consensus update recommend the consideration for antiplatelet discontinuation (ESC, Class 2a).[35,89] Both societies recommend the use of DOACs over vitamin K antagonists (ACC/AHA, 2a; ESC, 1) (Figure 1).[25,88,90]

Short DAPT – all comers and aspirin-free strategies

Since 2011 there have been numerous studies evaluating <12-month DAPT strategies. The studies prior to 2018 predominantly evaluated 6-month DAPT durations among patients with SIHD and demonstrated significant benefits; thus, guidelines recommend 6 months of DAPT in SIHD.[20,25] Since 2018, there have been 8 additional trials to evaluate DAPT durations of 3 months or less in predominantly all-comer populations. Throughout this period, there has been a shift from aspirin to $P2Y_{12}i$, specifically the more potent $P2Y_{12}i$, as the preferred agent for antiplatelet monotherapy. The rationale behind this shift is the thought $P2Y_{12}i$ provides ample antithrombotic effects with a lower risk of gastrointestinal bleeding.[91] Further, because aspirin has not been compared to placebo with regard to ischemic outcomes and because the early studies that led to the routine use of aspirin predate the widespread adoption of contemporary lipid-lowering therapies, the degree to which aspirin provides further ischemic benefit remains in question. In this context, 6 of the 8 trials evaluating monotherapy following 1 or 3 months of DAPT have used $P2Y_{12}i$ (Table 4).

The 2 trials which utilized aspirin monotherapy after short DAPT were REDUCES-ACS and the ONE-MONTH DAPT trial. REDUCE-ACS (2019) evaluated 3- versus 12-month DAPT among 1460 patients with ACS (47% STEMI), and the ONE-MONTH DAPT trial (2021) evaluated 1-month DAPT among 3020 patients with SIHD or unstable angina. Both trials met noninferiority for NACE and demonstrated no differences in individual ischemic outcomes, including stent thrombosis.[92,93]

The remaining 6 have evaluated $P2Y_{12}i$ monotherapy after DAPT strategies of 1 month[94–96] and 3 months.[97–99] Among the 3-month DAPT trials, SMART-CHOICE (2019) was the first, demonstrating noninferiority for the primary end point of MACCE at 1 year (2.9% vs 2.5%; $P < .007$), with significantly lower rates of bleeding among the 3-month DAPT population in nearly 3000 patients (58% ACS; 11% STEMI) using predominantly clopidogrel (77%) as $P2Y_{12}i$ monotherapy.[97] The 2 remaining trials of 3-month DAPT employed ticagrelor for $P2Y_{12}i$ monotherapy and included TWILIGHT, which met superiority for the primary bleeding end point without an increase in MACE in a population of patients at high ischemic and/or bleeding risk (64% ACS; STEMI excluded),[98] and TICO, which met superiority for the primary end point NACE without a difference in the rates of MACE among a purely ACS population (36% STEMI).[99]

Among the 1-month trials, the first was GLOBAL LEADERS (2018), which included nearly 16,000 patients (47% ACS) and compared ticagrelor monotherapy for 23 months to 12-month DAPT followed by aspirin monotherapy. It failed to reach superiority for the primary composite end point of all-cause death or MI at 2 years (3.8% vs 4.4%; $P=.07$), and it did not demonstrate a significant reduction in major bleeding.[94] Subsequently, STOPDAPT-2 (2019) found monotherapy with clopidogrel after 1-month DAPT was noninferior to 12-month DAPT for both NACE and MACE, with less bleeding among a population of over 3000 patients (38% ACS; 18% STEMI).[95] Finally, the most recent $P2Y_{12}i$ monotherapy trial, STOPDAPT-2 ACS (2022), ambitiously compared 1 to 2 months of DAPT followed by clopidogrel monotherapy to 12 months of DAPT in over 4000 patients (76% ACS; 54% STEMI) but failed to demonstrate noninferiority for the primary outcome of NACE.[96]

As a result of most of these studies, the most recent AHA/ACC revascularization guidelines now include 2a recommendations to consider the transition to $P2Y_{12}i$ monotherapy after 1 to 3 months of DAPT after weighing bleeding and ischemic risks for both SIHD and ACS populations.[25] The 2020 ESC NSTEMI guidelines similarly state ticagrelor monotherapy can be considered after 3 months of DAPT based on the balance between bleeding and ischemic risks.[88] Although neither guideline gives explicit guidance as to which patients should specifically be considered, caution should be taken when considering 1-month DAPT outside of the HBR population, especially among those with ACS, until the ongoing studies evaluating ticagrelor and prasugrel monotherapy following 1-month DAPT among purely ACS and STEMI populations are reported (NCT03971500, NCT04753749, NCT05066789, and NCT05491200).

DAPT de-escalation and tailored therapies

DAPT de-escalation, ie, switching from a more potent $P2Y_{12}i$ (ticagrelor or prasugrel) to either clopidogrel or a lower dose of ticagrelor or prasugrel, has been evaluated in parallel with shorter DAPT durations to optimize bleeding and ischemic events. To date, there have been 6 trials involving >500 post-PCI ACS patients evaluating DAPT de-escalation using either an unguided or a guided strategy.[100–105] A guided de-escalation strategy is specifically one whereby de-escalation is tailored by either platelet function testing (PFT) or genetic testing to identify patients with inadequate platelet inhibition after de-escalation to prevent thrombotic complications. This strategy emerged first due to the variable responses seen with clopidogrel and CYP2C19*2/*3 loss-of-function allele carriers.[106,107] Subsequently, PFTs and other genetic markers were also found potentially useful as means to predict thrombotic and bleeding events further.[108,109]

For the 3 studies that have evaluated guided de-escalation, the results have been mixed. The ANTARCTIC trial (2015) was the first to test a guided strategy and randomized 877 elderly (≥75 years) patients with ACS (34% STEMI) to either a guided arm based on PFTs at 2 and 4 weeks following PCI or continued prasugrel 5 mg/d.[100] Here the guided arm (39% clopidogrel, 55% prasugrel 5 mg at 1 month) failed to demonstrate superiority for NACE at 1 year, having an identical event rate of 28% with the conventional arm and no differences in bleeding or ischemic outcomes. The TROPICAL-ACS trial (2017) subsequently evaluated PFT guidance among a larger population of 2610 patients with ACS (56% STEMI), whereby the guided group had PFT-guided maintenance DAPT with clopidogrel or prasugrel 2 weeks post-PCI compared with a control of prasugrel 10 mg and demonstrated noninferiority but not superiority for NACE, again finding no difference in bleeding or ischemic outcomes.[102] Most recently, POPular Genetics (2019) employed CYP2C19 genotype-guided de-escalation from potent $P2Y_{12}i$ (ticagrelor or prasugrel) to clopidogrel among 2488 patients with STEMI, where 61% switched to clopidogrel and again demonstrated noninferiority without superiority for NACE; however, this time investigators found significantly less bleeding (9.8% vs 12.5%; $P = 0.04$) among the guided de-escalation group.[103]

Interestingly, the 3 de-escalation trials without PFT demonstrated more promising results when de-escalation occurred 1-month post-PCI. The first unguided trial, TOPIC (2017), randomized 645 patients with ACS (40% STEMI) to either clopidogrel or continued potent $P2Y_{12}i$ therapy (prasugrel or ticagrelor) at 1 month and met superiority for the primary end point NACE at 1 year (13% vs 26%; $P > .01$), with lower bleeding and no difference in ischemic outcomes.[101] Similarly, among a larger 2697 patients with ACS population (54% STEMI), the TALOS-AMI trial (2021) found unguided de-escalation to clopidogrel from ticagrelor at 1 month resulted in superior NACE outcomes (4.6% vs 8.2%;

Table 4. Trials evaluating ≤3 months of DAPT since 2018 in all comers.

Trial (y)	N	ACS % (STEMI %) of total population	Design	DAPT duration (study vs control)	DAPT $P2Y_{12}i$	Monotherapy	Outcomes primary (secondary)	Timepoint	Result	RR/HR (95% CI)	*P* value
GLOBAL LEADERS (2018)[95]	15,968	47% (13%)	Superiority	1 mo vs 12 mo	T vs C or T	T (24 mo)	All death or MI	2 y	3.8% vs 4.4%	RR 0.87 (0.75-1.01)	$P = 0.07$
							BARC 3 or 5		2.04% vs 2.12%	RR 0.97 (0.78-1.20)	$P = 0.78$
REDUCE-ACS (2019)[93]	1460	100% (47%)	Noninferiority	3 mo vs 12 mo	41% C, 49% T, 10% P	A	NACE	1 y	8.2% vs 8.4%	—	$P < 0.001$
							BARC 2, 3, or 5		3.3% vs 4.0%	HR 0.82 (0.48-1.41)	$P = 0.47$
STOPDAPT-2 (2019)[96]	3009	38% (18%)	Superiority	1 mo vs 12 mo	C	C	NACE	1 y	2.4% vs 3.7%	HR 0.64 (0.42-0.98)	$P = 0.04$
							Major + minor bleeding		0.41% vs 1.54%	HR 0.26 (0.11-0.64)	$P = 0.004$
SMART-CHOICE (2019)[98]	2993	58% (11%)	Noninferiority	3 mo vs 12 mo	77% C, 19% T, 4% P	$P2Y_{12}i$	MACCE	1 y	2.9% vs 2.5%	—	$P < 0.007$
							Bleeding		2.0% vs 3.4%	HR 0.58 (0.36-0.92)	$P = 0.02$
TWILIGHT[a] (2019)[99]	7119	64% (0%)	Superiority	3 mo vs 12 mo	T	T	BARC 2, 3, or 5 bleeding	1 y	4.0% vs 7.1%	HR 0.56 (0.45-0.68)	$P < 0.001$
							MACCE		3.9% vs 3.9%	HR 0.99 (0.78-1.25)	$P < 0.001$
TICO (2020)[100]	3056	100% (36%)	Superiority	3 mo vs 12 mo	T	T	NACE	1 y	3.9% vs 5.9%	HR 0.66 (0.48-0.92)	$P = 0.01$
							TIMI major bleeding		1.7% vs 3.0%	HR 0.56 (0.34-0.91)	$P = 0.02$
One-Month DAPT (2021)[94]	3020	39% (36%)	Noninferiority	1 mo vs 6-12 mo	93% C, 6% T or P	A	NACE	1 y	5.9% vs 6.5%	HR 0.90 (0.68-1.2)	$P < 0.001$
							Major bleeding		1.7% vs 2.5%	HR 0.69 (0.42-1.13)	$P = 0.136$
STOPDAPT-2 ACS (2022)[97]	4169	76% (56%)	Noninferiority	1-2 mo vs 12 mo	C	C	NACE	1 y	3.2% vs 2.8%	HR 1.14 (0.80-1.62)	$P = 0.06$
							TIMI major + minor bleeding		0.5% vs 1.2%	HR 0.46 (0.23-0.94)	—

A, aspirin; ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; C, clopidogrel; CV, cardiovascular; DAPT, dual antiplatelet therapy; HR, hazard ratio; MACCE, major adverse cardiac or cerebral events; MI, myocardial infarction; NACE, net adverse clinical events; P, prasugrel; $P2Y_{12}i$, P2Y purinoceptor 12 inhibitor; RR, rate ratio; STEMI ST-segment elevation myocardial infarction; T, ticagrelor; TIMI, thrombolysis in myocardial infarction.

[a] High-risk patients (high ischemic or bleeding risk, not a purely all-comer population).

$P = .001$) and again lowered bleeding without increasing ischemic events.[105] Finally, in a predominantly NSTE-AMI population (2338 patients, 14% STEMI), the HOST-REDUCE-POLYTECH-ACS trial (2020) found unguided de-escalation to prasugrel 5 mg at 1 month was non-inferior to continued prasugrel 10 mg with respect to NACE (7.2% vs 10.1%; $P = .0007$), with lower rates of bleeding.[104]

Based on these data, the most recent ESC NSTE-ACS guidelines have given a 2b recommendation to consider de-escalation from prasugrel or ticagrelor to clopidogrel for patients with ACS unsuitable for potent $P2Y_{12}$i, which can be done in an unguided or guided manner.[24] The AHA/ACC guidelines currently have not commented on de-escalation; however, a recently updated consensus statement on PFTs and genetic testing was developed in 2019.[110] There it was noted that PFT and genetic testing should not be routinely used; however, they can be considered as a supplemental tool to assist with $P2Y_{12}$i tailoring in select patients. Two subsequent meta-analyses have demonstrated the benefit of guided $P2Y_{12}$i selection. The first included nearly 21,000 patients with SIHD and ACS who were post-PCI and found that a guided strategy led to a reduction in MACE (RR, 0.78; 95% CI, 0.63-0.95) as well as its components and a trend toward reduced bleeding (RR, 0.88; 95% CI, 0.77-1.01; $P = .069$).[111] The second study compared guided and potent $P2Y_{12}$i therapy with clopidogrel among nearly 62,000 patients with ACS. The guided $P2Y_{12}$i selection was the only approach associated with a reduction in MACE (RR, 0.8; 95% CI, 0.65-0.98) without a significant difference in bleeding.[112]

Switching $P2Y_{12}$i

Beyond de-escalation, the reassessments of ischemic and bleeding risks and numerous other factors, including cost, availability, side effects/intolerances, and the use of intravascular $P2Y_{12}$i, result in a need transition between $P2Y_{12}$i agents. Due to the different pharmacologic properties of $P2Y_{12}$i, concerns exist over the potential for drug-drug interactions and excessive or inadequate antiplatelet inhibition, and subsequent adverse bleeding or thrombotic events. Currently, there are limited data evaluating the optimal switching between $P2Y_{12}$i agents, and thus the practice of switching is largely driven by pharmacologic studies, with general recommendations for switching being discussed in detail in a 2017 International Expert Consensus document.[113] In general, when transitioning between oral $P2Y_{12}$i in the acute/early phase (<30 days since PCI), a full-loading dose of the new $P2Y_{12}$i should be given 24 hours after the last dose of the former $P2Y_{12}$i; however, when transitioning from clopidogrel to the more potent $P2Y_{12}$i agents, the loading dose of ticagrelor or prasugrel should be given immediately, not 24 hours following the last dose of clopidogrel. Beyond 30 days of the index PCI, the transition between oral $P2Y_{12}$i agents can be done with a maintenance dose started 24 hours after the last dose of the former $P2Y_{12}$i, except when transitioning from ticagrelor, due to the shorter half-life, in which case a loading dose of either clopidogrel or prasugrel should be given 24 hours after the last dose of ticagrelor. When bridging to the intravascular $P2Y_{12}$i cangrelor from oral $P2Y_{12}$i agents, it is recommended there be a 4-day washout of prasugrel and a 2-day washout of clopidogrel and ticagrelor prior to initiation of the cangrelor infusion without bolus. When transitioning from cangrelor to oral $P2Y_{12}$i agents, it is recommended that clopidogrel or prasugrel loading doses be given immediately after, not before, the infusion is stopped; otherwise, there may be inadequate antiplatelet effect as the active metabolites are unable to bind the ADP receptor site when it is occupied by cangrelor and are subsequently excreted. Ticagrelor, however, can be given prior to termination of the cangrelor infusion as it reversibly binds at a distinct site and remains systemically available with a half-life of 8 to 12 hours without drug-drug interaction and, in real-world practice, is the most frequently utilized $P2Y_{12}$i with Cangrelor.[114,115]

Conclusion

Since first incorporated into clinical practice, DAPT recommendations have seen significant change with advances in DES technology and our understanding of bleeding and ischemic risks. Although current society guidelines continue to favor reducing thrombotic/ischemic events, they have continually trended toward shorter DAPT durations for many populations and more individually tailored DAPT therapy. Based on multiple large outcomes trials, we know that patients with HBR can reduce their duration of DAPT to shorter (1-3 month) durations without incurring excessive thrombotic or ischemic risk. Further, there now exists an abundance of data and risk stratification tools to help clinicians choose antiplatelet therapies to meet more specific patient risk profiles. Though there has been an abundance of data in recent years, many questions still linger, especially among patients with mixed moderate-to-high bleeding and ischemic risks or those with comorbid atrial fibrillation requiring anticoagulation. Fortunately, there are ongoing trials to address many of these questions that will further our ability to tailor antiplatelet therapies among patients undergoing PCI.

Declaration of competing interest

Samit Shah receives research support from Women's Health Research at Yale, Abbott Vascular Inc, and the US Food and Drug Administration to support projects within the Yale-Mayo Clinic Center of Excellence in Regulatory Science and Innovation (CERSI, U01FD005938). Yuichi Saito receives honoraria from Daiichi Sankyo. Daniela Tirziu, Alaide Chieffo, Giulio Stefanini, Alexandra Lansky, Alexander Thomas, and Mauro Gitto reported no financial interests.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics Statement and Patient Consent

The data utilized in the production of this review article came directly from already published and publicly available sources without any identifying datapoints and therefore was exempt from IRB review.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2023.100607.

References

1. Gibson P. Salicylic acid for coronary thrombosis? *Lancet*. 1948;1(6512):965. https://doi.org/10.1016/s0140-6736(48)91585-2
2. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet*. 1988; 2(8607):349–360.
3. Gori T, Polimeni A, Indolfi C, Räber L, Adriaenssens T, Münzel T. Predictors of stent thrombosis and their implications for clinical practice. *Nat Rev Cardiol*. 2019;16(4):243–256. https://doi.org/10.1038/s41569-018-0118-5
4. Schatz RA, Goldberg S, Leon M, et al. Clinical experience with the Palmaz-Schatz coronary stent. *J Am Coll Cardiol*. 1991;17(6 Suppl B):155B–159B. https://doi.org/10.1016/0735-1097(91)90952-6
5. Colombo A, Hall P, Nakamura S, et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. *Circulation*. 1995;91(6):1676–1688. https://doi.org/10.1161/01.cir.91.6.1676
6. Schömig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med*. 1996;334(17):1084–1089. https://doi.org/10.1056/NEJM199604253341702

7. Wiviott SD, Antman EM, Braunwald E. Prasugrel. *Circulation*. 2010;122(4):394–403. https://doi.org/10.1161/CIRCULATIONAHA.109.921502
8. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*. 2014;371(23):2155–2166. https://doi.org/10.1056/NEJMoa1409312
9. Doyle BJ, Rihal CS, Gastineau DA, Holmes DR. Bleeding, blood transfusion, and increased mortality after percutaneous coronary intervention: implications for contemporary practice. *J Am Coll Cardiol*. 2009;53(22):2019–2027. https://doi.org/10.1016/j.jacc.2008.12.073
10. CURRENT-OASIS 7 Investigators, Mehta SR, Bassand JP, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med*. 2010;363(10):930–942. https://doi.org/10.1056/NEJMoa0909475
11. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348(9038):1329–1339. https://doi.org/10.1016/s0140-6736(96)09457-3
12. Berger PB, Bell MR, Rihal CS, et al. Clopidogrel versus ticlopidine after intracoronary stent placement. *J Am Coll Cardiol*. 1999;34(7):1891–1894. https://doi.org/10.1016/s0735-1097(99)00442-8
13. de Carvalho HC. Effectiveness of clopidogrel and aspirin versus ticlopidine and aspirin in preventing stent thrombosis after coronary stent implantation. *Rev Port Cardiol*. 1999;18(6):657–658.
14. Müller C, Büttner HJ, Petersen J, Roskamm H. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents. *Circulation*. 2000;101(6):590–593. https://doi.org/10.1161/01.cir.101.6.590
15. Taniuchi M, Kurz HI, Lasala JM. Randomized comparison of ticlopidine and clopidogrel after intracoronary stent implantation in a broad patient population. *Circulation*. 2001;104(5):539–543. https://doi.org/10.1161/hc3001.093435
16. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345(7):494–502. https://doi.org/10.1056/NEJMoa010746
17. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358(9281):527–533. https://doi.org/10.1016/s0140-6736(01)05701-4
18. Steinhubl SR, Berger PB, Mann III JT, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288(19):2411–2420. https://doi.org/10.1001/jama.288.19.2411
19. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice guidelines. *J Am Coll Cardiol*. 2016;68(10):1082–1115. https://doi.org/10.1016/j.jacc.2016.03.513
20. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018;39(3):213–260.
21. Wallentin L, Varenhorst C, James S, et al. Prasugrel achieves greater and faster P2Y12receptor-mediated platelet inhibition than clopidogrel due to more efficient generation of its active metabolite in aspirin-treated patients with coronary artery disease. *Eur Heart J*. 2008;29(1):21–30. https://doi.org/10.1093/eurheartj/ehm545
22. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001–2015. https://doi.org/10.1056/NEJMoa0706482
23. Wiviott SD, Trenk D, Frelinger AL, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the prasugrel in Comparison to clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in myocardial infarction 44 trial. *Circulation*. 2007;116(25):2923–2932. https://doi.org/10.1161/CIRCULATIONAHA.107.740324
24. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42(14):1289–1367. https://doi.org/10.1093/eurheartj/ehaa575
25. Writing Committee M, Lawton JS, Tamis-Holland JE, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(2):e21–e129.
26. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045–1057. https://doi.org/10.1056/NEJMoa0904327
27. Schüpke S, Neumann FJ, Menichelli M, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. *N Engl J Med*. 2019;381(16):1524–1534. https://doi.org/10.1056/NEJMoa1908973
28. Schnorbus B, Daiber A, Jurk K, et al. Effects of clopidogrel vs. prasugrel vs. ticagrelor on endothelial function, inflammatory parameters, and platelet function in patients with acute coronary syndrome undergoing coronary artery stenting: a randomized, blinded, parallel study. *Eur Heart J*. 2020;41(33):3144–3152. https://doi.org/10.1093/eurheartj/ehz917
29. Angiolillo DJ, Capranzano P. Pharmacology of emerging novel platelet inhibitors. *Am Heart J*. 2008;156:S10–S15. https://doi.org/10.1016/j.ahj.2008.06.004 (2)(suppl).
30. Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013;368(14):1303–1313. https://doi.org/10.1056/NEJMoa1300815
31. Bhatt DL, Lincoff AM, Gibson CM, et al. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med*. 2009;361(24):2330–2341. https://doi.org/10.1056/NEJMoa0908629
32. Harrington RA, Stone GW, McNulty S, et al. Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med*. 2009;361(24):2318–2329. https://doi.org/10.1056/NEJMoa0908628
33. White HD, Chew DP, Dauerman HL, et al. Reduced immediate ischemic events with cangrelor in PCI: a pooled analysis of the CHAMPION trials using the universal definition of myocardial infarction. *Am Heart J*. 2012;163(2):182–190. https://doi.org/10.1016/j.ahj.2011.11.001. e4-190 e184.
34. Qamar A, Bhatt DL. Current status of data on cangrelor. *Pharmacol Ther*. 2016;159:102–109. https://doi.org/10.1016/j.pharmthera.2016.01.004
35. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40(2):87–165. https://doi.org/10.1093/eurheartj/ehy394
36. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med*. 2001;344(25):1895–1903. https://doi.org/10.1056/NEJM200106213442503
37. Kastrati A, Mehilli J, Schühlen H, et al. A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. *N Engl J Med*. 2004;350(3):232–238. https://doi.org/10.1056/NEJMoa031859
38. Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med*. 2002;346(13):957–966. https://doi.org/10.1056/NEJMoa013404
39. Winchester DE, Wen X, Brearley WD, Park KE, Anderson RD, Bavry AA. Efficacy and safety of glycoprotein IIb/IIIa inhibitors during elective coronary revascularization: A meta-analysis of randomized trials performed in the era of stents and thienopyridines. *J Am Coll Cardiol*. 2011;57(10):1190–1199. https://doi.org/10.1016/j.jacc.2010.10.030
40. Vaduganathan M, Harrington RA, Stone GW, et al. Evaluation of ischemic and bleeding risks associated with 2 parenteral antiplatelet strategies comparing cangrelor with glycoprotein IIb/IIIa inhibitors: an exploratory analysis from the CHAMPION trials. *JAMA Cardiol*. 2017;2(2):127–135. https://doi.org/10.1001/jamacardio.2016.4556
41. Yerasi C, Case BC, Chezar-Azerrad C, et al. Cangrelor vs. glycoprotein IIb/IIIa inhibitors during percutaneous coronary intervention. *Am Heart J*. 2021;238:59–65. https://doi.org/10.1016/j.ahj.2021.04.013
42. Moser M, Bertram U, Peter K, Bode C, Ruef J. Abciximab, eptifibatide, and tirofiban exhibit dose-dependent potencies to dissolve platelet aggregates. *J Cardiovasc Pharmacol*. 2003;41(4):586–592. https://doi.org/10.1097/00005344-200304000-00011
43. Tricoci P, Huang Z, Held C, et al. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. *N Engl J Med*. 2012;366(1):20–33. https://doi.org/10.1056/NEJMoa1109719
44. Capodanno D, Angiolillo DJ. Pretreatment with antiplatelet drugs in invasively managed patients with coronary artery disease in the contemporary era: review of the evidence and practice guidelines. *Circ Cardiovasc Interv*. 2015;8(3), e002301. https://doi.org/10.1161/CIRCINTERVENTIONS.114.002301
45. Sabatine MS, Cannon CP, Gibson CM, et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *JAMA*. 2005;294(10):1224–1232. https://doi.org/10.1001/jama.294.10.1224
46. Widimsky P, Motovská Z, Simek S, et al. Clopidogrel pre-treatment in stable angina: for all patients > 6 h before elective coronary angiography or only for angiographically selected patients a few minutes before PCI? A randomized multicentre trial PRAGUE-8. *Eur Heart J*. 2008;29(12):1495–1503. https://doi.org/10.1093/eurheartj/ehn169
47. Di Sciascio G, Patti G, Pasceri V, et al. Effectiveness of in-laboratory high-dose clopidogrel loading versus routine pre-load in patients undergoing percutaneous coronary intervention: results of the ARMYDA-5 preload (antiplatelet therapy for Reduction of myocardial Damage during angioplasty) randomized trial. *J Am Coll Cardiol*. 2010;56(7):550–557. https://doi.org/10.1016/j.jacc.2010.01.067
48. Bellemain-Appaix A, O'Connor SA, Silvain J, et al. Association of clopidogrel pretreatment with mortality, cardiovascular events, and major bleeding among patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *JAMA*. 2012;308(23):2507–2516. https://doi.org/10.1001/jama.2012.50788
49. Zeymer U, Amtz HR, Mark B, et al. Efficacy and safety of a high loading dose of clopidogrel administered prehospitally to improve primary percutaneous coronary intervention in acute myocardial infarction: the randomized CIPAMI trial. *Clin Res Cardiol*. 2012;101(4):305–312. https://doi.org/10.1007/s00392-011-0393-1
50. Montalescot G, Bolognese L, Dudek D, et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. *N Engl J Med*. 2013;369(11):999–1010. https://doi.org/10.1056/NEJMoa1308075
51. van Montalescot G, van 't Hof AW, Lapostolle F, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *N Engl J Med*. 2014;371(11):1016–1027. https://doi.org/10.1056/NEJMoa1407024
52. Tarantini G, Mojoli M, Varbella F, et al. Timing of oral P2Y12 inhibitor administration in patients with non-ST-segment elevation acute coronary syndrome. *J Am Coll Cardiol*. 2020;76(21):2450–2459. https://doi.org/10.1016/j.jacc.2020.08.053

53. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39(2):119–177. https://doi.org/10.1093/eurheartj/ehx393
54. O'gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127(4):e362–e425. https://doi.org/10.1161/CIR.0b013e3182742cf6
55. De Luca L. Pre-treatment with dual antiplatelet therapy in non-ST-segment elevation acute coronary syndromes: landing from guidelines recommendations to real-world ground. *Eur Heart J Cardiovasc Pharmacother*. 2021;7(5):442–444. https://doi.org/10.1093/ehjcvp/pvab045
56. Giustino G, Baber U, Sartori S, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. *J Am Coll Cardiol*. 2015;65(13):1298–1310. https://doi.org/10.1016/j.jacc.2015.01.039
57. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med*. 2011;364(3):226–235. https://doi.org/10.1056/NEJMoa1002358
58. Schoergenhofer C, Hobl EL, Schellongowski P, et al. Clopidogrel in critically ill patients. *Clin Pharmacol Ther*. 2018;103(2):217–223. https://doi.org/10.1002/cpt.878
59. Droppa M, Vaduganathan M, Venkateswaran RV, et al. Cangrelor in cardiogenic shock and after cardiopulmonary resuscitation: A global, multicenter, matched pair analysis with oral $P2Y_{12}$ inhibition from the IABP-SHOCK II trial. *Resuscitation*. 2019;137:205–212. https://doi.org/10.1016/j.resuscitation.2019.02.008
60. Prüller F, Bis L, Milke OL, et al. Cangrelor induces more potent platelet inhibition without increasing bleeding in resuscitated patients. *J Clin Med*. 2018;7(11). https://doi.org/10.3390/jcm7110442
61. Gorog DA, Price S, Sibbing D, et al. Antithrombotic therapy in patients with acute coronary syndrome complicated by cardiogenic shock or out-of-hospital cardiac arrest: a joint position paper from the European Society of Cardiology (ESC) Working Group on Thrombosis, in association with the Acute Cardiovascular Care Association (ACCA) and European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J Cardiovasc Pharmacother*. 2021;7(2):125–140. https://doi.org/10.1093/ehjcvp/pvaa009
62. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372(19):1791–1800. https://doi.org/10.1056/NEJMoa1500857
63. Connolly SJ, Eikelboom JW, Bosch J, et al. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet*. 2018;391(10117):205–218. https://doi.org/10.1016/S0140-6736(17)32458-3
64. Koo BK, Kang J, Park KW, et al. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. *Lancet*. 2021;397(10293):2487–2496. https://doi.org/10.1016/S0140-6736(21)01063-1
65. Kang J, Park KW, Lee H, et al. Aspirin versus clopidogrel for long-term maintenance monotherapy after percutaneous coronary intervention: the HOST-EXAM Extended Study. *Circulation*. 2023;147(2):108–117. https://doi.org/10.1161/CIRCULATIONAHA.122.062770
66. Valgimigli M, Costa F, Lokhnygina Y, et al. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. *Eur Heart J*. 2017;38(11):804–810. https://doi.org/10.1093/eurheartj/ehw525
67. Urban P, Meredith IT, Abizaid A, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N Engl J Med*. 2015;373(21):2038–2047. https://doi.org/10.1056/NEJMoa1503943
68. Ariotti S, Adamo M, Costa F, et al. Is bare-metal stent implantation still justifiable in high bleeding risk patients undergoing percutaneous coronary intervention?: A pre-specified analysis from the ZEUS trial. *JACC Cardiovasc Interv*. 2016;9(5):426–436. https://doi.org/10.1016/j.jcin.2015.11.015
69. Varenne O, Cook S, Sideris G, et al. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. *Lancet*. 2018;391(10115):41–50. https://doi.org/10.1016/S0140-6736(17)32713-7
70. Kandzari DE, Kirtane AJ, Windecker S, et al. One-month dual antiplatelet therapy following percutaneous coronary intervention with zotarolimus-eluting stents in high-bleeding-risk patients. *Circ Cardiovasc Interv*. 2020;13(11), e009565. https://doi.org/10.1161/CIRCINTERVENTIONS.120.009565
71. Windecker S, Latib A, Kedhi E, et al. Polymer-based or polymer-free stents in patients at high bleeding risk. *N Engl J Med*. 2020;382(13):1208–1218. https://doi.org/10.1056/NEJMoa1910021
72. Mehran R, Cao D, Angiolillo DJ, et al. 3- or 1-month DAPT in patients at high bleeding risk undergoing everolimus-eluting stent implantation. *JACC Cardiovasc Interv*. 2021;14(17):1870–1883. https://doi.org/10.1016/j.jcin.2021.07.016
73. Valgimigli M, Frigoli E, Heg D, et al. Dual antiplatelet therapy after PCI in patients at high bleeding risk. *N Engl J Med*. 2021;385(18):1643–1655. https://doi.org/10.1056/NEJMoa2108749
74. Pivato CA, Reimers B, Testa L, et al. One-month dual antiplatelet therapy after bioresorbable polymer everolimus-eluting stents in high bleeding risk patients. *J Am Heart Assoc*. 2022;11(6), e023454. https://doi.org/10.1161/JAHA.121.023454
75. Krucoff MW, Urban P, Tanguay JF, et al. Global approach to high bleeding risk patients with polymer-free drug-coated coronary stents: the LF II study. *Circ Cardiovasc Interv*. 2020;13(4), e008603. https://doi.org/10.1161/CIRCINTERVENTIONS.119.008603
76. Valgimigli M, Smits PC, Frigoli E, et al. Duration of antiplatelet therapy after complex percutaneous coronary intervention in patients at high bleeding risk: a Master DAPT trial sub-analysis. *Eur Heart J*. 2022;43(33):3100–3114. https://doi.org/10.1093/eurheartj/ehac284
77. Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention. *Circulation*. 2019;140(3):240–261. https://doi.org/10.1161/CIRCULATIONAHA.119.040167
78. Cao D, Mehran R, Dangas G, et al. Validation of the Academic Research Consortium high bleeding risk definition in contemporary PCI patients. *J Am Coll Cardiol*. 2020;75(21):2711–2722. https://doi.org/10.1016/j.jacc.2020.03.070
79. Costa F, Van Klaveren D, Feres F, et al. Dual antiplatelet therapy duration based on ischemic and bleeding risks after coronary stenting. *J Am Coll Cardiol*. 2019;73(7):741–754. https://doi.org/10.1016/j.jacc.2018.11.048
80. Hansen ML, Sørensen R, Clausen MT, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med*. 2010;170(16):1433–1441. https://doi.org/10.1001/archinternmed.2010.271
81. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med*. 2016;375(25):2423–2434. https://doi.org/10.1056/NEJMoa1611594
82. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet*. 2013;381(9872):1107–1115. https://doi.org/10.1016/S0140-6736(12)62177-1
83. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med*. 2017;377(16):1513–1524. https://doi.org/10.1056/NEJMoa1708454
84. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med*. 2019;380(16):1509–1524. https://doi.org/10.1056/NEJMoa1817083
85. Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet*. 2019;394(10206):1335–1343. https://doi.org/10.1016/S0140-6736(19)31872-0
86. Gargiulo G, Goette A, Tijssen J, et al. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. *Eur Heart J*. 2019;40(46):3757–3767. https://doi.org/10.1093/eurheartj/ehz732
87. Angiolillo DJ, Bhatt DL, Cannon CP, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: A North American perspective: 2021 update. *Circulation*. 2021;143(6):583–596. https://doi.org/10.1161/CIRCULATIONAHA.120.050438
88. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42(5):373–498.
89. Kumbhani DJ, Cannon CP, Beavers CJ, et al. 2020 ACC Expert Consensus decision pathway for anticoagulant and antiplatelet therapy in patients with atrial fibrillation or venous thromboembolism undergoing percutaneous coronary intervention or with atherosclerotic cardiovascular disease: A report of the American College of Cardiology solution set oversight committee. *J Am Coll Cardiol*. 2021;77(5):629–658. https://doi.org/10.1016/j.jacc.2020.09.011
90. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2019;74(1):104–132. https://doi.org/10.1016/j.jacc.2019.01.011
91. Tomaniak M, Storey RF, Serruys PW. Aspirin-free antiplatelet regimens after PCI: when is it best to stop aspirin and who could ultimately benefit? *EuroIntervention*. 2020;15(13):1125–1129. https://doi.org/10.4244/EIJY19M10_01
92. De Luca G, Damen SA, Camaro C, et al. Final results of the randomised evaluation of short-term dual antiplatelet therapy in patients with acute coronary syndrome treated with a new-generation stent (REDUCE trial). *EuroIntervention*. 2019;15(11):e990–e998. https://doi.org/10.4244/EIJ-D-19-00539
93. Hong SJ, Kim JS, Hong SJ, et al. 1-month dual-antiplatelet therapy followed by aspirin monotherapy after polymer-free drug-coated stent implantation: one-month DAPT trial. *JACC Cardiovasc Interv*. 2021;14(16):1801–1811. https://doi.org/10.1016/j.jcin.2021.06.003
94. Vranckx P, Valgimigli M, Jüni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet*. 2018;392(10151):940–949. https://doi.org/10.1016/S0140-6736(18)31858-0
95. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2

randomized clinical trial. *JAMA*. 2019;321(24):2414–2427. https://doi.org/10.1001/jama.2019.8145
96. Watanabe H, Morimoto T, Natsuaki M, et al. Comparison of clopidogrel monotherapy after 1 to 2 months of dual antiplatelet therapy with 12 months of dual antiplatelet therapy in patients with acute coronary syndrome: the STOPDAPT-2 ACS randomized clinical trial. *JAMA Cardiol*. 2022;7(4):407–417. https://doi.org/10.1001/jamacardio.2021.5244
97. Hahn JY, Song YB, Oh JH, et al. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. *JAMA*. 2019;321(24):2428–2437. https://doi.org/10.1001/jama.2019.8146
98. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med*. 2019;381(21):2032–2042. https://doi.org/10.1056/NEJMoa1908419
99. Kim BK, Hong SJ, Cho YH, et al. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. *JAMA*. 2020;323(23):2407–2416. https://doi.org/10.1001/jama.2020.7580
100. Cayla G, Cuisset T, Silvain J, et al. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (Antarctic): an open-label, blinded-endpoint, randomised controlled superiority trial. *Lancet*. 2016;388(10055):2015–2022. https://doi.org/10.1016/S0140-6736(16)31323-X
101. Cuisset T, Deharo P, Quilici J, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. *Eur Heart J*. 2017;38(41):3070–3078. https://doi.org/10.1093/eurheartj/ehx175
102. Sibbing D, Aradi D, Jacobshagen C, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. *Lancet*. 2017;390(10104):1747–1757. https://doi.org/10.1016/S0140-6736(17)32155-4
103. Claassens DMF, Vos GJA, Bergmeijer TO, et al. A genotype-guided strategy for oral P2Y12 inhibitors in primary PCI. *N Engl J Med*. 2019;381(17):1621–1631. https://doi.org/10.1056/NEJMoa1907096
104. Kim HS, Kang J, Hwang D, et al. Prasugrel-based de-escalation of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (HOST-REDUCE-POLYTECH-ACS): an open-label, multicentre, non-inferiority randomised trial. *Lancet*. 2020;396(10257):1079–1089. https://doi.org/10.1016/S0140-6736(20)31791-8
105. Kim CJ, Park MW, Kim MC, et al. Unguided de-escalation from ticagrelor to clopidogrel in stabilised patients with acute myocardial infarction undergoing percutaneous coronary intervention (TALOS-AMI): an investigator-initiated, open-label, multicentre, non-inferiority, randomised trial. *Lancet*. 2021;398(10308):1305–1316. https://doi.org/10.1016/S0140-6736(21)01445-8
106. Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA*. 2010;304(16):1821–1830. https://doi.org/10.1001/jama.2010.1543
107. Jeong YH, Tantry US, Kim IS, et al. Effect of CYP2C19*2 and *3 loss-of-function alleles on platelet reactivity and adverse clinical events in East Asian acute myocardial infarction survivors treated with clopidogrel and aspirin. *Circ Cardiovasc Interv*. 2011;4(6):585–594. https://doi.org/10.1161/CIRCINTERVENTIONS.111.962555
108. Stone GW, Witzenbichler B, Weisz G, et al. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet*. 2013;382(9892):614–623. https://doi.org/10.1016/S0140-6736(13)61170-8
109. Aradi D, Kirtane A, Bonello L, et al. Bleeding and stent thrombosis on P2Y12-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. *Eur Heart J*. 2015;36(27):1762–1771. https://doi.org/10.1093/eurheartj/ehv104
110. Sibbing D, Aradi D, Alexopoulos D, et al. Updated expert consensus statement on platelet function and genetic testing for guiding P2Y12 receptor inhibitor treatment in percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2019;12(16):1521–1537. https://doi.org/10.1016/j.jcin.2019.03.034
111. Galli M, Benenati S, Capodanno D, et al. Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *Lancet*. 2021;397(10283):1470–1483. https://doi.org/10.1016/S0140-6736(21)00533-X
112. Galli M, Benenati S, Franchi F, et al. Comparative effects of guided vs. potent P2Y12 inhibitor therapy in acute coronary syndrome: a network meta-analysis of 61 898 patients from 15 randomized trials. *Eur Heart J*. 2022;43(10):959–967. https://doi.org/10.1093/eurheartj/ehab836
113. Angiolillo DJ, Rollini F, Storey RF, et al. International expert consensus on switching platelet $P2Y_{12}$ receptor-inhibiting therapies. *Circulation*. 2017;136(20):1955–1975. https://doi.org/10.1161/CIRCULATIONAHA.117.031164
114. De Luca L, Steg PG, Bhatt DL, Capodanno D, Angiolillo DJ. Cangrelor: clinical data, contemporary use, and future perspectives. *J Am Heart Assoc*. 2021;10(13), e022125. https://doi.org/10.1161/JAHA.121.022125
115. Franchi F, Rollini F, Rivas A, et al. Platelet inhibition with cangrelor and crushed ticagrelor in patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Circulation*. 2019;139(14):1661–1670. https://doi.org/10.1161/CIRCULATIONAHA.118.038317