REVIEW ARTICLE

Antithrombotic therapy in patients with atrial fibrillation and acute coronary syndrome and / or undergoing percutaneous coronary intervention

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acute coronary syndrome, atrial fibrillation, dual antithrombotic therapy, percutaneous coronary intervention, triple antithrombotic therapy

ABSTRACT
The use of triple antithrombotic therapy (TAT) consisting of an oral anticoagulant (OAC), aspirin, and a P2Y12 inhibitor in patients with atrial fibrillation (AF) and acute coronary syndrome (ACS) and / or undergoing percutaneous coronary intervention (PCI) is associated with a high risk of bleeding. Recently, several randomized clinical trials tested the hypothesis as to whether dual antithrombotic therapy (DAT) regimens (consisting of an OAC and a single antiplatelet drug) may be safer in terms of bleeding events as compared with TAT. They also investigated the role of non–vitamin K antagonist oral anticoagulants (NOACs) as a part of DAT and TAT. The purpose of this review is to provide an overview of available evidence regarding the safety and efficacy of DAT compared with TAT regimens, international guidelines recommendations, knowledge gaps, and unmet needs in the management of patients with AF and ACS and / or undergoing PCI.

Introduction Atrial fibrillation (AF) is the most commonly sustained cardiac arrhythmia, with an estimated global prevalence of 3% in adults.[1] The prevalence of AF is increasing with age, ranging from 0.16% in those younger than 35 years to approximately 14% in those older than 85 years.[1] The principal therapy for prevention of cardioembolic stroke or systemic embolism in AF is oral anticoagulant (OAC) therapy, which includes vitamin K antagonist (VKA) oral anticoagulants or non–vitamin K antagonist oral anticoagulants (NOACs).[2] Hence, efforts are being made to improve uptake of stroke prevention in AF and to ensure persistence with therapy once initiated.[3,4] Given that AF and coronary artery disease (CAD) share many common risk factors, they often coincide, with the reported prevalence of CAD in patients with AF ranging from 6.4% to 46.5%.[5,6] The presence of CAD increases the risk of AF-related stroke.[7]

Patients with AF presenting with acute coronary syndrome (ACS) or undergoing elective percutaneous coronary intervention (PCI) require dual antiplatelet therapy (DAPT), including aspirin and a P2Y12 inhibitor to prevent stent thrombosis and recurrent coronary ischemia, and OACs for the prevention of AF-related cardioembolic stroke or systemic embolism (that is, triple antithrombotic therapy [TAT]). However, the use of TAT has been associated with a 2- to 4-fold increase in the risk of major bleeding in observational and randomized controlled trials (RCTs).[8,9] Practical decision-making in these patients therefore requires the assessment of stroke and bleeding risks in a pragmatic manner, using established risk stratification approaches.[10,11]

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Recent evidence from RCTs showed that the use of dual antithrombotic therapy (DAT), consisting of an OAC plus a P2Y12 inhibitor, was associated with a significant reduction in major bleeding events as compared with TAT, with no significant increase in the rate of trial-defined major adverse cardiovascular events (MACEs) including myocardial ischemia, stent thrombosis, and death. Nevertheless, the enthusiasm for the use of DAT early after ACS and/or PCI is counterbalanced by a note of caution, since these results come from trials focused on treatment safety, not powered to provide evidence on the efficacy of DAT compared with TAT. Whether DAT should be used as a default treatment option in all AF patients with ACS and/or undergoing PCI is currently intensely debated.

In this review, we provide an overview of available evidence concerning combined antithrombotic therapies in patients with AF and ACS and/or undergoing PCI, outline international guideline recommendations, and discuss knowledge gaps and unmet needs in the management of patients with AF and ACS and/or undergoing PCI.

Evidence summary

Randomized controlled trials Several RCTs have recently addressed the safety of omitting aspirin in combined antithrombotic treatment regimens in patients with ACS and/or undergoing PCI in whom long-term OAC use is indicated. The essential characteristics of those trials are shown in TABLE 1, whereas *Tables S1* and *S2* (Supplementary material) show the rates of safety and efficacy endpoints, respectively.

In the open-label WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) trial,[12] patients with an indication for long-term OAC use and undergoing PCI were randomized to receive DAT (a VKA plus clopidogrel) or standard TAT (a VKA, clopidogrel, and aspirin). At a 1-year follow-up, there were significantly less bleeding events in the DAT arm, although the difference was mostly driven by minor bleeding, without differences in major bleeding events and in the rates of thrombotic events. Notably, the overall major bleeding rates were low in the WOEST trial. In the trial cohort, 162 patients (69%) had AF, TAT was continued for 12 months only in those implanted with a drug-eluting stent (DES; 65% of patients), proton pump inhibitors (PPIs) were not routinely used, and the trial was underpowered to asses efficacy outcomes (ie, thrombotic events).

The first RCT that addressed the duration of TAT (a VKA, clopidogrel, and aspirin) was the ISAR-TRIPLE (Duration of Triple Therapy in Patients Requiring Oral Anticoagulation after Drug-Eluting Stent Implantation) trial.[13] It compared 6 weeks versus 6 months of TAT in patients after PCI and with an indication for VKA use (in 84% of patients, AF and/or atrial flutter was an indication for VKA use). After the prespecified TAT period, clopidogrel was discontinued and patients were receiving a VKA plus aspirin. During the 9-month follow-up, there was no significant difference in the primary endpoint (a composite of death, myocardial infarction [MI], definite stent thrombosis or Thrombolysis in Myocardial Infarction [TIMI] major bleeding). The trial was underpowered to address the individual components of the primary endpoint. Nevertheless, the ISAR-TRIPLE trial showed that duration of TAT could be shortened in selected patients at high risk of bleeding. Another analysis of this cohort showed that patients showing an enhanced response to clopidogrel (as measured by adenosine diphosphate–induced platelet aggregation) had significantly higher rates of major bleeding and death.[14]

Following the approval of NOACs for stroke prevention in patients with AF, several RCTs investigated the safety of NOACs and aspirin discontinuation in patients requiring a combined antithrombotic therapy for AF and ACS and/or PCI.

In the open-label PIONEER-AF (Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI) trial,[15] patients were randomized in a 1:1:1 ratio to: 1) rivaroxaban 15 mg (or rivaroxaban 10 mg in patients with moderate renal impairment) plus a P2Y12 inhibitor for 12 months; 2) rivaroxaban 2.5 mg twice daily and DAPT; or 3) standard TAT with a VKA plus DAPT in patients with AF and ACS (medically managed or with PCI) or elective PCI. A P2Y12 inhibitor was withdrawn from TAT after 1 month, 6 months, or 12 months, while aspirin was continued. After 12 months, the rates of bleeding events were significantly lower in the rivaroxaban-based treatment regimens compared with the standard TAT (ie, a VKA plus DAPT). Although there were no significant differences in ischemic events including stroke, MI, and stent thrombosis, the number of these events was small, and the trial was not sufficiently powered to address individual efficacy components. Notably, neither dose of rivaroxaban used in that trial (that is, a reduced dose of 15 mg once daily or a very low dose of 2.5 mg twice daily) was tested in the landmark ROCKET AF (Rivaroxaban Versus Warfarin in Nonvalvular Atrial Fibrillation) trial for the prevention of cardioembolic stroke or systemic embolism in patients with AF (of note, the ROCKET AF trial tested the 20-mg rivaroxaban dose once daily with dose reduction to 15 mg once daily in patients with creatinine clearance <50 ml/min).[16] Full-dose rivaroxaban was not used in the PIONEER-AF trial based on the ATLAS ACS-TIMI 46 (Rivaroxaban Versus Placebo in Patients with ACS) study results,[17] which showed an excess in the bleeding risk when rivaroxaban 20 mg was

TABLE 1 Main characteristics of the WOEST, PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, and ENTRUST-AF PCI trials

		WOEST	PIONEER AF-PCI	RE-DUAL PCI	AUGUSTUS	ENTRUST-AF PCI
Year of publication		2013	2016	2017	2019	2019
Cohort size, n		573	2124	2725	4614	1506
Randomization window after index event[a]		4 hrs	72 hrs	120 hrs	14 d	5 d
Treatment strategies		VKA + P2Y12 inhibitor vs VKA + DAPT	Rivaroxaban 15 mg once daily + P2Y12 inhibitor vs rivaroxaban 2.5 mg twice daily + DAPT vs VKA + DAPT	Dabigatran 110 mg twice daily + P2Y12 inhibitor vs dabigatran 150 mg twice daily + P2Y12 inhibitor vs VKA + DAPT	Apixaban 5 mg twice daily + DAPT vs apixaban 5 mg twice daily + P2Y12 inhibitor vs VKA + DAPT vs VKA + P2Y12 inhibitor	Edoxaban 60 mg once daily + P2Y12 inhibitor vs VKA + DAPT
Clinical settings, %	Elective PCI	72.5	61.5	49.5	38.8	48
	Primary PCI	27.5	38.5	50.5	37.3	52
	Medically managed ACS	0	0	0	23.9	0
P2Y12 inhibitor, %	Clopidogrel	100	94.4	87.9	92.6	92
	Ticagrelor	0	4.3	12.1	6.2	7
	Prasugrel	0	1.3	0	1.2	0.5
TAT regimen duration, mo		1–12 (BMS) or 12 (ACS and DES)	1, 6, or 12	1 (BMS) or 3 (DES)	6	1–12
DAPT regimen		VKA + clopidogrel	OAC + aspirin	OAC + P2Y12 inhibitor	OAC + P2Y12 inhibitor	OAC + P2Y12 inhibitor
Follow-up, mo		12	12	14	6	12
Safety endpoint		Any bleeding event	A composite of TIMI major bleeding or minor bleeding	Major or CRNM ISTH-defined bleeding	Major or CRNM ISTH--defined bleeding	Major or CRNM ISTH-defined bleeding
MACE definition		A composite of death, MI, stroke, target vessel revascularization, and ST	A composite of CV death, MI or stroke, and ST	A composite of all--cause death or an ischemic event (including stroke, MI, SE, or nonelective revascularization)	A composite of all-cause death or an ischemic event (including stroke, MI, definite or probable ST, and urgent revascularization)	A composite of CV death or an ischemic event (including stroke, MI, definite ST, SE)

a All patients received TAT in the period from the index event to randomization. In the AUGUSTUS and ENTRUST-AF PCI trials, the median (interquartile range) time from the index event to randomization was reported and was 6 (1–10) days and 45.1 (22.2–76.2) hours, respectively.[22,27]

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; BMS, bare-metal stent; CRNM, clinically relevant nonmajor; CV, cardiovascular; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; ISTH, International Society on Thrombosis and Haemostasis; MACE, major adverse cardiovascular event; MI, myocardial infarction; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; SE, systemic embolism; ST, stent thrombosis; TAT, triple antithrombotic therapy; TIMI, Thrombolysis in Myocardial Infarction; VKA, vitamin K antagonist

combined with DAPT. The very low–dose rivaroxaban regimen was chosen based on the ATLAS ACS 2–TIMI 51 (Rivaroxaban in Patients with a Recent Acute Coronary Syndrome)[18] trial results, which showed that adding rivaroxaban 2.5 mg twice daily to DAPT in patients with ACS resulted in significantly lower rates of the primary endpoint (a composite of cardiovascular death, MI, or stroke) in patients with ACS in sinus rhythm.

The RE-DUAL PCI (Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation) trial[19] compared dabigatran 150 mg twice daily or 110 mg twice daily plus a P2Y12 inhibitor versus standard TAT that included a VKA plus aspirin plus a P2Y12 inhibitor in patients with AF and ACS (medically managed or with PCI) or elective PCI. The rates of the primary endpoint of major or clinically relevant nonmajor (CRNM) bleeding were significantly lower with DAT consisting of dabigatran and a P2Y12 inhibitor. In contrast to the PIONEER-AF trial using the reduced 15-mg rivaroxaban dose, both dabigatran doses used in the RE-DUAL PCI trial were tested in the landmark RE-LY (Dabigatran Versus Warfarin in Patients with Atrial Fibrillation) trial for stroke prevention in patients with AF.[20] The RE-DUAL PCI trial was also underpowered to show the efficacy of DAT (dabigatran plus a P2Y12 inhibitor) in the prevention

of thromboembolic events. Of note, the rates of thrombotic events including stent thrombosis were numerically the highest among patients receiving DAT consisting of dabigatran 110 mg twice daily and a P2Y12 inhibitor, thus questioning the efficacy of this combination, particularly in patients at higher risk of ischemia.

These 2 NOAC trials compared DAT consisting of a NOAC plus a P2Y12 inhibitor and TAT including warfarin plus DAPT, but neither assessed whether TAT with a NOAC plus DAPT would lead to a lower incidence of bleeding events than TAT consisting of warfarin plus DAPT. Overall, it could not be determined based on firm evidence that the lower rates of bleeding were associated with the use of a NOAC, aspirin discontinuation, or both. There is the ongoing COACH-AF-PCI (Dabigatran Versus Warfarin with NVAF Who Undergo PCI) trial[21] that will compare dabigatran in TAT and the standard TAT with a VKA.

The double-blind AUGUSTUS (Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation) trial,[22] with a 2-by-2 factorial design, was the first to compare aspirin versus placebo and apixaban 5 mg twice daily (patients who met the prespecified criteria received a reduced dose of 2.5 mg twice daily)[23] versus a VKA in the respective DAT and TAT regimens. The study showed that patients who received apixaban-based treatments (either DAT or TAT) had significantly lower rates of International Society on Thrombosis and Haemostasis (ISTH) criteria–defined major or CRNM bleeding compared with the VKA-based DAT or TAT treatments. Nevertheless, the rates of bleeding-related hospitalizations were more than 2-fold higher in patients receiving TAT compared with DAT,[24] and the lowest bleeding rates were observed among patients receiving apixaban, a P2Y12 inhibitor, and placebo, and the highest in those receiving a VKA, aspirin, and a P2Y12 inhibitor. At 6 months, ischemic event rates including stent thrombosis were higher in the DAT regimens than in the TAT regimens. Most of stent thrombosis events (approximately 80%) occurred in the first 30 days of PCI; the event rates were lower in aspirin versus placebo arms and apixaban versus VKA arms, although the overall number was low.[25] The AUGUSTUS trial was also underpowered to assess the efficacy of DAT regimens for stent thrombosis and MI. Notably, the AUGUSTUS trial was the only one that included medically treated patients with ACS (n [%] = 1097 [23.9]), and prespecified subgroup analysis showed consistently better safety and similar efficacy of apixaban versus VKA regimens in patients with medically managed ACS.[26]

The open-label ENTRUST-AF PCI (Edoxaban-Based Versus Vitamin K Antagonist–Based Antithrombotic Regimen after Successful Coronary Stenting in Patients with Atrial Fibrillation) trial[27] investigated DAT consisting of edoxaban 60 mg once daily[28] and a P2Y12 inhibitor versus TAT consisting of a VKA plus DAPT in patients with AF and undergoing PCI. At 12 months, the primary endpoint (major or CRNM ISTH-defined bleeding) rate was significantly lower for DAT compared with TAT, with a nonsignificant difference in the rates of thrombotic events. Owing to the relatively small study population, the ENTRUST-AF PCI trial was underpowered to assess efficacy outcomes.

Meta-analysis Several meta-analyses of these RCTs were conducted in order to provide greater insight into the effects of specific treatment regimens regarding ischemic events. All of them have shown that DAT regimens are safer than TAT regimens not at the expense of the significantly higher rates of death, cardiovascular death, MACEs, and stroke, but have yielded conflicting results in terms of coronary ischemic events (ie, stent thrombosis and MI).

Lopes et al[29] analyzed the WOEST, PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS trials (including a total of 10 026 patients) and showed that, in comparison with VKA-based DAT and TAT regimens, the NOAC-based DAT regimen was the safest combination regarding the trial-defined primary safety outcome, with no significant difference in the efficacy outcomes including coronary ischemic events. Of note, this analysis also included 1097 medically managed patients with ACS from the AUGUSTUS trial, thus possibly underestimating the effect of aspirin discontinuation on stent thrombosis. Indeed, in a meta-analysis of the PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS trials (including a total of 9463 patients), Potpara et al[30] reported a significant, 67% higher risk for stent thrombosis with DAT versus TAT regimens when medically managed patients with ACS were excluded from the analysis.

After the publication of the ENTRUST-AF PCI trial, the meta-analyses including all 4 trials of NOAC use also showed conflicting results concerning coronary ischemic events. For example, the meta-analysis of the WOEST, PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, and ENTRUST-AF PCI trials by Lopes et al[31] (including a total of 11 542 patients) demonstrated lower bleeding rates and no significant difference in coronary ischemic events when DAT was compared with TAT. The results were consistent when the NOAC-based DAT was compared with the VKA-based TAT with regard to stent thrombosis (odds ratio [OR], 1.3; 95% CI, 0.61–2.64) and MI (OR, 1.15; 95% CI, 0.84–1.55). Another meta-analysis of the PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, and ENTRUST-AF PCI trials (including a total of 10 234 patients) by Gargiulo et al[32] showed that DAT regimens were safer than TAT in terms of the primary safety endpoint of ISTH-defined major or CRNM bleeding (risk ratio [RR], 0.66; 95% CI, 0.56–0.78;

P <0.001). This meta-analysis also demonstrated lower rates of intracranial hemorrhage (RR, 0.51; 95% CI, 0.24–1.11; P = 0.09) when DAT was compared with TAT, and this effect became statistically significant when the NOAC-based DAT was compared with the VKA-based TAT (RR, 0.33; 95% CI, 0.17–0.65; P = 0.001). In terms of efficacy outcomes, this meta-analysis indicated a trend towards a higher risk of MI (RR, 1.22; 95% CI, 0.99–1.52; P = 0.07) and a significantly higher risk of stent thrombosis (RR, 1.59; 95% CI, 1.01–2.5; P = 0.04) when DAT was compared with TAT. The trend remained consistent when the NOAC-based DAT was compared with the VKA-based TAT (MI: RR, 1.18; 95% CI, 0.93–1.52; P = 0.18; stent thrombosis: RR, 1.66; 95% CI, 0.99–2.41; P = 0.06).

In the end, to get firm evidence regarding the individual ischemic events, a large number of patients (tens of thousands) must be recruited in a trial, which is not practically feasible, because enrolling such a cohort would require several years of recruiting and result in overuse of funds. For example, in the PIONEER AF-PCI trial, around 2100 patients were recruited in a period of over 3 years.

What do international guidelines say? Current international guidelines and consensus documents agree that the duration of TAT should be minimized, balancing the patient's ischemic and bleeding risks (see TABLE 2). As ticagrelor and prasugrel were underrepresented in RCTs, guidelines recommend that these agents should be avoided in combination with OACs, except when there is a clear reason for such treatment choice (eg, early stent thrombosis in patients receiving clopidogrel).[33-38] Additional strategies that may mitigate the risk of bleeding in patients taking a combination of OACs and antiplatelet drugs include using the radial approach for coronary angiography, using the lowest dose of aspirin proven to be effective, adding a proton pump inhibitor, avoiding the concomitant use of nonsteroidal anti-inflammatory drugs, and optimizing the VKA therapy (see TABLE 2).[39]

Knowledge gaps **The timing of aspirin discontinuation after an index event** In the RCTs mentioned above, the use of aspirin was allowed until randomization (TABLE 1). Hence, these RCTs were not examining a true DAT from the very beginning of ACS / PCI or elective PCI, and a possible residual effect of aspirin could have influenced the results in terms of treatment safety and efficacy.

Dual antithrombotic therapy in patients at high risk of cardiac ischemic events Patients at high risk of coronary stent thrombosis and / or recurrent MI were largely underrepresented in the RCTs investigating the safety of antithrombotic therapy.

The prespecified subanalysis of the RE-DUAL PCI trial showed a reduced bleeding risk with no significant difference in the rates of ischemic events when the dabigatran-based DAT was compared with the VKA-based TAT, irrespective of clinical or procedural factors including a lesion, complexity, or both and irrespective of the modified DAPT[40] score (DAPT score ≥2 in 909 patients [33.4%]).[41] The clinical and / or procedural complexity factors used in this analysis were based on the DAPT (Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents) trial risk factors.[42] Clinical complexity factors included the presence of any of the following: ACS, acute ST-segment elevation MI, left ventricular ejection fraction <30%, and kidney failure (creatinine level ≥2 mg/dl or dialysis). The procedural (including lesion-related) factors included the presence of any of the following: more than 2 vessels stented, treatment of in-stent restenosis of a DES, prior brachytherapy applied to the target lesion, an unprotected left main lesion, more than 2 lesions in a single vessel, lesion length ≥30 mm, a bifurcation lesion with the side branch ≥2.5 mm, a vein bypass graft (segment or anastomosis), or a thrombus-containing lesion.[42,43] The modified DAPT score used in that subanalysis included the following factors with the prespecified scoring: age, MI at presentation, prior PCI or prior MI, vein graft PCI, current smoking status, diabetes mellitus, and history of congestive heart failure or left ventricular ejection fraction <30%.[41]

In another prespecified subanalysis of the RE-DUAL PCI trial, the risks of bleeding and stroke were higher in older (age ≥75 years) patients with AF and undergoing PCI compared with those younger (age <75 years). While DAT with the 110-mg dabigatran dose twice daily compared with the VKA-based TAT reduced the risk of bleeding in both older and younger patients, DAT with the 150-mg dabigatran dose twice daily did not reduce the risk of bleeding in older patients as compared with the VKA-based TAT, and the bleeding risk remained lower in younger individuals. There was a trend towards a higher risk of ischemic events in older patients receiving DAT with the 110-mg dabigatran dose twice daily as compared with the VKA-based TAT, with no increased ischemic risk noted in younger patients. In the study arm receiving DAT with the 150-mg dabigatran dose twice daily, there was no significant difference in ischemic events as compared with the VKA-based TAT in both older and younger patients.[44]

The use of more potent P2Y12 inhibitors in combination with non–vitamin K antagonist oral anticoagulants In the RCTs investigating the safety of antithrombotic therapy, clopidogrel was the main P2Y12 inhibitor used in more than 90% of participants. Clopidogrel is a prodrug that needs

TABLE 2 Formal guideline recommendations pertaining to the use of dual antithrombotic therapy or triple antithrombotic therapy in patients with atrial fibrillation and acute coronary syndrome and / or undergoing percutaneous coronary intervention

Guidelines	Highlights
2016 ESC AF Guidelines[33]	TAT duration from 1 month (for elective PCI), 1–6 months (for urgent PCI), to up to 12 months (for medically managed ACS), followed by DAT for up to 12 months In selected patients, DAT (any OAC and clopidogrel) could be considered. The lowest approved dose of NOACs for stroke prevention should be considered.
2017 ESC Focused update on dual antiplatelet therapy in coronary artery disease[34]	TAT duration from 1 month (for elective PCI, irrespective of stent type) to 6 months (for ACS / PCI), followed by DAT for up to 12 months DAT should be considered in patients in whom the bleeding risk outweighs the ischemic risk. The lowest approved dose of NOACs should be considered in TAT regimens and the lower part of recommended target INR (2 to 2.5) for VKA users. When rivaroxaban is used in combination with aspirin and / or clopidogrel, rivaroxaban 15 mg once daily may be used instead of rivaroxaban 20 mg once daily.
2018 ESC / EACTS Guidelines on myocardial revascularization[35]	TAT duration from 1 month (for elective PCI, irrespective of stent type) to 1 to 6 months (for ACS / PCI), followed by DAT for up to 12 months DAT should be considered in patients in whom the bleeding risk outweighs the ischemic risk. NOACs should be preferred over VKAs as a part of DAT or TAT regimens if not contraindicated. The lowest approved dose of NOACs should be considered in TAT regimens and the lower part of recommended target INR (2 to 2.5) for VKA users. When rivaroxaban is used in combination with aspirin and / or clopidogrel, rivaroxaban 15 mg once daily can be used instead of rivaroxaban 20 mg once daily. When dabigatran is used in combination with aspirin and / or clopidogrel, a dose of 150 mg twice daily may be preferred over a dose of 110 mg twice daily.
2018 EHRA Practical guide on the use of NOACs in patients with AF[36]	TAT duration from 1 month (for elective PCI) to 6 months (for ACS / PCI), followed by DAT for up to 12 months New-generation DES and radial access for interventional procedures should be preferred to reduce the risk of bleeding and duration of TAT.
2019 AHA / ACC / HRS Focused update of the 2014 AHA / ACC / HRS Guidelines for the management of patients with AF[37]	TAT duration from 4 to 6 weeks may be considered in patients with ACS with PCI, followed by DAT. In patients at high risk of bleeding, DAT containing a VKA and a P2Y12 inhibitor or rivaroxaban 15 mg once daily with a P2Y12 inhibitor or dabigatran 150 mg twice daily with a P2Y12 inhibitor can be considered in patients with ACS undergoing PCI.
2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes[38]	TAT duration for 1 week can be considered in patients at high risk of bleeding and low risk of stent thrombosis, followed by DAT (an OAC + a P2Y12 inhibitor). Otherwise TAT may last from 1 to 6 months. A NOAC is preferable over a VKA as a part of TAT or DAT regimens. The full approved dose of apixaban, rivaroxaban, edoxaban, and dabigatran for stroke prevention are recommended as a part of DAT and TAT regimens. In patients in whom the bleeding risk outweighs the ischemic risk, dabigatran 110 mg twice daily or rivaroxaban 15 mg once daily should be considered as a part of DAT or TAT. If a VKA is used, the dosage should be carefully adjusted with the target INR of 2 to 2.5 and TTR >70%. DAT with an OAC and either ticagrelor or prasugrel can be considered as an alternative to TAT in patients at moderate or high risk of stent thrombosis.

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; DAT, dual antithrombotic therapy; EACTS, European Association for Cardio-Thoracic Surgery; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; INR, international normalized ratio; NOAC, non–vitamin K antagonist oral anticoagulant; TTR, time in therapeutic range; others, see TABLE 1

biotransformation through hepatic cytochrome P-450 (CYP) enzymes into an active metabolite,[45,46] and around 30% of patients have a *CYP2C19* polymorphism with consequent resistance to clopidogrel and a higher risk of MACEs including stent thrombosis.[47] Whether this risk would be safely attenuated using a more potent P2Y12 inhibitor (ie, ticagrelor or prasugrel) in combination with an OAC is currently less well known, since patients receiving a more potent P2Y12 inhibitor were largely underrepresented in the RCTs of patients with AF and ACS and / or undergoing PCI.

A prespecified exploratory analysis of the RE-DUAL PCI trial showed that patients on ticagrelor (n [%] = 327 [12])compared with those who received clopidogrel had not only significantly higher rates of bleeding but also higher rates, of borderline significance, of ischemic events (a composite of death, thromboembolic events, or nonelective revascularization).[48] Notably, the use of ticagrelor in the RE-DUAL PCI trial was at the physician's discretion, and patients who received ticagrelor had a higher ischemic risk and clinical and procedural complexity (73% of patients in whom ticagrelor was prescribed presented with ACS) compared with those on clopidogrel.[48] The ongoing RT-AF (Rivaroxaban in Patients with Atrial Fibrillation and Coronary Artery Disease Undergoing Percutaneous Coronary Intervention) trial[49] will compare DAT

consisting of ticagrelor and rivaroxaban versus the VKA-based TAT in patients with AF undergoing PCI, and the CAPITAL PCI AF (The Safety and Efficacy of Rivaroxaban and Ticagrelor for Patients with Atrial Fibrillation after Percutaneous Coronary Intervention) nonrandomized study[50] will investigate rivaroxaban and ticagrelor use in patients with AF and undergoing PCI.

Other issues Given the predictable dose-related anticoagulant effect of NOACs, a routine measurement of NOAC blood levels is not justified. Whether highly selected patients (eg, those with recurrent bleeding and / or ischemia) would benefit from NOAC blood level measurement is presently unclear.[51]

Conclusions Optimizing antithrombotic therapy in patients with AF and ACS and / or undergoing PCI may be challenging and balancing the risks of bleeding and ischemic events is mandatory in each patient. The evidence shows that NOAC use, as an OAC strategy, is safer compared with the VKA-based treatment. This has been confirmed by results of clinical trials and real-world evidence supporting the safer profile of NOACs over VKAs, even in elderly patients with AF.[52,53]

Whereas the use of DAT consisting of an OAC (a NOAC in particular) and a P2Y12 inhibitor has been associated with a significant reduction in major bleeding and intracerebral hemorrhage in comparison with TAT, this safety benefit may be counterbalanced by an increased risk of coronary ischemic events with DAT, especially in high-risk patients. Notably, the risk of cerebrovascular ischemic events and mortality was broadly comparable across all treatment regimens in the pertinent RCTs.

No evidence is available to inform the use of a "true" DAT without at least a very short initial course of TAT. While early discontinuation of aspirin (eg, within a few days from presentation) may be considered as a default, caution is required in patients at high risk of recurrent coronary ischemic events who could benefit from a longer TAT course. More evidence is needed to better define the optimal timing of aspirin discontinuation and the use of more potent P2Y12 inhibitors in combination with OACs.

SUPPLEMENTARY MATERIAL

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

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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