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REVIEW

Personalized Approaches to Antiplatelet Treatment for Cardiovascular Diseases: An Umbrella Review

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Abstract: Antiplatelet therapy is the cornerstone of antithrombotic prevention in patients with established atherosclerosis, since it has been proven to reduce coronary, cerebrovascular, and peripheral thrombotic events. However, the protective effect of antiplatelet agents is counterbalanced by an increase of bleeding events that impacts on patients' mortality and morbidity. Over the last years, great efforts have been made toward personalized antithrombotic strategies according to the individual bleeding and ischemic risk profile, aiming to maximizing the net clinical benefit. The development of risk scores, consensus definitions, and the new promising artificial intelligence tools, as well as the assessment of platelet responsiveness using platelet function and genetic testing, are now part of an integrated approach to tailored antithrombotic management. Moreover, novel strategies are available including dual antiplatelet therapy intensity and length modulation in patients undergoing myocardial revascularization, the use of $P2Y_{12}$ inhibitor monotherapy for long-term secondary prevention, the implementation of parenteral antiplatelet agents in high-ischemic risk clinical settings, and combination of antiplatelet agents with low-dose factor Xa inhibitors (dual pathway inhibition) in patients suffering from polyvascular disease. This review summarizes the currently available evidence and provides an overview of the principal risk-stratification tools and antiplatelet strategies to inform treatment decisions in patients with cardiovascular disease.

Keywords: antiplatelet therapy, cardiovascular disease, $P2Y_{12}$ inhibitor, aspirin

Introduction

Antiplatelet therapy is the cornerstone of antithrombotic prevention in patients with established atherosclerosis, including those with coronary artery disease (CAD).[1–3] Although antiplatelet therapy is highly effective in reducing ischemic events and thrombotic complications, it invariably increases bleeding occurrence which may have a detrimental impact on patient mortality and morbidity.[4,5] Understanding the bleeding and ischemic risks balance is critical to inform decisions on antiplatelet therapy and efforts have been made toward finding the optimal compromise between prevention of thrombotic events and avoidance of bleeding complications.[6] Current guidelines stress the importance of risk stratification according to baseline characteristics and clinical presentation to identify those who could benefit from shorter or less intense antiplatelet therapy, and vice versa.[1–3] The aim of the present review is to summarize the evidence on antiplatelet therapy in patients with cardiovascular disease, providing an overview of the principal risk-stratification tools and antithrombotic available strategies, including novel emerging approaches (Figure 1). Given the preeminent role of antiplatelet therapy in patients with coronary artery disease undergoing percutaneous revascularization, we initially focused on this broad subset of patients; additionally, we also provided insights about personalized antiplatelet approaches in patients suffering from other specific cardiovascular conditions, including cerebrovascular and polyvascular disease.

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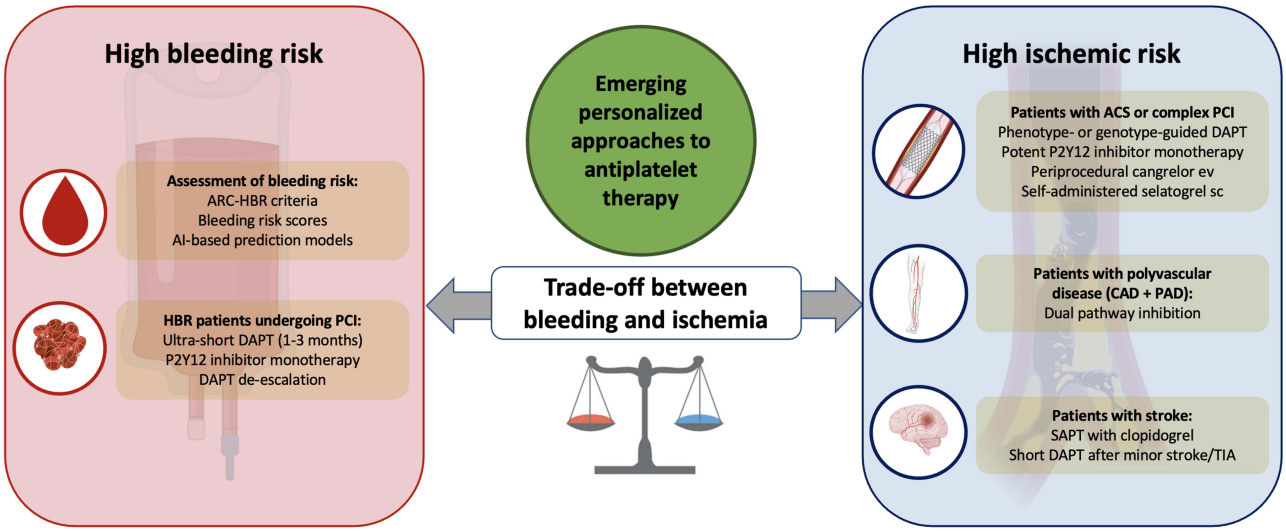

Figure 1 Emerging personalized approaches to antiplatelet therapy.

Antiplatelet Therapy in Patients with Coronary Artery Disease Undergoing Percutaneous Coronary Intervention

In the past years, dual antiplatelet therapy (DAPT), consisting of aspirin plus a $P2Y_{12}$-receptor inhibitor, was recommended for at least 12 months after percutaneous coronary intervention (PCI).[7] This default strategy was primarily driven by concerns about the risk of stent thrombosis with first-generation drug-eluting stents (DES) but gave little consideration to individual patient characteristics and risk factors. More recently, several randomized controlled trials (RCTs) have evaluated the safety and effectiveness of different DAPT strategies, tailoring the length and intensity of DAPT to optimize net clinical outcomes. Novel antithrombotic strategies, such as short DAPT followed by $P2Y_{12}$ inhibitor monotherapy and platelet function-guided or genotype-guided de-escalation or escalation of $P2Y_{12}$ inhibition, have been investigated. Moreover, in the context of antiplatelet therapy, risk scores have been developed to assess the risk of bleeding or ischemic events and inform decision-making on antiplatelet therapy. Assessment of bleeding and ischemic risks is achieved by the evaluation of clinical variables, including patient history, frailty, comorbidities, and laboratory examinations. In the PCI setting, procedural and technical features also play an important role in determining the subsequent ischemic or bleeding risks and should be taken into consideration.[8]

Stratification of Bleeding and Thrombotic Risk

The PARIS risk model is one of the first validated tools for prediction of out-of-hospital thrombotic and bleeding events in patients undergoing PCI with DES.[9] It consists of two different prediction models, one for coronary thrombotic events and the other for BARC (Bleeding Academic Research Consortium) 3 or 5 major bleeding, used to develop integer-based risk scores that categorize patients into three risk groups (low risk: <3, moderate risk: 3–7, and high risk: ≥8 points). Independent predictors of thrombotic complications included acute coronary syndrome (ACS), prior revascularization, diabetes mellitus, renal dysfunction, and current smoking. Independent predictors of major bleeding included older age, body mass index, concomitant use of anticoagulant at discharge, anemia, current smoking, and renal dysfunction. Each model displayed modest discrimination and adequate calibration. Other alternative scores assessing the long-term bleeding or thrombotic risk are summarized in Table 1 and include BleeMACS, the Dutch aspirin score, the PRECISE-DAPT score, the DAPT score, and the REACH score.[10–14] The PRECISE-DAPT score is a five-item risk score that incorporates the following clinical features: age, creatinine clearance, hemoglobin, white-blood-cell count, and previous spontaneous bleeding.[14] It provides a tool for the prediction of out-of-hospital TIMI (thrombolysis in myocardial infarction) major or minor bleeding during DAPT in patients undergoing PCI and has been endorsed by current guidelines.[1] The DAPT score was developed from 11,648 patients enrolled in the DAPT trial who tolerated DAPT during the first year post PCI without major adverse cardiovascular events (MACE) or bleeding. The DAPT score aimed to identify patients who could derive benefit from DAPT extension (beyond 1 year and up to 30 months) without bleeding-related harm and includes a combination of ischemic and bleeding predictors: age, heart failure/low left ventricular ejection fraction, vein

Table 1 Risk Scores for Evaluating Baseline Bleeding and/or Thrombotic Risk Among Patients with CAD

	REACH	Dutch ASA Score	DAPT	PARIS	PRECISE-DAPT	BleeMACS
Year	2010	2014	2016	2016	2017	2018
Development dataset	REACH registry (N=56,616)	Dutch ASA registry (N=235,531)	DAPT trial (N=11,648)	PARIS registry (N=4190)	Pooled analysis of 8 RCTs (N=14,963)	BleeMACS registry (N=15,401)
Patient population	Patients with established CAD, CVD, or PAD	New low-dose aspirin users	Event-free patients at 12 months after PCI	Stable CAD and ACS	Stable CAD and ACS	ACS patients undergoing PCI
Bleeding outcome	Non-fatal hemorrhagic stroke or bleeding leading to hospitalization and transfusion	Upper GI bleeding	GUSTO moderate or severe bleeding	BARC 3 or 5 major bleeding	Out-of-hospital TIMI major or minor bleeding	Post-discharge protocol-defined serious bleeding
Thrombotic outcome	–	–	MI or definite/ probable ST	MI or definite/ probable ST	–	–
Follow-up	2 years	530 days	30 months	2 years	552 days	1 year
Score range	0 to 23	0 to 15	–2 to 10	0 to 14	0 to 100	0 to 80
Development discrimination	AUC 0.68	AUC 0.64	AUC 0.68 (bleeding outcome) AUC 0.70 (thrombotic outcome)	AUC 0.72	AUC 0.73	AUC 0.71
Validating dataset	CHARISMA (N=15,603)	Dutch health insurance database (N=32,613)	PROTECT (N=8136)	ADAPT-DES (N=8130)	PLATO (N=8595) Bern PCI registry (N=6172)	SWEDEHEART (N=96,239)
Validation discrimination	AUC 0.64	AUC 0.63	AUC 0.64 (bleeding outcome) AUC 0.64 (thrombotic outcome)	AUC 0.64	AUC 0.70 (PLATO) AUC 0.66 (Bern PCI registry)	AUC 0.65

Abbreviations: CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; ACS, acute coronary syndrome; MI, myocardial infarction; ST, stent thrombosis; NSAID, non-steroidal anti-inflammatory drug; BARC, Bleeding Academic Research Consortium; GUSTO, Global Strategies for Opening Occluded Coronary Arteries; TIMI, thrombolysis in myocardial infarction; AUC, area under the curve.

graft stenting, myocardial infarction (MI) at presentation, prior MI or PCI, diabetes, stent diameter <3 mm, smoking, and paclitaxel-eluting stent.[11] The DAPT score has been externally validated in several studies with conflicting results.[15–18]

When interpreting risk scores, it must be remembered that they are all intrinsically influenced by the characteristics of the study populations used for their development and may not be applicable to the general population. In order to overcome these limitations, in 2019 an Academic Research Consortium (ARC) initiative proposed a consensus definition of high bleeding risk (HBR) patients based on the presence of well-recognized major and minor risk criteria in a PCI setting.[19] Patients should be considered HBR if at least 1 major or 2 minor criteria are met. A 1-year incidence of BARC 3 or 5 bleeding ≥4% or intracranial hemorrhage ≥1% has been arbitrarily proposed as a cut-off to define true HBR patients. The 2023 European guidelines for the management of ACS endorsed the use of ARC-HBR criteria to guide decisions on DAPT and, following the same approach, criteria for defining patients at high or moderate thrombotic risk were provided (Table 2).

Table 2 High Bleeding (ARC-HBR) and Thrombotic (ESC Guideline) Risk Definitions

Academic Research Consortium High Bleeding Risk Definition		European Society of Cardiology Thrombotic Risk Definition	
Major Criteria	**Minor Criteria**	**High Thrombotic Risk**	**Moderate Thrombotic Risk**
At Least 1 Criterion Needed	**At Least 2 Criteria Needed**	**Complex CAD + At Least 1 Criterion**	**Non-Complex CAD + At Least 1 Criterion**
		Risk enhancers	
Long-term use of oral anticoagulation	Age >75 years	Diabetes mellitus requiring medication	Diabetes mellitus requiring medication
Severe/end-stage CKD (eGFR <30 mL/min)	Moderate CKD (eGFR 30 to 59 mL/min)	History of recurrent MI	History of recurrent MI
Hemoglobin <11 g/dL	Hemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women	Multivessel CAD	Polyvascular disease (CAD + PAD)
Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months or at any time, if recurrent	Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months not meeting the major criterion	Polyvascular disease (CAD + PAD)	CKD with eGFR 15–59 mL/min
Moderate or severe thrombocytopenia (platelet count <100,000/dL)	Long-term use of oral NSAIDs or steroids	Premature (<45 years) or accelerated (new lesion within a 2-year time frame) CAD	
Chronic bleeding diathesis	Any ischemic stroke at any time not meeting the major criterion	Concomitant systemic inflammatory disease (eg, human immunodeficiency virus, systemic lupus erythematosus, chronic arthritis)	
Liver cirrhosis with portal hypertension		CKD with eGFR 15–59 mL/min	
Active malignancy		*Technical aspects*	
Previous spontaneous ICH (at any time)		At least 3 stents implanted	
Previous traumatic ICH (within 12 months)		At least 3 lesions treated	
Presence of a bAVM		Total stent length >60 mm	
Moderate or severe ischemic stroke within the past 6 months		History of complex revascularization (left main, bifurcation stenting with >2 stents implanted, chronic total occlusion, stenting of last patent vessel)	
Non-deferrable major surgery on DAPT		History of stent thrombosis on antiplatelet treatment	
Recent major surgery or major trauma within 30 days before PCI			

Notes: ESC thrombotic risk definition: CAD patients are stratified into 2 different risk groups (high versus moderately increased thrombotic or ischemic risk). Stratification of patients toward complex versus non-complex CAD is based on individual clinical judgment with knowledge of patients' cardiovascular history and/or coronary anatomy. Adapted from Byrne RA, Xavier Rossello JJC, Barbato E, et al. Roberto E, ESC Scientific Document Group, 2023 ESC guidelines for the management of acute coronary syndromes: developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC), *Eur Heart J.* 2023, ehad191, by permission of Oxford University Press.[3]
Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; bAVM, brain arteriovenous malformation; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; ICH, intracranial hemorrhage; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

Another well-known limitation of risk scores is that they are usually derived by applying classical statistic regression models and tend to underestimate interactions between variables in complex scenarios, especially when a large number of clinical, anatomical, and procedural features may be reciprocally influenced.[20] Novel opportunities may reside in the ability of artificial intelligence (AI) in generating decision pathways truly individualized for every single patient.[21] As an

example, the PRAISE score, a risk score aimed to predict 1-year post-discharge all-cause death, myocardial infarction, and major bleeding, was recently derived using a machine learning model trained on a cohort of 19,826 ACS patients from the BleeMACS and RENAMI registries.[22] AI-based approaches hold the promise of improving predictive model performance and could represent a turning point in the field of precision medicine; however, bigger studies and more evidence are warranted to implement their use in the clinical practice.

Strategies for Thrombotic Risk Reduction

Extended DAPT

In the early years after the spread of first-generation DES, safety concerns about the risk of late stent thrombosis were raised, highlighting the need for a more intense and prolonged DAPT.[23,24] The advent of newer-generation DES, associated with a very low incidence of stent thrombosis (<1%/year), mitigated this clinical issue.[25] However, the observation that patients with CAD remain at risk for recurrent spontaneous ischemic events provided the rationale for investigations on prolonged DAPT duration, even beyond one year.[26] To date, 9 RCTs have compared extended DAPT (up to 48 months) with standard 6–12-month DAPT (Table 3).[26–34] Most trials failed to demonstrate a clear benefit of extended DAPT, and pooled analyses showed that the reduction in myocardial infarction and stent thrombosis did not result in improved survival.[35] The DAPT study was the first large-scale, randomized clinical trial that evaluated a strategy of 30-month DAPT versus standard 12-month DAPT among 9961 participants with either stable CAD or ACS.[26] Extended DAPT significantly reduced the incidence of MACE and stent thrombosis, but at the expense of increased bleeding and mortality.

Altogether, these studies support an extended DAPT course in selected patients in whom thrombotic risk outweighs bleeding risk, but careful evaluation, especially in frail and older patients, is needed to avoid potential harm.[1–3]

Table 3 RCTs Comparing Extended versus Standard DAPT Regimens in Patients with CAD Undergoing PCI

Study	Year	DAPT Strategy	Patients (N)	ACS (%)	Follow-Up	Primary Endpoint	Results
PRODIGY	2012	6 vs 24 months	1970	75	24-month	All-cause death, MI, or stroke	10.1% vs 10.0% (*P*=0.910)
DAPT	2014	12 vs 30 months	9961	43	30-month	All-cause death, MI, or stroke	4.3% vs 5.9% (*P*<0.001)
ARCTIC-Interruption	2014	12 vs 18–24 months	1259	26	18-month	All-cause death, MI, ST, stroke, or urgent revascularization	4.0% vs 4.0% (*P*=0.580)
DES-LATE	2014	12 vs 36 months	5045	61	24-month	CV death, MI, or stroke	2.6% vs 2.4% (*P*=0.750)
OPTIDUAL	2015	12 vs 48 months	1385	36	36-month	All-cause death, MI, stroke, or major bleeding	5.8% vs 7.5% (*P*=0.170)
PEGASUS-TIMI54	2016	DAPT with Ticagrelor 90 mg or 60 mg versus placebo plus aspirin 1–3 years after MI	21,162	100	36-month	CV death, MI, or stroke	7.8% vs 9.0% (*P*=0.001)

(*Continued*)

Table 3 (Continued).

Study	Year	DAPT Strategy	Patients (N)	ACS (%)	Follow-Up	Primary Endpoint	Results
ITALIC	2017	6 vs 24 months	1894	44	12-month	All-cause death, MI, urgent TVR, stroke, or major bleeding	1.5% vs 1.6% (*P* non-inferiority<0.001)
NIPPON	2017	6 vs 18 months	3773	45	18-month	All-cause death, MI, stroke, and major bleeding	1.5% vs 2.1% (*P* non-inferiority<0.05)
THEMIS	2019	DAPT with ticagrelor versus placebo plus aspirin in stable patients with DM	19,271	0	40-month	CV death, MI, or stroke	6.9% vs 7.6% (*P*=0.04)

Abbreviations: DAPT, dual antiplatelet therapy; ACS, acute coronary syndrome; MI, myocardial infarction; ST, stent thrombosis; CV death, cardiovascular death; TVR, target vessel revascularization; DM, diabetes mellitus.

Strategies for Bleeding Risk Reduction

Short DAPT Followed by Aspirin Monotherapy

Twelve RCTs have explored the risks and benefits of short DAPT followed by aspirin as compared with standard DAPT (Table 4).[36–47] Eight trials compared 6-month versus 12-month DAPT, three trials 3-month versus 12-month DAPT, and one trial 1-month versus 6–12-month DAPT. Although most of these studies showed that early discontinuation of the $P2Y_{12}$ inhibitor reduces bleeding without a significant increase in thrombotic complications, caution should be exercised given the low ischemic risk profile of the patients enrolled, the lower-than-expected event rates, and the lack of power for hard ischemic endpoints for some RCTs. Overall, it seems reasonable to reserve a short DAPT duration followed by aspirin monotherapy to stable patients undergoing non-complex procedures.[1–3]

Table 4 RCTs Comparing Short DAPT Followed by Aspirin Monotherapy versus Standard DAPT in Patients with CAD Undergoing PCI

Study	Year	DAPT Strategy	Patients (N)	ACS (%)	Follow-Up	Primary Endpoint	Results
EXCELLENT	2012	6 vs 12 months	1443	51	12-month	CV death, MI, or ischemia-driven TVR	4.8% vs 4.3% (*P* non-inferiority=0.001)
RESET	2012	3 vs 12 months	2117	55	12-month	CV death, MI, ST, ischemia-driven TVR, or bleeding	4.7% vs 4.7% (*P* non-inferiority<0.001)
OPTIMIZE	2013	3 vs 12 months	3119	32	12-month	All-cause death, MI, stroke, or major bleeding	6.0% vs 5.8% (*P* non-inferiority=0.002)
SECURITY	2014	6 vs 12 months	1399	38	12-month	CV death, MI, ST, BARC 3 or 5 bleeding	4.5% vs 3.7% (*P* non-inferiority<0.05)
ISAR-SAFE	2015	6 vs 12 months	4000	40	9-month	All-cause death, MI, ST, stroke, and TIMI major bleeding	1.5% vs 1.6% (*P* non-inferiority<0.001)
I-LOVE-IT 2	2016	6 vs 12 months	1829	85	12-month	CV death, target vessel MI, or clinically indicated TLR	6.8% vs 5.9% (*P* non-inferiority=0.007)
IVUS-XPL	2016	6 vs 12 months	1400	49	12-month	CV death, MI, stroke, or TIMI major bleeding	2.2% vs 2.1% (*P*=0.854)

(*Continued*)

Table 4 (Continued).

Study	Year	DAPT Strategy	Patients (N)	ACS (%)	Follow-Up	Primary Endpoint	Results
SMART-DATE	2018	6 vs 12 months	2712	100	18-month	All-cause death, MI, or stroke	4.7% vs 4.2% (*P* non-inferiority=0.03)
DAPT-STEMI	2018	6 vs 12 months	870	100	18-month	All-cause death, MI, any revascularization, stroke, or TIMI major bleeding	4.8% vs 6.6% (*P* non-inferiority=0.004)
OPTIMA-C	2018	6 vs 12 months	1368	51	12-month	CV death, MI, or ischemia-driven TLR	1.2% vs 0.6 (*P* non-inferiority<0.05)
REDUCE	2019	3 vs 12 months	1496	100	12-month	All-cause death, MI, ST, stroke, TVR, or BARC 2/3/5 bleeding	8.2% vs 8.4% (*P* non-inferiority<0.001)
One-month DAPT	2021	1 vs 6–12 months in non-complex PCI patients	3020	39	12-month	CV death, MI, TVR, stroke, and major bleeding	5.9% vs 6.5% (*P* non-inferiority<0.001)

Abbreviations: DAPT, dual antiplatelet therapy; ACS, acute coronary syndrome; MI, myocardial infarction; ST, stent thrombosis; CV death, cardiovascular death; TVR, target vessel revascularization; TLR, target lesion revascularization; HBR, high bleeding risk; BARC, Bleeding Academic Research Consortium; TIMI, thrombolysis in myocardial infarction.

Ultra-short DAPT durations (1–3 months) have also been tested in HBR patients undergoing PCI with newer-generation DES platforms. Although bare-metal stents have been historically considered safer for HBR patients receiving an abbreviated DAPT, contemporary RCTs have challenged this practice.[48–51] The MASTER DAPT trial was the first large study testing different DAPT durations in a cohort of 4434 HBR patients undergoing implantation of a biodegradable-polymer sirolimus-eluting Ultimaster stent.[52] A short DAPT (1 month) regimen was shown to be non-inferior to standard DAPT with regard to net adverse clinical events and MACE. A recent meta-analysis comparing abbreviated (1–3 months) with standard (≥6 months) DAPT among 9006 HBR patients from 11 RCTs showed a significant reduction in major bleeding and cardiovascular mortality in HBR patients assigned to short DAPT.[53]

Short DAPT Followed by $P2Y_{12}$ Inhibitor Monotherapy

A strategy of $P2Y_{12}$ inhibitor monotherapy after a short DAPT has recently been proposed for PCI patients. RCTs comparing $P2Y_{12}$ inhibitor monotherapy versus DAPT are summarized in Table 5.[47,54–58] Clopidogrel monotherapy after 1-to-3 month DAPT was investigated as an alternative to standard 12-month DAPT in patients undergoing PCI in three different trials: SMART-CHOICE, STOPDAPT-2, and STOPDAPT-2 ACS.[47,57,59] In a pooled analysis of nearly 6000 patients, clopidogrel monotherapy was non-inferior to 12-month DAPT for the composite of cardiovascular death, MI, definite stent thrombosis, or any stroke, while it significantly reduced TIMI major or minor bleeding.[60] However, a numerical increase in cardiovascular events was noted among ACS on 1-month DAPT, warning about a possible safety issue in high ischemic risk patients.

With the advent of ticagrelor and prasugrel, pharmacodynamic studies have questioned the incremental antiplatelet effect of aspirin in the presence of potent $P2Y_{12}$ inhibitors, especially with ticagrelor.[61] GLOBAL LEADERS was the first trial to test a strategy of open-label 1-month DAPT followed by 23-month ticagrelor monotherapy versus 12-month DAPT followed by aspirin monotherapy among nearly 16,000 patients (of whom 46.9% had ACS).[54] The trial failed to meet its primary endpoint of reduction in all-cause death and non-fatal Q-wave MI despite a favorable numerical trend; meanwhile, no significant differences were observed in terms of site-reported BARC 3 or 5 bleeding. Opposing these negative results, the double-blind, placebo-controlled TWILIGHT trial enrolled high-risk PCI patients who completed an initial course of DAPT with ticagrelor for 3 months, and randomized them to ticagrelor monotherapy versus ticagrelor plus aspirin for an additional 12 months.[55] Ticagrelor monotherapy significantly reduced the primary outcome of BARC 2, 3, or 5 bleeding at 12 months and the key composite ischemic endpoint met the non-inferiority criterion. Results were

Table 5 RCTs Comparing Short DAPT Followed by $P2Y_{12}$ Inhibitor Monotherapy versus Standard DAPT in Patients with CAD Undergoing PCI

Study	Year	$P2Y_{12}$ Inhibitor Monotherapy Strategy	Patients (N)	ACS (%)	Follow-Up	Primary Endpoint	Results ($P2Y_{12}$ Inhibitor Monotherapy vs DAPT)
GLOBAL-LEADERS	2018	Ticagrelor monotherapy after 1-month DAPT	15,968	47	24-month	All-cause death or new Q-wave MI	3.8% vs 4.4% (*P*=0.07)
STOPDAPT-2	2019	Clopidogrel monotherapy after 1-month DAPT	3009	38	12-month	CV death, MI, stroke, ST, and TIMI major or minor bleeding	2.4% vs 3.7% (*P* non-inferiority<0.001)
SMART-CHOICE	2019	$P2Y_{12}$ inhibitor monotherapy strategy after 3-month DAPT	2993	58	12-month	All-cause death, MI, ST, stroke, or urgent revascularization	2.9% vs 2.5% (*P* non-inferiority=0.007)
TWILIGHT	2019	Ticagrelor monotherapy after 3-month DAPT	7119	65	15-month	BARC type 2, 3, or 5	4.0% vs 7.1% (*P*<0.001)
TICO	2020	Ticagrelor monotherapy after 3-month DAPT	3056	100	12-month	All-cause death, MI, ST, stroke, TVR, or TIMI major bleeding	3.9% vs 5.9% (*P*=0.01)
STOPDAPT-2 ACS	2022	Clopidogrel monotherapy after 1–2-month DAPT	4169	100	12-month	CV death, MI, stroke, ST, and TIMI major or minor bleeding	3.2% vs 2.8% (*P* non-inferiority=0.06)

Abbreviations: DAPT, dual antiplatelet therapy; ACS, acute coronary syndrome; MI, myocardial infarction; ST, stent thrombosis; CV death, cardiovascular death; TVR, target vessel revascularization; BARC, Bleeding Academic Research Consortium; TIMI, thrombolysis in myocardial infarction.

consistent among subgroups of high-risk patients such as those with diabetes mellitus, ACS, and HBR, and those undergoing complex PCI.[62–64] Finally, the TICO trial included only ACS patients who were randomized to 3-month DAPT followed by ticagrelor monotherapy or 12-month aspirin and ticagrelor.[65] Ticagrelor monotherapy significantly reduced the composite of death, MI, stent thrombosis, stroke, target vessel revascularization, or TIMI major bleeding at 12 months, a difference that was mainly driven by a reduction in TIMI major bleeding.

Results from studies investigating $P2Y_{12}$ inhibitor monotherapy versus standard DAPT, including those conducted among patients receiving coronary bypass, were pooled in a recent individual patient-level meta-analysis of nearly 24,000 patients. $P2Y_{12}$ inhibitor monotherapy significantly reduced bleeding without increasing the risk of death, myocardial infarction, or stroke.[66] Meta-analysis restricted to ticagrelor monotherapy RCTs yielded similar results.[67] Based on the available evidence, $P2Y_{12}$ inhibitor monotherapy after an initial short DAPT should be considered as an alternative to standard DAPT, especially when bleeding risk is a concern. In ACS patients, however, early DAPT discontinuation followed by clopidogrel monotherapy may not provide sufficient antithrombotic protection; thus, ticagrelor should remain the agent of choice.

Phenotype-Guided or Genotype-Guided Antiplatelet Strategies

Clopidogrel is a prodrug and requires conversion to an active metabolite by the hepatic cytochrome P450 enzyme (CYP2C19). Up to 30% of Caucasian patients show inadequate response to clopidogrel that can be partly explained by loss-of-function (LOF) polymorphisms of CYP2C19 alleles.[68] Carriers of LOF alleles exhibit high on-treatment platelet reactivity (HPR) that increases the risk of thrombotic events, MACE, and stent thrombosis; conversely, patients with low-platelet reactivity seem to have a higher risk for bleeding.[69] Because such genetic polymorphisms do not alter the pharmacokinetics of prasugrel and ticagrelor, it has been suggested that carriers of CYP2C19 LOF mutations might derive greater benefit from more potent

$P2Y_{12}$ inhibitors. The impact of CYP2C19 genotype on clinical outcomes with ticagrelor or prasugrel compared with clopidogrel was recently evaluated in a meta-analysis including 15,949 patients from 7 RCTs. Prasugrel or ticagrelor were shown to reduce major ischemic events in CYP2C19 LOF carriers, whereas no difference was observed in non-carriers.[70]

From a phenotype perspective, on-treatment platelet inhibition can be measured with dedicated essays. In vitro platelet function tests predict patients' clinical response to clopidogrel and have been shown to correlate with the risk of subsequent thrombosis and bleeding.[71] Theoretically, based on these tests, DAPT can be modulated choosing between more or less potent agents, depending on the predicted response to clopidogrel. Therefore, it is possible to define a functional-guided escalation (eg the use of a more potent $P2Y_{12}$ inhibitors in the setting of high platelet reactivity on clopidogrel) or de-escalation (eg, maintenance of clopidogrel in case of adequate platelet inhibition). At present, however, randomized trials assessing the clinical utility of standardized platelet function tests have generated contradictory results, and there is no consensus on the definition of resistance to antiplatelet therapy.[72–74]

In the TROPICAL-ACS trial, a platelet functional guided de-escalation strategy resulted non-inferior in terms of net-clinical benefit as compared with conventional therapy of DAPT with prasugrel among 2610 randomized ACS patients.[72] The rates of ischemic events were similar in the two groups and a numerical trend, albeit not significant, toward less bleeding in the platelet function-guided group was evident.

Non-inferiority for net clinical benefit was also met in the POPULAR GENETICS trial, in which a total of 2488 patients undergoing primary PCI for ST-elevation myocardial infarction (STEMI) were randomized to a genotype-guided DAPT strategy where carriers of CYP2C19 LOF alleles received ticagrelor or prasugrel and non-carriers received clopidogrel versus standard treatment with either ticagrelor or prasugrel.[73] The genotype-guided strategy was also associated with a significant reduction in major or minor bleeding, mainly driven by a reduction in minor bleeding.

Finally, in the TAILOR PCI trial, 5302 patients undergoing PCI for ACS (82%) or stable angina (18%) were randomized to standard treatment or use of a point-of-care genotyping test for the selection of ticagrelor or clopidogrel.[74] The genotype-guided strategy resulted in a numerically, but not statistically significant reduction of the primary endpoint, a composite of cardiovascular death, myocardial infarction, stroke, stent thrombosis, or severe recurrent ischemia at 12 months; however, the secondary endpoint of major or minor bleeding did not differ between the two study groups. The ABCD-GENE (age, body mass index, chronic kidney disease, diabetes mellitus, and genotyping) risk score was subsequently derived from a post-hoc analysis of the trial, to identify patients with HPR on clopidogrel at increased risk for adverse ischemic events, who may benefit from escalation of DAPT.[75]

Overall, in a large meta-analysis including 20,743 patients from 11 RCTs and 3 observational studies, a strategy of guided selection of antiplatelet therapy by means of genotyping or platelet function tests was associated with improved clinical outcomes.[76] Despite this significative piece of evidence and the potential role among HBR patients and patients with a recent ACS, routine adoption of phenotype-guided or genotype-guided antithrombotic therapies in clinical practice remains limited.

Long-Term Secondary Antithrombotic Prevention

Aspirin and DAPT

Aspirin is universally considered the foundation of life-long secondary prevention in patients with cerebrovascular, coronary, or peripheral artery disease and remains the drug of choice after discontinuation of DAPT post-PCI or ACS.[1,77] However, long-term aspirin use carries potential side-effects, including a well-established risk of gastrointestinal bleeding. In this setting, $P2Y_{12}$ inhibitors offer an alternative for chronic maintenance therapy. Initially, long-term maintenance therapy with $P2Y_{12}$ inhibitor was tested in combination with aspirin. In the PEGASUS-TIMI 54 trial, 21,162 high-risk patients presenting 1–3 years after ACS (54% STEMI) were randomized in a double-blind 1:1:1 fashion to ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily, or placebo, on top of aspirin.[31] At 3 years, ticagrelor 60 mg on top of aspirin was the most favorable regimen in terms of overall net benefit, and has therefore been endorsed by recent guidelines for long-term secondary prevention. The high-risk clinical features (age ≥65 years, diabetes mellitus, recurrent MI, multivessel disease, or chronic kidney disease) adopted as inclusion criteria in the PEGASUS-TIMI 54 trial serve to identify patients that may derive a clinical benefit from extended DAPT with low-dose of ticagrelor. On the other hand, in the setting of high-risk stable CAD, the THEMIS trial randomized 19,271 diabetic patients to ticagrelor 60 mg and aspirin versus aspirin alone.[34] At a median follow-up of 40 months, ticagrelor was associated with a borderline

reduction in MACE and a 2-fold increase in TIMI major bleeding. When the analysis was restricted to patients with previous PCI, ticagrelor seemed to yield a greater net benefit than in those without prior PCI.[78]

$P2Y_{12}$Inhibitor Monotherapy

More recently, several RCTs have compared $P2Y_{12}$ inhibitor monotherapy against aspirin for secondary prevention in patients with established atherosclerosis, yielding mixed results. A comprehensive meta-analysis encompassing 42,108 patients from 9 RCTs showed a significant, yet clinically modest, risk reduction in myocardial infarction with $P2Y_{12}$ inhibitor versus aspirin monotherapy, with no differences in death, stroke, and major bleeding.[79] In the HOST-EXAM trial, clopidogrel monotherapy was associated with a significant reduction in both thrombotic and bleeding events up to 5 years as compared to low-dose aspirin, among 5438 patients who were free from ischemic and bleeding adverse events 12 months after PCI.[80,81] These promising results were confirmed by an individual patient data meta-analysis of 7 large RCTs – including HOST-EXAM – with an overall population of nearly 35,000 patients with established coronary disease. $P2Y_{12}$ inhibitor monotherapy, including clopidogrel (62%) and ticagrelor (38%), showed a significant reduction of cardiovascular death, MI, or stroke with similar rate of major bleeding, as compared to aspirin, at a median follow-up of 552 days.[82] Despite the uncertain cost-effectiveness and the relatively low effect size of $P2Y_{12}$ inhibitor monotherapy, the use $P2Y_{12}$ inhibitors now represents a valid alternative to aspirin, especially in patients with coronary artery disease who are intolerant to aspirin or have experienced adverse events.

Personalized Approaches in Specific Cardiovascular Conditions

Complex PCI

Up to 30% of PCI procedures can be classified as complex owing to technical challenges and high rates of periprocedural complications, especially when multiple complexity features are present.[8,83] The definition of PCI complexity generally refers to coronary artery disease extent or lesion difficulty, but may also extend to patient comorbidities and frailty. Notably, bleeding and ischemic risk factors often coincide (eg, age, chronic kidney disease, anemia) and a large proportion (up to 45%) of patients undergoing complex PCI are at high-bleeding risk, making the management of DAPT even more challenging.[84]

In a pivotal study by Giustino et al, complex PCI was defined by the presence of at least one of the following criteria: 3 vessels treated, ≥3 lesions treated, ≥3 stents implanted, bifurcation with 2 stents implanted, total stent length >60 mm, or chronic total occlusion as the target lesion.[8] Using data from 6 RCTs and 9577 patients, the authors showed that long-term (≥12 months) versus short-term (3–6 months) DAPT significantly reduced MACE in complex PCI patients but not in those without complex features. On the other hand, long DAPT was associated with more major bleeding, irrespective of PCI complexity. A subsequent similar study, which accounted for not only PCI complexity but also HBR features, showed that long-term DAPT reduces ischemic events after complex PCI only when HBR features are not present.[85] Recently, in the ALPHEUS trial, 1910 elective high-risk PCI patients were randomized to DAPT with ticagrelor versus clopidogrel for 30 days after the procedure. Ticagrelor did not reduce the primary outcome, a composite of PCI-related type 4 myocardial infarction or major myocardial injury; major bleeding did not differ between the two groups, but minor bleeding was more frequent with ticagrelor at 30 days.[86] Finally, two different study-level meta-analyses and one patient-level meta-analysis evaluated the safety and efficacy of $P2Y_{12}$ inhibitor monotherapy among patients undergoing complex PCI including subgroup analysis from 5 different RCTs.[87–89] A short course of 1–3-month DAPT followed by $P2Y_{12}$ inhibitor monotherapy with either clopidogrel or ticagrelor was found to reduce bleeding complications without increasing ischemic events, irrespective of PCI complexity. On the basis of the available evidence, $P2Y_{12}$ inhibitor monotherapy after a short DAPT can be a valid alternative to standard and/or prolonged DAPT, especially in HBR patients.

Parenteral Antiplatelet Therapy

Glycoprotein IIb/IIIa Receptor Inhibitors

Glycoprotein IIb/IIIa receptor inhibitors (GPIs) were the first available intravenous antiplatelet agents providing nearly complete inhibition of platelet aggregation.[90] GPIs were first used in the acute setting to reduce the risk of ischemic complications during ACS or PCI. After the introduction of more potent oral $P2Y_{12}$ inhibitors and given the bleeding concerns associated with GPIs, their routine use has significantly decreased in clinical practice. Nowadays, GPIs are limited to a bailout use, in the presence of a large thrombus burden, slow flow, or "no reflow" complications of PCI.[90]

Cangrelor

Cangrelor is an intravenous direct reversible $P2Y_{12}$ receptor antagonist with a quick onset and a rapid offset of action after infusion discontinuation. Compared to oral $P2Y_{12}$ inhibitors, cangrelor achieves fast and consistent platelet inhibition, and it is effective in reducing periprocedural thrombotic complication of PCI.[90] In the CHAMPION PHOENIX trial, among 11,145 $P2Y_{12}$ inhibitor-naive patients undergoing PCI for stable CAD or non-ST-segment elevation ACS, pre-treatment with cangrelor reduced the primary endpoint of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 h, with no significant difference in severe bleeding, as compared to an oral loading dose of clopidogrel.[91] In a post-hoc analysis, cangrelor showed a greater absolute risk reduction of 48-h MACE and stent thrombosis in patients with high-risk periprocedural features, suggesting a greater benefit–risk profile in patients with complex coronary anatomies.[92] According to the current evidence, candidates for cangrelor administration include patients undergoing complex PCI who are not pretreated with oral $P2Y_{12}$ inhibitors. Those presenting with ACS who undergo emergency PCI can also be considered for cangrelor use. In the setting of STEMI and/or hemodynamic instability, the slow gut transit, morphine use, and presence of nausea, vomiting, intubation, or cardiogenic shock may impair absorption and efficacy of oral $P2Y_{12}$ inhibitors, making cangrelor a valid option to overcome the latency of an oral $P2Y_{12}$ inhibitor.[93] However, since cost and availability may limit its use, alternative strategies including parenteral administration of enoxaparin have been tested in this setting, with promising results.[94] Finally, given its rapid onset and offset of action, use of cangrelor is an attractive option for patients at high ischemic risk requiring non-deferrable surgery and in whom discontinuation of oral $P2Y_{12}$ inhibition is necessary.[95–97]

Selatogrel

A novel fascinating concept has been introduced with the development of the new parenteral $P2Y_{12}$ inhibitor, selatogrel. Selatogrel can be administered subcutaneously and has a rapid onset/offset effect, providing immediate platelet inhibition in patients with acute ischemic events including MI, stroke, or acute limb ischemia. As it is available in the form of an injector for self-administration, patients with very high ischemic risk could hypothetically derive benefit from an early self-administration when the first symptoms of ongoing ischemia are recognized.[98] Recently, a single subcutaneous administration of selatogrel was tested in a small phase 2 exploratory study among patients presenting with acute MI scheduled for an invasive strategy, showing a profound, rapid, and dose-related antiplatelet inhibition, with a good safety profile.[99] However, studies are needed to establish the efficacy and safety of selatogrel in patients with suspected MI.

Concomitant Oral Anticoagulation

Patients with an indication to chronic oral anticoagulation (OAC), mainly because of atrial fibrillation, represent a sizeable portion of those undergoing PCI and are by definition considered at HBR. Guidelines and consensus recommendations on the management of OAC and DAPT after PCI or ACS have changed significantly over the last years with introduction of non-vitamin K antagonist oral anticoagulants (NOACs) and with results of their respective RCTs: rivaroxaban (PIONEER AF-PCI), dabigatran (REDUAL-PCI), apixaban (AUGUSTUS), and edoxaban (ENTRUST-AF-PCI).[100–103] In order to minimize the risk of bleeding, a default strategy of triple antithrombotic therapy, consisting of aspirin, $P2Y_{12}$ inhibitor, and NOAC, should be given for one week (or up until hospital discharge) after PCI, followed by a combination of NAOC and a single antiplatelet agent (preferably, the $P2Y_{12}$ inhibitor clopidogrel) up to 12 months.[104] After 12 months, a single long-term therapy with NOAC alone should be the treatment of choice.[105] However, this strategy should be modulated according to the individual ischemic and bleeding risk of the patient. If thrombotic risk is a concern, the triple therapy may be extended up to one month after PCI and the use of more potent $P2Y_{12}$ inhibitors instead of clopidogrel may be considered in patients at low

bleeding risk. Meanwhile, if bleeding risk prevails, earlier discontinuation of dual antithrombotic therapy and transition to OAC alone after 3–6 months may be considered.

Cerebrovascular Disease

Anticoagulants represent the cornerstone of primary and secondary prevention among patients suffering from atrial fibrillation or atrial flutter at high risk for cardioembolic stroke. Nevertheless, in the absence of such indication to anticoagulation, antiplatelet therapy remains the treatment of choice for the secondary prevention of patients with a history of ischemic stroke or transient ischemic attack (TIA), and treatment initiation immediately after the acute event is essential for preventing recurrences.[106] The benefit of aspirin in this setting is well-established after it was tested in more than 40,000 patients, in the randomized CAST and IST studies.[107,108] Based on the results of the CAPRIE trial and subsequent meta-analysis of several studies, clopidogrel monotherapy was even more effective than aspirin in reducing ischemic stroke recurrence.[109,110] Similar rates of recurrent stroke were observed with the combination of aspirin plus dipyridamole versus clopidogrel in the PROFESS study.[110–112] Conversely, ticagrelor monotherapy failed to show superiority to aspirin in the SOCRATES trial, enrolling nearly 13,000 patients with non-severe ischemic stroke or high-risk TIA.[113] DAPT with aspirin and clopidogrel has been tested for long-term prevention after a stroke or TIA in the MATCH and SPS3 trials and in a subset of the CHARISMA trial, but it did not show better outcomes than monotherapy in terms of recurrent ischemic events, and was rather associated with increased bleeding.[111,114,115] By contrast, a short course of DAPT with clopidogrel has shown some advantages over monotherapy in patients with minor stroke or TIA in the CHANCE and POINT RCTs, probably due to the increased probability of reoccurrence of a major stroke, often disabling, within the first weeks after a minor event. On the other hand, DAPT with ticagrelor compared with aspirin alone significantly reduced the risk of 1-month stroke or death, at the expense of higher incidence of severe bleeding, among 11,016 patients enrolled in the THALES trial.[116]

For these reasons, current guidelines suggest short-term (up to 3 weeks) DAPT for patients with recent TIA or minor stroke, whereas antiplatelet monotherapy with clopidogrel over aspirin is recommended after moderate-to-severe strokes due to the potential risk of hemorrhagic transformation; antiplatelet monotherapy, or as alternative a combination of aspirin and dipyridamole, is warranted for long-term ischemic stroke secondary prevention.

Polyvascular Disease

A significant proportion of patients with CAD also have peripheral artery disease (PAD).[117] Presence of polyvascular disease renders these patients at increased risk of thrombotic events which may justify an intensified antithrombotic strategy.[117] Among patients with symptomatic PAD, single antiplatelet therapy with either aspirin or clopidogrel has been shown to reduce ischemic complications.[117] The effects of a more profound platelet inhibition with clopidogrel-based DAPT was evaluated in a post-hoc analysis of the CHARISMA trial among 3096 patients with PAD. DAPT was found to reduce the rate of MI and hospitalization for ischemic events at the cost of increased bleeding, and with no difference in ischemic limb events.[118] The newer $P2Y_{12}$ inhibitor ticagrelor failed to show a clinical benefit over clopidogrel among 13,885 patients with symptomatic PAD enrolled in the EUCLID trial.[119]

Taken together, the available evidence suggests that, despite a theoretical benefit of DAPT in PAD patients with a low bleeding risk being hypothesized, monotherapy with clopidogrel or aspirin remains the preferred approach. More recently, a new strategy of dual-pathway inhibition (DPI) consisting of a combination of an antiplatelet agent with a low-dose anticoagulant to achieve a synergistic antithrombotic effect has been proposed for patients with a high atherosclerotic burden. The COMPASS trial was the first study to investigate the use of low-dose NOAC in addition to antiplatelet therapy in stable atherosclerotic cardiovascular disease. A total of 27,395 patients were randomly assigned to rivaroxaban 2.5 mg twice daily plus aspirin (DPI group), rivaroxaban 5.0 mg twice daily alone, or aspirin alone. Patients assigned to a DPI strategy had fewer MACE but more major bleeding compared with those assigned to aspirin alone.[120] Among 7749 patients with a history of PAD, DPI with rivaroxaban plus aspirin reduced the occurrence of major adverse limb events including major amputation.[121] The benefit of DPI was even greater in terms of major adverse limb events, total vascular amputations, and peripheral vascular interventions when considering a restricted subgroup of 6391 patients with lower-extremity PAD.[121] The benefit of low-dose rivaroxaban in addition to aspirin in reducing major thrombotic

vascular events was also demonstrated in PAD patients undergoing peripheral revascularization from the VOYAGER PAD trial, with a significant reduction in thrombotic events with no apparent trade-off in major bleeding.[122] Therefore, adding "vascular protection" low-dose rivaroxaban to aspirin has been endorsed by recent expert consensus and guidelines as a feasible option in patients with PAD not deemed to be at HBR.[117]

Conclusions

Antiplatelet therapy has dramatically evolved over the last decades, aiming to reduce the risk of thrombotic complications while minimizing the risk of bleeding among patients with established cardiovascular disease. Among those with CAD undergoing PCI, different strategies are now available and include prolonging, shortening, escalating, or de-escalating DAPT, in a guided or unguided manner. $P2Y_{12}$ inhibitor monotherapy is a novel approach focused on reducing the bleeding risk perhaps maintaining ischemic protection. The use of parenteral antiplatelet agents, such as intravenous cangrelor or subcutaneous selatogrel, are emerging approaches to ensure adequate platelet inhibition in high-ischemic risk clinical settings. Finally, DPI can provide vascular protection in patients suffering from a complex, multidistrict polyvascular disease. However, a comprehensive assessment of the ischemic and bleeding risk profile, as well as of individual clinical features and possibly responsiveness to antiplatelet agents by the use of platelet function and genetic testing, is now crucial in defining the optimal regimen. The use of risk scores, consensus definitions, and the new promising AI tools is part of an integrated approach aimed to personalize the selection of the most appropriate antiplatelet therapy for each patient.

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