

Safety and efficacy of double vs. triple antithrombotic therapy in patients with atrial fibrillation with or without acute coronary syndrome undergoing percutaneous coronary intervention: a collaborative meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials

Giuseppe Gargiulo ⁽¹⁾, Christopher P. Cannon^{2,3}, Charles Michael Gibson⁴, Andreas Goette^{5,6,7}, Renato D. Lopes⁸, Jonas Oldgren ⁽¹⁾, Serge Korjian⁴, Stephan Windecker ⁽¹⁾, Giovanni Esposito¹, Pascal Vranckx¹¹, and Marco Valgimigli ⁽¹⁾*

¹Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy; ²Cardiovascular Division, Brigham and Women's Hospital, Heart and Vascular Center and Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA; ³Baim Institute for Clinical Research, 930-W Commonwealth Avenue, Boston, MA 02215, USA; ⁴Division of Cardiovascular Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; ⁵St. Vincenz-Hospital, Am Busdorf 2, 33098 Paderborn, Germany; ⁶Working Group of Molecular Electrophysiology, University Hospital Magdeburg, Leipziger Str. 44, 39120 Magdeburg, Germany; ⁷Atrial Fibrillation Network (AFNET), Mendel Str.11, 48149 Münster, Germany; ⁸Duke Clinical Research Institute, Duke University School of Medicine, 200 Morris Street, Durham, NC 27701, USA; ⁹Upsala Clinical Research Center and, Department of Medical Sciences, Uppsala University, Dag Hammarskjolds vag 38, SE-751 85 Uppsala, Sweden; and ; ¹⁰Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Freiburgstrasse 10, 3030 Bern, Switzerland; and ¹¹Department of Cardiology and Intensive Care Medicine, Jessa Ziekenhuis, Faculty of Medicine and Life Sciences, Hasselt University, Stadsomvaart 11, 3500 Hasselt, Belgium

Received 20 August 2020; revised 10 September 2020; editorial decision 14 September 2020; accepted 23 September 2020; online publish-ahead-of-print 29 October 2020

Aims	Safety and efficacy of antithrombotic regimens in patients with atrial fibrillation (AF) undergoing percutaneous cor- onary intervention (PCI) may differ based on clinical presentation. We sought to compare double vs. triple antith- rombotic therapy (DAT vs. TAT) in AF patients with or without acute coronary syndrome (ACS) undergoing PCI.
Methods and results	A systematic review and meta-analysis was performed using PubMed to search for non-vitamin K antagonist oral anticoagulant (NOAC)-based randomized clinical trials. Data on subgroups of ACS or elective PCI were obtained by published reports or trial investigators. A total of 10 193 patients from four NOAC trials were analysed, of whom 5675 presenting with ACS (DAT = 3063 vs. TAT = 2612) and 4518 with stable coronary artery disease (SCAD; DAT = 2421 vs. TAT = 2097). The primary safety endpoint of ISTH major bleeding or clinically relevant non-major bleeding was reduced with DAT compared with TAT in both ACS (12.2% vs. 19.4%; RR 0.63, 95% CI 0.56–0.71; $P < 0.0001$; $I^2 = 0\%$) and SCAD (14.6% vs. 22.0%; RR 0.68, 95% CI 0.55–0.85; $P = 0.0008$; $I^2 = 66\%$), without interaction (<i>P</i> -int = 0.54). Findings were consistent for secondary bleeding endpoints, including intra-cranial haemorrhage. In both subgroups, there was no difference between DAT and TAT for all-cause death, major adverse cardiovascular events, or stroke. Myocardial infarction and stent thrombosis were numerically higher with

^{*} Corresponding author. Tel: +41 91 805 3347, Email: marco.valgimigli@cardiocentro.org

[©] The Author(s) 2020. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

	DAT vs. TAT consistently in ACS and SCAD (<i>P</i> -int = 0.60 and 0.86, respectively). Findings were confirmed by mul- tiple sensitivity analyses, including a separate analysis on dabigatran regimens and a restriction to PCI population.
Conclusions	DAT, compared with TAT, is associated with lower bleeding risks, including intra-cranial haemorrhage, and a small non-significant excess of cardiac ischaemic events in both patients with or without ACS.
Keywords	Atrial fibrillation (AF) • Percutaneous coronary intervention (PCI) • Double therapy (DAT) • Triple therapy (TAT) • Non-vitamin K antagonist oral anticoagulant (NOAC) • Acute coronary syndrome (ACS)

Introduction

The optimal antithrombotic strategy for patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) remains debated.^{1–5} Four multicentre trials, focusing on AF patients undergoing PCI or with acute coronary syndromes (ACS), showed that double antithrombotic therapy (DAT) consisting of a non-vitamin K antagonist (VKA) oral anticoagulant (NOAC) plus a P2Y12 inhibitor (essentially clopidogrel) reduced bleeding complications without apparent increase in ischaemic risk compared with triple antithrombotic therapy (DAT), consisting of a VKA and dual antiplatelet therapy (DAPT).^{6–9} However, individual trials were powered for safety and not for efficacy and a recent pooled analysis of these four trials observed that the bleeding benefit was counterbalanced by a significant increase of stent thrombosis (ST) and a trend towards higher risk of myocardial infarction (MI) with DAT.¹⁰

All these trials have enrolled a variable number of AF patients with ACS or stable coronary artery disease (SCAD). The bleeding and ischaemic risks, as well as the optimal antithrombotic therapy, might differ according to the clinical presentation. We therefore investigated the safety and efficacy of DAT vs. TAT in AF patients undergoing PCI or affected by ACS according to the clinical presentation among the four NOAC-based randomized clinical trials.

Methods

The present systematic review and meta-analysis integrates the previous one by adding a stratification based on clinical presentation (ACS vs. SCAD).¹⁰ Data on clinical events in these subgroups were extracted by published reports or provided by investigators. A full description of the methodology was previously published.¹⁰ Briefly, a systematic search was performed on PubMed and led to identify four NOAC-based randomized clinical trials comparing DAT vs. TAT in AF patients with ACS or undergoing PCI, including AUGUSTUS (Open-Label, 2×2 Factorial, Randomized, Controlled Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention), ENTRUST-AF PCI (EdoxabaN TReatment versUS VKA in paTients with AF undergoing PCI), PIONEER-AF PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention), and RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention). The protocol followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting guidelines and was registered on PROSPERO (CRD42019142779).

Outcome measures

The primary safety bleeding endpoint was defined as ISTH major bleeding or clinically relevant non-major bleeding (CRNMB) at longest available follow-up (between 6 and 14 months). Secondary safety outcomes included alternative bleeding definitions (trial-defined primary safety bleeding endpoint; ISTH major bleeding, ISTH CRNMB, TIMI major or minor bleeding, intra-cranial haemorrhage).

Secondary efficacy endpoints included all-cause death; trial-defined major adverse cardiovascular event (MACE), MI, stroke, and ST. Main endpoint definitions are displayed in Supplementary material online, *Table S1*.

Statistical analysis

Effect sizes in the overall population and ACS and SCAD subgroups were calculated with the Mantel–Haenszel random-effects estimator and expressed as risk ratios (RRs) and 95% Cls. Heterogeneity was assessed by l^2 tests, with substantial heterogeneity defined as $l^2 > 50\%$. Number needed to treat for benefit (NNTB) or harm (NNTH) were also calculated according to Cochrane's recommendations: [1/ACR×(1-RR)], where ACR is the assumed control risk. Sensitivity analyses were performed to: (i) investigate the influence of individual trials on the results; (ii) test results with a fixed-effect model; (iii) investigate separately the doses of dabigatran 110 mg and 150 mg b.i.d. for the RE-DUAL PCI trial; and (iv) restrict the analysis to PCI only (due to the peculiar design of the AUGUSTUS trial, a secondary analysis on PCI population was also conducted by excluding patients presenting with ACS and managed medically).

As previously described, the methodological quality of the randomized trials was assessed by Cochrane's Collaboration tool for assessing risk of bias (low, unclear, or high risk of bias) and no publication bias was assessed due to the small number of studies (<10) included. Statistical significance was set at P < 0.05 (2-tailed). Data analysis was performed with Reviewer Manager (RevMan, version 5.3; Cochrane).

Results

Overall 10 193 patients (DAT = 5484 vs. TAT = 4709) from the four trials were analysed, of whom 5675 presented with ACS (DAT = 3063 vs. TAT = 2612) and 4518 with SCAD (DAT = 2421 vs. TAT = 2097).

The characteristics of the four included trials and of patients are reported in Supplementary material online, *Tables S1* and S2. All trials were of high quality (Supplementary material online, *Table S3*).

Safety endpoints

The primary safety bleeding endpoint of ISTH major bleeding or CRNMB was significantly reduced with DAT compared with TAT in both ACS (12.2% vs. 19.4%; RR 0.63, 95% CI 0.56–0.71; P < 0.0001; l²=0%) and SCAD (14.6% vs. 22.0%; RR 0.68, 95% CI 0.55-0.85; P = 0.0008; $l^2 = 66\%$) without interaction (interaction P = 0.54; Figure 1). In both ACS and SCAD subgroups, this benefit was consistently driven by reductions of both major (ACS: 3.9% vs. 6.4%; RR 0.60, 95% CI 0.48–0.75; P < 0.0001; I² = 0%; SCAD: 4.4% vs. 6.4%; RR 0.69, 95% CI 0.53–0.88; P = 0.004; $I^2 = 0\%$; interaction P = 0.42) and CRNMB (ACS: 9.1% vs. 14.3%; RR 0.64, 95% CI 0.56-0.75; P < 0.0001; l² = 0%; SCAD: 11.5% vs. 16.6%; RR 0.71, 95% CI 0.57-0.90; P = 0.004; $l^2 = 56\%$; interaction P = 0.48; Figures 1 and 2). The results remained consistent when alternative bleeding definitions were adopted (Figure 3). DAT was associated with a borderline 43% reduction of intra-cranial haemorrhage (P = 0.06, Figure 2) compared with TAT, with consistent effects among ACS (0.31% vs. 0.53%; RR 0.57, 95% CI 0.17–1.85; P = 0.35; $l^2 = 34\%$) and SCAD patients (0.38%) vs. 0.83%; RR 0.49, 95% CI 0.22-1.09; P=0.08; I²=0%; interaction P = 0.83; Figure 2).

Efficacy endpoints

In both ACS and SCAD subgroups, there was no significant difference between DAT and TAT for all-cause death (ACS: 4.5% vs. 4.0%; RR 1.13, 95% CI 0.88–1.45; P = 0.34; I² = 0%; SCAD: 3.5% vs. 3.3%; RR 1.05, 95% CI 0.77–1.44; P = 0.75; $I^2 = 0\%$; interaction P = 0.73; Figure 4), MACE (ACS: 9.6% vs. 8.9%; RR 1.08, 95% CI 0.92-1.27; P = 0.36; I² = 0%; SCAD: 7.3% vs. 6.9%; RR 1.06, 95% CI 0.86–1.32; P = 0.56; $l^2 = 0\%$; interaction P = 0.92; Figure 4) and stroke (ACS: 1.3%) vs. 1.3%; RR 0.93, 95% CI 0.55–1.56; P = 0.78; I² = 13%; SCAD: 0.9% vs. 0.8%; RR 1.15, 95% CI 0.59–2.21; P=0.68; l²=0%; interaction P = 0.62; Figure 4). The rates of MI and ST were slightly but not significantly higher with DAT in both ACS: (4.4% vs. 3.7%; RR 1.16, 95% CI 0.89–1.51; P = 0.26; l² = 0% and 1.1% vs. 0.7%; RR 1.59, 95% CI 0.89– 2.87; P = 0.12; $l^2 = 0\%$; respectively) and SCAD groups (2.8% vs. 2.1%; RR 1.31, 95% CI 0.89–1.93; P = 0.16; $l^2 = 0\%$; interaction P = 0.60 and 0.8% vs. 0.6%; RR 1.46, 95% CI 0.70-3.06; P = 0.31; I² = 0%; respectively; interaction P = 0.86; Figure 5).

Additional analyses

Bleeding endpoints remained consistent across clinical presentation subgroups when dabigatran 110 or 150 mg were analysed separately (Supplementary material online, *Figures S1–S6*). Ischaemic endpoints showed consistent results when dabigatran 110 or 150 mg were analysed separately (Supplementary material online, *Figures S7–S11*), although DAT with dabigatran 110 mg seemed to be associated with somewhat greater MI and ST risks in ACS but not SCAD patients (Supplementary material online, *Figures S10* and *S11*).

Results remained consistent when AUGUSTUS patients with ACS not undergoing PCI were excluded (Supplementary material online, *Figures S12–S16*), although the benefit of DAT in the ACS subgroup in terms of intra-cranial haemorrhage became greater (Supplementary material online, *Figure S13*) as the risk of MI, while the risk of ST slightly reduced (Supplementary material online, *Figure S16*).

When removing one study at a time, consistent results between ACS and SCAD subgroups were confirmed for the primary bleeding endpoint (Supplementary material online, *Table S4*). Results remained consistent when a fixed-effects model was adopted (Supplementary material online, *Table S5*).

The NNTB and NNTH were calculated for safety and efficacy endpoints in both ACS and SCAD (Supplementary material online, *Table S6*). We also calculated NNTB and NNTH for multiple risk strata for both ISTH major bleeding and MI and analysed the net benefit (NNTB<NNTH) or harm (NNTB>NNTH) in ACS and SCAD subgroups, observing that DAT had greater benefit than harm in ACS patients but not for SCAD patients in whom the bleeding benefit did not seem to exceed the higher MI rates (*Figure 6*; Supplementary material online, *Tables S7* and *S8*).

Discussion

In the present meta-analysis of the four NOAC-based multicentre randomized clinical trials, we investigated the safety and efficacy profile of DAT vs. TAT in 10 193 AF patients undergoing PCI according to clinical presentation (ACS or SCAD).

Main findings are summarized as follows (Figure 7):

- There was no difference in the treatment effects with respect to primary and secondary bleeding endpoints between ACS and SCAD patients treated with DAT or TAT, confirming a consistent reduction of bleeding with DAT in patients with or without ACS.
- There was no difference in treatment effects with respect to any cardiac or cerebrovascular ischaemic outcome between ACS and SCAD patients treated with DAT vs. TAT, suggesting that the small numerically higher rates of non-fatal cardiovascular ischaemic events with DAT may occur irrespective of the clinical presentation.

Aspirin has represented for decades the cornerstone for antiplatelet therapy in patients with cardiovascular diseases, however, in the last few years an alternative approach has emerged, the so called 'aspirin-free strategy', evaluating the safety and efficacy of a singleantiplatelet therapy with a P2Y12 inhibitor alone.^{5,11} The clinical setting of patients with AF undergoing PCI, who need both OAC and antiplatelet agents, has been among the first setting in which aspirin was withdrawn from DAPT while clopidogrel monotherapy was continued. After the WOEST trial, four NOAC-based trials of AF patients undergoing PCI or with ACS have been conducted and tested this approach. These studies demonstrated that DAT was consistently associated with lower bleeding risk compared with TAT in the absence of a significant trade-off in terms of main ischaemic endpoint.⁶⁻⁹ However, all of them were mostly underpowered for identifying differences of more rare, yet of major clinical relevance, bleeding events such as intra-cranial haemorrhages, or ischaemic endpoints, including MI or ST. A meta-analysis of these four trials detected a significant reduction of intra-cranial haemorrhage with DAT when compared with TAT, and showed that the bleeding benefit associated with DAT came with a trade-off of cardiac, but not cerebrovascular, ischaemic events.^{10,12}

Risks and benefits of antithrombotic regimens differ in patients with or without ACS. ACS patients suffer from higher risk of

	131111	IAJU	NON	CLIN	CALLI	RELEVANT NON	IVIAJOR BLEEDING
	DA	Г	TAT	Г		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
ACS							
AUGUSTUS	115	1410	194	1378	15.0%	0.58 [0.47, 0.72]	-
ENTRUST AF-PCI	59	388	79	389	9.7%	0.75 [0.55, 1.02]	
PIONEER AF-PCI	56	355	88	359	10.0%	0.64 [0.48, 0.87]	
RE-DUAL PCI	155	900	132	475	16.2%	0.62 [0.51, 0.76]	*
Subtotal (95% CI)		3053		2601	51.0%	0.63 [0.56, 0.71]	•
Total events	385		493				
Heterogeneity: Tau ²	= 0.00; Cl	$hi^2 = 1.$	83, df =	3 (P =	0.61); I ² :	= 0%	
Test for overall effec	t: Z = 7.42	2 (P < 0)	.00001)				
SCAD							
AUGUSTUS	89	864	170	888	13.6%	0.54 [0.42, 0.68]	-
ENTRUST AF-PCI	69	363	73	366	10.3%		
PIONEER AF-PCI	51	334	77	324	9.2%		
RE-DUAL PCI	150		132		16.0%		T
Subtotal (95% CI)		2405		2083	49.0%	0.68 [0.55, 0.85]	•
Total events	359		452				
Heterogeneity: Tau ²	= 0.03; Cl	$hi^2 = 8.$	81, df =	3 (P =	0.03); I ² =	= 66%	
Test for overall effec	t: $Z = 3.32$	7 (P = 0)	.0008)				
Total (95% CI)		5458		4684	100.0%	0.65 [0.58, 0.73]	•
Total events	744		945				
Heterogeneity: Tau ²	= 0.01; Cl	$hi^2 = 13$	1.16, df :	= 7 (P =	= 0.13); I ²	= 37%	0.01 0.1 1 10 100
Test for overall effec	t: Z = 7.33	3 (P < 0	.00001)				0.01 0.1 1 10 100 Favours DAT Favours TAT
Test for subgroup di	fferences:	$Chi^2 =$	0.38, df	= 1 (P)	= 0.54),	$l^2 = 0\%$	Tavouis DAT Favouis TAT

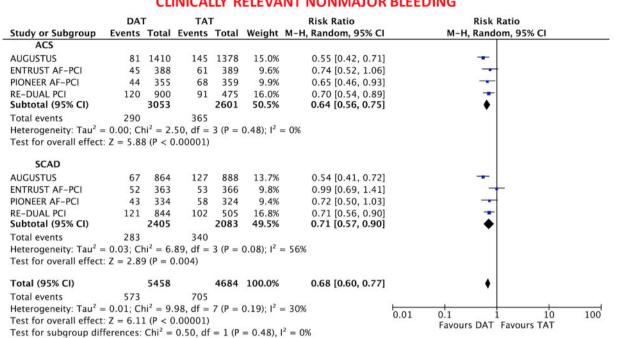
ISTH MAJOR OR CLINICALLY RELEVANT NONMAJOR BLEEDING

ISTH MAJOR BLEEDING

	DA	Г	TAT	Г		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
ACS							
AUGUSTUS	37	1410	58	1378	17.5%	0.62 [0.42, 0.94]	
ENTRUST AF-PCI	21	388	24	389	8.9%	0.88 [0.50, 1.55]	
PIONEER AF-PCI	14	355	23	359	6.8%	0.62 [0.32, 1.18]	
RE-DUAL PCI	51	900	55	475	21.6%	0.49 [0.34, 0.70]	
Subtotal (95% CI)		3053		2601	54.8%	0.60 [0.48, 0.75]	♦
Total events	123		160				Are 13
Heterogeneity: Tau ² =	= 0.00; Cl	$ni^2 = 2.$	96, df =	3 (P =	0.40); I ² :	= 0%	
Test for overall effect							
SCAD							
AUGUSTUS	28	864	50	888	14.0%	0.58 [0.37, 0.91]	
ENTRUST AF-PCI	24	363	24	366	9.6%	1.01 [0.58, 1.74]	
PIONEER AF-PCI	13	334	23	324	6.5%	0.55 [0.28, 1.06]	
RE-DUAL PCI	41	844	35	505	15.0%	0.70 [0.45, 1.09]	
Subtotal (95% CI)		2405		2083	45.2%	0.69 [0.53, 0.88]	•
Total events	106		132				28.
Heterogeneity: Tau ² =	= 0.00; Cl	ni ² = 2.	93, df =	3 (P =	0.40); I ² =	= 0%	
Test for overall effect	: Z = 2.9	1 (P = 0)	0.004)				
							72-60
Total (95% CI)		5458		4684	100.0%	0.64 [0.54, 0.75]	◆
Total events	229		292				
Heterogeneity: Tau ² =	= 0.00; Cl	$ni^2 = 6.$	53, df =	7 (P =	0.48); I ² :	= 0%	
Test for overall effect	: Z = 5.22	2 (P < 0)).00001)				0.01 0.1 1 10 100 Favours DAT Favours TAT
Test for subgroup dif	ferences:	$Chi^2 =$	0.64, df	= 1 (P)	= 0.42),	$l^2 = 0\%$	Favours DAT Favours TAT

Figure I Main bleeding endpoints in double antithrombotic therapy vs. triple antithrombotic therapy according to clinical presentation. Randomeffects risk ratios and 95% confidence intervals for main bleeding endpoints. DAT, double antithrombotic therapy; ISTH, International Society on Thrombosis and Haemostasis; M–H, Mantel–Haenszel; TAT, triple antithrombotic therapy.

ischaemic events compared with SCAD patients and benefit more from prolonged DAPT duration, suggesting that a more potent and/ or prolonged DAPT is beneficial among ACS patients.¹³ Thus, clinical presentation is an important driver for the decision-making on type and duration of DAPT.⁴ In patients with AF undergoing PCI, who require oral anticoagulation for the prevention of thrombo-embolic complications, the balance of benefits and risks of different antithrombotic regimens is more complex and the supporting evidence



CLINICALLY RELEVANT NONMAJOR BLEEDING

INTRACRANIAL HAEMORRHAGE

	DAT	г	TA	г		Risk Ratio	Risk Ratio
Study or Subgroup					Weight	M-H, Random, 95% CI	
ACS							
AUGUSTUS	6	1410	4	1378	22.6%	1.47 [0.41, 5.18]	· · · · · · · · · · · · · · · · · · ·
ENTRUST AF-PCI	2	388	3	389	11.3%	0.67 [0.11, 3.98]	
PIONEER AF-PCI	0	355	1	359	3.5%	0.34 [0.01, 8.25]	
RE-DUAL PCI	1	900	5	475	7.8%	0.11 [0.01, 0.90]	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)		3053		2601	45.3%	0.57 [0.17, 1.85]	
Total events	9		13				
Heterogeneity: Tau ² =	= 0.50; Cł	$ni^2 = 4.$	57, df =	3 (P =	0.21); I ² =	= 34%	
Test for overall effect							
SCAD							
AUGUSTUS	4	864	4	888	18.9%	1.03 [0.26, 4.10]	· · · · · · · · · · · · · · · · · · ·
ENTRUST AF-PCI	2	363	6	366	14.2%	0.34 [0.07, 1.65]	·
PIONEER AF-PCI	0	334	2	324	3.9%	0.19 [0.01, 4.03]	
RE-DUAL PCI	3	844	5	505	17.7%	0.36 [0.09, 1.50]	
Subtotal (95% CI)		2405		2083	54.7%	0.49 [0.22, 1.09]	-
Total events	9		17				
Heterogeneity: Tau ² =	= 0.00; Cl	ni ² = 1.	86, df =	3 (P =	0.60); I ² =	= 0%	
Test for overall effect	: Z = 1.74	4 (P = 0)	0.08)				
Total (95% CI)		5458		4684	100.0%	0.57 [0.31, 1.03]	•
Total events	18		30				
Heterogeneity: Tau ² =	= 0.00; Cl	$ni^2 = 6.$	71, df =	7 (P =	0.46); I ² =	= 0%	0.01 0.1 1 10 100
Test for overall effect							0.01 0.1 1 10 100 Favours DAT Favours TAT
Test for subgroup dif	ferences:	$Chi^2 =$	0.05, df	= 1 (P)	= 0.83), 1	$^{2} = 0\%$	FAVOUIS DAT FAVOUIS TAT

Figure 2 Clinically relevant non-major bleeding and intra-cranial haemorrhage in double antithrombotic therapy vs. triple antithrombotic therapy according to clinical presentation. Random-effects risk ratios and 95% confidence intervals clinically relevant non-major bleeding and intra-cranial haemorrhage.

more limited. In a sub-analysis of the PIONEER-AF PCI, Kerneis et al.,¹⁴ observed consistent findings in several subgroups including those who required urgent revascularization, although a specific subanalysis for ACS vs. SCAD was not performed. In the sub-analysis

from the RE-DUAL trial, Oldgren et al.,¹⁵ found that the benefits of both dabigatran 110 and 150 mg DAT compared with warfarin TAT in reducing bleeding risks were consistent across subgroups of patients with or without ACS, as were the results on ischaemic

	DA	Т	TA	г		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
ACS								
AUGUSTUS	115	1410	194	1378	15.1%	0.58 [0.47, 0.72]	-	
ENTRUST AF-PCI	59	388	79	389	9.8%	0.75 [0.55, 1.02]		
PIONEER AF-PCI	55	355	85	359	9.8%	0.65 [0.48, 0.89]		
RE-DUAL PCI	155		132		16.2%	0.62 [0.51, 0.76]	T	
Subtotal (95% CI)		3053		2601	50.9%	0.63 [0.56, 0.71]	•	
Total events	384		490					
Heterogeneity: Tau ²	= 0.00; Cl	$hi^2 = 1.$	87, df =	3 (P =	0.60); I ² :	= 0%		
Test for overall effec	t: $Z = 7.36$	6 (P < 0	0.00001)					
SCAD								
AUGUSTUS	89	864	170	888	13.6%	0.54 [0.42, 0.68]	-	
ENTRUST AF-PCI	69	363	73	366	10.3%	0.95 [0.71, 1.28]	+	
PIONEER AF-PCI	51	334	77	324	9.2%	0.64 [0.47, 0.88]	-	
RE-DUAL PCI	150	844	132	505	16.0%	0.68 [0.55, 0.84]	-	
Subtotal (95% CI)		2405		2083	49.1%	0.68 [0.55, 0.85]	•	
Total events	359		452				0.00%	
Heterogeneity: Tau ²	= 0.03; Ch	$hi^2 = 8.$	81, df =	3 (P =	0.03); I ² :	= 66%		
Test for overall effec	t: Z = 3.32	7 (P = 0)	.0008)					
Total (95% CI)		5458		4684	100.0%	0.66 [0.59, 0.73]	▲ ¹	
	743		942				10 I	
Total events	745							

TIMI MAJOR OR MINOR

	DA	Г	TAT	Г		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
ACS							
AUGUSTUS	52	1410	82	1378	16.1%	0.62 [0.44, 0.87]	
ENTRUST AF-PCI	57	388	75	389	17.0%	0.76 [0.56, 1.04]	
PIONEER AF-PCI	11	355	17	359	6.8%	0.65 [0.31, 1.38]	
RE-DUAL PCI	35	900	39	475	12.9%	0.47 [0.30, 0.74]	
Subtotal (95% CI)		3053		2601	52.9%	0.64 [0.53, 0.78]	♦
Total events	155		213				
Heterogeneity: Tau ² =	= 0.00; Cl	$ni^2 = 3.$	00, df =	3 (P =	0.39); I ² =	= 0%	
Test for overall effect	: Z = 4.44	4 (P < 0)	0.00001)				
SCAD							
AUGUSTUS	28	864	63	888	13.1%	0.46 [0.30, 0.71]	
ENTRUST AF-PCI	67	363	69	366	17.4%	0.98 [0.72, 1.33]	+
PIONEER AF-PCI	10	334	15	324	6.3%	0.65 [0.29, 1.42]	
RE-DUAL PCI	21		30		10.3%		
Subtotal (95% CI)		2405		2083	47.1%	0.60 [0.37, 0.97]	•
Total events	126		177				
Heterogeneity: Tau ² =	= 0.17; Cl	$ni^2 = 1$	1.90, df =	= 3 (P =	= 0.008);	$I^2 = 75\%$	
Test for overall effect	Z = 2.02	7 (P = 0)	0.04)				
Total (95% CI)		5458		4684	100.0%	0.62 [0.50, 0.78]	•
Total events	281		390				
Heterogeneity: Tau ² =	= 0.05; Cl	$hi^2 = 1!$	5.07, df =	= 7 (P =	= 0.04); I ²	= 54%	
Test for overall effect							0.01 0.1 1 10 100 Favours DAT Favours TAT
Test for subgroup dif	ferences:	$Chi^2 =$	0.05. df	= 1 (P)	= 0.82).	$ ^2 = 0\%$	FAVOUIS DAT FAVOUIS TAT

Figure 3 Alternative bleeding definitions in double antithrombotic therapy vs. triple antithrombotic therapy according to clinical presentation. Random-effects risk ratios and 95% confidence intervals for primary bleeding endpoint trial-defined and thrombolysis in myocardial infarction major or minor bleeding.

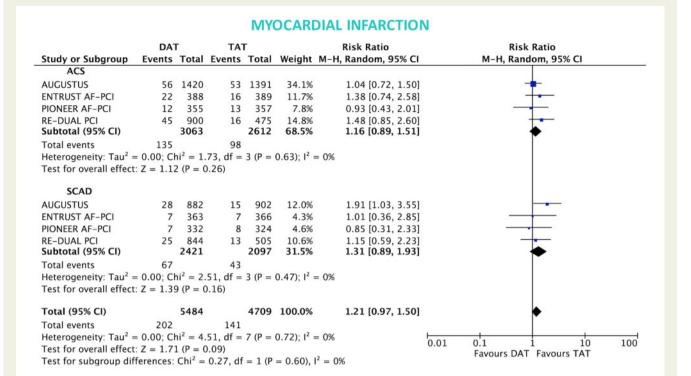
÷

endpoints. Windecker *et al.*,¹⁶ recently reported AUGUSTUS trial results stratified by clinical presentation (ACS managed medically, ACS undergoing PCI, elective PCI) demonstrating that the superior

safety and similar efficacy of DAT was consistent across subgroups. Also, Vranckx *et al.*,¹⁷ recently reported that the edoxaban-based regimen provided consistent safety and similar efficacy irrespective of

				ALL	-CAL	JSE DEATH		
Study or Subgroup	DAT Events		TAT ents To	tal Wei	ight M-	Risk Ratio H, Random, 95% CI		Risk Ratio M-H, Random, 95% Cl
ACS								
AUGUSTUS ENTRUST AF-PCI	49	1420 388	47 13		4.9% 4.8%	1.02 [0.69, 1.51] 1.34 [0.80, 2.23]		
PIONEER AF-PCI	13	355			5.1%	1.63 [0.69, 3.89]		
RE-DUAL PCI	46	900			5.6%	1.01 [0.63, 1.64]		+
Subtotal (95% CI) Total events	140	3063	103	612 61	1.4%	1.13 [0.88, 1.45]		Ť
Heterogeneity: Tau ² =		$i^2 = 1.57$,		P = 0.67); $ ^2 = 09$	6		
Test for overall effect:								
SCAD								
AUGUSTUS	30	882	25 9	02 14	4.1%	1.23 [0.73, 2.07]		+
ENTRUST AF-PCI	14	363 332			7.0% 1.9%	1.09 [0.52, 2.28]		
PIONEER AF-PCI RE-DUAL PCI		844			5.6%	0.59 [0.14, 2.43] 0.97 [0.59, 1.60]		
Subtotal (95% CI)		2421			3.6%	1.05 [0.77, 1.44]		+
Total events	86	2 - 1 00	67	0 - 0 79), 1 ² - 06	,		
Heterogeneity: Tau ² = Test for overall effect:				P = 0.78); 1- = 02	b		
Total (95% CI)	r	5484	47	09 100	0%	1.10 [0.90, 1.34]		
Total events	226	5404	170 47	55 100		1.10 [0.50, 1.34]		T
Heterogeneity: Tau ² =	= 0.00; Chi		df = 7 (P = 0.91); $ ^2 = 09$	6	0.01	0.1 1 10 10
Test for overall effect: Test for subgroup diff				1 (P = 0)	73), l ² –	0%		Favours DAT Favours TAT
. est for subgroup uni	crences. c					AL-DEFINED		
	DAT		TAT	VIAC	LINI	Risk Ratio		Risk Ratio
Study or Subgroup ACS				tal Wei	ght M-	H, Random, 95% CI		M-H, Random, 95% CI
AUGUSTUS	114		105 13		5.0%	1.06 [0.82, 1.37]		+
ENTRUST AF-PCI		388			7.2%	1.18 [0.73, 1.92]		<u>+</u>
PIONEER AF-PCI RE-DUAL PCI		355 900			5.7% 3.6%	1.39 [0.81, 2.39] 1.00 [0.77, 1.31]		T
Subtotal (95% CI)		3063			2.5%	1.08 [0.92, 1.27]		•
Total events Heterogeneity: Tau ² =	309	2 1 2 2	224		. 12 . 01	,		
Test for overall effect:				r = 0.74	1, 1 = 09	0		
SCAD AUGUSTUS	5.4	007	44 0	02 11	1 20/	1 26 [0 95 1 95]		-
ENTRUST AF-PCI	54 16	882 363			1.2% 3.9%	1.26 [0.85, 1.85] 0.90 [0.46, 1.73]		
PIONEER AF-PCI		332			3.0%	0.84 [0.39, 1.78]		
RE-DUAL PCI Subtotal (95% CI)		844 2421			9.4% 7 .5%	1.04 [0.77, 1.40] 1.06 [0.86, 1.32]		1
Total events	188		137	5, 5,		1.00 [0.00, 1.52]		
Heterogeneity: Tau ² = Test for overall effect:				P = 0.71	$ _{1}^{2} = 09$	6		
Total (95% CI)		5484	47	09 100	0.0%	1.07 [0.94, 1.22]		
Total events	497	- 101	361			101 [0134] 1166]		ľ
Heterogeneity: Tau ² =	0.00; Chi			P = 0.92); $I^2 = 09$	6	0.01	0.1 1 10 10
Test for overall effect: Test for subgroup diff				L (P = 0.9)	92), I ² =	0%	02565.771	Favours DAT Favours TAT
					ST	ROKE		
	DAT		TAT			Risk Ratio		Risk Ratio
	DAT							
Study or Subgroup			ents Te	otal we	ight M-	H, Random, 95% CI		M-H, Random, 95% CI
Study or Subgroup ACS AUGUSTUS	Events				1ght M- 8.8%	H, Random, 95% CI		M-H, Random, 95% Cl
ACS AUGUSTUS ENTRUST AF-PCI	Events	Total Ev 1420 388	15 1 7	391 28 389 8	8.8% 8.1%	0.98 [0.48, 2.00] 0.43 [0.11, 1.65]		M-H, Random, 95% Cl
ACS AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI	Events 15 3 6	Total Ev 1420	15 1 7 2	391 28 389 8 357 5	8.8% 8.1% 5.7%	0.98 [0.48, 2.00] 0.43 [0.11, 1.65] 3.02 [0.61, 14.85]		M-H, Random, 95% CI
ACS AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI Subtotal (95% CI)	Events 15 3 6 16	Total Ev 1420 388 355	15 1 7 2 10 2	391 28 389 8 357 9 475 23	8.8% 8.1%	0.98 [0.48, 2.00] 0.43 [0.11, 1.65]		M-H, Random, 95% CI
ACS AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI	Events	Total Ex 1420 388 355 900 3063 i ² = 3.44	15 1 7 2 10 2 34 , df = 3 (391 28 389 8 357 9 475 23 5 12 66	8.8% 8.1% 5.7% 3.8% 5.4%	0.98 [0.48, 2.00] 0.43 [0.11, 1.65] 3.02 [0.61, 14.85] 0.84 [0.39, 1.85] 0.93 [0.55, 1.56]		M-H, Random, 95% CI
ACS AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI Subtotal (95% CI) Total events Heterogeneity: Tau ² Test for overall effect	Events	Total Ex 1420 388 355 900 3063 i ² = 3.44	15 1 7 2 10 2 34 , df = 3 (391 28 389 8 357 9 475 23 5 12 66	8.8% 8.1% 5.7% 3.8% 5.4%	0.98 [0.48, 2.00] 0.43 [0.11, 1.65] 3.02 [0.61, 14.85] 0.84 [0.39, 1.85] 0.93 [0.55, 1.56]		M-H, Random, 95% CI
ACS AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI Subtotal (95% CI) Total events Heterogeneity: Tau ² =	Events	Total Ex 1420 388 355 900 3063 i ² = 3.44	15 1 7 2 10 20 34 , df = 3 (8)	391 28 389 8 357 5 475 23 5 12 66 P = 0.33	8.8% 8.1% 5.7% 3.8% 5.4%	0.98 [0.48, 2.00] 0.43 [0.11, 1.65] 3.02 [0.61, 14.85] 0.84 [0.39, 1.85] 0.93 [0.55, 1.56]		M-H, Random, 95% CI
ACS AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect SCAD AUGUSTUS ENTRUST AF-PCI	Events 15 3 6 16 40 = 0.04; Chi t: Z = 0.28 4 7	Total Ev 1420 388 355 900 3063 $i^2 = 3.44$ $i (P = 0.74)$ 882 363 363	15 1 7 2 10 2 34 , df = 3 (8) 5 1	391 28 389 8 357 9 475 23 512 66 P = 0.33 902 8 366 12	8.8% 8.1% 5.7% 3.8% 5.4%); I ² = 13 8.5% 1.2%	0.98 [0.48, 2.00] 0.43 [0.11, 1.65] 3.02 [0.61, 14.85] 0.84 [0.39, 1.85] 0.93 [0.55, 1.56] 3%		M-H, Random, 95% CI
ACS AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect SCAD AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI	Events 15 3 6 16 40 = 0.04; Chi t: Z = 0.28 4 7 2	Total Ev 1420 388 355 900 3063 $i^2 = 3.44$ $i (P = 0.74)$ 882 363 332	15 1 7 2 10 2 34 , df = 3 (8) 5 4	391 24 389 4 357 5 475 23 512 66 P = 0.33 902 4 366 11 324 5	8.8% 8.1% 5.7% 3.8% 5.4% i); i ² = 13 8.5% 1.2% 5.1%	0.98 [0.48, 2.00] 0.43 [0.11, 1.65] 3.02 [0.61, 14.85] 0.84 [0.39, 1.85] 0.93 [0.55, 1.56] 3% 0.82 [0.22, 3.04] 1.41 [0.45, 4.41] 0.49 [0.09, 2.65]		M-H, Random, 95% CI
ACS AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect SCAD AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI Subtotal (95% CI)	Events 15 3 6 16 40 = 0.04; Chi t: Z = 0.28 4 7 2 10	Total Ev 1420 388 355 900 3063 $i^2 = 3.44$ $i (P = 0.74)$ 882 363 363	15 1 7 2 10 2 34 , df = 3 (8) 5 4 3	391 24 389 8 357 2 312 66 P = 0.33 902 8 366 11 324 9 505 8	8.8% 8.1% 5.7% 3.8% 5.4%); I ² = 13 8.5% 1.2%	0.98 [0.48, 2.00] 0.43 [0.11, 1.65] 3.02 [0.61, 14.85] 0.84 [0.39, 1.85] 0.93 [0.55, 1.56] 3%		M-H, Random, 95% CI
ACS AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect SCAD AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI Subtotal (95% CI) Total events Heterogeneity: Tau ² =	Events 15 3 6 16 40 = 0.04; Chi t: Z = 0.28 4 7 7 10 23 = 0.00; Chi	Total Ev 1420 388 355 900 3063 $i^2 = 3.44$ (P = 0.7i) 882 363 332 844 2421 $i^2 = 2.08$	15 1 7 2 10 20 34 , df = 3 (8) 5 4 3 20 17 , df = 3 (391 24 389 4 357 5 512 66 P = 0.33 902 8 366 1 324 5 505 8 9097 33	8.8% 8.1% 5.7% 3.8% 5.4%); l ² = 13 8.5% 1.2% 5.1% 8.8% 3.6%	0.98 [0.48, 2.00] 0.43 [0.11, 1.65] 3.02 [0.61, 14.85] 0.84 [0.39, 1.85] 0.93 [0.55, 1.56] 3% 0.82 [0.22, 3.04] 1.41 [0.45, 4.41] 0.49 [0.09, 2.65] 1.99 [0.55, 7.21] 1.15 [0.59, 2.21]		M-H, Random, 95% CI
ACS AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect SCAD AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI Subtotal (95% CI) Total events	Events 15 3 6 16 40 = 0.04; Chi t: Z = 0.28 4 7 7 10 23 = 0.00; Chi	Total Ev 1420 388 355 900 3063 $i^2 = 3.44$ (P = 0.7i) 882 363 332 844 2421 $i^2 = 2.08$	15 1 7 2 10 20 34 , df = 3 (8) 5 4 3 20 17 , df = 3 (391 24 389 4 357 5 512 66 P = 0.33 902 8 366 1 324 5 505 8 9097 33	8.8% 8.1% 5.7% 3.8% 5.4%); l ² = 13 8.5% 1.2% 5.1% 8.8% 3.6%	0.98 [0.48, 2.00] 0.43 [0.11, 1.65] 3.02 [0.61, 14.85] 0.84 [0.39, 1.85] 0.93 [0.55, 1.56] 3% 0.82 [0.22, 3.04] 1.41 [0.45, 4.41] 0.49 [0.09, 2.65] 1.99 [0.55, 7.21] 1.15 [0.59, 2.21]		M-H, Random, 95% CI
ACS AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect SCAD AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect Total (95% CI)	Events 15 3 6 17 16 1	Total Ev 1420 388 355 900 3063 $i^2 = 3.44$ (P = 0.7i) 882 363 332 844 2421 $i^2 = 2.08$	$ \begin{array}{c} 15 \\ 2 \\ 10 \\ 2 \\ 34 \\ , df = 3 \\ 8 \\ \end{array} $ $ \begin{array}{c} 5 \\ 5 \\ 4 \\ 3 \\ 2 \\ 6 \\ 17 \\ , df = 3 \\ 8 \\ \end{array} $	391 24 389 4 357 5 512 66 P = 0.33 902 8 366 1 324 5 505 8 9097 33	8.8% 8.1% 5.7% 3.8% 5.4% (); $l^2 = 1$ 8.5% 1.2% 5.1% 8.8% 3.6% (); $l^2 = 0$	0.98 [0.48, 2.00] 0.43 [0.11, 1.65] 3.02 [0.61, 14.85] 0.84 [0.39, 1.85] 0.93 [0.55, 1.56] 3% 0.82 [0.22, 3.04] 1.41 [0.45, 4.41] 0.49 [0.09, 2.65] 1.99 [0.55, 7.21] 1.15 [0.59, 2.21]		M-H, Random, 95% CI
ACS AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect SCAD AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect Total (95% CI) Total events	Events 15 3 6 16 40 = 0.04; Chi t: Z = 0.28 4 7 2 10 23 = 0.00; Chi t: Z = 0.41 63	Total Ex 1420 388 388 355 9003063 i² = 3.44 i² = 3.44 (P = 0.7i 882 363 332 844 2421 i² = 2.08 i² = 2.08 (P = 0.6i 5484 5484	15 1 7 2 10 2 34 , df = 3 (8) 5 5 4 3 2 4 3 2 (17 , df = 3 (8) 4 5 5 , 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	391 24 389 4 357 5 475 2 475 2 475 2 602 4 366 1 366 1 364 1 355 4 902 4 903 10 904 10 905 10 907 10	8.8% 8.1% 5.7% 3.8% 5.4% (); $l^2 = 13$ 8.5% 1.2% 8.8% 3.6% (); $l^2 = 09$ 0.0%	0.98 [0.48, 2.00] 0.43 [0.11, 1.65] 3.02 [0.61, 14.85] 0.84 [0.39, 1.85] 0.93 [0.55, 1.56] 3% 0.82 [0.22, 3.04] 1.41 [0.45, 4.41] 0.49 [0.09, 2.65] 1.99 [0.55, 7.21] 1.15 [0.59, 2.21] 6 1.00 [0.68, 1.46]		
ACS AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect SCAD AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect Test for overall effect Test for overall effect	Events 15 3 6 16 9 9 10 2 10 23 9 0.00; Chit t: Z = 0.41 63 9 0.00; Chit t: Z = 0.02; Chit	Total Ex 1420 388 355 900 3063 $i^2 = 3.44$ (P = 0.7i) 882 363 332 844 2421 $i^2 = 2.08$ (P = 0.6i) 5484 $i^2 = 5.79$ (P = 0.9i)	15 1 7 2 10 2 34 , df = 3 (8) 5 5 4 3 20 , df = 3 (8) 47 , df = 3 (8) 47 8) 47 81 8)	391 28 389 8 387 9 475 25 512 66 902 8 366 11 324 9 505 8 997 33 997 33 907 100 P = 0.566 0 P = 0.566 0 99 0.56	8.8% 8.1% 5.7% 3.8% 5.4% (); $I^2 = 13$ 8.5% 1.2% 5.1% 8.8% 3.6% (); $I^2 = 09$ 0.0% (); $I^2 = 09$	0.98 [0.48, 2.00] 0.43 [0.11, 1.65] 3.02 [0.61, 14.85] 0.84 [0.39, 1.85] 0.93 [0.55, 1.56] 3% 0.82 [0.22, 3.04] 1.41 [0.45, 4.41] 0.49 [0.05, 7.21] 1.15 [0.59, 2.21] 6 1.00 [0.68, 1.46] 6	0.01	
ACS AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI Subtotal (95% CI) Total events Heterogeneity: Tau ² = SCAD AUGUSTUS ENTRUST AF-PCI PIONEER AF-PCI RE-DUAL PCI Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect Total (95% CI) Total events Heterogeneity: Tau ² =	Events 15 3 6 16 9 9 10 2 10 23 9 0.00; Chit t: Z = 0.41 63 9 0.00; Chit t: Z = 0.02; Chit	Total Ex 1420 388 355 900 3063 $i^2 = 3.44$ (P = 0.7i) 882 363 332 844 2421 $i^2 = 2.08$ (P = 0.6i) 5484 $i^2 = 5.79$ (P = 0.9i)	15 1 7 2 10 2 34 , df = 3 (8) 5 5 4 3 20 , df = 3 (8) 47 , df = 3 (8) 47 8) 47 81 8)	391 28 389 8 387 9 475 25 512 66 902 8 366 11 324 9 505 8 997 33 997 33 907 100 P = 0.566 0 P = 0.566 0 99 0.56	8.8% 8.1% 5.7% 3.8% 5.4% (); $I^2 = 13$ 8.5% 1.2% 5.1% 8.8% 3.6% (); $I^2 = 09$ 0.0% (); $I^2 = 09$	0.98 [0.48, 2.00] 0.43 [0.11, 1.65] 3.02 [0.61, 14.85] 0.84 [0.39, 1.85] 0.93 [0.55, 1.56] 3% 0.82 [0.22, 3.04] 1.41 [0.45, 4.41] 0.49 [0.05, 7.21] 1.15 [0.59, 2.21] 6 1.00 [0.68, 1.46] 6	0.01	

Figure 4 Death, major adverse cardiovascular events, and stroke in double antithrombotic therapy vs. triple antithrombotic therapy according to clinical presentation. Random-effects risk ratios and 95% confidence intervals for all-cause death, major adverse cardiovascular events, and stroke.



STENT THROMBOSIS

	DA	г	TAT	г		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
ACS							
AUGUSTUS	13	1420	7	1391	25.2%	1.82 [0.73, 4.55]	
ENTRUST AF-PCI	5	388	5	389	13.9%	1.00 [0.29, 3.44]	· · · · · · · · · · · · · · · · · · ·
PIONEER AF-PCI	3	355	3	357	8.3%	1.01 [0.20, 4.95]	
RE-DUAL PCI	15	900	3	475	13.9%	2.64 [0.77, 9.07]	
Subtotal (95% CI)		3063		2612	61.3%	1.59 [0.89, 2.87]	◆
Total events	36		18				
Heterogeneity: Tau ² =	= 0.00; Cl	$ni^2 = 1.$	60, df =	3 (P =	0.66); I ² =	= 0%	
Test for overall effect	: Z = 1.50	5 (P = 0)).12)				
10.49 Carl 10.00							
SCAD							
AUGUSTUS	8	882	4	902	14.7%	2.05 [0.62, 6.77]	
ENTRUST AF-PCI	3	363	1	366	4.1%	3.02 [0.32, 28.94]	
PIONEER AF-PCI	2	332	1	324	3.7%	1.95 [0.18, 21.42]	· · · · · · · · · · · · · · · · · · ·
RE-DUAL PCI	7	844	5	505	16.2%	0.84 [0.27, 2.63]	
Subtotal (95% CI)		2421		2097	38.7%	1.46 [0.70, 3.06]	
Total events	20		11				
Heterogeneity: Tau ² =	= 0.00; Cl	$ni^2 = 1.$	67, df =	3 (P =	0.64); I ² =	= 0%	
Test for overall effect	z = 1.0	1 (P = 0)).31)				
		F 4 9 4		4700	100.0%	1 54 [0 07 3 44]	
Total (95% CI)		5484		4709	100.0%	1.54 [0.97, 2.44]	-
Total events	56		29				
Heterogeneity: Tau ² =			•	7 (P =	0.86); l ² =	= 0%	0.01 0.1 1 10 100
Test for overall effect						 Market (1997) 	Favours DAT Favours TAT
Test for subgroup dif	ferences:	$Chi^2 =$	0.03, df	= 1 (P	= 0.86),	$l^2 = 0\%$	

Figure 5 Myocardial infarction and stent thrombosis in double antithrombotic therapy vs. triple antithrombotic therapy according to clinical presentation. Random-effects risk ratios and 95% confidence intervals for myocardial infarction and stent thrombosis. Note: stent thrombosis definition was definite ST for the RE-DUAL PCI, ENTRUST-AF PCI and PIONEER-AF PCI trials, and definite or probable ST for AUGUSTUS.

clinical presentation. However, these individual sub-analyses have limited power to identify whether clinical presentation is a treatment modifier for the effects of DAT vs. TAT.

Patients with ACS are at higher risks of ST and recurrent MI after PCI. Therefore, despite the absence of supporting evidence, multiple international guidelines or position papers have suggested caution in

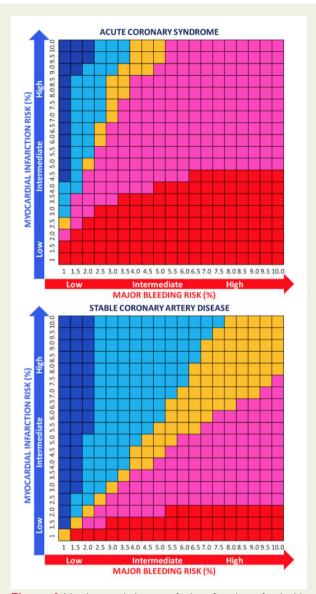


Figure 6 Number needed to treat for benefit or harm for double antithrombotic therapy vs. triple antithrombotic therapy according to risk of major bleeding and myocardial infarction in acute coronary syndrome and stable coronary artery disease subgroups. At each risk (%) ranging from 1% to 10% for both major bleeding and MI, the difference between NNTB and NNTH was calculated. Red indicates that the net benefit of double antithrombotic therapy vs. triple antithrombotic therapy is in favour of bleeding (NNTB < NNTH, thus reduction of bleeding is higher than the risk of MI) and its intensity refers to greater (dark red) or lower (light red/pink) benefit (with the cut-off range selected arbitrarily to be -100-100), while blue indicates a net ischaemic harm (NNTB > NNTH, thus the reduction of bleeding is lower than the risk of MI) and its intensity refers to greater (dark blue) or lower (light blue) harm (with the cut-off range selected arbitrarily to be -100-100). Orange indicates a neutral effect (NNTB = NNTH; we arbitrarily selected a range from -10 to 10 to consider the effect as neutral).

selecting a DAT instead of a TAT regimen early after intervention in this patient population. $^{3,4,18-20}$ While there is large consensus that

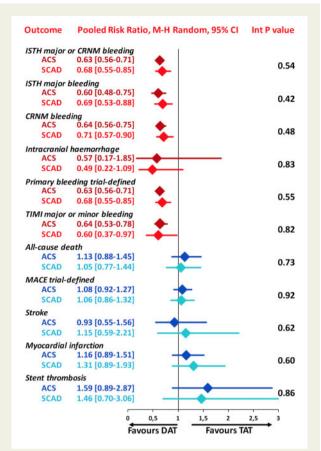


Figure 7 The summary of safety and efficacy endpoints in double antithrombotic therapy vs. triple antithrombotic therapy demonstrating there is a consistent effect across acute coronary syndrome and stable coronary artery disease subgroups. Pooled randomeffects risk ratios with 95% confidence intervals and interaction *P* values for safety and efficacy endpoints. CRNM, clinically relevant non-major; DAT, double antithrombotic therapy; ISTH, International Society on Thrombosis and Haemostasis; MACE, major adverse cardiovascular events; TAT, triple antithrombotic therapy; TIMI, thrombolysis in myocardial infarction.

the trade-off between predicted ischaemic and bleeding risks should guide the early vs. late adoption of a DAT regimen in AF patients undergoing PCI, some guidelines and position statements endorsed ACS presentation *per se* among the drivers for a TAT instead of a DAT regimen.^{3,4,18–20}

Although several meta-analyses have been conducted on patients with AF undergoing PCI,^{10,21,22} this is the first one to specifically address the subgroups of ACS and SCAD and does not support this position for two main observations. First, ACS patients also suffer from heightened major bleeding risk and they derived, in this pooled analysis, slightly greater absolute risk benefit with DAT instead of TAT, resulting in a slightly lower number needed to treat for benefit compared with SCAD patients. Secondly, the absolute risk difference as well as the relative risk increase for MI or ST with DAT compared with TAT was not higher in ACS compared with SCAD patients. These observations were unexpected and might reflect the synergistic role of NOACs, when administered at full doses, with a P2Y12

inhibitor monotherapy for the prevention of coronary ischaemic events. Interestingly, the only signal that DAT was associated with higher MI (RR: 1.87; 95% CI 1.04–3.36) and ST (RR: 3.73; 95%CI 1.06–13.15) risks compared with TAT was observed in patients treated with dabigatran 110 mg, but not dabigatran 150 mg.

Hence, ACS or SCAD presentation *per se* does not justify the default adoption of a given post-PCI antithrombotic regimen in patients taking NOAC at FDA approved stroke prevention regimens, rather concurs, together with other established ischaemic, and bleeding risk factors, to the decision-making on the optimal secondary prevention antithrombotic regimens.

Study limitations

This is a study-level meta-analysis without access to individual patient data, which carries well-known inherent limitations. Due to missing information on ACS or SCAD presentation, the present analysis excluded 41 (0.4%) among the 10 234 originally included patients across the four selected trials, which explains the apparently inconsistent findings on ST in this compared with a prior meta-analysis.¹⁰ Randomization was stratified according to clinical presentation only in the ENTRUST-AF PCI and AUGUSTUS trials. Finally, our results mainly apply to a clopidogrel-based therapy (>90% of patients received this P2Y12 inhibitor), therefore, whether the use of strategies to identify poor-responders (such as genotype or platelet function tests or risk score application)^{23,24} or the use of alternative P2Y12 inhibitors, such as ticagrelor or prasugrel, might reduce thrombotic risks while preserving the bleeding benefit remains to be investigated.

Conclusions

DAT is associated with a reduction in bleeding complications, including major and intra-cranial haemorrhages compared with TAT, irrespective of clinical presentation and is associated with a small increase of non-fatal cardiovascular ischaemic events in both ACS and SCAD patients.

Supplementary material

Supplementary material is available at European Heart Journal – Cardiovascular Pharmacotherapy online.

Funding

The present study did not receive any funding.

Conflict of interest: G.G. reports consultant/speaker fees from Daiichi Sankyo, outside the submitted work. C.P.C. reports research grants from Amgen, Boehringer-Ingelheim (BI), Bristol-Myers Squibb (BMS), Daiichi Sankyo, Janssen, Merck, and Pfizer; and consulting fees from Aegerion, Alnylam, Amarin, Amgen, Applied Therapeutics, Ascendia, BI, BMS, Corvidia, Eli Lilly, HLS Therapeutics, Innovent, Janssen, Kowa, Merck, Pfizer, Rhoshan, and Sanofi. C.M.G. receives research funds from Janssen and Johnson & Johnson. He receives consulting funds from Janssen, Johnson & Johnson, and Bayer. 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. R.D.L. reports grants and personal fees from Bristol-Myers Squibb and Pfizer, personal fees from Boehringer Ingelheim and Bayer AG and grants from Amgen Inc., GlaxoSmithKline, Medtronic PLC, and Sanofi-aventis. S.W. reports research and educational grants to the institution from Abbott, Amgen, BMS, Bayer, Boston Scientific, Biotronik, Cardinal Health, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Johnson&Johnson, Medtronic, Querbet, Polares, Sanofi, Terumo, and Sinomed, outside the submitted work. P.V. discloses personal fees from Daiichi Sankyo, AstraZeneca, Bayer Health Care, and Terumo outside the submitted work. M.V. reports grants and personal fees from Abbott, Terumo, and Astrazeneca and personal fees from Chiesi, Bayer, Daiichi Sankyo, Amgen, Alvimedica, grants from Medicure, Biosensors, and Idorsia, outside the submitted work. J.O. reports consultant/advisory boards (including study steering committees and data safety monitoring boards) and lecture fees to his institution from AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daichii-Sankyo, Pfizer, Portola, Roche Diagnostics, and Sanofi.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

References

- Angiolillo DJ, Goodman SG, Bhatt DL, Eikelboom JW, Price MJ, Moliterno DJ, Cannon CP, Tanguay JF, Granger CB, Mauri L, Holmes DR, Gibson CM, Faxon DP. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a North American perspective-2018 update. *Circulation* 2018;**138**:527–536.
- Capodanno D, Huber K, Mehran R, Lip GYH, Faxon DP, Granger CB, Vranckx P, Lopes RD, Montalescot G, Cannon CP, Ten Berg J, Gersh BJ, Bhatt DL, Angiolillo DJ. Management of antithrombotic therapy in atrial fibrillation patients undergoing PCI: JACC state-of-the-art review. J Am Coll Cardiol 2019;**74**:83–99.
- Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferović PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019;40:87–165.
- 4. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann F-J, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN; ESC Scientific Document Group. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39:213–260.
- Gargiulo G, Windecker S, Vranckx P, Gibson CM, Mehran R, Valgimigli M. A critical appraisal of aspirin in secondary prevention: is less more? *Circulation* 2016; 134:1881–1906.
- 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. Committee R-DPS and investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med 2017;377:1513–1524.
- 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.
- 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 and Investigators A. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med 2019;**380**:1509–1524.

- 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.
- 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;**40**:3757–3767.
- Capodanno D, Mehran R, Valgimigli M, Baber U, Windecker S, Vranckx P, Dangas G, Rollini F, Kimura T, Collet JP, Gibson CM, Steg PG, Lopes RD, Gwon HC, Storey RF, Franchi F, Bhatt DL, Serruys PW, Angiolillo DJ. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. *Nat Rev Cardiol* 2018;**15**:480–496.
- Gargiulo G, Goette A, Vranckx P, Valgimigli M. Higher risk of stent thrombosis with double therapy with direct oral anticoagulants: cherry picking the populations of interest does not help. *Eur Heart J* 2020;**41**:1701–1702.
- 13. Costa F, Vranckx P, Leonardi S, Moscarella E, Ando G, Calabro P, Oreto G, Zijlstra F, Valgimigli M. Impact of clinical presentation on ischaemic and bleeding outcomes in patients receiving 6- or 24-month duration of dual-antiplatelet therapy after stent implantation: a pre-specified analysis from the PRODIGY (Prolonging Dual-Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) trial. *Eur Heart J* 2015;**36**:1242–1251.
- 14. Kerneis M, Gibson CM, Chi G, Mehran R, AlKhalfan F, Talib U, Pahlavani S, Mir M, Bode C, Halperin JL, Nafee T, Peterson ED, Verheugt FWA, Wildgoose P, van Eickels M, Lip GYH, Fox KAA, Cohen M. Effect of procedure and coronary lesion characteristics on clinical outcomes among atrial fibrillation patients undergoing percutaneous coronary intervention: insights from the PIONEER AF-PCI trial. *JACC Cardiovasc Interv* 2018;11:626–634.
- 15. Oldgren J, Steg PG, Hohnloser SH, Lip GYH, Kimura T, Nordaby M, Brueckmann M, Kleine E, Ten Berg JM, Bhatt DL, Cannon CP. Dabigatran dual therapy with ticagrelor or clopidogrel after percutaneous coronary intervention in atrial fibrillation patients with or without acute coronary syndrome: a subgroup analysis from the RE-DUAL PCI trial. *Eur Heart J* 2019;40:1553–1562.
- 16. Windecker S, Lopes RD, Massaro T, Jones-Burton C, Granger CB, Aronson R, Heizer G, Goodman SG, Darius H, Jones WS, Aschermann M, Brieger D, Cura F, Engstrom T, Fridrich V, Halvorsen S, Huber K, Kang HJ, Leiva-Pons JL, Lewis BS, Malaga G, Meneveau N, Merkely B, Milicic D, Morais J, Potpara TS, Raev D, Sabate M, de Waha-Thiele S, Welsh RC, Xavier D, Mehran R, Alexander JH and Investigators A. Antithrombotic therapy in patients with atrial fibrillation and acute coronary syndrome treated medically or with percutaneous coronary intervention or undergoing elective percutaneous coronary intervention: insights from the AUGUSTUS trial. *Circulation* 2019;**140**:1921–1932.
- Vranckx P, Valgimigli M, Eckardt L, Lewalter T, Unikas R, Marin F, Schiele F, Laeis P, Reimitz PE, Smolnik R, Zierhut W, Tijssen J. Goette A. Edoxaban in atrial fibril-

lation patients with percutaneous coronary intervention by acute or chronic coronary syndrome presentation: a pre-specified analysis of the ENTRUST-AF PCI trial. *Eur Heart J* 2020;doi: 10.1093/eurheartj/ehaa617.

- Goette A. Antithrombotic therapy after coronary artery stenting in atrial fibrillation: dual therapy encompassing NOAC plus P2Y12 inhibitor is ready for prime time! Ann Transl Med 2019;7:S270–S270.
- 19. Lip GYH, Collet J-P, Haude M, Byrne R, Chung EH, Fauchier L, Halvorsen S, Lau D, Lopez-Cabanillas N, Lettino M, Marin F, Obel I, Rubboli A, Storey RF, Valgimigli M, Huber K, Potpara T, Blomström Lundqvist C, Crijns H, Steffel J, Heidbüchel H, Stankovic G, Airaksinen J, Ten Berg JM, Capodanno D, James S, Bueno H, Morais J, Sibbing D, Rocca B, Hsieh M-H, Akoum N, Lockwood DJ, Gomez Flores JR, Jardine R; ESC Scientific Document Group. 2018 joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS). Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). Europace 2019:21:192-193.
- Rubboli A, Valgimigli M, Capodanno D, Lip GYH. Choices in antithrombotic management for patients with atrial fibrillation undergoing percutaneous coronary intervention. Questions (and answers) in chronological sequence. *Eur Heart J Cardiovasc Pharmacother* 2021;**7**:68–73.
- 21. Capodanno D, Di Maio M, Greco A, Bhatt DL, Gibson CM, Goette A, Lopes RD, Mehran R, Vranckx P, Angiolillo DJ. Safety and efficacy of double antithrombotic therapy with non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation undergoing percutaneous coronary intervention: a systematic review and meta-analysis. J Am Heart Assoc 2020;9:e017212.
- 22. Lopes RD, Hong H, Harskamp RE, Bhatt DL, Mehran R, Cannon CP, Granger CB, Verheugt FWA, Li J, Ten Berg JM, Sarafoff N, Vranckx P, Goette A, Gibson CM, Alexander JH. Optimal antithrombotic regimens for patients with atrial fibrillation undergoing percutaneous coronary intervention: an updated network meta-analysis. JAMA Cardiol 2020;5:582.
- Angiolillo DJ, Capodanno D, Danchin N, Simon T, Bergmeijer TO, Ten Berg JM, Sibbing D, Price MJ. Derivation, validation, and prognostic utility of a prediction rule for nonresponse to clopidogrel: the ABCD-GENE score. *JACC Cardiovasc Interv* 2020;**13**:606–617.
- 24. Sibbing D, Aradi D, Alexopoulos D, Ten Berg J, Bhatt DL, Bonello L, Collet JP, Cuisset T, Franchi F, Gross L, Gurbel P, Jeong YH, Mehran R, Moliterno DJ, Neumann FJ, Pereira NL, Price MJ, Sabatine MS, So DYF, Stone GW, Storey RF, Tantry U, Trenk D, Valgimigli M, Waksman R, Angiolillo DJ. Updated expert consensus statement on platelet function and genetic testing for guiding P2Y12 receptor inhibitor treatment in percutaneous coronary intervention. JACC Cardiovasc Interv 2019;12:1521–1537.