A Critical Appraisal of Aspirin in Secondary Prevention

Is Less More?

Giuseppe Gargiulo, MD
Stephan Windecker, MD
Pascal Vranckx, MD, PhD
Charles Michael Gibson, MD
Roxana Mehran, MD, PhD
Marco Valgimigli, MD, PhD

"The unexamined life is not worth living."
—Socrates[1]

ABSTRACT: Aspirin represents the *sine qua non* for antiplatelet pharmacotherapy in patients with cardiovascular diseases because of its well-established role in secondary prevention and its widespread availability and affordability. Historical studies, conducted in an era that bears little resemblance to contemporary clinical practice, demonstrated large reductions in thrombotic risk when aspirin was compared with placebo, thus forming the evidence base promulgated in practice guidelines and recommendations. $P2Y_{12}$ inhibitors have mostly been studied in addition to aspirin; dual-antiplatelet therapy proved superiority compared with aspirin monotherapy for the prevention of ischemic events, despite increased bleeding risks. An alternative approach currently under investigation includes evaluation of single-antiplatelet therapy with $P2Y_{12}$ inhibitors alone versus dual-antiplatelet therapy after acute coronary syndromes or coronary stent implantation. As the availability of more effective antiplatelet agents increases, it is time to revisit the existing and long-standing paradigm supporting aspirin use for secondary prevention of atherothrombotic events. Ongoing trials will provide new evidence whether the less-is-more strategy is justified.

Every year millions of patients worldwide undergo percutaneous coronary intervention (PCI) for treatment of coronary artery disease (CAD). To date, dual-antiplatelet therapy (DAPT), consisting of low-dose acetylsalicylic acid (ASA or aspirin) and an inhibitor of the adenosine diphosphate (ADP) $P2Y_{12}$ platelet receptor, is mandatory to prevent thrombosis among patients with stable CAD after stent implantation and following acute coronary syndromes (ACS), irrespective of final management (invasive or noninvasive).[2–6] An alternative approach currently under investigation includes evaluation of single-antiplatelet therapy with $P2Y_{12}$ inhibitors alone after ACS or coronary stent implantation.

The aim of this article is to critically review the available evidence for aspirin use after ACS and PCI and to discuss the scientific rational for ongoing studies testing the risks and benefits of omission or early discontinuation of aspirin in favor of $P2Y_{12}$ inhibitor monotherapy.

PLATELET PATHOPHYSIOLOGY AND ROLE OF ANTIPLATELET AGENTS

Platelets are critical modulators of hemostasis following tissue trauma and vascular injury. Thus, inhibition of platelet adhesion and aggregation consistently resulted in an

Correspondence to: Marco Valgimigli, MD, PhD, Department of Cardiology, Bern University Hospital, CH-3010 Bern, Switzerland. E-mail marco.valgimigli@insel.ch

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increased risk of bleeding.[7] Platelet activation plays a crucial role in the development of atherosclerosis and ACS; thus, its inhibition is pivotal to prevent ischemic complications after stent implantation, including stent thrombosis (ST). Platelets adhere to the injured endothelium of blood vessels at sites of endothelial cell activation and contribute to the development of chronic atherosclerotic plaques. Moreover, platelets trigger the acute onset of arterial thrombosis in response to atherosclerotic plaque rupture.[7] Although platelet adhesion and activation is a physiological response to the fissuring or rupture of atherosclerotic plaques, eventually contributing to repair, uncontrolled progression of this process, through a series of self-sustaining amplification loops, may lead to intraluminal thrombus formation and vascular occlusion.[8] Platelet activation determines several responses, including shape change; dense granule secretion of ATP, 5-hydroxytryptamine, and ADP (it binds to $P2Y_{12}$ receptors that have a potent effect on amplification of platelet activation); α-granule secretion of chemokines (leading to activation of leukocytes and endothelial cells) and coagulation factors; and procoagulant changes in the platelet surface membrane supporting thrombin generation and activation of GPIIb/IIIa leading to platelet aggregation and outside-in signaling further amplifying platelet activation.[8] Consequently, platelet inhibition is the mainstay in the prevention of recurrent ischemic events (Figure 1), and current guidelines recommend a period of DAPT ranging from a minimum of 1 month to well beyond 1 year among patients undergoing PCI.[2–6,9] The pharmacopeia of $P2Y_{12}$ antagonists has rapidly expanded in recent years. [10,11] In comparison with clopidogrel, which has been shown to improve outcomes vis-à-vis placebo on a background therapy of aspirin[12] as well as aspirin monotherapy,[13] the new $P2Y_{12}$ inhibitors, prasugrel and ticagrelor, are characterized by faster onset of action and more consistent and potent inhibition of platelet function. Unlike aspirin, $P2Y_{12}$ inhibitors block the amplification process of platelet activation.[7,11] Both prasugrel and ticagrelor have been tested thus far in clinical trials involving ACS patients with ASA serving as background therapy. Accordingly, the safety and efficacy of monotherapy with these potent agents remains unknown. Prasugrel, an irreversible inhibitor of $P2Y_{12}$ receptor, was associated with a lower risk of major adverse cardiovascular events (MACE), largely driven by reduction in myocardial infarction (MI), but a higher risk of spontaneous and coronary artery bypass grafting (CABG)–related major bleeding compared with clopidogrel among ACS patients[14] already on background ASA therapy. Notably, fatal bleeding was slightly but significantly increased in prasugrel in comparison with clopidogrel-treated patients.

The direct and reversible $P2Y_{12}$ antagonist ticagrelor offers at least similar inhibition of the $P2Y_{12}$ receptor as prasugrel,[15] but yields faster offset of platelet inhibition in comparison with prasugrel and clopidogrel. Ticagrelor significantly reduced the risk of MACE, but also all-cause and cardiovascular mortality in comparison with clopidogrel in ACS patients, irrespective of the final management strategy (invasive or noninvasive).[16] Ticagrelor increases nonprocedural but not CABG-related or fatal bleeding in comparison with clopidogrel. Prasugrel or ticagrelor, when used with background aspirin therapy, are therefore preferred over clopidogrel in ACS patients, based on superior prevention of ischemic events despite both carrying higher risk of spontaneous (ie, nonprocedural) bleeding hazard.[2,3,5]

Given the delicate balance between ischemic and bleeding risks in patients receiving DAPT and notwithstanding the recent evidence that long-term DAPT further decreases the risk of MACE, [17,18] there remains uncertainty on the optimal DAPT duration after ACS or stent implantation.[19] As a result, a personalized approach to administration and duration of DAPT therapy is advocated, integrating anticipated ischemic over bleeding risks. Remarkably, such a treatment strategy has never been tested prospectively. At the time of DAPT discontinuation, current guidelines recommend indefinite aspirin monotherapy as a secondary prevention measure.[2–6]

Recently, exploration of novel strategies for patients with ACS has yielded mixed results. The use of low-dose rivaroxaban at 2.5 mg twice daily in the ATLAS-ACS 2 trial (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome ACS 2),[20] and vorapaxar in the TR A2°P-TIMI50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events-Thrombolysis in Myocardial Infarction 50)[21] and TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome)[22] trials have been shown to reduce the risk of ischemic adverse events at the cost of greater bleeding in comparison with DAPT consisting of aspirin and clopidogrel. Conversely, less favorable results were observed for rivaroxaban at a dose of 5 mg twice daily (ATLAS-ACS), for dabigatran (twice daily administration of 50, 75, 110, or 150 mg) in the RE-DEEM study (Dabigatran Versus Placebo in Patients With ACS on DAPT: A Randomized, Double-Blind, Phase II Trial),[23] apixaban (5 mg twice daily) in the APPRAISE-2 study (Apixaban for Prevention of Acute Ischemic and Safety Events),[24] and darexaban (all doses) in the RUBY-1 trial (Study Evaluating Safety, Tolerability and Efficacy of YM150 in Subjects With Acute Coronary Syndromes).[25] More specifically, these trials generally showed a magnitude of incremental bleeding risk that was not counterbalanced by a concordant reduction in thrombotic events thereby rendering a neutral or negative net benefit. Because these strategies were examined by adding the novel agent to a background of DAPT, inferences surrounding the omission of ASA in the experimental arm are not possible based on these studies.

Given the well-recognized trade-off between ischemic prevention and bleeding risk in patients receiving DAPT

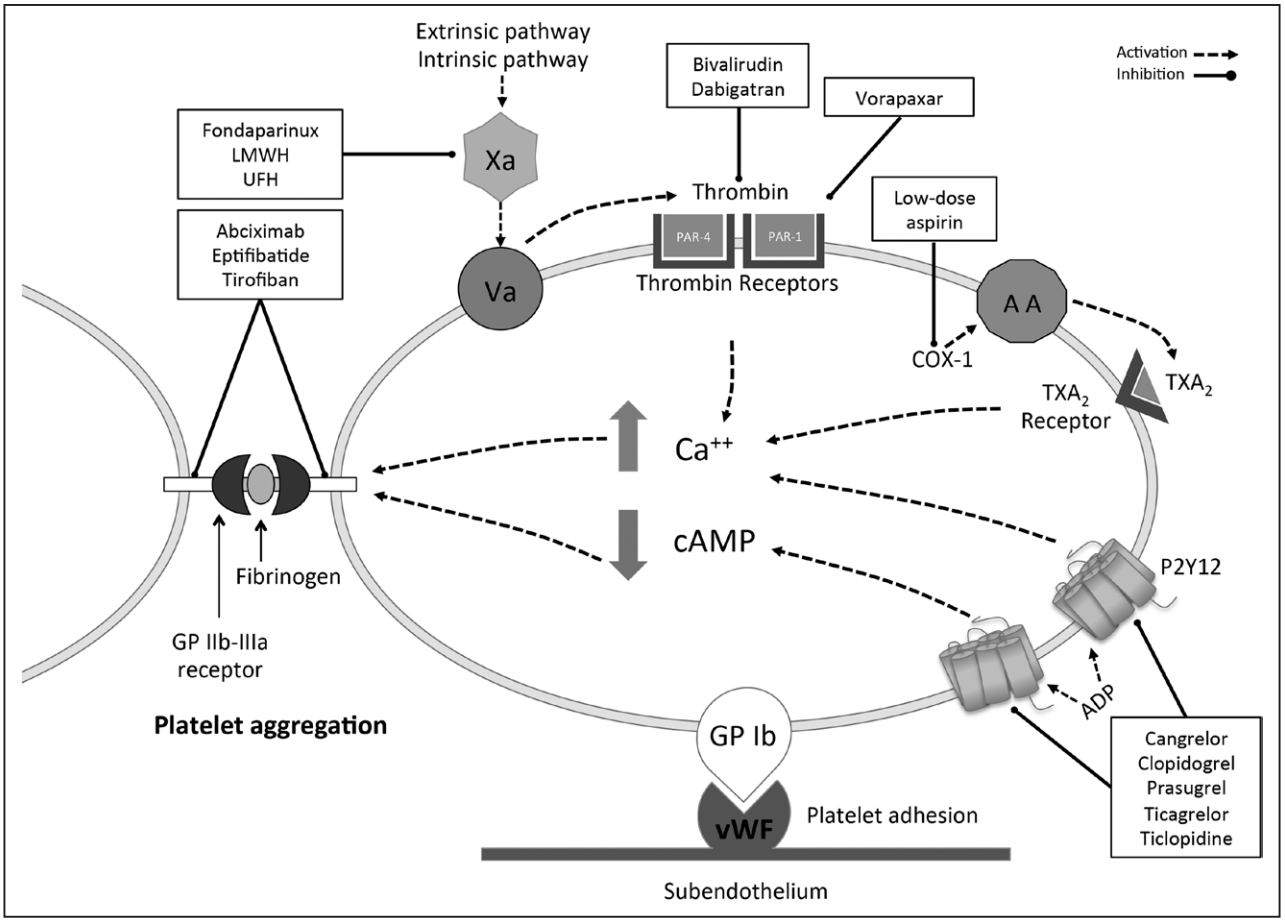

Figure 1. Antithrombotic agents.
Illustration of the process of platelet aggregation and the mechanism of actions of the main antithrombotic agents. AA indicates arachidonic acid; ADP, adenosine diphosphate; Ca, calcium; COX, cyclooxygenase; GP, glycoprotein; LMWH, low-molecular-weight heparin; PAR, protease-activated receptor; TXA_2, thromboxane A_2; UFH, unfractionated heparin; and vWF, von Willebrand factor.

or triple therapy, alternative strategies that optimize net clinical benefit by preserving ischemic reduction without increasing bleeding harm are needed. An intriguing and emerging area of research is to avoid aspirin therapy altogether in favor of long-term $P2Y_{12}$ inhibitor monotherapy. Ongoing studies aim to discern whether monotherapy with a $P2Y_{12}$ inhibitor can safely and effectively replace conventional DAPT regimens after ACS or PCI, or even replace ASA for long-term secondary prevention.

ASPIRIN

Mechanism of Action

ASA was synthesized in 1897 and then commercialized as aspirin in 1899. It was used worldwide because of its anti-inflammatory/analgesic effects until the 1970s when its antiplatelet effects became apparent. For this latter mechanism of action, aspirin has become the cornerstone in the antithrombotic therapy for the prevention and treatment of wide range of cardiovascular diseases worldwide.

Arachidonic acid is released from membrane phospholipids by several isoforms of phospholipase A2 (Figure 2). Free arachidonic acid is converted to the unstable intermediates prostaglandin G2 and prostaglandin H2 by cytosolic prostaglandin H synthases through its cyclooxygenase (COX) and hydroperoxidase activities, respectively.[26–29] Prostaglandin H2 is converted by tissue-specific isomerases to multiple prostanoids that activate specific cell membrane receptors. Although high-dose aspirin inhibits both COX-1 and COX-2, low-dose aspirin selectively and irreversibly inhibits COX-1 in the arachidonic acid pathway (Figure 2), subsequently blocking the production of thromboxane A2 (TXA2), a platelet agonist (rapidly transformed in TXB2), thereby reducing thrombus formation.[26,29] More specifically, aspirin first binds to an arginine 120 residue, as do other nonsteroidal anti-inflammatory drugs, but unlike these, aspirin then acetylates the serine 529 residue of human COX-1 (serine 516 in human COX-2 for higher doses of aspirin) located in the narrowest section of the channel, irreversibly inhibiting access to the COX catalytic site by

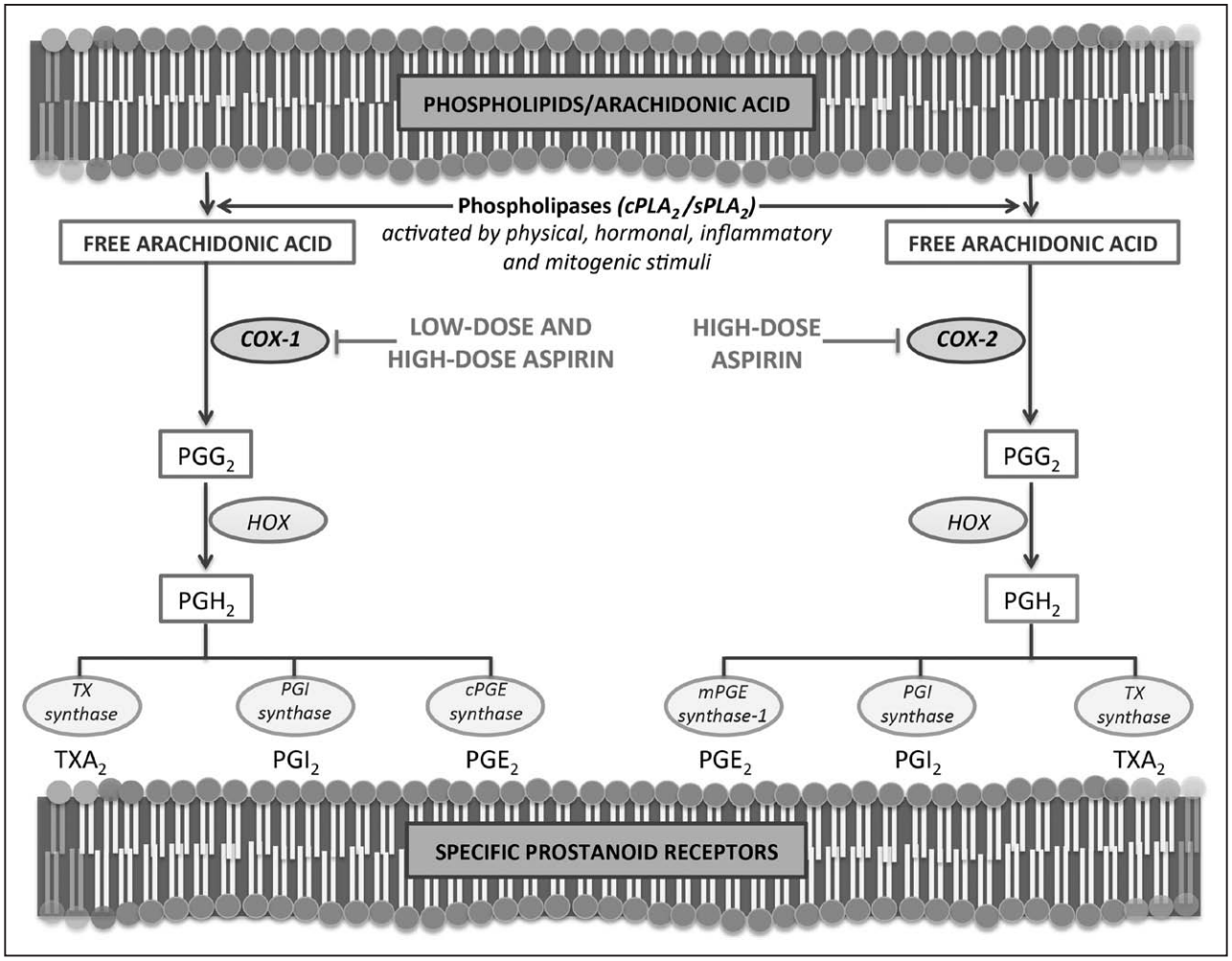

Figure 2. Aspirin mechanism of antiplatelet action.
Illustration of the process of formation and action of prostanoids and the mechanism of action of aspirin. COX indicates cyclooxygenase; cPGE, cytosolic prostaglandin E; $cPLA_2$, cytosolic phospholipase A_2; HOX, hydroperoxidase; mPGE, microsomal prostaglandin E; PG, prostaglandin; $sPLA_2$, secretory phospholipase A_2; and TX, thromboxane.

arachidonic acid.[26,29] This antiplatelet effect persists for the lifespan of platelets because the permanent inactivation of the platelet COX-1 can be reversed only through the generation of new platelets.[28] Although aspirin is characterized by a very short half-life (≈15 minutes in plasma), it needs to be administered only once daily for the purpose of platelet inhibition.

Importantly, there is a nonlinear relationship between low-dose aspirin-induced inactivation of platelet COX-1 and inhibition of TXA2-dependent platelet function.[8] This translates into crucial implications: (1) a less than maximal inactivation of COX-1 determines a significant reduction in platelet inhibition; (2) after aspirin discontinuation, the recovery of platelet function is disproportionately rapid, occurring within 3 to 4 days; (3) most traditional nonsteroidal anti-inflammatory drugs are not able to completely and persistently inhibit platelet COX-1. Additionally, the selective inhibition by ASA of TXA2-dependent platelet function alone, without any effect on other pathways of platelet activation (ADP-$P2Y_{12}$, thrombin-protease–activated receptor-1) forms the physiological rationale for dual- or triple-antiplatelet therapy in high-risk settings where further platelet inhibition is necessary (Figure 1).[8]

The gastrointestinal adverse effects of aspirin and nonsteroidal anti-inflammatory drugs (erosive gastritis and bleeding) are mainly a result of COX-1 inhibition.[29] Indeed, COX-1 is ubiquitous, constitutively expressed in the human body and able to produce prostaglandins involved in platelet aggregation (mainly TXA2), but also in the maintenance of gastrointestinal mucosal integrity (mainly prostaglandin E_2 and prostaglandin I_2).[29]

Clinical Outcomes

Numerous studies have clearly demonstrated that low-dose aspirin reduces cardiovascular morbidity and mortality in patients with ACS or previous MI and confers

a durable long-term benefit.[30,31] Most randomized trials have been summarized by the Antithrombotic Trialists' Collaboration, which included 16 secondary prevention randomized trials (17 000 individuals at high-risk, 43 000 person-years, 3306 serious vascular events) and compared long-term aspirin versus control.[30] Aspirin significantly reduced the risk of serious vascular events (6.7% versus 8.2% per year, $P<0.0001$), with a nonsignificant increase in intracranial hemorrhage but reductions in total stroke (2.08% versus 2.54% per year, $P=0.002$) and coronary events (4.3% versus 5.3% per year, $P<0.0001$). Among the 16 secondary prevention trials, only 6 included post-MI patients (overall 10 859 patients), whereas the other 10 trials enrolled post–transient ischemic attack (TIA)/stroke patients. Convincing results notwithstanding, these findings must be interpreted within the context of several important limitations that might limit generalizability to contemporary clinical practice. First and perhaps most relevant, most studies were conducted several decades ago and do not reflect the modern-day clinical settings, therapeutics, and event rates (Tables 1 and 2).[31] Second, most included young and predominantly male patients. Third, the ASA regimens used in most of these studies differ significantly from current clinical norms in terms of dosing frequency and amount. As a result, it is unclear whether the benefits associated with ASA use in these studies would be replicated in the contemporary era.

Further evidence supporting the preventive role of aspirin was yielded by a meta-analysis exploring the hazards inherent to aspirin withdrawal or noncompliance in subjects at risk for, or with established, CAD.[32] Overall, the nonadherence or withdrawal of aspirin was associated with a 3-fold increased risk of MACE. However, reasons for aspirin discontinuation were not accounted for in this aggregate data analysis, which may explain the higher ischemic hazards at least as much as aspirin withdrawal.

Resistance and Hypersensitivity

Treatment with aspirin confers a long-lasting functional defect in platelets, which is detectable with laboratory tests for platelet reactivity[26,33] and also prolongs the bleeding time. The effect of ASA on platelet COX-1 has also been characterized through measurements of serum TXB2 and urinary metabolites of TXB2.[33–35] Given that the maximal biosynthetic capacity of human platelets is several thousand times as high as the basal rate of TXA2 biosynthesis in healthy subjects, the relationship between the inhibition of platelet COX-1 activity and TXA2 biosynthesis in vivo is nonlinear. The inhibition of platelet COX-1 has functional relevance when a reduction by at least 95% in the maximal capacity to generate TXA2 is reached. However, it should be noted that, recently, the nonlinear relationship between COX-1 inhibition and platelet function has been questioned.[36] In this study, a linear relationship was observed between aggregation and TXA2 production for all combinations of arachidonic acid or collagen and aspirin, and similar relationships were found in combinations of aspirin-treated and naïve platelets, and in blood from individuals taking an antithrombotic dose of aspirin.[36]

The term aspirin resistance has been used to describe the inability of aspirin to produce a measurable response on ex vivo tests of platelet function, to inhibit TXA2 biosynthesis in vivo, or to protect individual patients from thrombotic complications. A large body of data has reported lower-than-expected inhibition of platelet function in a variable proportion of patients treated with aspirin.[35,37] Some data showed that patients defined to have aspirin resistance were found to be at increased risk for recurrent cardiovascular events with greater clinically relevant long-term morbidity and mortality.[38,39]

The interpatient variability in aspirin response (aspirin resistance) has been mainly attributed to the variable turnover rate of its target receptor (platelet COX-1). Remarkably, the dosage of TXB2 serum levels at different time points was used to identify patients with a faster recovery of COX-1 activity and consequently characterized by aspirin resistance.[40] In this study, some factors were associated with resistance: younger age, higher mean platelet volume and body mass index in diabetic patients, whereas only higher body mass index was a predictor in patients without diabetes mellitus. A twice-daily regimen of low-dose aspirin was originally proposed for patients with high platelet turnover rates,[41] this has also been shown to rescue the limited duration of the antiplatelet effect in patients with aspirin resistance.[40,42]

Although several studies have been published on the topic of aspirin resistance, its definition, diagnosis, causes, and clinical consequences remain controversial.[43] The term resistance should be used when the drug is unable to bind to its pharmacological target, either because of the inability to reach it (as a consequence of reduced bioavailability, in vivo inactivation, or negative interaction with other substances) or alterations of the target.[43] Accordingly, it is inappropriate to consider all patients experiencing atherothrombotic events while on aspirin treatment to be resistant. This phenomenon has been called clinical resistance, but it should be more properly named treatment failure.[43] Given that arterial thrombosis is multifactorial, an arterial thrombotic event in a patient may reflect treatment failure rather than resistance.[44] Additionally, the finding of high residual platelet reactivity in vitro in patients on aspirin treatment has often been confused with aspirin resistance, but may not necessarily imply that these patients are resistant to treatment, particularly if platelet function is measured through laboratory tests that are not specific for the effect of aspirin on its pharmacological target. Doubtless, unspecific tests are useful to

Table 1. Secondary Prevention Trials of Aspirin Versus Control in Patients With Previous Myocardial Infarction

Trial Name	Starting Year	Publication Year	Aspirin Daily Dose, mg	No. of Patients	Study Duration	Age	Male, %	Htn, %	Diabetes Mellitus, %	β-Blocker, %	Time From MI to Enrollment	Revascularization (PCI/CABG), %
Prior MI												
Cardiff I	1971	1974	300	1239	13 mo	55	100	NA	NA	NA	10 wk	0
Cardiff II	NA	1979	900	1725	12 mo	56	85	NA	0.5	NA	95% <7days	0
PARIS I*	1975	1980	972	1216	41 mo	56	87	NA	10	15.4	8 wk to 60 mo	0
AMIS	1975	1980	1000	4524	38 mo	55	89	NA	11	12	8 wk to 60 mo	0
CDP-A†	1972	1976	972	1529	22 mo	56	100	NA	14	NA	75% >60 mo	0
GAMIS‡	1970	1980	1500	626*	24 mo	59	78	19	20	NA	30–42 days	0
Micristin	NA	1979	1500	1340	24 mo	NA	NA	NA	NA	NA	NA	NA
Acute MI												
ISIS-pilot§	1983	1987	162.5	619	1 mo	60	80	22	5	40	<24 h	0
ISIS-2‖	1985	1988	162.5	17187	35 days	NA	NA	NA	NA	NA	<24 h	0
Dutch-aspirin	NA	1990	100	100	3	62.5	74	NA	NA	32	<12 h	Rare, none within 1 wk
Huddinge	NA	1988	167 (500 every 3 days)	20	1 mo (12 mo)	63	80	NA	NA	20	<24 h	10
Frankfurt	NA	1976	1320	39	14 days	NA	NA	NA	NA	NA	NA	NA
APRICOT¶	NA	1993	325	192	3 mo	57	81	NA	NA	43	48 h	10.4
Unstable angina												
VA-pilot	1974	1986	324	50	3 mo	NA	100	NA	NA	NA	NA	NA
VA-main	1974	1983	324	1266	3 mo	56	100	41	17	74	48 h	3.5
RISC	1985	1990	75	796	12 mo	58	100	30	8	88	72 h	3.9
ALDUSA-pilot#	NA	1987	324–340	84	12 mo	NA	NA	NA	NA	NA	NA	NA
Thèroux**	1986	1988	650	479	6 days (3 mo)	58	71	38	13	96	<24 h	48
ATACS-pilot††	1987	1990	325–380	93	3 mo	62	60	49	37	39	<48 h	50
Coronary angioplasty												
Perth‡‡	1986	1991	100	212	6 mo	55	84	34	4	58	–	100% PCI for stable CAD
M-HEART III‖‖	NA	1995	325	503	6 mo	58	83	50	18	NA	–	100% PCI for stable CAD
Stable CAD												
SAPAT¶¶	1985	1992	75	2035	50	67	52	41	7	100	–	3.9
VA bypass IV-B##	1983	1989	325	502	24	58	100	46	NA	NA	–	100% enrolled after CABG

ALDUSA-pilot indicates Aspirin at Low Dose in Unstable Angina; AMIS, Aspirin Myocardial Infarction Study; APRICOT, Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis; ASA, aspirin; ATACS-pilot, Antithrombotic Therapy in Acute Coronary Syndromes; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CDP-A, Coronary Drug Project-Aspirin; GAMIS, German-Austrian Myocardial InfarctionStudy; Htn, hypertension; ISIS, International Studies of Infarct Survival; M-HEART II, Multi-Hospital Eastern Atlantic Restenosis Trialists II; MI, myocardial infarction; NA, not available; PARIS I, Persantine-Aspirin Reinfarction Study I; PCI, percutaneous coronary intervention; RISC, Research Group on Instability in Coronary Artery Disease; SAPAT, Swedish Angina Pectoris Aspirin Trial; and VA, Veterans Administration.

*PARIS I included 3 groups (ASA+dipyridamole=810; ASA=810; placebo=406).

†Patients enrolled were all those previously enrolled in the CDP study that included 3 groups (dextrothyroxine, estrogen 5 mg/d and estrogen 2.5 mg/d)

‡GAMIS included 3 groups (ASA=317, placebo=309, phenprocoumon=320).

§ISIS-pilot: patients with suspected acute MI were randomly assigned to receive either a high-dose short-term intravenous infusion of streptokinase or placebo. Using a 2×2×2 factorial design, patients were also randomly assigned to receive either oral ASA (325 mg on alternate days for 28 days) or placebo, and separately randomly assigned to receive either intravenous heparin (1000 IU h^{-1} for 48 h) or no heparin.

‖Patients up to 24 h after the onset of suspected acute MI were randomly assigned to 4 groups: 1-hour intravenous infusion of streptokinase; 1 month of 162.5 mg/d enteric-coated ASA; both active treatments or neither.

¶Patients treated with intravenous thrombolytic therapy followed by intravenous heparin were eligible when a patent infarct-related artery was demonstrated at angiography <48 h. Patients were randomly assigned to either 325 mg ASA daily (n=102) or placebo (n=90) with discontinuation of heparin or to Coumadin (n=92).

#ALDUSA-pilot: In the 40-mg arm, patients were to receive ASA 120 mg on day 1 and 40 mg daily thereafter.

**Patients were randomly assigned to 4 groups: ASA (n=121), heparin (n=118), ASA+heparin (n=122) or placebo (n=118).

††Patients were randomly assigned to receive ASA (325 mg daily; n=32), or full-dose heparin followed by warfarin (n=24), or the combination of ASA (80 mg/d) plus heparin and then warfarin (n=37).

‡‡After angioplasty of a previously untreated native coronary artery and after 2 wk of ASA therapy, 216 subjects (aged <70 y without acute MI) were randomly assigned to treatment with soluble ASA (n=108), 100 mg/d, or placebo (n=104) to study the effect on restenosis.

‖‖Patients were randomly assigned to ASA (325 mg daily; n=248), sulotroban (800 mg 4 times a day; n=249), or placebo (n=255), started within 6 h before PTCA and continued for 6 mo.

¶¶Patients with symptoms of chronic stable angina pectoris treated with increasing doses of sotalol were randomly assigned to ASA 75 mg daily (n=1009) or placebo (1026).

##The study determined how to improve saphenous vein graft patency after coronary artery bypass grafting by comparing ASA (325 mg once daily; n=104), ASA (325 mg 3 times daily; n=96), ASA+dipyridamole (325 mg and 75 mg, respectively, 3 times daily; n=99), sulfinpyrazone (267 mg 3 times daily; n=96), and placebo (3 times daily; n=107).

Table 2. Individual Results of Trials of Aspirin Versus Control

Trial Name	Treatment Regimen	Patients		Nonfatal MI		Nonfatal Stroke		Vasc Deaths		Vasc Events		Nonvasc Deaths		Major Bleeds			
		APT	Ctrl	APT	Ctrl	APT	Ctrl	APT	Ctrl	APT	Ctrl	APT	Ctrl	APT		Ctrl	
Prior MI																	
Cardiff-I	A300	615	624	10	15	–	–	47	61	57	76	2	4	–	(0)	–	(0)
Cardiff-II	A900	847	878	31	65	0	0	98	122	129	187	5	5	–	(0)	–	(0)
PARIS-I	A972 + D225	1620	406	105	34	15	3	147	45	265	82	26	7	–	(0)	–	(0)
AMIS	A1000	2267	2257	140	173	29	49	214	199	379	411	32	20	–	(0)	–	(0)
CDP-A	A972	758	771	27	32	7	9	43	61	76	102	2	4	–	(0)	–	(0)
GAMIS	A1500	317	309	11	15	0	0	22	30	33	45	5	2	–	(0)	–	(0)
Micristin	A1500	672	668	22	35	9	15	34	56	65	106	15	15	2	(1)	2	(1)
Acute MI																	
ISIS-pilot	A325 (SK), A325, A325 (H), A325 (H + SK)	313	306	7	9	1	2	25	35	33	46	0	0	1	(0)	1	(0)
ISIS-2	A162.5 (SK), A162.5	8587	8600	74	161	29	52	815	1026	915	1236	2	7	24	(2)	18	(3)
Dutch-aspirin	A100 (H)	50	50	2	6	1	0	9	12	12	18	0	0	0	(0)	0	(0)
Huddinge	A167	10	10	0	0	0	0	0	0	0	0	0	1	0	(0)	0	(0)
Frankfurt	A1320 + D300, A1320	25	14	0	0	0	0	1	1	1	1	0	0	0	(0)	0	(0)
APRICOT	A325 (H + FIB)	107	95	3	10	0	0	1	2	4	12	0	0	–	(–)	–	(–)
Unstable angina																	
VA-pilot	A324	26	24	0	1	0	0	1	3	1	4	0	0	0	(0)	0	(0)
VA-main	A324	661	677	27	49	3	2	15	24	45	75	0	0	0	(0)	0	(0)
RISC	A75	474	471	36	69	0	0	9	16	45	85	2	2	0	(0)	0	(0)
ALDUSA-pilot	A325, A40	56	28	5	0	1	0	1	1	7	1	0	0	–	(0)	–	(0)
Théroux	A650, A650 (H)	243	236	6	12	0	0	0	2	6	14	0	0	4	(0)	2	(0)
ATACS-pilot	A80 (H + W)	37	24	0	3	–	–	0	1	0	4	0	0	1	(0)	0	(0)
Coronary angioplasty																	
Perth	A100	124	128	0	2	–	–	–	–	0	2	–	–	–	(–)	–	(–)
M-HEART II	A325, ST	497	255	5	10	–	–	1	1	6	11	–	–	–	(–)	–	(–)
Stable CAD																	
SAPAT	A75	1009	1026	40	61	21	27	53	71	111	159	29	35	18	(9)	11	(5)
VA bypass IV-B	A325	161	173	3	3	–	–	3	4	6	7	0	0	–	(–)	–	(–)

The number of patients per group or the total number of patients could not correspond to Table 1 because ATT had access to individual patient data for many of the trials. Numbers of nonfatal major (extracranial) bleeds are shown first, with fatal bleeds in parentheses. Nonfatal stroke includes ischemic and hemorrhagic strokes, together with strokes of unknown etiology. Vascular deaths includes deaths that were known to have a vascular cause, and deaths of unknown cause. A indicates aspirin; ALDUSA-pilot, Aspirin at Low Dose in Unstable Angina; AMIS, Aspirin Myocardial Infarction Study; APRICOT, Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis; APT, antiplatelet; ATACS-pilot, Antithrombotic Therapy in Acute Coronary Syndromes; CAD, coronary artery disease; CDP-A, Coronary Drug Project-Aspirin; Ctrl, control; D, dipyridamole; FIB, fibrinolytic therapy; GAMIS, German-Austrian Myocardial Infarction Study; H, heparin; ISIS, International Studies of Infarct Survival; M-HEART II, Multi-Hospital Eastern Atlantic Restenosis Trialists II; MI, myocardial infarction; Nonvasc, nonvascular; PARIS-I, Persantine-Aspirin Reinfarction Study I; RISC, Research Group on Instability in Coronary Artery Disease; SAPAT, Swedish Angina Pectoris Aspirin Trial; SK, streptokinase; ST, sulotroban; W, warfarin; VA, Veterans Administration; Vasc, vascular; and –, data unavailable.

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identify patients with high residual platelet reactivity, but only specific tests measuring the pharmacological effect of aspirin can clarify whether platelet hyperreactivity is attributable to insufficient pharmacological effect of aspirin or to other causes. Consequently, resistance to aspirin should be limited to situations in which aspirin is unable to inhibit COX-1–dependent TXA2 production (and thus, TXA2-dependent platelet functions). Measuring the capacity of platelets to directly synthesize TXA2 has been recommended to monitor the effect of aspirin.[45] The measurement of serum TXB2 to assess aspirin response showed that the prevalence of poor responders is extremely low.[45] Confounding problems may contribute to inappropriate use of the term resistance. The most frequent and plausible cause of insufficient inhibition of COX-1 by aspirin is probably poor patient compliance to therapy. Furthermore, genetic considerations, increased platelet turnover in some diseases (with a more rapid recovery of COX-1–dependent platelet function) and interference with the aspirin mechanism (ie, competition of aspirin with other nonsteroidal anti-inflammatory drugs, such as ibuprofen, can prevent aspirin irreversible acetylation and inactivation of the COX-1) could also account for interindividual variability of response to aspirin.[45]

Currently, aspirin resistance is not evaluated in routine clinical practice and efforts to enhance susceptibility to ASA, for instance, by increasing the aspirin daily regimen, should not be pursued given the lack of outcome data in this specific population.[30,31]

Aspirin may also be associated with hypersensitivity or intolerance, challenging secondary prevention.[46–49] Hypersensitivity refers to a history of respiratory, cutaneous, or systemic reactions, whereas the term intolerance refers to a history of severe indigestion incurred by low-dose aspirin.[47] Aspirin intolerance may be frequent, varying from 6% to 20%, whereas true hypersensitivity is rare at 0.6% to 2.4% of the general population.[47] These patients may be managed via desensitization protocols, which have been shown to be effective, but remain underused.[47–49] However, potentially fatal systemic reactions are rare and the number of patients with a true contraindication to low-dose aspirin is rather low.[47] In a study of patients with CAD undergoing cardiac catheterization and coronary stent implantation, Rossini et al[50] found that 2.6% reported histories of aspirin sensitivity characterized by respiratory or cutaneous manifestations (no anaphylactic reactions). The authors tested a novel rapid desensitization procedure (6 sequential doses of aspirin [1, 5, 10, 20, 40, and 100 mg] over 5.5 hours without corticosteroids or antihistamines) before cardiac catheterization (ST-segment–elevation MI patients underwent desensitization before hospital discharge) and found that this was safe and effective (success in 89%, during 1-year follow-up aspirin was tolerated well, without developing allergic reactions).[50]

Dosage

It is known that aspirin inhibition of platelet TXA2 is cumulative on repeated daily dosing and saturable at low doses (daily administration of ASA 30 mg determines a virtually complete suppression of platelet TXA2 after 1 week) in healthy individuals because of its irreversible nature, but some clinical conditions (diabetes mellitus, metabolic syndrome, CABG, etc) are associated with suboptimal antiplatelet inhibition by aspirin.[26] Thus, typical regimens of 75 to 100 mg daily clearly exceed the minimal effective dose required for a full pharmacodynamic effect, but accommodate some degree of interindividual variability.[26]

It has been suggested that aspirin doses <75 mg daily may be more effective than higher doses because they spare prostacyclin (an antiplatelet and vasodilator) and cause less gastrointestinal toxicity. In the Antithrombotic Trialists' meta-analysis, no significant differences in outcomes were observed when ASA ≥75 mg was compared with ASA <75 mg among 3570 patients in 3 trials.[31] However, aspirin doses of <75 mg have been less widely assessed than doses of 75 to 150 mg daily, and uncertainty remains as to whether such low doses are as effective as daily doses of ≥75 mg. Among trials evaluating higher daily doses of ASA versus no-ASA, the relative reduction in vascular events was 19% with doses of 500 to 1500 mg daily, 26% with doses of 160 to 325 mg daily, and 32% with doses of 75 to 150 mg daily, whereas daily doses <75 mg seemed to have a somewhat smaller effect (proportional reduction 13%).[31] In trials comparing ASA with control, the proportional increase in the risk of a major extracranial bleed was similar with all daily aspirin doses <325 mg (odds ratios 1.7 [95% confidence interval [CI] 0.8–3.3] for <75 mg; 1.5 [1.0–2.3] for 75–150 mg; and 1.4 [1.0–2.0] for 160–325 mg). Two trials that compared 75 with 325 mg aspirin daily with <75 mg daily also found no significant difference in major extracranial bleeds (2.5% with 75–325 mg versus 1.8% with <75 mg; *P*=nonsignificant).

A systematic review of clinical trials in 2007 suggested that available clinical data did not support the routine, long-term use of aspirin dosages >75 to 81 mg daily in the setting of cardiovascular disease prevention and that higher dosages, which were commonly prescribed, were not more effective at preventing events, but rather were associated with increased risks of gastrointestinal bleeding.[51] A subanalysis of the CURE trial (Clopidogrel in Unstable Angina to Prevent Recurrent Events) stratified patients based on ASA dosage (≤100, 101–199, and ≥200) demonstrating that the higher ASA doses did not reduce ischemic events but significantly increased the risk of major or life-threatening bleeding.[52] The CURRENT-OASIS 7 trial (Double-Dose Versus Standard-Dose Clopidogrel And High-Dose Versus Low-Dose Aspirin in Individuals Undergoing PCI for ACS) confirmed no sig-

nificant differences in MACE between patients with ACS randomly assigned to high-dose (300–325 mg) versus low-dose (75–100 mg) ASA.[53] Although overall bleeding complications were nonsignificantly different, there was a higher incidence of gastrointestinal bleeding with high-dose ASA.[53] Interestingly, in the PLATO trial (Platelet Inhibition and Patient Outcomes), variation in ASA dose emerged as a possible explanation for observed regional differences (lower effect of ticagrelor in North America than in the rest of the world) and the lowest risk of cardiovascular death, MI, or stroke with ticagrelor in comparison with clopidogrel was associated with a low maintenance dose of concomitant aspirin.[54] Importantly, high-dose ASA also reduced the benefits of ticagrelor outside the United States.[54] On the contrary, an analysis from the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38) showed that, although North American patients received high-dose ASA more frequently than in other countries, the bleeding and ischemic events of prasugrel in comparison with those of clopidogrel were directionally consistent regardless of ASA dose.[55]

More recent data from US clinical practice still reflects uncertainty regarding the optimal aspirin dose for secondary prevention.[56] Indeed, despite previous data supporting lower doses of ASA, an analysis from 2014 showed that ≈60% of US patients with heart disease were discharged with 325-mg aspirin doses, whereas most of the remainder received lower doses (81 mg daily in 36%). Even among patients who experienced major in-hospital bleeding, 57% received the 325-mg dose. Furthermore, high-dose ASA was also commonly adopted in patients treated without revascularization (45%), in those treated with CABG (48%), or in those prescribed triple therapy (44%).[56] Similarly, the recent analysis from the Treatment with ADP Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome study (TRANSLATE-ACS) showed that among 10 213 patients with MI who underwent PCI, 63% were discharged on ASA 325 mg and 37% with ASA 81 mg daily.[57] The adjusted risk of MACE was nonsignificantly different between the 2 regimens, but high-dose ASA was associated with greater risk of any Bleeding Academic Research Consortium–defined bleeding, driven mostly by minor Bleeding Academic Research Consortium type 1 or 2 events not requiring hospitalization.[57]

Recently, American guidelines have incorporated the low-dose ASA recommendation stating that a daily aspirin dose of 81 mg (range 75–100 mg) is recommended in patients treated with DAPT.[6] However, the ADAPTABLE trial (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness; NCT02697916) is expected to offer additional information on optimal ASA dosages. This study is funded by a Patient-Centered Outcomes Research Institute Award and will be conducted through PCORnet (National Patient-Centered Clinical Research Network).[58] The primary composite outcome (death, hospitalization for nonfatal MI, or stroke) and a primary safety end point of major bleeding complications were chosen with input from patients. The trial will compare a daily dose of ASA 81 versus 325 mg in 20 000 high-risk patients with atherosclerotic heart disease (defined as MI, or catheter ≥75% stenosis of ≥1 epicardial vessel, or PCI/CABG) and at least one of the following: age >65 years, creatinine 1.5 mg/dL, diabetes mellitus, 3-vessel disease, cerebrovascular disease or peripheral arterial disease, ejection fraction <50% (by echocardiogram, catheter or nuclear imaging), or current smoking. Patients will be excluded if they are <18 years of age, have a documented ASA allergy or contraindication (including pregnancy or nursing), a significant gastrointestinal bleed within the past 12 months, a significant bleeding disorder, need warfarin or non-Vitamin K oral anticoagulants or ticagrelor. Enrollment is planned to occur over 24 months, and the maximum follow-up will be 30 months.

Dual-Antiplatelet Therapy

The activation of platelets by a primary agonist, such as exposed collagen or thrombin at a site of vessel injury or plaque rupture, triggers platelet production of TXA2 and the release of ADP from platelet-dense granules, as well. TXA2 and ADP then act as autocrine and paracrine agonists via activation of platelet thromboxane-prostanoid and ADP ($P2Y_1$ and $P2Y_{12}$) receptors, respectively. By targeting both COX-1 and $P2Y_{12}$ pathways of platelet activation, aspirin and $P2Y_{12}$ inhibitors yield an additive or even synergistic effect when used in concert.[59]

Twenty years ago, the ISAR study (Intracoronary Stenting and Antithrombotic Regimen) first demonstrated that DAPT was superior to anticoagulant therapy in patients undergoing to PCI.[60,61] Subsequently, the CURE trial showed the benefits of adding clopidogrel to ASA monotherapy in ACS patients and also in those undergoing PCI, although at the cost of increased bleeding.[12,62] Over the past 2 decades, the coadministration of $P2Y_{12}$ inhibitors with aspirin has been shown to further reduce the risk of acute thrombotic events in several clinical settings, albeit always at the price of greater bleeding.[2,8,12] As a result, equipoise and controversy persist surrounding the optimal duration of DAPT after PCI.[63] Multiple studies have consistently shown the feasibility of reducing DAPT duration to 6 (PRODIGY, EXCELLENT, SECURITY, ITALIC, ISAR-SAFE, I-LOVE-IT 2, IVUS-XPL, NIPPON) or even 3 months (OPTIMIZE, RESET), resulting in lower bleeding hazards without any incremental increase in ischemic events.[64] Nevertheless, other trials investigated the value of prolonging DAPT beyond 12 months (ARCTIC Interruption, DAPT, DES-LATE, OPTIDUAL), providing partially conflicting results as it relates to

the benefit to reduce nonfatal ischemic events including MI and very late ST at the expense of greater bleeding and potentially fatal outcomes. A meta-analysis of 10 thienopyridine trials including 31 666 patients showed that shorter DAPT was associated with a lower risk of major bleeding, but a higher risk of MI and ST.[63] Notably, this analysis also demonstrated that longer DAPT was associated with a significantly increased risk of all-cause mortality that was attributable to noncardiac mortality.[63] The caveat of this analysis, however, is that by pooling all available thienopyridine studies, a 12-month DAPT duration was included in both control and experimental groups, thereby failing to provide information on optimal DAPT duration. As an alternative approach, these 10 thienopyridine trials have been stratified more recently based on DAPT duration in the control group, by keeping 12 months as the control therapy and contrasting it to either a shortened (ie, 6 or 3 months) or a prolonged (ie, ≥18 months) DAPT regimen.[19] This analysis showed that DAPT discontinuation before 12 months after PCI with drug-eluting stent (DES) yielded fewer bleeding events without an apparent increase of ischemic complications. DAPT continuation beyond 12 months reduced ischemic and thrombotic events at the expense of more frequent major bleeding and all-cause mortality. Hence, it has been suggested that the currently recommended 12-month DAPT duration after DES implantation is a compromise between ischemic and bleeding risk of uncertain value, and it highlights the challenge of identifying a uniformly ideal DAPT duration across patient ischemic and bleeding risk profiles in practice.

Although it has been suggested that early-generation DES, in comparison with new-generation DES, may amplify the need for prolonged DAPT,[65] an emerging new paradigm is that the benefit of prolonged DAPT may largely be stent independent. DAPT consisting of aspirin and clopidogrel beyond 12 months has been shown to reduce the risk of MI not related to stented segments.[18] The benefits and risks of aspirin and ticagrelor at doses of 60 mg twice daily and 90 mg twice daily beyond 1-year treatment was investigated in patients with established CAD, revealing a reduced risk of ischemic events, including myocardial infarction and stroke, again at the expense of increased bleeding risk. The paradigm shift (from stent to patient protection) supports the notion of extending DAPT beyond the vulnerability window intrinsic to and related to stents (subacute or late ST). Yet this benefit must be interpreted in the context of the continuous increase in bleeding risk observed during the course of DAPT duration. Previous evidence that, in patients on DAPT bleeding, may decrease over time (ie, CHARISMA) has been challenged by recent studies (DAPT, PRODIGY, PEGASUS [Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin]) suggesting a linear relationship between DAPT duration and bleeding risk. Although a high risk of bleeding is somewhat expected soon after the initiation of DAPT, multiple long-term DAPT studies have clearly shown that this risk never abates over time, even after several years of treatment. A recent subanalysis from PEGASUS explored the reasons for and timing of discontinuation of ticagrelor among stable patients with prior MI and found that bleeding was the main cause of discontinuation. The rate of treatment discontinuation because of bleeding was 3.5% in the ticagrelor 60 mg arm and 5% in the ticagrelor 90 mg arm (in comparison with <1% in the placebo group) and it increased to ≈5% and 6.5%, respectively, at an average 3-year follow-up (in comparison with ≈1.2% in the placebo group).[66]

In a pooled analysis of trials comparing short versus prolonged DAPT durations, bleeding was potentially more causally associated with all-cause mortality than ST, which highlights the need to minimize the risks of bleeding to optimize the fatality rate.[67] This appears consistent with the results of a large survey capturing DAPT prescription practices, where attempts to individualize DAPT duration based on conventional ischemic and bleeding risk factors emerged as the most common prescription pattern.[68]

It remains unclear whether the type of DAPT (ie, the type of $P2Y_{12}$ inhibitor paired with aspirin) affects the comparative effectiveness/safety profile of a shortened versus a prolonged DAPT duration.

The PEGASUS study randomly assigned 21 162 patients with an MI 1 to 3 years earlier to ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily, or placebo.[17] All patients received low-dose aspirin and were followed for a median of 33 months. In comparison with placebo, both ticagrelor doses reduced the rate of the primary efficacy end point, with cumulative event rates at 3 years of 7.85% in the 90 mg twice daily group, 7.77% in the 60 mg twice daily group, and 9.04% in the placebo group (hazard ratio [HR] for 90 mg of ticagrelor versus placebo, 0.85; 95% CI, 0.75–0.96; *P*=0.008; HR for 60 mg of ticagrelor versus placebo, 0.84; 95% CI, 0.74–0.95; *P*=0.004). Both ticagrelor doses significantly reduced rates of MI, whereas the 60 mg twice daily ticagrelor regimen also reduced the risk of stroke and trended toward a reduction in cardiovascular mortality. When pooling both doses, there was no signal of harm related to all-cause mortality, which is at variance with the previously discussed results of the pooled analysis using clopidogrel for DAPT.[69] Whether the observed heterogeneity with respect to overall mortality after prolonged DAPT reflects the characteristics of the $P2Y_{12}$ inhibitor used in the DAPT regimen (ie, a thienopyridine versus a nonthienopyridine agent) or rather different patient selections across studies (ie, a uniform post-MI population in PEGASUS versus a mix of stable and unstable CAD patients undergoing stent implantation in other thienopyridine trials) is unclear and warrants subsequent investigation.[69–72]

SINGLE-ANTIPLATELET $P2Y_{12}$ INHIBITOR THERAPY AFTER PCI

Rationale

Under the assumption that aspirin is the default antiplatelet therapy, all the studies in the past decades investigating, among others, $P2Y_{12}$ antagonists or oral anticoagulants, both in patients with or without an established indication to systemic anticoagulation, have been conducted as add-on therapy in the context of background aspirin treatment. A prolonged DAPT, despite being efficacious in mitigating the risks of MI and ST, may disproportionally increase bleeding liability, leading to unfavorable effects on noncardiovascular and total mortality. Although the addition of rivaroxaban to a DAPT regimen consisting of aspirin and clopidogrel was effective in reducing a composite ischemic end point, including a significant reduction in cardiovascular mortality, relevant increases in overall, life-threatening, and intracranial bleeding were also observed.

These findings may reflect the ceiling effect associated with further intensification of antithrombotic drugs wherein additional exposure increases bleeding toxicity without any reduction in thrombosis. Consequently, the less-is-more concept has been proposed in an effort to mitigate bleeding potential while preserving antithrombotic efficacy achieved through the concomitant inhibition of multiple platelet activation pathways, thereby optimizing net clinical benefit. Recently, a stand-alone $P2Y_{12}$ inhibition strategy has been proposed to replace long-term DAPT regimens for long-term secondary prevention. Interestingly, Rollini et al[73] compared the antiplatelet effect of aspirin monotherapy and clopidogrel monotherapy in patients with atherosclerotic disease in a prospective pharmacodynamics study and showed that clopidogrel was associated with increased platelet inhibition in heavy smokers.

Although the results of large randomized studies are awaited to validate this potentially new treatment modality, 3 large-scale studies testing different anticoagulants in ACS patients have shown that bleeding prevention may be causally linked to mortality benefit, despite slightly higher risks of ST or catheter thrombosis.[74–76] The net clinical effect of adding aspirin in patients receiving newer more potent $P2Y_{12}$ antagonists is unknown and aspirin may increase bleeding while not further mitigating the ischemic risk. This may be particularly true in patients treated with newer $P2Y_{12}$ antagonists,[11] which unlike ticlopidine[77] or clopidogrel,[78,79] exert a predictable inhibition of the target receptor.

Biochemical Considerations

Several lines of evidence suggest that $P2Y_{12}$ antagonists might also affect TXA2 platelet production, thereby minimizing any additional antiplatelet effect realized with aspirin use.[80–85] Experiments with platelet-rich plasma from healthy volunteers have shown that prasugrel active metabolites inhibit platelet release of both TXA2 and ATP+ADP, and the addition of aspirin to prasugrel failed to provide any additional inhibition of platelet aggregation.[82] However, the study had some limitations, particularly in how the effect of aspirin was assessed. These findings are related to the strong $P2Y_{12}$ inhibition, so they also can be extended to ticagrelor. Indeed, in a recent pharmacodynamics study in diabetic patients, both prasugrel and ticagrelor were associated with inhibitory effects on measures of non–ADP-induced platelet reactivity (ie, thromboxane-, collagen-, and thrombin-induced).[86] Nevertheless, it remains to be proven whether these in vitro and ex vivo observations will translate into clinical implications. However, the overall effect of adding aspirin (particularly at daily doses >100 mg) to new $P2Y_{12}$ antagonists could be deleterious because of its inhibition of protective prostanoids in other cells and tissues, including vascular endothelium, stomach, and kidney.[80] High-dose aspirin does not provide greater treatment efficacy but increases bleeding risks in comparison with a low-dose aspirin regimen.[54,87] In the PLATO trial, geographical differences in clinical outcomes were observed, namely, an apparent lack of superior treatment effect of ticagrelor over clopidogrel in the study cohort recruited in the United States.[15,54] Of the 37 baseline and postrandomization factors explored, aspirin maintenance dose was found to be the most important covariate explaining at least in part these regional differences.[54] In particular, the lowest risk of cardiovascular death, MI, or stroke with ticagrelor in comparison with clopidogrel, was associated with a low maintenance dose of concomitant aspirin, whereas the higher maintenance dose of aspirin used in the United States in comparison with other regions (≥300 mg/d in 53.6% versus 1.7% of patients, respectively) seemed to be responsible for these geographic differences. This study suggested that high-dose aspirin added to ticagrelor could be deleterious and could blunt ticagrelor benefits, in the United States, and in the as non-United States, as well.[54] Notably, 2 small studies showed that aspirin had no direct effect on ticagrelor pharmacokinetics or its platelet inhibition.[88]

Evidence contradicting the possible biochemical interaction between $P2Y_{12}$ and COX-1 inhibition has also been provided. Cattaneo et al[89] assessed whether $P2Y_{12}$ antagonists have off-target/indirect inhibitory effects on platelet TXA2 production. They studied 3 patients with inherited deficiency of $P2Y_{12}$ receptors and 33 healthy subjects, demonstrating that $P2Y_{12}$ inhibition did not affect the platelet capacity to synthesize TXA2: (1) serum TXB2 (TXA2 metabolite) levels were similar in $P2Y_{12}$R-deficient patients and healthy subjects and were not decreased by $P2Y_{12}$ antagonists in vitro; (2) serum TXB2 levels did not decrease in patients treated with prasugrel

(10 mg) or placebo for 14 days; (3) ASA inhibited TXB2 production more effectively than a $P2Y_{12}$ antagonist, and only the combination of ASA plus $P2Y_{12}$ antagonist inhibited platelet aggregation induced by high concentrations of collagen.

Clinical guidelines supporting the prophylactic use of aspirin for purposes of secondary prevention acknowledge the cardiovascular benefits, weighed against the potential risks of bleeding.

However, it should be mentioned that new aspirin formulations have a better pharmacokinetic/pharmacodynamic profile and gastrointestinal tolerability that may open new avenues for aspirin in the future.

Furthermore, there is also relevant evidence supporting other benefits related to low-dose aspirin use, including chemoprevention and reduced risk of dementia, and these effects would be lost in case of long-term treatment with new $P2Y_{12}$ antagonists instead of aspirin.[90–93] It has been suggested that low-dose aspirin is associated with decreased incidence and mortality for colorectal cancer, potentially because of its interference with neoplastic transformation of a normal intestinal epithelium (mainly in the colorectal region) toward a sporadic adenoma and its progression to cancer.[90–92] It has also been speculated that even a 10% reduction in overall cancer incidence starting in the first 10 years of treatment may favorably tip the balance of benefits and risks in average-risk populations.[91] Preliminary evidence also suggests that low-dose aspirin reduces cognitive decline in the elderly, possibly by reducing brain inflammation (inhibition of platelet-related inflammation and release of lipoxins).[93] Long-term studies comparing aspirin versus $P2Y_{12}$ inhibitors alone would be required to confirm or disprove these potential aspirin-specific effects.

Clinical Evidence

Initial experience supporting the use of $P2Y_{12}$ inhibitors over aspirin was provided by the TASS (Ticlopidine Aspirin Stroke Study) and the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) trials.[13,94] Ticlopidine was more effective than aspirin in preventing strokes in a high-risk population with similar bleeding risk.[94] In the CAPRIE trial, long-term administration of clopidogrel among patients with atherosclerotic vascular disease was as safe as, but more effective than aspirin in reducing the combined risk of ischemic stroke, MI, or vascular death.[13] The recent SOCRATES (Acute Stroke or TIA Treated with Aspirin or Ticagrelor and Patient Outcomes) was an international double-blind controlled trial in 674 centers in 33 countries, in which 13199 patients with a nonsevere ischemic stroke or high-risk TIA were randomly assigned within 24 hours after symptom onset, in a 1:1 ratio, to receive either ticagrelor (180 mg loading dose on day 1 followed by 90 mg twice daily for days 2–90) or aspirin (300 mg on day 1 followed by 100 mg daily for days 2–90).[95] The primary end point (stroke, MI, or death within 90 days) occurred in 442 of the 6589 patients (6.7%) treated with ticagrelor, versus 497 of the 6610 patients (7.5%) treated with aspirin (HR, 0.89; 95% CI, 0.78–1.01; P=0.07).[95] Approximately 32% of patients were taking aspirin before randomization, and the prespecified subgroup analysis of the primary end point showed that these patients tended to derive greater benefit from ticagrelor (previous aspirin patients: HR, 0.76; 95% CI, 0.61–0.95; no previous aspirin patients: HR, 0.96; 95% CI, 0.82–1.12), although the interaction P value was nonsignificant (interaction P=0.10). Interestingly, major bleeding occurred in 0.5% of patients treated with ticagrelor and in 0.6% of patients treated with aspirin, intracranial hemorrhage in 0.2% and 0.3%, respectively, and fatal bleeding in 0.1% and 0.1%.[95] This study failed to conclusively show superiority of ticagrelor versus aspirin in poststroke/TIA patients; however, it adds to the growing evidence that a $P2Y_{12}$ inhibitor monotherapy strategy may result in greater protection from ischemic recurrences than aspirin, with a similar bleeding profile.

Further evidence supporting the use of $P2Y_{12}$ inhibitors without aspirin in patients with established atherosclerotic disease was provided in the context of the MATCH trial (Molecular Analysis for Therapy Choice).[96] In MATCH, 7599 high-risk patients with recent ischemic stroke or TIA and at least 1 additional vascular risk factor, who were already receiving clopidogrel 75 mg/d, were randomly assigned to aspirin 75 mg/d or placebo.[96] This study showed that adding aspirin to clopidogrel did not decrease major vascular events but increased the risk of major and life-threatening, including intracranial, bleeding complications.[96] This supported the concept that adding ASA to clopidogrel was more dangerous than adding clopidogrel to ASA as was previously observed in the CURE trial.

Finally, evidence suggesting an improved safety profile of aspirin omission after PCI comes from the proof-of-concept WOEST study (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) that compared the use of clopidogrel alone in patients on vitamin K antagonist and showed fewer bleeding complications without an apparent increase of thrombotic events, including a lower mortality risk in comparison with triple therapy.[97] It should be emphasized, however, that concomitant oral anticoagulant therapy largely increases bleeding risk, but it also mitigates thrombotic risks, including the reduction of ST incidence. Therefore, caution should be used in extrapolating the effect of aspirin removal in patients taking oral anticoagulants to those not in need of such therapy (ie, who have indication to DAPT only) after ACS or PCI.

Table 3. Characteristics of Trials Assessing Anticoagulation Therapy in Patients With AF Undergoing PCI

	REDUAL-PCI	PIONEER AF-PCI	AUGUSTUS	ENTRUST-AF-PCI
Title	A Prospective Randomised, Open Label, Blinded End point (PROBE) Study to Evaluate DUAL Antithrombotic Therapy With Dabigatran Etexilate (110 mg and 150 mg BID) Plus Clopidogrel or Ticagrelor vs Triple Therapy Strategy With Warfarin (INR 2.0–3.0) Plus Clopidogrel or Ticagrelor and Aspirin in Patients With Non Valvular Atrial Fibrillation (NVAF) That Have Undergone a Percutaneous Coronary Intervention (PCI) With Stenting	An Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention	An Open-label, 2×2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs Vitamin K Antagonist and Aspirin vs Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention	Evaluation of the Safety and Efficacy of an Edoxaban-based Compared to a Vitamin K Antagonist-based Antithrombotic Regimen in Subjects With Atrial Fibrillation Following Successful Percutaneous Coronary Intervention (PCI) With Stent Placement
ClinicalTrials.gov identifier	NCT02164864	NCT01830543	NCT02415400	NCT02866175
Sponsor	Boehringer Ingelheim	Janssen Scientific Affairs, LLC	Bristol-Myers Squibb	Daiichi Sankyo Inc.
Estimated enrollment	2502	2127	4600	1500
Study start date	July 2014	May 2013	June 2015	February 2017
Estimated completion date	March 2017	July 2016	September 2017	February 2019
Allocation	Randomized	Randomized	Randomized	Randomized
End point classification	Safety/efficacy study	Safety study	Safety study	Safety/efficacy study
Intervention model	Parallel assignment	Single-group assignment	Factorial assignment	Parallel assignment
Masking	Open label	Open label	Open label	Open label
Active comparator	Warfarin 5 or 3 or 1 mg plus aspirin plus clopidogrel or ticagrelor	Dose-adjusted VKA once daily (target INR 2.0–3.0) plus low-dose aspirin, 75 to 100 mg/d, and clopidogrel 75 mg once daily (or prasugrel 10 mg once daily or ticagrelor 90 mg twice daily) followed by dose-adjusted VKA once daily (target INR 2.0–3.0 or 2.0–2.5 at the investigator discretion) plus low-dose aspirin for 12 mo	VKA orally once daily plus aspirin film-coated tablet orally once daily (81 mg or placebo)	VKA plus clopidogrel 75 mg once daily (or in the presence of a documented clinical need prasugrel [5 mg or 10 mg once daily] or ticagrelor [90 mg twice daily] may be used).

(*Continued*)

Table 3. Continued

	REDUAL-PCI	PIONEER AF-PCI	AUGUSTUS	ENTRUST-AF-PCI
Experimental comparator	Dabigatran etexilate 110 mg plus clopidogrel or ticagrelor Dabigatran etexilate 150 mg plus clopidogrel or ticagrelor	Rivaroxaban 2.5 mg twice daily plus low-dose aspirin 75–100 mg once daily and clopidogrel 75 mg once daily (or prasugrel 10 mg once daily or ticagrelor 90 mg twice daily) followed by rivaroxaban 15 mg (10 mg if moderate CKD) once daily plus low-dose aspirin for 12 mo Rivaroxaban 15 mg (10 mg if moderate CKD) once daily plus clopidogrel 75 mg once daily (or prasugrel 10 mg once daily or ticagrelor 90 mg twice daily) for 12 mo	Apixaban 2.5 or 5 mg orally twice per day plus aspirin film coated tablet orally once daily (81 mg or placebo)	Edoxaban 60 mg once daily or 30 mg once daily in selected subjects
Primary outcome	First ISTH major or CRNM bleeding (up to 30 mo)	Clinically significant bleeding at 12 mo (composite of TIMI major bleeding, minor bleeding, and bleeding requiring medical attention)	Occurrence of ISTH major or CRNM bleeding during the time the patient is taking the medicine which is 6 mo (between apixaban and VKA; between aspirin and no-aspirin)	Number of ISTH major or CRNM bleeding (≤12 mo)
Secondary outcome	At 30 mo: Undetermined cause of death; noncardiovascular death; cardiovascular death; all death; MI; stroke; ST; SE; death+MI+stroke; unplanned revascularization (PCI or CABG); death or first thrombotic event (all death, MI, stroke/SE); death or first thrombotic event or unplanned revascularization	Clinically significant bleeding and adverse cardiovascular events, and adverse events at 10 d, 30 d, 3 mo, 6 mo, 9 mo, 12 mo. Composite of clinically significant bleeding and adverse cardiovascular events at the end of DAPT period (1 mo or 6 mo or 12 mo) and at 12 mo	Superiority on major+CRNM bleeding between apixaban versus VKA at 6 mo Composite of death and ischemic events (stroke, MI, ST, urgent revascularization) between apixaban versus VKA and between aspirin and no-aspirin at 6 mo First rehospitalization for any cause between apixaban versus VKA and between aspirin and no-aspirin at 6 mo	At 12 mo: composite number of cardiovascular death, stroke, SE, MI, and ST events; composite number of cardiovascular death, stroke, SE, MI, ST events, and ISTH-defined bleeding events; Number of ISTH major bleeding
Inclusion criteria	1. Male or female patients aged ≥18 y 2. Patients with nonvalvular AF 3. Patient presenting with: an ACS (STEMI, NSTEMI, or UA) that was successfully treated by PCI and stenting (either BMS or DES) or stable coronary artery disease with at least 1 lesion eligible for PCI that was successfully treated by elective PCI and stenting (either BMS or DES) 4. The patient must be able to give informed consent	1. History of paroxysmal, persistent, or permanent nonvalvular AF 2. Have undergone PCI with stent placement for primary atherosclerotic disease 3. INR of ≤2.5 to be randomized 4. Women must be postmenopausal before entry or practicing a highly effective method of birth control when heterosexually active 5. Be willing and able to adhere to the prohibitions and restrictions specified in the study protocol	1. Adults with either active or a history of nonvalvular AF or flutter with the planned or existing use of an oral anticoagulant for prophylaxis of thromboembolism. In addition, subjects must have had an ACS or PCI with a stent within the previous 14 days 2. Planned use of antiplatelet agents for at least 1 to 6 mo 3. Men and women ≥18 y 4. Women of childbearing potential must have a negative serum or urine pregnancy test within 24 h before the start of study drug	Oral anticoagulant therapy indication for AF for a period of at least 12 mo following successful PCI with stenting. Eligibility is assessed 4 h after sheath removal and within 5 days after successful PCI with stent placement. If a staged PCI is planned, eligibility is assessed after completion of the last stage.

(*Continued*)

Table 3. Continued

	REDUAL-PCI	PIONEER AF-PCI	AUGUSTUS	ENTRUST-AF-PCI
Exclusion criteria	1. Mechanical or biological heart valve prosthesis 2. Cardiogenic shock during current hospitalization 3. Stroke within 1 mo before screening visit 4. Major surgery within the month before screening 5. Gastrointestinal hemorrhage within 1 mo before screening, unless, in the opinion of the Investigator, the cause has been permanently eliminated 6. Major bleeding episode including life-threatening bleeding episode in 1 mo before screening visit 7. Anemia (Hb <10g/dL) or thrombocytopenia including heparin-induced thrombocytopenia (platelet count <100×109/L) at screening 8. Severe CKD (estimated CrCl by Cockcroft-Gault <30 mL/min at screening 9. Active liver disease	1. Any condition that contraindicates anticoagulant or antiplatelet therapy or would have an unacceptable risk of bleeding, such as, but not limited to: platelet count <90 000/μL at screening, history of intracranial hemorrhage, 12 mo history of clinically significant gastrointestinal bleeding, non-VKA-induced elevated prothrombin time (PT) at screening 2. Anemia of unknown cause with a Hb level <10 g/dL 3. History of stroke or TIA 4. Calculated CrCl <30 mL/min at screening 5. Known significant liver disease or liver function test abnormalities 6. Any severe condition that would limit life expectancy to <12 mo	1. Conditions other than AF that require chronic anticoagulation (eg, prosthetic mechanical heart valve) 2. Severe CKD (serum creatinine >2.5 mg/dL or a calculated CrCl < 30 mL/min 3. History of intracranial hemorrhage 4. Patients have had or will undergo CABG for their index ACS event 5. Known ongoing bleeding or coagulopathies 6. Any contraindications or allergies to VKA, apixaban, or to intended $P2Y_{12}$ antagonists or to aspirin	1. Bleeding risks or systemic conditions 2. Known bleeding diathesis, including but not limited to: a. Uncontrolled active bleeding, encompassing both ISTH major and clinically relevant nonmajor bleeding, preceding randomization. Lesion or condition, if considered to be a significant risk for major bleeding. This may include but is not limited to: unresolved gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding (eg, malignancies with metastasis), recent unresolved brain or spinal injury, recent brain, spinal, or ophthalmic surgery, any intracranial hemorrhage, known or suspected esophageal varices, arteriovenous malformations, vascular aneurysms (of >3.5 cm) or major intraspinal or intracerebral vascular abnormalities. b. Medication-related 3. INR > 2.5 (the subject can be reconsidered at a later time, but within 5 days of sheath removal). 4. Contraindication to edoxaban, VKA, ASA. and $P2Y_{12}$ antagonists; 5. Concomitant treatment with other antithrombotic agents, fibrinolytic therapy. and chronic nonsteroidal anti-inflammatory drugs (NSAIDs). 6. Critically ill or hemodynamically unstable subjects (at the time of randomization) including: a. Cardiogenic shock or acute decompensated heart failure, with the requirement for vasopressor agents or inotropic support or mechanical support to support circulation b. Respiratory failure requiring endotracheal intubation and mechanical ventilation. 7. Any prior mechanical valvular prosthesis; 8. Planned coronary or vascular intervention or major surgery within 12 mo; Randomization must be deferred to the last stage in a multistep, multivessel PCI procedure; 9. Moderate or severe mitral stenosis; 10. Ischemic stroke within 2 wk before randomization;

(*Continued*)

Table 3. Continued

	REDUAL-PCI	PIONEER AF-PCI	AUGUSTUS	ENTRUST-AF-PCI
Exclusion criteria (Continued)				11. Uncontrolled severe hypertension with a systolic blood pressure (BP) ≥180 mm Hg and diastolic BP≥120 mm Hg; 12. Severe renal impairment with estimated CrCl <15 mL/min or on dialysis; 13. Known abnormal liver function before randomization (including hepatic disease or biochemical evidence of significant liver derangement known before randomization). 14. Any of the following abnormal local laboratory results prior to randomization: a. Platelet count < 50×109/L b. Hemoglobin <8 mg/dL 15. Unable to provide written IC; Female subjects of childbearing potential without using adequate contraception (female of childbearing potential is defined as one who has not been postmenopausal for at least 1 y, or has not been surgically sterilized, or has not had a hysterectomy at least 3 mo before the start of this study [Visit 1]). Females taking oral contraceptives should have been on therapy for at least 3 mo. Adequate contraceptives include hormonal intrauterine devices, hormonal contraceptives (oral, depot, patch, or injectable), and double-barrier methods such as condoms or diaphragms with spermicidal gel or foam. 16. Pregnant or breastfeeding subjects; 17. Assessment that the subject is not likely to comply with the study procedures or have complete follow-up; 18. Participating in another clinical trial that potentially interferes with the current study; 19. Previous randomization in this study; 20. Known drug or alcohol dependence within the past 12 mo as judged by the Investigator; 21. Life expectancy <12 mo.

ACS indicates acute coronary syndrome; AF, atrial fibrillation; BID, twice daily; BMS, bare metal stent; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CrCl, creatinine clearance; CRNM, clinically relevant nonmajor; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; Hb, hemoglobin; IC, informed consent; INR, international normalized ratio; ISTH, international society on thrombosis and hemostasis; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; SE, systemic embolism; ST, stent thrombosis; STEMI, ST-segment–elevation myocardial infarction; TIA, transient ischemic attack; UA, unstable angina; and VKA, vitamin-K antagonist.

Table 4. Characteristics of GLOBAL LEADERS, TWILIGHT, and TICO Trials

	GLOBAL LEADERS	TWILIGHT	TICO
Title	Comparative Effectiveness of 1 mo of Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy Versus a Current-day Intensive Dual Antiplatelet Therapy in All-comers Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and BioMatrix Family Drug-eluting Stent Use	Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention	Ticagrelor Monotherapy After 3 mo in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome
ClinicalTrials.gov identifier	NCT01813435	NCT02270242	NCT02494895
Sponsor	European Cardiovascular Research Institute (ECRI)	Mount Sinai School of Medicine	Yonsei University
Estimated enrollment	16 000	9000	3056
Study start date	May 2013	July 2015	July 2015
Estimated completion date	June 2016	October 2018	July 2020
Allocation	Randomized	Randomized	Randomized
End point classification	Safety/efficacy study	Safety/efficacy study	Safety/efficacy study
Intervention model	Parallel assignment	Parallel assignment	Parallel assignment
Masking	Open label	Double blind	Open label
Active comparator	Aspirin (≤100 mg qd) + Ticagrelor (90 mg bid) for 12 mo followed by aspirin monotherapy for 12 mo in case of ACS; Aspirin (≤100 mg qd) + clopidogrel (75 mg qd) for 12 mo followed by aspirin monotherapy for 12 mo in case of stable CAD	Aspirin (81 mg daily for 12 mo) + ticagrelor (90 mg bid for 15 mo)	Aspirin + ticagrelor
Experimental comparator	Aspirin (≤100 mg qd) + ticagrelor (90 mg bid) for 1 mo followed by 23 mo of ticagrelor monotherapy.	Placebo (daily for 12 mo)+ ticagrelor (90 mg bid for 15 mo)	Ticagrelor monotherapy at 3 mo after PCI
Primary outcome	Composite of all-cause mortality or nonfatal new Q-wave MI up to 2 y	Bleeding: the time to first occurrence of clinically relevant bleeding, defined as BARC types 2, 3, or 5 bleeding at 1 y (15 mo after PCI)	Major adverse cardiovascular clinical events (MACCE) 1 y after the procedure Major bleeding (TIMI) 1 y after the procedure
Secondary outcome	Bleeding: The composite of investigator-reported BARC3 or BARC5 bleeding up to 2 y	Ischemic episode: the time to first occurrence of confirmed cardiovascular death, nonfatal MI, ischemic stroke, or IDR at 1 y (15 mo after PCI)	

(*Continued*)

Table 4. Continued

	GLOBAL LEADERS	TWILIGHT	TICO
Inclusion criteria	All-comer patients: 1. Age ≥18 y; 2. Presence of ≥1coronary artery stenoses of ≥50% in a native coronary artery or in a saphenous venous or arterial bypass conduit suitable for coronary stent implantation. The vessel should have a reference vessel diameter of at least 2.25 mm (no limitation on the number of treated lesions, vessels, or lesion length); 3. Able to provide informed consent and willing to participate in 2-y follow-up period.	High-risk patients who have undergone successful elective or urgent PCI with at least one locally approved drug-eluting stent discharged on DAPT with aspirin and ticagrelor of at least 3 mo intended duration will be eligible. Enrollment into the study will require meeting at least one clinical inclusion, one angiographic inclusion, and none of the exclusion criteria. Clinical Inclusion Criteria: 1. Adult patients ≥ 65 y of age 2. Recent (≥3 days) presentation with acute coronary syndrome with clinical stabilization and decreasing cardiac enzymes 3. Established vascular disease defined as previous MI, documented PAD or CAD/PAD revascularization 4. Diabetes mellitus treated with medications (oral hypoglycemic, subcutaneous injection of insulin) 5. CKD defined as an eGFR <60 mL·min^{-1}·1.73m^{-2} or creatinine clearance (CrCl) <60 mL/min Angiographic Inclusion Criteria: 1. Multivessel CAD 2. Target lesion requiring total stent length >30 mm 3. SYNTAX score ≥23 4. Bifurcation lesions with Medina X:X:1 classification requiring at least 2 stents 5. Left main (≥50%) or proximal LAD (≥70%) lesion 6. Calcified target lesion requiring atherectomy	1. Patients ≥19 y old 2. Patients who received new-generation sirolimus-eluting (Osiro) stent implantation for treating ACS 3. Patients without significant clinical events such as MI, stent thrombosis, or revascularization until 3 mo after PCI 4. Provision of informed consent
Exclusion criteria	1. Known intolerance to aspirin, $P2Y_{12}$ inhibitors, bivalirudin, stainless steel, or biolimus; 2. Known intake of a strong CYP3A4 inhibitor (eg, ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir), because coadministration may lead to a substantial increase in exposure to ticagrelor; 3. Known moderate to severe hepatic impairment (alanine-aminotransferase ≥3×ULN); 4. Planned surgery, including CABG as a staged procedure (hybrid) within 12 mo of the index procedure, unless dual-antiplatelet therapy is maintained throughout the perisurgical period;	1. Under 18 y of age 2. Contraindication to aspirin 3. Contraindication to ticagrelor 4. Planned surgery within 90 days 5. Planned coronary revascularization (surgical or percutaneous) within 90 days 6. Need for chronic oral anticoagulation 7. Prior stroke 8. Dialysis-dependent renal failure 9. Active bleeding or extreme risk for major bleeding (eg, active peptic ulcer disease, gastrointestinal pathology with a raised risk for bleeding, malignancies with a raised risk for bleeding)	1. Age > 80 y 2. Increased risk of bleeding, anemia, thrombocytopenia 3. A need for oral anticoagulation therapy 4. Pregnant women or women with potential childbearing 5. Life expectancy <1 y 6. Patients treated with strong CYP3A4 inhibitors (eg, ketoconazole, clarithromycin, nefazodone, ritonavir, or atazanavir) 7. Patients who had history of intracranial hemorrhage

(*Continued*)

Table 4. Continued

	GLOBAL LEADERS	TWILIGHT	TICO
Exclusion criteria (Continued)	5. Need for chronic oral anticoagulation therapy; 6. Active major bleeding or major surgery within the past 30 days; 7. Known history of intracranial hemorrhagic stroke or intracranial aneurysm; 8. Known stroke (any type) within the past 30 days; 9. Known pregnancy at time of randomization; 10. Female who is breastfeeding at time of randomization; 11. Currently participating in another trial and not yet at its primary end point	10. Emergent or salvage PCI or STEMI presentation. 11. Liver cirrhosis 12. Life expectancy <1 y 13. Unable or unwilling to provide informed consent 14. Women of childbearing potential (as determined by hospital standard of care) 15. Fibrinolytic therapy within 24 h of index PCI 16. Concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer 17. Platelet count <100 000 mm^3 18. Requiring ongoing treatment with aspirin >325 mg daily	8. Moderate to severe hepatic dysfunction 9. Increased risk of bradycardia-related symptom (guidance and reference)

ACS indicates acute coronary syndrome; BARC, bleeding academic research consortium; bid, twice daily; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; DAPT, dual-antiplatelet therapy; eGFR, estimated glomerular filtration rate; IDR, ischemia-driven revascularization; LAD, left anterior descending artery; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; qd, every day; STEMI, ST-segment–elevation myocardial infarction; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; and ULN, upper limit normal.

Ongoing Studies

Based on the considerations outlined above and to further evaluate the contemporary value of aspirin as a secondary prevention medication, numerous randomized trials are currently being conducted in patients with (Table 3) or without (Table 4) an established indication for concomitant oral anticoagulation.

Table 3 shows the trials testing the less-is-more approach (ie, clopidogrel monotherapy in the absence of concomitant aspirin therapy) after PCI in patients with atrial fibrillation.

Table 4 shows ongoing trials in patients without atrial fibrillation. The GLOBAL LEADERS (GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation; NCT01813435) is a superiority all-comers (with the exception of patients with an indication for oral anticoagulant) study among patients undergoing PCI. It is designed to assess whether a 24-month antithrombotic regimen with ticagrelor and 1-month aspirin, in comparison with 12-month conventional DAPT followed by aspirin monotherapy, improves outcome.[98] This is an investigator-initiated, randomized, open-label, outcome trial, which recruited 16 001 patients admitted for stable CAD or ACS undergoing PCI under standardized treatment consisting of bivalirudin-supported biolimus-eluting stent implantation. Patients were enrolled in >100 interventional cardiology sites in Europe, Asia, Brazil, Australia, and Canada from July 2013 to November 2015. Patients were randomly assigned (1:1 ratio) to ticagrelor 90 mg twice daily for 24 months plus ASA ≤100 mg for 1-month versus conventional DAPT with either ticagrelor in ACS patients or clopidogrel for 12 months plus ASA ≤100 mg for 24 months in stable CAD patients (Figure 3). Under the assumption that less may be more, this study is powered to show the superiority of ticagrelor monotherapy in terms of all-cause mortality or Q-wave MI. Results are to be released in the first or second quarter of 2018.

The TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention; NCT02270242) is a double-blind, multicenter trial enrolling ≈9000 high-risk patients undergoing elective or urgent PCI (emergent or salvage PCI or ST-segment–elevation MI presentation is an exclusion criterion) with DES (Table 4). Subjects meeting eligibility criteria at 3 months after enrollment are randomly assigned to ticagrelor (90 mg twice daily) and aspirin (81–100 mg/d) or ticagrelor and placebo for an additional 12 months. It is powered to show a reduction of bleeding with ticagrelor monotherapy (Figure 4). The first patient was enrolled in July 2015, and results are expected in 2019.

In the TICO study (Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome; NCT02494895), 3056 patients with ACS treated with new-generation sirolimus-eluting stent implantations are randomly assigned to ticagrelor monotherapy or ticagrelor plus aspirin at 3 months after PCI. The primary end point is the rate of major adverse cardiovascular

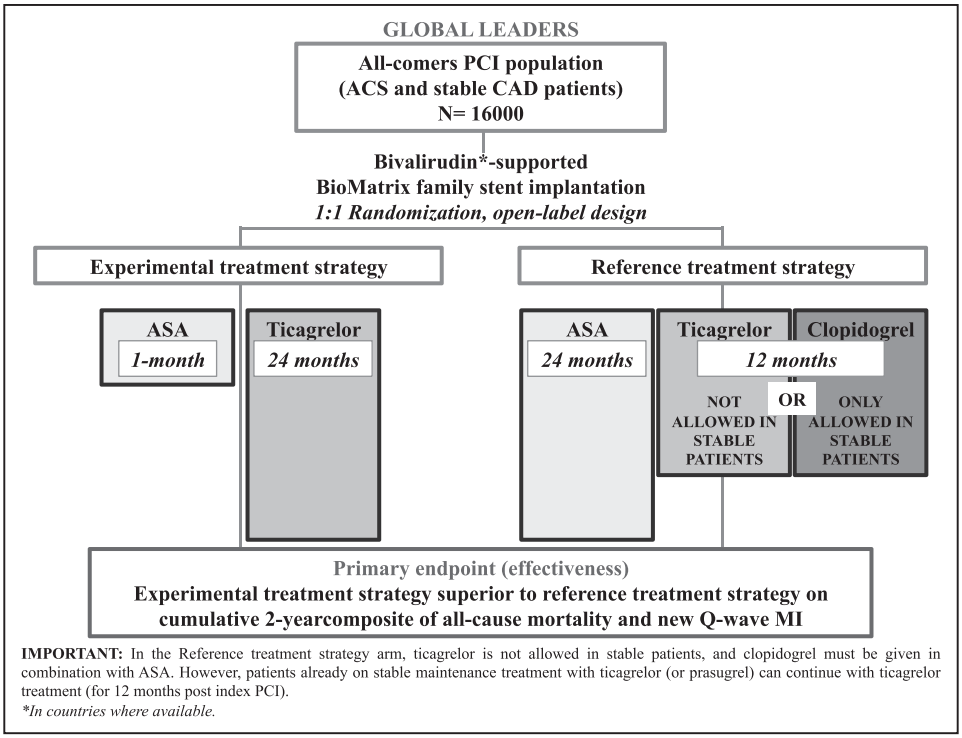

Figure 3. Design of the GLOBAL LEADERS trial.
Illustration of the study diagram of the GLOBAL LEADERS trial. Adapted from Figure 1 of Vranckx et al[97] with permission of the publisher. Copyright © 2016, Europa Digital & Publishing. ACS indicates acute coronary syndromes; ASA, aspirin; CAD, coronary artery disease; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

clinical events and major bleeding at 1 year after the procedure (Table 4).

Following the encouraging results of a 2.5 mg twice daily rivaroxaban regimen added to aspirin and clopidogrel,[20] the COMPASS (Rivaroxaban for the Prevention of MACE in Coronary or Peripheral Artery Disease; NCT01776424) is recruiting (from February 2013 to March 2018) 27 400 patients with coronary or peripheral artery disease randomly allocated to rivaroxaban and aspirin or rivaroxaban alone in comparison with aspirin monotherapy for the prevention of recurrent ischemic events, stroke, or cardiovascular death. The primary

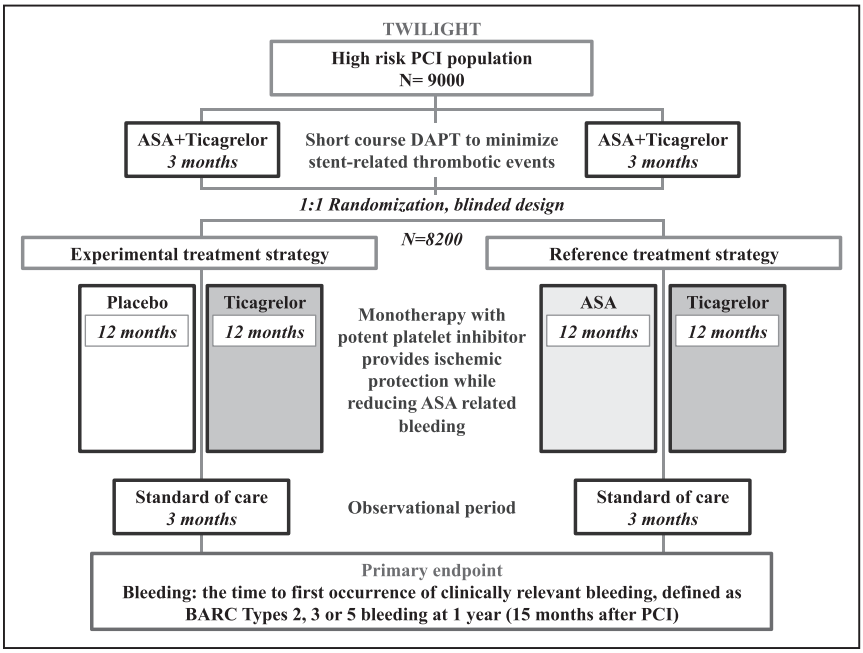

Figure 4. Design of the TWILIGHT trial.
Illustration of the study diagram of the TWILIGHT trial. ASA indicates aspirin; BARC, Bleeding Academic Research Consortium; DAPT, dual-antiplatelet therapy; and PCI, percutaneous coronary intervention.

efficacy end point is the occurrence of MI, stroke, or cardiovascular death at 5 years, and the occurrence of major bleeding is the primary safety end point. On the other hand, the GEMINI-ACS1 trial (A Study to Compare the Safety of Rivaroxaban Versus Acetylsalicylic Acid in Addition to Either Clopidogrel or Ticagrelor in Participants With Acute Coronary Syncrome; NCT02293395) is a phase II prospective, randomized, double-dummy, double-blind, active-controlled trial testing the safety of dual-antithrombotic therapy (rivaroxaban 2.5 mg twice daily plus $P2Y_{12}$ inhibitor) in comparison with DAPT (aspirin 100 mg plus $P2Y_{12}$ inhibitor) within 10 days of an ACS event in 3000 patients.[99] Patients will be randomly assigned in a 1:1 ratio stratified by intended $P2Y_{12}$ inhibitor use (clopidogrel 75 mg daily or ticagrelor 90 mg twice daily), with 1500 patients expected in each $P2Y_{12}$ inhibitor strata. The primary end point is TIMI clinically significant bleeding (major, minor, or requiring medical attention). The exploratory efficacy determination will be a composite of cardiovascular death, MI, ischemic stroke, and ST.

Similar to PCI setting, ASA alternatives are also being explored in patients undergoing transcatheter aortic valve implantation (ie, GALILEO, ATLANTIS, and POPULAR-TAVI trials), in whom the balance between ischemic and bleeding risks may be more challenging because of advanced age and comorbidities.[100]

CONCLUSION

Single-antiplatelet therapy with $P2Y_{12}$ inhibitors is being explored as a potential alternative to a DAPT regimen after ACS or coronary stent implantation, and a potentially more effective long-term treatment than aspirin monotherapy, as well. Given the well-established role of aspirin as a secondary prevention medication, its widespread availability and affordability, aspirin should remain a critical antithrombotic compound in patients with established coronary or cardiovascular disorders. However, as the availability of newer, potentially safer and more effective antiplatelet or antithrombotic agents increases, the quest for the ideal long-term secondary prevention medication mandates reappraising the value of aspirin, an historical antiplatelet agent whose efficacy was proven largely versus placebo in the setting of studies that appear largely outdated in comparison with contemporary cardiovascular practice.

The optimal duration of a DAPT regimen post-ACS or stent implantation remains unresolved and is most likely variable from patient to patient. The results of ongoing trials appraising the value of dropping aspirin in favor of $P2Y_{12}$ inhibitor monotherapy will soon shed new light on the less-is-more approach for long-term secondary prevention.

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AFFILIATIONS

From Department of Cardiology, Bern University Hospital, University of Bern, Switzerland (G.G., S.W., M.V.); Department of Advanced Biomedical Sciences, Federico II University of Naples, Italy (G.G.); Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Belgium (P.V.); Division of Cardiology, Beth Israel Deaconess Medical Center, Boston, MA (C.M.G.); The Zena and Michael A Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY (R.M.); and Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands (M.V.).

FOOTNOTES

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