ENTRUST-AF PCI

Edoxaban- vs vitamin-K-antagonist-based anti-thrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): A randomised, open-label, phase 3b trial

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ESC Congress Paris 2019 Together with World Congress of Cardiology

CARDIALYSIS Clinical Trial Management - Core Laboratories

AFNET

Daiichi-Sankyo

Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Served as a consultant for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and Pfizer; and a speaker for AstraZeneca, Bayer, Berlin-Chemie, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, and Omeicos.)

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Disclosures

Honoraria:

- Astra Zeneca
- Bayer Healthcare
- Berlin Chemie
- Biotronik
- BMS/Pfizer
- Boehringer Ingelheim
- Boston Scientific
- Cordis
- Daiichi-Sankyo
- Medtronic
- Omeicos

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Background

- Approximately 15% of AF patients also require PCI with stent placement to treat obstructive coronary artery disease
- Current guidelines recommend oral anticoagulation for AF and dual antiplatelet therapy (DAPT) with acetylsalicylic acid (aspirin) and $P2Y_{12}$ inhibitors after PCI
- DAPT in combination with oral anticoagulation (triple therapy) is associated with high rates of bleeding
- Edoxaban has established efficacy and safety for stroke prevention in AF
- Three randomised trials evaluated standard or reduced doses of NOAC in AF patients undergoing PCI while aspirin was abandoned
- The effects of edoxaban in combination with a $P2Y_{12}$ inhibitor in the setting of PCI are unexplored

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Study Objectives

Primary objective: To compare a 12-month antithrombotic regimen of

- edoxaban plus a $P2Y_{12}$ inhibitor versus
- VKA plus a $P2Y_{12}$ inhibitor plus aspirin for 1-12 months

in patients with AF and ACS or stable CAD following successful PCI with stent placement for the incidence of major or clinically relevant non-major bleeding (ISTH)

Two hypotheses for the primary bleeding objective are tested consecutively:

1. The edoxaban-based antithrombotic regimen is non-inferior to the VKA-based antithrombotic regimen
2. The edoxaban-based antithrombotic regimen is superior to the VKA-based antithrombotic regimen

Secondary objectives (exploratory):

- Main efficacy endpoint: Composite of cardiovascular (CV) death, stroke, systemic embolic events (SEE), spontaneous myocardial infarction (MI), and definite stent thrombosis

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Study Design

PROBE design: Prospective, Randomized, Open label, Blinded endpoint Evaluation in 1500 AF patients with ACS or stable CAD

Inclusion Criteria:

- ***OAC indication for AF for at least 12 months***
- ***Successful PCI with stent placement (goal of at least 25% ACS)***

4 hours – 5 days after sheath removal

RANDOMIZE

Edoxaban 60 mg/day*

$P2Y_{12}$ inhibitor** (without aspirin)

Vitamin K Antagonist***

$P2Y_{12}$ inhibitor aspirin 1 - 12 months****

12 m.

**Edoxaban dose reduction to 30 mg OD*
- *if CrCL≤50 ml/min*
- *BW≤60 kg*
- *certain P-gp inhibitors*

***Clopidogrel 75mg once-daily or if documented need prasugrel 5 or 10mg once-daily or ticagrelor 90mg twice-daily . Predeclared at randomization*

**** VKA, target INR 2-3*

*****aspirin 100mg OD for 1-12 months guided by clinical presentation (ACS or stable CAD), $CHA_2DS\text{-}VASc_2$ and HAS_BLED*

Primary outcome:
ISTH major or clinically relevant non-major bleeding

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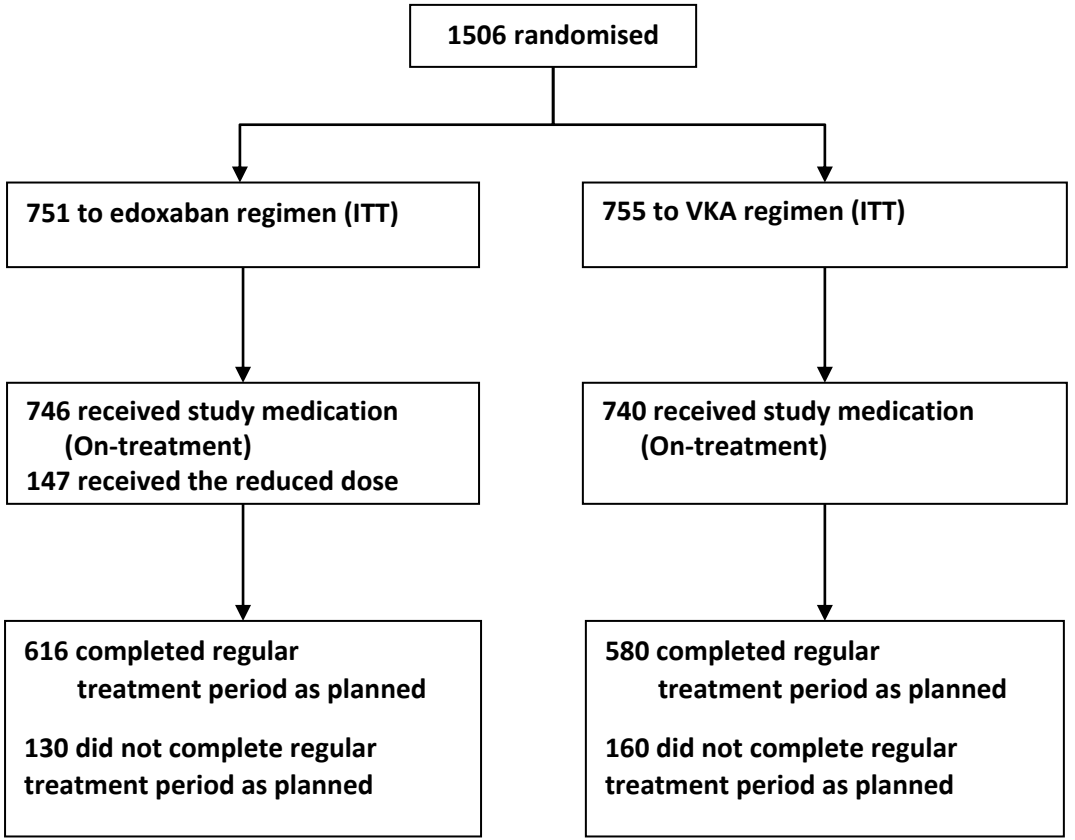
Consort Diagram



186 centres
18 countries

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Baseline Demographics

	Edoxaban regimen (N=751)	VKA regimen (N=755)
Age (years), median (Q1; Q3)	69 (63; 77)	70 (64; 77)
Sex, female	194 (25.8)	192 (25.4)
Weight (kg), median (Q1; Q3)	80 (71; 93)	83 (72; 94)
Type of AF, n (%)		
Paroxysmal	402 (53.5)	358 (47.5)
Persistent	140 (18.6)	146 (19.4)
Long-standing persistent or permanent	209 (27.8)	250 (33.2)
CHA_2DS_2-VASc score, median (Q1; Q3)	4.0 (3; 5)	4.0 (3; 5)
HAS-BLED score, median (Q1; Q3)	3.0 (2; 3)	3.0 (2; 3)
CrCL (mL/min), median (Q1; Q3)	71.8 (53.7, 91.1)	71.7 (54.0, 90.9)
Clinical presentation, n (%)		
ACS	388 (51.7)	389 (51.5)
Stable CAD	363 (48.3)	366 (48.5)
OAC prior to index PCI, n (%)	408 (68.0)	413 (65.1)
Time (hours) between end of PCI and randomisation, median (Q1; Q3)	45.1 (22.3; 75.6)	44.8 (22.1; 76.5)
Type of $P2Y_{12}$ antagonist, n (%)		
Clopidogrel	696 (92.8)	695 (92.1)
Prasugrel or Ticagrelor	54 (7.2)	60 (7.9)

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Primary Study Endpoint

ITT Analysis (N=1506), overall study period

	Edoxaban regimen	VKA regimen	Hazard Ratio (2-sided 95% CI)	P-value
Primary outcome of major or CRNM bleeding (ISTH)				
Intent-to-treat analysis:				
Number of patients	751	755		
Number of patients with event (%)	128 (17)	152 (20)		
Annualised event rate (% per year)	20.7	25.6	0.83 (0.65; 1.05)	Non-inferiority: P=0.0010 Superiority: P=0.1154

Hierarchical test procedure (*confirmatory statistics*):

STEP 1: **1.047 < 1.20** ➔ **The edoxaban regimen is non-inferior to the VKA regimen**

STEP 2: **1.047 > 1.00** ➔ **superiority of edoxaban regimen could not be demonstrated**

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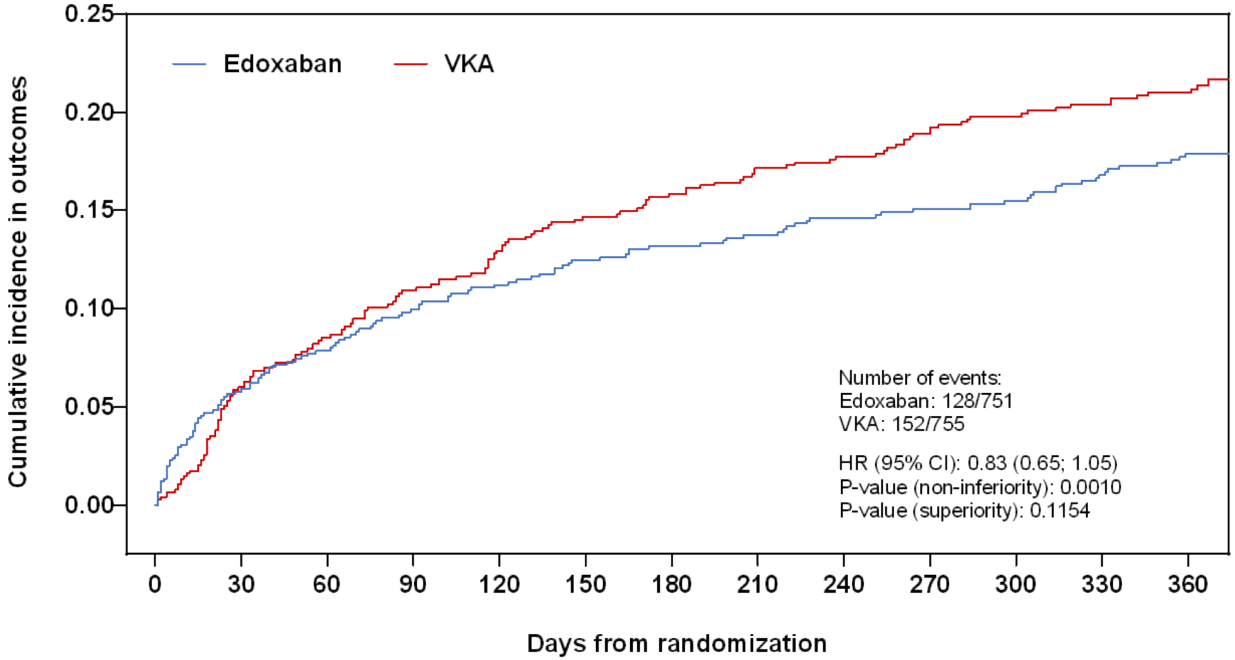
Primary Study Endpoint

ITT Analysis (N=1506), overall study period



Number at risk:

EDOXABAN	751	688	665	646	629	618	609	600	590	584	575	565	506
VKA	755	678	648	625	603	588	578	568	561	552	543	538	485

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Main Efficacy Endpoint

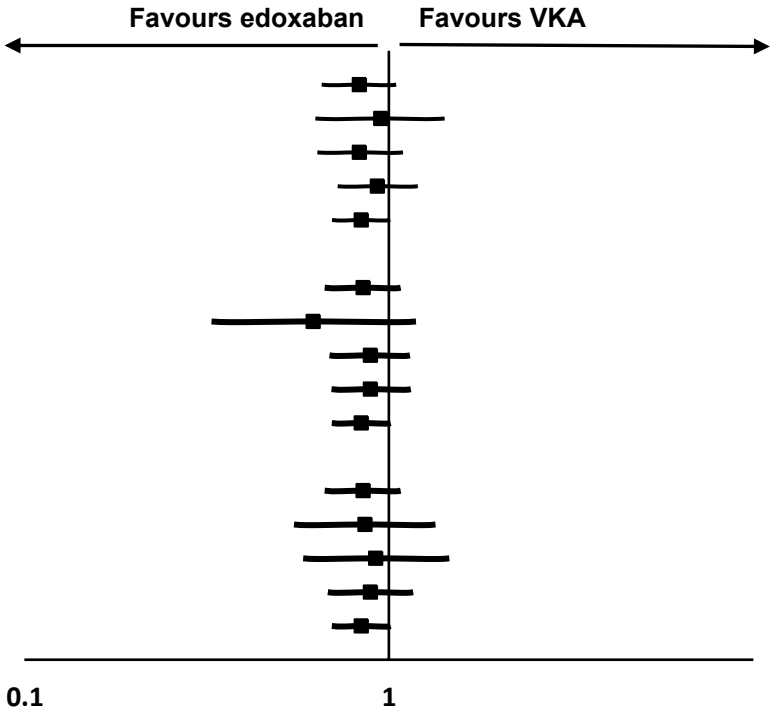
ITT Analysis (N=1506), overall study period

	Edoxaban regimen	VKA regimen	Hazard Ratio (2-sided 95% CI)
Main efficacy outcome (composite of CV death, stroke, SEE, MI or definite stent thrombosis)			
Intent-to-treat analysis:			
Number of patients	751	755	
Number of patients with event (%)	49 (7)	46 (6)	
Annualised event rate (% per year)	7.3	6.9	1.06 (0.71; 1.69)

Bleeding Outcomes (ISTH, TIMI, BARC)

ITT Analysis (N=1506), overall study period

Bleeding (ISTH, TIMI, BARC): Time to first event	95% CI Lower Limit	HR	95% CI Upper Limit
Major or CRNM bleeding (ISTH)	0.654	0.83	1.047
Major bleeding (ISTH)	0.628	0.95	1.422
CRNM bleeding (ISTH)	0.636	0.83	1.093
Minor bleeding (ISTH)	0.723	0.93	1.200
Any bleeding (ISTH)	0.698	0.84	1.009
Major or minor bleeding (TIMI)	0.666	0.85	1.077
Major bleeding (TIMI)	0.326	0.62	1.186
Minor bleeding (TIMI)	0.687	0.89	1.142
Minimal bleeding (TIMI)	0.696	0.89	1.148
Any bleeding (TIMI)	0.697	0.84	1.011
Type 2, 3, or 5 bleeding (BARC)	0.666	0.85	1.077
Type 3 or 5 bleeding (BARC)	0.549	0.86	1.342
Type 3 bleeding (BARC)	0.582	0.92	1.464
Type 2 bleeding (BARC)	0.680	0.89	1.165
Type 1, 2, 3, or 5 bleeding (BARC)	0.697	0.84	1.011



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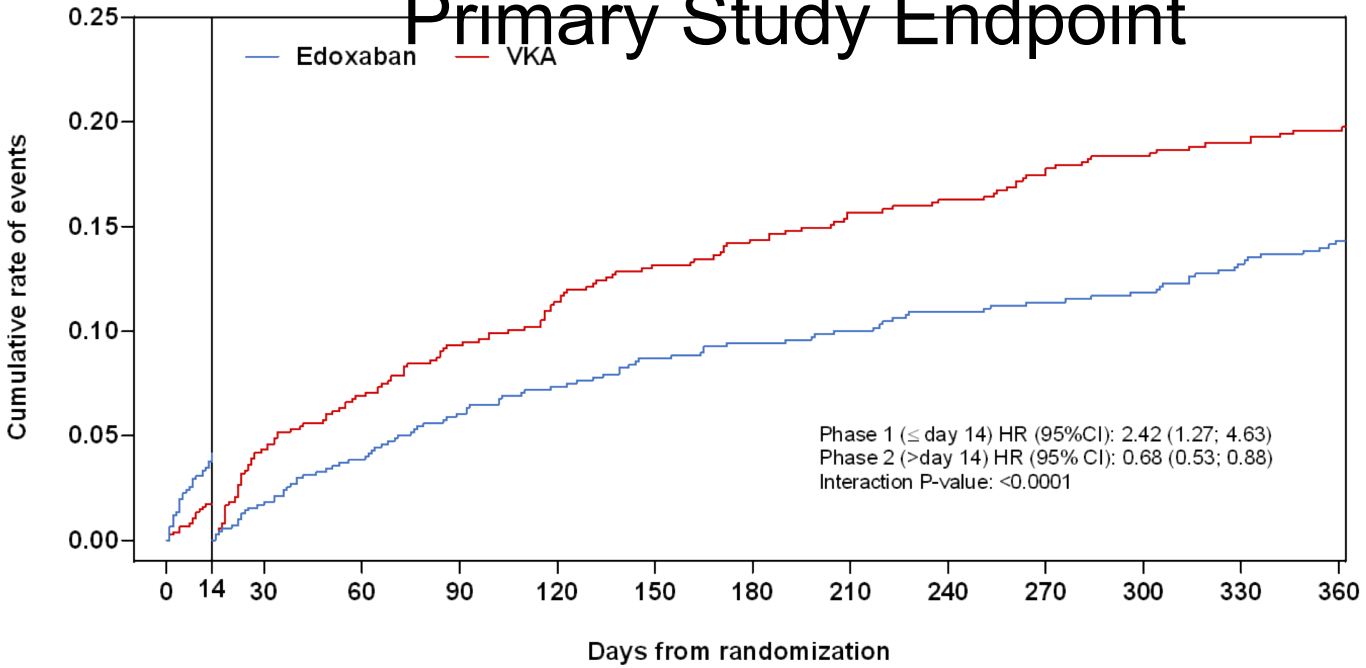
Post Hoc Landmark Kaplan Meier Analysis
Primary Study Endpoint

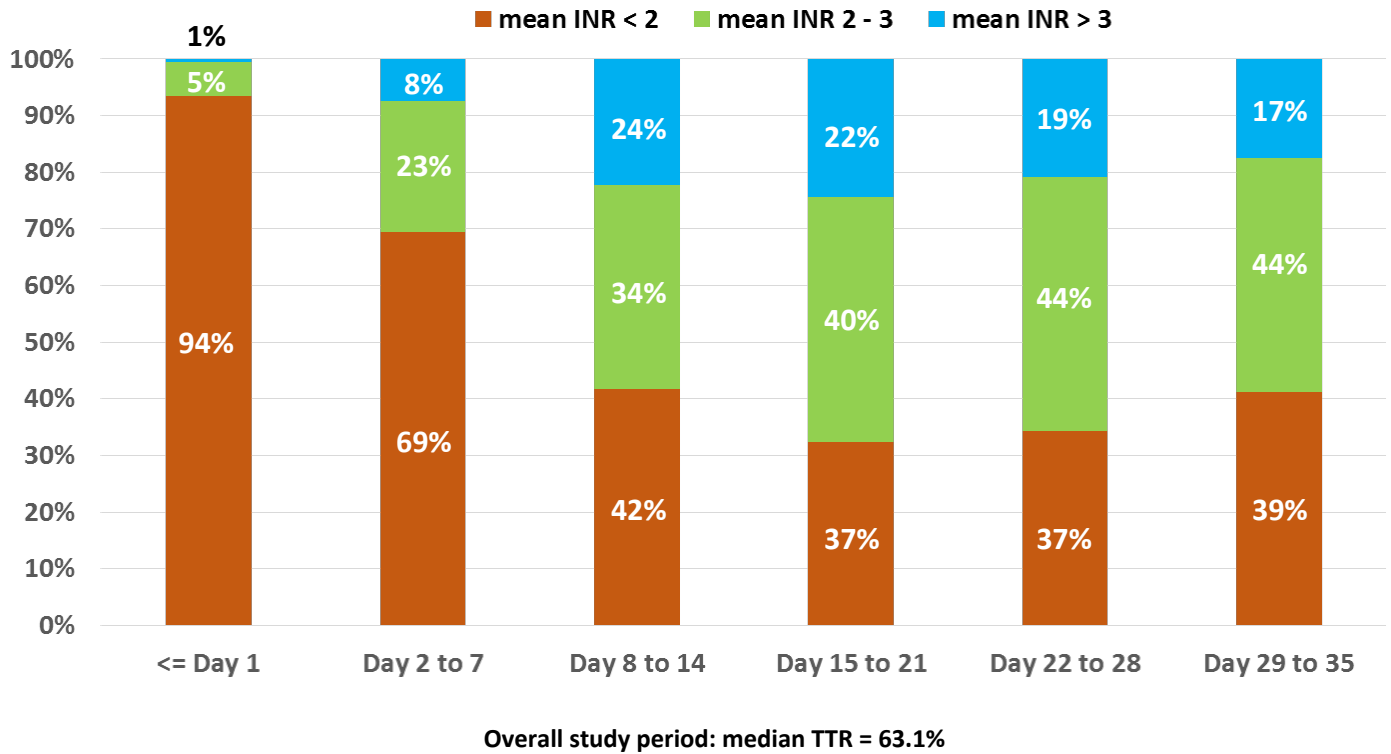


Number at risk:

EDOXABAN	751	707	688	665	646	629	618	609	600	590	584	575	565	506
VKA	755	721	678	648	625	603	588	578	568	561	552	543	538	485

INR in VKA regimen in first 5 weeks

Time from PCI to Randomisation:
- shortest – 0.2 h
- median – 45 h



Overall study period: median TTR = 63.1%

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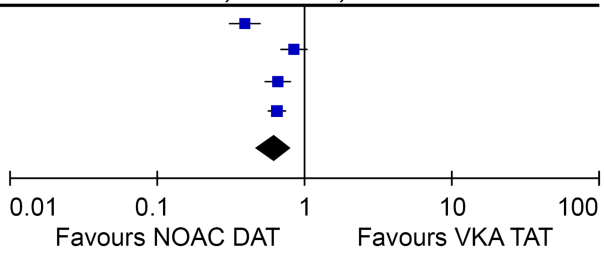
Meta-Analysis:
Comparative NOAC AF PCI trials
ISTH Major or CRNM Bleeding

ISTH Major or Clinically Relevant Non-Major Bleeding

Study or Subgroup	NOAC DAT Events	NOAC DAT Total	VKA TAT Events	VKA TAT Total	Weight	Risk Ratio M–H, Random, 95% CI
AUGUSTUS	84	1143	210	1123	23.7%	0.39 (0.31, 0.50)
ENTRUST AF-PCI	128	751	152	755	24.7%	0.85 (0.68, 1.05)
PIONEER AF-PCI	117	696	178	697	24.8%	0.66 (0.53, 0.81)
RE-DUAL PCI	305	1744	264	981	26.8%	0.65 (0.56, 0.75)
Total (95% CI)		**4334**		**3556**	**100.0%**	**0.62 (0.47, 0.81)**
Total events	634		804			

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 22.84$, df = 3 (P <0.0001); $I^2 = 87\%$

Test for overall effect: Z = 3.47 (P = 0.0005)



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Myocardial Infarction and Stent Thrombosis

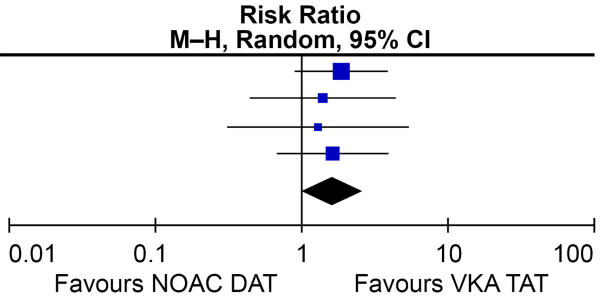
- Endpoints as defined by each of the NOAC AF PCI trials -

Stent Thrombosis

Study or Subgroup	NOAC DAT Events	Total	VKA TAT Events	Total	Weight	Risk Ratio M–H, Random, 95% CI
AUGUSTUS	21	1153	12	1154	40.0%	1.75 (0.87, 3.54)
ENTRUST AF-PCI	8	751	6	755	17.9%	1.34 (0.47, 3.84)
PIONEER AF-PCI	5	694	4	695	11.6%	1.25 (0.34, 4.64)
RE-DUAL PCI	22	1744	8	981	30.6%	1.55 (0.69, 3.46)
Total (95% CI)		**4342**		**3585**	**100.0%**	**1.55 (0.99, 2.41)**
Total events	56		30			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.29$, df = 3 (P = 0.96); $I^2 = 0\%$

Test for overall effect: Z = 1.92 (P = 0.06)



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Limitations

- TTR for the patients who received VKA was modestly lower than in ENGAGE AF-TIMI 48 but comparable to other NOAC AF PCI studies. The observed TTR in NOAC AF PCI trials reflects the challenges with VKA treatment in routine clinical practice.
- The number of patients on a more potent $P2Y_{12}$ inhibitor is limited; therefore, our trial must primarily be viewed as a comparison of clopidogrel-based antiplatelet therapies, which is consistent with all prior NOAC AF PCI trials.
- Furthermore, our study was designed as an open-label study, with potential treatment or reporting bias, which may explain why more patients withdrew from the VKA arm. However, patient data were 100% monitored for unreported events and all potential events were blindly adjudicated.
- Finally, in concert with the other trials, the enrolment of 1506 patients in ENTRUST-AF PCI was not large enough to detect small but potentially important differences in the incidence of the main efficacy outcome.

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Conclusions

- The ENTRUST-AF PCI trial showed that, among patients with AF who underwent successful PCI, a full-dose anticoagulation therapy with edoxaban 60 mg once daily plus a P2Y12 inhibitor is noninferior to a triple therapy with VKA (ASA given for 1 to 12 months) regarding the risks of major or CRNM bleeding events at 12 months.
- The edoxaban-based dual therapy regimen, as compared to the triple VKA-based regimen, showed similar rates with respect to the main efficacy outcome, a composite of death from cardiovascular causes, stroke or SEE, MI, or definite stent thrombosis.
- *Of note, all NOAC AF PCI trials show numerically increased rates of MI and stent thrombosis in patients with early withdrawal of aspirin.*
- In conclusion, in patients with AF who underwent PCI, the edoxaban-based dual antithrombotic therapy was noninferior for bleeding compared with VKA-based triple antithrombotic regimen without significant differences in ischaemic events.

ENTRUST-AF PCI Study Boards and Board Members

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THE LANCET

Articles

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

Pascal Vranckx, Marco Valgimigli, Lars Eckardt, Jan Tijssen, Thorsten Lewalter, Giuseppe Gargiulo, Valerii Batushkin, Gianluca Campo, Zoreslava Lysak, Igor Vakaliuk, Krzysztof Milewski, Petra Laeis, Paul-Egbert Reimitz, Rüdiger Smolnik, Wolfgang Zierhut, Andreas Goette

Summary

Background We aimed to assess the safety of edoxaban in combination with P2Y12 inhibition in patients with atrial fibrillation who had percutaneous coronary intervention (PCI).

Methods ENTRUST-AF PCI was a randomised, multicentre, open-label, non-inferiority phase 3b trial with masked outcome evaluation, done at 186 sites in 18 countries. Patients had atrial fibrillation requiring oral anticoagulation, were aged at least 18 years, and had a successful PCI for stable coronary artery disease or acute coronary syndrome. Participants were randomly assigned (1:1) from 4 h to 5 days after PCI using concealed, stratified, and blocked web-based central randomisation to either edoxaban (60 mg once daily) plus a P2Y12 inhibitor for 12 months or a vitamin K antagonist (VKA) in combination with a P2Y12 inhibitor and aspirin (100 mg once daily, for 1–12 months). The

Published Online
September 3, 2019
http://dx.doi.org/10.1016/S0140-6736(19)31872-0

See Online/Comment
http://dx.doi.org/10.1016/PII

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