Cardiovascular Drugs and Therapy (2019) 33:711–724
https://doi.org/10.1007/s10557-019-06916-7

REVIEW ARTICLE

Omitting aspirin in PCI patients: Myth or reality?

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Published online: 6 December 2019

Abstract

In the current era of percutaneous coronary intervention (PCI), with the use of contemporary drug-eluting stents, refined techniques, and adjunctive pharmacotherapy, the role of aspirin peri-PCI remains undisputable. Beyond the initial period, dual antiplatelet therapy (DAPT) consisting of aspirin and a $P2Y_{12}$ receptor inhibitor for 6 months in stable coronary artery disease and 12 months in acute coronary syndromes is the standard of care. However, concerns regarding bleeding adverse events caused by aspirin have led to shortened DAPT duration or even omission of aspirin. Aspirin free-strategies have been increasingly encountered in several studies and showed a significant reduction in bleeding events, without any sign of increased ischemic risk. Individualization of DAPT duration particularly in high bleeding risk patients appears therefore mandatory, making aspirin not necessary in several cases. Moreover, recent randomized trials have shed light on how to treat PCI patients in the presence of concomitant anticoagulant treatment with $P2Y_{12}$ monotherapy and excluding aspirin. These aspirin-free strategies have been proved safer than the "older" standard triple antithrombotic treatment, without compromising safety. Ongoing studies may further dispel the myths and establish real facts regarding post-PCI-tailored treatment with or without aspirin.

Keywords Aspirin · Percutaneous coronary intervention · Anticoagulation · Dual antiplatelet therapy

Introduction

Aspirin is considered the cornerstone of pharmacological therapies for cardiovascular atherothrombotic disease. In patients undergoing percutaneous coronary intervention (PCI) with stent implantation, peri-procedural aspirin and $P2Y_{12}$ receptor inhibitor administration is mandatory and constitutes the so-called dual antiplatelet therapy (DAPT) [1]. Afterwards, DAPT is recommended for duration of 6 months in patients with stable coronary artery disease (CAD) and for 12 months in patients with an acute coronary syndrome (ACS) [2, 3].

However, concerns regarding accompanying bleeding adverse events have led to shortened DAPT duration and adoption of a single antiplatelet treatment (SAPT) in different clinical scenarios [4, 5]. This is a particular issue in patients in whom bleeding risk prevails ischemic risk, as SAPT reduces the number of bleeding hazards, while providing comparable to DAPT antithrombotic protection. A SAPT could be either a $P2Y_{12}$ receptor inhibitor-omitting or an aspirin-omitting therapy. Issues like those of aspirin resistance or aspirin allergy may impact on the choice of antiplatelet agent post-PCI. Furthermore, recent understanding that DAPT concomitant with anticoagulant drugs (known as triple antithrombotic therapy) greatly enhances the bleeding risk compared with dual antithrombotic therapy, has led investigators to study strategies of reduced antithrombotic intensity, mainly by omitting aspirin [6–10]. Dual antithrombotic therapy without aspirin has been recently suggested as the default strategy for most atrial fibrillation patients undergoing PCI [11, 12]. The role of aspirin peri- and post-PCI, and scenarios for aspirin omission in PCI patients in the current era, are the focus of this review.

Aspirin Peri-PCI

Several early studies of patients with coronary stent implantation established aspirin as an essential component of peri-PCI pharmacotherapy together with a $P2Y_{12}$ receptor inhibitor

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[13–15]. More recently, the value of peri-PCI aspirin has been indirectly demonstrated. Among 65,175 patients undergoing PCI from January 2010 to December 2011 at 44 hospitals in Michigan, 4640 (7.1%) did not receive aspirin within 24 h prior to PCI. A history of gastrointestinal bleeding, cardiogenic shock, or post-cardiac arrest predicted absence of aspirin treatment. In propensity-matched analysis, a higher rate of death and stroke was observed in non-aspirin group vs those pre-treated with aspirin, 3.9% vs. 2.8%, odds ratio (OR), 95% confidence interval (CI) 1.89 (1.32–2.71), $p < 0.001$, and 0.5% vs. 0.1%, OR (95%CI) 4.24 (1.49–12.11), $p = 0.007$, respectively [16]. In another study in patients on 100-mg daily aspirin, the addition of a 1000-mg bolus aspirin 1 day prior to PCI reduced the platelet activation state before and after intervention [17]. In patients also on chronic low dose aspirin undergoing elective PCI, 325-mg loading dose of aspirin prior to PCI attenuated the increase in serum thromboxane B2 and improved reperfusion and myocardial injury indices [18]. Overall, current evidence supports the catholic use of aspirin peri-PCI.

Aspirin for Secondary Prevention in Post-PCI Patients-Guidelines Recommendations

Meta-analyses by the Antithrombotic Trialists' Collaboration have established the role of aspirin for secondary prevention by describing significant absolute reductions in the risk of having a serious vascular event by 36 per 1000 for 2 years among patients with previous MI and by 38 per 1000 patients treated for 1 month among patients with acute MI [19, 20]. Although the usefulness of aspirin following PCI in patients with stent implantation was not assessed in the above meta-analyses, practice guidelines are based on them and suggest post-PCI with class IA recommendation the life-long treatment with aspirin [1] or SAPT, usually aspirin [3].

DAPT Discontinuation Post-PCI—The Role of Aspirin Removal

Post-PCI antiplatelet therapy discontinuation has been for long associated with stent thrombosis and ischemic events. Discontinuation may take the form of treatment with aspirin alone, treatment with $P2Y_{12}$ receptor inhibitor alone or both antiplatelet agents' discontinuation. In the era of the first generation drug-eluting stents (DES), DAPT discontinuation was evaluated up to 5 years in 12,812 patients undergoing sirolimus-eluting stents implantation in the j-Cypher registry [21]. Discontinuation of both thienopyridine and aspirin was associated with an increased incidence of late and very late stent thrombosis up to 5 years post-PCI. However, patients who discontinued either $P2Y_{12}$ receptor inhibitor only or aspirin only did not have an excess of stent thrombosis in any of the study time intervals. In the CREDO-Kyoto Registry Cohort-2 among 10,470 patients undergoing PCI either with bare metal stents only ($N = 5392$) or sirolimus-eluting stents only ($N = 5078$), adverse events were linked to the antiplatelet status just 1-day before the events. Discontinuation of both aspirin and thienopyridines was associated with increased risk for serious cardiovascular events including stent thrombosis, MI and stroke beyond 1-month after coronary stenting. A SAPT was not associated with higher risk for serious adverse events compared with DAPT, except for a marginally higher risk for stent thrombosis in the sirolimus eluting stent group. However, the thienopyridine-only, without aspirin group, was small-sized consisting of 2.9–3.4% of the 5078 patients [22]. The above studies may mitigate the need of aspirin post-PCI in the DES era, as soon as a $P2Y_{12}$ receptor inhibitor is maintained.

Aspirin Resistance

Indirect evidence on the role of aspirin discontinuation post-PCI may be obtained by outcome studies in patients with aspirin resistance. Although the correlation between high on-clopidogrel treatment platelet reactivity and clinical outcome is well established, data for high on-aspirin treatment platelet reactivity are conflicting. In the Intracoronary Stenting and Antithrombotic Regimen-ASpirin and Platelet Inhibition (ISAR-ASPI) registry and among 7090 consecutive PCI patients pre-treated with aspirin (intravenous dose of 500 mg) and $P2Y_{12}$ receptor inhibitor, on-aspirin treatment platelet aggregation was measured immediately before PCI by a multiplate analyzer (Roche Diagnostics, Basel, Switzerland) [23]. Arachidonic acid–induced platelet aggregation > 203AU X min was observed in the upper quintile of patients and was considered as index of aspirin resistance. Patients with aspirin resistance showed a significantly higher risk of death or stent thrombosis at 1 year, compared with the no-resistance group, 6.2% vs. 3.7%, respectively, OR (95%CI) 1.78 (1.39–2.27), $p < 0.0001$. Aspirin resistance independently predicted the composite of death from any cause or stent thrombosis at 1 year with adjusted hazard ratio (HR) (95% CI) 1.46 (1.12–1.89), $p = 0.005$. However, results in the opposite direction have been obtained in the Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents (ADAPT-DES) prospective multicenter registry involving 8583 patients with DES implantation, where high platelet reactivity on aspirin, defined as > 550 ARU by VerifyNow (Accumetrics, San Diego, CA, USA) was determined at a mean time of 20.3 ± 8.3 h after PCI [24]. High platelet reactivity on aspirin, which was observed in 478 (5.6%) patients, was not significantly associated with stent thrombosis, MI, or death at 1 year [adjusted HR (95% CI) 1.46 (0.58–3.64), 0.81 (0.46–1.42), 1.42 (0.83–2.43), respectively] but was inversely related to bleeding, 0.65 (0.43–0.99), $p = 0.04$. In patients on aspirin monotherapy between years 1 and 2, aspirin hyporesponsiveness was not associated

with adverse outcomes [25]. The role of aspirin resistance in the DES era and in $P2Y_{12}$ receptor inhibitor–treated patients appears therefore rather limited.

Clinical Scenarios for Aspirin-Free Strategies

Aspirin Hypersensitivity in Patients Undergoing PCI

In everyday practice in patients undergoing PCI, several clinical scenarios may arise where omitting or withdrawal of aspirin may be considered (Fig. 1), with aspirin hypersensitivity being one of them. The prevalence of aspirin hypersensitivity ranges from 0.07 to 0.2% for aspirin-induced urticaria in the general population, to 10% for aspirin-exacerbated respiratory tract disease in patients with asthma. The diagnosis is based mainly on history with little use of biological tests [26, 27]. Provocation tests can be potentially dangerous, are best avoided and therefore a careful and comprehensive clinical history is paramount. Potential treatment options for aspirin hypersensitivity in patients undergoing PCI include desensitization or omission of aspirin and use of a SAPT with a $P2Y_{12}$ receptor inhibitor like clopidogrel, prasugrel, or ticagrelor [26, 28, 29]. In a recent, retrospective analysis of 70 patients (representing 0.3% of the total PCI population during a 10-year period) who were discharged without aspirin because of aspirin intolerance/hypersensitivity/allergy, 46 (65.7%) were treated with clopidogrel and 24 (34.3%) with new $P2Y_{12}$ receptor inhibitors [30]. Patient-oriented composite endpoints at 12 months occurred in 25.7% of patients. No significant differences were found between patients treated with clopidogrel monotherapy and new $P2Y_{12}$ receptor inhibitors monotherapy, except for target lesion revascularization (TVR, 9 vs 0, $p = 0.02$). In another case series, 12 stented patients with aspirin hypersensitivity were discharged with ticagrelor monotherapy [31]. During 6-month follow-up 11 (92%) of patients had neither ischemic nor bleeding events, suggesting that ticagrelor monotherapy could be a viable option for patients who cannot tolerate aspirin. Therefore, if aspirin desensitization is not performed or is ineffective, aspirin could be omitted, and a $P2Y_{12}$ receptor inhibitor alone could be used instead, preferably prasugrel or ticagrelor to avoid the pitfall of commonly observed clopidogrel resistance.

Aspirin Discontinuation Post-PCI Following a Very-Short (1–3 months) Period of DAPT

Post-PCI aspirin administration in the context of DAPT is not without concerns, raising the issue of the value of aspirin-free strategies in this clinical scenario. The rationale behind these strategies appears to be multifactorial. Bleeding adverse effects, in the form of intracranial and major extracranial bleeding events, mostly gastrointestinal, may accompany the use of aspirin. This is especially true if aspirin is co-administered with other antiplatelet agents (which is by default the case in DAPT), non-steroidal anti-inflammatory drugs, and in patients with the history of peptic ulcer. Intensive contemporary secondary prevention measures like controlling blood

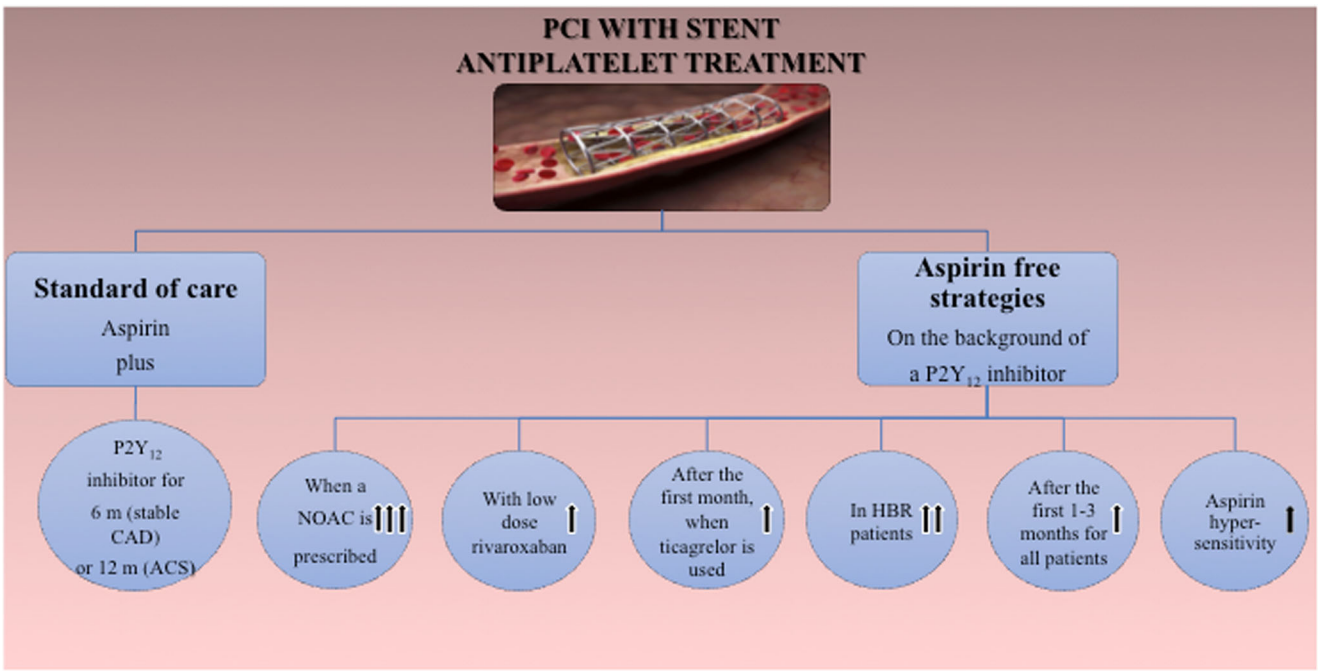

Fig. 1 Antiplatelet treatment in patients undergoing PCI with stent implantation—aspirin-free strategies

pressure, lipid profiles, blood glucose levels, and use of beta blockers have also challenged the pivotal role of aspirin especially in the prevention of cardiovascular events post-PCI [4, 5]. Furthermore, the refinements in DES technology has led to shorter DES re-endothelialization time, thinner struts, and the use of stents with biodegradable polymer or polymer-free stents thereby support the clinical use of shorter DAPT durations [32–34]. The introduction of novel generation $P2Y_{12}$ receptor inhibitors such as prasugrel and ticagrelor, which are associated with more potent and consistent pharmacodynamic effect and improved clinical outcomes compared with clopidogrel, may have degraded the role of aspirin. In vitro examination of individual and combined effects of aspirin and $P2Y_{12}$ receptor antagonism showed that a potent $P2Y_{12}$ receptor blockade alone is able to inhibit thromboxane A2–dependent pathways of platelet activation with little additional inhibition provided by aspirin [35]. This has led to the speculation that $P2Y_{12}$ inhibitor monotherapy may maintain antiischemic efficacy while reducing the bleeding risk, compared with DAPT [5]. Other investigators, however, suggest that pharmacological rational for treating ACS patients with a $P2Y_{12}$ receptor inhibitor only is missing [36].

Several recently published or ongoing trials lighten the issue of aspirin discontinuation post-PCI following a very-short (1–3 months) period of DAPT (Table 1). The ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 (STOPDAPT-2) was a randomized controlled trial to determine whether a short DAPT regimen (1 month) followed by clopidogrel monotherapy was non-inferior to the standard 12-month DAPT therapy after implantation of a cobalt-chromium DES [37]. Regarding the primary endpoint of clinically significant bleeding and cardiovascular events (composite of cardiovascular death, MI, definite stent thrombosis, stroke, or thrombolysis in myocardial infarction (TIMI) major/minor bleeding) at 1 year non-inferiority was met for the short DAPT over standard DAPT strategy with absolute difference, − 1.34% (95%CI, − 2.57% to − 0.11%), relative 50% non-inferiority margin and $p < 0.001$. A short DAPT was also superior over standard DAPT strategy, $p = 0.04$. TIMI major/minor bleeding was greatly reduced in patients who received treatment with clopidogrel monotherapy after 1 month of DAPT (1-month group 0.4% vs. 12-month group 1.5%, log rank $p = 0.002$; HR (95% CI) 0.26 (0.11–0.64), p superiority = 0.004). It is worth noting that intravascular imaging of the final angioplasty result after the implantation of stent was almost uniform, (97% in 1-month group, 98% in 12-month group). Overall, the observed benefit was driven by a highly significant reduction in bleeding events without increase in ischemic events.

The comparison between $P2Y_{12}$ antagonist monotherapy and dual antiplatelet therapy after DES (SMART-CHOICE) trial was a prospective, open-label study, which compared the $P2Y_{12}$ inhibitor monotherapy with the standard DAPT therapy in a broad spectrum of patients undergoing PCI with current generation DES and receiving DAPT at least for 3 months [38]. For the primary endpoint (all-cause mortality, MI, and cerebrovascular events) at a mean of 12 months, the $P2Y_{12}$ inhibitor monotherapy after 3 months DAPT was non-inferior to 12-month DAPT: 3-month group 2.9% vs. 12-month group 2.5%; difference, 0.4% (1-sided 95%CI, – ∞% to 1.3%), non-inferiority margin 1.8% and $p = 0.007$. The rate of major cardiovascular events (defined as MI, stent thrombosis, cardiac death) did not differ across strategies. There was a reduction in bleeding BARC type 2–5 with short-duration DAPT and then $P2Y_{12}$ monotherapy, 2.0% vs. 3.4%, HR (95%CI) 0.58 (0.36–0.92), $p = 0.02$. It is notable that in the $P2Y_{12}$ monotherapy group clopidogrel was used in 76.9% and prasugrel/ ticagrelor in 23.1% of patients, while approximately 10% of patients were still on aspirin at 12 months.

In the comparative effectiveness of 1 month of ticagrelor plus aspirin followed by ticagrelor monotherapy versus a current-day intensive DAPT in all-comers patients undergoing PCI with bivalirudin and BioMatrix family DES use (GLOBAL LEADERS) study, patients were randomized to aspirin 75–100 mg plus ticagrelor 90 mg bid for 1 month, followed by 23 months of ticagrelor monotherapy, or standard DAPT with aspirin 75–100 mg plus either clopidogrel 75 mg od (for stable CAD patients) or ticagrelor 90 mg bid (for ACS patients) for 12 months, followed by aspirin monotherapy for 12 months [39]. The primary endpoint (a composite of all-cause mortality or non-fatal new Q-wave MI) rate at 2 years was 3.81% vs 4.37% in the experimental group vs standard DAPT group, respectively with rate ratio (95%CI) 0.87 (0.75–1.01), $p = 0.073$. BARC 3 or 5 bleeding events occurred in 2.04% of patients treated with aspirin for 1 month and extended ticagrelor and 2.12% of patients treated with conventional DAPT with rate ratio (95%CI) 0.97 (0.78–1.20), $p = 0.77$. Notably, a pre-specified landmark analysis at 1 year revealed a significant reduction of the primary endpoint rate in the experimental group (1.95%) vs the reference group (2.47%), with risk ratio (95% CI) 0.79 (0.64–0.98), $p = 0.028$. From 1 to 2 years, primary endpoints occurred in 1.89% vs 1.95% of patients in the experimental and the reference groups, respectively, with a risk ratio 0.97 (0.77–1.22), $p = 0.79$. LEADERS is the largest trial so far testing 1-month of DAPT versus a more prolonged DAPT after DES implantation and is a negative trial as it was designed as a superiority trial hypothesizing that ticagrelor monotherapy could improve outcomes over conventional DAPT. Although the trial was not designed as a non-inferiority trial, there was no safety signal of the experimental strategy. In addition, a higher non-adherence rate to ticagrelor monotherapy was observed in the second year of the study, which may have contributed to study and aforementioned landmark analysis results. Furthermore, as suggested by a non-prespecified subanalysis of GLOBAL LEADERS according to the complexity of PCI, ticagrelor monotherapy

Table 1 Aspirin discontinuation post-PCI following a very-short (1–3 months) period of DAPT

Study	STOPDAPT-2 [37]	SMART-CHOICE [38]	GLOBAL LEADERS [39]
Year	2019	2019	2019
Design	RCT, open label	RCT, open label	RCT, open label
Size (n)	3009	2993	15,968
Comparison	-DAPT for 1 month followed by clopidogrel for 59 months -DAPT for 12 months followed by aspirin for 48 months	-DAPT for 3 months followed by $P2Y_{12}$ inhibitor monotherapy -DAPT for 12 months	-1 month of aspirin plus ticagrelor followed by ticagrelor monotherapy for 23 months (experimental group) -1 year of DAPT followed by 1 year of aspirin monotherapy (control group)
Hypothesis	-Non-inferiority of 1-month DAPT to 12-month DAPT for the primary endpoint at 1-year.	-Non-inferiority of 3-month DAPT to 12-month DAPT for the primary endpoint at 1-year.	-Superiority of the experimental over control strategy for the primary endpoint at 2 years.
Exclusion criteria	-Oral anticoagulants; prior intracranial hemorrhage; serious complications (MI, stroke, and major bleeding) during hospital stay after PCI; DES other than cobalt chromium everolimus eluting stents	-Active bleeding; DES implantation within 12 months; contraindication to study medication	-Intolerance to aspirin or ticagrelor; use of fibrinolytic therapy within 24 h of PCI; Need for anticoagulation; known overt major bleeding; prior intracranial hemorrhage; stroke within last 30 days.
Primary endpoint	-Composite of cardiovascular death, MI, definite stent thrombosis, stroke, TIMI major/minor bleeding	-Composite of death, MI, stroke	-Composite of death or non-fatal Q wave MI
Secondary endpoints	-Ischemic composite endpoint -Bleeding composite endpoint	-Individual components of the primary endpoints; cardiac death; stent thrombosis, bleeding BARC 2–5; net adverse clinical and cerebral events.	-Individual components of the primary endpoint; a composite endpoint of death, new Q-wave MI, or stroke; MI; stroke; target vessel or any revascularization; stent thrombosis Bleeding BARC 3 or 5
Follow up	59 months	12 months	24 months
Results	-Primary endpoint 2.4% in the 1-month DAPT group vs 3.7% in the 12-month DAPT group at 1 year, absolute difference, − 1.34% (95%CI, − 2.57% to − 0.11%), *p* non-inferiority < 0.001, *p* superiority 0.04. -Secondary endpoints: ischemic composite endpoint at 1 year: 2.0% in the 1-month DAPT group vs 2.5% in 12-month DAPT group, *p* non-inferiority = 0.005 bleeding composite endpoint at 1 year 0.4% in the 1-month DAPT group vs 1.5% in the 12-month DAPT group, HR (95%CI) 0.26 (0.11–0.64), *p* superiority = 0.004.	-Primary endpoint 2.9% vs. 2.5%, for 3 months vs. 12 months of DAPT, at 12 months, difference, 0.4% (1-sided 95%CI, – ∞% to 1.3%), p non-inferiority = 0.007; -Secondary endpoints all-cause death 1.4% vs. 1.2% *p* = 0.61; MI 0.8% vs 1.2% *p* = 0.28 -Bleeding BARC 2–5 2.0% vs 3.4%, HR (95%CI) 0.58 (0.36–0.92), *p* = 0.02.	-xPrimary endpoint 3.8% in the experimental group vs 4.4% in the control group, rate ratio (95%CIs) 0.87(0.75–1.01), *p* = 0. 073. Secondary endpoints: all-cause mortality: 2.8% in the experimental group vs. 3.2% in the control group (*p* = 0.18); Q wave MI: 1.0% in the experimental group vs. 1.3% in the control group (*p* = 0.14); Bleeding BARC grade 3 or 5: 2.0% in the experimental group vs. 2.1% in the control group, *p* = 0.77
Study	**GLASSY** (41, 42)	**TWILIGHT** (43)	**TICO** (44)
Year	2019	2019	2019
Design	Sub-study of GLOBAL LEADERS	RCT, double blind aspirin and matching placebo	RCT, open label
Size (n)	7585	9000	
Comparison		Ticagrelor plus aspirin for 3 months followed by - Ticagrelor monotherapy for an additional 12 months or	-Ticagrelor monotherapy after 3-month DAPT -12-month ticagrelor plus aspirin group

Table 1 (continued)

Study	STOPDAPT-2 [37]	SMART-CHOICE [38]	GLOBAL LEADERS [39]
		-Ticagrelor plus aspirin for 12 months	
Hypothesis	Efficacy: Non-inferiority of the experimental over control strategy for the primary endpoint at 2 years Safety: Superiority of the experimental over control strategy for the primary endpoint at 2 years	Ticagrelor monotherapy is superior regarding the primary endpoint of BARC type 2, 3, or 5, while maintaining non-inferiority for ischemic events compared with ticagrelor plus aspirin	Ticagrelor monotherapy following 3-month DAPT is superior to 12-month ticagrelor plus aspirin
Exclusion criteria		Intolerance to aspirin or ticagrelor; need for anticoagulation; prior stroke; active bleeding or extreme risk for major bleeding; fibrinolytic therapy within 24 hours of PCI.	Age > 80 years; Increased risk of bleeding (prior hemorragic stroke, ischemic stroke within a year, active bleeding, bleeding diathesis); need for oral anticoagulation therapy; Increased risk of bradycardia-related symptoms.
Primary endpoint	Efficacy: death, MI, stroke, or urgent TVR Safety: BARC grade 3 or 5 bleeding	BARC grades 2, 3 or 5 bleeding.	Net adverse cardiovasular events (a composite of death, MI, stent thrombosis, stroke, TVR and TIMI major bleeding.
Secondary endpoints		Death, non-fatal MI or stroke	Each component of primary endpoint
Follow up		15 months	12 months
Results	-Primary efficacy endpoint: 7.1% in the experimental group vs. 8.4% in the control group, RR (95% CI) 0.85(0.72–0.99), $p < 0.001$ for non-inferiority -Safety endpoint: 2.5% in both groups ($p = 0.99$)	N/A	N/A

BARC, bleeding academic research consortium; *CI*, confidence interval; *DAPT*, dual antiplatelet therapy; *DES*, drug eluting stents; *HR*, hazard ratio; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *RCT*, randomized controlled trial; *TIMI*, thrombolysis in myocardial infarction, *TVR*, target vessel revascularization

following 1-month DAPT was associated with a significantly lower risk of death/Q-wave MI with similar risk of BARC type 3 or 5 bleeding, thereby achieving a significant net clinical benefit, in patients with, but not in those without complex PCI [40].

The GLOBAL LEADERS Adjudication Sub-StudY (GLASSY) is a sub-study of the GLOBAL LEADERS study having randomized 7585 patients, (47.4% of the overall trial), in order to assess whether 23-month ticagrelor monotherapy after 1-month DAPT is non-inferior to a standard DAPT for 12 months followed by aspirin monotherapy for the primary efficacy endpoint of death, non-fatal MI, non-fatal stroke, or urgent TVR, and superior for the primary safety endpoint of BARC type 3 or 5 bleeding [41, 42]. At 2 years, the ticagrelor monotherapy strategy was non-inferior to conventional DAPT (7.14% vs 8.41%, relative risk (RR) (95%CI) 0.85 (0.72–0.99), $p < 0.001$ for non-inferiority) for the efficacy endpoint. Bleeding events BARC 3 or 5 were identical in the two study groups (2.46%). Overall, GLASSY results suggest that discontinuation of aspirin after 30 days while continuing ticagrelor alone does not expose patients to a higher ischemic risk, as compared with a standard DAPT for 1 year.

Ongoing studies are expected to further contribute in the field of aspirin withdrawal post-PCI. The ticagrelor with aspirin or alone in high-risk patients after coronary intervention (TWILIGHT) trial (NCT02270242) is a double-blind placebo-controlled trial, which—following 3-month treatment with ticagrelor and aspirin—evaluates the comparative efficacy and safety of antiplatelet monotherapy with ticagrelor versus DAPT consisting of ticagrelor and aspirin, in up to 9000 high-risk patients undergoing PCI with DES. The primary hypothesis is that a strategy of ticagrelor monotherapy will be superior with respect to the primary endpoint of BARC type 2, 3, or 5, while maintaining non-inferiority for ischemic events compared with ticagrelor plus aspirin. Results are expected in the second quarter of 2019 [43]. The ticagrelor monotherapy after 3 months in the patients treated with new generation sirolimus stent for acute coronary syndrome (TICO study) (NCT02494895) is another randomized open-label trial in ACS patients treated with ultrathin bioresorbable polymer sirolimus–eluting stents, which evaluates whether ticagrelor monotherapy following 3-month DAPT is superior to 12-month ticagrelor plus aspirin. The primary endpoint is net adverse cardiovascular events (a composite of all-cause death, MI, stent thrombosis, stroke, and TVR and TIMI major bleeding) at 12-month post-PCI [44].

Aspirin Replacement with an Anticoagulant

An aspirin-free strategy has also been tested in ACS patients by replacing aspirin with an anticoagulant in the background of treatment with a $P2Y_{12}$ receptor inhibitor [45]. In the study to compare the safety of rivaroxaban versus acetylsalicylic acid in addition to either clopidogrel or ticagrelor in participants with ACS (GEMINI-ACS 1) trial, 3037 patients (87% with a PCI at index event) were randomized double-blindly, after having been started on DAPT (aspirin and $P2Y_{12}$ receptor inhibitor) 1-10 days following an ACS, to either continuing aspirin 100 mg/day or to rivaroxaban 2.5 mg bid on top of pre-randomization $P2Y_{12}$ receptor inhibitor. The low dose of rivaroxaban arm had a similar risk of TIMI non-CABG clinically significant bleeding up to day 390 compared with the aspirin arm, 5% vs 5% with HR (95% CI) 1.09 (0.80–1.50), $p = 0.584$. The efficacy and safety of this dual pathway antithrombotic regimen, not-involving aspirin, is worth of further investigation.

Aspirin-Free Strategies in Patients Treated with Anticoagulants

In patients with an indication for anticoagulation, most commonly atrial fibrillation men with CHA_2DS_2-VASc score ≥ 1 (congestive heart failure, hypertension, age ≥ 75 [2 points], diabetes mellitus, prior stroke or transient ischemic attack [2 points], vascular disease, age 65–74, sex category female) and women with atrial fibrillation and CHA_2DS_2-VASc score ≥ 2, and concomitant need of DAPT because of recent PCI with stent implantation, the triple antithrombotic therapy has been considered for years us unavoidable. However, the understanding in recent years of the greatly increased bleeding potential of such a strategy has led to attempts of diminishing the intensity of the antithrombotic therapy and studying aspirin-free strategies (Table 2).

The What is the Optimal antiplatElet and anticoagulation therapy in patients with oral anticoagulation and coronary StenTing (WOEST) trial, an open-label, randomized, controlled trial of 573 patients, was the first to study the safety of omitting aspirin from the "standard" triple scheme [6]. After 1-year follow-up, any bleeding occurred in 19.4% patients in the dual therapy group and in 44.4% of patients in the triple therapy group, HR (95% CI) 0.36 (0.26–0.50), $p < 0.0001$. Patients in the aspirin-free group also experienced significantly lower risk of the composite secondary endpoint (death, MI, stroke, TVR, and stent thrombosis) with HR (95%CI) 0.60 0.38–0.94, $p = 0.025$.

The 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 (PIONEER AF-PCI) trial enrolled 2124 patients with non-valvular atrial fibrillation who required stent implantation [7]. Patients were randomized in three groups: an aspirin-free strategy consisting of rivaroxaban 15 mg od (or 10 mg for those with moderate renal impairment) plus $P2Y_{12}$ receptor inhibitor for 12 months, low-dose rivaroxaban 2.5 mg bid plus DAPT for 1, 6, or 12 months and standard triple

Table 2 Randomized clinical trials comparing dual versus triple antithrombotic therapy

Study	WOEST [6]	PIONEER AF PCI [7]	REDUAL PCI [9]
Year	2013	2016	2017
Design	RCT, open label	RCT, open label	RCT, open label
Size (*n*)	573	2124	2725
AF (%)	70	100	100
ACS (%)	27	52	51
PCI (%)	100	100	100
DES (%)	64	68	83
Comparison	-Double therapy: clopidogrel 75 mg od for 1–12 months plus OAC -Triple therapy: aspirin 80–100 mg od plus clopidogrel 75 mg od for 1–12 months plus OAC	-Group 1: rivaroxaban 15 mg od plus a $P2Y_{12}$ inhibitor for 12 months -Group 2: rivaroxaban 2.5 mg bid plus DAPT for 1, 6, or 12 months -Group 3:Warfarin plus DAPT for 1, 6, or 12 months	-Dabigatran (110 mg or 150 mg bid) plus clopidogrel or ticagrelor -Dose-adjusted VKA plus DAPT (TAT group)
Exclusion criteria	History of intracranial bleeding; cardiogenic shock; contraindication to aspirin, clopidogrel, or both; peptic ulcer in previous 6 months; thrombocytopenia; major TIMI bleed in previous 12 months; age > 80	History of stroke or TIA; history of intracranial hemorrhage; clinically significant gastrointestinal bleeding within 1 year prior to index hospitalization; CrCl < 30 mL/min; Hgb < 10 g/dL; any condition increasing the risk of bleeding	Bioprosthetic/mechanical heart valves; gastrointestinal or other major bleeding, stroke, or major surgery within 1 month prior to screening; Anemia or thrombocytopenia; severe renal insufficiency; conditions leading to increased risk of bleeding
Primary endpoint	All bleeding episodes	Clinically significant bleeding (composite of major and minor TIMI bleeding)	Major or clinically relevant non-major bleeding
Secondary endpoints	Death, MI, stroke, target vessel revascularization and stent thrombosis	Cardiovascular death, MI, stroke, stent thrombosis and major bleeding	Death, MI, stroke, systemic embolism, revascularization, stent thrombosis
Follow up	12 months	12 months	14 months
Results	-Primary endpoint: Double therapy 19.4% vs triple therapy 44.4%, HR (95%CI) 0.36 (0.26–0.50), $p < 0.0001$). -Secondary endpoint double therapy 11.1% vs triple therapy HR (95%CI) 17.6% (0.38–0.94), $p = 0.025$	-Primary endpoint: 16.8% in group 1, 18.0% in group 2, 26.7% in group 3 HR group 1 vs group 3 (95%CI) 0.59 (0.47–0.76) HR for group 2 vs group 3, (95%CI) 0.63 (0.50–0.80). -Secondary endpoint 6.5% in group 1, 5.6% in group 2 and 6.0% in group 3	-Primary endpoint: 15.4% in the 110 mg dabigatran group and 26.9% in the TAT group HR (95%CI) 0.52 (0.42-0.63); 20.2% in the 150 mg dabigatran group and 25.7% in the TAT group HR (95%CI) 0.72 (0.58–0.88). -Secondary endpoint 13.7% in combined dabigatran groups and 13.4% in TAT groups
Comments	-Not powered for efficacy -30% other indications than AF -Small number of patients	-Not powered for efficacy -Not-approved rivaroxaban dose for stroke prevention	-Not powered for efficacy -Increase in MI and stent thrombosis in the dabigatran 110 mg group
Study	**AUGUSTUS** [10]	**ENTRUST-AF PCI** [46]	
Year	2019	2019	
Design	RCT, open label, 2 by 2 factorial	RCT, open label	
Size (n)	4614	1506	
AF (%)	100	100	
ACS (%)	61	51	
PCI (%) DES (%)	76.2	100	

Table 2 (continued)

Study	WOEST [6]	PIONEER AF PCI [7]	REDUAL PCI [9]
Comparison	On the background of $P2Y_{12}$ inhibitor: -First randomization, apixaban 5 mg bid (or 2.5 mg bid) vs VKA -Second randomization, aspirin 81 mg vs matching placebo	-Edoxaban 60 mg od* plus $P2Y_{12}$ inhibitor -TAT: warfarin (INR 2–3), $P2Y_{12}$ inhibitor, aspirin (100 mg for 1–12 months)	
Exclusion criteria	Bioprosthetic/mechanical heart valve; anticoagulation for other indications (venous thromboembolism, mitral stenosis); history of intracranial hemorrhage; severe renal insufficiency; recent or planned coronary artery bypass grafting; coagulopathy or ongoing bleeding.	Bioprosthetic/mechanical heart valve; bleeding risk; uncontrolled severe hypertension; moderate or severe mitral stenosis; ischemic stroke within 2 weeks; severe renal insufficiency; abnormal liver function.	
Primary endpoint	Major or clinically relevant non-major bleeding	Major or clinically relevant non-major bleeding	
Secondary endpoints	The composite of death or hospitalization and the composite of death or ischemic events (stroke, MI, stent thrombosis, or urgent revascularization).	The composite of cardiovascular death, stroke, systemic embolic events, MI, definite stent thrombosis	
Follow up	6 months	12 months	
Results	-Primary endpoint: 10.5% in apixaban vs 14.7% in VKA group, HR (95%CI) 0.69(0.58-0.81), p < 0.001; 16.1% in aspirin vs 9.0% in placebo group HR (95%CI) 1.89 (1.59–2.24), $p < 0.001$. -Death or hospitalization 23.5% in apixaban vs 27.4% in VKA group, HR (95%CI) 0.83 (0.74–0.93), $p = 0.002$; similar incidence of ischemic events	-Primary endpoint: 17% (annualized event rate 20.7%) with the edoxaban regimen vs 20% (annualized event rate 25·6%) with the VKA regimen, HR(95%CI) 0.83(0.65–1.05), $p = 0.001$ for non-inferiority, margin HR 1.20 and $p = 0.1154$ for superiority. -Secondary endpoint: 7% (annualized event rate 7.3%) in the edoxaban regimen group vs 6% (annualized event rate 6.9%) in the VKA regimen group, HR (95%CI) 1.06 (0.71–1.69)	
Comments	-Proved beneficial adding apixaban to a $P2Y_{12}$ inhibitor in patients with AF and recent ACS or PCI	-Edoxaban-based dual antithrombotic therapy did not show superiority for bleeding reduction compared with TAT	

ACS, acute coronary syndrome; *AF*, atrial fibrillation; *DES*, drug eluting stents; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *RCT*, randomized controlled trial; *TAT*, triple antithrombotic treatment; *VKA*, vitamin K antagonist

*30 mg if moderate or severe renal impairment (calculated creatinine clearance 15–50 mL/min), ≤ 60 kg, concurrent use of specific potent P-glycoprotein inhibitors

antithrombotic therapy consisting of dose-adjusted vitamin K antagonist plus DAPT for 1, 6, or 12 months. Both rivaroxaban-based strategies were associated with improved safety compared with the standard triple antithrombotic therapy, as the clinically significant bleeding was reduced in both groups receiving rivaroxaban. The aspirin-free arm was associated with a 41% risk reduction in clinically significant bleeding rate versus the triple antithrombotic therapy arm (360-day Kaplan–Meier estimate, 16.8% vs 26.7%; $p < 0.001$) and rivaroxaban 2.5 mg bid plus DAPT was associated with a 37% risk reduction (360-day Kaplan–Meier estimate, 18.0% vs 26.7%; $p < 0.001$). Furthermore, the risk of major adverse cardiovascular events did not differ between the three treatment groups even though the trial was underpowered for this endpoint.

The randomized evaluation of dual therapy with dabigatran vs triple therapy with warfarin in patients with atrial fibrillation that undergo a percutaneous coronary intervention with stenting (RE-DUAL PCI) trial was a multicenter trial of 2725 patients with atrial fibrillation who had undergone PCI [9]. Patients were randomized in an aspirin-free dual therapy strategy with dabigatran (150 mg or 110 mg bid) plus a $P2Y_{12}$ receptor inhibitor (mainly clopidogrel) or in standard triple antithrombotic therapy consisting of dose-adjusted vitamin K antagonist plus DAPT. The primary endpoint was major or clinically relevant non-major bleeding according to International Society on Thrombosis and Hemostasis (ISTH) criteria which occurred at lower rates in both dabigatran strategies through a mean follow-up of 14 months: 15.4% in the 110-mg dabigatran dual-therapy group as compared with 26.9% in the triple-therapy group [HR (95%CI), 0.52 (0.42–0.63), $p < 0.001$ for non-inferiority and $p < 0.001$ for superiority] and 20.2% in the 150-mg dabigatran dual-therapy group as compared with 25.7% in the corresponding triple-therapy group [HR (95%CI), 0.72 (0.58–0.88), $p < 0.001$ for non-inferiority]. In addition, the aspirin-free dual therapy groups combined were non-inferior to the standard triple therapy group in regard to the rate of thromboembolic events (MI, stroke, systemic embolic), death or unplanned revascularization, 13.7% and 13.4%, HR (95% CI) 1.04(0.84–1.29), $p = 0.005$ for non-inferiority.

The study of apixaban in patients with atrial fibrillation, not caused by a heart valve problem, who are at risk for thrombosis due to having had a recent coronary event, such as a heart attack or a procedure to open the vessels of the heart (AUGUSTUS) trial evaluated apixaban versus vitamin K antagonist (open-label) plus $P2Y_{12}$ receptor inhibitor along with aspirin versus no aspirin (blinded) in a 2 × 2 factorial design, thus allowing directly testing the benefit and risk of omitting aspirin with both warfarin and apixaban [10]. AUGUSTUS is, therefore, the first randomized trial comparing directly two different aspirin-free strategies, namely apixaban plus $P2Y_{12}$ receptor inhibitor vs vitamin K antagonist plus $P2Y_{12}$ receptor inhibitor. Among the 4614 randomized patients, the primary end point rate of major or clinically relevant non-major bleeding at 6 months was reduced in the group receiving apixaban compared with the group receiving vitamin K antagonist, 10.5% vs 14.7%, HR (95%CI) 0.69 (0.58–0.81), $p < 0.001$ for both non-inferiority and superiority). The primary end point rate was 16.1% of the patients receiving aspirin, as compared with 9.0% of those receiving placebo HR (95% CI)1.89 (1.59–2.24), $p < 0.001$. The rate of major adverse cardiovascular events (defined as a composite of death from cardiovascular causes or hospitalization) was lower in the patients in apixaban group than those in warfarin group, 23.5% vs. 27.4%, HR (95% CI) 0.83 (0.74–0.93), $p = 0.002$. By contrast, the rate of death or hospitalization did not differ across the strategies of aspirin and placebo. Overall, AUGUSTUS proved that an aspirin-free strategy with apixaban plus a $P2Y_{12}$ receptor inhibitor is accompanied by less bleeding and fewer hospitalizations without significant differences in ischemic events than strategies including a vitamin K antagonist, aspirin, or both.

The 2019 updated guidelines—published prior to AUGUSTUS results—adopted the above key findings and especially the fact that the dual therapy was associated with reduction of bleeding risk and similar prevention of a new episode or stent thrombosis as the standard triple therapy [12]. Very recently, the ENTRUST-AF PCI (edoxaban-based versus vitamin K antagonist–based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation) trial results were published: edoxaban 60 mg plus a $P2Y_{12}$ inhibitor were compared with triple therapy with warfarin plus a $P2Y_{12}$ inhibitor and aspirin 100 mg for 1–12 months [46]. Regarding the primary endpoint of major or clinically relevant non-major bleeding, the aspirin-free edoxaban strategy was proved to be non-inferior to triple therapy strategy, 17% vs 20% of patients, HR (95%CI) 0.83 (0.65–1.05), $p = 0{\cdot}0010$ for non-inferiority, margin HR 1.20, but not superior either ($p = 0.1154$ for superiority). Concerning the main efficacy outcome (the composite of cardiovascular death, stroke, systemic embolic events, MI, and definite stent thrombosis), there were no significant differences between strategies (Table 2). The early omitting of aspirin (50% of patients discontinued aspirin at 1 month), the sub-therapeutic anticoagulation in triple therapy arm (INR < 2 in 69% of patients between 2 and 7 days) and the use of the full dose of edoxaban may have been implicated in the observed results.

Perspectives

Scenarios in need for aspirin-free strategies are increasingly encountered in PCI patients. Treating an aging population, with more comorbidities and high-bleeding risk features,

makes it more imperative to decrease the intensity of antithrombotic treatment, without compromising efficacy, while simultaneously increasing safety. Aspirin-free strategies appear as a useful tool of tailoring antithrombotic therapy for individual patient. DES technology refinements, as mentioned, further reinforce the use of lower antithrombotic intensity strategies, at least in the high-bleeding risk PCI patients [32–34]. While omitting aspirin post-PCI, options include either its replacement by low-dose rivaroxaban, a GEMINI-ACS 1-strategy [45], or, more importantly and more convincingly, shortening aspirin duration to 1–3 months. A significant reduction in bleeding could be expected by maintaining only clopidogrel beyond the 1–3 months post-PCI. Although no sign of an increased ischemic potential was apparent, this should be considered in the context of a very meticulous PCI technique applied with liberal use of intravascular imaging and the careful extrapolation of these findings in higher thrombotic risk, e.g., ST elevation myocardial infarction patients. The introduction of a potent $P2Y_{12}$ receptor inhibitor, namely ticagrelor monotherapy, also without aspirin, after the first month post-PCI, does not appear to harm patients compared with a standard DAPT for 1 year. No relevant data regarding prasugrel are available.

The issue of antiplatelet monotherapy beyond 12 months from PCI and aspirin replacement by a $P2Y_{12}$ receptor inhibitor is even more unexplored. In a retrospective study of 3243 patients receiving DES between January 2003 and December 2010 and completing 12-month DAPT, analysis according to further 36-month antiplatelet monotherapy showed that clopidogrel was associated with a reduction in risk for a composite of cardiac death, MI, or stroke over aspirin [47]. The risk of cardiac death was also lower with clopidogrel monotherapy than with aspirin monotherapy, 1.4% vs 0.5%, HR (95%CI) 0.31 (0.11–0.93), $p = 0.04$, while TIMI major bleeding occurred with a similar frequency between groups. The harmonizing optimal strategy for treatment of coronary artery stenosis–extended antiplatelet monotherapy (HOST-EXAM)) is an ongoing prospective, randomized, multicenter trial, to compare clopidogrel 75 mg od vs aspirin 100 mg od in patients with no clinical events during combined antiplatelet therapy for 12 ± 6 months after index PCI (NCT02044250) [48]. The primary endpoint is the composite of all-cause death, non-fatal MI, stroke, readmission due to ACS, or major bleeding at 2-year post-randomization. HOST-EXAM has completely enrolled 5500 patients and expected to report results in the next year (Dr Hyo-Soo Kim personal communication). Of note, landmark analysis of GLASSY has suggested that ticagrelor beyond the first year may reduce the rates of MI and definite stent thrombosis as compared with aspirin alone [42]. In patients with atrial fibrillation and stable CAD beyond 1 year after stenting the OAC-ALONE (Optimizing Antithrombotic Care in patients with AtriaL fibrillatiON and coronary stEnt) trial also failed to demonstrate non-inferiority of an aspirin-free strategy with anticoagulant alone to combined anticoagulant and antiplatelet (aspirin 86.4%/clopidogrel 13.9% of patients) because patient enrollment was prematurely terminated, leading to an underpowered sample size [49].

Regarding aspirin omission in cases in need of the "older" standard triple antithrombotic treatment, data are convincing that this is associated with greatly reduced risk of bleeding, without any apparent compromise in safety. This is reflected into the more recent relevant American Practice Guidelines, with an aspirin-free, dual antithrombotic therapy consisting of a novel anticoagulant and a $P2Y_{12}$ inhibitor representing the default strategy for most patients [12]. No signals of an increased ischemic risk have been encountered so far with such a strategy, with the caveat that respective trials were not powered for efficacy and uncommon endpoints like MI or stent thrombosis [50]. The safety and efficacy of different aspirin-free strategies using a network meta-analysis of randomized controlled trials was recently reported [51]. TIMI major bleeding was reduced with vitamin K antagonist plus $P2Y_{12}$ inhibitor without aspirin and non-vitamin K oral anticoagulant plus $P2Y_{12}$ inhibitor without aspirin, compared with triple therapy (vitamin K antagonist plus DAPT involving aspirin), with OR (95% CI) 0.58 (95%CI, 0.31–1.08) and 0.49 (95%CI, 0.30–0.82), respectively. There were no significant differences in ischemic events between different treatment arms. Most importantly, no clear signal of increased stent thrombosis in the groups taking antithrombotic regimens without aspirin was observed. Of note, European Consensus Documents Guidelines still suggests triple antithrombotic therapy as a default strategy in atrial fibrillation patients after stent implantation, excluding those on very high bleeding risk (HAS-BLED [hypertension, abnormal renal and liver function, stroke, bleeding history or predisposition, labile INR, elderly (> 65 years), drugs and alcohol] ≥ 3, recent bleeding event) and relatively low ischemic risk [52].

Conclusions

In the current era of PCI with the use of contemporary DES, refined PCI techniques and adjunctive pharmacotherapy the role of aspirin peri-PCI remains undisputable. However, following the initial period (1 week–1 month) post-PCI, scenarios for aspirin-free strategies are commonly encountered. Recent randomized trials have shed light on how to treat patients, e.g., in the presence of concomitant anticoagulant more safely with $P2Y_{12}$ monotherapy and excluding aspirin. Individualization of DAPT duration particularly in high bleeding risk patients appears as mandatory also making aspirin not necessary in several cases. Ongoing studies may further dispel

the myths and establish real facts regarding post-PCI-tailored treatment with aspirin.

Compliance with Ethical Standards

Conflict of Interest Dr. Alexopoulos discloses lecturing honoraria/advisory board fees from Astrazeneca, Bayer, Boehringer Ingelheim, Biotronik, Medtronic, Chiesi Hellas. Other authors have no disclosure.

Abbreviations ACS acute coronary syndrome ; CAD coronary artery disease ; HBR high bleeding risk ; NOAC non-vitamin K anticoagulant

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