European Heart Journal Supplements (2020) **22** (Supplement I), I22-I31
The Heart of the Matter
doi:10.1093/eurheart/suaa101

ESC European Society of Cardiology

Atrial fibrillation patients undergoing percutaneous coronary intervention: dual or triple antithrombotic therapy with non-vitamin K antagonist oral anticoagulants

Andreas Goette[1,2,3]* and Pascal Vranckx[4]

[1]*St. Vincenz-Hospital, Paderborn, Germany;*
[2]*Working Group of Molecular Electrophysiology, University Hospital Magdeburg, Magdeburg, Germany;*
[3]*Atrial Fibrillation Network (AFNET), Münster, Germany;*
[4]*Department of Cardiology and Intensive Care Medicine, Jessa Ziekenhuis, Faculty of Medicine and Life Sciences at the Hasselt University, Hasselt, Belgium*

KEYWORDS
Atrial fibrillation (AF);
Percutaneous coronary intervention (PCI);
Antithrombotic therapy;
Triple therapy;
Non-vitamin K antagonist oral anticoagulant;
NOAC;
Review

About 20% of all atrial fibrillation (AF) patients develop coronary artery disease, which requires coronary stenting [percutaneous coronary intervention (PCI)]. Thus, this subcohort of AF patients may require aggressive antithrombotic therapy encompassing vitamin K antagonist (VKA) or non-vitamin K antagonist oral anticoagulants (NOAC) plus aspirin and a P2Y12 inhibitor. At present, four clinical Phase IIIb trials using dabigatran, rivaroxaban, apixaban, or edoxaban, were published. These studies assessed the impact of NOACs as a part of DAT therapy vs. triple therapy. Compared with triple therapy, NOAC-based DAT has been shown to be associated with reduced major bleeding as well as intracranial haemorrhages. The benefit, however, is somewhat counterbalanced by a higher risk of stent-related ischaemia during the early phase of dual therapy. Thus, triple therapy after stenting is appropriate for at least 14 days with a maximum of 30 days. Thereafter, DAT including a NOAC is the therapy of choice in AF PCI patients to reduce the risk of bleeding during a 1 year of follow-up compared to VKA-based regimes. The present review summarizes the published study results and demonstrates differences in trial design and reported outcomes.

Introduction

Non-vitamin K antagonist oral anticoagulants (NOACs) have been proven in patients with atrial fibrillation (AF) to prevent stroke and peripheral embolism.[1] The risk for stroke in AF depends on concomitant clinical factors, which are represented in the CHA_2DS_2-Vasc risk score.[2] In most patients with AF, the arrhythmia appears to be the consequence of an atrial cardiomyopathy, which triggers atrial thrombogenesis at the endocardium. The thrombogenic endocardial remodelling is characterized by expression of adhesion molecules and inflammatory markers in particular in the left atrial appendage.[2-6] About 20% of all AF patients develop coronary artery disease, which may require coronary stenting [percutaneous coronary intervention (PCI)]. After coronary stenting dual antiplatelet therapy (aspirin and P2Y12 inhibitors; DAPT) is necessary to prevent stent thrombosis.[7-9] In AF patients with recent stent implantation, triple antithrombotic regime (TAT) encompassing vitamin K antagonist (VKA) or NOAC plus aspirin and P2Y12 inhibitor was considered to be therapy of choice to prevent stroke and stent thrombosis. Recently, the so called dual therapy (DAT) consisting of VKA/NOAC plus a P2Y12

*Corresponding author. Tel: +40 5251 861651, Fax: +495251861652, Email: andreas.goette@vincenz.de

inhibitor has been found as safe alternative in this clinical setting.[10] At present, four clinical trials using dabigatran, rivaroxaban, apixaban, or edoxaban, were published.[8,11-13] These trials assessed the impact of NOACs as a part of DAT therapy vs. TAT encompassing VKA. However, none of these studies was powered to assess the effect of treatment on mortality or ischaemic events (*Table 1*).

Study outcomes of atrial fibrillation percutaneous coronary intervention trials

The four NOAC AF PCI trials used safety parameters as main endpoint (*Table 1*). The primary bleeding endpoint was typically defined as major bleeding or clinically relevant non-major bleeding (CRNMB) at longest available follow-up. Secondary safety endpoints consisted of bleeding endpoints according to various definitions. Secondary efficacy endpoints included all-cause death; cardiovascular death; trial-defined major adverse cardiovascular event (MACE); myocardial infarction (MI); stroke; and stent thrombosis (ST).

PIONEER-AF PCI trial

The PIONEER-AF trial was an open-label, randomized, controlled, multicentre trial assessing two treatment strategies of rivaroxaban and a dose-adjusted VKA strategy in AF patients who undergo PCI.[12] A total of 2124 AF patients were assigned after PCI to low-dose rivaroxaban (15 mg once daily) plus a $P2Y_{12}$ inhibitor for 12 months, very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months, or standard therapy with a dose-adjusted VKA plus DAPT for 1, 6, or 12 months. The rates of clinically significant bleeding were lower in the rivaroxaban groups compared to VKA-based TAT.[12] The rates of death from cardiovascular causes, myocardial infarction, or stroke were 6.5% in the 15 mg rivaroxoban group, 5.6% in the 2×2.5 mg rivaroxaban group, and 6.0% in the VKA-triple therapy arm. Thus, the administration of either low-dose rivaroxaban plus a $P2Y_{12}$ inhibitor for 12 months or very-low-dose rivaroxaban plus DAPT for 1, 6, or 12 months was associated with a lower rate of clinically significant bleeding than was standard therapy with a VKA plus DAPT during follow-up.

RE-DUAL PCI

The RE-DUAL PCI trial was a randomized evaluation of DAT with dabigatran vs. triple therapy (TAT) with warfarin in patients with non-valvular AF undergoing PCI,[11] In this multicentre trial, 2725 patients with AF who had undergone PCI to TAT with warfarin plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and aspirin (for 1–3 months) (TAT group) or dual therapy with dabigatran (110 or 150 mg twice daily) plus a P2Y inhibitor (clopidogrel or ticagrelor) and no aspirin (DAT groups). There was no individualized dabigatran dose adjustment in this trial. The primary endpoint occurred in 15.4% in the 110-mg DAT group as compared with 26.9% in the TAT group and in 20.2% in the 150-mg DAT group as compared with 25.7% in the corresponding TAT group. The incidence of the composite efficacy Endpoint was 13.7% in the two DAT groups combined as compared with 13.4% in the TAT group. Thus, among AF PCI patients, the risk of bleeding was lower among those who received DAT with dabigatran and a $P2Y_{12}$ inhibitor than among those who were assigned to TAT with warfarin, a $P2Y_{12}$ inhibitor, and aspirin.

AUGUSTUS trial

The AUGUSTUTS trial was randomized controlled clinical trial to evaluate the safety of apixaban vs. VKA and aspirin vs. aspirin placebo in patients with AF and acute coronary syndrome and/or PCI.[13] The AUGUSTUS trial had a two-by-two factorial design. Atrial fibrillation patients with an acute coronary syndrome (ACS) or PCI were randomly assigned to receive apixaban or a VKA and to receive aspirin or matching placebo for 6 months. The primary endpoint was major or CRNM bleeding. Secondary endpoints encompassed death or hospitalization and a composite of ischaemic events. However, the Augustus trial randomized patients 6.6 days after the coronary event. Thus, the first week of antithrombotic therapy was not covered in the trial. Furthermore, several AF patients did not receive a PCI and the follow-up was rather short (6 months), although TAT was applied for 6 months, which appears to be rather aggressive. Of note, there were no significant interactions between the two randomization factors on the primary or secondary outcomes. Major or CRNM bleeding was noted in 10.5% of the patients receiving apixaban, as compared with 14.7% of those receiving VKA. Bleeding events occurred in 16.1% of the patients receiving aspirin, as compared with 9.0% of those receiving placebo. Patients in the apixaban group had a lower incidence of death or hospitalization than those treated with VKA.[13] Patients in the aspirin group had an incidence of death or hospitalization and of ischaemic events that was similar to that in the placebo group. The AUGUSTUS investigators concluded that an antithrombotic regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in the incidence of ischaemic events.[13]

ENTRUST AF PCI trial

The EdoxabaN TReatment versUS VKA in paTients with AF undergoing PCI (ENTRUST-AF PCI) trial examined the role of edoxaban in AF patients undergoing PCI with and without ACS.[8] The study was a randomized, multicentre, open-label, non-inferiority Phase 3b trial with masked outcome evaluation. Atrial fibrillation patients were included in the study if they were at least 18 years, and had a successful PCI for stable coronary artery disease or acute coronary syndrome. Patients were randomly assigned from 4 h to 5 days after PCI to either edoxaban (60 mg once daily) plus a P2Y12 inhibitor for 12 months or a VKA in combination with a P2Y12 inhibitor and aspirin (100 mg once daily, for 1–12 months). A total of 1506 patients were enrolled. Time from PCI to randomization was rather short (median: 45.1 h). Major or CRNM bleeding events occurred in 17% of patients with the edoxaban and to 20% of patients with VKA. Thus, in AF PCI patients DAT with edoxaban was non-inferior for bleeding compared with VKA-based TAT.

Table 1 NOAC AF PCI trials

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
	RE-DUAL PCI (completed)	PIONEER AF-PCI (completed)	AUGUSTUS (completed)	ENTRUST-AF PCI (completed)
Patients (*n*)	2725	2124	4600	≅1500
Randomization	1:1:1	1:1:1	2 × 2 factorial design	1:1
Treatment arms	Warfarin + $P2Y_{12}$ inhibitor + aspirin Dabigatran (110 mg or 150 mg BID) + $P2Y_{12}$ inhibitor	Rivaroxaban (15 mg OD) + $P2Y_{12}$ inhibitor Rivaroxaban (2.5 mg BID) + $P2Y_{12}$ antagonist + aspirin Vitamin K antagonist + $P2Y_{12}$ antagonist + aspirin (standard therapy)	Warfarin + $P2Y_{12}$ inhibitor Apixaban + $P2Y_{12}$ inhibitor combined with aspirin or without aspirin (placebo)	Vitamin K antagonist+ $P2Y_{12}$ antagonist + aspirin (standard therapy) Edoxaban + $P2Y_{12}$ antagonist
Primary endpoint	First ISTH major or CRNM bleeding	Composite of major bleeding or minor bleeding according to TIMI criteria or bleeding requiring medical attention	Time to first occurrence of ISTH major or CRNM bleeding	ISTH major and CRNM bleeding
Secondary endpoint	Composite of thrombo-embolic events (MI, stroke, or SEE), death, or unplanned revascularization	The incidence of each component of the primary safety endpoint, and the following efficacy end points: the occurrence of MACE, each component of MACE and stent thrombosis	Composite of all-cause death, stroke, MI, stent thrombosis, urgent revascularization, and first hospitalization for any cause	Composite of CV death, stroke, SEE, spontaneous MI, and definite stent thrombosis
Key inclusion	• Patients ≥18 years with paroxysmal, persistent, or permanent NVAF • ACS successfully treated by PCI and stenting • Stable CAD with ≥1 lesion eligible for PCI successfully treated by elective PCI and stenting	• Patients ≥18 years with paroxysmal, persistent, or permanent NVAF • ACS successfully treated by PCI and stenting • Stable CAD with ≥1 lesion eligible for PCI successfully treated by elective PCI and stenting	• Patients ≥18 years with history of AF or flutter with planned or existing use of OAC • ACS and/or PCI within prior 14 days • Planned use of P2Y12 inhibitor for ≥6 months	• Patients ≥18 years with paroxysmal, persistent, or permanent NVAF • OAC indication for AF for at least 12 months • Successful PCI with stent placement
Key exclusion	• Cardiogenic shock during current hospitalization • Use of fibrinolytics within 24 h of randomization that would put patient at high risk of bleeding • Stroke or major bleeding event within 1 month before screening • CrCl <30 mL/min	• History of stroke or TIA • Clinically significant GI bleeding within 12 M before randomization • CrCL <30 mL/min • Anaemia of an unknown cause with a haemoglobin concentration <10 g/dL, or any other condition known to increase the risk of bleeding	• Condition other than AF for chronic anticoagulation • Serum creatinine >2.5 or CrCL <30 mL per minute • History of ICH, ongoing bleeding, or coagulopathies • Recent or planned CABG surgery for index ACS	• Patients with mechanical heart valves, moderate to severe mitral stenosis • Known bleeding diathesis • End-stage renal disease (CrCl < 15 mL/min)

ACS, acute coronary syndrome; AF, atrial fibrillation; BMI, body mass index; BMS, bare-metal stent; CAD, coronary artery disease; DAPT, dual antiplatelet therapy (P2Y12 inhibitor +aspirin); DES, drug-eluting stent; MI, myocardial infarction; PCI, percutaneous coronary intervention; VKA, vitamin K antagonist.

Differences between non-vitamin K antagonist oral anticoagulant atrial fibrillation percutaneous coronary intervention trials

All trials were designed differently and used various treatment strategies encompassing low and very low dose of NOAC, different duration of TAT in the control arm, possibility to adjustment NOAC dose if appropriate and time points of randomization after PCI. Of note, not all patients in the NOAC AF PCI trials received a stent. In particular, the AUGUSTUS trial included a large group of patients with conservative management of an acute coronary syndrome.[13] These differences must be considered if

Table 2 Comparison of trial demographics

	PIONEER AF-PCI			RE-DUAL PCI		AUGUSTUS		ENTRUST AF PCI	
Treatment	Rivaroxaban + $P2Y_{12}$-inhibitor	Rivaroxaban + DAPT	VKA + DAPT	Dabigatran + $P2Y_{12}$-inhibitor	VKA + DAPT	Apixaban + $P2Y_{12}$-inhibitor + aspirin	VKA + $P2Y_{12}$-inhibitor + aspirin	Edoxaban + $P2Y_{12}$-inhibitor	VKA + DAPT
N (randomization)	709	709	706	763	764	2306	2308	751	755
CHA_2DS_2-VASc	3.7	3.8	3.8	3.3	3.6	3.9	4.0	3.9	3.9
(SD)	n.a.	n.a.	n.a.	1.5	1.5	1.6	1.6	1.7	1.5
HAS-BLED score	3.0	2.9	3.0	2.6	2.7	2.9	2.9	2.8	2.9
(SD)	n.a.	n.a.	n.a.	0.7	0.8	1.0	0.9	0.9	0.8
Non-STEMI	130/701	129/703	123/691	179	151	n.a.	n.a.	163	157
(%)	(18.5%)	(18.3%)	(17.8%)	(23.5%)	(19.8%)	n.a.	n.a.	(21.8%)	(20.9%)
STEMI	86/701	97/703	74/691	114	112	n.a.	n.a.	133	132
(%)	(12.3%)	(13.8%)	(10.7%)	(14.9%)	(14.7%)	n.a.	n.a.	(17.8%)	(17.6%)
Unstable angina	145/701	148/703	164/691	126	138	n.a.	n.a.	112	123
(%)	(20.7%)	(21.1%)	(23.7%)	(16.5%)	(18.1%)	n.a.	n.a.	(15.0%)	(16.4%)
ACS and PCI	n.a.	n.a.	n.a.	n.a.	n.a.	873/2297	841/2298	388/751	389/755
(%)	n.a.	n.a.	n.a.	n.a.	n.a.	38	37	52	52
Medically managed	None	None	None	None	None	547/2297	550/2298	None	None
Elective PCI	n.a.	n.a.	n.a.	n.a.	n.a.	877/2297	907/2298	363/751	366/755
(%)	n.a.	n.a.	n.a.	n.a.	n.a.	38	40	48	48

VKA, vitamin K antagonist; HR, hazard ratio; CRNM, clinically relevant non-major bleeding; n.a., no information provided in primary publication of phase IIIb trial; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; DAPT, dual antiplatelet therapy (P2Y12 inhibitor +aspirin).

Table 3 Endpoints parameters provided by the main trial publication

	PIONEER AF-PCI		RE-DUAL PCI		AUGUSTUS		ENTRUST AF PCI	
Treatment	Rivaroxaban + $P2Y_{12}$-inhibitor	VKA + DAPT	Dibigatran + $P2Y_{12}$-inhibitor	VKA + DAPT	Apixaban + $P2Y_{12}$-inhibitor + aspirin	VKA + $P2Y_{12}$-inhibitor + aspirin	Edoxaban + $P2Y_{12}$-inhibitor	VKA + DAPT
N (in analysis)	696	697	763	764	2290	2259	751	755
Major bleeding (ISTH)	27 (3.9)	48 (6.9)	43 (5.6)	64 (8.4)	69 (3.0)	104 (4.6)	45 (6.0)	48 (6.4)
Event rate/year (%)					6.7	10.5	6.7	7.2
HR (95% CI)	n.a.		0.64 (0.43-0.94)		0.64 (0.47-0.86)		0.95 (0.63-1.42)	
CRNM bleeding (%)	90 (12.9)	130 (18.7)			180 (7.9)	246 (10.9)	97 (12.9)	114 (15.1)
Event rate/year (%)					18.2	26.1	15.3	18.7
HR (95% CI)	n.a.		n.a.		0.69 (0.57-0.84)		0.83 (0.64-1.09)	
Minor bleeding (%)	123 (17.7)	163 (23.4)					116 (15.4)	125 (16.6)
Event rate/year (%)							19.0	20.8
HR (95% CI)	n.a.		n.a.		n.a.		0.93 (0.72-1.20)	
Any bleeding (%)			254 (33.3)	316 (41.4)			210 (28.0)	246 (32.6)
Event rate/year (%)							38.0	47.1
HR (95% CI)	n.a.		0.72 (0.61-0.84)		n.a.		0.84 (0.70-1.01)	

VKA, vitamin K antagonist; HR, hazard ratio; CRNM, clinically relevant non-major bleeding; n.a., no information provided in primary publication of phase IIIb trial; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; DAPT, dual antiplatelet therapy (P2Y12 inhibitor +aspirin).

Table 4 Key secondary efficacy outcomes provided by the main trial publication

	PIONEER		RE-DUAL		AUGUSTUS		ENTRUST	
Treatment	Rivaroxaban+ $P2Y_{12}$-inhibitor	VKA + DAPT	Dabigatran + $P2Y_{12}$-inhibitor	VKA + DAPT	Apixaban + $P2Y_{12}$-inhibitor + aspirin	VKA + $P2Y_{12}$-inhibitor + aspirin	Edoxaban + $P2Y_{12}$-inhibitor	VKA + DAPT
N (in analysis)	694	695	763	764	2306	2308	751	755
Stroke	8	7	9 (1.2)	8 (1.0)	13 (0.6)	26 (1.1)	10 (1.3)	12 (1.6)
Event rate/year (%)	1.3	1.2			1.2	2.4	1.5	1.8
HR (95% CI)	1.07 (0.39-2.96)		1.09 (0.42-2.83)		0.50 (0.26-0.97)		0.84 (0.36-1.95)	
Myocardial infarction	19	21	26 (3.4)	22 (2.9)	72 (3.1)	80 (3.5)	29 (3.9)	23 (3.0)
Event rate/year (%)	3.0	3.5			6.6	7.4	4.3	3.4
HR (95% CI)	0.86 (0.46-1.59)		1.16 (0.66-2.04)		0.89 (0.65-1.23)		1.26 (0.73-2.17)	
Definite stent thrombosis	5	4	7 (0.9)	7 (0.9)			8 (1.1)	6 (0.8)
Event rate/year (%)	0.8	0.7					1.2	0.9
HR (95% CI)	1.20 (0.32-4.45)		0.99 (0.35-2.81)		n.a.		1.32 (0.46-3.79)	

VKA, vitamin K antagonist; HR, hazard ratio; CRNM, clinically relevant non-major bleeding; n.a., no information provided in primary publication of Phase IIIb trial; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; DAPT, dual antiplatelet therapy (P2Y12 inhibitor +aspirin).

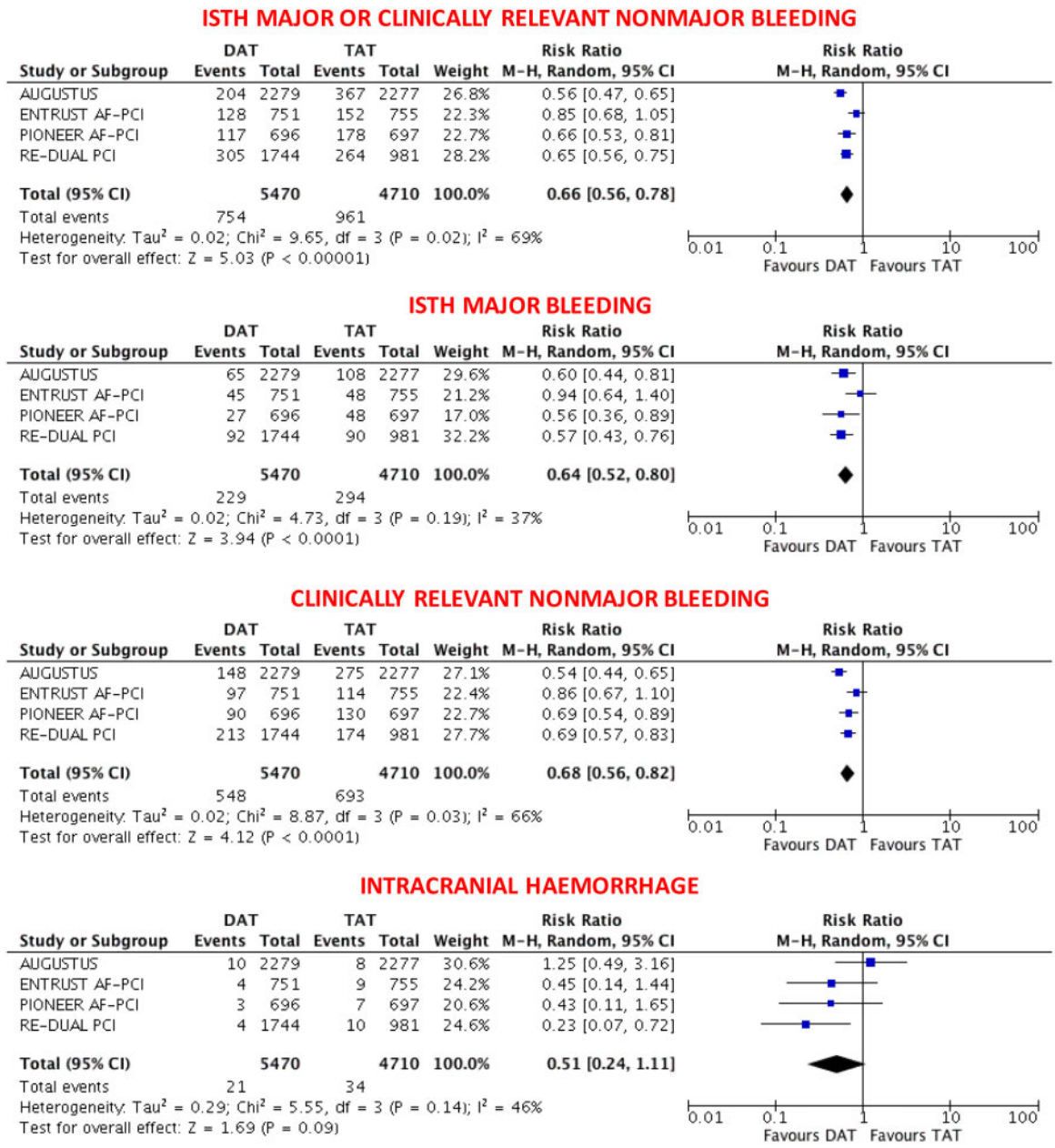

Figure 1 Main bleeding endpoints in dual antithrombotic therapy vs. triple antithrombotic therapy. Random-effects risk ratios for main bleeding endpoints. DAT, dual antithrombotic therapy; ISTH, International Society on Thrombosis and Haemostasis; M-H, Mantel-Haenszel; TAT, triple antithrombotic therapy. With permission Gargiulo *et al.*[9]

trials and trial results are compared with each other (*Tables* 2, 3, *and* 4). Time in therapeutic range (TTR) during VKA therapy differed between trials (RE-Dual PCI TTR: mean 64%, PIONEER AF-PCI TTR: mean 65 ± 25%; AUGUSTUS TTR: mean 56 ± 31%; ENTRUST AF PCI TTR: mean 60 ± 21%), which may have contributed to differences in bleeding events.

Meta-analyses

A recent meta-analysis encompassing all patients (10 234 AF patients) from the four AF PCI trials showed that there was no significant difference between DAT and TAT in terms of all-cause death, cardiovascular death, MACE, and stroke, while DAT was associated with a borderline higher risk of MI, and a higher risk of coronary stent thrombosis.[8,9] Of note, the results were still consistent when the analysis was restricted to NOAC-based DAT vs. VKA-based TAT (*Figures* 1, 2, *and* 3). Another, meta-analysis, which included the WOEST trial plus the four AF PCI trials showed included a total of 11 542 patients.[14] The primary safety outcome of that study was thrombolysis in myocardial infarction (TIMI) major bleeding and the primary efficacy outcome was trial-defined major adverse cardiovascular events (MACE). Compared with VKA plus dual antiplatelet therapy (TAT), odds ratios for TIMI major bleeding were

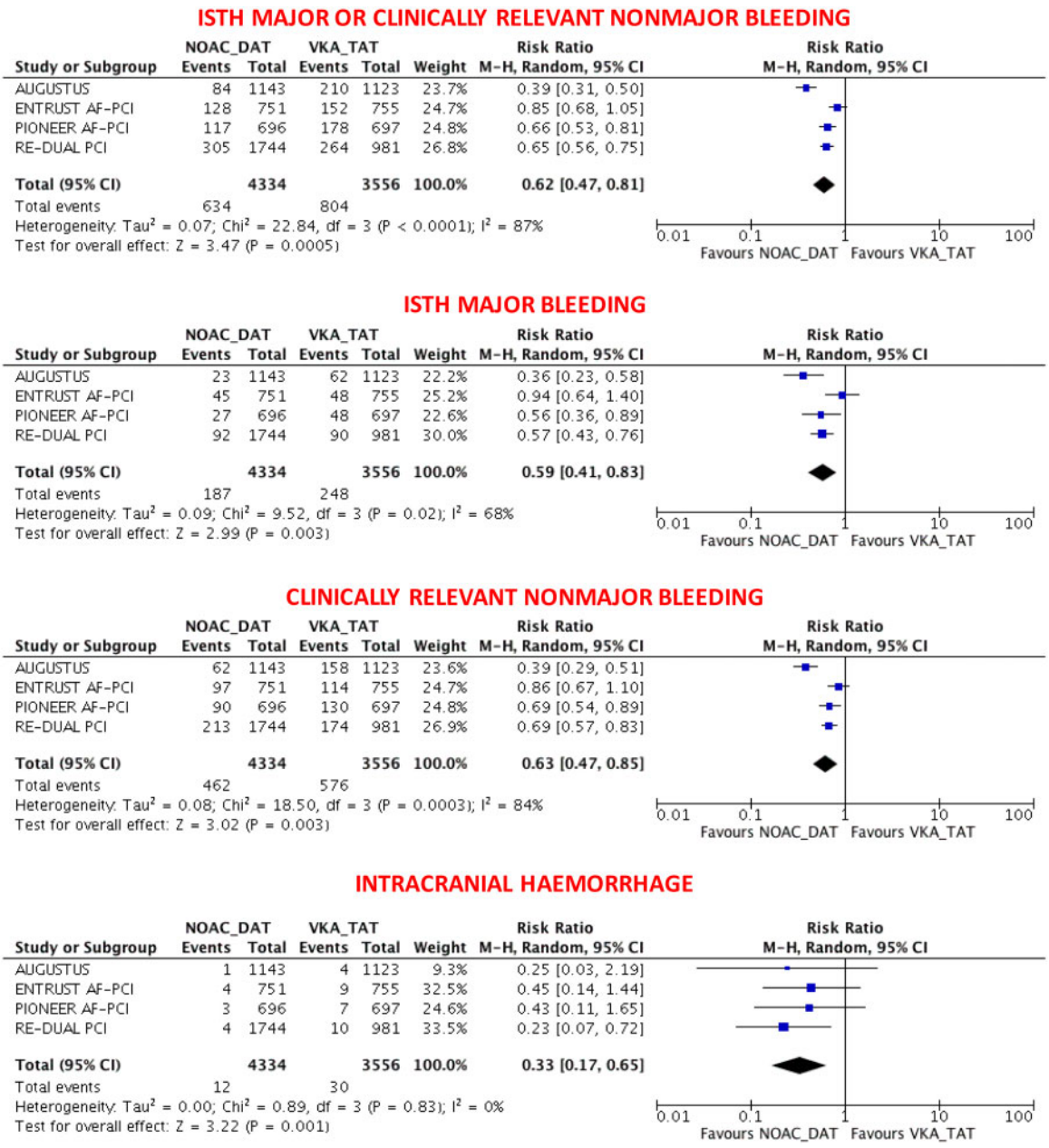

Figure 2 Main bleeding endpoints in non-vitamin K antagonist oral anticoagulant-based dual antithrombotic therapy vs. vitamin K antagonist-based triple antithrombotic therapy. Random-effects risk ratios for main bleeding endpoints. DAT, dual antithrombotic therapy; ISTH, International Society on Thrombosis and Haemostasis; M-H, Mantel-Haenszel; TAT, triple antithrombotic therapy; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist. With Gargiulo *et al.*[9]

0.57 for VKA plus P2Y12 inhibitor, 0.69 for NOAC-based TAT, and 0.52 for NOAC-based DAT. The findings of this meta-analysis suggest that VKA-based TAT should be avoided, because DAT in which aspirin is discontinued lowers bleeding rates without an increase in ischaemic risk. Therefore, the use of a NOAC-based DAT without aspirin was considered to be the favourable treatment in AF patients undergoing PCI.

Thus, the four NOAC AF PCI trials show that DAT, compared to VKA-TAT, reduces major and CRNM bleeding. Furthermore, NOAC-based DAT are associated with reduced rates of intracranial haemorrhage. DAT is not associated with higher rates of trial-defined MACE, all-cause or cardiovascular death, and stroke as compared with TAT throughout the follow-up period. However, the risk of myocardial infarction and stent thrombosis is increased in AF patients if aspirin therapy (despite ongoing therapy with clopidogrel) is stopped early after stenting. Thus, TAT is of importance in all AF patients after coronary artery stenting for some weeks to prevent stent thrombosis.[8,9,15] The mechanism through which early aspirin discontinuation expose AF patients to more ischaemic events remains unknown. Whether ticagrelor or prasugrel reduce the ischaemic risks in DAT warrants further investigations. Nevertheless, the results of the four AF PCI trials will

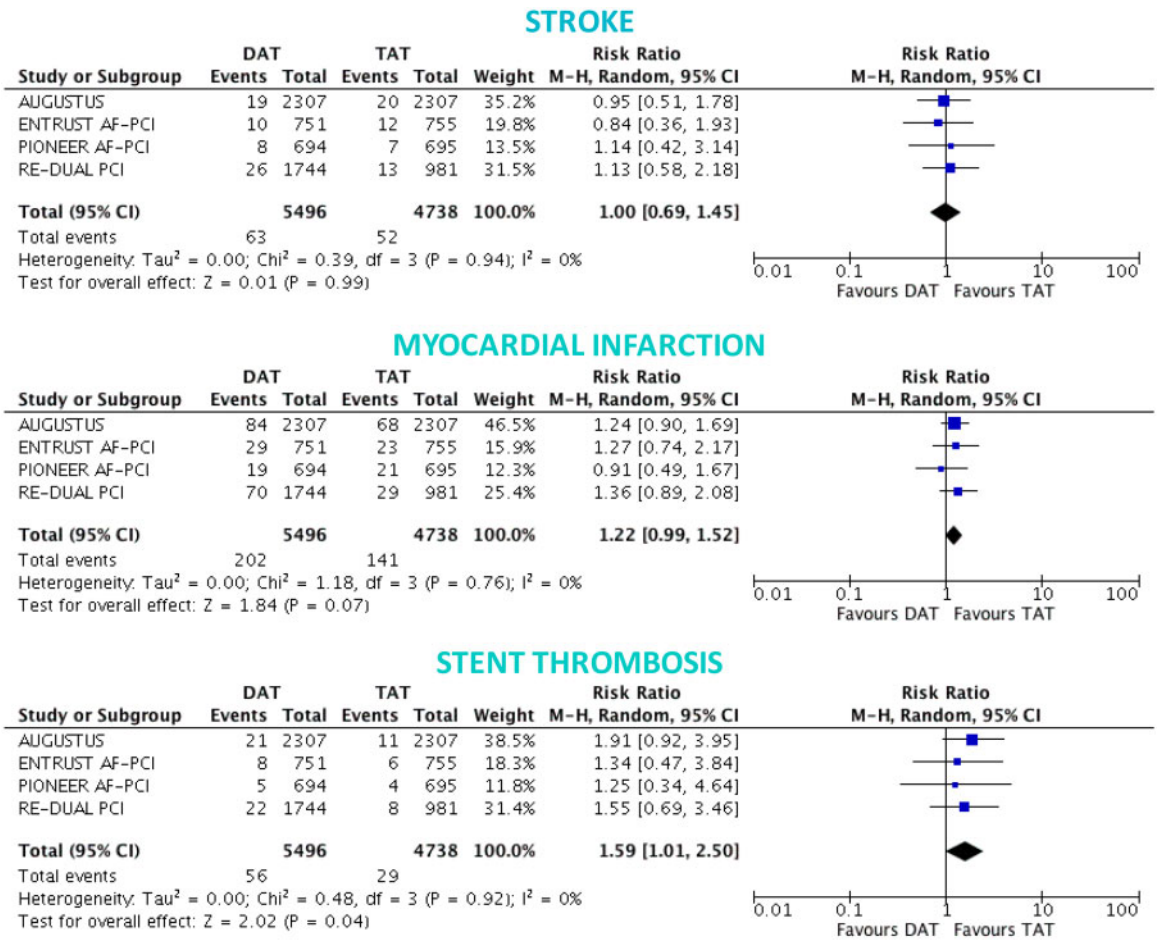

Figure 3 Ischaemic endpoints in dual antithrombotic therapy vs. triple antithrombotic therapy. Random-effects risk ratios for stroke, myocardial infarction and stent thrombosis. With permission Gargiulo *et al.*[9]

influence clinical routine (*Figure 4*). Further sub-studies are warranted to access differences between various subgroups of AF patients like ACS and stable coronary artery disease. A *post hoc* study from AUGUSTUS suggests that aspirin should be provided up to 30 days in AF patients at high risk for stent thrombosis.[15] Of note, many patients stent in the AUGUSTUS trial did not receive a, and therefore, stent thrombosis is not a good outcome parameter for the total study population. In addition, a recent substudy from AUGUSTUS could show that incidence of bleeding events tend to differ between patients undergoing elective PCI and ACS patients with AF. Furthermore, the ENTRUST AF PCI trial suggests that rates of bleeding after PCI differ between radial and femoral artery puncture.[8] The periprocedural antithrombotic regime might address this aspect: in case of femoral artery puncture, VKA and NOACs might be paused 24 h prior to the procedure. Re-initiation of therapy might start about 24 h after the procedure to reduce bleeding from the femoral access site. This temporary pause of VKA/NOACs might not be necessary if the radial route is used for PCI.[8]

In addition to the NOAC AF PCI trials, all other published Phase III trials (RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48, ENSURE AF, X-VERT, and PIONEER AF-PCI) have also shown that NOACs are not inferior to VKA therapy.[16-21] Nevertheless, the study results are based on the correct intake of the NOACs. Thus, adherence and persistence to medical therapy appears of major importance for adequate anticoagulation.[22,23] Recently, Andrade *et al.*[24] published a study on self-reported adherence to various NOACs. Non-adherence, however, is likely to be a significant problem and a reason for concern when prescribing NOACs for long-term anticoagulation.[24]

Conclusion

Compared with TAT, NOAC-based DAT has been shown to be associated with reduced major bleeding as well as intracranial haemorrhages. The benefit is somewhat counterbalanced by a higher risk of stent-related ischaemia during the early phase of DAT. Thus, TAT after stenting is appropriate for at least 14 days with a maximum of 30 days. Thereafter, DAT including a NOAC is the therapy of choice in AF PCI patients to reduce the risk of bleeding during a 1 year of follow-up (*Figure 4*).

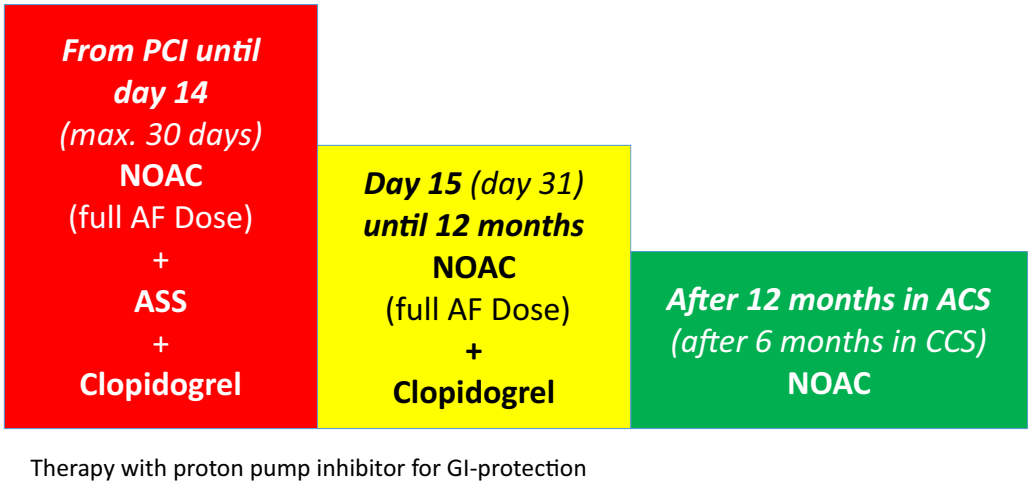

Figure 4 Antithrombotic therapy in atrial fibrillation patients after successful percutaneous coronary intervention. NOAC, non-vitamin K antagonist; full AF dose, dose of non-vitamin K antagonist oral anticoagulant approved by Phase III trials to prevent stroke in atrial fibrillation patients (AF); PCI, percutaneous coronary intervention; ACS, acute coronary syndrome; CCS, chronic coronary syndrome.

Funding

Research grant from the Josef-Freitag-Stiftung Paderborn and Deutsche Herzstiftung. This paper was published as part of a supplement financially supported by an unrestricted educational grant from Daiichi Sankyo Europe GmbH.

Conflict of interest: A.G. discloses honoraria and speaker fees from Astra Zeneca, Bayer Health Care, Berlin-Chemie, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, Boston Scientific, Daiichi Sankyo, Medtronic, Novartis, and Omeicos. Research has been supported by Josef-Freitag Stiftung and Deutsche Herzstiftung e. V. outside the submitted work. P.V. discloses personal fees from Daiichi Sankyo, AstraZeneca, Bayer Health Care, and Terumo outside the submitted work.

Data availability

No new data were generated or analysed in Support of this Research

References

1. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;**383**:955–962.
2. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, Chugh SS, Corradi D, D'Avila A, Dobrev D, Fenelon G, Gonzalez M, Hatem SN, Helm R, Hindricks G, Ho SY, Hoit B, Jalife J, Kim Y-H, Lip GYH, Ma C-S, Marcus GM, Murray K, Nogami A, Sanders P, Uribe W, Van Wagoner DR, Nattel S. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Europace* 2016;**18**:1455–1490.
3. Bukowska A, Lendeckel U, Krohn A, Keilhoff G, Have S. T, Neumann KH, Goette A. Atrial fibrillation down-regulates renal neutral endopeptidase expression and induces profibrotic pathways in the kidney. *Europace* 2008;**10**:1212–1217.
4. Goette A, Jentsch-Ullrich K, Lendeckel U, RöCken C, Agbaria M, Auricchio A, Mohren M, Franke A, Klein HU. Effect of atrial fibrillation on hematopoietic progenitor cells: a novel pathophysiological role of the atrial natriuretic peptide? *Circulation* 2003;**108**:2446–2449.
5. Merino JL, Lip GYH, Heidbuchel H, Cohen AA, De Caterina R, de Groot JR, Ezekowitz MD, Le Heuzey JY, Themistoclakis S, Jin J, Melino M, Winters SM, Merkely B, Goette A. Determinants of left atrium thrombi in scheduled cardioversion: an ENSURE-AF study analysis. *Europace* 2019;**21**:1633–1638.
6. Bukowska A, Zacharias I, Weinert S, Skopp K, Hartmann C, Huth C, Goette A. Coagulation factor Xa induces an inflammatory signalling by activation of protease-activated receptors in human atrial tissue. *Eur J Pharmacol* 2013;**718**:114–123.
7. Vranckx P, Lewalter T, Valgimigli M, Tijssen JG, Reimitz PE, Eckardt L, Lanz HJ, Zierhut W, Smolnik R, Goette A. Evaluation of the safety and efficacy of an edoxaban-based antithrombotic regimen in patients with atrial fibrillation following successful percutaneous coronary intervention (PCI) with stent placement: rationale and design of the ENTRUST-AF PCI trial. *Am Heart J* 2018;**196**:105–112.
8. Vranckx P, Valgimigli M, Eckardt L, Tijssen J, Lewalter T, Gargiulo G, Batushkin V, Campo G, Lysak Z, Vakaliuk I, Milewski K, Laeis P, Reimitz PE, Smolnik R, Zierhut W, Goette A. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet* 2019;**394**:1335–1343.
9. Gargiulo G, Goette A, Tijssen J, Eckardt L, Lewalter T, Vranckx P, Valgimigli M. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. *Eur Heart J* 2019;2019;40:3757–3767.
10. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GYH, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K; ESC Scientific Documents Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.
11. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, Maeng M, Merkely B, Zeymer U, Gropper S, Nordaby M, Kleine E, Harper R, Manassie J, Januzzi JL, ten Berg JM, Steg PG, Hohnloser SH. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med* 2017;**377**:1513–1524.

12. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Birmingham M, Ianus J, Burton P, van Eickels M, Korjian S, Daaboul Y, Lip GY, Cohen M, Husted S, Peterson ED, Fox KA. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016;**375**:2423–2434.
13. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, Goodman SG, Windecker S, Darius H, Li J, Averkov O, Bahit MC, Berwanger O, Budaj A, Hijazi Z, Parkhomenko A, Sinnaeve P, Storey RF, Thiele H, Vinereanu D, Granger CB, Alexander JH. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med* 2019;**380**:1509–1524.
14. Lopes RD, Hong H, Harskamp RE, Bhatt DL, Mehran R, Cannon CP, Granger CB, Verheugt FWA, Li J, ten Berg JM, Sarafoff N, Gibson CM, Alexander JH. Safety and efficacy of antithrombotic strategies in patients with atrial fibrillation undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials. *JAMA Cardiol* 2019;**4**:747.
15. Lopes RD, Leonardi S, Wojdyla DM, Vora AN, Thomas L, Storey RF, Vinereanu D, Granger CB, Goodman SG, Aronson R, Windecker S, Thiele H, Valgimigli M, Mehran R, Alexander JH. Stent thrombosis in patients with atrial fibrillation undergoing coronary stenting in the AUGUSTUS Trial. *Circulation* 2020;**141**:781–783.
16. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093–2104.
17. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener H-C, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–1151.
18. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–992.
19. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KAA, Califf RM; the ROCKET AF Steering Committee. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–891.
20. Cappato R, Ezekowitz MD, Klein AL, Camm AJ, Ma CS, Le Heuzey JY, Talajic M, Scanavacca M, Vardas PE, Kirchhof P, Hemmrich M, Lanius V, Meng IL, Wildgoose P, van Eickels M, Hohnloser SH; X-VeRT Investigators. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *Eur Heart J* 2014;**35**:3346–3355.
21. Goette A, Merino JL, Ezekowitz MD, Zamoryakhin D, Melino M, Jin J, Mercuri MF, Grosso MA, Fernandez V, Al-Saady N, Pelekh N, Merkely B, Zenin S, Kushnir M, Spinar J, Batushkin V, de Groot JR, Lip GY. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. *Lancet* 2016;**388**:1995–2003.
22. Goette A, Hammwohner M. How important is it for therapy adherence to be once a day? *Eur Heart J Suppl* 2016;**18**:I7–I12.
23. Vrijens B, Heidbuchel H. Non-vitamin K antagonist oral anticoagulants: considerations on once- vs. twice-daily regimens and their potential impact on medication adherence. *Europace* 2015;4**17**: 514–523.
24. Andrade J G, Hawkins N M, Fordyce C B, Deyell M W, Er L, Djurdjev O, Macle L, Virani S A, Levin A.Variability in Non-Vitamin K Antagonist Oral Anticoagulants Dose Adjustment in Atrial Fibrillation Patients With Renal Dysfunction: The Influence of Renal Function Estimation Formulae. Canadian Journal of Cardiology 2018;**34**: 1010–1018. 10.1016/j.cjca.2018.04.019