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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Antiplatelet Agents for the Treatment and Prevention of Coronary Atherothrombosis

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ABSTRACT

Antiplatelet drugs provide first-line antithrombotic therapy for the management of acute ischemic syndromes (both coronary and cerebrovascular) and for the prevention of their recurrence. Their role in the primary prevention of atherothrombosis remains controversial because of the uncertain balance of the potential benefits and risks when combined with other preventive strategies. The aim of this consensus document is to review the evidence for the efficacy and safety of antiplatelet drugs, and to provide practicing cardiologists with an updated instrument to guide their choice of the most appropriate antiplatelet strategy for the individual patient presenting with different clinical manifestations of coronary atherothrombosis, in light of comorbidities and/or interventional procedures. (J Am Coll Cardiol 2017;70:1760–76) © 2017 by the American College of Cardiology Foundation.

Antiplatelet drugs have an established role in the management and prevention of coronary and cerebrovascular events associated with atherothrombosis, whereas their role in primary prevention of these events remains less clear. In this consensus document, the European Society of Cardiology Working Group on Thrombosis reviews the evidence for different antiplatelet drugs to provide

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clinicians with a guide to appropriate antiplatelet strategies.

CLINICAL PHARMACOLOGY OF ANTIPLATELET DRUGS

Multiple pathways contribute to platelet activation and aggregation, and although pharmacological interference with these pathways reduces the risk of atherothrombotic complications, it is also associated with an increased risk of bleeding (**Figure 1**). It is important to emphasize that the thromboxane (TX) A_2-, adenosine diphosphate (ADP)-, and thrombin-activated pathways transduce independent signals of platelet activation and represent nonredundant targets for its pharmacological modulation. This is reflected by the additive nature of the effects of combined antiplatelet therapy, as discussed later.

CYCLOOXYGENASE-1 INHIBITORS. Aspirin irreversibly inactivates platelet cyclooxygenase (COX)-1 and suppresses TXA_2 generation by selectively acetylating a serine residue (Ser-529) close to the catalytic pocket of the enzyme (**Figure 2**) (1). Whereas a virtually complete and long-lasting inhibition of platelet COX-1 by low-dose aspirin is associated with reduced risk of atherothrombotic events (1), this is not achieved by most nonsteroidal anti-inflammatory drugs (NSAIDs), unmasking their COX-2–dependent cardiotoxicity (2). For more details, please see the Online Appendix.

$P2Y_{12}$ INHIBITORS. Oral inhibitors of the platelet ADP receptor, $P2Y_{12}$, include the thienopyridines (ticlopidine, clopidogrel, and prasugrel) and ticagrelor. Major characteristics of $P2Y_{12}$ inhibitors are summarized in **Table 1**. Thienopyridines are prodrugs, generating short-lived active metabolites (Online Figures 1A and 1B) that irreversibly inactivate the receptor and consequently inhibit ADP-induced platelet activation.

Ticagrelor is an adenosine triphosphate analogue. It directly and reversibly binds the $P2Y_{12}$ receptor, acting as an allosteric antagonist that noncompetitively prevents ADP-induced $P2Y_{12}$ activation (1).

When added to COX-1 suppression by low-dose aspirin, $P2Y_{12}$ blockade by clopidogrel produces an additional 10% to 20% relative risk reduction of major vascular events in high-risk patients (1). This relatively modest benefit may reflect the low degree of $P2Y_{12}$ inactivation achieved by clopidogrel in most patients. A faster and more complete $P2Y_{12}$ blockade by prasugrel or ticagrelor produced additional benefit versus clopidogrel in acute coronary syndromes (ACS) (3,4), supporting the clinical relevance of effectively targeting 2 nonredundant platelet signaling pathways. For more details please see the Online Appendix.

PROTEASE-ACTIVATED RECEPTOR INHIBITORS. At least 2 protease-activated receptors (PAR1 and PAR4) are present on human platelets, with PAR1 showing the highest affinity for thrombin. Vorapaxar competes with the tethered ligand of PAR1 generated by thrombin-catalyzed proteolysis, disrupting downstream signaling (1). Targeting this pathway in addition to aspirin and clopidogrel produced a nonsignificant reduction in major vascular events in ACS, associated with a disproportionate increase in bleeding (5). For more details, please see the Online Appendix.

INTERINDIVIDUAL VARIABILITY IN DRUG RESPONSES. At variance with drug resistance, interindividual variability in drug response is largely related to the mechanism(s) of drug absorption and biotransformation, and/or patient characteristics (6).

Clopidogrel has less than optimal pharmacokinetics: ~85% is inactivated by carboxylesterases before liver first pass; it is a substrate of the P-glycoprotein (P-gp) efflux transporter (also known as *ABCB1*) and is bio-activated by 2 sequential oxidative reactions involving several cytochrome P450 (CYP450) isozymes (1A2, 2B6, 2C9, 2C19, 3A4, and 3A5) (Online Figure 1A) with <10% systemic bioavailability. CYP2C19 and P-gp polymorphisms significantly affect the concentration of clopidogrel active metabolite and clinical efficacy, such that patients with the P-gp 3435 TT genotype and/or poor metabolizers (i.e., patients with any 2 loss-of-function CYP2C19 alleles) have a reduced drug efficacy and consequent poor clinical outcome (7–10). Interestingly, a recent trial in patients with symptomatic peripheral artery disease (PAD), which excluded poor metabolizers, showed superimposable efficacy and safety of clopidogrel and ticagrelor (11). The P-gp and CYP3A4, 2B6, 2C9, and 2C19 pathways account for clinically relevant drug-drug interactions with omeprazole, statins, and strong CYP3A4/P-gp inducers or inhibitors, which increase variability in response to clopidogrel, and likely affect its safety and efficacy (Online Figure 1A) (12). Prasugrel has simpler and more efficient pharmacokinetics than clopidogrel, resulting in less variability in drug response and no clinically relevant drug-drug interactions.

Ticagrelor has a half-life of 7 to 12 h and ~36% bioavailability (1). Ticagrelor is biotransformed by

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndromes

CABG = coronary artery bypass graft

CAD = coronary artery disease

COX = cyclooxygenase

DAPT = dual antiplatelet therapy

ICH = intracranial hemorrhage

MI = myocardial infarction

OAC = oral anticoagulation

PAD = peripheral artery disease

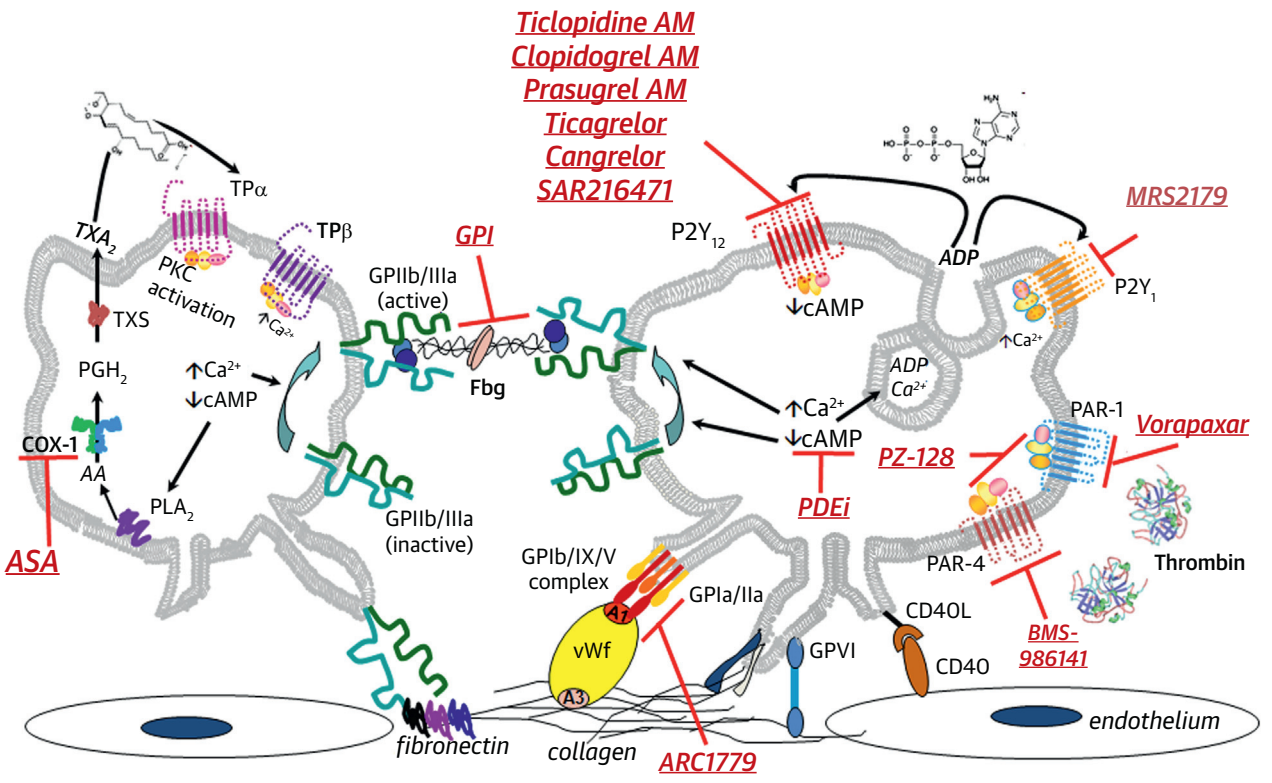
PAR = protease-activated receptor

PCI = percutaneous coronary intervention

SAPT = single antiplatelet therapy

TX = thromboxane

FIGURE 1 Platelet Activation Pathways and Targets of Current and Novel Antiplatelet Drugs



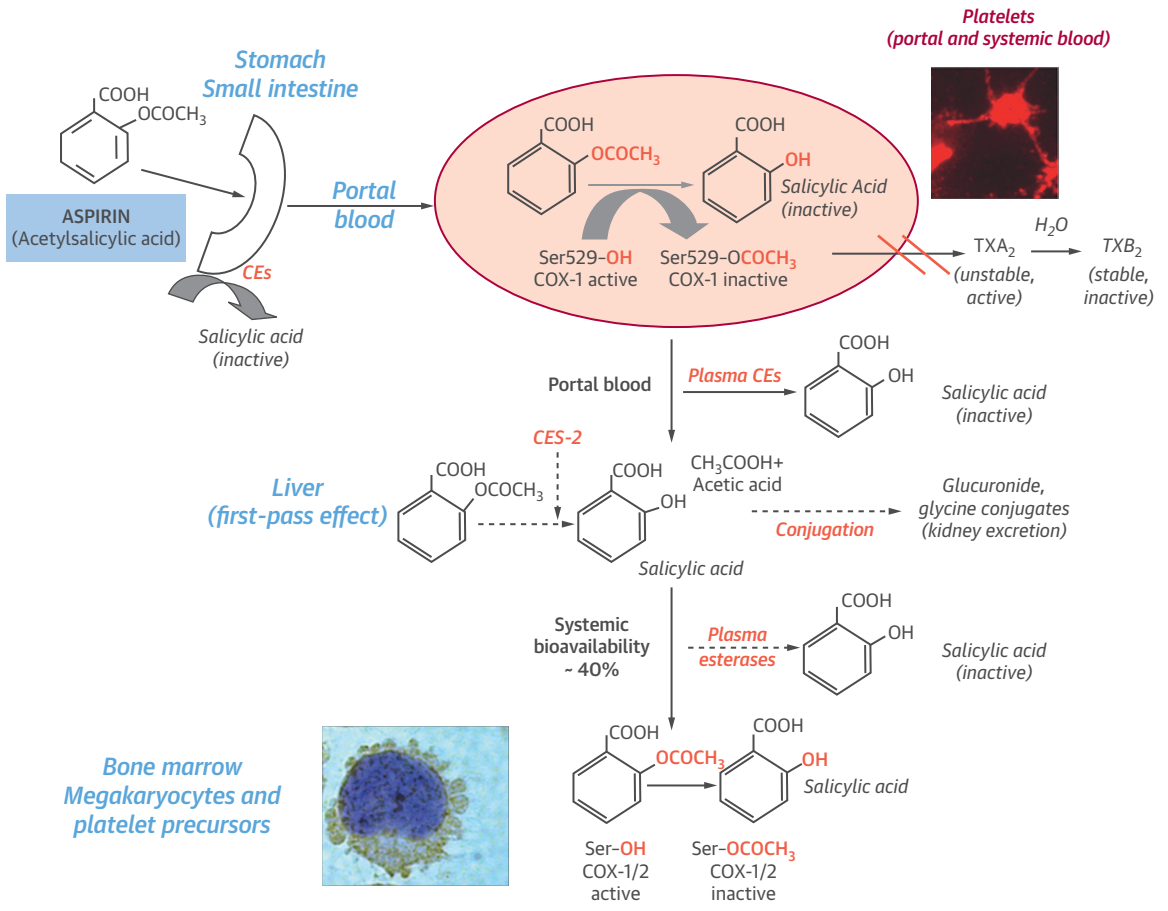
Platelet activation via multiple pathways leads to numerous responses including: secretion of ADP and its binding to $P2Y_1$ and $P2Y_{12}$ receptors; changes in the surface membrane supporting thrombin generation and activation of its PAR1 and PAR4 receptors; increased intraplatelet calcium; reduced cAMP concentrations; activation of phospholipases and release of arachidonic acid as a substrate for COX-1 and TXA_2 formation; and final activation of α2bβ3 (GP IIb/IIIa) leading to fibrinogen binding and platelet aggregation, as well as to amplification signals. Antiplatelet drugs already marketed or under different stages of development (ARC1779, MRS2179, PZ-128, BMS-986141, SAR216471) are shown, together with the targets they interfere with. Adapted from Patrono C, Rocca B. The future of antiplatelet therapy in cardiovascular disease. Ann Rev Med 2010;61:49–61. AA = arachidonic acid; ADP = adenosine diphosphate; AM = active metabolite; ASA = aspirin; Ca^{2+} = calcium; cAMP = cyclic adenosine monophosphate; COX = cyclooxygenase; Fbg = fibrinogen; GP = glycoprotein; GPI = GPIIb/IIIa inhibitors; PAR = protease-activated receptor; PDEi = phosphodiesterase inhibitors; PGH_2 = prostaglandin H_2; PKC = protein kinase C; PL = phospholipase; PLA_2 = phospholipase A_2; TP = thromboxane receptor; TX = thromboxane; TXS = thromboxane synthase; vWf = von Willebrand factor.

CYP3A4/A5 to a main active (AR-C124910XX) and an inactive (AR-C133913XX) metabolite (Online Figure 1C). AR-C124910XX is equipotent to ticagrelor, has similar pharmacokinetics, and contributes approximately 30% of the antiplatelet effect (1). P-gp or CYP2C19 polymorphisms do not affect ticagrelor pharmacokinetics or clinical efficacy (13). Clinically relevant drug-drug interactions may occur with strong CYP3A4 inhibitors or inducers, which are contraindicated (1). A clinically relevant P-gp-related interaction might occur with digoxin, due to its narrow therapeutic window (1).

Vorapaxar is biotransformed by CYP2J2 and 3A4 to an equipotent metabolite (M20), which approximates 25% of vorapaxar (Online Figure 2) (14). CYP3A4/A5 forms the major M19 inactive metabolite. Consequently, the coadministration of strong inducers or inhibitors of CYP3A4 may produce clinically relevant interactions (14).

The relatively simple pharmacokinetics of aspirin (**Figure 2**) explains the lack of pharmacokinetic interactions. Mutagenesis studies showed that Arg-120 of COX-1 is a docking site for aspirin, at which NSAIDs containing a carboxylic acid moiety may compete with aspirin, thereby preventing subsequent acetylation of Ser-529 (Online Table 1) (15). The pharmacodynamic interaction between some NSAIDs (e.g., ibuprofen) and low-dose aspirin, by limiting the

FIGURE 2 **Pharmacokinetics and Pharmacodynamics of Aspirin**



Aspirin is absorbed in the stomach and small intestine, exerts its pharmacodynamic effect, that is, the permanent acetylation of a Ser-529 residue of COX-1, already in the portal blood, and is biotransformed to inactive salicylic acid by intestine, plasma, and liver carboxylesterases, mainly the isoenzyme 2. On average, its systemic bioavailability is approximately 50% of the administered dose. Once in the systemic circulation, aspirin reaches bone marrow megakaryocytes and platelet precursors, inhibiting COX-1 and -2. The COX-1–dependent arachidonic acid pathway in platelets generates mainly TXA_2, which amplifies platelet activation by binding to its platelet receptors. TXA_2 is nonenzymatically hydrolyzed to TXB_2, which is biologically inactive but stable, and can be measured in ex vivo assays, or undergoes further hepatic enzymatic biotransformation in vivo. The potential pharmacodynamic drug–drug interaction site is indicated. Adapted from Rocca B, Dragani A, Pagliaccia F. Identifying determinants of variability to tailor aspirin therapy. Exp Rev Cardiovasc Ther 2013;11:365–79. CE = carboxylesterase; MK = megakaryocytes; other abbreviations as in Figure 1.

degree of platelet COX-1 inhibition, might further increase the cardiovascular risk associated with the use of NSAIDs (2).

TESTING ANTIPLATELET DRUG PHARMACODYNAMICS. The measurement of serum TXB_2 was instrumental to characterizing the clinical pharmacology of platelet COX-1 inhibition by aspirin and accurately predicted the range of daily doses (30 to 160 mg) that were shown to be effective in randomized clinical trials, where much higher doses showed no additional benefit, consistent with the saturability of platelet COX-1 inactivation at low doses (16). Serum TXB_2 may be measured to assess noncompliance, detect a pharmacodynamic interaction with some NSAIDs, or investigate the extent and duration of COX-1 inhibition in a specific clinical setting associated with reduced oral bioavailability of the inhibitor or accelerated renewal of the drug target (1).

Different platelet function assays have been used to measure the degree of $P2Y_{12}$ inhibition (17). In the case of clopidogrel, the concordance among the functional assays and between each assay and plasma

TABLE 1 Main Properties of $P2Y_{12}$ Inhibitors

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Bioavailability	50%	80%	36%	100%
Half-life (active metabolite)	30–60 min	Distribution half-life 30–60 min; elimination half-life 2–15 h	7–9 h	3–6 min
Binding reversibility	Irreversible	Irreversible	Reversible	Reversible
Onset of action	2–6 h	30 min	30 min	2 min
Frequency of administration	Once daily	Once daily	Twice daily	Intravenous infusion
Duration of effect	3–10 days	7–10 days	3–5 days	1–2 h
Antidote	No	No	No	No
Clinical indication	PCI, ACS, ACS-PCI, and SCAD	ACS-PCI	ACS, ACS-PCI	PCI, bridging in patient at high ischemic risk who is undergoing an invasive procedure
Discontinuation before nonacute surgery	At least 5 days	At least 7 days	At least 3 days	1 h

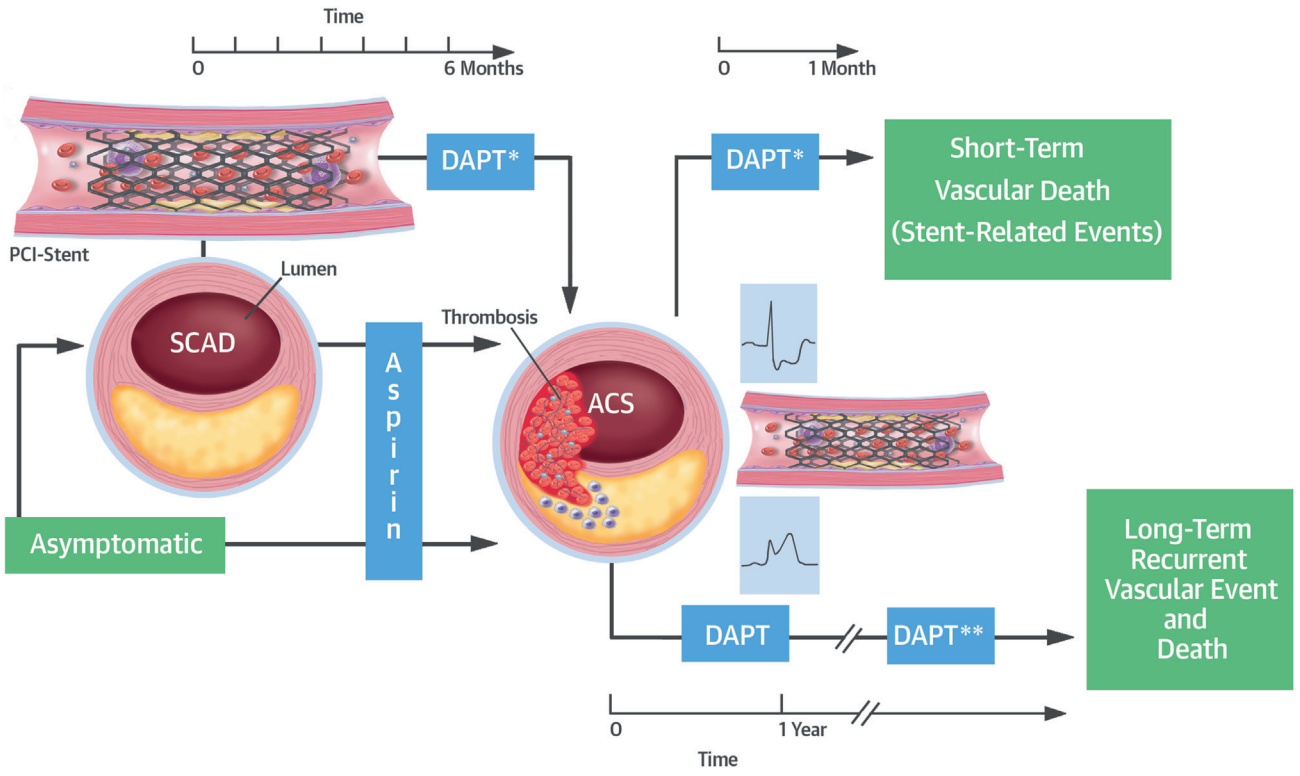
ACS = acute coronary syndromes; PCI = percutaneous coronary intervention; SCAD = stable coronary artery disease.

active metabolite concentrations is poor to moderate; the intrasubject variability is relatively high and largely depends on pharmacokinetic factors. Several trials in patients undergoing elective coronary stenting for stable coronary artery disease (CAD) showed no significant improvement in clinical outcomes with treatment adjustment according to platelet-function testing (VerifyNow $P2Y_{12}$ and aspirin point-of-care assays, Accriva Diagnostics, San Diego, California) compared with standard antiplatelet therapy without testing (18-20). Moreover, in the ANTARCTIC (Assessment of a Normal versus Tailored dose of prasugrel after stenting in patients Aged >75 years to Reduce the Composite of bleeding, stent Thrombosis and Ischemic Complications) study, platelet function monitoring with treatment adjustment did not improve the clinical outcome of elderly patients treated with coronary stenting for ACS (21). A pure de-escalation strategy with a stage-adapted treatment approach in the early phase of ACS, with the possibility of switching from prasugrel to clopidogrel, is being investigated in the TROPICAL-ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes) trial (22). Such a strategy may be of particular benefit when bleeding complications occur on prasugrel or ticagrelor. Conversely, TAILOR-PCI (Tailored Antiplatelet Therapy Following PCI) (NCT01742117) is assessing the hypothesis that genetic testing can identify the best antiplatelet therapy for patients who undergo a coronary stent placement and do not adequately activate clopidogrel. Routine use of platelet function testing is not recommended for patients undergoing elective or urgent percutaneous coronary intervention (PCI) (23), and its use should be restricted to the investigational setting. However, testing may be considered to: 1) assess (non)compliance with treatment; and 2) de-escalate or escalate treatment when deemed necessary after an unwanted/unexpected event. An observational study in patients who discontinued ticagrelor <5 days before coronary artery bypass graft (CABG) surgery (24) suggested that platelet function testing may be used to avoid unwanted bleeding and to reduce waiting time.

OTHER ANTIPLATELET DRUGS AND NEW TARGETS. For more information on additional antiplatelet drugs and new targets in antiplatelet therapy, please see the Online Appendix.

FUTURE CHALLENGES. The pharmacological and genetic determinants of the interindividual variability in response to antiplatelet agents have only been partially characterized. Two areas appear to deserve further investigation: 1) assessing the influence of variable platelet turnover on the pharmacodynamics of thienopyridines through in silico modeling and ex vivo confirmation; and 2) exploring the influence of obesity and bariatric surgery on the pharmacokinetics of aspirin and $P2Y_{12}$ inhibitors. Moreover, the ANDAMAN (Aspirin Twice a Day in Patients With Diabetes and Acute Coronary Syndrome) trial (NCT02520921) is currently investigating the efficacy and safety of a twice-daily low-dose aspirin regimen that was previously shown to improve the persistence of the antiplatelet effect of aspirin throughout the 24-h dosing interval in diabetic subjects with accelerated renewal of platelet COX-1 (25).

CENTRAL ILLUSTRATION **Coronary Atherothrombosis and its Prevention**



Patrono, C. et al. J Am Coll Cardiol. 2017;70(14):1760–76.

Different pathways in the natural history of coronary atherothrombosis and evidence-based interventions with antiplatelet agents for its treatment and prevention (both primary and secondary) that are reviewed throughout the paper. The time scales are intended to represent the timeframe within which particular combinations of antiplatelet agents were shown to be effective in reducing any given outcome illustrated in the figure. ACS = acute coronary syndrome; DAPT = dual antiplatelet therapy with aspirin + clopidogrel/ticagrelor/prasugrel; DAPT* = dual antiplatelet therapy with aspirin + clopidogrel; DAPT** = dual antiplatelet therapy with aspirin + ticagrelor 60 mg or aspirin + vorapaxar; PCI = percutaneous coronary intervention; SCAD = stable coronary artery disease.

SINGLE ANTIPLATELET THERAPY

Long-term single antiplatelet therapy (SAPT) with aspirin reduces the risk of first or recurrent major cardiovascular events with absolute effects proportional to the baseline risk (**Central Illustration**) (26,27).

FOR PRIMARY PREVENTION. Making the decision for long-term aspirin therapy in asymptomatic subjects remains challenging. There is no approved indication for primary cardiovascular prevention in most countries, and there are inconsistencies between treatment guidelines (**Table 2**) due to the substantial heterogeneity of the study subjects enrolled in the aspirin trials and their conflicting results in terms of the benefit/risk balance (28–32). Different recommendations range from considering no threshold (28), to a very high threshold of cardiovascular risk (i.e., ≥2%/year) (33), up to simply stating that it cannot be recommended (31). All recommendations listed in **Table 2** are relatively weak (none are Class I), reflecting: 1) a substantial lack of aspirin trials in high-risk, asymptomatic subjects (34); 2) differential value given to ischemic versus bleeding events (31,33); and 3) inconsistent consideration given to a potential chemopreventive effect of aspirin against colorectal cancer (28–33). **Table 3** shows the rate ratios for various clinical outcomes according to traditional risk factors, demonstrating that serious vascular events and major extracranial bleeding events are largely predicted by the same risk factors (34). Therefore, the net clinical benefit is not in favor of systematic treatment according to risk factors, given the associated bleeding risk of SAPT (35). It is reasonable to use aspirin in individuals with diabetes whose 10-year risk of events is >10%, which corresponds to men

TABLE 2 Guidelines on the Use of Aspirin in Primary Prevention

Organization (Year)	Recommendation	Class (Level of Evidence)	First Author (Ref. #)
ACCP (2012)	Low-dose aspirin (75–100 mg/day) in patients >50 yrs of age over no aspirin therapy.	II (B)	Vandvik et al. (28)
ESC/EASD (2013)	Antiplatelet therapy with aspirin in patients with DM at low CVD risk is not recommended.	III (A)	Rydén et al. (29)
ESC/EASD (2013)	Antiplatelet therapy for primary prevention may be considered in high-risk patients with DM on an individual basis.	IIb (C)	Rydén et al. (29)
AHA/ADA (2015)	Low-dose aspirin (75–162 mg/day) is reasonable among those with a 10-yr CVD risk of at least 10% and without an increased risk of bleeding.	IIa (B)	Fox et al. (30)
AHA/ADA (2015)	Low-dose aspirin is reasonable in adults with diabetes mellitus at intermediate risk (10-yr CVD risk, 5%–10%).	IIb (C)	Fox et al. (30)
ESC (2016)	Aspirin is not recommended in individuals without CVD due to the increased risk of major bleeding.	III (B)	Piepoli et al. (31)
USPSTF (2016)	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of CVD and CRC in adults 50 to 59 yrs of age who have a 10% or greater 10-yr CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 yrs, and are willing to take low-dose aspirin daily for at least 10 yrs.	B	Bibbins-Domingo et al. (32)
USPSTF (2016)	The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults 60 to 69 yrs of age who have a 10% or greater 10-yr CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 yrs, and are willing to take low-dose aspirin daily for at least 10 yrs are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.	C	Bibbins-Domingo et al. (32)

ACCP = American College of Chest Physicians; ADA = American Diabetes Association; AHA = American Heart Association; CRC = colorectal cancer; CVD = cardiovascular disease; DM = diabetes mellitus; EASD = European Association for the Study of Diabetes; ESC = European Society of Cardiology; MI = myocardial infarction; USPSTF = United States Preventive Services Task Force.

>50 years of age and women >60 years of age with at least 1 additional risk factor and who are not at increased risk of bleeding (no history of gastrointestinal [GI] bleeding or peptic ulcer disease, no concurrent use of other medications that increase bleeding risk) (30).

Overall, the absolute reduction in nonfatal myocardial infarction (MI) has been calculated to be approximately twice as large as the absolute increase in nonfatal GI bleeding in a primary prevention population, irrespective of age, sex, and baseline cardiovascular risk (34). The absolute benefits of antiplatelet prophylaxis are an order of magnitude lower than in secondary prevention (26,34). The benefit of aspirin in primary prevention is blunted by other preventive interventions, such as statin therapy, which are less harmful and display an additive effect on the reduction of cardiovascular events (36).

A more difficult situation is when asymptomatic arterial lesions have been identified with noninvasive imaging, computed tomography, or measurements such as the ankle-brachial index (ABI). Asymptomatic lesions are a major driver of the decision to initiate SAPT as a primary prevention intervention. The benefit of SAPT to prevent stroke in asymptomatic patients with carotid artery disease has not been established, as opposed to statin therapy. However, low-dose aspirin (75 to 100 mg daily) may be used in these patients to reduce the occurrence of other cardiovascular events (26). Indeed, asymptomatic carotid stenosis is associated with twice the long-term risk of MI (37).

There is no dedicated trial assessing the potential benefits and risks of SAPT according to the full spectrum of lower-extremity arterial disease (LEAD). A meta-analysis of randomized trials comparing SAPT to placebo included a subgroup of 5,269 patients with mainly symptomatic LEAD and a follow-up ranging from 10 days up to 6.7 years (38). The analysis demonstrated a nonsignificant reduction in cardiovascular events, defined as nonfatal MI, nonfatal stroke, and cardiovascular mortality (relative risk [RR]: 0.75; 95% confidence interval [CI]: 0.48 to 1.18), a significant reduction in nonfatal stroke (RR: 0.64; 95% CI: 0.42 to 0.99), and no statistically significant changes in nonfatal MI, cardiovascular mortality, or major bleeding (38). However, the available evidence from the ATT (Antithrombotic Trialists') Collaboration meta-analysis of antiplatelet trials is that the relative risk reductions are consistent in all high-risk populations, including those with asymptomatic LEAD (26). According to the 2016 American Heart Association (AHA)/American College of Cardiology (ACC) guideline on the management of patients with

TABLE 3 Rate Ratios (95% CI) Associated With Risk Factors for Selected Outcomes in People With No Known Vascular Disease in Primary Prevention Trials

Risk Factor	Major Coronary Event	Probable Ischemic Stroke	Hemorrhagic Stroke	Major Extracranial Bleed
Age (per decade)	1.84 (1.74–1.95)	2.46 (2.27–2.65)	1.59 (1.33–1.90)	2.15 (1.93–2.39)
Male*	2.43 (1.94–3.04)	1.44 (1.14–1.82)	1.11 (0.52–2.34)	1.99 (1.45–2.73)
Diabetes mellitus	2.66 (2.28–3.12)	2.06 (1.67–2.54)	1.74 (0.95–3.17)	1.55 (1.13–2.14)
Current smoker	2.05 (1.85–2.28)	2.00 (1.72–2.31)	2.18 (1.57–3.02)	1.56 (1.25–1.94)
Mean blood pressure (per 20 mm Hg)†	1.73 (1.59–1.89)	2.00 (1.77–2.26)	2.18 (1.65–2.87)	1.32 (1.09–1.58)
Cholesterol (per 1 mmol/l)	1.18 (1.12–1.24)	1.02 (0.95–1.09)	0.90 (0.77–1.07)	0.99 (0.90–1.08)
Body mass index (per 5 kg/m^2)	1.09 (1.03–1.15)	1.06 (0.98–1.14)	0.85 (0.71–1.02)	1.24 (1.13–1.35)

*Analyses are stratified by trial. The relevance of male sex can therefore be assessed only in the 2 trials that included both men and women, so the 95% CIs for it are wide, particularly for stroke. †Mean of systolic and diastolic blood pressure. Associations with measured values are not corrected for the effects of regression dilution. Reproduced with permission from the Antithrombotic Trialists' (ATT) Collaboration (34).

CI = confidence interval.

lower-extremity PAD, in asymptomatic patients with PAD (ABI ≤0.90), use of SAPT is reasonable to reduce the risk of MI, stroke, or vascular death (39).

Coronary artery calcium examined through electron beam or multislice computed tomography is considered as a modifier of cardiovascular risk assessment, especially in individuals with calculated SCORE (Systematic COronary Risk Evaluation) risks around the 5% and 10% thresholds (31). It is associated with CAD, but its negative predictive value has been questioned, given that significant stenosis may be present in the absence of coronary artery calcium (31). The effect of SAPT has not been tested in patients exceeding some threshold of coronary artery calcium score.

FOR SECONDARY PREVENTION. This usually corresponds to a situation where cardiovascular risk is >20% in 10 years, in which case SAPT with low-dose aspirin is recommended. In symptomatic extracranial carotid or vertebral atherosclerosis, SAPT is recommended and preferred over oral anticoagulation (OAC) (28,40). Clopidogrel (75 mg daily) provides an alternative antiplatelet agent in patients with prior MI, prior stroke, or symptomatic PAD (41). The benefit of long-term SAPT after coronary revascularization or in stabilized patients with ACS is well established. In addition, there is consistent evidence demonstrating that SAPT disruption in symptomatic patients with CAD is harmful (42–44).

Whether one antiplatelet agent is more effective than another as SAPT is a matter of debate. Clopidogrel was not consistently more effective than aspirin in patients with different clinical presentations of atherothrombosis (41). Terutroban (a TXA_2 receptor antagonist) and ticagrelor failed to show any statistically significant superiority over aspirin in patients with stroke (45,46). It should be emphasized that, besides reducing vascular mortality by about one-quarter during the first 5 weeks after an acute MI (47), aspirin is highly effective in reducing early recurrent events after a transient ischemic attack (TIA) or ischemic stroke (48). More recently, the EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease) trial compared, in a randomized double-blind approach, ticagrelor versus clopidogrel in 13,885 patients ≥50 years of age (mean age 66 years) with symptomatic PAD (11). Patients were eligible if they had an ABI ≤0.80 (57%) or had undergone previous revascularization of the lower limbs (43%). CYP2C19*2 homozygous carriers were excluded to avoid poor clopidogrel metabolizers. The primary efficacy endpoint, a composite of adjudicated cardiovascular death, MI, or ischemic stroke evaluated at a median follow-up of 30 months, occurred in 751 of 6,930 patients (10.8%) receiving ticagrelor and in 740 of 6,955 (10.6%) receiving clopidogrel (hazard ratio [HR]: 1.02; 95% CI: 0.92 to 1.13; p = 0.65). In each group, acute limb ischemia occurred in 1.7% of the patients (HR: 1.03; 95% CI: 0.79 to 1.33; p = 0.85) and major bleeding in 1.6% (HR: 1.10; 95% CI: 0.84 to 1.43; p = 0.49) (11).

FUTURE CHALLENGES. There is an intermediate area of cardiovascular risk (10% to 20% at 10 years) where data from aspirin trials are lacking, but the benefits may outweigh the risks (27). There are 4 ongoing primary prevention trials on this specific issue that may have an effect on the guidelines (49–52). Another interesting development is represented by the apparent long-term benefits of aspirin therapy to reduce GI cancer incidence and cancer-related mortality, as consistently suggested by several lines of evidence (53). Inhibition of platelet activation at sites of GI mucosal lesions could be the primary mechanism of action of low-dose aspirin (54), although other explanations have been proposed (53). Several adjuvant trials of low-dose aspirin versus placebo in patients with cancer are currently ongoing (53).

Whether factor Xa inhibitors used at low dose may be superior to aspirin to prevent recurrent major

cardiovascular events is another unsolved question. COMPASS (Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease; NCT01776424) is a double-blind, randomized, controlled trial aimed at evaluating whether rivaroxaban 2.5 mg twice a day (b.i.d.) in addition to aspirin 100 mg once daily or rivaroxaban 5 mg b.i.d. alone is better than aspirin 100 mg alone at preventing MI, stroke, or cardiovascular death among patients with CAD or PAD (55). Rivaroxaban 2.5 mg b.i.d. plus aspirin 100 mg once daily reduced CV outcomes (HR: 0.76; 95% CI: 0.66 to 0.86; $p < 0.001$), but increased major bleeding events (HR: 1.70; 95% CI: 1.40 to 2.05; $p < 0.001$) without a significant increase in fatal, intracranial or critical organ bleeding (55). Rivaroxaban 5 mg b.i.d. alone did not result in better cardiovascular outcomes than aspirin alone and resulted in more major bleeding events (55). Finally, several ongoing trials (i.e., GLOBAL LEADERS [A Clinical Study Comparing Two Forms of Antiplatelet Therapy After Stent Implantation; NCT01813435] (56); TWILIGHT [Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention; NCT02270242] (57); and TICO [Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome; NCT02494895]) are evaluating the so-called "less-is-more" approach to antiplatelet therapy in over 28,000 patients without atrial fibrillation undergoing PCI (58). These trials are testing the hypothesis that ticagrelor monotherapy may be superior in terms of efficacy and/or safety over conventional dual antiplatelet therapy (DAPT), largely based on the controversial assumption that effective blockade of $P2Y_{12}$ may also affect platelet TXA_2 production, thereby minimizing any additional antiplatelet effect of aspirin (58).

COMBINATION ANTIPLATELET THERAPY

Most studies of antiplatelet therapy in secondary prevention to date have used aspirin in combination with 1 or 2 other antiplatelet drugs, although there is strong interest in studies that challenge this status quo. Currently, the dominant strategy for high-risk individuals is DAPT with aspirin and an oral $P2Y_{12}$ antagonist. The use of vorapaxar in combination with DAPT consisting of aspirin and clopidogrel or SAPT has also been explored in ACS (5). Alternatively, the combination of aspirin and dipyridamole has been established in secondary prevention after TIA or stroke and has yet to be successfully challenged (40).

ASPIRIN AND CLOPIDOGREL. The CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) study provided proof-of-concept for the use of DAPT with aspirin and clopidogrel in the management of ACS: compared with aspirin alone, DAPT reduced the rate of the composite endpoint of MI, stroke, or cardiovascular death by 20% (9.3% vs. 11.4%; RR: 0.80; 95% CI: 0.72 to 0.90; $p < 0.001$), but increased the risk of major bleeding (3.7% vs. 2.7%; RR: 1.38; 95% CI: 1.13 to 1.67; $p < 0.001$) (59,60). Numerous other studies in patients undergoing PCI have supported this DAPT regimen as the default strategy for preventing stent thrombosis (61). Aspirin and clopidogrel remain the recommended combination for patients undergoing elective PCI for stable CAD (62). However, the interindividual variability in response to clopidogrel is associated with a high proportion of cases of stent thrombosis during DAPT in adherent patients (63,64). This variability, combined with slower onset of action, has led to the displacement of clopidogrel by ticagrelor and prasugrel in higher-risk patients with ACS, as detailed later. However, safety considerations have led to recommendations for preferentially using clopidogrel in ACS patients who also require OAC in view of the increased bleeding hazard with this combination (23,65).

ASPIRIN AND PRASUGREL. The pharmacokinetic and pharmacodynamic advantages of prasugrel explain its higher antithrombotic efficacy compared with clopidogrel, particularly with regard to prevention of stent thrombosis in patients with ACS undergoing PCI (3,66,67). Consequently, DAPT with aspirin and prasugrel is recommended as a first-line option in patients with ACS planned for PCI, in preference to aspirin and clopidogrel (23,68). DAPT with prasugrel, compared with clopidogrel, was also associated with higher rates of CABG-related bleeding (3) and, in another study, did not significantly reduce ischemic events in patients with ACS who were medically managed (69). Consequently, prasugrel is not recommended in patients with ACS who are not planned for PCI. Pre-treatment of ACS patients with a prasugrel loading dose before coronary angiography was not found to be more effective than treatment at the time of PCI (70) and is therefore also not recommended (23). Concern about possible harm in patients with prior history of cerebrovascular disease has led to contraindication for prasugrel in this subgroup, and lack of net benefit observed in patients >75 years of age has also led to a recommendation to avoid prasugrel in these patients (23,68). Prasugrel is also not recommended in patients who require OAC (23,65). In contrast to clopidogrel, the pharmacokinetics of prasugrel are not significantly affected by inhibitors of CYP2C19 or CYP3A, and this should be taken into consideration when selecting DAPT in patients who require ongoing treatment with strong inhibitors of these CYP pathways (71).

EXTENDED THIENOPYRIDINE-BASED DAPT. Prolonged therapy with aspirin and either clopidogrel or prasugrel after PCI (more than 12 months) is associated with reduced risks of stent thrombosis and MI, but increased risk of major bleeding (72). $P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year after ACS may be considered after careful assessment of the ischemic and bleeding risks of the patient (23). A treatment algorithm for duration of $P2Y_{12}$ inhibitor therapy in patients with recent ACS (non-ST-segment elevation ACS or ST-segment elevation MI) has been proposed by the 2016 ACC/AHA guideline focused update (73).

ASPIRIN AND TICAGRELOR. DAPT with aspirin and ticagrelor reduces major vascular events, including cardiovascular death, compared with DAPT with aspirin and clopidogrel in the first year after ACS (9.8% vs. 11.7%; HR: 0.84; 95% CI: 0.77 to 0.92; $p < 0.001$) with consistent benefit seen across a wide range of management strategies (PCI, CABG surgery, or conservative management) (4). Consequently, ticagrelor is recommended in preference to clopidogrel as first-line therapy in patients with either ST-segment elevation MI undergoing primary PCI or non-ST-segment elevation ACS, regardless of management strategy (23,68). Ticagrelor increases the risk of non-CABG-related major bleeding compared with clopidogrel (PLATO [Platelet Inhibition and Patient Outcomes]-defined major non-CABG bleeding: 4.5% vs. 3.8%, respectively; $p = 0.03$), including intracranial hemorrhage (ICH), and is contraindicated in those with prior history of ICH (4). Despite its greater antiplatelet effect, ticagrelor did not increase CABG-related bleeding compared with clopidogrel, likely related to its faster offset of action (4). Ticagrelor should also be avoided in combination with aspirin and OAC (65).

Dyspnea is a common adverse effect (approximately 10% of patients), usually occurring early during treatment, and sometimes necessitates switching to clopidogrel or prasugrel (74,75).

EXTENDED TICAGRELOR-BASED DAPT. Longer-term treatment with ticagrelor-based DAPT beyond 1 year following MI has also been shown to reduce serious vascular events compared with aspirin alone in patients without prior history of cerebrovascular disease (ticagrelor 60 mg b.i.d. vs. placebo: 7.8% vs. 9.0%; HR: 0.84; 95% CI: 0.74 to 0.95; $p = 0.004$), albeit at the expense of increased risk of nonfatal bleeding (Thrombolysis In Myocardial Infarction [TIMI] major bleeding, 2.3% vs. 1.1%; HR: 2.32; 95% CI: 1.68 to 3.21; $p < 0.001$) (76,77). An extended duration of ticagrelor-based DAPT beyond 1 year post-MI is likely to be beneficial in those at high risk of cardiovascular death who do not have a high risk of fatal bleeding (73).

COMBINATION THERAPY WITH VORAPAXAR. Vorapaxar added to standard-of-care treatment (predominantly aspirin and/or clopidogrel) was shown to reduce serious vascular event rates in patients with a history of atherosclerotic disease, but with a significant increase in the risk of ICH and other major bleeding, particularly in those with a history of ischemic stroke, so that benefits appeared to be confined to subgroups with MI or PAD without a history of stroke (78). Acute treatment of non-ST-segment elevation ACS patients with vorapaxar, in addition to standard-of-care treatment (predominantly clopidogrel-based DAPT), failed to show significant reduction in the primary endpoint and was associated with increased risk of ICH and other major bleeding, particularly in those with a history of ischemic cerebrovascular disease (5). The addition of vorapaxar to aspirin or clopidogrel may be considered as an option in patients with stable atherosclerotic disease, particularly PAD, who do not have a history of cerebrovascular disease or other factors that may increase the risk of ICH; however, this recommendation is limited by the lack of a prospective trial in this specific population. According to the 2016 AHA/ACC guideline, the overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain (39).

ASPIRIN AND DIPYRIDAMOLE. The combination of low-dose aspirin and dipyridamole remains a first-line option for secondary prevention in those with a history of noncardioembolic ischemic stroke or TIA (1,28). There is no evidence to support this combination for other indications.

COMBINATION THERAPY WITH LOW-DOSE RIVAROXABAN. Rivaroxaban at a dose of 2.5 mg b.i.d., representing one-quarter of the approved anticoagulant dose in patients with atrial fibrillation and normal renal function, has been shown to reduce ischemic events and cardiovascular death in patients treated with aspirin and clopidogrel following ACS, at the expense of increased major bleeding (79). The safety and efficacy of this regimen has not been studied with ticagrelor or prasugrel instead of clopidogrel, which has prevented a strong recommendation of this strategy as first-line therapy in ACS (23). Rivaroxaban 2.5 mg b.i.d. has also shown potential for replacing aspirin in patients who are stable following PCI and treated with an oral $P2Y_{12}$ inhibitor, but further work would be required before this approach could be recommended (80).

TABLE 4 High-Risk Features of Stent-Driven Recurrent Ischemic Events

Prior stent thrombosis on adequate antiplatelet therapy
Stenting of the last remaining patent coronary artery
Diffuse multivessel disease, especially in patients with diabetes
Chronic kidney disease (i.e., creatinine clearance <60 ml/min)
At least 3 stents implanted
At least 3 lesions treated
Bifurcation with 2 stents implanted
Total stent length >60 mm
Treatment of a chronic total occlusion

FUTURE CHALLENGES. The benefit/risk ratio of short (i.e., ≤6 months) triple therapy duration, compared with double therapy consisting of clopidogrel and OAC, remains unknown and requires a patient-by-patient decision (23). Ongoing trials are comparing non-vitamin K antagonists (non-VKA) versus VKA in this particular setting. The PIONEER AF-PCI (A Study Exploring Two Strategies of Rivaroxaban [NCT01830543] and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) study of 2,124 participants with atrial fibrillation undergoing PCI with placement of stents demonstrated better safety of rivaroxaban versus VKA, although it was largely underpowered for assessing realistic differences in the incidence of relevant ischemic events (81). Data on the timing of cessation of any antiplatelet agents in patients with stented arteries requiring chronic OAC are scarce.

Studies demonstrating that OAC alone is superior to aspirin post-ACS and that OAC + aspirin may not be more protective, but is associated with excess bleeding, should encourage cessation of all antiplatelet agents in stabilized patients who are at low risk of further ischemic events (82). These patients can be defined as those without any high-risk features, as described in **Table 4** (23).

Furthermore, the substantial burden of late vascular events after ACS (approximately 10% at 1 year) despite optimal pharmacological treatment, including effective $P2Y_{12}$ inhibitors and statins, calls for reappraisal of the pathophysiology of these adverse outcomes and innovative preventive strategies (23).

PREDICTING BLEEDING COMPLICATIONS

Antiplatelet therapies alone and in combination are associated with an increased risk of bleeding, estimated at 4 to 7 events/100 patient-years, particularly during the acute in-hospital phase of treatment. Efforts to predict bleeding have focused on clinical factors, but also laboratory testing of platelet function, genetics, and biomarkers (83,84). As outlined throughout this review, specific circumstances and antiplatelet therapies are particularly associated with an increased risk of bleeding. Thus, cerebrovascular disease (prior stroke or TIA) and a prior history of ICH are associated with a higher risk of bleeding (particularly ICH), as are escalating regimens of different or more effective antiplatelet therapies. This is particularly the case for combinations of antiplatelet therapies that include vorapaxar or when antiplatelet therapy is combined with OAC, and is related to the duration of treatment. Other factors, including older age, female sex, low body weight (<60 kg), renal dysfunction, and a history of bleeding, have consistently been found to be predictors of bleeding complications in CAD patients, as the age-related and kidney dysfunction-related major bleeding risks are amplified by antiplatelet drugs. A number of bleeding scores have been developed (e.g., CRUSADE [Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines], ACUITY [Acute Catheterization and Urgent Intervention Triage strategy], and HAS-BLED [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly] [85–87]), and such scoring systems are recommended in several guidelines (23,65,88). These scoring systems were compared in the PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) trial (89). All 3 scoring systems predicted bleeding events, although the CRUSADE score was more specific in low-risk patients. The results were consistent across bleeding scales and duration of treatment (89). Nevertheless, the predictability is poor, and further refinement and comparison of different bleeding risk scores are needed (90).

Other approaches have focused on the degree of platelet inhibition versus the risk of bleeding. Patients with the lowest residual platelet activity are at a greater risk of bleeding (91). However, it should be noted that clinical factors may influence platelet function assays, including patient characteristics, such as diabetes mellitus, age, and smoking, that can independently affect platelet reactivity. Genetic tests are designed to detect common variants in drug-metabolizing enzymes, specifically CYP2C19. Patients with the gain-of-function CYP2C19*17 allele are fast metabolizers of clopidogrel, form higher amounts of its active metabolite, and have lower platelet reactivity on the drug. Although patients with this

allele may be at higher risk of bleeding (92), the outcomes of other studies on bleeding risk show a variable association with this allele. This may be due to ethnic differences, clinical factors, or the presence of other genetic variants. However, there are no randomized trials that have looked at the effect on bleeding risk of adjusting therapy based on platelet function assays or genetic testing while on DAPT.

TAILORING ANTIPLATELET THERAPY IN SPECIAL POPULATIONS

TYPE 2 DIABETES MELLITUS. Type 2 diabetes mellitus is associated with increased atherothrombotic risk due to accelerated atherosclerosis and prothrombotic changes in blood coagulability and platelet function (29). Platelet turnover may be increased, which, in turn, can promote faster recovery from platelet inhibition during the 24-h dosing interval of irreversibly acting drugs, such as aspirin (25). Consequently, there is interest in the use of b.i.d. low-dose aspirin, but the efficacy and safety of this approach is unknown and is being currently tested (see earlier discussion). Diabetes also mildly reduces the response to clopidogrel due to impaired formation of its active metabolite, as well as increased platelet turnover (93,94). This fact, along with the increased atherothrombotic risk of patients with diabetes, supports the use of ticagrelor or prasugrel in preference to clopidogrel for the management of MI, as well as for subsequent long-term secondary prevention (29).

CHRONIC KIDNEY DISEASE. Both ischemic and bleeding risks are increased in patients with severe chronic kidney disease (CKD). A systematic review and meta-analysis of antiplatelet trials in persons with CKD concluded that the benefits of antiplatelet therapy are statistically uncertain and potentially outweighed by bleeding hazards (95). The available oral antiplatelet drugs are not dependent on renal excretion, and therefore do not require dose adjustment according to renal function. CKD has been associated with reduced response to clopidogrel in patients with diabetes mellitus, but not in patients without diabetes, suggesting that renal function per se is not a determinant of clopidogrel response (96). Ticagrelor is associated with a mild increase in serum creatinine, but remains efficacious in those with non-dialysis-dependent CKD and is therefore recommended in this population (97,98). There are limited data on the safety and efficacy of oral $P2Y_{12}$ inhibitors in patients with dialysis-dependent renal failure, but no evidence to suggest that tailoring of therapy is required in this population.

The intravenous small-molecule glycoprotein (GP) IIb/IIIa antagonists are partly excreted via the kidneys, and therefore should be used with caution in patients with acute renal failure or moderate-to-severe CKD. Eptifibatide and tirofiban infusion rates should be reduced by 50% for creatinine clearances of 30 to 59 ml/min and 15 to 30 ml/min, respectively, and are not recommended when creatinine clearance is <30 and <15 ml/min, respectively (23). Careful evaluation of bleeding risk, but no specific recommendation or dose adjustment, is needed for abciximab (23). Cangrelor clearance is not dependent on renal function (23).

BODY WEIGHT. There is insufficient evidence to suggest a need for dose adjustment of aspirin, clopidogrel, ticagrelor, vorapaxar, or dipyridamole in those who are underweight or with different degrees of obesity. Prasugrel should either be avoided or used at a dose of 5 mg daily in those with body weight <60 kg (99). Dosing of intravenous GP IIb/IIIa antagonists and cangrelor is weight-adjusted (23).

HIGH-RISK OR COMPLICATED PCI. Clopidogrel in combination with aspirin is standard therapy for patients with stable CAD undergoing PCI, but poor pharmacodynamic response may be deemed an increased risk in patients undergoing high-risk procedures (**Table 4**) or those with periprocedural thrombotic complications. Even in high-risk patients, platelet function testing failed to show any benefit in guiding antiplatelet therapy, but may be considered when there is an unwanted event, such as acute stent thrombosis on treatment; alternatively, off-label use of prasugrel or ticagrelor may be considered (17,64).

PATIENTS WITH RECENT GI BLEEDING OR PRIOR ICH. The management of antithrombotic therapy after bleeding is reviewed in detail elsewhere (100). Prasugrel and ticagrelor should generally be avoided, and the antithrombotic regimen should be decided on the basis of individual ischemic and bleeding risks.

ELDERLY PATIENTS. Beyond 75 years of age, the rate of upper GI bleeding increases from approximately 0.5/100 patient-years without antiplatelet treatment to approximately 1/100 patient-years with aspirin (101). Secondary prevention of cardiovascular events by aspirin is more favorable among patients 64 to 74 years of age than among patients 50 to 59 years of age (approximately 2.2 vs. 1.4 events prevented per 100 patient-years) (28). Thus, older age does not contraindicate the use of aspirin for secondary cardiovascular prevention. Upper GI pain or prior uncomplicated ulcer warrant gastroprotection with a proton pump inhibitor, especially in patients 65 years

of age or older who are on DAPT (101). Aspirin avoidance should be considered in the presence of bleeding ulcer or ICH, especially for those above 75 years of age (101).

Clopidogrel (if bleeding risk is high) or ticagrelor are recommended instead of prasugrel for patients ≥75 years of age, given their favorable benefit/risk profile (102). If prasugrel is deemed necessary, a 5-mg daily maintenance dose should be considered (101). Despite an overall higher non-CABG TIMI major bleeding rate with ticagrelor than with clopidogrel (2.8% vs. 2.2%/year; $p = 0.03$) (4), the survival benefit with ticagrelor versus clopidogrel is maintained in patients >75 years of age (102). Thus, unless bleeding risk is excessive, ticagrelor is recommended over clopidogrel in the older population (101).

The benefit/risk ratio of intravenous cangrelor is more favorable in elderly than in younger patients (101). The opposite is true for intravenous GP IIb/IIIa inhibitors and vorapaxar (101).

DISCONTINUATION OF ANTIPLATELET THERAPY

The risk of bleeding in patients treated with antithrombotic drugs who either undergo surgical or other invasive procedures or experience a bleeding event is a matter of concern in daily practice. However, premature discontinuation of antiplatelet drugs, especially DAPT after ACS or within the first 3 to 6 months after drug-eluting stent (DES) implantation, has been associated with an increased risk of stent thrombosis or new, non-stent-related acute events (103). Furthermore, bleeding may heighten thrombotic risk by mechanisms that are distinct from the risk associated with discontinuation of antiplatelet therapy (100).

The most recent meta-analysis that evaluated the use of aspirin in patients undergoing CABG surgery included 13 randomized trials with a total of 2,399 participants (104). The investigators found that the continuation of aspirin reduced the risk of perioperative MI by nearly one-half. However, there was evidence of increased bleeding, and an increased need for red cell transfusions and surgical re-exploration. In patients who are at low bleeding risk undergoing CABG, low-dose aspirin (75 to 100 mg daily) should be maintained. In patients with increased bleeding risk and in those who refuse blood transfusion, withdrawal of aspirin 3 to 5 days before surgery is recommended based on individualized assessment of ischemic and bleeding risks (105). Continuation of aspirin is also recommended for patients undergoing noncardiac surgery (106).

Whereas withdrawal of aspirin monotherapy may be harmful, cessation of aspirin rather than $P2Y_{12}$ inhibitor in DAPT-treated patients will lead to improved hemostasis and may be considered for management of bleeding or bleeding risk. Ongoing studies are assessing the effect of withdrawal of aspirin at 1 to 3 months after PCI to determine how this influences the balance of ischemic and bleeding risk compared with DAPT (58). Because cessation of aspirin in a DAPT regimen leads to less platelet inhibition and, therefore, potentially higher ischemic risk, the results of these studies should be awaited before this strategy can be recommended other than in patients presenting with bleeding.

Regarding $P2Y_{12}$ inhibitors, the bleeding risk associated with surgery or interventions is closely related to the time period of withdrawal. In the CURE trial, a total of 2,072 patients underwent CABG at any time after randomization. Among these, major bleeding occurred in 9.6% and 7.5% in the clopidogrel and placebo arms, respectively (relative risk: 1.27; 95% CI: 0.96 to 1.69; $p = 0.095$) (107). Whereas no excess bleeding was observed for those stopping the drug for >5 days before surgery (clopidogrel 4.4% vs. placebo 5.3%), a 53% increase in major bleeding was recorded in those who continued the drug within 5 days of surgery (clopidogrel 9.6% vs. placebo 6.3%) (107). Ticagrelor should be discontinued 4 to 5 days before CABG surgery or longer for other types of surgery that require absence of $P2Y_{12}$ inhibition (106). Among ACS patients undergoing CABG, the rate of TIMI major bleeding was higher with prasugrel than with clopidogrel (3). The difference in CABG-related TIMI major or minor bleeding between prasugrel and clopidogrel was remarkable when the time from the last dose of the study drug was ≤3 days pre-CABG (26.7% vs. 5.0%; $p < 0.001$), but also when the drug was discontinued within 4 to 7 days (11.3% vs. 3.4%; $p < 0.001$) (3). A time period of 7 days to discontinue prasugrel is recommended for patients undergoing noncardiac surgery (106).

In summary, patients should be counseled about the risk of premature discontinuation of prescribed antiplatelet therapy and clinicians should avoid, when possible, discontinuation of therapy in the event of non-life-threatening bleeding. For those undergoing surgery following PCI, a minimum of 1 month of DAPT should be considered, independently of the type of implanted stent (i.e., bare-metal stent or newer-generation DES), in cases when surgery cannot be delayed for a longer period (108). In patients who are at higher than average ischemic risk because of the type of presentation (e.g., high-risk ACS) and/or complexity of the revascularization

procedures, delaying surgery up to 6 months after the index ACS or PCI may be reasonable as an additional safeguard to minimize the risk of perisurgical MI, if the risks of further delaying surgery are acceptable (109).

BRIDGING THERAPY

For patients scheduled for invasive or surgical procedures for whom a temporary interruption of $P2Y_{12}$ inhibitors is advised, the risk of stent thrombosis or new thrombotic events should be managed. To minimize both risks, several protocols of bridging therapy have been proposed. To be effective, the bridging agent should be able to achieve platelet inhibition similar to that of the oral $P2Y_{12}$ receptor inhibitor, with a rapid onset of action and rapid offset. Two unapproved options are currently available: small-molecule GP IIb/IIIa inhibitors (tirofiban and eptifibatide) and the intravenous $P2Y_{12}$ inhibitor cangrelor. In a series of 30 patients with a recently implanted DES and high-risk characteristics for stent thrombosis who underwent urgent major surgery or eye surgery (110), clopidogrel was to be withdrawn 5 days before surgery, and tirofiban was started 24 h later, continued until 4 h before surgery, and resumed 2 h post-surgery until clopidogrel was resumed. There was no death, MI, stent thrombosis, or surgical re-exploration due to bleeding during the index admission, with a risk estimate of 0% to 11.6% (1-tailed 97.5% CI). The same investigators (110) developed a protocol of bridging therapy with tirofiban started 3 days before the procedure and stopped 4 h before. An alternative bridging regimen with cangrelor has been proposed, started on the same day of stopping oral agents and infused until 1 to 6 h before surgery (111). Given the experimental and often nonrandomized nature of these small studies, bridging therapy should be considered on an individual basis.

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KEY WORDS aspirin, cangrelor, clopidogrel, prasugrel, ticagrelor, vorapaxar

APPENDIX For supplemental material as well as figures and a table, please see the online version of this article.