

Non-Vitamin K Antagonist Oral Anticoagulants in Coronary Artery Disease

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Abstract

Keywords

- ▶ coronary artery disease
- ▶ non-vitamin K antagonist
- ▶ oral anticoagulants
- ▶ direct antithrombin agents
- ▶ atherosclerosis

Zusammenfassung

Schlüsselwörter

- ▶ koronare Herzkrankheit
- ▶ Nicht-Vitamin-K-Antagonist
- ▶ orale Antikoagulantien (NOAKs)
- ▶ direkte Antithrombinmittel
- ▶ Arteriosklerose

The prevention of atherothrombotic events is the primary goal in the treatment of patients with arteriosclerotic disorders. Despite recent improvements in the management of coronary artery disease (CAD) with revascularization techniques and antiplatelet therapy, some patients remain at risk of recurrent cardiovascular events. This could be related to additional thrombin generation. As a result, there has been interest in developing novel therapies to prevent thromboembolic events, targeting thrombin-mediated pathways. These include non-vitamin K antagonist oral anticoagulants (NOACs). This article aims to summarize the recent clinical studies that investigated the role of NOACs in CAD.

Die Prävention atherothrombotischer Ereignisse ist das primäre Ziel bei der Behandlung von Patienten mit arteriosklerotischen Erkrankungen. Trotz aktueller Fortschritte bei der Behandlung der koronaren Herzkrankheit mit Revaskularisationstechniken und Thrombozytenaggregationshemmung leiden einige Patienten weiterhin unter kardiovaskulären ischämischen Ereignissen. Dies könnte mit einer übermäßigen Thrombinbildung zusammenhängen. Infolgedessen bestand Interesse an der Entwicklung neuer Therapien zur Verhinderung thromboembolischer Ereignisse, die auf Thrombin-vermittelte Signalwege abzielen. Dazu gehören Nicht-Vitamin-K-Antagonist-orale Antikoagulantien (NOAKs). Dieser Artikel soll die aktuellen klinischen Studien zusammenfassen, in denen die Rolle von NOACs bei koronarer Herzerkrankung untersucht wurde.

Introduction

Despite the remarkable advances in the management of cardiac diseases during the last decades, coronary artery disease (CAD) remains the leading cause of death world-

wide.¹ The various clinical presentations of CAD can be classified into chronic coronary syndrome (CCS) and acute coronary syndromes (ACSs).^{2,3} The three main categories of ACS are unstable angina, non-ST-elevation myocardial infarction, and ST-elevation myocardial infarction.^{2–4}

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Thromboembolic events in patients with CAD are attributed not only to platelet accumulation but also to plasma coagulation with thrombin-mediated fibrin production.⁵ Thus, anticoagulation agents such as vitamin K antagonists (VKAs) have been administered as secondary preventive treatment to reduce atherothrombotic recurrences in patients with recent ACS.^{6,7} However, VKAs are reported to increase risk of hemorrhage in these patients.⁸ Moreover, VKAs present many limitations such as dietary restrictions and extensive interactions with other agents,⁹ engendering the development of non-vitamin K antagonist oral anticoagulants (NOACs). NOACs offer many advantages compared with VKAs, achieving a dose-dependent direct inhibition of thrombin or activated factor Xa, key enzymes in the pathways of coagulation, which qualifies their administration of fixed doses.^{8,9} Four NOACs have been compared with VKAs in recent years: rivaroxaban, apixaban, and edoxaban act by blocking the activated factor X, while dabigatran directly inhibits thrombin. NOACs are generally safer than VKAs, as they are associated with significant reduction of intracranial hemorrhage and mortality.^{10,11} This article presents an overview of the potential role of NOACs in patients with CAD and summarizes the recent clinical studies on antithrombotic therapy for CAD (►Table 1).

Potential Interactions between Plasmatic and Cellular Hemostasis

Cellular and plasmatic coagulation work in tandem to achieve hemostasis and clot formation.¹² The intrinsic and extrinsic pathways within the coagulation cascade create the prothrombinase complex formed by FXa and its cofactor FVa, which drives the enzymatic cleavage of prothrombin into thrombin.¹² Thrombin's primary role is to catalyze the conversion of fibrinogen to fibrin, which is primarily responsible for thrombus stabilization.^{12,13} Moreover, thrombin is the most effective platelet activator and one of the most important methods of attracting platelets into a developing hemostatic plug.¹³ NOACs inhibit thrombin either directly (dabigatran) or indirectly by inhibiting activated factor X (Xa) (rivaroxaban, apixaban, and edoxaban). However, whether NOACs affect platelet hemostasis remains incompletely known.¹⁴ A recent study showed that the thrombin-induced aggregation of platelets is decreased in patients with nonvalvular atrial fibrillation (AF) receiving edoxaban.¹⁵ These results are in line with other published studies showing that edoxaban is a potent inhibitor of tissue factor-induced platelet aggregation and clot-bound FXa.^{16,17} Similar results regarding the aggregation of platelets in patients with AF have also been published for

Table 1 Summary of the recent clinical studies on the role of NOACs for coronary artery disease

Indication	Study	NOAC	Comparison
Chronic coronary syndrome	COMPASS	Rivaroxaban (two arms) <ul style="list-style-type: none"> • 2.5 mg BD and aspirin 100 mg OD • 5 mg BD and + aspirin-matched placebo 	Rivaroxaban-matched placebo BD and aspirin 100 mg OD
Acute coronary syndrome	RE-DEEM	Dabigatran (four arms) <ul style="list-style-type: none"> • 50 mg BD + DAPT • 75 mg BD + DAPT • 110 mg BD + DAPT • 150 mg BD + DAPT 	Dabigatran-matched placebo BD + DAPT
	APPRAISE-2	Apixaban (two arms) <ul style="list-style-type: none"> • Normal renal function: 5 mg BD + DAPT • CrCl < 40 mL/min: 2.5 mg BD + DAPT 	Apixaban-matched placebo BD + DAPT
	ATLAS-ACS	Rivaroxaban (two arms) <ul style="list-style-type: none"> • 2.5 mg BD + DAPT • 5 mg BD + DAPT 	Rivaroxaban-matched placebo BD + DAPT
Atrial fibrillation patients undergoing PCI	PIONEER AF-PCI	Rivaroxaban (two arms) <ul style="list-style-type: none"> • Low dose: 15 mg OD + SAPT • Very low dose: 2.5 mg BD + DAPT 	Warfarin + DAPT
	RE-DUAL-PCI	Dabigatran (two arms) <ul style="list-style-type: none"> • Low dose: 110 mg BD + SAPT • High dose: 150 mg BD + SAPT 	Warfarin + DAPT
	AUGUSTUS	Apixaban (5 mg BD) + P2Y12 inhibitor and + either: <ul style="list-style-type: none"> • Aspirin or • Placebo 	Warfarin + P2Y12 inhibitor and + either: <ul style="list-style-type: none"> • Aspirin or • Placebo
	ENTRUST PCI	Edoxaban (60 mg OD) + P2Y12 inhibitor	Warfarin + DAPT

Abbreviations: BD, twice daily; DAPT, dual-antiplatelet therapy; NOAC, non-vitamin K antagonist oral anticoagulant; OD, once daily; PCI, percutaneous coronary intervention; SAPT, single-antiplatelet therapy.

dabigatran,^{18,19} while platelet activation with other agonists rather than thrombin was not found to be affected by dabigatran.²⁰ On the contrary, a study by Olivier et al reported an enhanced platelet aggregation in patients receiving dabigatran and no effect in patients treated with rivaroxaban.²¹ The antiplatelet effects of ASA and clopidogrel measured by AA- or ADP-induced platelet aggregation were not substantially altered by NOAC therapy with neither dabigatran nor rivaroxaban in patients with AF receiving both NOACs and platelet inhibitors.²² More in-depth study is clearly required to further explore the situation.

Role of NOACs in Chronic Coronary Syndrome

The prevention of atherothrombotic events is the primary goal in the treatment of patients with arteriosclerotic disorders. Platelet aggregation inhibitors, acetylsalicylic acid (ASA) and clopidogrel, were until recently the only available agents used in the primary and secondary prophylaxis of patients with CCS.⁸ However, ASA reduces the risk of serious cardiovascular events by 19% and cardiovascular death by 9% only.²³ Previous efforts to enhance the efficiency of antithrombotic treatment in CCS using combinations of antiplatelet drugs with or without warfarin have had little success.^{24,25} There is evidence for a persistent hypercoagulable state in CCS, which may explain the elevated risk of cardiovascular events in some patients.²³ Therefore, it was hypothesized that patients with CCS would benefit from a long-term therapy with oral anticoagulants. Monotherapy with VKAs significantly reduced cardiovascular events. However, VKAs were associated with an increased risk of bleeding.²⁶ Similarly, VKAs in combination with ASA have not consistently demonstrated a benefit on cardiovascular events and have shown a significant increase in major bleeding compared with monotherapy with ASA.³ As a result, the use of VKAs in CCS was abandoned in clinical practice. The role of NOACs in CCS has been investigated in a recent randomized clinical trial.

COMPASS Trial

The COMPASS study in 2017 randomly assigned 27,395 patients with CCS (91%) and/or peripheral artery disease (27%) into three cohorts, treating them with either rivaroxaban 2.5 mg twice daily in combination with ASA 100 mg once daily or rivaroxaban 5 mg twice daily or a standard therapy consisting of aspirin 100 mg once daily alone. The trial included high-risk patients with relevant primary arteriosclerotic disease (i.e., multivessel disease, prior MI). To be included into the study, patients had to be either 65 years or older or to match two of the following criteria: smoking, diabetes mellitus, creatinine clearance less than 60 mL/minute, heart failure NYHA I/II, or prior ischemic stroke. Key exclusion criteria were a high risk of bleeding, severe cardiac insufficiency (NYHA III/IV), renal failure (creatinine clearance <15 mL/min), and an indication for dual-antiplatelet therapy or therapeutic anticoagulation (especially AF).²⁷ The trial was terminated

prematurely due to the significantly superior results in the rivaroxaban 2 × 2.5 mg + ASS 100 mg arm. Over a medium of 23 months, the primary endpoint (composed of cardiovascular death, stroke, or myocardial infarction) occurred only in 4.1% of patients in the aspirin + rivaroxaban 2 × 2.5 mg group compared with 5.4% in the aspirin group.

Similarly, the overall mortality (4.1% in the ASS 100 group vs. 3.4% in the ASS 100 + rivaroxaban 2 × 2.5 mg group) and the incidence of ischemic strokes (1.4% ASS 100 group vs. 0.7% in the ASS 100 + rivaroxaban 2 × 2.5 mg group) were reduced. On the contrary, there was an increase in major bleeding events in the aspirin + rivaroxaban cohort to 3.1% from 1.4% in the group treated only with aspirin. Although half of those bleedings were of gastrointestinal origin, a treatment with a proton-pump inhibitor had no significant effect on reducing these bleedings.²⁸

The number of fatal bleedings did not increase significantly (0.1% in the aspirin group vs. 0.2% in the aspirin + rivaroxaban group) and the incidence of intracranial bleedings was equally common in both groups (0.3%).¹⁴ Furthermore, the combined endpoint consisting of cardiovascular death, stroke, myocardial infarction, fatal bleeding, and symptomatic bleeding in a critical organ was reduced from 5.9% in the group treated only with aspirin to 4.7% in the group with combined treatment. Treatment with rivaroxaban alone did not decrease cardiovascular events and the overall mortality but resulted in a higher risk of bleeding.²⁹

The trial showed a substantial net benefit with a 20% relative risk reduction. However, the reported net benefit did not include the primary safety endpoint of major bleeding defined by modified criteria of ISTH (International Society on Thrombosis and Haemostasis) but only fatal or critical organ bleeding. Due to the inclusion of a high number of less severe bleeding events, substituting life-threatening and fatal bleeding events with all major bleeding events according to the modified ISTH criteria resulted in no significant difference in net clinical benefit outcomes between the two trial groups.³⁰

Role of NOACs in Acute Coronary Syndrome

Following an ACS, the plasma coagulation cascade becomes more active than usual months after the initial coronary event.^{5–8} In addition to platelet aggregates, large amounts of fibrin can also be stained in aspirated coronary thrombi of patients with acute myocardial infarction, which illustrates the importance of plasmatic anticoagulation for the prevention of atherothrombotic events.⁸ Despite platelet inhibition after ACS, there remains a risk of recurrent ischemic events due to thrombin formation.^{5–8} The addition of VKAs to ASA to reduce atherothrombotic recurrences after ACS is accordingly effective and prevents reinfarction, but it also leads to relevant bleeding complications.⁸ Consequently, NOACs were examined for treatment after ACS.

The phase II RE-DEEM trial showed no clinical benefit of dabigatran in combination with dual-antiplatelet therapy (DAPT) in patients with a recent myocardial infarction at high risk of new ischemic cardiovascular events. Dabigatran

(in different doses ranging between 50 and 150 mg twice daily), in addition to DAPT, was associated with an increase in bleeding events without reducing the incidence of major adverse cardiac events, as compared with DAPT alone.³¹ These findings are similar to those noted in the APPRAISE-2 study with apixaban. The addition of 5-mg apixaban twice daily to DAPT with ASA and clopidogrel significantly increased the risk of bleeding without additional protection against ischemic events. The use of full-dose apixaban and the inclusion of a high-risk population may explain the negative results of this trial.³²

ATLAS-ACS Trial

The ATLAS-ACS2-TIMI 51 trial investigated the hypothesis that inhibiting factor Xa, and thereby the thrombotic cascade, would help prevent cardiovascular events in patients after ACS. For this purpose, the authors randomized 15,526 ACS patients (50.3%—ST-segment elevation myocardial infarction [STEMI], 25.6%—non-STEMI [NSTEMI], 24%—unstable angina) into three cohorts. All patients received the standard medical treatment of the time consisting of a low dose of aspirin and a thienopyridine (clopidogrel or ticlopidine). In addition to that, the first group was treated with 2 × 2.5 mg rivaroxaban, the second group received 2 × 5 mg rivaroxaban, and the third group was given a placebo twice per day. The study included patients older than 55 years. Patients younger than 55 years must also have had either diabetes mellitus or a prior MI in addition to the presenting ACS event. Major exclusion criteria were medical conditions contraindicating anticoagulant therapy or an increased risk of bleeding as well as severe renal or liver disease.³³ Both rivaroxaban doses showed a significant reduction in the primary efficacy endpoint defined as a composite of death from cardiovascular causes, myocardial infarction, or stroke (9.1% in the 2 × 2.5 mg group, 8.8% in the 2 × 5 mg group vs. 10.7% in the placebo group). In the same way, the rate of the secondary endpoint (death from any cause, myocardial infarction, or stroke) was significantly reduced in the 2 × 2.5 mg rivaroxaban (9.3%) and the 2 × 5 mg rivaroxaban cohort (9.1%) as compared with the placebo arm (11.0%). On the other hand, both rivaroxaban doses increased the number of major bleedings (1.8% in the 2 × 2.5 mg group, 2.4% in the 2 × 5 mg group vs. 0.6% in the placebo arm) as well as intracranial hemorrhages (0.4% in the 2 × 2.5 mg rivaroxaban, 0.7% in the 2 × 5 mg rivaroxaban vs. 0.2% in the placebo group). However, the number of fatal bleedings was 0.1% in the patients treated with the lower rivaroxaban group, as compared with 0.2% in the placebo group and 0.4% in the higher dose rivaroxaban group. More importantly, the 2 × 2.5 mg rivaroxaban dose also showed a significant reduction in overall mortality. Death from any causes occurred in only 2.9% of patients in the 2 × 2.5 mg rivaroxaban group as compared with 4.4% in the 2 × 5 mg group and 4.5% in the placebo group.^{34,35}

A subgroup analysis of patients with STEMI showed a reduction in the overall mortality from 4.2 to 2.0% in the 2 × 2.5 mg rivaroxaban group. Based on these findings, rivaroxaban was approved in 2013 by the European Medicines Agency (EMA) for secondary prophylaxis of ACS. The current

European guidelines recommend the addition of a very low dose of rivaroxaban to the standard DAPT therapy with aspirin and clopidogrel in high-risk patients at low risk of bleeding following STEMI (class IIb recommendation).²

In summary, these trials have demonstrated that there is a very small ideal therapeutic window between enhanced antithrombotic activity and elevated bleeding events in CCS patients. The risk–benefit profile tended to be unfavorable at therapeutic NOACs doses (equivalent to VKAs at the international standardized ratio of 2.0–3.0). It is important to mention that the potent P2Y₁₂ inhibitors (prasugrel and ticagrelor) were not widely available when the ATLAS trial was conceived. Therefore, rivaroxaban has rarely been used after ACS, as ticagrelor or prasugrel is largely preferred for DAPT in ACS patients.

Role of NOACs in AF Patients Undergoing PCI

Percutaneous coronary intervention (PCI) is the most common invasive procedure performed in patients with coronary heart disease.³⁶ A background of AF is seen in up to 1 in 10 people undergoing PCI.³⁷ The anticoagulation strategy in people with AF requiring PCI can pose a dilemma. On the one hand, DAPT consisting of aspirin and P2Y₁₂ inhibitor is prescribed post-PCI to prevent stent thrombosis.³⁸ On the other hand, oral anticoagulation is needed to prevent stroke in AF patients.¹¹ A triple antithrombotic therapy, comprising DAPT with an oral anticoagulant, is associated with a high risk of bleeding.³⁹ A diligent balancing of the risk of bleeding and thrombosis is, therefore, crucial in AF patients undergoing PCI. As a result, various antithrombotic treatment regimens and drug combinations have been investigated to maintain anticoagulation while minimizing bleeding complications.

One of these strategies is to pull off ASA. The What is the Optimal antiplatelet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting (WOEST) trial showed that the combination of VKAs and clopidogrel reduces the bleeding risk, without a significant difference in thrombotic events compared with conventional triple therapy.³⁸ In the triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation (ISAR-TRIPLE) trial, a 6-week triple therapy was not inferior to the 6-month duration with regard to ischemic and hemorrhagic events.⁴⁰ The role of NOACs in AF patients undergoing PCI has been recently assessed in several randomized controlled trials (RCTs).

The PIONEER AF-PCI (A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) trial evaluated two dosing regimens of rivaroxaban: 15 mg once daily (10 mg once daily if creatinine clearance was 30–50 mL/min) with a P2Y₁₂ inhibitor and 2.5 mg twice daily with DAPT. Rivaroxaban in both doses reduced the rates of clinically significant bleeding, compared with conventional triple therapy with warfarin plus DAPT.⁴¹ In REDUAL-PCI (Evaluation of Dual Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With Atrial Fibrillation That

Undergo a PCI With Stenting), both high-dose dabigatran (150 mg twice daily) and low-dose dabigatran (110 mg twice daily) in combination with single-antiplatelet therapy is associated with a reduced risk of bleeding compared with warfarin and DAPT.⁴² The AUGUSTUS (An Open-label, 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban versus Vitamin K Antagonist and Aspirin versus Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention) trial compared apixaban with a VKA as well as aspirin with placebo in a two-by-two factorial design. Apixaban caused lower rates of major or clinically relevant non-major bleeding compared with VKA.⁴³ Moreover, the addition of aspirin was associated with significantly more bleedings.⁴³ ENTRUST-AF-PCI (Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial showed that a dual-antithrombotic

therapy with edoxaban plus P2Y12 inhibitor is noninferior compared with a triple treatment with warfarin in terms of major and non-major clinically relevant bleeding events⁴⁴ (→ Tables 1 and 2).

These RCTs showed that dual-antithrombotic therapy with NOAC and a P2Y12 inhibitor is safer than triple therapy with VKAs and DAPT with respect to major bleeding. However, none of these studies were sufficiently powered to detect differences in key efficacy endpoints, like ischemic stroke and stent thrombosis. All participants had nonvalvular AF as the indication for long-term oral anticoagulation. Male participants were predominant in these RCTs and the populations were a mixture of CCS and ACS patients. While all patients in PIONEER-PCI, RE-DUAL-PCI, and ENTRUST-PCI underwent PCI, 23.9% of patients with ACS in the AUGUSTUS trial were medically managed. The follow-up time in the AUGUSTUS trial was shorter than that in the PIONEER-AF PCI,

Table 2 Comparisons of the recent randomized trials on the role of NOACs in patient with AF undergoing PCI

Study	PIONEER-AF-PCI	RE-DUAL-PCI	AUGUSTUS	ENTRUST PCI
Participants	2,124	2,725	4,614	1,506
Age (mean)	70.2	70.8	70.7	69.5
Treatment duration	12 mo	12.3 mo	6 mo	12 mo
Indication for PCI	STEMI: 12.3%, in rivaroxaban 15-mg dual-therapy group, 13.8% in rivaroxaban 2.5-mg triple therapy group, and 10.7% in warfarin triple group. NSTEMI: 18.5% in rivaroxaban 15-mg dual-therapy group, 18.3% in rivaroxaban 2.5-mg triple therapy group, and 17.8% in warfarin triple group. Unstable angina: 20.7% in rivaroxaban 15-mg dual-therapy, 21.1% in rivaroxaban 2.5-mg triple therapy group, and 23.7% in warfarin triple therapy group	STEMI: 9.3% in dabigatran 110-mg dual-therapy group and 8.2% in corresponding triple therapy group; 9.7% in dabigatran 150-mg dual-therapy group, and 8.1% in corresponding triple therapy group. NSTEMI: 20.7% in dabigatran 110-mg dual-therapy group and 21.0% in corresponding triple therapy group; 23.5% in dabigatran 150-mg dual-therapy group and 19.8% in corresponding triple therapy group. Unstable angina pectoris: 19.9% in dabigatran 110-mg dual-therapy group and 16.9% in corresponding triple therapy group. 16.5% in dabigatran 150-mg dual-therapy group and 18.1% in corresponding triple therapy group	ACS: 37.3%; medically managed ACS: 23.9%; elective PCI: 38.8%	ACS: 51.6% and CCS: 48.4%
Median time till randomization	1 (1–2) d	1 (1–2) d	6 (3–10) d	1.9 (0.9–3.2) d
Ticagrelor	4.3%	12%	6.2%	7%
Prasugrel	1.3%	0	1.1%	0.5%
Primary outcome	Clinically relevant bleeding at 12 mo	Major or CRNM bleeding through follow-up (mean: 14 mo)	Major or CRNM bleeding at 6 mo	Major or CRNM bleeding at 12 mo
Treatment effect for intervention vs. control	HR, 0.59 (95% CI, 0.47–0.76); $p < 0.001$ for superiority	HR, 0.72 (95% CI, 0.58–0.88); $p < 0.001$ for noninferiority, $p = 0.002$ for superiority (dabigatran 150 mg bid); HR, 0.52 (95% CI, 0.42–0.63); $p < 0.001$ for noninferiority, $p < 0.001$ for superiority (dabigatran 110 mg bid)	HR, 0.53 (95% CI, 0.45–0.63); $p < 0.001$ for superiority	HR, 0.83 (95% CI, 0.65–1.05); $p = 0.001$ for noninferiority, $p = 0.1154$ for superiority
NNT for primary safety outcome	10	9 (110 mg)/18 (150 mg)	24	33

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; CCS, chronic coronary syndrome; CI, confidence interval; CRNM, clinically relevant non-major; HR, hazard ratio; NNT, number needed to treat; NOAC, non-vitamin K antagonist oral anticoagulant; NSTEMI, non-STEMI; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

the RE-DUAL PCI, and ENTRUST AF-PCI trials (6 vs. 12 months). The mean time in therapeutic range (TTR) of warfarin in the AUGUSTUS trial was 59%, while in the RE-DUAL PCI and the PIONEER AF trials TTR was 64 to 65%. The higher the TTR quality, the more reliable the safety outcomes. Moreover, some outcome definitions, such as stent thrombosis, were not uniform across trials. It should be noted that triple therapy with a NOAC was not performed in all these studies with the exception of the AUGUSTUS study. The use of aspirin throughout the peri-PCI period was required in all trials, meaning that all patients received triple treatment. However, the interval between PCI and the first intake of the randomized therapy varied significantly among the included trials (on average for 1–2 days after PCI in PIONEER AF-PCI, REDUAL-PCI, and ENTRUST-AF-PCI and for 6 days in AUGUSTUS). Finally, individual participant data are not publicly available (–Table 2).

Several meta-analyses of NOAC post-PCI studies showed an advantage of NOAC dual therapy over warfarin triple therapy with regard to major bleeding, without any differences in efficacy outcomes.^{45,46} Importantly, however, recent meta-analyses raised an important concern about a significant increase in the risk of stent thrombosis with double therapy.^{47–49} These findings have sparked controversy over the best time to stop taking aspirin in AF patients undergoing PCI. Stent thrombosis occurs mostly within 30 days after PCI.^{47,48} Since the introduction of new-generation drug-eluting stents, the risk of late and very late stent thrombosis has decreased significantly.⁵⁰ The more potent P2Y12 inhibitors prasugrel and ticagrelor are more effective than clopidogrel in lowering stent thrombosis in patients undergoing PCI for ACS.^{2–4} However, limited data are available for the combination of the more potent P2Y12 inhibitors with NOAC. The usage of prasugrel and ticagrelor in the four RCTs was minimal, with clopidogrel administered to the vast majority of patients.

Although the safety and efficacy findings were consistent with the overall trial results, in AF-PCI patients, potent P2Y12 inhibitors increase the risk of bleeding without reducing the ischemic risk.⁴⁹ Therefore, recent guidelines still advise against using the more potent P2Y12 inhibitors (prasugrel or ticagrelor) in AF patients post-PCI.^{3,51,52}

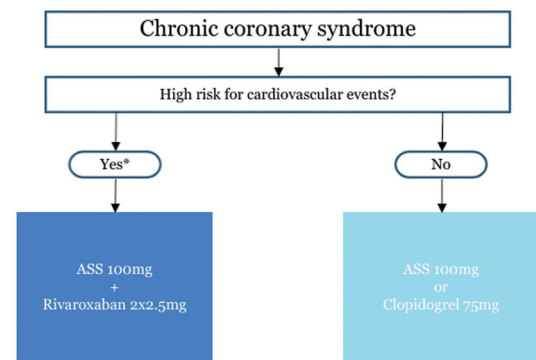
Since there are no head-to-head trials that compared NOACs directly against each other, there is no evidence to suggest one NOAC in preference to another for the management of individuals with the indication for anticoagulation after PCI. An indirect comparison of NOAC agents using a network meta-analysis also did not show superiority of one NOAC over another for AF patients post-PCI.⁴⁶

The decision to select a certain NOAC drug should take into consideration features of the trial design that best fit the patient's characteristics (–Table 2). PIONEER-AF-PCI was the only trial that excluded participants who had previously experienced a cerebrovascular incident.⁴¹ ENTRUST-PCI was the only trial that did not reveal superiority in bleeding reduction of a NOAC-based dual-antithrombotic therapy compared with a VKA, although noninferiority was met.⁴⁴ AUGUSTUS, the trial with the largest population, was the only trial to test aspirin in a placebo-controlled setting and

the only one to indicate a decreased bleeding with the NOAC (apixaban) against VKA in a factorial comparison.⁴³ RE-DUAL PCI was the only study with randomized testing of two NOACs doses that were tested in AF.⁴² Despite encouraging findings on the safety of a NOAC in patients with significant renal failure, these individuals were excluded from the studies of patients with AF receiving PCI. The four NOACs were investigated in patients with a GFR greater than 30 mL/min. Thus, no data are available on patients with severe renal impairment.

Current Guidelines of AF-PCI

The findings of the AF-PCI trials are supported by the North American consensus.⁵⁰ According to the American recommendations, triple therapy should be used solely during the in-hospital stay, followed by oral anticoagulant and clopidogrel for 6 to 12 months depending on the bleeding risk, and this should be the treatment of choice for the vast majority of AF-PCI patients, including those with ACS.⁵⁰ In individuals with a high ischemic risk, it is acceptable to take aspirin for up to 1 month following PCI.⁵⁰ Nonetheless, continuing aspirin treatment for more than 1 month post-PCI is not advised.⁵⁰ The European approach is still more cautious, recommending to terminate the triple treatment at discharge, 1 month, or 3 to 6 months depending on the individual's thrombotic and



* Either polyvascular disease (affecting at least 2 vascular beds) or coronary artery disease plus
 - diabetes mellitus or
 - renal impairment or
 - heart failure

Fig. 1 Treatment of chronic coronary syndrome according to Compass trial.

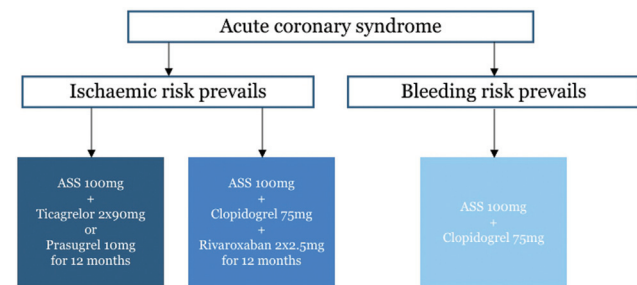


Fig. 2 Antithrombotic therapy in patients after acute coronary syndrome.

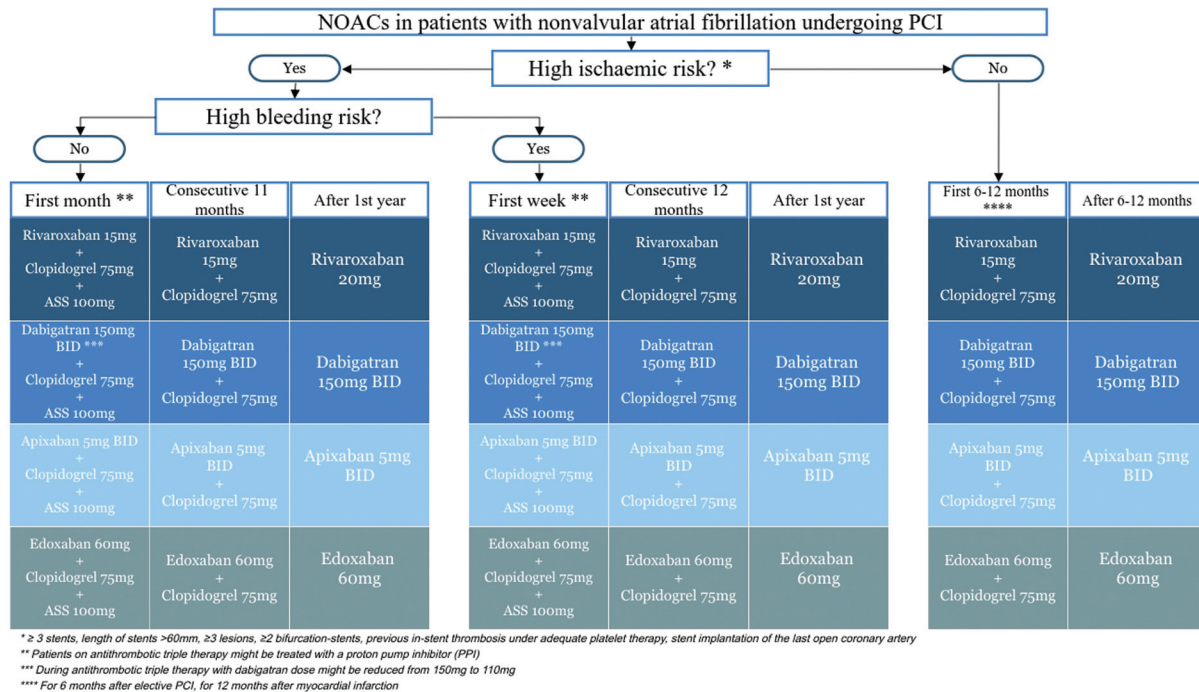


Fig. 3 Antithrombotic treatment in patients treated with NOACS after PCI.

bleeding profile.³⁻⁵⁴ Patients with a high thrombotic risk should be treated with triple treatment for even up to 6 months, according to European guidelines.³⁻⁵⁴ In general, both European and North American guidelines agree that NOAC should be preferred over VKAs in patients with AF undergoing PCI and the triple antithrombotic treatment should be as brief as feasible.^{3,51,52} NOAC should be taken at the same dose as that recommended for thromboembolic protection in people with AF; lower doses are not recommended in dual-antithrombotic treatment.^{50,52}

Ongoing Trials

Several ongoing trials are awaited to fill some of the current knowledge gap. The RT-AF, APPROACH-ACS-AF, and NCT03536611 trials are studying rivaroxaban, apixaban, and dabigatran, respectively.⁵⁵⁻⁵⁷

Conclusion

Atherothrombotic processes in CAD are promoted not only by platelets activation but also by plasmatic factors. Therefore, a better understanding of how these plasma components contribute to undesirable outcomes in CAD is critical to developing tailored treatment strategies. The decision to add a very low dose of rivaroxaban to standard-antiplatelet therapy with aspirin in CCS patients should be based on the patient's characteristics. In particular, patients with multiple ischemic risk factors, who are not at increased risk of bleeding, will benefit from this treatment option (→Fig. 1). After an appropriate selection of the patients, combination therapy can be used to offer life-prolonging therapy. In ACS patients, a very low dose of rivaroxaban in

combination with clopidogrel and aspirin can be an option for high-risk patients if prasugrel and ticagrelor are not available (→Fig. 2).

The findings of the AF-PCI trials argue against routine use of triple antithrombotic regimen with VKA. Therefore, triple therapy will no longer be the standard of treatment in all AF patients undergoing PCI. In fact, aspirin might be given only in the periprocedural phase and does not appear to be mandatory after PCI in most AF patients. However, triple antithrombotic therapy might still be indicated in selected patients at highest risk for stent thrombosis such as those with STEMI or complex PCI (e.g., bifurcation or left main PCI or PCI with multiple stents) (→Fig. 3). In summary, the best strategy appears to identify the individual ischemic and bleeding risk profile of each patient to achieve a net benefit of NOACs in CAD.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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References

- 1 Finegold JA, Asaria P, Francis DP. Mortality from ischaemic heart disease by country, region, and age: statistics from World Health Organisation and United Nations. *Int J Cardiol* 2013;168(02): 934-945
- 2 Ibanez B, James S, Agewall S, et al; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the

- Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;39(02):119–177
- 3 Knuuti J, Wijns W, Saraste A, et al; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;41(03):407–477
 - 4 Roffi M, Patrono C, Collet J-P, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37(03):267–315
 - 5 Merlini PA, Bauer KA, Oltrona L, et al. Persistent activation of coagulation mechanism in unstable angina and myocardial infarction. *Circulation* 1994;90(01):61–68
 - 6 van Es RF, Jonker JJC, Verheugt FWA, Deckers JW, Grobbee DE. Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2) Research Group. Aspirin and Coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. *Lancet* 2002;360(9327):109–113
 - 7 Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med* 2002;347(13):969–974
 - 8 Al Said S, Bode C, Duerschmied D. Anticoagulation in atherosclerotic disease. *Hamostaseologie* 2018;38(04):240–246
 - 9 Mekaj YH, Mekaj AY, Duci SB, Miftari EI. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. *Ther Clin Risk Manag* 2015;11:967–977
 - 10 Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383(9921):955–962
 - 11 Hindricks G, Potpara T, Dagres N, et al; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;42(05):373–498 [Erratum in: *Eur Heart J*. 2021 Feb 1;42(5):507, 546–547, 541–543]
 - 12 Sang Y, Roest M, de Laat B, de Groot PG, Huskens D. Interplay between platelets and coagulation. *Blood Rev* 2021;46:100733
 - 13 Brass LF. Thrombin and platelet activation. *Chest* 2003;124(03, Suppl):18S–25S
 - 14 Steppich B, Dobler F, Brendel LC, et al. Effect of the FXa inhibitors rivaroxaban and apixaban on platelet activation in patients with atrial fibrillation. *J Thromb Thrombolysis* 2017;43(04):490–497
 - 15 Sokol J, Nehaj F, Ivankova J, et al. Impact of edoxaban on thrombin-dependent platelet aggregation. *Clin Appl Thromb Hemost* 2020;26:1076029620948585
 - 16 Honda Y, Kamisato C, Morishima Y. Edoxaban, a direct factor Xa inhibitor, suppresses tissue-factor induced human platelet aggregation and clot-bound factor Xa in vitro: comparison with an antithrombin-dependent factor Xa inhibitor, fondaparinux. *Thromb Res* 2016;141:17–21
 - 17 Nehaj F, Sokol J, Ivankova J, Mokan M, Mokan M, Stasko J. Edoxaban affects TRAP-dependent platelet aggregation. *J Thromb Thrombolysis* 2020;49(04):578–583
 - 18 Sokol J, Nehaj F, Ivankova J, Mokan M, Mokan M, Stasko J. Dabigatran affects thrombin-dependent platelet aggregation after a week-long therapy. *Scand Cardiovasc J* 2018;52(04):227–231
 - 19 Shimizu M, Natori T, Tsuda K, et al. Thrombin-induced platelet aggregation -effect of dabigatran using automated platelet aggregometry. *Platelets* 2020;31(03):360–364
 - 20 Vinholt PJ, Nielsen C, Söderström AC, Brandes A, Nybo M. Dabigatran reduces thrombin-induced platelet aggregation and activation in a dose-dependent manner. *J Thromb Thrombolysis* 2017;44(02):216–222
 - 21 Olivier CB, Weik P, Meyer M, et al. TRAP-induced platelet aggregation is enhanced in cardiovascular patients receiving dabigatran. *Thromb Res* 2016;138:63–68
 - 22 Olivier CB, Weik P, Meyer M, et al. Dabigatran and rivaroxaban do not affect AA- and ADP-induced platelet aggregation in patients receiving concomitant platelet inhibitors. *J Thromb Thrombolysis* 2016;42(02):161–166
 - 23 Eikelboom JW, Connolly SJ, Bosch J, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;377(14):1319–1330
 - 24 Bhatt DL, Fox KAA, Hacke W, et al; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354(16):1706–1717
 - 25 Sorbets E, Steg PG. Direct-acting anticoagulants in chronic coronary syndromes. *Eur Cardiol* 2020;15:1–7
 - 26 De Caterina R, Husted S, Wallentin L, et al. Oral anticoagulants in coronary heart disease (Section IV). Position paper of the ESC Working Group on Thrombosis - Task Force on Anticoagulants in Heart Disease. *Thromb Haemost* 2016;115(04):685–711
 - 27 Bosch J, Eikelboom JW, Connolly SJ, et al. Rationale, design and baseline characteristics of participants in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Trial. *Can J Cardiol* 2017;33(08):1027–1035
 - 28 Moayyedi P, Eikelboom JW, Bosch J, et al; COMPASS Investigators. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. *Gastroenterology* 2019;157(03):682–691.e2
 - 29 Alsaid S, Bode C, Duerschmied D. Perspektive nach der COMPASS-Studie für KHK- und AVK-Patienten: Die neue Rolle der oralen Antikoagulationstherapie bei atherosklerotischer Erkrankung. *Der Klinikarzt* 2019;48(03):73–77. Doi: 10.1055/a-0861-1036
 - 30 Steffel J, Eikelboom JW, Anand SS, Shestakovska O, Yusuf S, Fox KAA. The COMPASS trial: net clinical benefit of low-dose rivaroxaban plus aspirin as compared with aspirin in patients with chronic vascular disease. *Circulation* 2020;142(01):40–48 [Erratum in: *Circulation*. 2020 Jul 7;142(1):e23. PMID: 32436455]
 - 31 Oldgren J, Budaj A, Granger CB, et al; RE-DEEM Investigators. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. *Eur Heart J* 2011;32(22):2781–2789
 - 32 Alexander JH, Lopes RD, James S, et al; APPRAISE-2 Investigators. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med* 2011;365(08):699–708
 - 33 Gibson CM, Mega JL, Burton P, et al. Rationale and design of the anti-Xa therapy to lower cardiovascular events in addition to standard therapy in subjects with acute coronary syndrome-thrombolysis in myocardial infarction 51 (ATLAS-ACS 2 TIMI 51) trial: a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of rivaroxaban in subjects with acute coronary syndrome. *Am Heart J* 2011;161(05):815–821.e6
 - 34 Mega JL, Braunwald E, Wiviott SD, et al; ATLAS ACS 2-TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;366(01):9–19
 - 35 Mega JL, Braunwald E, Wiviott SD, et al. Comparison of the efficacy and safety of two rivaroxaban doses in acute coronary syndrome (from ATLAS ACS 2-TIMI 51). *Am J Cardiol* 2013;112(04):472–478
 - 36 Khera S, Kolte D, Bhatt DL. Percutaneous Coronary Intervention [Internet]. *Translational Research in Coronary Artery Disease*; 2016:179–194. Doi: 10.1016/b978-0-12-802385-3.00016-4
 - 37 Al Said S, Katus HA, Alabed S. Cochrane corner: NOACs in atrial fibrillation patients post-percutaneous coronary intervention. *Heart* 2020;106(17):1293–1295

- 38 Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. [in Polish]. *Kardiol Pol* 2017;75(12):1217–1299
- 39 Dewilde WJM, Oirbans T, Verheugt FWA, et al; WOEST study investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;381(9872):1107–1115
- 40 Fiedler KA, Maeng M, Mehilli J, et al. Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation: the ISAR-TRIPLE trial. *J Am Coll Cardiol* 2015;65(16):1619–1629
- 41 Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016;375(25):2423–2434
- 42 Cannon CP, Bhatt DL, Oldgren J, et al; RE-DUAL PCI Steering Committee and Investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med* 2017;377(16):1513–1524
- 43 Lopes RD, Heizer G, Aronson R, et al; AUGUSTUS Investigators. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med* 2019;380(16):1509–1524
- 44 Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet* 2019;394(10206):1335–1343
- 45 Lopes RD, Hong H, Harskamp RE, et al. Optimal antithrombotic regimens for patients with atrial fibrillation undergoing percutaneous coronary intervention: an updated network meta-analysis. *JAMA Cardiol* 2020;5(05):582–589
- 46 Al Said S, Alabed S, Kaier K, et al. Non-vitamin K antagonist oral anticoagulants (NOACs) post-percutaneous coronary intervention: a network meta-analysis. *Cochrane Database Syst Rev* 2019;12:CD013252
- 47 Gargiulo G, Goette A, Tijssen J, et al. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. *Eur Heart J* 2019;40(46):3757–3767
- 48 Galli M, Andreotti F, Porto I, Crea F. Intracranial haemorrhages vs. stent thromboses with direct oral anticoagulant plus single antiplatelet agent or triple antithrombotic therapy: a meta-analysis of randomized trials in atrial fibrillation and percutaneous coronary intervention/acute coronary syndrome patients. *Europace* 2020;22(04):538–546
- 49 Sullivan AE, Nanna MG, Rao SV, et al. A systematic review of randomized trials comparing double versus triple antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention. *Catheter Cardiovasc Interv* 2020;96(02):E102–E109
- 50 Moon JY, Franchi F, Rollini F, Angiolillo DJ. Evolution of coronary stent technology and implications for duration of dual antiplatelet therapy. *Prog Cardiovasc Dis* 2018;60(4-5):478–490
- 51 Lopes RD, Leonardi S, Wojdyla DM, et al. Stent thrombosis in patients with atrial fibrillation undergoing coronary stenting in the AUGUSTUS trial. *Circulation* 2020;141(09):781–783
- 52 Casula M, Fortuni F, Ferlini M, Fabris F, Oltrona Visconti L, Leonardi S. Meta-analysis comparing potent oral P2Y₁₂ inhibitors versus clopidogrel in patients with atrial fibrillation undergoing percutaneous coronary intervention. *Am J Cardiovasc Drugs* 2021;21(02):231–240
- 53 Angiolillo DJ, Bhatt DL, Cannon CP, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a North American perspective: 2021 update. *Circulation* 2021;143(06):583–596
- 54 Lip GYH, Collet JP, Haude M, et al; ESC Scientific Document Group. 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). *Europace* 2019;21(02):192–193
- 55 Gao F, Shen H, Wang ZJ, Yang SW, Liu XL, Zhou YJ. Rationale and design of the RT-AF study: combination of rivaroxaban and ticagrelor in patients with atrial fibrillation and coronary artery disease undergoing percutaneous coronary intervention. *Contemp Clin Trials* 2015;43:129–132
- 56 U.S. National Library of Medicine. Apixaban vs. phenprocoumon in patients with ACS and AF: APPROACH-ACS-AF (approach)., 2016. Available at: <https://clinicaltrials.gov/ct2/show/NCT02789917>. [Last update posted: August 14, 2020]
- 57 Dabigatran versus warfarin with NVAf who undergo PCI. 2018. Available: clinicaltrials.gov/ct2/show/NCT03536611 [Last update posted: January 4, 2019]