REVIEW ARTICLE

Patients with atrial fibrillation undergoing percutaneous coronary intervention

Current concepts and concerns: part I

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ABSTRACT

Atrial fibrillation (AF) and coronary artery disease (CAD) often coexist. Both conditions confer an increased risk of acute thrombotic complications. However, the pathogenesis of thrombus development in AF and CAD is different. Coagulation activation is the main pathway in AF, and platelet activation is the hallmark of coronary thrombosis. Antithrombotic prophylaxis is essential in both conditions.

In patients with AF undergoing percutaneous coronary intervention (PCI), a combination of oral anticoagulation and antiplatelet therapy is required, which elevates the risk of major bleeding. This has to be balanced against the risk of stroke and stent thrombosis.

In the first part of the present review, the prerequisites for antithrombotic management in AF patients undergoing PCI are discussed. We cover the epidemiology of concomitant presentation of AF and CAD as well as differences in the pathogenesis of thrombus formation in both conditions. We evaluate data regarding a variety of antithrombotic regimens including triple therapy in line with stroke and bleeding risk assessment.

Overall, triple therapy is often warranted but should be for the shortest possible duration. Although much of the current guidance comes from observational data, well designed, adequately powered randomized clinical trials are emerging to further inform practice in this challenging area.

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Introduction Atrial fibrillation (AF) and coronary artery disease (CAD) often coexist. The pattern of this comorbidity has not changed significantly over the last decade.[1-5] In 2 recent registries (the EURObservational Research Programme AF [EORP-AF] Pilot General Registry and PREvention oF thromboembolic events—European Registry in AF [PREFER in AF]), which together collected prospective data from 16 participating European countries (over 10000 patients), approximately 20% to 35% of the patients were found to have CAD.[2,3] This was consistent across different types of AF (eg, new onset, paroxysmal, persistent, and permanent).[2] Up to half of these patients have had myocardial infarction (MI) or undergone coronary revascularization or both.[2,3]

Both AF and CAD confer an increased risk of acute thrombotic complications, that is, stroke or systemic embolism in AF, and acute coronary syndrome, in CAD. In the latter, percutaneous coronary intervention (PCI) with stent implantation is the standard of care.[6] It is also widely used in patients with stable CAD to relieve symptoms of myocardial ischemia due to flow-limiting coronary disease.[6-8] Patients undergoing PCI are at risk of stent thrombosis, particularly in the case of first-generation drug-eluting stents.[9] Antiproliferative substances profoundly inhibit the reparative response to arterial injury and delay endothelialization, thus leading to persistent prothrombotic and proinflammatory reactions as well as neointimal atherosclerotic change (neoatherosclerosis).[10,11]

Pathogenesis of thrombosis in atrial fibrillation and coronary artery disease The pathogenesis of thrombus development in AF and CAD is slightly

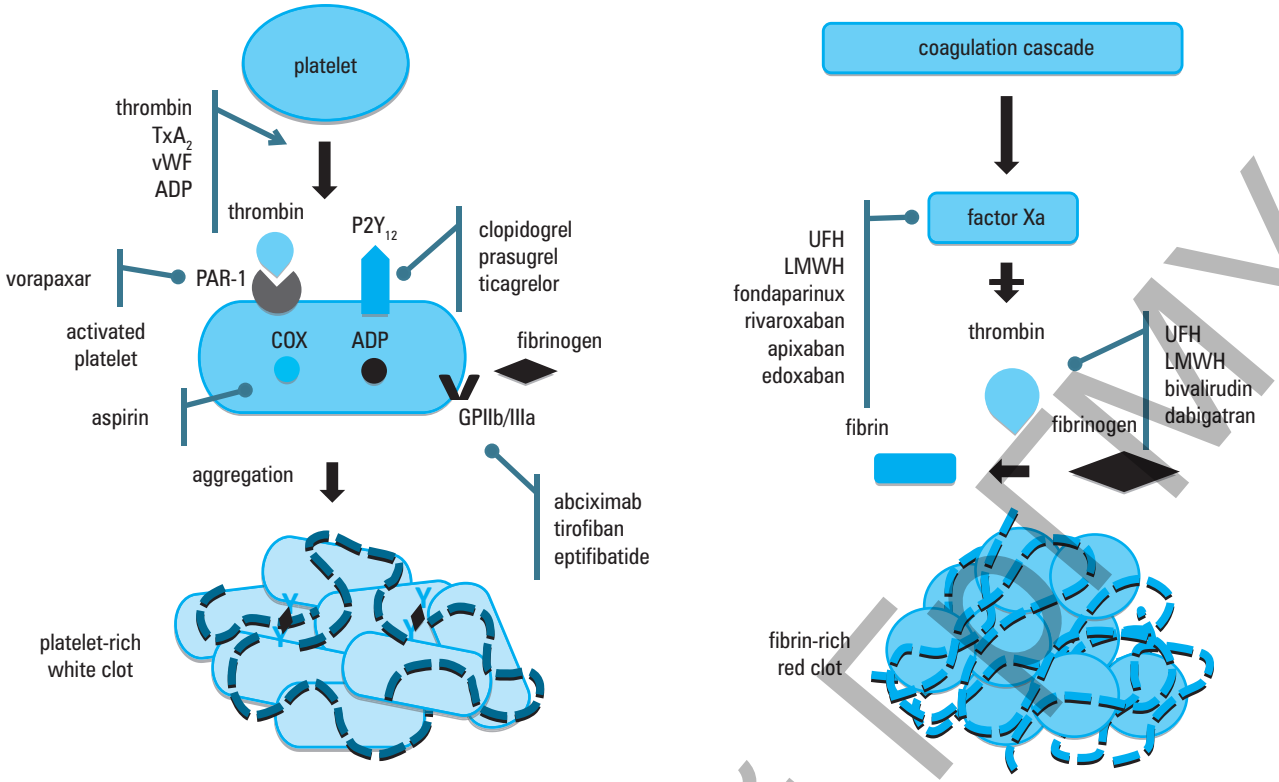

FIGURE Mechanisms of thrombogenesis and targets for antithrombotic drugs in atrial fibrillation and coronary artery disease Abbreviations: ADP, adenosine diphosphate; COX, cyclooxygenase; GPIIb/IIIa, glycoprotein IIb/IIIa; LMWH, low-molecular-weight heparin; PAR-1, protease activated receptor 1; TxA_2, thromboxane A_2; UFH, unfractionated heparin; vWF, von Willebrand factor

different (FIGURE). Clot structure is known to be affected by the velocity of blood flow and wall shear rates, which vary widely along blood vessels of different caliber and type and were found to reach the highest levels in the arteries, particularly at sites of stenotic lesions. Coagulation activation against the background of low flow, blood stasis, and increased expression of procoagulant factors, leading to fibrin-rich thrombus formation is the main pathway in AF, and platelet activation at sites of vascular injury under high flow resulting in platelet-rich thrombus development is a hallmark of coronary thrombosis.[12-15]

This results in differences to antithrombotic prevention, which is essential in both conditions. While patients with nonvalvular AF and 1 additional stroke risk factor (ie, the vast majority of AF population) clearly benefit from oral anticoagulation (OAC),[16-20] notwithstanding a sufficient protective effect of OAC in stable CAD,[21] those with ACS or stable CAD but undergoing stent implantation require antiplatelet therapy (FIGURE).[6]

Thus, AF patients undergoing PCI require a period of treatment with OAC and either single or dual antiplatelet therapy to inhibit both pathways, the combination of which increases the risk of major bleeding.[22-25] This must be weighed against the risk of stroke and stent thrombosis. Recent studies have focused on finding the ideal combination of antithrombotic therapy while maintaining efficacy and safety for patients.[22,23]

Current guidelines consist mainly of an expert opinion based on observational data, and prospective randomized clinical trials (RCTs) are warranted to inform modern clinical practice.[22,23] As a result, attempts to standardize antithrombotic therapy in AF patients undergoing PCI have proved difficult.[24,26-28]

The first part of the present review discusses some concerns related to combination antithrombotic therapy in patients with AF who need PCI in the acute or chronic setting (ie, balancing the risk of ischemic and hemorrhagic complications) as well as opportunities to reduce the risks, for example, with a combination of OAC and single antiplatelet therapy in lieu of dual antiplatelet therapy.

Concomitant atrial fibrillation and coronary artery disease New-onset AF, particularly if uncontrolled, may exacerbate preexisting CAD by causing an abrupt increase in myocardial oxygen demand, leading to ischemia that during sinus rhythm remains compensated. In turn, ion currents are particularly sensitive to oxygen supply, and hypoxia may cause ectopic flow in the atria and generate AF.[29,30]

In several studies, either new-onset or pre-existing AF was shown to have a negative impact on prognosis in patients with CAD treated with PCI (TABLE 1).[31-35] AF may result in progressive deterioration of systolic function if heart rate is not controlled. It confers an increased stroke risk and requires OAC (with or without antiplatelets), which, in turn, is associated with a risk of hemorrhage. Despite adjustment for possible confounders, AF appeared to be an independent predictor of death, stroke, and other adverse events. Baseline characteristics of AF patients were usually different from patients in sinus rhythm (eg, older age, worse renal function, lower left ventricular ejection fraction). Hence, it is not always obvious

TABLE 1 Studies on impact of atrial fibrillation on prognosis of patients with coronary artery disease

Study	No. of patients	Study design	Follow-up	Population	Clinical outcomes[a]							
					death, %	CV death, %	MI, %	TVR, %	stent thrombosis, %	ischemic stroke, %	MACE, %	major bleeding, %[b]
Chan et al. 2012[31]	3307	prospective, multicentre	1 month	PCI AF (prevalent) 4.9% ACS 64.7%	9.9 / 2.2[c] 2.78 (1.35–5.72)	8 / 1.7[c]	3.7 / 2.3	1.2 / 2.2	0.6 / 0.9	0.6 / 0.2[c]	13 / 5.5[c]	5 / 2.1[c,d]
Lopes et al. 2009[32]	5745	post hoc analysis of the APEX-AMI trial (prospective, double--blind, multicentre RCT)	90 days	STEMI, PCI AF (incident) 6.3%	1.81 (1.06–3.09)[c]	NR	NR	NR	NR	2.98 (1.47–6.04)[c]	NR	13.8 / 4.6[d,e] 1.95 (0.93–4.09)
Lopes et al. 2012[33]	69255	retrospective, multicentre, ACTION registry	in-hospital stay	STEMI, NSTEMI, AF (prevalent) 7.1% PCI 68.7%	9.9 / 4.2[c]	NR	1.2 / 1.0	NR	NR	1.3 / 0.7[c]	NR	14.6 / 9.9[c]
Pilgrim et al. 2013[34]	6308	prospective, single-centre	4 years	PCI, DES AF (prevalent) 5.3% ACS 54.5%	22.5 / 9.6[c] 1.67 (1.27–2.20)	11.8 / 4.7[c] 1.84 (1.26–2.71)	6.5 / 4.8	16.3 / 14.8	6.8 / 6.5	3.4 / 0.8[c] 3.08 (1.45–6.56)	NR	3.7 / 1.7
Rene et al. 2014[35]	3281	post hoc analysis of the HORIZONS-AMI (prospective, open-label, multicentre RCT)	3 years	STEMI, PCI AF (incident) 4.5%	11.9 / 6.3[c] 1.91 (1.16–3.14)	6.3 / 3.7	16.4 / 7.0[c] 2.56 (1.66–3.94)	24.2 / 14.0[b] 1.90 (1.34–2.70)	10.2 / 4.8[c] 2.22 (1.26–3.91)	5.8 / 1.3[c] 4.49 (2.10–9.60)	38.4 / 21.2[e] 2.05 (1.56–2.69)	20.9 / 8.2[c] 2.67 (1.83–3.89)

a event rate in patients with AF vs patients with sinus rhythm, hazard ratios (95% confidence interval) for significant associations when available
b various definitions across the studies
c significant difference in event rates
d in-hospital event rate
e trend toward between-group difference

Abbreviations: ACS, acute coronary syndrome; ACTION, National Cardiovascular Data Registry's Acute Coronary Treatment and Intervention Outcomes Network Registry – Get With the Guidelines; AF, atrial fibrillation; APEX-AMI, Assessment of Pexelizumab in Acute Myocardial Infarction; CV, cardiovascular; DES, drug-eluting stents; HORIZONS-AMI, Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; MACE, major adverse cardiac events; MI, myocardial infarction; NR, not reported; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; STEMI, ST-segment elevation myocardial infarction; TVR, target vessel revascularization

TABLE 2 Stroke and bleeding risk stratification with the CHA_2DS_2-VASc[38] and HAS-BLED scores[39]

CHA_2DS_2-VASc[a]	Score	HAS-BLED[b]	Score
congestive heart failure/LV dysfunction	1	hypertension (systolic blood pressure >160 mmHg)	1
hypertension	1	abnormal renal or liver function	1 or 2
age ≥75 years	2	stroke	1
diabetes mellitus	1	bleeding tendency or predisposition	1
stroke/TIA/TE	2	labile INRs (if on warfarin)	1
vascular disease (prior MI, PAD, or aortic plaque)	1	age (eg, >65, frail condition)	1
aged 65–74 years	1	drugs (eg, concomitant antiplatelet or NSAIDs) or alcohol excess/abuse	1 or 2
sex category (ie, female)	1		
maximum score	9		9

a CHA_2DS_2-VASc: heart failure (moderate-to-severe left ventricular systolic dysfunction refer to left ventricular ejection fraction ≤40% or recent decompensated heart failure requiring hospitalization), hypertension, age ≥75 years, diabetes, stroke/TIA, vascular disease (specifically, myocardial infarction, complex aortic plaque, and peripheral artery disease), age 65–74 years, female sex
b HAS-BLED: uncontrolled hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly patients (eg, age >65 years, frail condition), drugs (eg, antiplatelet, NSAIDs)/excessive alcohol

Abbreviations: INR, international normalized ratio; LV, left ventricular; NSAIDs, nonsteroidal anti-inflammatory drugs; TE, thromboembolism; TIA, transient ischemic attack; PAD, peripheral artery disease; others, see **TABLE 1**

whether AF directly affects the clinical course of CAD or merely reflects a poorer baseline state.

In any scenario, AF forces amendments in the management of CAD patients, with the antithrombotic therapy for thromboprophylaxis perhaps being the most challenging area.

Stroke and bleeding risk assessment The impact of AF on stroke risk depends on the presence of other vascular risk factors, and appropriate risk stratification is important.[36,37] The CHA_2DS_2-VASc score[38] (**TABLE 2**) is now recommended by the European and other guidelines for decision making with respect to OAC in patients with nonvalvular AF.[16,22]

Vascular disease in the CHA_2DS_2-VASc score includes peripheral artery disease, aortic plaque, and prior MI or coronary revascularization. Hence, patients with AF undergoing PCI are at a risk of stroke and require OAC with either a well-adjusted vitamin K antagonist (VKA) or one of novel OACs.

The CHA_2DS_2-VASc score reliably predicts all-cause mortality (hazard ratio [HR], 1.16; 95% confidence interval [CI], 1.02–1.32) and major adverse cardiac and cerebrovascular events (MACCE, defined as composite of all-cause death, MI, target vessel revascularization, definite/probable stent thrombosis, transient ischemic attack or stroke; HR, 1.17; 95% CI, 1.06–1.28) among AF patients undergoing PCI in the prospective observational, multicentre registry including patients with AF who are referred for the PCI AFCAS registry (Management of Patients With Atrial Fibrillation Undergoing Coronary Artery Stenting).[40] An important finding from this registry was that only approximately 10% of AF patients were at a low risk for stroke prior to registry entrance.[40]

Antithrombotic prevention, of any description is associated with an increased risk of hemorrhage. The HAS-BLED score (**TABLE 2**)[39] is recommended for the assessment of risk of major bleeding with the score of 3 as a cut-off for high risk.[16,22] It is important to note that a HAS-BLED score of 3 or higher alone should not be used as a reason to withhold OAC. An elevated HAS-BLED score rather highlights the requirement for closer monitoring (international normalized ratio [INR] in case of anticoagulation with VKAs, kidney function when NOACs are used) and correction of modifiable bleeding risk factors, for example, removal of unnecessary concomitant antiplatelet therapy / nonsteroidal anti-inflammatory drugs, reduction in excessive alcohol intake, tight blood pressure control.[36,37]

The HAS-BLED score is simple, practical, and has been well-validated in multiple cohorts; however, in AF patients undergoing PCI, combined multiple antithrombotic drugs are likely to interfere with its predictive ability. Thus, it should be used for the assessment of baseline bleeding risk to define the most appropriate combination and duration of antithrombotic therapy.[16,22]

Once combination therapy has been started, the HAS-BLED score appears to be less useful and shows inconsistent performance. In a retrospective analysis of a cohort with ACS who received OAC in addition to dual antiplatelet therapy due to various indications (predominantly AF and apical akinesia), the HAS-BLED score reliably predicted spontaneous bleeding events with a *c* statistic of 0.67 (95% CI, 0.54–0.79).[41] More contemporary data from the AFCAS registry showed no statistically significant difference in hemorrhage between distinct risk strata as classified via the HAS-BLED score as well as other

TABLE 3 Meta-analyses on efficacy and safety of triple antithrombotic therapy versus dual antiplatelet therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention with stent implantation

Reference	Number of studies included	Clinical outcomes, odds ratio (95% confidence interval)				
		MACE	ischemic stroke	MI	all-cause death	major bleeding
Gao et al. 2011[71]	9	NR	0.29 (0.15–0.58)	0.84 (0.57–1.23)	1.20 (0.63–2.27)	2.00 (1.41–2.83)
Saheb et al. 2013[72]	10	0.76 (0.54–1.07)[a]	0.27 (0.13–0.57)	0.57 (0.22–1.50)	NR	1.47 (1.22–1.78)
Zhao et al. 2011[73]	9	0.60 (0.42–0.86)[b]	0.38 (0.12–1.22)	NR	0.59 (0.39–0.90)	2.12 (1.05–4.29)

a cardiac death, acute myocardial infarction, stent thrombosis, or target lesion revascularization
b death, myocardial infarction/reinfarction, stent thrombosis, target vessel revascularization, stroke and bleeding

Abbreviations: MACE, major adverse cardiovascular events (composite of death, myocardial infarction/reinfarction, stent thrombosis, target vessel revascularization, stroke, and bleeding); others, see **TABLE 1**

available bleeding risk assessment schemes (eg, $HEMORR_2HAGES$, ATRIA, etc.).[42,43] This is not unexpected since the HAS-BLED score was derived and validated in cohorts of "stable" anticoagulated AF patients.[36,37]

ACS-specific risk scores such as the GRACE 2.0 ACS Risk Calculator[44-46] for predicting death or death/MI following an initial ACS, CRUSADE score[47,48] for bleeding risk assessment, and stent thrombosis scores[49,50] may be used; however, they have not been validated in AF cohorts and do not impact on decision making with respect to antithrombotic management in AF patients undergoing PCI.

Overall, the vast majority of AF patients undergoing PCI have a high risk both for stroke and major bleeding.[51] Thus, antithrombotic therapy in this group of patients has to carefully balance thromboembolism versus bleeding.

Triple antithrombotic therapy: is there an alternative? Triple antithrombotic therapy (namely OAC in combination with dual antiplatelet therapy) for patients with AF undergoing PCI developed as a result of OAC is indicated for AF patients, and dual antiplatelet therapy is indicated for ACS patients.[7,8,16,22,24] It is also supported by the pathology of clot formation and is generally deemed to be appropriate but until recently has not been tested in an RCT.[12-15]

However, adding antiplatelet agents on top of OAC inevitably results in elevation of bleeding risk.[52-54] In a large analysis from the nationwide Danish registry including over 80,000 AF patients, HRs of fatal or nonfatal bleeding were as follows: 1.66 (95% CI, 1.34–2.04) for dual antiplatelet therapy; 1.83 (95% CI, 1.72–1.96) for warfarin and aspirin; 3.08 (95% CI, 2.32–3.91) for warfarin and clopidogrel, and 3.70 (95% CI, 2.89–4.76) for triple therapy versus warfarin monotherapy as a reference.[52] Consistent results were obtained in the meta-analysis included 18 studies with patients receiving triple therapy after PCI and stenting: odds ratio (OR), 2.38; 95% CI, 1.05–5.38 at 30 days, and 2.87; 95% CI, 1.47–5.62 at 6 months compared with dual antiplatelet therapy.[53]

Studies on triple therapy in AF patients undergoing PCI are mostly observational, often retrospective, single-centre, and hence underpowered to reveal a difference in event rates between groups with different strategies of antithrombotic therapy. The proportion of AF and ACS patients included, event definitions and follow-up duration also varied widely. In the absence of robust evidence finding the equilibrium between the risk of serious bleeding on the one hand, and stroke, recurrent cardiac ischemia, stent thrombosis on the other, is particularly challenging.

There have been plenty of such studies weighing pros and cons of triple antithrombotic therapy against other antithrombotic regimens (*Supplementary material online*, *Table S1*) as well as a few meta-analyses (**TABLE 3**) that have been published.

Dual antiplatelet therapy with aspirin and clopidogrel is inferior to triple antithrombotic therapy in AF patients undergoing PCI particularly for ischemic stroke. Strokes in AF are usually severe and associated with poorer outcomes compared with non-AF-related strokes. Thus, OAC cannot be omitted. OAC was beneficial even in patients with high bleeding risk (HAS-BLED score, ≥3) and octogenarians: subsets of patients in whom OAC is often withheld by clinicians for fear of bleeding complications, particularly intracranial hemorrhage, even in chronically anticoagulated patients with no need for combination antithrombotic therapy.[51,56]

The choice between triple therapy and OAC plus single antiplatelet is less well-defined. The WOEST trial (What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing) was open-label, intention-to-treat RCT, in which triple therapy was compared with double therapy of OAC and clopidogrel (thus omitting aspirin).[58] At 1-year follow-up, lower bleeding and mortality rates were revealed in the warfarin-plus-clopidogrel arm compared with the triple-therapy arm (HR, 0.36; 95% CI, 0.26–0.50, and HR, 0.39; 95% CI, 0.16–0.93, respectively) with no significant differences in the rate of thrombotic events.[58] However, the WOEST trial had many limitations. First, the lower bleeding rate with dual therapy was driven by a reduction of minor bleeding

events while major bleedings were not different between the groups. Indeed, no difference with respect to major bleeding was found when TIMI (Thrombolysis In Myocardial Infarction) definition was used. With the BARC (Bleeding Academic Research Consortium) definition, serious bleeding (BARC 3) was significantly lower in the double-therapy than in the triple-therapy group (6.5% vs 12.7%; HR, 0.49; 95% CI, 0.28–0.86).[58] Other limitations included enrolment not only of patients with AF, but also those with mechanical heart valves, heart aneurysm, pulmonary embolism as indications for OAC; triple therapy was unnecessarily extended up to 1 year; femoral access was used more commonly; proton-pump inhibitors were not routinely used; most of PCIs were elective; study was underpowered to reveal difference in the rate of stent thrombosis between 2 antithrombotic regimens. Hence, the WOEST trial did not provide all the answers and was deemed hypothesis-generating.

Comparable 1-year efficacy (MACCE) and safety (bleeding) of 3 antithrombotic regimens, namely, triple therapy, dual antiplatelet therapy, and OAC plus clopidogrel were observed in the AFCAS registry.[74] Seivani et al.[75] considered the combination of OAC and clopidogrel effective and safe in high-risk AF patients treated with PCI and drug-eluting stents even with shorter than recommended duration (clopidogrel was stopped after a mean duration of 9 months).

A retrospective analysis of the biggest AF cohort available thus far, extracted from the Danish nationwide registry, yielded both early (within 3 months) and delayed (3 to 12 months) bleeding risk after an index event (MI or PCI) to be higher (HR, 1.47; 95% CI, 1.04–2.08, and HR, 1.36; 95% CI, 0.95–1.95, respectively) with triple therapy versus OAC plus single antiplatelet agent while no significant difference in thromboembolic risk was observed with 2 strategies.[76] Lamberts et al.[65] further confirmed an increase in bleeding rates with an increasing intensity of antithrombotic treatment. Bleeding risk was nonsignificantly lower for OAC plus clopidogrel (HR, 0.78; 95% CI, 0.55–1.12) and significantly lower for OAC plus aspirin (HR, 0.69; 95% CI, 0.53–0.90), and dual antiplatelet therapy (HR, 0.48; 95% CI, 0.38–0.61) versus triple therapy.

In terms of efficacy outcomes, no difference between different strategies but a trend toward the benefit of OAC plus clopidogrel (HR, 0.69; 95% CI, 0.48–1.00) in comparison with triple therapy was observed with regard to MI and coronary death. Higher risk with dual antiplatelet therapy (HR, 1.50; 95% CI, 1.03–2.20) and comparable risk with OAC plus any antiplatelet agent versus triple therapy was found for ischemic stroke. Finally, OAC plus aspirin and dual antiplatelet therapy were associated with a significantly increased risk of all-cause death (HR, 1.52; 95% CI, 1.17–1.99, and HR, 1.60; 95% CI, 1.25–2.05, respectively). That was not the case for OAC with clopidogrel. Thus, given a nonsignificant reduction of coronary death, MI, and major bleeding together with similar efficacy for stroke prevention and no increase in mortality, OAC plus clopidogrel appears to be the most attractive option.[65]

In summary, based on available evidence, triple antithrombotic therapy in patients with AF and CAD undergoing PCI with stenting is a "necessary evil", where necessity is determined by an elevated risk of ischemic and embolic events with "lighter" antithrombotic combinations (eg, dual antiplatelet therapy or OAC plus single antiplatelet agent, particularly clopidogrel) and elevated bleeding risk is the main threat. Thus, attempts should be made to shorten exposure to such a regimen as much as possible depending on the clinical scenario, type of stent, baseline bleeding and stroke risk.[77] Also, while dual antiplatelet therapy appeared to be the least effective in this group of patients, as a lower bleeding rate is usually accompanied by a higher stroke rate, the choice between triple therapy and OAC plus clopidogrel remains a controversial issue.

Conclusions The trade-off between bleeding, embolic complications, and coronary thrombosis represents a complex and challenging area. Evidence informing the management of AF patients undergoing PCI is gradually increasing but we are still lacking large randomized trials testing various combinations of antithrombotic therapy. Thus far, triple antithrombotic therapy is warranted to prevent thrombotic and embolic events at the cost of increased risk of bleeding. Intentions to reduce its duration or replace with OAC combined with single antiplatelet therapy have been made, and they are deemed appropriate, particularly in a subset of patients with moderate stroke and/or high bleeding risk. Therefore, baseline stroke and bleeding risk assessment are important for the final judgment as well as clinical setting.

Supplementary material online Supplementary material online is available with the online version of the paper at www.pamw.pl.

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Przezskórne interwencje wieńcowe u chorych z migotaniem przedsionków

Aktualne koncepcje i obawy: część 1

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STRESZCZENIE

Migotanie przedsionków (*atrial fibrillation* – AF) i choroba wieńcowa (*coronary artery disease* – CAD) często współistnieją. Oba stany niosą zwiększone ryzyko ostrych powikłań zakrzepowych, jednak patogeneza powstawania zakrzepu w AF i w CAD jest odmienna. W AF głównym szlakiem jest aktywacja kaskady krzepnięcia, natomiast w zakrzepicy wieńcowej kluczową rolę odgrywa aktywacja płytek. W obu stanach podstawowe znaczenie ma profilaktyka przeciwzakrzepowa.

U chorych z AF poddawanych przezskórnej interwencji wieńcowej (*percutaneous coronary intervention* – PCI) konieczne jest kojarzenie doustnych antykoagulantów i leków przeciwpłytkowych, co zwiększa ryzyko poważnego krwawienia. Trzeba je odnieść do ryzyka udaru i zakrzepicy w stencie.

W części 1. niniejszego przeglądu przeanalizowano wymogi leczenia przeciwzakrzepowego u chorych z AF poddawanych PCI. Omówiono epidemiologię współwystępowania AF i CAD, a także różnice w patogenezie zakrzepicy w obu stanach. Poddano ocenie dane dotyczące różnych wariantów leczenia przeciwzakrzepowego, w tym terapii potrójnej, w aspekcie oceny ryzyka krwawienia i udaru.

Ogólnie – terapia potrójna jest często uzasadniona, ale powinna być stosowana jak najkrócej. Większość aktualnych zaleceń opiera się na danych obserwacyjnych, ale pojawiają się dobrze zaplanowane, o odpowiedniej mocy badania z randomizacją, które pozwolą nam poszerzyć wiedzę w tej trudnej dziedzinie.

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TABLE S1 Summary of studies comparing triple antithrombotic therapy with dual antiplatelet therapy or oral anticoagulation plus single antiplatelet therapy

Study	N	Design	Follow-up	Population	Compared regimes	Clinical outcomes[a]										
						major bleeding	minor bleeding	any bleeding	death	CV death	MI	TVR	stent thrombosis	stroke	SE	MAC(C)E overall
Bernard et al. 2013[55]	417	retrospective, single-center	650 days	AF, PCI-S ACS 61.9%	OAC/no OAC at discharge	4.3/3.4	NR	NR	5.2/11.9	NR	MI	5.2/3.4	NR	5.2/9.1[i]	5.2/9.1[i]	23.7/32.5[d] 0.58 (0.32-1.05)
Caballero et al. 2013[56]	604	retrospective, two-center	17 months	AF, PCI-S ACS 75.8% octogenarians 15.7%	OAC/no OAC at discharge	20.9/21.2	9.7/15.4	NR	22.2/44.4[d] 3.75 (0.97-14.53)	NR	20.6/25.0	NR	NR	NR	8.9/18.9	28.9/58.3[c] 4.30 (1.26–14.56)
Dąbrowska et al. 2013[57]	104	prospective, single-center	1 year	AF, PCI-S ACS NR	TT/DAPT	11.1/6.9	27.8/10.3	38.9/17.2	0/13.8	NR	2.2/19.4[c]	NR	0/0	NR	NR	NR
Dewilde et al. 2013[58]	573	rct, open-label, multicenter	1 year	PCI-S AF 69% ACS NR	TT/OAC+clopidogrel	5.6/3.2	NR	44.4/19.4[c] 0.36 (0.26–0.50)	6.3/2.5[c] 0.39 (0.16–0.93)	2.5/1.1	3.4/11.1[b]	6.7/7.2	3.2/1.4	2.8/0.7[d] 0.25 (0.05–1.17)	NR	NR
Fosbol et al. 2013[59]	1648	retrospective, multicenter	1 year	AF, NSTEMI, PCI-S	TT/DAPT	15.5/12.8[d] 1.29 (0.96-1.74)	NR	NR	12.9/13.3	NR	4.6/3.2	NR	NR	1.6/2.2	NR	19.4/20.6
Gao et al. 2010[60]	622	prospective, single-center	1 year	AF, DES ACS 14.1%	TT/DAPT/OAC+AT[e]	2.9/1.8/2.5	8.8/3.3/5.0[c]	11.8/5.1/7.4[c]	4.4/9.0/5.8	NR	6.3/6.8	3.7/4.5/4.1	0.7/0.9/1.7	0.7/3.6/0.8[d]	NR	8.8/20.1/14.9[c]
Gilard et al. 2009[61]	359	prospective, multicenter	1 year	PCI-S AF 69.1% ACS NR	TT/DAPT	5.6/2.1[c]	NR	18.4/16.0	8/5.6	4.0/2.6	2.9/5.4/5.8	NR	1.6/1.7	0.8/3	0.8/0	NR
Ho et al. 2013[62]	602	retrospective, single-center	2 years	AF, PCI-S ACS NR	TT/DAPT	24.5/20.4	NR	NR	1.6/5.3 ($CHADS_2 \leq 2$) 11.4/10.0 ($CHADS_2 > 2$)[c]	NR	5.0/4.3[b]	NR	NR	2.2/1.8	NR	NR
Mutuberria et al. 2013[63]	640	prospective, multicenter	1 year	AF, PCI-S ACS NR	TT vs DAPT	5.3/0	NR	NR	8.4/1.3[c]	8.4/0[c]	NR	NR	NR	NR	1.1/1.3	13.7/9.3
Karjalainen et al. 2007[64]	478	retrospective, multicenter	1 year	PCI-S AF 35.1% ACS 53.8%	TT/DAPT	8.2/2.6[c] 3.3 (1.3–8.6)	NR	NR	8.7/1.8[c] 5.3 (1.8–16.0)	NR	NR	11.0/7.5	4.1/1.3	3.2/2.2[d] 3.2 (0.8–12.1)	NR	21.9/11.0[c] 2.3 (1.3–3.8)
Lamberts et al. 2013[65]	12165	retrospective, nationwide	1 year	AF, PCI MI 77.2%	TT/DAPT/OAC+ASA/ OAC+clopidogrel[f]	14.3[c] /6.9/9.7[c] /10.9[c] 2.08 (1.64–2.65) 1.44 (1.14–1.83) 1.63 (1.15–2.30)	NR	NR	8.9[c] /17.5/15.6/7.1[c] 0.61 (0.47–0.77) 0.54 (0.35–0.76)	2.5[c] /5.3/3.9/1.2[g] 0.58 (0.36–0.92)	10.0/4.8[c] 2.2 (1.0–4.7)	NR	NR	4.1[c] /6.3/5.6[c] /2.8[c] 0.67 (0.46–0.98) 0.81 (0.61–1.08) 0.51 (0.28–0.95)	NR	NR
Rossini et al. 2008[66]	204	prospective, single-center	18 months	PCI-S AF 66.6% ACS 78.9%	TT/DAPT	2.9/2	7.8/2.9	10.8/4.9	2.9/1.0	1/1	16.2[d] /21.3/17.7[c] /9.6[c,h] 0.83 (0.68–1.00) 0.78 (0.66–0.91) 0.56 (0.40–0.79)	1/2.9	1/2	1/2	NR	5.8/4.9
Rubboli et al. 2012[67]	632	prospective, multicenter	1 year	PCI-S AF 58% ACS 63%	TT/DAPT/OAC+ASA	5.0/2.0/2.6	NR	NR	9.9/8.5/10.2	NR	2/2	12.3/10.3/11.9	2.7/1.7/2.0	1.0/4.1/1.1[d]	1.8/2.8/0[d]	NR
Ruiz-Nodar et al. 2008[68]	426	retrospective, two-center	594 days	AF, PCI-S ACS 83.9%	TT/DAPT	14.9/9.0	12.6/9.0	NR	17.8/27.8[c]	NR	11.3/5.5/9.3[d]	7.1/8.4	1.2/1.3	NR	1.7/6.9[c]	26.5/38.7 4.9 (2.17–11.09)
Ruiz-Nodar et al. 2012[51]	420	retrospective, two-center	1 year	AF, PCI-S ACS 86.4% HAS-BLED ≥3	OAC/no OAC at discharge	11.8/4.0[c] 3.03 (1.24–7.38)	NR	NR	9.3/20.1[c] 0.45 (0.26–0.78)	NR	6.5/10.4	NR	NR	NR	NR	13.0/26.4[c] 0.48 (0.29–0.77)
Sambola et al. 2009[69]	405	prospective, multicenter	6 months	PCI-S AF 67.6% ACS NR	TT/DAPT/OAC+AT[e]	4.3/1.2/6.5	11.2/2.5/6.5[c]	15.5/3.7/13[c]	6.8/1.2/10.9[d]	4.3/0/8.7[c]	NR	3.6/0/4.3	4.0/0/8.7[c]	0.3/1.2/2.2[i]	0.3/1.2/2.2[i]	7.9/1.2/15.2[a]
Smith et al. 2012[41]	318	etrospective, single center	1 year	ACS, PCI-S AF 19.8%	TT/DAPT	13.4/3.8[c]	NR	NR	4.5/2.5	NR	NR	NR	NR	1.9/1.9	0/0	NR
Uchida et al. 2010[70]	575	prospective, single-center	459 days	DES AF 5% ACS 39.1%	TT/DAPT	20/2.7[c] 8.02 (3.34-19.15)	20/9.9[c]	40/12.8[c]	8/3.4	NR	3.8/1.3[b]	14/7.4[d]	0/0	4/1.1	NR	22/12[c] 1.74 (0.91-3.35)[d]

a rate of events in groups, %; odd or hazard ratio (95% confidence interval) for significant associations when available; **b** acute coronary syndrome; **c** significant difference in event rates; **d** trend toward between-groups difference; **e** over 80% of patients in OAC plus single antiplatelet group were receiving clopidogrel; **f** TT and OAC plus single antiplatelet therapy vs DAPT; **g** coronary death or fatal stroke; **h** MI/coronary death; **i** stroke or systemic embolism

For a list of references, see the main article.

Abbreviations: ACS, acute coronary syndrome; AT, single antiplatelet therapy; AF, atrial fibrillation; ASA, acetylsalicylic acid; $CHADS_2$, congestive heart failure, hypertension, age, diabetes, stroke; CV, cardiovascular; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; MAC(C)E, major adverse cardiac (and cerebral) events; MI, myocardial infarction; NR, not reported; NSTEMI, non-ST-segment elevation myocardial infarction; OAC, oral anticoagulation; PCI(-S), percutaneous coronary intervention (with stenting); RCT, randomized controlled trial; SE, systemic embolism; TT, triple antithrombotic therapy; TVR, target vessel revascularization