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A novel risk score to identify the need for triple antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention: a post hoc analysis of the RE-DUAL PCI trial

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KEYWORDS

- antithrombotic treatment
- atrial fibrillation
- myocardial infarction
- percutaneous coronary intervention
- risk stratification
- stent thrombosis

Abstract

Background: Current guidelines recommend treating atrial fibrillation (AF) patients who undergo percutaneous coronary intervention (PCI) with triple antithrombotic therapy (TAT) for up to one month in patients at high thrombotic risk. It is unclear how to select these high-risk patients.

Aims: The aim of this study was to identify patients at high thrombotic risk who might benefit from TAT over double antithrombotic therapy (DAT).

Methods: This study was a *post hoc* subanalysis of the RE-DUAL PCI trial. A Cox proportional hazards model was built by stepwise selection of plausible predictor variables for a composite ischaemic endpoint, defined as cardiovascular death, myocardial infarction (MI), stent thrombosis (ST) or ischaemic stroke. The effect of TAT versus DAT was calculated for those patients with the highest proportion of predicted thrombotic risk. A simplified risk score was constructed based on beta-coefficients.

Results: For 209 patients (7.7%) the composite ischaemic endpoint occurred during the first year. The simplified risk score contained six variables. In patients with a score ≥5 (n=154, 5.7%), a significant reduction in the composite of MI and ST was observed with TAT versus DAT (6.3% vs 21.0%, p=0.041), without a penalty in terms of bleeding. In patients at low thrombotic risk, a significant increase in bleeding was observed without a reduction of ischaemic events.

Conclusions: Our findings support the use of DAT in the majority of patients. A small subgroup of patients might benefit from TAT and we propose a novel clinical risk score to select these patients.

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Abbreviations

ACS	acute coronary syndrome
AF	atrial fibrillation
BARC	Bleeding Academic Research Consortium
BMS	bare metal stent
CI	confidence interval
DAT	double antithrombotic therapy
DES	drug-eluting stent
eGFR	estimated glomerular filtration rate
IQR	interquartile range
LVEF	left ventricular ejection fraction
MI	myocardial infarction
NOAC	non-vitamin K oral anticoagulants
NSTEMI	non-ST-segment elevation myocardial infarction
NYHA	New York Heart Association
OAC	oral anticoagulation
PCI	percutaneous coronary intervention
ST	stent thrombosis
STEMI	ST-segment elevation myocardial infarction
TAT	triple antithrombotic therapy
VKA	vitamin K antagonist

Introduction

Antithrombotic regimens in patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) represent one of the most challenging topics for cardiologists in daily practice. In AF patients with a CHA_2DS_2-VASc score ≥1 in males and ≥2 in females, oral anticoagulation (OAC) is warranted to reduce the risk of systemic thromboembolic events, including stroke, whereas patients undergoing PCI have an indication for dual antiplatelet therapy, consisting of aspirin and a $P2Y_{12}$ inhibitor, in order to reduce the risk of stent thrombosis (ST) or other recurrent atherothrombotic events[1-3]. Approximately one in five patients with AF undergo PCI at some point, illustrating the relevant overlap in clinical practice[4]. From the PCI perspective, one in twelve patients undergoing coronary stenting has concomitant AF and an indication for OAC[3]. The combination of dual antiplatelet therapy and OAC is referred to as triple antithrombotic therapy (TAT). A drawback of TAT is that it confers at least a two-times higher risk of bleeding as compared to double antithrombotic therapy (DAT), i.e., with the omission of aspirin[5,6].

Current international guidelines and consensus documents recommend TAT for one week and up to one month in patients at high thrombotic risk[2,7,8]. To date, it is unclear how to select patients at high thrombotic risk.

Five randomised controlled trials compared TAT with the combination of (N)OAC and an antiplatelet agent. The WOEST study was the first to investigate a regime of omitting aspirin in anticoagulated patients undergoing PCI[9]. The WOEST study showed that treatment with a vitamin K antagonist (VKA) and the $P2Y_{12}$ inhibitor clopidogrel (DAT) was associated with a reduction of bleeding without an increase in ischaemic events, compared to patients treated with TAT. Four more recent studies, which used the same approach of TAT versus DAT with non-vitamin K oral anticoagulants (NOAC), did not show any differences in ischaemic outcomes, whereas all but the ENTRUST-AF PCI study showed a reduction of bleeding complications in patients treated with DAT[10-13].

Although no differences in ischaemic outcomes were observed in the individual trials, it must be noted that all studies were largely underpowered for thromboembolic endpoints and the trials included mostly low-risk patients, with a small proportion of patients with acute coronary syndrome (ACS)[14,15]. Some meta-analyses suggested a significant but small increase of myocardial infarction (MI) and ST in patients treated with DAT[14,16]. A subanalysis of the AUGUSTUS trial pointed to a trade-off in ischaemic versus bleeding risks. A significant reduction in ischaemic events was observed when TAT was used in the first month after PCI, but at the equal cost of bleeding[17]. After 30 days, TAT continued to increase bleeding without significantly reducing ischaemic events. The authors propose a patient-centric decision-making strategy for the use of TAT. The recent meta-analysis by Gargiulo et al[14] supports this concept of a personalised strategy. The authors found evidence for a subgroup of patients who had a net benefit from TAT versus DAT in favour of reducing ischaemic events; however, they could not provide tools for the identification of this subgroup of patients, nor do international guidelines provide specific guidance for patient selection.

In this study, we sought to find subgroups of patients at high thrombotic risk, and to develop a risk score to identify the high-risk patients who might benefit from TAT.

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Methods

PATIENT COHORTS

This study was a *post hoc* subanalysis of the RE-DUAL PCI trial. The study protocol for this trial has been previously published[18]. In short, in the RE-DUAL PCI trial, the DAT group was treated with dabigatran, 110 mg b.i.d. or 150 mg b.i.d., in combination with a $P2Y_{12}$ inhibitor (actual treatment: clopidogrel in 87% and ticagrelor in 12% of patients). The TAT group consisted of VKA, aspirin and a $P2Y_{12}$ inhibitor (actual treatment: clopidogrel in 90% and ticagrelor in 8% of patients). TAT was given for three months in patients undergoing PCI with drug-eluting stents (DES) and for one month in patients receiving a bare metal stent (BMS). The study received the proper ethical oversight; the study protocol and any amendments were approved by the ethics committee at each participating centre.

ISCHAEMIC AND BLEEDING ENDPOINTS

The composite ischaemic endpoint was defined as cardiovascular death, MI, ST (definite or probable according to Bleeding Academic Research Consortium [BARC] criteria) or ischaemic stroke. The bleeding endpoint was defined as the first BARC 2, 3 or 5 bleeding within 365 days. Also, separate components of these endpoints were explored. For the purpose of a sensitivity analysis, follow-up was truncated after the first event (either ischaemic or bleeding event).

FOLLOW-UP

The mean follow-up after PCI was 14 months. For this analysis follow-up was truncated at 365 days to obtain risk estimates for the first year of DAT versus TAT. Groups were compared according to the intention-to-treat principle.

STATISTICAL ANALYSIS

Baseline characteristics were compared between patients with and without ischaemic events during the one-year follow-up by t-tests or chi-square tests, or their non-parametric equivalents, as appropriate.

PREDICTORS

Based on clinical plausibility and availability in both trial datasets, variables were considered as candidate predictors. The variables included age, sex, body mass index, hypertension, hypercholesterolaemia, diabetes mellitus including subgroups of insulin dependent diabetes, smoking, alcohol use, medical history (bleeding, MI, PCI, coronary bypass artery grafting, stroke, venous thrombo-embolisms or systemic embolism, renal failure, malignancy, peripheral artery disease [with intervention, or ankle-brachial index <90], heart failure), MI at presentation, left ventricular ejection fraction (LVEF), laboratory tests at presentation (haemoglobin, haematocrit, platelet count, leukocyte count, creatinine, estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]), and angiographic and procedural characteristics (number of diseased vessels [>50% diameter stenosis], left main disease, thrombus-containing lesion, number of stented vessels, stented vessel/graft, bifurcation PCI, lesion length >30 mm and in-stent restenosis stenting). We did not include modifiable factors like medication use, periprocedural heparin use, factors of which reporting might be unreliable like New York Heart Association classification, and factors with uncertain causal relation like index electrocardiogram (ECG) rhythm and type of atrial fibrillation.

MODEL DEVELOPMENT

Since we wanted to characterise the patients' thrombotic risk based on their single clinical features, irrespective of receiving DAT or TAT, individual candidate variables for the model were selected from a univariate Cox regression, stratified for randomisation arm and BMS placement (the latter directly influenced aspirin treatment duration). Variables showing a p-value <0.30 for the ischaemic events model were considered as candidate variables. A Cox model for the composite ischaemic endpoint was constructed with forced entry of the stratification variables. Stepwise selection from the candidate variables using a 0.05 significance level was performed. Missing values in the dataset for stepwise model selection were imputed by simple means **(Supplementary Table 1)**. Based on the beta coefficients of the Cox model, a point score was constructed using the methods as proposed in the Framingham Study risk scores[19]. Continuous variables were at that point categorised, based on clinically relevant categories. After dichotomisation, the least prevalent category would be retained in the model.

VALIDATION

With the Cox model, the expected hazard of the ischaemic endpoint, given the covariates, was predicted at 365 days. Also, the point score was calculated for each patient. Predictive accuracy of the model and point score were evaluated by the area under the receiver operating curve (C-statistic). The cohort was divided into quintiles, deciles and demi-deciles based on the expected hazards, or grouped by point score to assess calibration. Also, goodness-of-fit was assessed by the Hosmer-Lemeshow test.

Observed risks within the different risk categories and risk scores of ischaemic events, bleeding, and mortality were compared between the patients that received TAT or DAT, to evaluate if a benefit of TAT over DAT could be found in patients at higher thrombotic risk.

To compare the performance of the new risk score in relation to existing risk scores, an assessment of the C-statistic of the CHA_2DS_2-VASc for the ischaemic endpoint in the RE-DUAL PCI cohort was performed.

External validation was performed in the WOEST 2 registry (ClinicalTrials.gov: NCT02635230). The (as yet unpublished) WOEST 2 registry is a cohort of 1,059 patients treated with OAC undergoing PCI. Baseline characteristics of this cohort are summarised in **Supplementary Table 2**. Differences in outcomes between TAT and DAT cohorts were not evaluated, as an inherent indication bias exists between the groups due to the observational design of this cohort.

Results

A total of 2,725 patients were included in this analysis. In 209 patients (7.7%) the composite ischaemic endpoint occurred during the first year. Baseline characteristics of patients with and without ischaemic events are depicted in **Table 1**. Approximately half of the cohort (50.5%) underwent PCI for the indication of ACS. Patients with an ischaemic event during follow-up were more likely to have a medical history of MI, heart failure, diabetes, renal failure, peripheral artery disease or prior stroke and were more likely to have presented with ACS. LVEF was lower in patients with an ischaemic event during follow-up and multivessel disease was more prevalent. Furthermore, there were significant differences in haemoglobin levels, white blood cell counts, platelet counts and creatinin clearance. BARC 2, 3 or 5 bleedings were documented in 520 patients (19.1%).

Table 2 shows results of the stratified univariate Cox regression. Strong predictors for ischaemic events were: decreased LVEF, multivessel disease or multivessel stenting, MI, diabetes mellitus, peripheral artery disease or stroke and a history of heart failure or renal failure.

After the stepwise selection, the multivariable Cox regression model predicting ischaemic events contained the LVEF, number of diseased vessels, MI as an indication for index-PCI, platelet count, peripheral artery disease and creatinine clearance **(Table 3)**. The discriminatory capacity of the ischaemic model was fair (C-statistic 0.68, 95% CI: 0.64-0.72) **(Supplementary Figure 1)**.

Table 1. Baseline characteristics. Stratified by occurrence of ischaemic endpoint during one-year follow-up.

		Ischaemic endpoint		*p*-value
		No n=2,516	Yes n=209	
Demographics				
Age (median [IQR])		71.00 [65.00, 77.00]	71.50 [65.00, 78.00]	0.46
Female sex (%)		611 (24.3)	44 (21.1)	0.33
Body mass index (median [IQR])		28.10 [25.30, 31.70]	28.10 [25.10, 31.40]	0.49
Cardiovascular risk factors				
Hypertension (%)		2,114 (84.1)	180 (86.1)	0.49
Hypercholesterolaemia (%)		1,640 (65.2)	130 (62.2)	0.42
Smoker (%)		310 (12.3)	27 (12.9)	0.89
Diabetes mellitus (%)		902 (35.9)	91 (43.5)	0.032
Insulin-dependent (%)		248 (9.9)	29 (13.9)	0.089
Alcohol abuse (%)		1,276 (50.7)	99 (47.4)	0.39
Medical history				
Prior myocardial infarction (%)		623 (24.8)	76 (36.4)	<0.001
Congestive heart failure (%)		849 (33.8)	88 (42.1)	0.018
Prior bleeding (%)		32 (1.3)	0 (0.0)	0.19
Prior gastro-intestinal bleeding (%)		167 (6.6)	16 (7.7)	0.68
Stroke (%)		200 (8.0)	26 (12.4)	0.033
Prior coronary revascularisation (%)		951 (37.8)	92 (44.0)	0.089
History of malignancy (%)		225 (9.1)	16 (7.8)	0.60
Peripheral artery disease (%)		161 (6.9)	27 (13.8)	0.001
Admission and procedural characteristics				
ACS at baseline (%)		1,253 (49.8)	122 (58.4)	0.021
Type of ACS	STEMI	280 (22.8)	25 (20.8)	<0.001
	NSTEMI	509 (41.4)	73 (60.8)	
	Unstable angina	440 (35.8)	22 (18.3)	
NYHA 3/4 (%)		237 (28.1)	33 (37.5)	0.084
LVEF at baseline (median [IQR])		54.00 [45.00, 60.00]	47.00 [35.00, 55.00]	<0.001
Atrial fibrillation or flutter at presentation (%)		1,162 (46.2)	103 (49.3)	0.43
Haemoglobin (mmol/L) (median [IQR])		8.50 [7.76, 9.18]	8.32 [7.51, 8.94]	0.050
Haematocrit (%) (median [IQR])		41.00 [38.00, 44.00]	40.00 [37.00, 44.00]	0.13
Platelet count ($\times 10^9$/L) (median [IQR])		201.00 [169.00, 243.00]	212.00 [182.00, 252.00]	0.006
Creatinin (mg/dL) (median [IQR])		1.00 [0.85, 1.19]	1.08 [0.91, 1.22]	0.001
Creatinin (µmol/L) (median [IQR])		88.00 [75.00, 106.00]	96.00 [80.00, 108.00]	0.001
eGFR (CKD-EPI) (median [IQR])		76.00 [61.00, 89.00]	68.00 [59.00, 83.00]	<0.001
White blood cell count (median [IQR])		7.33 [6.09, 8.92]	7.70 [6.45, 9.30]	0.021
Femoral access (%)		889 (35.6)	83 (40.3)	0.20
3-vessel disease (%)		418 (17.0)	63 (30.9)	<0.001
Complex procedure (%)		506 (20.1)	43 (20.6)	0.95
>2 vessels stenting (%)		77 (3.1)	9 (4.3)	0.43
In-stent restenosis stenting (%)		42 (1.7)	4 (1.9)	1.00
Prior brachytherapy lesion stenting (%)		2 (0.1)	0 (0.0)	1.00
Unprotected left main stenting (%)		44 (1.7)	4 (1.9)	1.00
>2 lesions per vessel stenting (%)		144 (5.7)	12 (5.7)	1.00
>30 mm stenting (%)		220 (8.7)	20 (9.6)	0.78
Bifurcation stenting (%)		88 (3.5)	4 (1.9)	0.31
Venous graft stenting (%)		53 (2.1)	5 (2.4)	0.98
Thrombus-containing lesion stenting (%)		37 (1.5)	6 (2.9)	0.20

Table 1. Baseline characteristics. Stratified by occurrence of ischaemic endpoint during one-year follow-up. (cont'd)

		Ischaemic endpoint		*p*-value
		No n=2,516	Yes n=209	
Admission and procedural characteristics				
Number of stented vessels (%)	1	2,016 (81.7)	162 (78.6)	0.12
	2	382 (15.5)	33 (16.0)	
	3	70 (2.8)	11 (5.3)	
Stented coronary vessel (%)	LAD	1,191 (47.3)	94 (45.0)	0.56
	LCX	648 (25.8)	69 (33.0)	0.027
	RCA	869 (34.5)	67 (32.1)	0.52
	Graft	68 (2.7)	9 (4.3)	0.26
	Arterial graft	9 (0.4)	2 (1.0)	0.46
	Venous graft	53 (2.1)	5 (2.4)	0.98
Randomisation arm (%)	Triple therapy	907 (36.0)	74 (35.4)	0.91
Bleeding outcomes during follow-up				
BARC 2, 3, or 5 bleeding (%)		465 (18.5)	55 (26.3)	0.007
BARC 3 or 5 bleeding (%)		100 (4.0)	27 (12.9)	<0.001
Haemorrhagic stroke (%)		0 (0.0)	6 (2.9)	<0.001

ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium criteria; BMS: bare metal stent; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration rate; IQR: interquartile range; LAD: left anterior descending artery; LCX: left circumflex artery; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-segment elevation myocardial infarction; NYHA: New York Heart Association classification of heart failure; RCA: right coronary artery; STEMI: ST-segment elevation myocardial infarction

Observed ischaemic and bleeding outcomes and mortality rates by percentiles and quintiles for predicted hazards are depicted in **Figure 1** and **Supplementary Table 3**. Goodness-of-fit as assessed by the Hosmer-Lemeshow test was found to be good (p=1.00). Incidence of ischaemic events ranged from 3.9% for the lowest quintile of thrombotic risk to 15.8% for the highest risk quintile. In comparing high-risk patients to low-intermediate risk patients, significantly more thromboembolic events were found in the high-risk patients (15.8% vs 5.6%; p<0.001) **(Supplementary Table 3)**.

A numerical reduction of the ischaemic endpoint was observed in patients at the highest thrombotic risk treated with TAT as compared to DAT **(Figure 1A)**. This effect was most pronounced in patients in the >95th percentile of thrombotic risk **(Figure 1B)**.

The simplified risk score based on the Cox regression model contained six variables **(Central illustration)** and retained fair accuracy comparable to the original Cox regression model (C-statistic 0.66, 95% CI: 0.62-0.70) **(Supplementary Figure 2)**. The total risk score ranged from one point to eight points. Higher

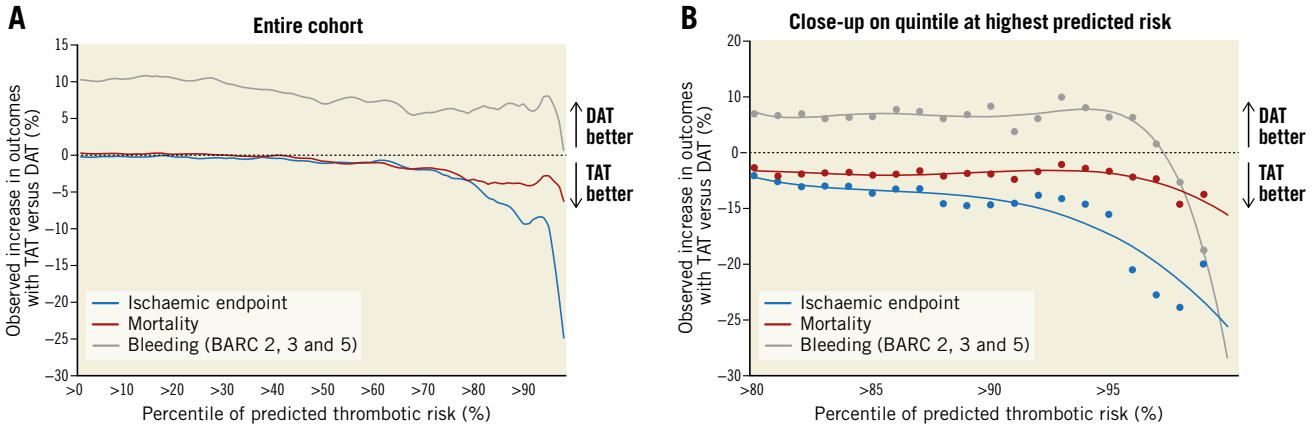


Figure 1. *Treatment effect of TAT versus DAT on ischaemic endpoint, mortality, and bleeding per percentile of predicted thrombotic risk. Farther to the right = higher thrombotic risk and smaller fraction of patients. A) In the entire cohort. B) Close-up on quintile at highest predicted risk. BARC: Bleeding Academic Research Consortium criteria; DAT: double antithrombotic therapy; TAT: triple antithrombotic therapy*

Table 2. Univariate analysis for composite ischaemic endpoint. Analysis adjusted for treatment arm and stent type.

	HR (95% CI for HR)	*p*-value
LVEF (per % increase)	0.97 (0.96-0.98)	<0.001
3-vessel disease	2.1 (1.5-2.8)	<0.001
Number of diseased vessels (per 1 vessel increase)	1.5 (1.3-1.8)	<0.001
Myocardial infarction at baseline	1.9 (1.5-2.5)	<0.001
History of myocardial infarction	1.7 (1.3-2.2)	<0.001
1-vessel disease	0.60 (0.45-0.79)	<0.001
Peripheral artery disease	2.1 (1.4-3.1)	<0.001
eGFR (CKD-EPI, per point increase)	0.99 (0.98-0.99)	<0.001
Heart failure or LVEF <30%	1.6 (1.2-2.1)	<0.001
Creatinin (per µmol/L increase)	1.0 (1.0-1.0)	<0.001
Platelet count (per 10^9/L increase)	1.0 (1.0-1.0)	0.001
NYHA classification (per Class increase)	1.5 (1.1-2.0)	0.006
History of renal failure	1.5 (1.1-2.1)	0.010
Heart failure	1.4 (1.1-1.9)	0.010
ACS at baseline	1.4 (1.1-1.9)	0.010
History of stroke	1.7 (1.1-2.5)	0.015
Graft stenting	1.6 (0.82-3.1)	0.170
LCx stenting	1.4 (1.1-1.9)	0.021
NYHA Class 4	2.4 (1.1-5.3)	0.025
Haematocrit (per % increase)	0.97 (0.94-1.0)	0.032
Diabetes mellitus	1.3 (1.0-1.8)	0.035
White blood cell count (per 10^9/L increase)	1.1 (1.0-1.1)	0.035
Haemoglobin (per mmol/L increase)	0.86 (0.75-0.99)	0.038
3 vessels stented	1.9 (1.0-3.4)	0.046
NYHA Class 3/4	1.5 (1.0-2.4)	0.048
Prior coronary revascularisation	1.3 (0.99-1.7)	0.057
Number of vessels stented (per vessel increase)	1.3 (0.97-1.6)	0.088
Insulin-dependent diabetes mellitus	1.4 (0.94-2.1)	0.095
Body mass index (per kg/m^2 increase)	0.98 (0.95-1.0)	0.12
Thrombus containing lesion	1.9 (0.84-4.3)	0.12
Prior PCI	1.2 (0.91-1.6)	0.19
Prior CABG	1.3 (0.86-1.9)	0.21
1 vessel stented	0.81 (0.58-1.1)	0.22
Alcohol abuse	0.85 (0.64-1.1)	0.23
Bifurcation stenting	0.55 (0.20-1.5)	0.24
Arterial graft stenting	2.3 (0.57-9.2)	0.25
NYHA Class 3	1.3 (0.82-2.0)	0.28
Hypercholesterolaemia	0.86 (0.65-1.1)	0.30
>2 vessel stented	1.4 (0.71-2.7)	0.34
Age (per year increase)	1.0 (0.99-1.0)	0.39
RCA stenting	0.89 (0.66-1.2)	0.41
Female sex	0.88 (0.63-1.2)	0.44
Hypertension	1.2 (0.78-1.7)	0.48
Atrial fibrillation or flutter at baseline ECG	1.1 (0.83-1.4)	0.51
LAD stented	0.91 (0.7-1.2)	0.52
Past or active smoker	1.1 (0.83-1.4)	0.54
Hyper coagulable condition	0.57 (0.079-4.0)	0.57
Prior systemic embolism	0.58 (0.081-4.2)	0.59
History of malignancy	0.88 (0.53-1.5)	0.61
Total stent length >30 mm	1.1 (0.71-1.8)	0.62
Venous graft stenting	1.2 (0.47-2.8)	0.76
In-stent restenosis stenting	1.1 (0.42-3.0)	0.81
STEMI at baseline	1.1 (0.69-1.6)	0.82
Prior VTE/SE	0.92 (0.43-2.0)	0.83
Complex lesion stented	1.0 (0.74-1.5)	0.83
Active smoker	1.0 (0.69-1.5)	0.89
History of venous thromboembolism	0.95 (0.42-2.1)	0.91
>2 lesions per vessel stenting	1.0 (0.57-1.8)	0.96
Unprotected left main stenting	1.0 (0.38-2.7)	0.97
Prior major bleeding or predisposition to bleeding	0.00 (0.00-inf)	0.99
Prior brachytherapy lesion stenting	0.00 (0.00-inf)	0.99

ACS: acute coronary syndrome; BMS: bare metal stent; CABG: coronary artery bypass grafting; CI: confidence interval; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration rate; HR: hazard ratio; IQR: interquartile range; LAD: left anterior descending artery; LCx: left circumflex artery; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association classification of heart failure; PCI: percutaneous coronary intervention; RCA: right coronary artery; STEMI: ST-segment elevation myocardial infarction; SE: systemic embolism; VTE: venous thromboembolism

Table 3. Cox proportional hazards model. Analysis adjusted for treatment arm and stent type.

Predictor of events	HR (95% CI)	*p*-value
LVEF at baseline (per % increase)	0.973 (0.963-0.984)	<0.001
Number of diseased vessels (per vessel increase)	1.376 (1.162-1.631)	<0.001
MI as indication for index-PCI	1.693 (1.284-2.233)	<0.001
Platelet count (per 10^9/L increase)	1.003 (1.001-1.005)	0.002
Peripheral artery disease	1.739 (1.152-2.627)	0.008
Creatinin clearance (per ml/min increase)	0.990 (0.983-0.998)	0.011

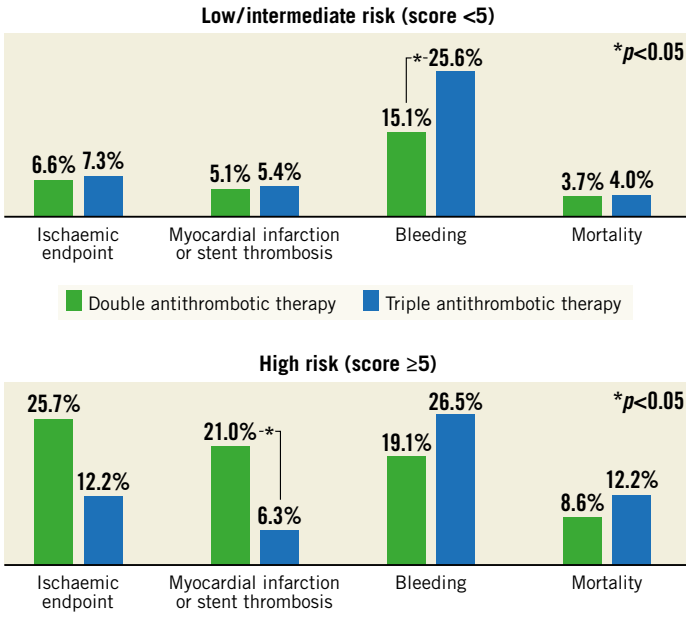
CI: confidence interval; HR: hazard ratio; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention

scores were associated with a higher risk of ischaemic events (p_{trend}<0.001). The calibration curve demonstrated excellent calibration for the composite ischaemic endpoint **(Supplementary Figure 3)**.

When using a >5 point cut-off, a trend towards a reduction of the composite ischaemic endpoint in patients treated with TAT as compared to DAT was observed (p=0.092) **(Figure 2A)**. A significant reduction of MI or ST was also observed (6.3% vs 21.0%, p=0.041) **(Figure 2B)**. When considering other outcomes, bleeding events outnumbered ischaemic events across all risk categories, with a significant increase in patients using TAT as compared with DAT in patients with low thrombotic risk **(Figure 2C, Supplementary Figure 4)**.

CENTRAL **ILLUSTRATION** Score for thrombotic risk in AF-PCI patients.

Thrombotic risk in AF-PCI patients		
Feature		**Score**
	LVEF <30%	+3
	LVEF 30-50%	+1
	3-vessel disease	+2
	MI as indication for index PCI	+2
	History of peripheral artery disease	+2
	Platelet count ≥400 *10^9/L	+3
	eGFR ≥90 ml/min	–1



The score contains six clinical variables to predict ischaemic events after PCI in patients with AF (LVEF, three-vessel disease, MI as indication for index PCI, history of peripheral artery disease, platelet count ≥400×109/L and eGFR ≥90 ml/min). In patients with low and intermediate risk (score <5) the use of TAT was significantly associated with higher bleeding rates than DAT (25.6% vs 15.1%, p<0.001) without benefits regarding ischaemic endpoints. In patients with high risk (score ≥5) the use of TAT was associated with significantly less myocardial infarction and stent thrombosis (6.3% vs 21.0%, p=0.041). Thus, the score identifies a minority of high-risk patients that might benefit from TAT after PCI. AF: atrial fibrillation; DAT: double antithrombotic therapy; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; TAT: triple antithrombotic therapy

EXTERNAL VALIDATION

The risk score was externally validated in the WOEST 2 registry. Discriminative capacity was similar to the internal validation (C-statistic 0.63, 95% CI: 0.56-0.70) **(Supplementary Figure 5)**.

The score had an excellent overall ability to identify high-risk patients, with higher scores corresponding to a higher risk of ischaemic endpoints (p_{trend}<0.001) **(Figure 3)**. A score ≥5 identified 11.8% of all patients at high thrombotic risk. Thrombotic risk in these high-risk patients was significantly higher as compared to the remainder of the cohort (16.3% vs 6.7%, p=0.001).

DURATION OF TRIPLE THERAPY

To study the timing of ischaemic events, a Kaplan-Meier curve was constructed **(Supplementary Figure 6)** with separate outcomes for high-risk patients (risk score ≥5) and patients not at high risk (risk score <5). Interestingly, the curves of high-risk patients continued to diverge beyond the first month, up to 90 days after PCI. Although this study cannot provide a definitive answer to the question of optimal treatment duration when TAT is given, this observation suggests that a substantial proportion of events continue to take place after the first month in patients treated with DAT but not in those treated with TAT. Therefore, when TAT is prescribed in patients at high thrombotic risk and is well tolerated by the patient in the first month, continuing TAT up to three months might be considered.

PERFORMANCE OF THE CHA_2DS_2-VASC SCORE

When applying the CHA_2DS_2-VASc in the RE-DUAL PCI cohort, it showed only modest accuracy for the composite ischaemic endpoint (C-statistic 0.58, 95% CI: 0.54-0.62) **(Supplementary Figure 7)**.

Discussion

This study sought to identify AF patients undergoing PCI at high risk for recurrent ischaemic events who might benefit from TAT. The model was able to identify patients with high thrombotic risk. A simplified risk score found a significant reduction in MI/ST with TAT in patients with a risk score >5. However, this subgroup of "high-risk" patients comprised only ~5% of all patients. In the majority of patients, no benefit with TAT was observed. Importantly, the lower incidence of ischaemic events with TAT as compared to DAT was outnumbered by an increase in bleeding events in the overall population, but not in patients at the highest thrombotic risk.

The observation of a possible reduction in ischaemic events in high-risk patients is in line with some meta-analyses and subgroup

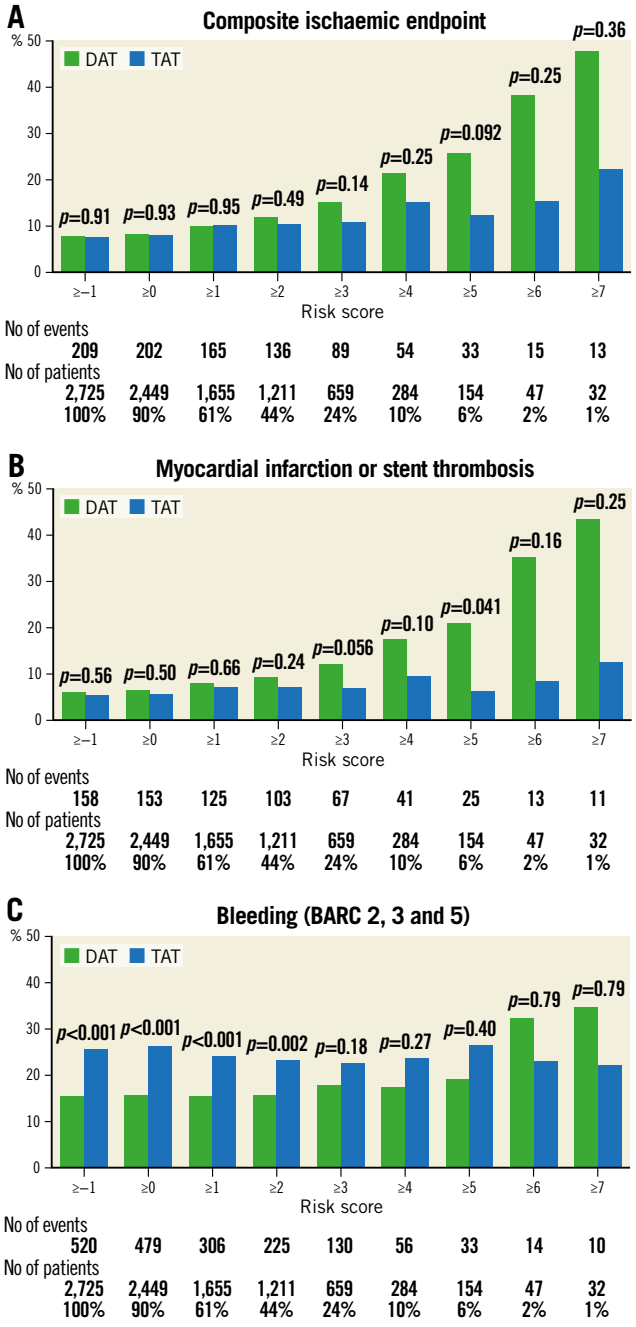


Figure 2. *Observed outcomes with DAT and TAT for different risk score cut-offs. A) Composite ischaemic endpoint. B) Myocardial infarction or stent thrombosis. C) Bleeding. BARC: bleeding academic research consortium criteria; DAT: double antithrombotic therapy; TAT: triple antithrombotic therapy*

analyses which pointed to a possible benefit of TAT, especially in high-risk patients. Two meta-analyses of randomised controlled trials signalled a reduction in terms of ST (and a trend for MI) associated with TAT[14,16]. Although incidence rates were very low, ST was significantly reduced. Other meta-analyses did not support this finding[5,20,21].

Our study is the first study to investigate the effect of TAT in patients at high thrombotic risk, represented by a combination of

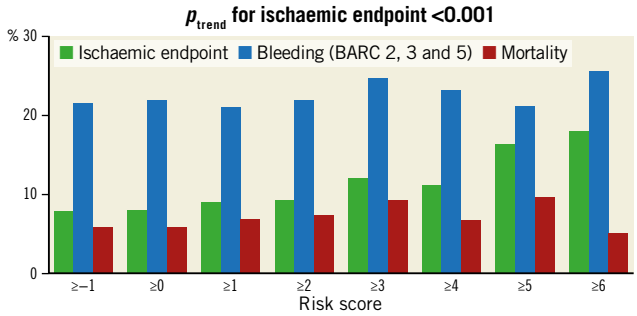


Figure 3. *Outcomes for different risk score cut-offs in the external validation cohort (WOEST 2 registry). BARC: bleeding academic research consortium*

high-risk characteristics. Several subgroup analyses of the randomised controlled trials based on single clinical variables (e.g., diabetes, age ≥80 years, ACS patients) could not demonstrate a reduction in ischaemic events associated with TAT[22-24]. This illustrates the complex and multifactorial aspect of high thrombotic risk, which was adequately addressed in the current study by combining multiple patients' characteristics.

Further randomised controlled studies will be needed to adequately address the question of TAT versus DAT, particularly in high-risk patients. Of note, the MASTER DAPT trial enrolled 4,434 patients with high bleeding risk, of whom 1,666 used OAC. The subgroup using OAC was randomised to a duration of one month of TAT versus at least three months of TAT before switching to DAT. The shorter duration of TAT had a lower risk of bleeding without an additional ischaemic risk[25]. Similar results were observed in a *post hoc* analysis of the AUGUSTUS trial[17]. This demonstrates that, if TAT is prescribed, it should be limited to one month.

CLINICAL IMPLICATIONS

Using this risk score containing seven clinical, angiographical and procedural parameters, a significant reduction in MI/ST associated with TAT was seen in a small subgroup of patients at high thrombotic risk undergoing PCI. Our findings are an important "proof of concept", which is in line with the general beliefs of many cardiologists with regard to high-risk patients.

On the other hand, for the majority of the population, no benefit of TAT was found - and it could even harm patients at low thrombotic risk, in whom only an increase in bleeding was observed. Therefore, our findings support the utilisation of DAT rather than TAT in the majority of AF patients undergoing PCI, while reserving TAT for a small proportion of patients – as was adapted in the most recent ESC guideline on non-ST-segment elevation myocardial infarction (NSTEMI)[7]. If TAT is prescribed, it should be limited to 30 days, as its antithrombotic effect shows no clear value beyond 30 days post-PCI[17,25].

Limitations

The TAT arm in this study comprised vitamin K antagonists whereas in contemporary clinical practice NOACs are standard

care for their favourable safety profile. In the RE-DUAL PCI trial, DAT including a NOAC was compared to TAT using a VKA, which might have exaggerated the bleeding risk in the latter group.

We did adjust the analyses for the duration of TAT, which was directly related to the use of BMS (one month) or DES (three months). However, we did not evaluate the effect of different dabigatran dosages (110 mg b.i.d. or 150 mg b.i.d.). Generally, as per international guidelines, the lowest approved dose should be applied in this population with multiple antithrombotic agents.

Although an overall increase of bleeding associated with TAT was observed, numerically fewer bleeding events were observed in patients with a risk score of ≥5. This is an interesting observation that could be due to greater degrees of thrombin activation or might be a play of chance due to small patient numbers. However, a similar asymmetrical treatment effect was observed in the PRECISE-DAPT bleeding score, in whom patients at high bleeding risk no longer had a benefit in terms of reduction in ischaemic events.

The performance of the score was good in the WOEST 2 registry which served as an external validation cohort. Although the C-statistic of 0.63 was modest (and typical of risk scores based on clinical factors), this applies to the overall fit of the risk score and does not necessarily correspond to the ability of the score to identify the patients at the highest risk. Finally, differences between DAT and TAT could not be tested, due to the indication bias inherent in the design of an observational registry. Before adapting this novel risk score into daily clinical practice, further external validation in randomised controlled trials such as the AUGUSTUS, PIONEER AF-PCI, or ENTRUST PCI is needed.

Conclusions

A clinical risk score was developed to estimate thrombotic risk in AF patients undergoing PCI. The model identified a small subgroup of high-risk patients comprising ~5% of all patients, in whom a significant reduction in MI/ST was observed with TAT. For patients not at high thrombotic risk, no benefit was observed and even harm was found.

Our findings support the use of DAT in the majority of AF patients undergoing PCI, while reserving TAT for a small and selected subgroup of high-risk patients. We propose a risk score which might aid in identifying these patients.

Impact on daily practice

The majority of AF patients undergoing PCI do not benefit from TAT. However, we identified a small subset (~5%) of patients at high thrombotic risk in whom a significant reduction in myocardial infarction and stent thrombosis was observed with TAT. A risk score is proposed which might aid in identifying these patients.

Funding

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Conflict of interest statement

B. Zwart reports having received consultancy/speakers' fees from Bayer, AstraZeneca and Sanofi. A.J.W.M. de Veer reports advisory/consulting/speakers' fees from Bayer and Boehringer Ingelheim. G.Y.H. Lip reports consultancy fees for Bayer/Janssen, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo and Verseon; speakers' fees from Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer and Daiichi-Sankyo although no fees are directly received personally. D.L. Bhatt serves on the advisory boards of Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Level Ex, Medscape Cardiology, MyoKardia, PhaseBio, PLx Pharma, and Regado Biosciences; serves on the Board of Directors of the Boston VA Research Institute, the Society of Cardiovascular Patient Care, and Tobesoft; is the Chair of the American Heart Association Quality Oversight Committee; serves on the Data Monitoring Committees of the Baim Institute for Clinical Research, the Cleveland Clinic, Contego Medical, Duke Clinical Research Institute, the Mayo Clinic, Mount Sinai School of Medicine, and the Population Health Research Institute; has received honoraria from the American College of Cardiology, the Baim Institute for Clinical Research, Belvoir Publications, the Canadian Medical and Surgical Knowledge Translation Research Group, Duke Clinical Research Institute, HMP Global, Journal of the American College of Cardiology, K2P, Level Ex, Medtelligence/ReachMD, MJH Life Sciences, Population Health Research Institute, Slack Publications, the Society of Cardiovascular Patient Care, and WebMD; has other affiliations with Clinical Cardiology, the NCDR-ACTION Registry Steering Committee, and the VA CART Research and Publications Committee; has received research funding from Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, MyoKardia, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi, Synaptic, and The Medicines Company; has received royalties from Elsevier; is a Site Co-Investigator for Biotronik, Boston Scientific, CSI, St. Jude Medical, and Svelte; is a Trustee of the American College of Cardiology; and has done unfunded research for FlowCo, Merck, Novo Nordisk, and Takeda. C.P. Cannon reports research grants and personal fees from Amgen, Applied Therapeutics, Ascendia, Better Therapeutics, Boehringer-Ingelheim, Bristol-Myers Squibb, Corvidia, Daiichi Sankyo, Eli Lilly, HLS Therapeutics, Innovent, Kowa, Lexicon, Janssen, Merck, Pfizer, Rhoshan, and Sanofi; consulting fees from Aegerion/Amryt, Alnylam, Amarin, Amgen, and grants from NovoNordisk, outside the submitted work. J.M. ten Berg reports having received research grants and personal fees from, Accumetrics, AstraZeneca, Boehringer-Ingelheim, Bayer, Bristol-Myers Squibb, CeleCor, Daiichi Sankyo, Eli Lilly, Ferrer, The Medicines Company, Pfizer and ZonMw. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Missing in dataset for the selected variables in the model.

Supplementary Table 2. Baseline characteristics of the external validation cohort (WOEST 2 registry).

Supplementary Table 3. Observed outcomes for quintiles of predicted thrombotic risk.

Supplementary Figure 1. Predictive accuracy of the model.

Supplementary Figure 2. Predictive accuracy of the simplified risk score.

Supplementary Figure 3. Calibration curve of the model.

Supplementary Figure 4. Observed outcomes with DAT and TAT for different risk score cut-offs.

Supplementary Figure 5. Predictive accuracy in the external validation cohort (WOEST 2 registry).

Supplementary Figure 6. Kaplan-Meier curves of the composite ischaemic endpoint.

Supplementary Figure 7. Predictive accuracy of the CHA_2DS_2-VASc.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00165

Supplementary data

Supplementary Table 1. Missing in dataset for the selected variables in the model.

	Missing (n)	
LVEF	188	6.90%
Number of diseased vessels	63	2.31%
Myocardial infarction at baseline	26	0.95%
Platelet count	3	0.11%
Creatinine clearance	12	0.44%
Peripheral artery disease	179	6.57%

LVEF: left ventricular ejection fraction

Supplementary Table 2. Baseline characteristics of the external validation cohort (WOEST 2 registry).

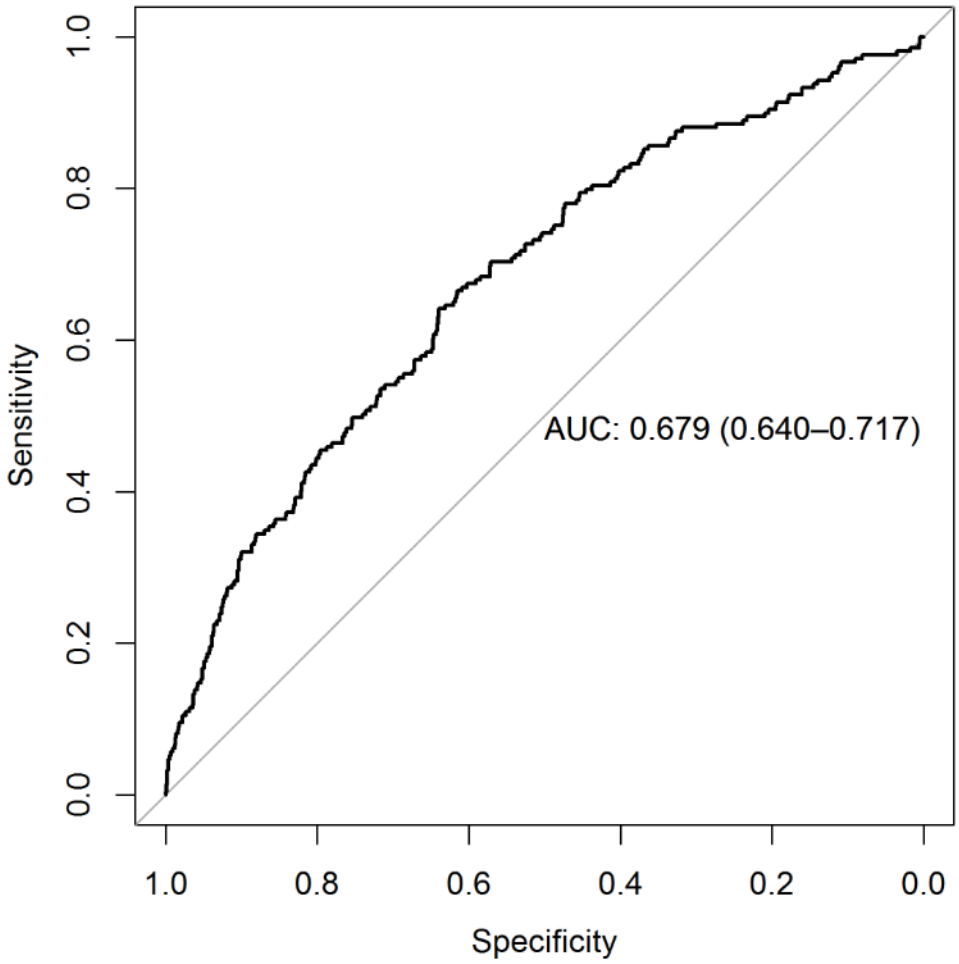
		Triple therapy 415	Dual therapy 644	*p*-value
Demographics				
Age, mean (SD)		73.53 (8.11)	73.85 (8.21)	0.52
Female (%)		101 (24.3)	160 (24.8)	0.91
Body-mass index, mean (SD)		28.16 (5.03)	27.54 (4.39)	**0.04**
Caucasian ethnicity (%)		325 (94.2)	527 (95.1)	0.65
Indication for OAC				
Atrial fibrillation (%)		379 (91.3)	613 (95.2)	**0.02**
de novo (%)		28 (7.9)	54 (9.7)	0.42
Mechanical heart valve prosthesis (%)		22 (5.3)	27 (4.2)	0.50
Not specified (%)		20 (4.8)	20 (3.1)	0.21
Medical history				
CHA_2DS_2-VASc, mean (SD)		3.83 (1.57)	4.19 (1.60)	**<0.001**
CHA_2DS_2-VASc ≥5 (%)		142 (34.2)	265 (41.1)	**0.03**
HAS-BLED, mean (SD)		3.08 (1.11)	3.03 (1.01)	0.46
HAS-BLED ≥3 (%)		293 (70.8)	444 (69.2)	0.63
Myocardial infarction (%)		105 (25.3)	177 (27.5)	0.47
PCI (%)		143 (34.5)	243 (37.8)	0.30
CABG (%)		84 (20.2)	129 (20.1)	1.00
Congestive heart failure (%)		71 (17.1)	169 (26.3)	**0.001**
Stroke (%)		58 (14.0)	122 (19.0)	**0.04**
Peripheral artery disease (%)		61 (14.7)	103 (16.0)	0.63
Chronic kidney disease (%)		151 (36.4)	249 (38.7)	0.48
Bleed requiring medical attention (%)		42 (10.1)	92 (14.3)	0.06
Active malignancy (%)		8 (1.9)	19 (3.0)	0.40
Diabetes mellitus (%)		112 (27.0)	186 (29.0)	0.52
Hypertension (%)		282 (68.0)	498 (77.8)	**<0.001**
Hypercholesterolaemia (%)		262 (63.7)	431 (67.4)	0.24
Smoking (%)		57 (14.0)	87 (13.9)	1.00
Admission and procedural characteristics				
Indication for PCI (%)	elective	237 (58.4)	424 (68.1)	**0.001**
	unstable angina	30 (7.4)	51 (8.2)	
	non-STEMI	118 (29.1)	113 (18.1)	
	STEMI	21 (5.2)	35 (5.6)	
Prior OAC use (%)		357 (86.0)	577 (89.6)	0.10
Interruption of OAC (%)		154 (45.6)	134 (24.8)	**<0.001**
Complex PCI (any criterion, %)		70 (16.9)	129 (20.0)	0.23
3 vessels treated (%)		5 (1.2)	6 (0.9)	0.92
≥3 lesions treated (%)		22 (5.3)	28 (4.4)	0.59
≥3 stents implanted (%)		54 (13.1)	85 (13.3)	1.00
bifurcation with 2 stents implanted (%)		11 (5.2)	20 (4.1)	0.66
total stent length >60 mm (%)		37 (13.8)	64 (11.7)	0.46
chronic total occlusion (%)		9 (4.3)	35 (7.2)	0.20
Discharge medication				
Vitamin K antagonist (%)		182 (43.9)	314 (48.8)	0.13
NOAC	apixaban (%)	76 (18.3)	111 (17.2)	0.71
	dabigatran (%)	39 (9.4)	46 (7.1)	0.23
	edoxaban (%)	24 (5.8)	19 (3.0)	**0.03**
	rivaroxaban (%)	93 (22.4)	155 (24.1)	0.58
$P2Y_{12}$ inhibitor	clopidogrel (%)	391 (94.2)	604 (93.8)	0.88
	ticagrelor (%)	19 (4.6)	40 (6.2)	0.32
	prasugrel (%)	5 (1.2)	0 (0.0)	**0.02**

BARC: Bleeding Academic Research Consortium; CABG: coronary artery bypass grafting; NOAC: non-vitamin K oral anticoagulant; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; SD: standard deviation; STEMI: ST-segment elevation myocardial infarction

Supplementary Table 3. Observed outcomes for quintiles of predicted thrombotic risk.

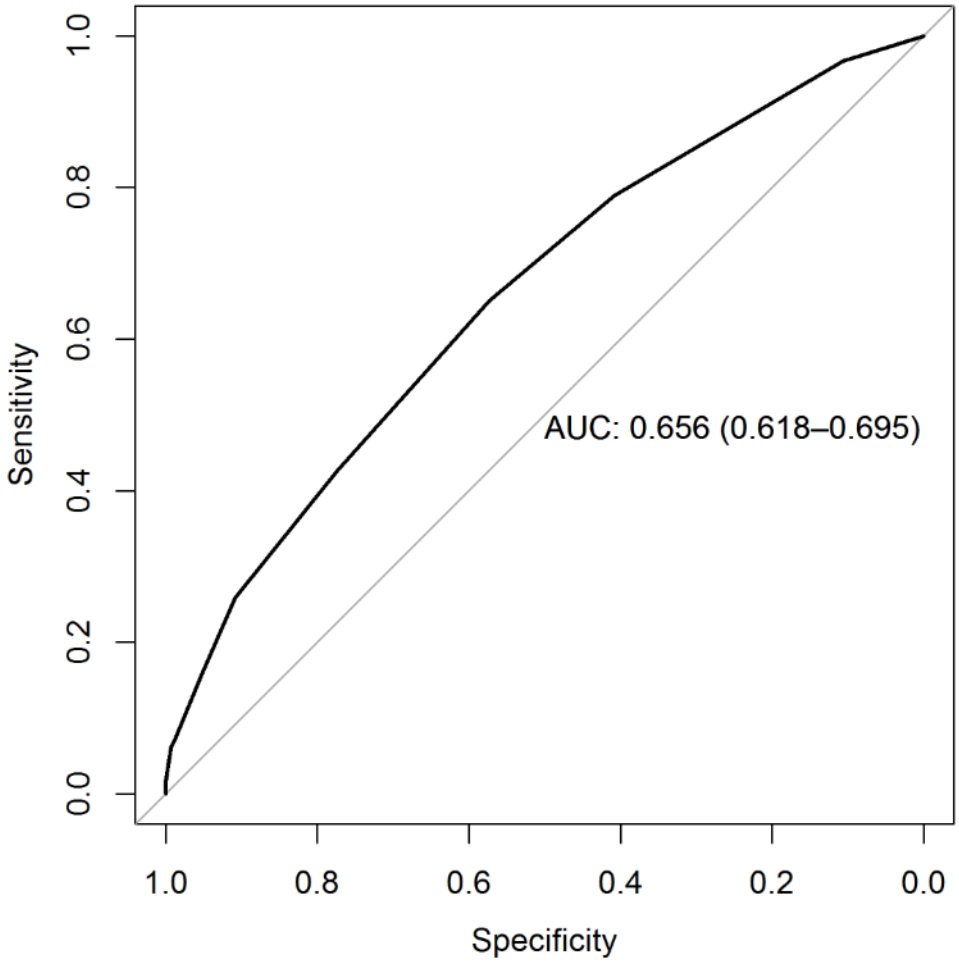
	Quintile	N	Ischaemic endpoint (%)		p-value	Bleeding (%)		p-value	Mortality (%)		p-value
			DAT	TAT		DAT	TAT		DAT	TAT	
	1	545	3.92	3.72	1.000	15.41	26.06	0.004	1.40	2.66	0.481
	2	545	3.52	3.92	0.995	14.96	29.9	<0.001	2.35	2.94	0.885
	3	545	6.05	6.06	1.000	15.27	25.76	0.004	2.02	4.04	0.264
	4	545	7.95	10.88	0.324	13.35	21.76	0.016	4.55	5.18	0.902
High risk	5	545	17.29	13.13	0.246	17.87	24.75	0.071	9.80	7.07	0.356
Low-intermediate risk	1-4	2,180	5.37	6.13	0.520	14.75	25.93	<0.001	2.58	3.70	0.176

DAT: double antithrombotic therapy; TAT: triple antithrombotic therapy



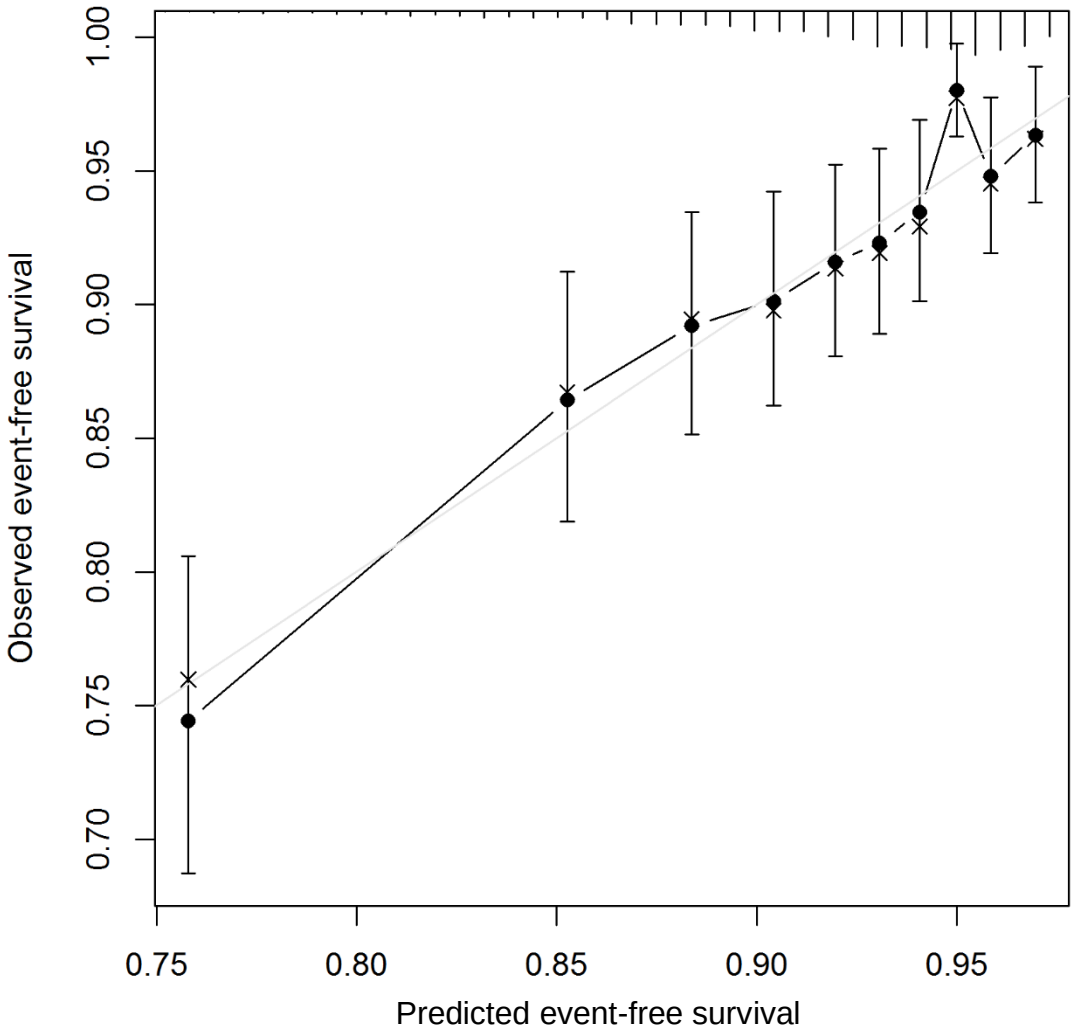
Supplementary Figure 1. Predictive accuracy of the model.

In the derivation cohort, AUC of the ROC curve = C-statistic



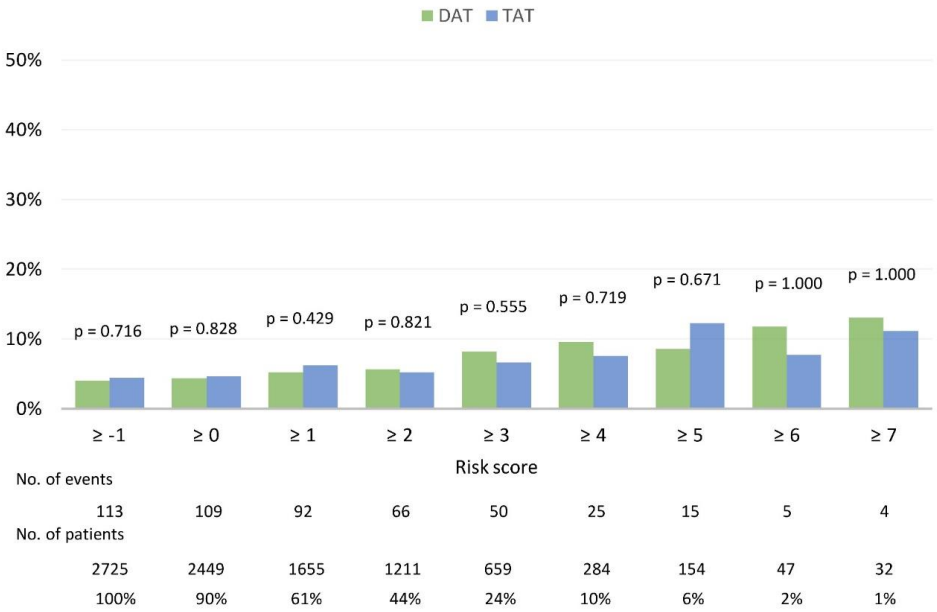
Supplementary Figure 2. Predictive accuracy of the simplified risk score.

In the derivation cohort, AUC of the ROC curve = C-statistic

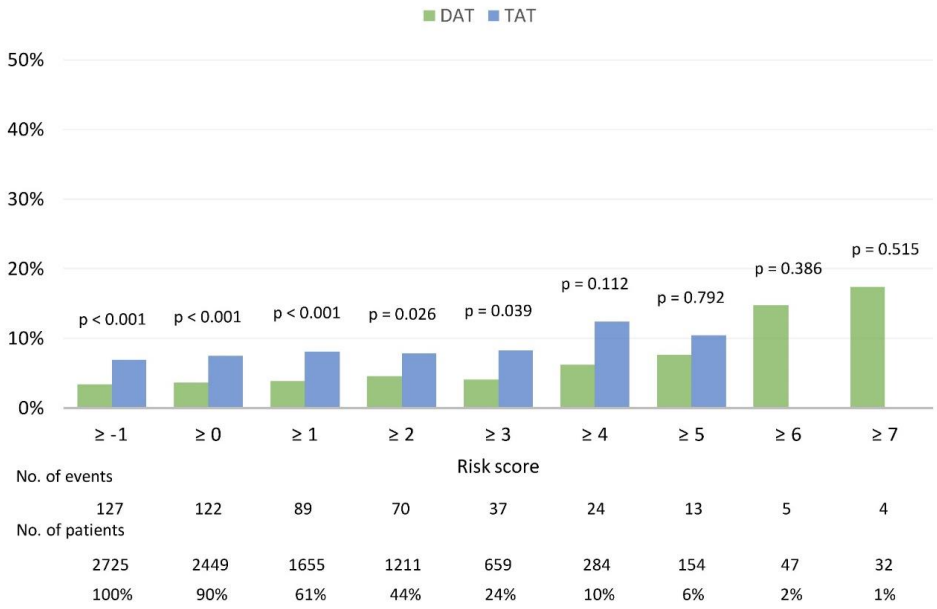


Supplementary Figure 3. Calibration curve of the model. Grey line: ideal.

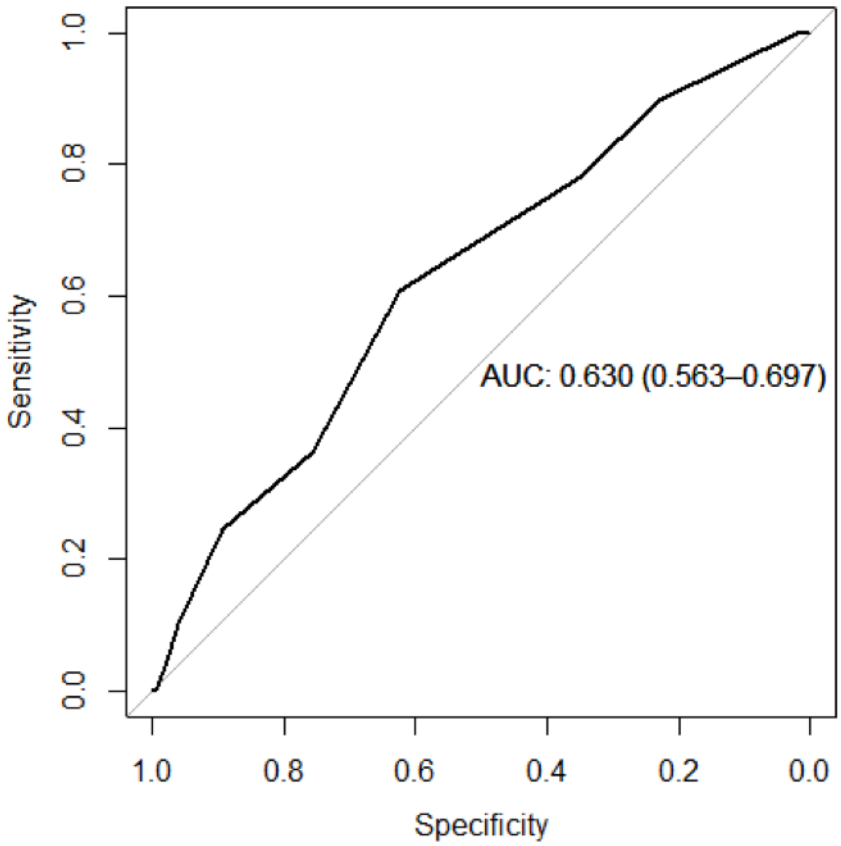
A) Mortality



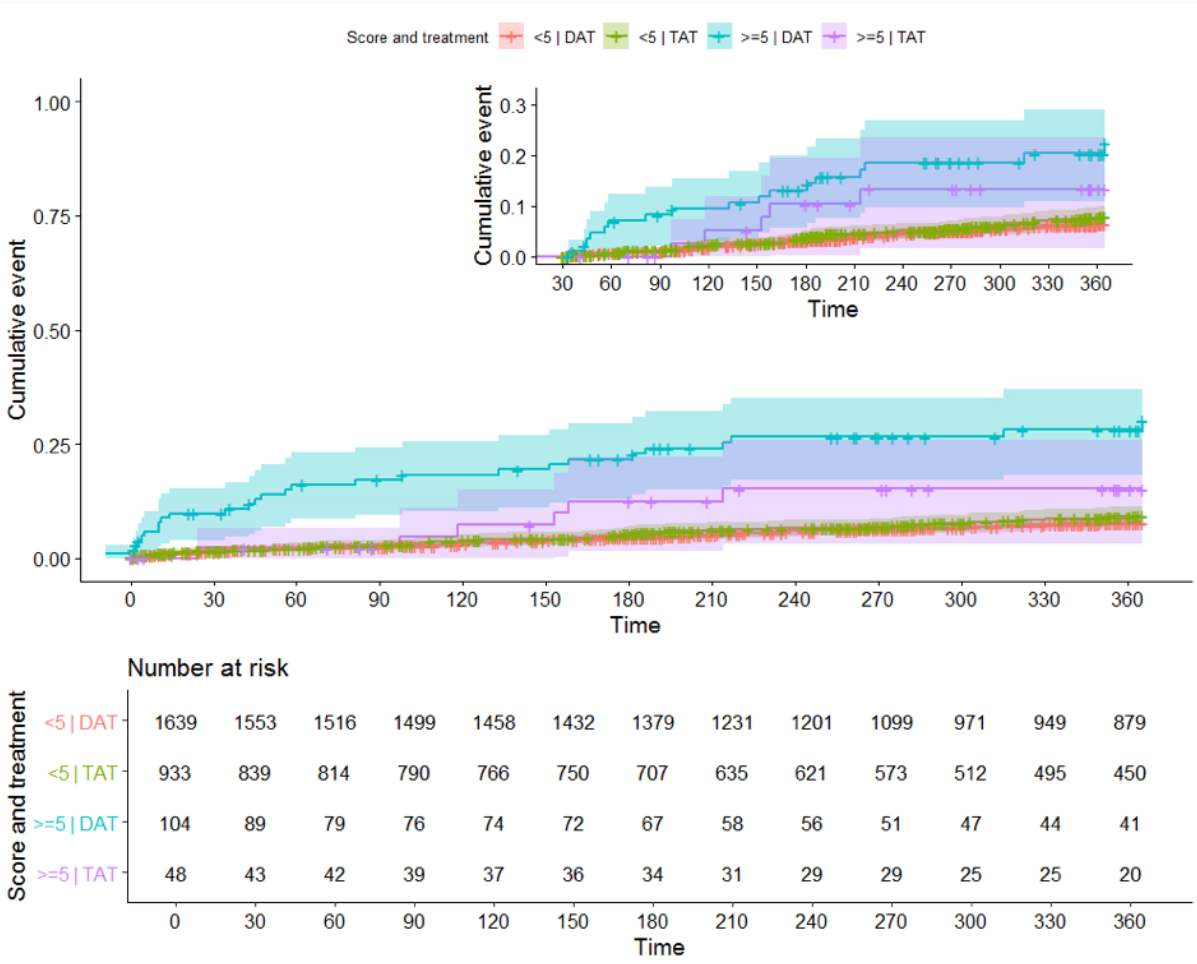
B) Major bleeding (BARC 3 and 5)



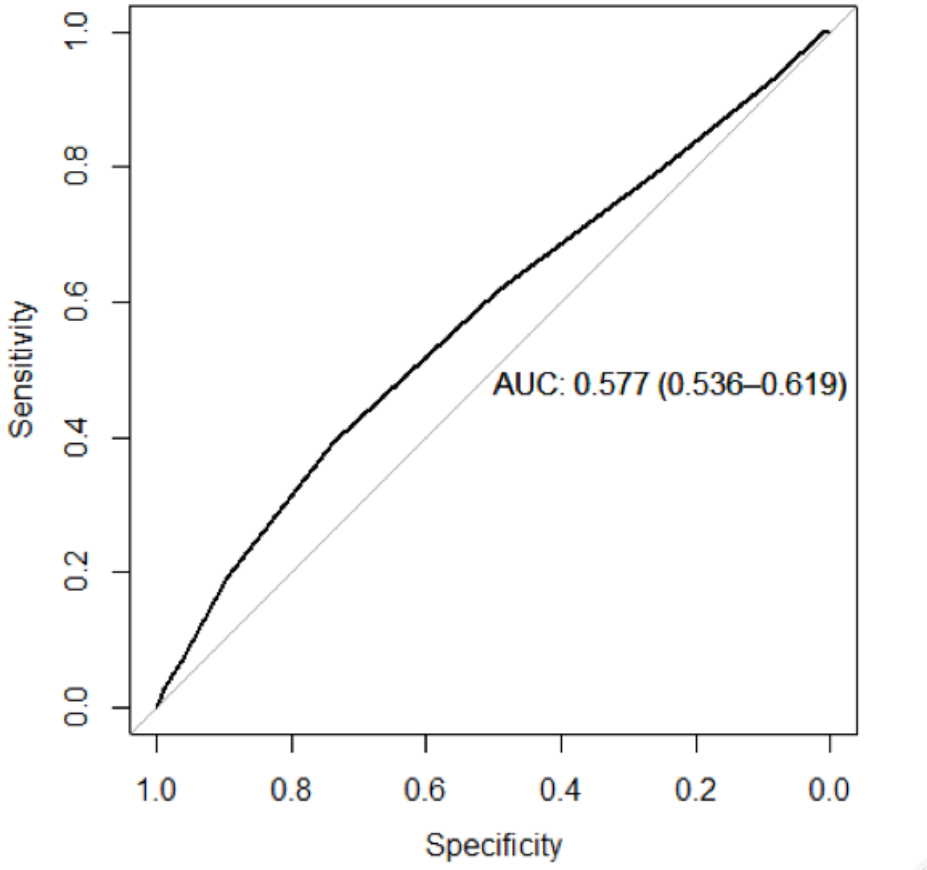
Supplementary Figure 4. Observed outcomes with DAT and TAT for different risk score cut-offs. BARC: bleeding academic research consortium criteria; DAT: double antithrombotic therapy; TAT: triple antithrombotic therapy



Supplementary Figure 5. Predictive accuracy in the external validation cohort (WOEST 2 registry). Simplified risk score. AUC of the ROC curve = C-statistic



Supplementary Figure 6. Kaplan-Meier curves of the composite ischaemic endpoint. With landmark analysis for events >30 days. Stratified for thrombotic risk and treatment strategy. DAT: double antithrombotic therapy; TAT: triple antithrombotic therapy



Supplementary Figure 7. Predictive accuracy of the CHA_2DS_2-VASc.

For the composite ischaemic endpoint, in the derivation cohort, AUC of the ROC curve = C-statistic.