

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) A₂-, 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 TXA₂ 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](#).

P2Y₁₂ INHIBITORS. Oral inhibitors of the platelet ADP receptor, P2Y₁₂, include the thienopyridines (ticlopidine, clopidogrel, and prasugrel) and ticagrelor. Major characteristics of P2Y₁₂ 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 P2Y₁₂ receptor, acting as an allosteric antagonist that noncompetitively prevents ADP-induced P2Y₁₂ activation (1).

When added to COX-1 suppression by low-dose aspirin, P2Y₁₂ 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 P2Y₁₂ inactivation achieved by clopidogrel in most patients. A faster and more complete P2Y₁₂ 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).

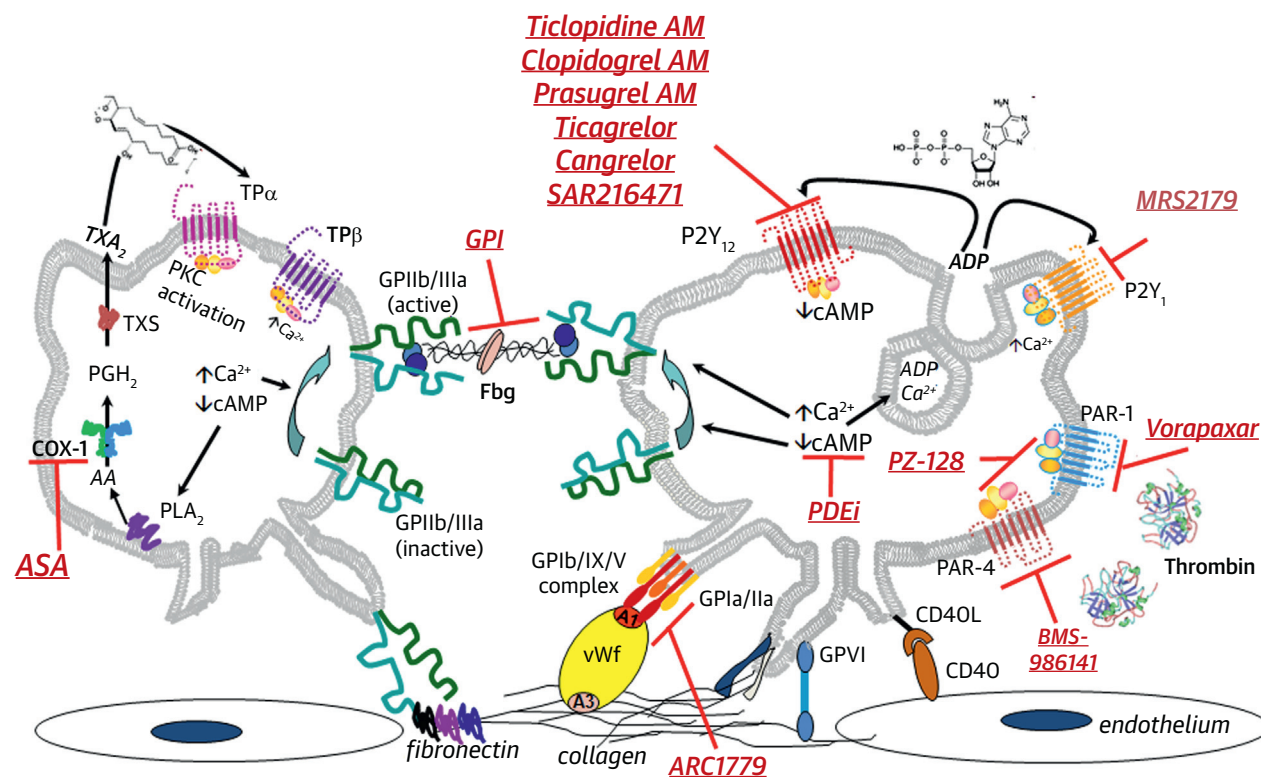
Clopidogrel has less than optimal pharmacokinetics: ~85% is inactivated by carboxylesterases before liver first pass; it is a substrate of the P-glycoprotein (P-gp) efflux transporter (also known as ABCB1) and is bio-activated by 2 sequential oxidative reactions involving several cytochrome P450 (CYP450) 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 P2Y₁ and P2Y₁₂ 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 TXA₂ formation; and final activation of α 2b β 3 (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; Ca²⁺ = calcium; cAMP = cyclic adenosine monophosphate; COX = cyclooxygenase; Fbg = fibrinogen; GP = glycoprotein; GPI = GPIIb/IIIa inhibitors; PAR = protease-activated receptor; PDEi = phosphodiesterase inhibitors; PGH₂ = prostaglandin H₂; PKC = protein kinase C; PL = phospholipase; PLA₂ = phospholipase A₂; TP = thromboxane receptor; TX = thromboxane; TXS = thromboxane synthase; vWf = von Willebrand factor.

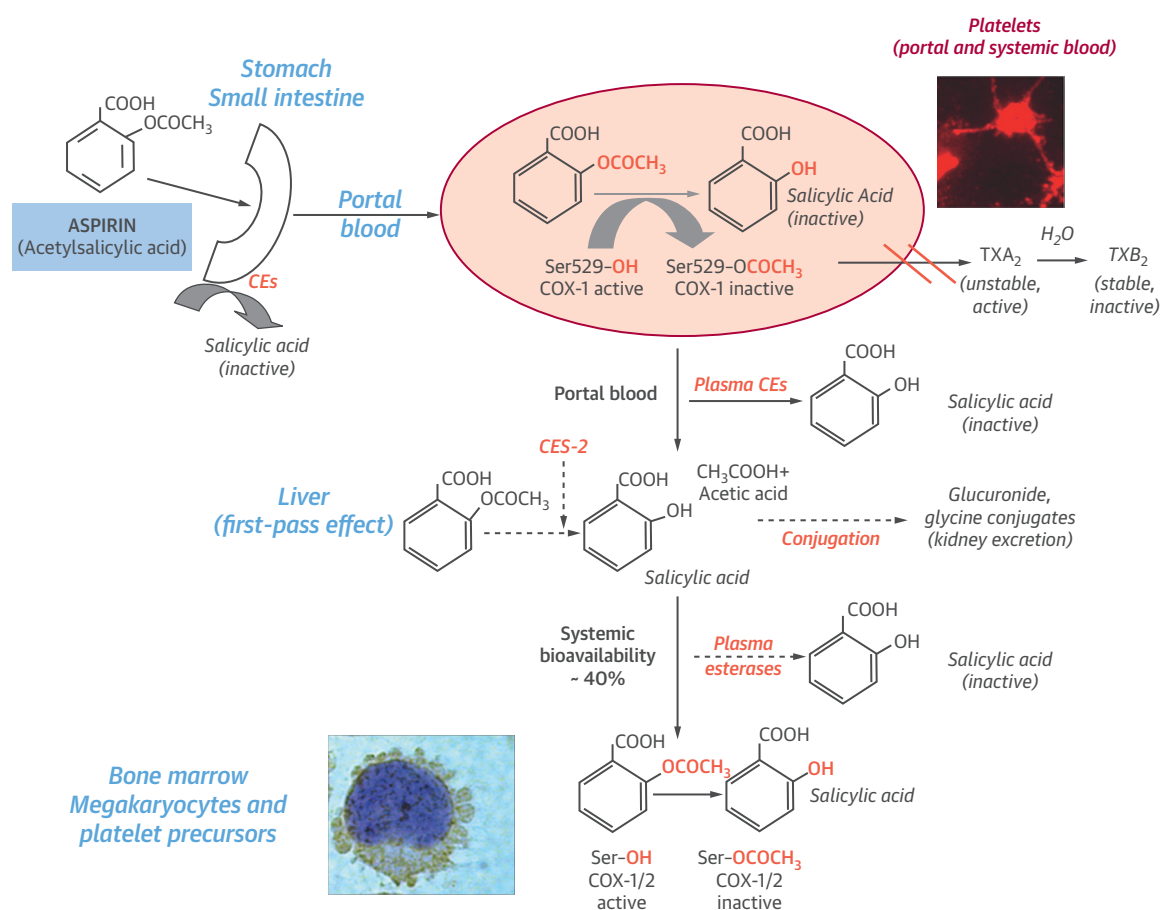
CYP3A4/A5 to a main active (AR-C124910XX) and an inactive (AR-C133913XX) metabolite (Online Figure 1C). AR-C124910XX is equipotent to ticagrelor, has similar pharmacokinetics, and contributes approximately 30% of the antiplatelet effect (1). P-gp or CYP2C19 polymorphisms do not affect ticagrelor pharmacokinetics 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 TXA₂, which amplifies platelet activation by binding to its platelet receptors. TXA₂ is nonenzymatically hydrolyzed to TXB₂, 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 TXB₂ 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 TXB₂ 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 P2Y₁₂ inhibition (17). In the case of clopidogrel, the concordance among the functional assays and between each assay and plasma

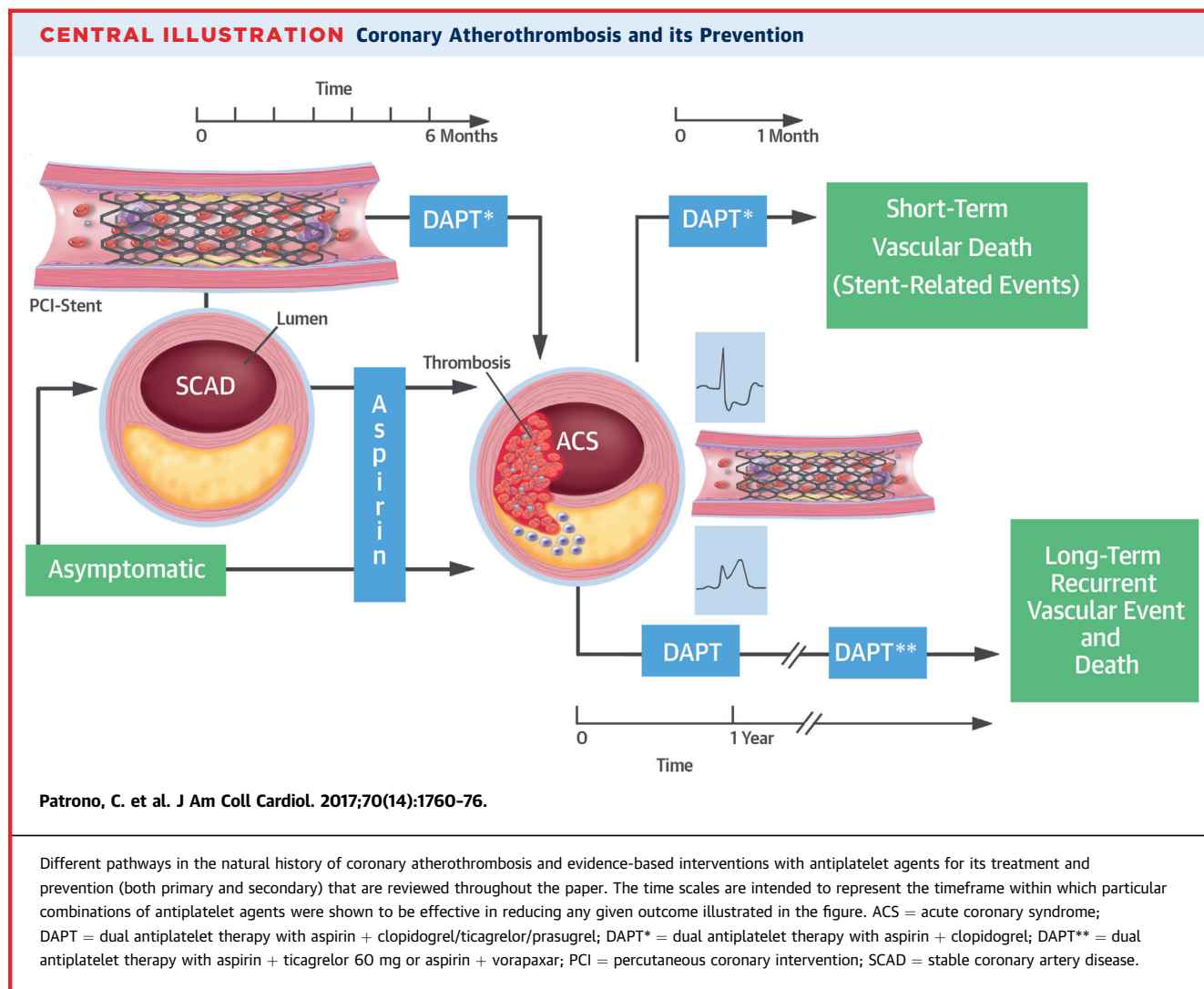
TABLE 1 Main Properties of P2Y ₁₂ Inhibitors				
	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Bioavailability	50%	80%	36%	100%
Half-life (active metabolite)	30–60 min	Distribution half-life 30–60 min; elimination half-life 2–15 h	7–9 h	3–6 min
Binding reversibility	Irreversible	Irreversible	Reversible	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 P2Y₁₂ 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 P2Y₁₂ 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).



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., $\geq 2\%$ /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 TXA₂ 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 P2Y₁₂ may also affect platelet TXA₂ 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 P2Y₁₂ 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). P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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], ACUTY [Acute Catheterization and Urgent Intervention Triage strategy], and HAS-BLED [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or pre-disposition, 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 P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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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REFERENCES

- Patrono C, Andreotti F, Arnesen H, et al. Antiplatelet agents for the treatment and prevention of atherothrombosis. *Eur Heart J* 2011;32:2922–32.
- Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013;382:769–79.
- Wiviott SD, Braunwald E, McCabe CH, et al., for the TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001–15.
- Wallentin L, Becker RC, Budaj A, et al., for the PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045–57.
- Tricoci P, Huang Z, Held C, et al., for the TRACER Investigators. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. *N Engl J Med* 2012;366:20–33.
- Rocca B, Patrono C. Determinants of the inter-individual variability in response to antiplatelet drugs. *J Thromb Haemost* 2005;3:1597–602.
- Mega JL, Close SL, Wiviott SD, et al. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. *Lancet* 2010;376:1312–9.
- Simon T, Verstuyft C, Mary-Krause M, et al., for the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) Investigators. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009;360:363–75.
- Mega JL, Close SL, Wiviott SD, et al. Cytochrome P-450 polymorphisms and response to clopidogrel. *N Engl J Med* 2009;360:354–62.
- Roberts JD, Wells GA, Le May MR, et al. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. *Lancet* 2012;379:1705–11.
- Hiatt WR, Fowkes FGR, Heizer G, et al., for the EUCLID Trial Steering Committee and Investigators. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med* 2017;376:32–40.
- Hulot JS, Collet JP, Montalescot G. Thienopyridine-associated drug-drug interactions: pharmacologic mechanisms and clinical relevance. *Curr Cardiol Rep* 2011;13:451–8.
- Wallentin L, James S, Storey RF, et al., for the PLATO Investigators. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet* 2010;376:1320–8.
- Hawes BE, Zhai Y, Hesk D, et al. In vitro pharmacological characterization of vorapaxar, a novel platelet thrombin receptor antagonist. *Eur J Pharmacol* 2015;762:221–8.
- Li X, Fries S, Li R, et al. Differential impairment of aspirin-dependent platelet cyclooxygenase acetylation by nonsteroidal antiinflammatory drugs. *Proc Natl Acad Sci U S A* 2014;111:16830–5.
- Patrono C. Aspirin as an antiplatelet drug. *N Engl J Med* 1994;330:1287–94.
- Aradi D, Storey RF, Komócsi A, et al., for the Working Group on Thrombosis of the European Society of Cardiology. Expert position paper on the role of platelet function testing in patients undergoing percutaneous coronary intervention. *Eur Heart J* 2014;35:209–15.
- Collet JP, Cuisset T, Rangé G, et al., for the ARCTIC Investigators. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med* 2012;367:2100–9.
- Price MJ, Berger PB, Teirstein PS, et al., for the GRAVITAS Investigators. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA* 2011;305:1097–105.
- Trenk D, Stone GW, Gawaz M, et al. A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents: results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel) to Guide Alternative Therapy With Prasugrel Study. *J Am Coll Cardiol* 2012;59:2159–64.
- Cayla G, Cuisset T, Silvain J, et al., for the ANTARCTIC Investigators. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. *Lancet* 2016;388:2015–22.

22. Sibbing D, Aradi D, Jacobshagen C, et al., for the TROPICAL-ACS Investigators. A randomised trial on platelet function-guided de-escalation of antiplatelet treatment in ACS patients undergoing PCI. Rationale and design of the Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes (TROPICAL-ACS) Trial. *Thromb Haemost* 2017;117:188-95.
23. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37:267-315.
24. Malm CJ, Hansson EC, Åkesson J, et al. Pre-operative platelet function predicts perioperative bleeding complications in ticagrelor-treated cardiac surgery patients: a prospective observational study. *Br J Anaesth* 2016;117:309-15.
25. Rocca B, Santilli F, Pitocco D, et al. The recovery of platelet cyclooxygenase activity explains interindividual variability in responsiveness to low-dose aspirin in patients with and without diabetes. *J Thromb Haemost* 2012;10:1220-30.
26. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86.
27. Patrono C, García Rodríguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med* 2005;353:2373-83.
28. Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:e637S-68S.
29. Rydén L, Grant PJ, Anker SD, et al. ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2013;34:3035-87.
30. Fox CS, Hill Golden S, Anderson C, et al., for the American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health, Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Cardiovascular Surgery and Anesthesia, Council on Quality of Care and Outcomes Research, American Diabetes Association. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation* 2015;132:691-718.
31. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). *Eur Heart J* 2016;37:2315-81.
32. Bibbins-Domingo K, for the U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2016;164:836-45.
33. Halvorsen S, Andreotti F, ten Berg JM, et al. Aspirin therapy in primary cardiovascular disease prevention: a position paper of the European Society of Cardiology working group on thrombosis. *J Am Coll Cardiol* 2014;64:319-27.
34. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373:1849-60.
35. Patrono C. Low-dose aspirin in primary prevention: cardioprotection, chemoprevention, both, or neither? *Eur Heart J* 2013;34:3403-11.
36. Hennekens CH, Sacks FM, Tonkin A, et al. Additive benefits of pravastatin and aspirin to decrease risks of cardiovascular disease: randomized and observational comparisons of secondary prevention trials and their meta-analyses. *Arch Intern Med* 2004;164:40-4.
37. Pickett CA, Jackson JL, Hemann BA, Atwood JE. Carotid bruits as a prognostic indicator of cardiovascular death and myocardial infarction: a meta-analysis. *Lancet* 2008;371:1587-94.
38. Berger JS, Krantz MJ, Kittelson JM, Hiatt WR. Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials. *JAMA* 2009;301:1909-19.
39. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017;69:e71-126.
40. Sacco RL, Diener HC, Yusuf S, et al., for the PROFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 2008;359:1238-51.
41. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-39.
42. Mehran R, Baber U, Steg PG, et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. *Lancet* 2013;382:1714-22.
43. Collet JP, Montalescot G, Blanchet B, et al. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. *Circulation* 2004;110:2361-7.
44. Biondi-Zoccai GG, Lotrionte M, Agostoni P, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. *Eur Heart J* 2006;27:2667-74.
45. Boussier MG, Amarenco P, Chamorro A, et al., for the PERFORM Study Investigators. Terutroban versus aspirin in patients with cerebral ischaemic events (PERFORM): a randomised, double-blind, parallel-group trial. *Lancet* 2011;377:2013-22.
46. Johnston SC, Amarenco P, Albers GW, et al., for the SOCRATES Steering Committee and Investigators. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. *N Engl J Med* 2016;375:35-43.
47. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;2:349-60.
48. Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. *Lancet* 2016;388:365-75.
49. De Berardis G, Sacco M, Evangelista V, et al., for the ACCEPT-D Study Group. Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D): design of a randomized study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins. *Trials* 2007;8:21.
50. ASPREE Investigator Group. Study design of ASPIrin in Reducing Events in the Elderly (ASPREE): a randomized, controlled trial. *Contemp Clin Trials* 2013;36:555-64.
51. Bayer HealthCare. Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE). Available at: <https://clinicaltrials.gov/ct2/show/NCT00501059>. Accessed August 19, 2016.
52. British Heart Foundation. A Study of Cardiovascular Events in Diabetes (ASCEND) Trial Website. Available at: <http://www.ctsu.ox.ac.uk/ascend>. Accessed August 13, 2017.
53. Patrignani P, Patrono C. Aspirin and cancer. *J Am Coll Cardiol* 2016;68:967-76.
54. Thun MJ, Jacobs EJ, Patrono C. The role of aspirin in cancer prevention. *Nat Rev Clin Oncol* 2012;9:259-67.
55. Eikelboom JW, Connolly SJ, Bosch J, et al., for the COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017 Aug 27 [E-pub ahead of print].
56. Vranckx P, Valgimigli M, Windecker S, et al. Long-term ticagrelor monotherapy versus standard dual antiplatelet therapy followed by aspirin monotherapy in patients undergoing biolimus-eluting stent implantation: rationale and design of the GLOBAL LEADERS trial. *EuroIntervention* 2016;12:139-45.
57. Baber U, Dangas G, Cohen DJ, et al. Ticagrelor with aspirin or alone in high-risk patients after coronary intervention: rationale and design of the TWILIGHT study. *Am Heart J* 2016;182:125-34.

58. Gargiulo G, Windecker S, Vranckx P, Gibson CM, Mehran R, Valgimigli M. A critical appraisal of aspirin in secondary prevention: is less more? *Circulation* 2016;134:1881-906.
59. Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502.
60. Mehta SR, Yusuf S, Peters RJG, et al., for the Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;358:527-33.
61. Müller C, Büttner HJ, Petersen J, Roskamm H. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents. *Circulation* 2000;101:590-3.
62. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;35:2541-619.
63. Sibbing D, Braun S, Morath T, et al. Platelet reactivity after clopidogrel treatment assessed with point-of-care analysis and early drug-eluting stent thrombosis. *J Am Coll Cardiol* 2009;53:849-56.
64. Stone GW, Witzensichler B, Weisz G, et al., for the ADAPT-DES Investigators. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet* 2013;382:614-23.
65. Lip GY, Windecker S, Huber K, et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). *Eur Heart J* 2014;35:3155-79.
66. Wiviott SD, Trenk D, Frelinger AL, et al., for the PRINCIPLE-TIMI 44 Investigators. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation Thrombolysis in Myocardial Infarction 44 Trial. *Circulation* 2007;116:2923-32.
67. Brandt J, Payne C, Wiviott S, et al. A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. *Am Heart J* 2007;153:66.e9-16.
68. Steg PG, James SK, Atar D, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology (ESC). *Eur Heart J* 2012;33:2569-619.
69. Roe MT, Armstrong PW, Fox KAA, et al., for the TRILOGY ACS Investigators. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med* 2012;367:1297-309.
70. Montalescot G, Bolognese L, Dudek D, et al., for the ACCOAST Investigators. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. *N Engl J Med* 2013;369:999-1010.
71. Farid N, Payne C, Small D, et al. Cytochrome P450 3A inhibition by ketoconazole affects prasugrel and clopidogrel pharmacokinetics and pharmacodynamics differently. *Clin Pharmacol Ther* 2007;81:735-41.
72. Mauri L, Kereiakes DJ, Yeh RW, et al., for the DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;371:2155-66.
73. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2016;68:1082-115.
74. Storey RF, Becker RC, Harrington RA, et al. Characterization of dyspnoea in PLATO study patients treated with ticagrelor or clopidogrel and its association with clinical outcomes. *Eur Heart J* 2011;32:2945-53.
75. Bonaca MP, Bhatt DL, Oude Ophuis T, et al. Long-term tolerability of ticagrelor for the secondary prevention of major adverse cardiovascular events: a secondary analysis of the PEGASUS-TIMI 54 Trial. *JAMA Cardiol* 2016;1:425-32.
76. Bonaca MP, Bhatt DL, Cohen M, et al., PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;372:1791-800.
77. Bhatt DL, Bonaca MP, Bansilal S, et al. Reduction in ischemic events with ticagrelor in diabetic patients with prior myocardial infarction in PEGASUS-TIMI 54. *J Am Coll Cardiol* 2016;67:2732-40.
78. Morrow DA, Braunwald E, Bonaca MP, et al., for the TRA 2P-TIMI 50 Steering Committee and Investigators. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med* 2012;366:1404-13.
79. Mega JL, Braunwald E, Wiviott SD, et al., for the ATLAS ACS 2-TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;366:9-19.
80. Ohman EM, Roe MT, Steg PG, et al. Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial. *Lancet* 2017;389:1799-808.
81. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016;375:2423-34.
82. Lamberts M, Gislason GH, Lip GY, et al. Antiplatelet therapy for stable coronary artery disease in atrial fibrillation patients taking an oral anticoagulant: a nationwide cohort study. *Circulation* 2014;129:1577-85.
83. Hijazi Z, Oldgren J, Lindbäck J, et al., for the ARISTOTLE and RE-LY Investigators. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. *Lancet* 2016;387:2302-11.
84. Vries MJ, van der Meijden PE, Henskens YM, ten Cate-Hoek AJ, ten Cate H. Assessment of bleeding risk in patients with coronary artery disease on dual antiplatelet therapy. A systematic review. *Thromb Haemost* 2016;115:7-24.
85. Subherwal S, Bach RG, Chen AY, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. *Circulation* 2009;119:1873-82.
86. Mehran R, Pocock SJ, Nikolsky E, et al. A risk score to predict bleeding in patients with acute coronary syndromes. *J Am Coll Cardiol* 2010;55:2556-66.
87. Pisters R, Lane DA, Nieuwlaar R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138:1093-100.
88. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 2011;58:2550-83.
89. Costa F, Tijssen JG, Ariotti S, et al. Incremental value of the CRUSADE, ACUITY, and HAS-BLED risk scores for the prediction of hemorrhagic events after coronary stent implantation in patients undergoing long or short duration of dual antiplatelet therapy. *J Am Heart Assoc* 2015;4:e002524.
90. Costa F, van Klaveren D, James S, et al., for the PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* 2017;389:1025-34.
91. Choi SY, Kim MH, Serebruany V. The challenge for predicting bleeding events by assessing platelet reactivity following coronary stenting. *Int J Cardiol* 2016;207:128-31.
92. Siller-Matula JM, Delle-Karth G, Lang IM, et al. Phenotyping vs. genotyping for prediction of

- clopidogrel efficacy and safety: the PEGASUS-PCI study. *J Thromb Haemost* 2012;10:529–42.
93. Storey RF, Parker WAE. Choices for potent platelet inhibition in patients with diabetes mellitus. *Circulation* 2016;134:793–6.
 94. Stratz C, Bömicke T, Younas I, et al. Comparison of immature platelet count to established predictors of platelet reactivity during thienopyridine therapy. *J Am Coll Cardiol* 2016;68:286–93.
 95. Palmer SC, Di Micco L, Razavian M, et al. Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2012;156:445–59.
 96. Angiolillo DJ, Bernardo E, Capodanno D, et al. Impact of chronic kidney disease on platelet function profiles in diabetes mellitus patients with coronary artery disease taking dual antiplatelet therapy. *J Am Coll Cardiol* 2010;55:1139–46.
 97. James S, Budaj A, Aylward P, et al. Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the Platelet Inhibition and Patient Outcomes (PLATO) Trial. *Circulation* 2010;122:1056–67.
 98. Magnani G, Storey RF, Steg PG, et al. Efficacy and safety of ticagrelor for long-term secondary prevention of atherothrombotic events in relation to renal function: insights from the PEGASUS-TIMI 54 trial. *Eur Heart J* 2016;37:400–8.
 99. Erlinge D, Ten Berg J, Foley D, et al. Reduction in platelet reactivity with prasugrel 5 mg in low-body-weight patients is noninferior to prasugrel 10 mg in higher-body-weight patients: results from the FEATHER trial. *J Am Coll Cardiol* 2012;60:2032–40.
 100. Halvorsen S, Storey RF, Rocca B, et al. Management of antithrombotic therapy after bleeding in patients with coronary artery disease and/or atrial fibrillation: expert consensus paper of the European Society of Cardiology Working Group on Thrombosis. *Eur Heart J* 2017;38:1455–62.
 101. Andreotti F, Rocca B, Husted S, et al. Antithrombotic therapy in the elderly: expert position paper of the European Society of Cardiology Working Group on Thrombosis. *Eur Heart J* 2015;36:3238–49.
 102. Husted S, James S, Becker RC, et al. Ticagrelor versus clopidogrel in elderly patients with acute coronary syndromes: A substudy from the prospective randomized PLATeT Inhibition and Patient Outcomes (PLATO) Trial. *Circ Cardiovasc Qual Outcomes* 2012;5:680–8.
 103. Zeymer U, Becher A, Jennings E, Johansson S, Westergaard M. Systematic review of the clinical impact of dual antiplatelet therapy discontinuation after acute coronary syndromes. *Eur Heart J Acute Cardiovascular Care* 2016 May 3 [E-pub ahead of print].
 104. Hastings S, Myles P, McIlroy D. Aspirin and coronary artery surgery: a systematic review and meta-analysis. *Br J Anaesth* 2015;115:376–85.
 105. Sousa-Uva M, Storey R, Huber K, et al., for the ESC Working Group on Cardiovascular Surgery and ESC Working Group on Thrombosis. Expert position paper on the management of antiplatelet therapy in patients undergoing coronary artery bypass graft surgery. *Eur Heart J* 2014;35:1510–4.
 106. Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management. The Joint Task Force on non-cardiac surgery; cardiovascular assessment and management of the European Society of Cardiology (ESC) and European Society of Anaesthesiology (ESA). *Eur Heart J* 2014;35:2383–431.
 107. Fox KA, Peters R, Zhao F, Lakkis N, Gersh BJ, Yusuf S. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. *Circulation* 2004;110:1202–8.
 108. Egholm G, Kristensen SD, Thim T, et al. Risk associated with surgery within 12 months after coronary drug-eluting stent implantation. *J Am Coll Cardiol* 2016;68:2622–32.
 109. Holcomb CN, Graham LA, Richman JS, Itani KM, Maddox TM, Hawn MT. The incremental risk of coronary stents on postoperative adverse events: a matched cohort study. *Ann Surg* 2016;263:924–30.
 110. Savonitto S, Caracciolo M, Cattaneo M, De Servi S. Management of patients with recently implanted coronary stents on dual antiplatelet therapy who need to undergo major surgery. *J Thromb Haemost* 2011;9:2133–42.
 111. Angiolillo DJ, Firstenberg MS, Price MJ, et al., for the BRIDGE Investigators. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. *JAMA* 2012;307:265–74.

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.