Non–vitamin K antagonist oral anticoagulants in the treatment of coronary and peripheral atherosclerosis

Expert Consensus of the Association for Cardiovascular Interventions, Working Group on Intensive Cardiac Care and Resuscitation, and Working Group on Cardiovascular Pharmacotherapy of the Polish Cardiac Society

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ABSTRACT

Oral anticoagulants (OACs) are widely used for prevention of systemic thromboembolism, including the reduction of the risk of stroke in patients with atrial fibrillation (AF) and prosthetic heart valves. There is also an increasing population of patients who require not only OACs, but also double antiplatelet therapy (DAPT). A typical example is a patient with AF and stable coronary artery disease or acute coronary syndrome (ACS), treated by percutaneous coronary intervention. In recent years, with the introduction of NOACs, triple or dual therapy has become safer. Regardless of these indications for the use of NOACs, rivaroxaban at a reduced dose has proved to efficiently reduce the risk of further thrombotic events when added to DAPT in patients who have suffered an ACS. However, such therapy increases the incidence of bleeding complications. Interesting was also the potential impact of the pleiotropic mechanism of action of non–vitamin K antagonist oral anticoagulants (NOACs) through protease-activated receptors 1 and 2, present on the platelets and many other cells, and changing the course of arterial atherosclerosis. The COMPASS trial has shown that in the group treated with rivaroxaban combined with aspirin, the primary outcome (cardiovascular death, stroke, and myocardial infarction) occurred significantly less frequently than in the group treated only with aspirin. However, a significantly higher number of bleedings was observed. In the subgroup of patients with peripheral artery disease, a significant reduction of the incidence of amputations was shown. The outcomes of the COMPASS trial might be a breakthrough in the treatment of coronary and peripheral atherosclerosis.

The rationale behind the experts' opinion

The need for an experts' opinion arises directly from the rapid development of pharmacology and clinical cardiology, and from the fact that an increasing group of patients requires treatment with both antiplatelet drugs and oral anticoagulants (OACs). This is related to the aging of society, concomitant coronary artery disease (CAD), peripheral artery disease (PAD), heart failure, and atrial fibrillation (AF). Additionally,

TABLE 1 Clinical application of non–vitamin K antagonist oral anticoagulants

Clinical application	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Stroke and systemic embolism prevention in patients with nonvalvular atrial fibrillation	+	+	+	+
Management/ prevention of deep vein thrombosis and pulmonary embolism	+	+	+	+
Prevention of ischemic events in patients with atherosclerosis of coronary and peripheral arteries	-	-	-	+

there is also a significant impact of the bleeding risk based on validated scores on the decision on the type of antithrombotic treatment.

Combination therapy with antiplatelet drugs and OACs is used not only because of coexisting CAD and AF, but also as a secondary prevention following acute coronary syndromes (ACSs) in patients who do not require long-term anticoagulation for stroke prevention. The similarities between activation of the coagulation system and inflammatory mediators in coronary and peripheral atherosclerosis justify the use of OACs combined with antiplatelet drugs in patients with PAD. It has been shown that despite aggressive antiplatelet treatment, the residual risk of thrombosis persists but can be reduced with anticoagulants.

Clinical observations of patients with CAD, in particular after ACS, have shown that despite dual antiplatelet therapy (DAPT), the recurrence of cardiovascular events is frequent, which indicates a need for improving secondary prevention strategies. The insight into coagulation disorders, which can persist after an acute phase of an ischemic episode, has given rise to the idea of combined antiplatelet and anticoagulation therapy. Such an approach is possible because non–vitamin K antagonist oral anticoagulants (NOACs) are less likely than vitamin K antagonists (VKAs) to cause clinically significant bleeding. This has made it possible to conduct randomized clinical trials to assess DAPT or single antiplatelet therapy combined with NOAC after ACS and in patients undergoing percutaneous coronary intervention (PCI), both with coexisting AF and without. Based on the outcomes of those trials, it can be concluded that the combined treatment (NOAC + DAPT or NOAC + single antiplatelet drug) after ACS reduces the incidence of recurrent ischemic cardiovascular events, although at the cost of increased risk of bleeding in long-term follow-up. However, there was a reduced incidence of bleeding observed with NOACs after PCI as compared with standard treatment with VKA + DAPT.[1,2] Furthermore, the recently published COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies) documented the role of rivaroxaban in the prevention of cardiovascular events in patients with stable CAD and PAD.[3]

In this document, we discuss the novel indications for NOACs based on recently published trials. Also, we highlight the differences in dosing regimens dependent not only on renal function and bleeding risk but also on the indication and the presence of AF. We also believe that it is increasingly important for clinicians to be familiar with the mechanisms of action and pharmacokinetics of NOACs. These drugs do not require routine monitoring of international normalized ratio (INR), which is an unquestionable advantage. However, in the event of an urgent surgery or a bleeding episode, monitoring the effect of NOACs is more difficult and also depends on the time elapsed from the drug ingestion. Given that 4 NOACs are now available, clinicians should familiarize themselves with the impact of renal function on the metabolism of each of these drugs to choose the optimal treatment for their patients.

The relevance of this group of drugs is highlighted by the fact that they are discussed in detail in the guidelines and experts' opinion of the European Heart Rhythm Association, the guidelines for treatment of myocardial infarction and cardiac revascularization, and in the European Society of Cardiology (ESC) clinical practice guidelines on the use of antiplatelet drugs.[4-7] The main indications for NOACs are listed in TABLE 1.

Additionally, the outcomes of the COMPASS trial provide a basis for using rivaroxaban (2.5 mg twice daily) combined with acetylsalicylic acid (ASA) as an effective method for the prevention of mortality, stroke, and myocardial infarction in patients with stable CAD and PAD who have sinus rhythm. However, it should be remembered that bleeding risk increases with this treatment, meaning that it should be always individualized depending on the risk of ischemic and hemorrhagic incidents. Effective prevention of ischemic complications is the primary objective of treatment in patients with atherosclerosis. The use of this lower "vascular" dose of rivaroxaban is the beginning of a new age of pharmacological prevention of atherosclerotic complications. In the following experts' opinion, we will attempt to explain why we believe this statement to be true.

Molecular mechanisms of action and pharmacokinetics and pharmacodynamics of non–vitamin K antagonist oral anticoagulants (NOACs). Differences between oral anticoagulants and NOACs In the 20th century, the only OAC available in Poland, and other Eastern European countries, was acenocoumarol. In 2006, warfarin was registered in Poland as the second VKA. From the viewpoint of therapeutic
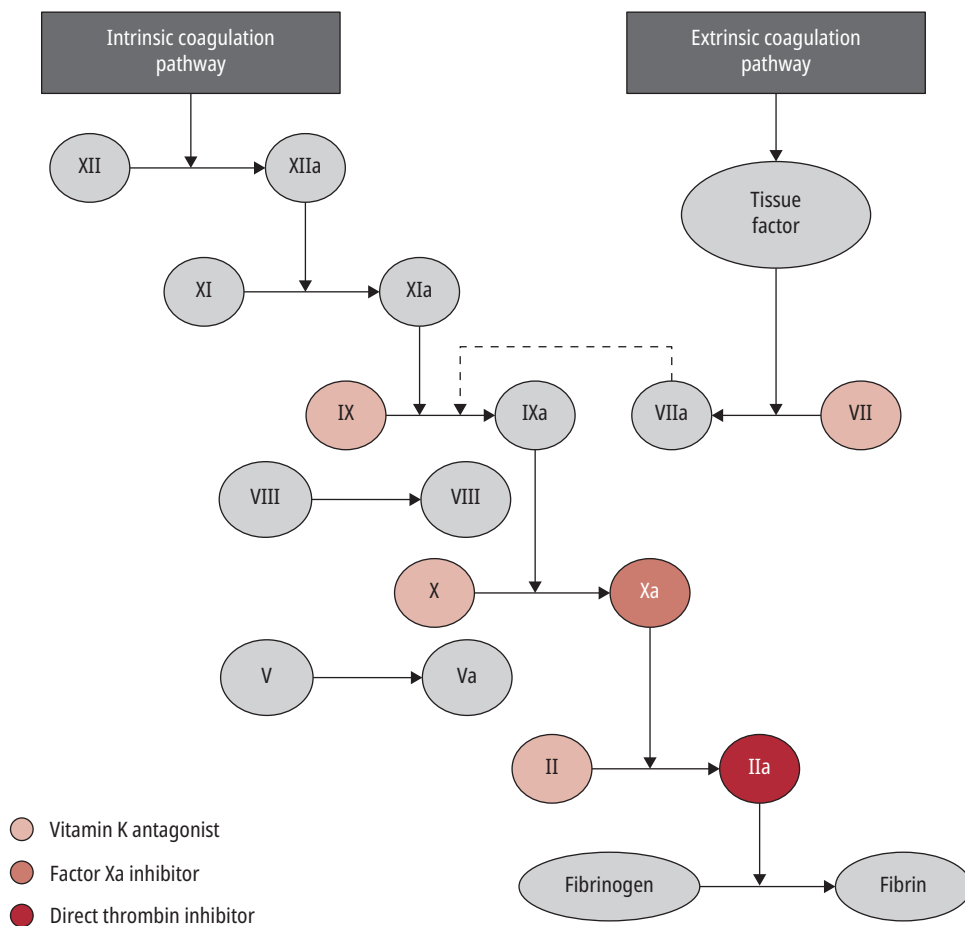
efficiency, there is not much difference between the 2 medications; however, because warfarin was more often used in most Western European countries, it was tested in clinical trials on anticoagulation and is listed in guidelines.

NOACs made their debut on the pharmaceutical market in the first decade of the 21st century. Unlike VKAs, which reduce the synthesis of coagulation factors from the prothrombin group (factors II, VII, IX, and X) and of anticoagulant proteins C and S, the novel drugs are highly selective towards the individual components of the coagulation cascade, namely, factor Xa or thrombin (factor IIa), which are common elements of the extrinsic and the intrinsic coagulation pathways.[8] A simplified diagram of the mechanisms of action of VKAs and NOACs is provided in FIGURE 1.

NOACs do not require routine monitoring of coagulation parameters, and changes in the INR do not necessitate dose adjustments. However, the quantitative assessment of the action of these drugs and their anticoagulant activity might be necessary in life-threatening conditions, such as severe thrombotic or bleeding events, the need for urgent surgery, acute hepatic or renal failure, interaction with other drugs, or overdose.

Compared with VKAs, monitoring the action of NOACs is much more difficult. The INR assays are not relevant in this group of patients.[9] Furthermore, all of the above medications have a different impact on coagulation parameters, depending on the current plasma levels of the drug. Therefore, in order to correctly interpret coagulation parameters during treatment with NOACs, the physician must know the time elapsed from the last dose of the drug, and also the time to peak and trough plasma levels of the drug. The results obtained from a blood sample collected 3 hours after taking the drug will be significantly different from those obtained after 12 or 24 hours, or even 6 hours after the drug has been taken. TABLE 2 provides the expected ranges of the peak and trough plasma levels of specific NOACs, and of the blood coagulation parameters impacted by those drugs.[4] Furthermore, depending on the patient's general condition, sometimes it is necessary to consider also the changes in the half-life of the drug, which depend, among other, on renal function. This is particularly important for dabigatran, which is metabolized mostly in the kidneys.

In the case of NOACs, fewer interactions with food have been observed as compared with VKAs. The food ingestion does not affect the action of dabigatran and apixaban, and those 2 medications can be taken with or without food.[10,11] The absorption of dabigatran depends on the acid-alkaline balance in

TABLE 2 Plasma levels of non–vitamin K antagonist oral anticoagulants (NOACs), and blood coagulation parameters in patients treated with NOACs[4]

Parameter	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Expected peak plasma level range, ng/ml	64–443	69–321	91–321	184–343
Expected trough plasma level range, ng/ml	31–225	34–230	31–230	12–137
PT	↑	(↑)	↑(↑)	↑↑(↑)
aPTT	↑↑(↑)	(↑)	↑	↑
ACT	↑(↑)	↑	↑	↑
dTT	↑↑↑↑	–	–	–

Abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; PT, prothrombin time

the gastrointestinal tract, but drugs such as proton pump inhibitors and H_2 receptor antagonists have only a minor impact on its absorption. Thus, dabigatran can be taken concomitantly with those agents.[12,13] On the other hand, taking rivaroxaban with food increases its absorption and bioavailability by around 39%, so it is recommended to take this drug with food. Detailed information on the absorption, bioavailability, and metabolism of specific NOACs is provided in TABLE 3.

Despite the fact that, compared with VKAs, NOACs have markedly fewer interactions, adverse reactions caused by concomitant use of other substances cannot be ruled out for those

agents. This issue has been discussed in detail in the new 2018 practical guidelines of the European Hearth Rhythm Association.[4]

The mechanism of action of NOACs is also related to the inhibition of protease-activated receptors (PARs). Inhibition of PAR1 and PAR2 impacts multiple cells other than platelets and hampers a number of processes leading to atherosclerosis. Importantly, rivaroxaban affects not only PAR1 (as do VKAs and the direct thrombin inhibitor dabigatran), but also PAR2, thus reducing local inflammation, migration of leukocytes through endothelium, angiogenesis, and the volume of the atherosclerotic plaque in animal models, translating directly into anti-inflammatory and antiatherosclerotic action. However, although the PAR2 inhibition hypothesis is based on experimental in vitro models, the analysis of other clinical trials of PAR-affecting drugs appears to confirm that medications devoid of impact on PA2 are less beneficial. One example of such a drug is vorapaxar, a PAR1 antagonist which reduces the risk of revascularization in patients with PAD, while increasing bleeding risk due to the dominant PAR1 distribution on platelets.[14] The pleiotropic effect of rivaroxaban seems most likely if we consider the fact that beneficial effects can be observed even for small, "vascular" doses of the drug (2 × 2.5 mg), and the reduction of the primary endpoint, namely, all-cause mortality, in the COMPASS trial is characteristic for pleiotropic drugs. The mechanism of action of NOACs through PAR1 and PAR2 is illustrated in FIGURE 2.[15]

TABLE 3 Absorption and metabolism of non–vitamin K antagonist oral anticoagulants[4]

Properties	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Bioavailability, %	3–7	50	62	66 when taken without food; 80–100 with food
Prodrug	Yes	No	No	No
Nonrenal/renal clearance in percentages of the dose (with nonimpaired renal function), %	20/80	73/27	50/50	65/35
Binding to plasma proteins, %	35	87	55	95
Hepatic metabolism: using CYP3A4	No	Yes (elimination, moderate participation of CYP3A4 ~25%	Minimal (elimination <4%)	Yes (hepatic elimination ~18%)
Absorption depending on food intake	No impact	No impact	Absorption improved by 6%–22%	Absorption improved by 39%
Absorption depending on the use of H2 receptor antagonists and proton pump inhibitors, %	–12 to –30	No impact	No impact	No impact
Asian patient effect, %	+25	No impact	No impact	No impact
Half-life, h	12–17	12	10–14	5–9 in younger patients; 11–13 in older patients
Other	Dyspepsia (5%–10%)	–	–	15 mg/20 mg doses – obligatory taking with food

Outcomes of randomized trials comparing vitamin K antagonists and non–vitamin K antagonist oral anticoagulants in patients with atrial fibrillation undergoing percutaneous coronary intervention Optimal combined antiplatelet and anticoagulant therapy and the length of the combined treatment in patients with AF undergoing PCI is still extensively studied. Initiating 1 or 2 antiplatelet agents after PCI in patients who require anticoagulant treatment increases the bleeding risk. Dual antiplatelet treatment can be shortened or extended, depending on the clinical and angiographic assessment of the patient, rather than the type of the stent used (drug-eluting stent or bare metal stent). Drug-eluting stents are associated with a lower risk of stent thrombosis in the long-term than bare metal stents. Furthermore, recent studies suggest that short DAPT (1 month after the procedure in patients with stable angina, or 6 months after ACS) is safe for elderly patients and those with a high risk of bleeding complications.[16-19] The currently applicable treatment strategies for patients after elective PCI, published in the guidelines are constantly evolving according to the outcomes of the latest research. The trend of those changes especially in patients with high bleeding risk leans towards a more

frequent use of NOACs than VKAs, and use dual therapy, that is, OACs combined with only 1 antiplatelet agent, to reduce the risk of hemorrhagic complications. At the same time, such an approach seems to be safe and does not increase the risk of recurrent ischemia and mortality.[4,6,7]

The first randomized trial to demonstrate the benefits of a single antiplatelet drug combined with warfarin was WOEST (What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing).[1] The trial assessed treatment with clopidogrel and warfarin as compared with standard triple therapy with the addition of ASA. The risk of bleeding events was reduced in the group treated only with clopidogrel and VKA compared with the standard triple therapy, mainly due to lower rates of minor bleeding (major and minor bleedings, 14.0% vs 31.3%, respectively, P <0.0001; major bleedings, 3.2% vs 5.6%, P = 0.16). The rate of myocardial infarctions (3.25% vs 4.6%), stroke (1.1% vs 2.8%), repeated target vessel revascularization (7.2% vs 6.7%), and stent thrombosis (1.4% vs 3.2%) did not differ significantly between the groups. Total mortality after 1 year was significantly lower in the dual therapy group (2.6% vs 0% to 6.4%, P = 0.027).[1] Nevertheless, the study lacked statistical power to allow a reliable assessment of the impact of the applied therapies on long-term clinical outcomes.

Further studies compared strategies of standard triple therapy (VKA + DAPT), NOAC and a single antiplatelet agent versus NOACs and

FIGURE 2 Illustration of protease-activated receptors (PAR) 1 and 2 cellular locations, and the potential impact of thrombin- or Xa-mediated PAR activation on the blood vessel wall and the myocardium, and the resulting atherosclerotic process and atrial fibrillation (modified from Spronk et al[15])
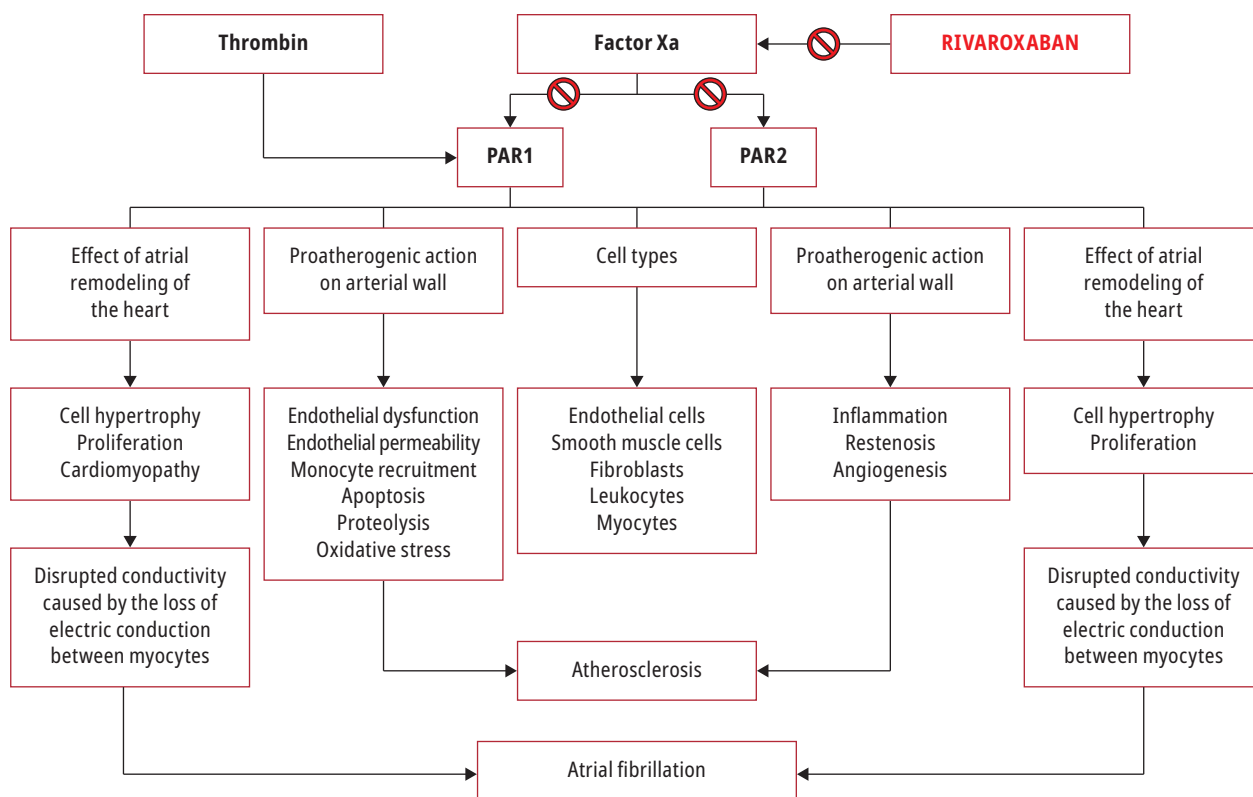
DAPT. The PIONEER AF-PCI trial (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention) assessed the safety of 3 treatment strategies after PCI with stent implantation in 2124 patients with paroxysmal, persistent, or permanent AF.[20] The applied treatment regimens were as follows: 1) rivaroxaban in small doses, ie, 15 mg once daily (10 mg if creatinine clearance was 30 to 50 ml/min) plus a $P2Y_{12}$ inhibitor for 12 months; 2) rivaroxaban in very small doses (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months. After the completion of 1- or 6-month DAPT, the patient received 15 mg once daily of rivaroxaban (10 mg if creatinine clearance was 30 to 50 ml/min) plus a small dose of ASA (75 to 100 mg/d) for the remaining part of the 12-month treatment; 3) standard triple therapy with VKA (warfarin) once daily (target INR, 2.0–3.0) plus DAPT for 1, 6, or 12 months. The patients treated with 1- or 6-month regimens were subsequently treated with warfarin and ASA in doses as specified above for the remaining part of the 12-month treatment.

The PIONEER AF-PCI trial showed that both dosing regimens of rivaroxaban reduced the risk of clinically relevant bleeding complications after 1 year of treatment, as compared with standard triple therapy with VKA and variable duration of DAPT (16.8% in group 1, 18.0% in group 2, and 26.7% in group; hazard ratio [HR] 1 vs 2, 0.59; 95% CI, 0.47–0.76; HR 2 vs 3, 0.63; 95% CI, 0.50–0.80). In both groups treated with rivaroxaban, there was also a much lower incidence of bleeding episodes requiring medical attention than in the standard therapy group (HR 1 vs 3, 0.61; 95% CI, 0.47–0.80; HR 2 vs 3, 0.67; 95% CI, 0.52–0.86). The rate of cardiovascular death, myocardial infarction, and stroke was comparable across the 3 groups. Nevertheless, the statistical power of the trial for the assessment of these secondary endpoints was insufficient to draw definite conclusions. The rate of stent thrombosis was low and similar across all groups. It should also be pointed out that rivaroxaban 2.5 mg twice daily had not been previously studied in the context of stroke prevention in patients with AF.[20]

The RE-DUAL PCI trial (Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting) assessed the safety of 2 doses of dabigatran (110 mg or 150 mg twice daily) combined with clopidogrel or ticagrelor (dual therapy without aspirin), as compared with standard triple therapy (VKA, ASA, and clopidogrel or ticagrelor) in 2725 patients with AF who were undergoing PCI.[2] The rate of the composite endpoint major bleeding and clinically overt nonmajor bleeding, as well as of major bleeding events assessed separately, was significantly reduced in groups receiving dual therapy with 110 mg and 150 mg of dabigatran, as compared with standard triple therapy with VKA and DAPT. Although the lack of statistical power of the trial did not allow for a reliable assessment of individual components of the endpoint separately, it showed that NOAC and single antiplatelet drug are noninferior to standard triple therapy regarding the composite endpoint (death, stroke, thromboembolic events, or unplanned revascularization) (P = 0.005). In patients with AF who were undergoing PCI, both doses of dabigatran used in the RE-DUAL PCI trial, combined with a $P2Y_{12}$ inhibitor, significantly reduced bleeding complications as compared to triple therapy with warfarin, a $P2Y_{12}$ inhibitor, and ASA.[2] There was also equivalence in observed prevention of thromboembolic events. Additionally, a meta-analysis of the WOEST, PIONEER AF-PCI, and RE-DUAL PCI studies suggested that the probability of an increased risk of thromboembolic events during dual therapy is low compared to triple therapy.[21]

Two ongoing studies with NOACs (ENTRUST-AF PCI [Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention] and AUGUSTUS [A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart]) will undoubtedly expand our knowledge and should provide answers to the questions of how long triple therapy should be used after PCI in patients with AF, and whether it should be used at all.[22,23] In particular, the AUGUSTUS trial with apixaban should provide insight into whether administering dual therapy with apixaban and clopidogrel, and dual therapy with warfarin and clopidogrel, has comparable or higher efficacy than respective triple therapies, and if so, then which of the 4 studied treatment strategies is optimal in terms of benefits and protection against ischemic events and the risk of bleeding complications. The difficulties with providing the clear guidelines also arise from the fact that the studies with both rivaroxaban and dabigatran did not have sufficient statistical power to confirm the equivalence of reduced doses of those agents in the prevention of stent thrombosis and other ischemic events.

Additionally, data supporting the combination of NOACs with ticagrelor or prasugrel are limited. NOACs are currently not recommended for triple therapy regimens with these more potent $P2Y_{12}$ inhibitors by the latest ESC guidelines. Nevertheless, the situation may be different in dual therapy regimens.[7] In a subgroup of

TABLE 4 Summary of the outcomes of randomized trials on the use of oral anticoagulants and non–vitamin K antagonist oral anticoagulants after percutaneous coronary intervention in patients with atrial fibrillation (continued on the next page)

Trial / drug	Purpose	No. of patients	Selected inclusion criteria	Selected exclusion criteria	Endpoints	Conclusions
WOEST[1] VKA	Assessment of treatment with clopidogrel alone compared with ASA combined with clopidogrel in patients treated with oral anticoagulation after PCI	573	• Age 18–80 y • Long-term indication for OACs (at least 1 year after the end of study) • Significant coronary artery disease (at least 75% occlusion confirmed by angiography, or FFR <0.80), with an indication for PCI	• Intracranial bleeding episodes • Cardiogenic shock • Peptic ulcer within the previous 6 months • Thrombocytopenia (PLT levels <50 × 10^9/l) • Major bleeding within the previous 12 months (according to TIMI score)	Primary endpoint: • Occurrence of any bleeding episode during 1-year follow-up Additional endpoints: • Death • Myocardial infarction • Stroke • Repeated revascularization of artery after pci • Stent thrombosis	In patients taking OACs and undergoing PCI, the use of clopidogrel without aspirin significantly reduced hemorrhagic complications and did not increase the incidence of thrombotic events.
PIONEER AF-PCI[20] Rivaroxaban	Assessment of 3 management strategies in patients with nonvalvular AF who were undergoing PCI: 1. Rivaroxaban 15 mg or 10 mg once daily + P2Y$_{12}$ inhibitor for 12 months 2. Rivaroxaban 2.5 mg twice daily + DAPT for 1, 6, or 12 months, followed by rivaroxaban 15 mg or 10 mg once daily + ASA for up to 12 months 3. Standard triple therapy with warfarin once daily (INR 2.0–3.0) + DAPT for 1, 6, or 12 months, followed by warfarin + ASA for up to 12 months	2124	• Paroxysmal, persistent, or permanent nonvalvular AF • Current PCI with stent implantation	• History of stroke or TIA • Clinically relevant gastrointestinal bleeding within the previous 12 months • Creatinine clearance below 30 ml/min • Anemia of unknown etiology with hemoglobin levels below 10 g/dl • Other conditions known to increase bleeding risk	Primary safety endpoint: • Occurrence of clinically relevant bleeding during 1-year follow-up Secondary endpoints: • Major bleeding, minor bleeding, bleeding episodes requiring medical consultation, analyzed separately • Cardiovascular death, heart attack or stroke, analyzed jointly	In patients with AF who were undergoing PCI with stent implantation, treatment with rivaroxaban in small dose combined with P2Y$_{12}$ inhibitor for 12 months, and rivaroxaban in very small dose combined with DAPT for 1, 6, or 12 months was associated with a lower percentage of clinically overt bleeding episodes than standard treatment with OACs combined with DAPT. The efficacy of treatment was similar across the 3 groups; nevertheless, due to the broad CIs, the trial was inconclusive in this aspect.
RE-DUAL PCI[24] Dabigatran	Assessment of safety and efficacy of dual regimen (P2Y$_{12}$-inhibitor without ASA + dabigatran) compared with triple regimen (2 antiplatelet agents + warfarin) in patients with nonvalvular AF who were undergoing PCI: 1. Dabigatran 110 mg twice daily + P2Y$_{12}$ inhibitor 2. Dabigatran 150 mg twice daily + P2Y$_{12}$ inhibitor 3. Warfarin + P2Y$_{12}$ inhibitor + ASA <100 mg for 3 months (BMS) / 6 months (DES)	2725	• Patients with nonvalvular AF who were treated with VKAs or not before PCI, but had indications for long-term anticoagulant therapy • ACS treated with PCI with stent implantation, or stable coronary artery disease with ≥1 lesion effectively treated by PCI with stent implantation	• Cardiogenic shock or thrombolytic therapy of ACS • Stroke within the previous month • Major surgery within the previous month • Major bleeding within the previous month • Anemia • Kidney failure (eCrCl <30 ml/min), active liver disease	Primary endpoint: occurrence of a major or clinically relevant bleeding during 1-year follow-up Secondary endpoint: thromboembolic complications (heart attack, stroke or other embolism), death, or unplanned revascularization, assessed jointly	Among patients with AF who were undergoing PCI, the bleeding risk was lower in dual regimen with dabigatran and P2Y$_{12}$ inhibitor than in triple regimen with warfarin, P2Y$_{12}$ inhibitor, and aspirin. The dual therapy was noninferior to triple therapy in terms of thromboembolic events risk.

Trial / drug	Purpose	No. of patients	Selected inclusion criteria	Selected exclusion criteria	Endpoints	Conclusions
ENTRUST-AF PCI[22] Edoxaban	Assessment whether anticoagulation strategy based on edoxaban reduced the risk of hemorrhagic complications of PCI compared with OACs combined with standard dual antiplatelet regimen in patients with AF who required continuous OAC. Additionally, the relative risk of ischemic events was compared between the study groups. 1. Edoxaban 60 mg (or 30 mg) once daily + P2Y$_{12}$ inhibitor (clopidogrel) 2. VKA + P2Y$_{12}$ inhibitor (clopidogrel) + ASA 100 mg for 30 days	1500	• Nonvalvular AF with an indication for chronic antithrombotic therapy after a successful PCI with stent implantation • Angiographically and clinically successful PCI	• High risk of major bleeding or a history of major hemorrhagic complications • Ischemic stroke within the previous 2 weeks • Uncontrolled hypertension • Anemia (Hb <8 mg/dl) • Kidney failure (CrCl <15 ml/min)	Primary safety endpoint: incidence of major and clinically overt nonmajor bleeding Primary efficacy endpoint: cardiovascular death, stroke, thrombotic episodes, myocardial infarction, and some stent thrombosis, assessed jointly	The outcomes have not been published. The trial is ongoing, with planned end in March 2019.
AUGUSTUS[23] Apixaban	Comparison of apixaban and warfarin, and the assessment of the risks and benefits of ASA in patients with AF who were treated with PCI for ACS 1. Apixaban 5 mg twice daily (2×2.5 mg) + P2Y$_{12}$ inhibitor + ASA 2. Apixaban 5 mg twice daily (2×2.5 mg) + P2Y$_{12}$ inhibitor 3. Warfarin + P2Y$_{12}$ inhibitor + ASA 4. Warfarin + P2Y$_{12}$ inhibitor*P2Y$_{12}$ inhibitor for 6 months, ASA from the date of ACS to PCI/ randomization to PCI	4600	• Paroxysmal, persistent, or permanent AF requiring antithrombotic therapy • ACS (heart attack, unstable angina) treated with PCI within the previous 14 days	• Indications for chronic anticoagulation other than AF • Kidney failure (CrCl <30 ml/min) • Intracranial bleeding • History of or planned CABG due to the presence of ACS • Coagulopathy, active bleeding	Primary endpoint: • Major or clinically overt non-major bleeding within the previous 6 months Main secondary endpoint: • All-cause death or hospitalization Other secondary endpoints: • DeathHeart attack • StrokeStent thrombosis • Urgent revascularization • Hospitalization	The outcomes have not been published. The trial is ongoing, with planned end in December 2018.

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; ASA, acetylsalicylic acid; BMS, bare metal stent; CABG, coronary artery bypass grafting; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; eCrCl, estimated creatine clearance; FFR, fractional flow reserve; Hb, hemoglobin; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; PLT, platelets; VKA, vitamin K antagonist

RE-DUAL PCI, the use of ticagrelor combined with dabigatran proved that both treatment regimens are safe and efficient.[24] The outcomes of randomized trials on the use of OACs and NOACs after PCI in patients with AF are summarized in TABLE 4.

In summary, it should be noted that at the moment, there is no definite evidence supporting the routine use of dual therapy regimens (NOAC + P2Y$_{12}$ inhibitor) in patients with AF who are undergoing PCI. In patients at very high risk of recurrent ischemia, first-line treatment should be based on 1- to 6-month triple therapy regimens, as recommended by the current guidelines. If the bleeding risk dominates, as an alternative to the current regimens, dual therapy initiated immediately after PCI should be considered for patients with nonvalvular AF who require chronic anticoagulation treatment: 1) with rivaroxaban: 15 mg once daily combined with clopidogrel (10 mg with creatinine clearance of 30 to 49 ml/min); 2) with dabigatran: 150 mg twice daily or 110 mg twice daily combined with clopidogrel or ticagrelor.

Randomized trials with non–vitamin K antagonist oral anticoagulants (NOACs) in acute coronary syndromes and their clinical implications. The role of NOACs in acute coronary syndrome treatment: current guidelines of the European Society of Cardiology

The essential component of the treatment after ACS, regardless of the adopted strategy (pharmacological treatment, PCI, and/or CABG), is 12-month DAPT, with the combination of ASA and more potent P2Y$_{12}$ inhibitors (ticagrelor, prasugrel) as the preferred regimen. Combining ASA with clopidogrel is recommended only for patients taking chronic OACs (VKAs, NOACs), with contraindications to new P2Y$_{12}$ inhibitors, when such drugs are not available, or the patient refuses the regimen due to economic reasons.

Despite implementation of the current guideline recommendations, including myocardial revascularization, DAPT, and secondary prevention including aggressive reduction of low-density lipoprotein cholesterol, patients after ACS are still exposed to high risk of recurrent cardiovascular events. This might be partially related to prolonged increased thrombin production, which is observed in patients after ACS.[25] There is evidence that OACs can efficiently reduce the rate of ischemic events after ACS, and that the combination of OACs and antiplatelet agents is more efficient than using each of the class of drugs separately. However, combined therapy with warfarin or acenocoumarol is related to increased risk of bleeding complications.[26] Therefore, using OACs combined with antiplatelet drugs is recommended only in patients after ACS who have other indications for chronic anticoagulation (AF, mechanical valve prosthesis, left

ventricular thrombus, venous thromboembolism, etc). To reduce the bleeding risk, it is also recommended to shorten the triple therapy after drug-eluting stent implantation to 6 months, and in the case of a high risk of bleeding complications, to 1 month, or to use double therapy only. After early termination of triple therapy, it is recommended to continue treatment with dual therapy for up to 12 months after an ACS, with an anticoagulant (VKA or NOAC) combined with clopidogrel or ASA. After 12 months, it is recommended to switch the patient to monotherapy (VKA or NOAC).[7]

The introduction of NOACs into clinical practice triggered a series of studies assessing their safety and efficacy in the prevention of recurrent ischemic events in patients after ACS.

The APPRAISE II trial (Apixaban for Prevention of Acute Ischemic Events 2) assessed the outcome of treatment with apixaban, 5 mg twice daily, in patients after ACS who were receiving standard antiplatelet therapy. A total of 7392 patients were enrolled, but the trial was terminated early due to the lack of effect of the study treatment on the incidence of cardiac mortality, myocardial infarction, and ischemic stroke, with a significantly increased risk of hemorrhagic complications, including intracranial hemorrhages and severe fatal bleeding episodes.[27]

The RE-DEEM trial (Dose Finding Study for Dabigatran Etexilate in Patients With Acute Coronary Syndrome) assessed the impact of 4 different doses of dabigatran (50 mg, 75 mg, 110 mg, and 150 mg twice daily), as compared with placebo, on the risk of hemorrhagic complications and coagulation activity in 1861 patients after myocardial infarction (ST-segment and non–ST-segment elevation myocardial infarction) who were receiving standard antiplatelet therapy.[28] During 6-month follow-up in the dabigatran group, a dose-dependent 2- to 4-fold increase of the risk of bleeding complications was observed, as well as a reduction of the procoagulation activity of plasma, with an average reduction of D-dimer levels by 45% at 4 weeks of treatment. However, the trial did not have sufficient statistical power to assess the impact of different doses of dabigatran on the incidence of ischemic complications (death, myocardial infarction, ischemic stroke) and to evaluate in detail the risk to benefit ratio for the study treatment.[28]

Then the ATLAS ACS 2–TIMI 51 trial (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis In Myocardial Infarction-51) assessed the impact of treatment with rivaroxaban 2.5 mg twice daily and 5 mg twice daily versus placebo on the risk of ischemic and bleeding complications in 15 526 stable patients after ACS who were treated with DAPT.[29] Both doses of rivaroxaban

reduced the incidence of the primary efficacy endpoint (cardiac death, myocardial infarction, and stroke), but increased the risk of bleeding not related to coronary artery bypass grafting and of intracranial bleeding, with no differences in the incidence of fatal bleeding. The impact of treatment with rivaroxaban was dose dependent. The dosing regimen of 2.5 mg twice daily significantly reduced the incidence of cardiac death (2.7% vs 4.5%, P = 0.002), as compared with placebo. This effect was not observed for the regimen of 5 mg twice daily.[29]

Considering the outcomes of the above studies, the ESC guidelines for the management of ACSs without persistent ST-segment elevation in 2015, the management of acute myocardial infarction with ST-segment elevation in 2017, and for myocardial revascularization in 2018[5,6,30] recommended considering of adding rivaroxaban, 2.5 mg twice daily, to DAPT (grade of recommendation, IIb; level of evidence, B) only in patients: 1) without a history of stroke or transient ischemic attack; 2) treated with clopidogrel; and 3) in whom an increased risk of ischemic complications is identified, with a low risk of bleeding complications.

Clinical implications of randomized trials with non–vitamin K antagonist oral anticoagulants in chronic stable coronary artery disease and peripheral artery disease

In the ESC guidelines on PAD, antiplatelet monotherapy with ASA or clopidogrel is recommended for all symptomatic patients (IA). For asymptomatic patients with atherosclerosis of the lower extremities, antiplatelet therapy is not indicated (IIIA), while in asymptomatic patients with carotid stenosis exceeding 50%, antiplatelet treatment with a low ASA dose should be considered (IIaC).[31] Similarly, patients after peripheral artery interventions who underwent 1-month DAPT have indications for treatment with ASA or clopidogrel. Chronic OAC treatment is applied only in the event of concomitant indications for such therapy: in the case of AF or prosthetic heart valve implantation. Oral anticoagulants can be combined with antiplatelet agents in patients with a recent history of revascularization.

The purpose of antiplatelet therapy is to prevent ischemia of extremities, but also to prevent cardiovascular events, which are a common cause of death in this population.[32] However, the authors of the guidelines did not refer to the outcomes of the COMPASS trial, as the results had not been published at the time. But, being aware of the early termination of the study due to the confirmed benefits of low-dose treatment with rivaroxaban + ASA, the authors of the guidelines took into consideration the need for further updating the guidelines.

The European guidelines for the management of stable CAD were published in 2013, that

is, several years before the COMPASS trial.[33] The guidelines for antiplatelet therapy in stable CAD are similar to those for PAD, recommending a single antiplatelet agent: ASA (IA) or clopidogrel (IB). Dual antiplatelet therapy is applied only to patients after PCI, and OACs are administered only if there are additional indications.[33]

The COMPASS trial outcomes, published in 2017, might change the way of management of atherosclerosis, both in stable CAD and in PAD.[3] The objective of the trial was to assess the safety and efficacy of rivaroxaban in monotherapy, rivaroxaban in the vascular dose with aspirin, and monotherapy with aspirin in reducing the risk of myocardial infarction, stroke, and cardiovascular death in CAD or PAD. It was a randomized, controlled, double-blinded trial conducted until the specified number of cardiovascular events had occurred. A total of 27395 patients with stable atherosclerosis (CAD and/or PAD) were enrolled in the trial and randomized into 3 groups: 1) rivaroxaban, 2.5 mg twice daily, and ASA, 100 mg; 2) rivaroxaban, 5 mg twice daily; and 3) ASA, 100 mg once daily.

Combined treatment is always associated with an increased risk of bleeding complications. Therefore, the dose of rivaroxaban for the study arm receiving combined treatment with ASA was adjusted according to the outcomes of the earlier ATLAS ACS 2-TIMI 51 trial, as described in the previous section.[29]

The COMPASS inclusion criteria provided detailed definitions of PAD and CAD. The PAD definition was as follows (one of the following criteria met):

1 History of aortofemoral bypass
2 History of limb bypass surgery
3 History of percutaneous angioplasty of iliac arteries
4 History of percutaneous angioplasty of subinguinal arteries
5 History of limb or foot amputation due to arterial disease
6 History of intermittent claudication, with at least one of the following criteria, met:
   a Ankle-brachial index <0.90
   b Significant (≥50%) peripheral artery occlusion, as confirmed by angiography or Doppler ultrasound examination
7 History of revascularization of carotid arteries
8 Asymptomatic stenosis of carotid artery (≥50%), as confirmed by Doppler ultrasound examination or angiography.

CAD was defined as follows (one of the following criteria):

1 Myocardial infarction over the past 20 years;
2 Multivessel CAD with current or a history of stable or unstable angina symptoms
3 Multivessel PCI
4 Multivessel CABG.

The inclusion criteria of the COMPASS trial were PAD or CAD. The CAD criterion was
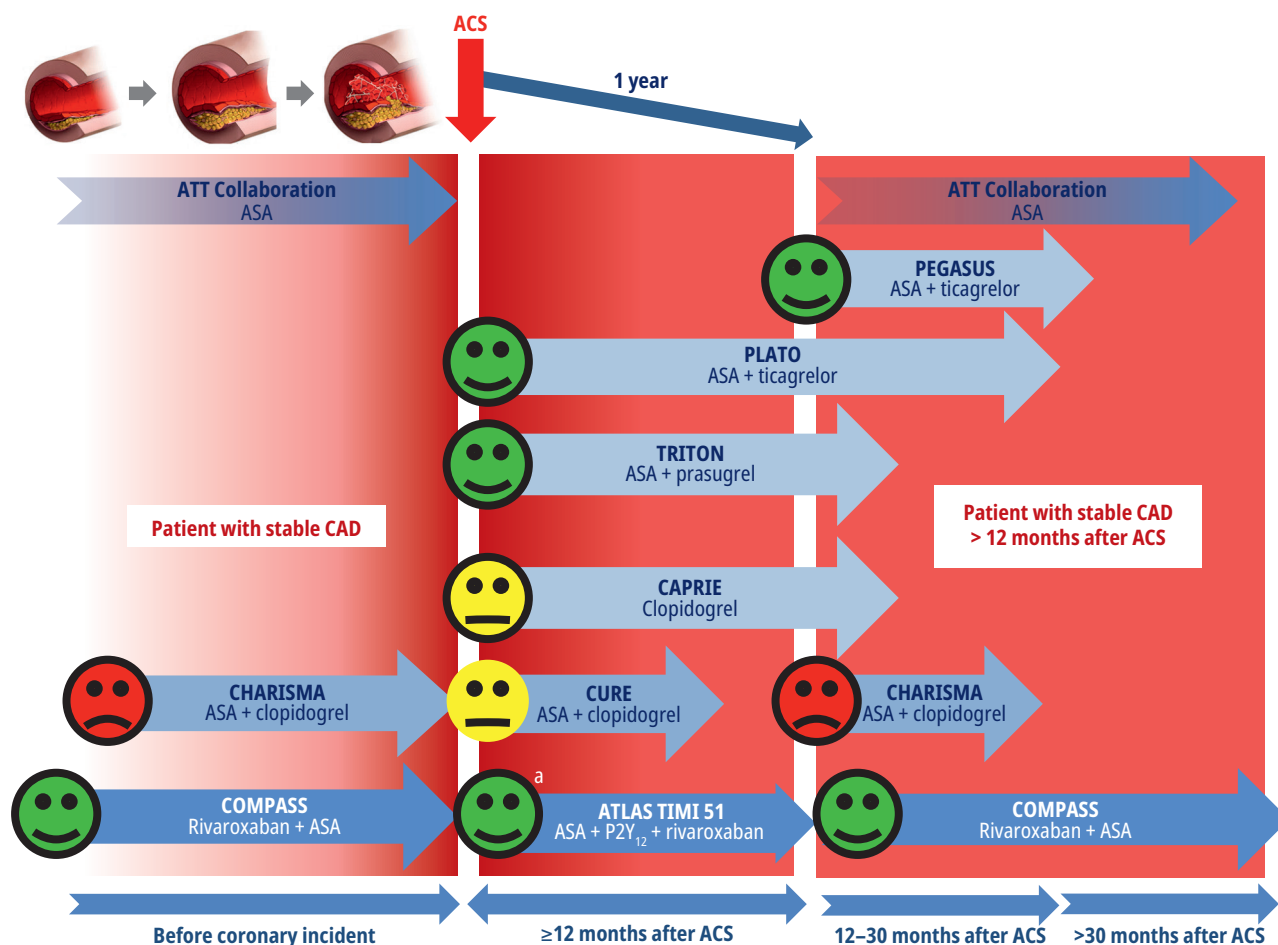
FIGURE 3 Key illustration of the experts' opinion on the use of non–vitamin K antagonist oral anticoagulants in patients with atherosclerosis of coronary and peripheral arteries in the context of other trials on antiplatelet and anticoagulation therapies. Description: The application of optimal models of antiplatelet / anticoagulant therapy in patients with coronary artery disease (CAD) was the objective of multiple randomized clinical trials. The treatment can be divided into 3 phases: before an acute coronary syndrome (ACS) in patients with stable CAD, immediately after ACS (adopting the most common model of a 1-year antiplatelet therapy after ACS), and follow-up treatment, ie, more than 1 year after ACS. Given that long-term management after ACS would not differ considerably from patient management before an ACS, the proposed figure could take the form of a circular model, where a patient who experienced an ACS many years earlier receives the same treatment as a patient under a coronary incident prevention strategy. In the figure, the "green smiley faces" indicate the outcomes of clinical trials that currently provide the strongest evidence, in an evidence-based medicine setting, for the preference of that model of treatment. The "red faces" indicate the trials in which the proposed model did not prove to be significantly better than the compared alternative (eg, CHARISMA trial). It should be noted that not all of the trials were randomized, prospective clinical programs (eg, ATT Collaboration); consequently, the use of acetylsalicylic acid (ASA) in monotherapy arises from an experts' consensus based on extensive meta-analysis of the trials, which are not marked with "faces"; some of the trials are marked as "neutral faces": these trials provide evidence for the proposed therapy, eg, ASA + clopidogrel after ACS, or clopidogrel instead of ASA after ACS), but the outcomes of more recent trials have degraded them to less preferred management strategies than, eg, ASA + ticagrelor or ASA + prasugrel.

a An alternative only for patients without a history of stroke or transient ischemic attack, who are treated with aspirin and clopidogrel; class IIbB recommendation according to the European Society of Cardiology guidelines[6]

applicable to patients aged 65 or older; for younger patients, concomitant atherosclerosis in 2 or more vascular beds was required, or 2 or more additional risk factors, such as active smoking, diabetes, kidney failure (estimated glomerular filtration rate <60 ml/min), heart failure, and nonlacunar ischemic stroke 1 month before or earlier.

Due to those inclusion criteria, the patients who were enrolled in the trial had very advanced atherosclerosis. It should be noted that patients requiring OACs or DAPT were excluded. It means

that AF patients as well as patients within 1 year after ACS or stent implantation were excluded from the trial.

Other exclusion criteria in the COMPASS trial included a stroke within the previous month or any hemorrhagic or lacunar stroke, advanced heart failure: New York Heart Association functional class III or IV, significant left ventricular dysfunction (ejection fraction <30%), advanced kidney failure (estimated glomerular filtration rate <15 ml/min), and use of antiplatelet agents other than ASA.

The trial was prematurely stopped due to confirmation of the efficacy of rivaroxaban, 2.5 mg twice daily, combined with ASA. The group receiving rivaroxaban, 5 mg twice daily, did not differ from ASA in terms of the occurrence of the composite endpoint, but the number of major bleeding episodes was higher in that group. The average follow-up was 23 months. In the group receiving rivaroxaban with ASA, the primary endpoint of cardiovascular death, stroke, and myocardial infarction occurred in 379 patients (4.1%) vs 496 (5.4%) in the ASA group (P <0.001). The relative reduction of events was 24% (HR, 0.76). Interestingly, the highest reduction of major events was related to stroke, which occurred in 142 patients (1.6%) in the ASA group, and in 83 (0.9%) in the ASA + rivaroxaban group (HR, 0.58; P <0.001). In the combined treatment group, a higher incidence of major bleeding was observed, that is, in 288 patients (3.1%) vs 170 patients (1.9%), P <0.001. The relative increase in major bleeding incidence was 70% (HR, 1.7). The number of fatal bleeding episodes and intracranial bleeding episodes did not differ significantly between the groups. The number of deaths was lower in the rivaroxaban + ASA group than in the ASA group: 313 (3.4%) vs 378 (4.1%), respectively (HR, 0.82; P = 0.01). Despite the significantly higher number of bleeding complications, considering the reduction of the composite endpoint, treatment with rivaroxaban, 2.5 mg twice daily, combined with ASA, 100 mg once daily, provided a clinical net benefit of 20% relative reduction of cardiovascular events.

In the population of the COMPASS trial, 90.5% to 90.8% of patients in each group had CAD, while PAD was present in 27.1% to 27.4% of the population. Peripheral artery disease was often accompanied by CAD. Aside from the outcomes for the entire COMPASS population, the trial outcomes were also assessed separately in the stable CAD population and the peripheral or carotid atherosclerosis group.[34,35] The outcomes of these cohorts were consistent with the outcomes of the entire COMPASS trial. There are some aspects warranting closer attention in the assessed populations. The most common hemorrhagic complication was gastrointestinal bleeding. The trial also assessed the suitability of proton pump inhibitors for reducing the incidence of gastrointestinal bleeding, using pantoprazole as the study drug. This part of the trial has not yet been published but may be useful for interpreting the outcomes.

Interestingly, a significant reduction of deaths was observed in patients with CAD treated with rivaroxaban and ASA, as compared to monotherapy with ASA: 262 (3%) of 8313 vs 339 (4%) of 8261, respectively (HR, 0.77; P = 0.0012), which was not observed in the PAD group. The difference may be caused by the size of the population.

For PAD, the number of deaths was 129 out of 2492 patients (5%) in the rivaroxaban + ASA group vs 142 out of 2504 patients (6%) in the ASA group. Additionally, a significant reduction in the incidence of major adverse limb events was shown, including amputations, which occurred in 32 patients (1%) treated with rivaroxaban + ASA vs 60 (2%) in the group treated with ASA alone (HR, 0.54; P = 0.0037).

It should be added that COMPASS was the first and thus far the only randomized trial assessing the action of NOACs in patients with chronic symptomatic atherosclerosis. Two earlier trials assessed the efficacy of warfarin in similar patient groups. The WARIS II trial (Warfarin-Aspirin Reinfarction Study II) assessed the action of warfarin, warfarin combined with ASA, and monotherapy with ASA in the treatment of 3630 patients who had experienced a myocardial infarction.[26] During 4 years of follow-up, a significant reduction in the incidence of the composite endpoint (death, myocardial infarction, or ischemic stroke) was shown compared with monotherapy with ASA, both in patients receiving monotherapy with warfarin and in the combined therapy group. However, the use of warfarin increased the risk of major bleeding complications (P <0.001). In the WAVE trial (Warfarin Antiplatelet Vascular Evaluation Trial I), 2161 patients with PAD were randomized to groups treated with OACs combined with an antiplatelet agent, or monotherapy with an antiplatelet agent.[36] During 3 years of follow-up, in the combined therapy group, no significant reduction in the incidence of the composite endpoint (cardiovascular death, myocardial infarction, or stroke) or peripheral atherosclerosis was shown, while an increase of the risk of life-threatening bleeding was observed (relative risk, 3.41; 95% CI, 1.84–6.35; P <0.001).[36]

In January 2018, enrollment into the VOYAGER PAD trial (Efficacy and Safety of Rivaroxaban in Reducing the Risk of Major Thrombotic Vascular Events in Subjects With Symptomatic Peripheral Artery Disease Undergoing Peripheral Revascularization Procedures of the Lower Extremities) was completed; 6500 patients with PAD referred for surgical or interventional treatment, who were receiving ASA, 100 mg/d, were randomized to receive rivaroxaban, 2 × 2.5 mg, or placebo. In this study, it is acceptable to simultaneously administer, for a short time following the intervention, $P2Y_{12}$ inhibitors. The study will end after reaching the specified number of 1015 events included in the composite efficacy endpoint of cardiovascular death, myocardial infarction, ischemic stroke, acute limb ischemia, or amputation. VOYAGER PAD is an international, multicenter, double-blinded randomized trial.[37]

In conclusion, the outcomes of the COMPASS trial might be a breakthrough in the management of atherosclerosis. Combined treatment

with rivaroxaban, 2.5 mg twice daily, and ASA, 100 mg, provides long-term clinical benefits both in stable CAD and in symptomatic PAD. Rivaroxaban, 2.5 mg twice daily, coadministered with ASA was registered for the prevention of atherothrombotic events in adult patients with CAD or symptomatic PAD at high risk of ischemic events.

Summary Oral anticoagulants are widely used for prevention of systemic thromboembolism, including the aim to reduce the risk of stroke in patients with AF and prosthetic heart valves. On the other hand, there is an increasing population of patients who require not only OACs but also DAPT. A typical example is a patient with AF and stable CAD or ACS, treated by PCI. The decision on the duration of triple therapy with OACs and DAPT is not an easy one and must be made based on the individual risk assessment of further thrombotic events, such as death, myocardial infraction, or ischemic stroke, and balancing the effect of treatment on the risk of major bleeding complications, such as hemorrhagic stroke and gastrointestinal bleeding, to determine the safety of the selected therapy. In recent years, with the introduction of NOACs, triple or dual therapy (NOAC + $P2Y_{12}$ inhibitor) has become safer and its efficacy is at least comparable to older drugs, namely, VKAs. This has been confirmed for 2 NOACs available on the Polish market: dabigatran (thrombin inhibitor) and rivaroxaban (coagulation factor Xa inhibitor). The outcomes of randomized trials with apixaban and edoxaban (both factor Xa inhibitors) will be published soon.

Regardless of the indications for the use of NOACs arising from the risk of stroke, and different concepts for treatment of patients who require simultaneous administration of antiplatelet agents due to PCI, rivaroxaban in the reduced ("vascular") dose has been proved to efficiently reduce the risk of further thrombotic events when added to DAPT in patients who have suffered an ACS. However, the ECS guidelines recommend caution, because such therapy increases the incidence of bleeding complications. The importance of an individual risks and benefits assessment cannot be overstated, hence the class of recommendation IIb ("may be considered"). The fact that it was no longer necessary to periodically assay INR and adjust the dose accordingly, as with the older generation of anticoagulants, acenocoumarol and warfarin, has also bolstered the popularity of NOACs.

The most interesting development, however, was the one nobody had anticipated, namely, the potential impact of the pleiotropic mechanism of action of NOACs through PAR1 and PAR2, present on the platelets and many other cells, and changing the course of atherosclerosis of coronary and peripheral arteries. These clinical benefits arising from the newly discovered action of NOACs have thus far been confirmed for one drug from this group, rivaroxaban. In the randomized, multicenter COMPASS trial, conducted on a study population of over 27 000 patients with stable CAD and/or PAD, it was shown that in the group treated with rivaroxaban combined with ASA, the primary outcome (composed of cardiovascular death, stroke, and myocardial infarction) occurred significantly less frequently than in the group treated only with ASA.[1] The relative reduction of events was 24%, with the incidence of stroke reduced the most. Also, the number of deaths was significantly lower in the rivaroxaban + ASA group than in the ASA alone group. Despite the significantly higher number of bleeding complications, considering the reduction of the composite endpoint, treatment with rivaroxaban, 2.5 mg twice daily, combined with ASA, 100 mg, provided a clinical net benefit of 20% relative reduction of cardiovascular events. In the subgroup of patients with PAD, a significant reduction of the incidence of major adverse limb events was shown, including amputations.

It appears that the outcomes of the COMPASS trial might be a new era in the treatment of atherosclerosis. Given the huge population of patients with CAD (approx. 3 million individuals) and/or PAD in Europe and in Poland, and the fact that cardiovascular diseases remain the main cause of death in Poland (51% in women and 41% in men, including patients in their productive age, ie, 18–65 years), any new therapy reducing the number of deaths and disabilities caused by arterial diseases is very important.[38] All the more so, the excess of the mortality rate in Poland is very high: 38% of men and 17% of women die before reaching the age of 65, which is the highest rate in the European Union.[39,40] The majority of those deaths are caused by cardiovascular diseases, mostly atherosclerosis. Therefore, the outcomes of the COMPASS trial can be expected to be included in the next edition of the ESC guidelines on the diagnosis and management of stable CAD and PAD. FIGURE 3 is the key illustration of the experts' opinion on the use of NOACs in patients with atherosclerosis of coronary and peripheral arteries in the context of other trials on antiplatelet and anticoagulation therapies. It should be also pointed out that the figure does not address stroke prevention in patients with AF. These trials are discussed in the section "Outcomes of randomized trials comparing vitamin K antagonists and non–vitamin K antagonist oral anticoagulants in patients with atrial fibrillation undergoing percutaneous coronary intervention."

Finally, the outcomes of the COMMANDER HF trial (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of

Death, Myocardial Infarction or Stroke in Participants With Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure), announced and simultaneously published at the 2018 ESC Congress, should be briefly discussed.[41] A total of 5022 patients with heart failure and increased levels of natriuretic peptides and left ventricular ejection fraction of 40% or less, CAD, and sinus rhythm, were treated with rivaroxaban, 2.5 mg twice daily, or placebo. Patients took drugs prescribed for heart failure (99.5%) and ASA (93.1%) or DAPT (34.8%). The incidence of the composite endpoint (all-cause death, stroke, and myocardial infarction) was similar in both groups, with similar levels of safety of both therapies. These outcomes show that both the basic mechanism of action of rivaroxaban (impact on the coagulation system) and the potential impact of pleiotropic mechanisms, that is, the drug's action through the aforementioned PAR1 and PAR2, are probably not the source of cardiovascular events in patients with heart failure.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/kardiologiapolska.

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