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 edoxaban dose was reduced to 30 mg per day if one or more factors (creatinine clearance 15–50 mL/min, bodyweight ≤60 kg, or concomitant use of specified potent P-glycoprotein inhibitors) were present. The primary endpoint was a composite of major or clinically relevant non-major (CRNM) bleeding within 12 months. The primary analysis was done in the intention-to-treat population and safety was assessed in all patients who received at least one dose of their assigned study drug. This trial is registered with ClinicalTrials.gov, NCT02866175, is closed to new participants, and follow-up is completed.

Findings From Feb 24, 2017, through May 7, 2018, 1506 patients were enrolled and randomly assigned to the edoxaban regimen (n=751) or VKA regimen (n=755). Median time from PCI to randomisation was 45·1 h (IQR 22·2–76·2). Major or CRNM bleeding events occurred in 128 (17%) of 751 patients (annualised event rate 20·7%) with the edoxaban regimen and 152 (20%) of 755 patients (annualised event rate 25·6%) patients with the VKA regimen; hazard ratio 0·83 (95% CI 0·65–1·05; p=0·0010 for non-inferiority, margin hazard ratio 1·20; p=0·1154 for superiority).

Interpretation In patients with atrial fibrillation who had PCI, the edoxaban-based regimen was non-inferior for bleeding compared with the VKA-based regimen, without significant differences in ischaemic events.

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Department of Cardiology and Intensive Care, Jessa Ziekenhuis, Faculty of Medicine and Life Sciences at the Hasselt University, Hasselt, Belgium (Prof P Vranckx MD); **Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland** (Prof M Valgimigli MD, G Gargiulo MD); **Atrial Fibrillation Network, Munster, Germany** (Prof L Eckardt MD, Prof T Lewalter MD, Prof A Goette MD); **Department of Cardiology and Angiology, Division of Electrophysiology, University of Munster, Munster, Germany** (Prof L Eckardt); **Department of Cardiology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, Netherlands** (Prof J Tijssen PhD); **Cardialysis, Rotterdam, Netherlands** (Prof J Tijssen); **Department of Cardiology, Hospital Munich South, Munich, Germany** (Prof T Lewalter); **University of Bonn, Bonn, Germany** (Prof T Lewalter); **Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy** (G Gargiulo); **Department of Cardiology, Kyiv City Clinical Hospital #5, Kiev, Ukraine** (Prof V Batushkin MD); **Cardiovascular Institute, Azienda Ospedaliero-Universitaria di Ferrara, Cona, Venice, Italy** (G Campo MD); **Maria Cecilia Hospital, GVM Care and Research, Cotignola, Italy** (G Campo); **Department of Cardiac Rehabilitation,**

Introduction

Non-vitamin K antagonist oral anticoagulants (NOAC) are rapidly replacing vitamin K antagonists (VKAs) as the treatment of choice for stroke prevention in patients with non-valvular atrial fibrillation who are at increased thromboembolic risk (ie, CHA_2DS_2-VASc score ≥2).[1,2] About 15% of patients with atrial fibrillation might require percutaneous coronary interventions (PCIs) with stent placement to treat obstructive coronary artery disease.[3] The coexistence of atrial fibrillation with acute coronary syndrome or stable coronary artery disease raises concern about co-treatment with different antithrombotic drugs in the case of PCI. Dual antiplatelet therapy (DAPT) with acetylsalicylic acid (aspirin) and P2Y12 antagonist is recommended after PCI and patients requiring DAPT often also require treatment with oral anticoagulation, including patients with atrial fibrillation.[4,5] DAPT in combination with oral anticoagulation (triple therapy) is associated with high risk of bleeding.[6,7] Three randomised trials evaluated standard or reduced doses of NOACs in patients with atrial fibrillation who had undergone PCI and cumulatively added strength to the concept that abandoning aspirin might improve safety towards bleeding in these patients.[8–10]

Edoxaban is as effective as a VKA with respect to the prevention of stroke or systemic embolism and is associated with significantly lower incidence of bleeding and death from cardiovascular causes.[11] From the patient perspective, edoxaban therapy has been shown to be more

Oleksandrivska Kyiv City Clinical Hospital, Kiev, Ukraine (Z Lysak MD)**; Center for Cardiovascular Research and Development, American Heart of Poland Katowice, Poland; and The Jerzy Kukuczka Academy of Physical Education, Faculty of Physiotherapy, Katowice, Katowice, Poland** (Prof K Milewski MD)**; Department Internal Medicine No2 and Nursing, Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine** (I Vakaliuk MD)**; Department of Anesthesiology with Wards of Intensive Care, Ivano-Frankivsk Regional Clinical Cardiological Clinic, Ivano-Frankivsk, Ukraine** (I Vakaliuk)**; Daiichi Sankyo Europe, Munich, Germany** (P Laeis PhD, P-E Reimitz PhD, R Smolnik MD, W Zierhut MD)**; Cardiology and Intensive Care Medicine, St Vincenz-Hospital, Paderborn, Germany** (Prof A Goette)**; and Working Group of Molecular Electrophysiology, University Hospital Magdeburg, Magdeburg, Germany** (Prof A Goette)

Correspondence to:
Prof Pascal Vranckx, Department of Cardiology and Intensive Care, Jessa Ziekenhuis, Faculty of Medicine and Life Sciences at the Hasselt University, Hasselt, Belgium
pascal.vranckx@jessazh.be

or

Prof Andreas Goette, Cardiology and Intensive Care Medicine, St Vincenz-Hospital, Paderborn, Germany
andreas.goette@vincenz.de

Research in context

Evidence before this study

We did a systematic search on PubMed for studies published up to July 13, 2019, with no language restrictions. The following keywords were used in different combinations: "percutaneous coronary intervention", "PCI", "coronary stenting", "acute coronary syndrome", "ACS", "atrial fibrillation", "AF", "apixaban", "rivaroxaban", "edoxaban", "dabigatran", "vitamin K antagonist", "warfarin", "phenprocoumon", "oral anticoagulation", "oral anticoagulants", "dual antithrombotic therapy", "dual therapy", "triple therapy", "triple antithrombotic therapy", "dual antiplatelet therapy", "clopidogrel", "aspirin", and "randomised trial". References of previous systematic reviews and meta-analyses were also screened for relevant studies. For this meta-analysis, we included all randomised controlled trials in patients with atrial fibrillation who received percutaneous coronary intervention (PCI) in at least 50% of the sample and were allocated to dual antithrombotic therapy (DAT) consisting of any non-vitamin K antagonist oral anticoagulant (NOAC) in combination with a P2Y12 inhibitor or triple antithrombotic therapy (TAT) consisting of any vitamin K antagonist (VKA) in combination with dual antiplatelet therapy (DAPT). Three completed trials (PIONEER-AF PCI, RE-DUAL PCI, and AUGUSTUS) were identified. The PIONEER-AF PCI (N=2124) trial showed either low-dose rivaroxaban (15 mg once daily) plus a P2Y12 inhibitor for 12 months or very-low-dose rivaroxaban (2·5 mg twice daily) plus DAPT for 1, 6, or 12 months was associated with lower rate of clinically significant bleeding (a composite of major bleeding or minor bleeding according to TIMI criteria or bleeding requiring medical attention) compared with standard therapy with a VKA plus DAPT for 1, 6, or 12 months. In the RE-DUAL PCI (N=2725) trial the ISTH classification bleeding risk was lower among those who received dual therapy with dabigatran (110 or 150 mg twice daily) and a P2Y12 inhibitor than those who received TAT. The AUGUSTUS (N=4614) trial assessed the safety and efficacy of standard-dose apixaban (5 mg twice daily) compared with a VKA and of low-dose acetylsalicylic acid (aspirin) compared with placebo, on a background of concomitant P2Y12 inhibitor therapy for 6 months in patients with atrial fibrillation and recent acute coronary syndrome or PCI. DAT use was associated with a greater than 40% reduction of ISTH-defined major or clinically relevant non-major (CRNM) bleeding compared with TAT.

Added value of this study

This is the first trial testing an edoxaban-based DAT versus a VKA-based TAT in patients with atrial fibrillation who had PCI. This study showed that DAT consisting of edoxaban in combination with an oral P2Y12 inhibitor is non-inferior to TAT (VKA, oral P2Y12 inhibitor, and 1-month to 12-month aspirin) with respect to the occurrence of major or CRNM bleeding at 12 months. The composite of cardiovascular death, stroke, myocardial infarction, definite stent thrombosis, or systemic embolic events, as well as its individual components, did not differ between groups.

Implications of all the available evidence

We pooled the four trials using crude number of events retrieved from each study and a random-effects model (Mantel-Haenszel method). Given the objective of this meta-analysis, we only selected treatment groups with NOAC-based DAT or VKA-based TAT from the included trials. Treatment effect was reported as risk ratio and 95% CI. A DAT consisting of a NOAC and an oral P2Y12 inhibitor compared with TAT based on VKA and DAPT was associated with lower risks of major or CRNM bleeding events and similar risks of major adverse cardiovascular events, all-cause death, stroke, stent thrombosis, or myocardial infarction. Thus, NOAC-based DAT was safer and as effective as VKA-based TAT (appendix p 41).

convenient to use than VKA.[12,13] However, the effects of edoxaban in combination with a P2Y12 inhibitor in the setting of PCI are unexplored.[14]

We conducted a trial for the evaluation of the safety and efficacy of an edoxaban-based antithrombotic regimen in patients with atrial fibrillation following successful percutaneous coronary intervention (the ENTRUST-AF PCI trial) to assess the safety and efficacy of an edoxaban-based versus a VKA-based antithrombotic regimen among patients with atrial fibrillation who had undergone PCI.[14]

Methods

Study design and participants

The ENTRUST-AF PCI trial was a randomised, multicentre, open-label, phase 3b study with masked outcome assessments by an independent clinical event committee done at 186 sites in 18 countries (appendix pp 8–14).[14] Eligible 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.[14] Patients with non-valvular atrial fibrillation not secondary to a reversible disorder were included and patients with mechanical heart valves, moderate-to-severe mitral stenosis, end-stage renal disease, and other major comorbidities were excluded. Full inclusion and exclusion criteria are listed in the appendix (pp 21–22).

The trial was performed in compliance with the protocol, the ethical principles of the Declaration of Helsinki, the International Conference on Harmonisation guidelines for Good Clinical Practice, and applicable regulatory requirements. The protocol and its amendments were approved by national regulatory agencies in participating countries and by the institutional review board or ethics committee at each participating institution. All patients provided written informed consent before participation in

See Online for appendix

the study. The trial protocol and a list of committee members and participating investigators are in the appendix (pp 3–32).

Randomisation and masking

Eligible patients were centrally randomly assigned (1:1) to the edoxaban-based regimen or VKA-based regimen between 4 h after arterial sheath removal and 5 days after successful PCI. If a staged PCI was planned, consent and random group assignment took place after completion of the last stage.

Randomisation was concealed from study nurses and physicians enrolling patients via a locked web-based system. The allocation sequence was computer generated by an external programmer who was not otherwise involved in the trial. Randomisation was stratified by geographic region (Asia *vs* eastern Europe *vs* western Europe), clinical presentation (stable coronary artery disease *vs* acute coronary syndrome), and requirement for dose adjustment according to edoxaban label and blocked with randomly varied block sizes of four per stratum. Treatment allocation was open to participants, the clinicians caring for them in primary and secondary care, and local investigators. Outcome event adjudicators were masked to participant identity, treatment allocation, and drug use. Masking of the clinical events adjudication committee was managed by the clinical research organisation (CRO) (Chiltern). Study statisticians were not masked to the treatment allocation. However, they did not generate any table or study report during the actual study. The statistical analysis plan was written without knowledge of outcome data. A statistician, contracted from the CRO (Chiltern) and firewalled from the study team, generated all tables for the data safety monitoring board.

Procedures

The assigned anticoagulation therapy was to be implemented as soon as possible after participants were enrolled and randomly assigned. Patients were transitioned from other oral or parenteral anticoagulants to edoxaban (Daiichi Sankyo, Japan) using an algorithm provided in the protocol (appendix p 23) and previously described.[14]

Patients assigned to the edoxaban regimen received a dose of 60 mg once daily and by default clopidogrel 75 mg once daily for 12 months. At the investigator's discretion, either prasugrel (5 mg or 10 mg once daily) or ticagrelor (90 mg twice daily) could be used instead of clopidogrel. The antiplatelet therapy in the ENTRUST-AF PCI trial was provided by the funder (packaged and labelled), the transition to the study antiplatelet therapy at time of randomisation is described in the appendix (p 23). The periprocedural antiplatelet therapy was per routine practice.

The edoxaban dose was reduced to 30 mg once daily for patients with any of the following characteristics at randomisation or during the study: moderate or severe renal impairment (calculated creatinine clearance 15–50 mL/min), bodyweight 60 kg or less, or concurrent use of specific potent P-glycoprotein inhibitors (cyclosporine, dronedarone, erythromycin, or ketoconazole). At the end of the trial, patients in the edoxaban group could transition to VKA by receiving both edoxaban 30 mg once daily (15 mg for patients qualifying for dose reduction) and a VKA until an international normalised ratio (INR) of 2·0 was reached. At that point, edoxaban was stopped and the VKA was continued at the discretion of the treating physician, aiming for an INR of 2·0–3·0.

Patients who were randomly assigned to the VKA regimen received a VKA in combination with clopidogrel 75 mg once daily (or at the discretion of the investigator, prasugrel 5 mg or 10 mg once daily or ticagrelor 90 mg twice daily) for 12 months and aspirin (100 mg once daily) for a minimum of 1 month and up to 12 months' duration at the discretion of the investigator. The dose of VKA was adjusted to achieve and maintain a therapeutic INR of 2·0–3·0. INR measurements were taken once every 2–3 days until the value reached the therapeutic range; thereafter, ad-hoc INR measurements were performed at the discretion of the investigator. The choice of P2Y12 inhibitor and duration of aspirin treatment was predeclared by the investigator before random group assignment as guided by the clinical presentation (acute coronary syndrome or stable coronary artery disease), CHA_2DS_2-VASc score (composite score with the following categories: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke or transient ischaemic attack or thromboembolism, vascular disease, age 65–74 years, and female sex) and HAS-BLED score (composite score with the following categories: hypertension, abnormal renal and liver function, stroke, bleeding history or predisposition, labile INR, elderly, and drugs or alcohol).[1] The use of gastric protection drugs that do not interact with cytochrome P450 2C19 (such as pantoprazole) was strongly recommended.

All patients who were assigned to a group were followed for 12 months after randomisation and every effort was made to complete the clinical follow-up. For this purpose, onsite visits could be replaced by telephone contact at the patient's request, and clinical follow-up information was collected from hospital records and national death registries unless explicitly forbidden by the patient. Trial medications were dispensed every 3 months.

Adherence was assessed by direct pill counts and self-reporting. Adherence counselling by the study team was the default strategy to improve drug adherence.

Clinical follow-up of the patient was conducted through onsite visits at 1, 3, 6, 9, and 12 months after randomisation, and telephone assessments at 2, 4, 5, 7, 8, 10, and 11 months after randomisation.[14] A tabular summary of the visits scheduled and a description of follow-up procedures is in the appendix (pp 17–19).

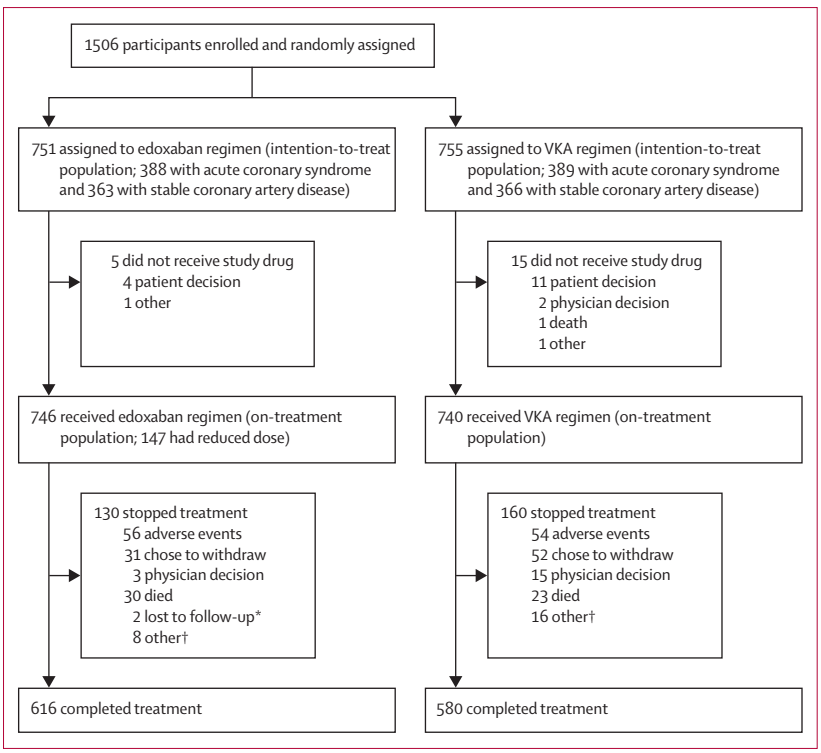

Figure 1: **Trial profile**
VKA=vitamin K antagonist. *One participant was lost to follow-up on day 14 and the other one on day 57. †Includes no efficacy and progressive disease.

Outcomes

The primary outcome was the composite of major or clinically relevant non-major (CRNM) bleeding defined according to the International Society of Thrombosis and Haemostasis (ISTH) between randomisation and 12 months thereafter (appendix p 29).[14,15] The main efficacy outcome was the composite of cardiovascular death, stroke (modified Valve Academic Research Consortium-2 definition),[16] systemic embolic events (SEE), myocardial infarction, and definite stent thrombosis (according to the academic research consortium criteria).[14,17] Other secondary outcomes reported in this manuscript were net clinical benefit, ISTH-defined major, CRNM, and minor bleeding and any ISTH-defined bleeding, intracranial and fatal bleeding, and bleeding as per the Bleeding Academic Research Consortium (BARC)[18] and Thrombosis in Myocardial Infarction (TIMI)[19] definitions (appendix p 34). Secondary efficacy outcomes were stroke, ischaemic stroke, haemorrhagic stroke, systemic embolic events, myocardial infarction, definite stent thrombosis, probable stent thrombosis, all-cause death, cardiovascular death, and cardiovascular or unexplained death (appendix p 35). Other secondary outcomes (appendix p 20) will be analysed and reported elsewhere.

The single components of the composite primary and secondary outcomes and specific subcategories (eg, haemorrhagic, ischaemic, and undetermined stroke) were analysed as exploratory outcomes. Bleeding events were classified according to BARC and TIMI classifications, for descriptive purposes only. More detailed outcome definitions are in the appendix (pp 24–32).

Statistical analysis

Under the VKA-based antithrombotic regimen, the 1-year event rate for major and CRNM bleeding is expected to be approximately 24%.[1,5,20] We estimated a sample size of 750 patients per group providing more than 80% power to show non-inferiority with a non-inferiority margin of 1·20 at a one-sided significance level of 2·5%. The margin of 1·20 was selected on the basis of clinical appropriateness. This sample size provides 80% power to detect an 18% relative risk reduction at 1 year under an edoxaban-based anticoagulation regimen at a two-sided α of 0·05.[14]

The trial was designed to test the safety hypothesis that the edoxaban-based regimen would be non-inferior to the VKA-based regimen with respect to the rate of the primary outcome of major or CRNM bleeding. To satisfy non-inferiority, the upper boundary of the two-sided 95% CI for the hazard ratio (HR) should not exceed the margin of 1·20. If non-inferiority was established, the edoxaban-based regimen was to be tested for superiority against the VKA-based regimen. Both analyses were done in the intention-to-treat (ITT) population of all participants irrespective of whether they received their assigned treatment. The analyses were repeated for sensitivity reasons in the on-treatment population; events were counted from the first intake of the study medication through 3 days after the permanent discontinuation of the assigned study medication (edoxaban or VKA). Intention-to-treat and on-treatment analyses were also done for secondary endpoints.

The time from randomisation to the first adjudicated event of major or CRNM bleeding was analysed using a Cox proportional hazards model including treatment regimen and the three stratification factors as covariates (geographic region, clinical presentation, and requirement for dose adjustment according to the edoxaban label). The HR for edoxaban versus VKA, p values, and corresponding 95% CIs were estimated from the model.

The main efficacy outcome was statistically analysed in a similar manner to the primary outcome. No formal statistical hypothesis testing was performed for these outcomes; HRs and 95% CIs are presented.

Subgroup analyses of the primary outcome were performed with tests for treatment-by-subgroup interaction for prespecified baseline characteristics.[14]

To assess the possibility that the low INR rates soon after randomisation led to the apparent violation of the proportional hazards assumption, we performed a post-hoc landmark analysis with a landmark in the first 14 days. The 14 days was selected based on the INR distribution over time and inspection of the Kaplan-Meier curve.

All statistical analyses were performed in SAS, version 9.4. The primary statistical analysis was performed

by statisticians contracted by the CRO (Chiltern) and checked for consistency by a second statistician employed by the sponsor. An independent data and safety monitoring board reviewed unmasked patient-level data at regular intervals during the trial to monitor safety of the study participants. No formal interim analyses for early termination of the trial were planned.

Onsite monitoring visits were done at individual sites with events checked against source documents. Additionally, the trial was remote monitored for event under-reporting. All suspected outcomes were adjudicated by a masked independent clinical event committee. The trial is registered with ClinicalTrials.gov (NCT02866175).

Role of the funding source

The funder of the study was involved in study design, data collection, data analysis, and data interpretation, but not writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From Feb 24, 2017, to May 7, 2018, 1506 PCI patients with atrial fibrillation were randomly assigned to receive an open-label edoxaban-based regimen (n=751) or a VKA-based regimen (n=755); 746 (99%) patients assigned to the edoxaban-based regimen and 740 (98%) assigned to the VKA regimen received at least one dose of their assigned drug (figure 1).

The characteristics of the patients at baseline were well balanced between the groups (table 1). The indication for the index PCI was acute coronary syndrome in 777 (52%) of 1506 patients. The median age was 70 years (IQR 63–77) and 386 (26%) patients were women. 189 (13%) patients had a previous stroke. The median CHA_2DS_2-VASc score was 4·0 (IQR 3·0–5·0), and the median HAS-BLED score was 3·0 (IQR 2·0–3·0). 456 (30%) patients had previously used VKAs and 365 (24%) had used NOACs. The median time from PCI to randomisation was 45·1 h (IQR 22·2–76·2).

After random group assignment, 1391 (92%) of 1506 patients were treated with clopidogrel (table 1). 147 (20%) of 746 patients assigned to the edoxaban regimen started with an adjusted dose of 30 mg. Among patients assigned to the VKA regimen, triple antithrombotic therapy was taken for a median of 66 days (IQR 33–188; appendix pp 36–38). The median time in therapeutic range (INR 2·0–3·0) was 63·1% (IQR 46·3–75·6). 130 (17%) of 746 patients prematurely discontinued the edoxaban-based regimen and 160 (22%) of 740 patients prematurely discontinued the VKA regimen. Adherence to the intended aspirin duration is reported in the appendix (p 33). Two patients in the edoxaban regimen were lost to follow-up (figure 1). The median follow-up time in the ENTRUST-AF PCI trial was 364 days (IQR 361–368).

	Edoxaban regimen (n=751)	VKA regimen (n=755)
Age, years	69 (63–77)	70 (64–77)
Sex		
Female	194 (26%)	192 (25%)
Male	557 (74%)	563 (75%)
Bodyweight, kg	80 (71–93)	83 (72–94)
Type of atrial fibrillation		
Paroxysmal	402 (54%)	358 (47%)
Persistent	140 (19%)	146 (19%)
Long-standing persistent or permanent	209 (28%)	250 (33%)
Recalculated CHA_2DS_2-VASc score	4·0 (3·0–5·0)	4·0 (3·0–5·0)
Recalculated HAS-BLED score	3·0 (2·0–3·0)	3·0 (2·0–3·0)
Recalculated creatinine clearance, mL/min*	71·8 (53·7–91·1)	71·7 (54·0–90·9)
Data missing	3 (<1%)	5 (1%)
Medical history		
Myocardial infarction	188 (25%)	177 (23%)
Previous PCI	199 (26%)	195 (26%)
Previous CABG	46 (6%)	49 (6%)
Congestive heart failure	418 (56%)	408 (54%)
Stroke	97 (13%)	92 (12%)
Peripheral artery disease	76 (10%)	82 (11%)
Non-CNS systemic embolic event	12 (2%)	10 (1%)
Diabetes mellitus	259 (34%)	258 (34%)
Hypertension	674 (90%)	687 (91%)
Hypercholesterolaemia	497 (66%)	484 (64%)
Bleeding events	56 (7%)	49 (6%)
Valvular heart disease	210 (28%)	221 (29%)
Malignancy	43 (6%)	46 (6%)
Geographic region		
Asia	82 (11%)	87 (12%)
Eastern Europe	350 (47%)	349 (46%)
Western Europe	319 (42%)	319 (42%)
Clinical presentation (documented in IXRS)		
Acute coronary syndrome	388 (52%)	389 (52%)
Stable coronary artery disease	363 (48%)	366 (48%)
Type of therapy before index PCI		
VKA	232 (31%)	224 (30%)
NOAC	176 (23%)	189 (25%)
None	192 (26%)	221 (29%)
Data missing	151 (20%)	121 (16%)
Duration between end of PCI and randomisation, h	45·1 (22·3–75·6)	44·8 (22·1–76·5)
Type of P2Y12 antagonist (documented in IXRS)		
Clopidogrel	696 (93%)	695 (92%)
Prasugrel 5 mg	2 (<1%)	1 (<1%)
Prasugrel 10 mg	3 (<1%)	2 (<1%)
Ticagrelor	49 (7%)	57 (8%)

Data are median (IQR), n (%), or n. CABG=coronary artery bypass grafting. IXRS=interactive voice web response system. NOAC=non-vitamin K antagonist oral anticoagulant. PCI=percutaneous coronary intervention. VKA=vitamin K antagonist. *Minimum of the recalculated local lab creatinine clearance and the recalculated central lab creatinine clearance value has been used.

Table 1: **Baseline patient characteristics**

	Edoxaban regimen	VKA regimen	Hazard ratio (two-sided 95% CI)	p value
Primary outcome of major or CRNM bleeding (ISTH)				
Intention-to-treat analysis				
Number of patients	751	755	..	..
Number of patients with event	128 (17%)	152 (20%)	..	..
Annualised event rate	20·7	25·6	0·83 (0·65–1·05)	Non-inferiority p=0·0010; superiority p=0·1154
On-treatment analysis				
Number of patients	746	740	..	..
Number of patients with event	124 (17%)	142 (19%)	..	..
Annualised event rate	20·7	25·5	0·84 (0·66–1·06)	Non-inferiority p=0·0016; superiority p=0·1434
Major bleeding (ISTH)				
Intention-to-treat analysis				
Number of patients	751	755	..	..
Number of patients with event	45 (6%)	48 (6%)	..	..
Annualised event rate	6·7	7·2	0·95 (0·63–1·42)	..
On-treatment analysis				
Number of patients	746	740	..	..
Number of patients with event	42 (6%)	42 (6%)	..	..
Annualised event rate	6·5	6·8	0·98 (0·64–1·49)	..
Main efficacy outcome (composite of cardiovascular death, stroke, systemic embolic event, myocardial infarction, or definite stent thrombosis)				
Intention-to-treat analysis				
Number of patients	751	755	..	..
Number of patients with event	49 (7%)	46 (6%)	..	..
Annualised event rate	7·3	6·9	1·06 (0·71–1·69)	..

CRNM=clinically relevant non-major. ISTH=International Society of Thrombosis and Haemostasis. VKA=vitamin K antagonist.

Table 2: **Study outcomes**

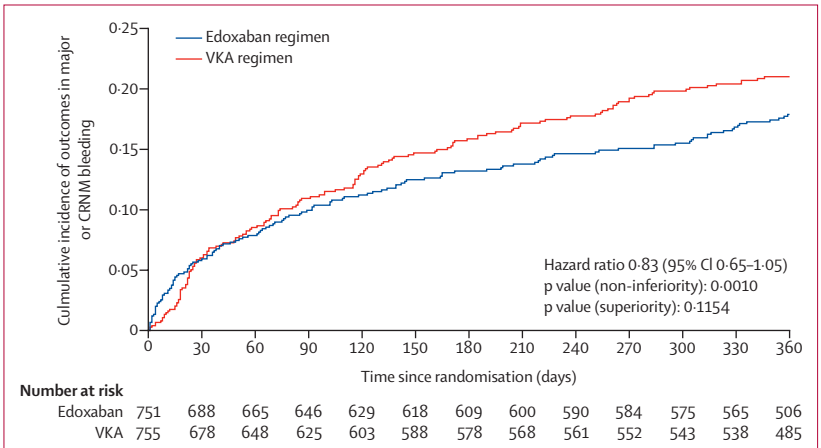

Figure 2: **Primary outcome events of major or CRNM bleeding (intention-to-treat population; n=1506)**
CRNM=clinically relevant non-major. VKA=vitamin K antagonist.

The primary outcome of ISTH-defined major or CRNM bleeding events occurred in 128 (17%) of 751 patients (annualised event rate 20·7%) with the edoxaban regimen and in 152 (20%) of 755 patients (annualised event rate 25·6%) with the VKA regimen (HR for edoxaban 0·83 [95% CI 0·65–1·05], p=0·0010 for non-inferiority, margin HR 1·20, p=0·1154 for superiority; table 2, figure 2). Fatal bleeding occurred in one (<1%) patient receiving the edoxaban regimen and seven (1%) patients receiving the VKA regimen. Intracranial bleeding occurred in four (1%; 0·6% per year) and nine (1%; 1·3% per year) patients. Rates of bleeding according to ISTH, TIMI, and BARC definitions were consistent (appendix pp 29–31, 43). Subgroup analyses showed no variation in treatment effects for the primary bleeding outcome by prespecified baseline characteristics (appendix pp 39–40). An analysis of the primary bleeding outcomes occurring while the patient was on study medication showed consistent results (HR for edoxaban 0·84 [95% CI 0·66–1·06], p=0·0016 for non-inferiority, p=0·1434 for superiority; table 2; appendix p 42).

At 12 months, the main efficacy outcome (the composite of cardiovascular death, stroke, SEE, myocardial infarction, and definite stent thrombosis) occurred in 49 (7%) of 751 patients (annualised event rate 7·3%) receiving the edoxaban regimen compared with 46 (6%) of 755 (annualised event rate 6·9%) patients receiving the VKA regimen (HR for edoxaban 1·06 [95% CI 0·71–1·69]; table 2; appendix p 44). The rates for each component of the main secondary efficacy outcome were similar between treatments (appendix p 35).

A post-hoc analysis with a landmark at 14 days for the primary bleeding outcome provided clear signal of heterogeneity with respect to the treatment effect ($p_{interaction}$<0·0001). Non-significantly lower bleeding rates were noted for the VKA regimen versus the edoxaban regimen (HR for edoxaban 2·42 [95% CI 1·27–4·63]) followed by a significant reduction in the rate of the primary bleeding outcome favouring the edoxaban regimen (HR for edoxaban 0·68 [95% CI 0·53–0·88]; figure 3A). The proportion of VKA-treated patients with subtherapeutic INR less than 2 was 559 (94%) of 592 patients with this data available at the day of randomisation, 340 (69%) of 491 on days 2–7, and 296 (42%) of 700 on days 8–14 (figure 3B).

Discussion

The ENTRUST-AF PCI trial showed that, among patients with atrial fibrillation who had successful PCI, a full-dose anticoagulation therapy with edoxaban 60 mg once daily plus a P2Y12 inhibitor is non-inferior to a triple therapy with VKA (aspirin given for 1–12 months) regarding the risks of major or CRNM bleeding events at 12 months. This difference for the primary bleeding outcome was mainly attributable to the CRNM bleeding events. The edoxaban dual therapy regimen and the triple VKA regimen showed similar rates for the main efficacy outcome, a composite of death from cardiovascular causes, stroke, SEE, myocardial infarction, or definite stent thrombosis.

The edoxaban dose (60 mg once daily) investigated in the ENTRUST-AF PCI trial is approved for the prevention of stroke and SEE in patients with atrial fibrillation and has been shown to be both safe and efficacious in the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction) trial.[11] The ENTRUST-AF PCI trial was projected to show superiority in addition to non-inferiority of edoxaban in combination with a P2Y12 inhibitor compared with a VKA regimen in terms of bleeding. We found a numerically lower rate of bleeding with no significant evidence for superiority. The Kaplan-Meier curves showed an unexpected pattern with an unfavourable HR for edoxaban relative to VKA in the first 2 weeks that converted to an HR that continuously favoured edoxaban throughout the remainder of the study period. The bleeding rate with VKA was unexpectedly low in the first 2 weeks. This result might be explained by the high proportion of patients with an INR less than 2 (69% in the first week and 42% in the second week). By contrast, the full anticoagulation effect of edoxaban is present within 2 h of drug intake.[21] Of note, the 14-day bleeding rates in the VKA regimen correspond to the ones encountered in DAPT-treated patients, pointing towards possible under-anticoagulation.[22,23] ENTRUST-AF PCI is the fourth trial in a series testing a NOAC in patients with atrial fibrillation after PCI, providing consistent findings (appendix p 41).[8–10] Given the important differences in trial design, it is impossible to conclude whether the reduction in risk of bleeding that was seen with the NOAC was due to the use of the new drug, the reduced dose, or the discontinuation of aspirin. The primary bleeding outcomes were analysed primarily for the intention-to-treat population and repeated, for sensitivity reasons, for the on-treatment population. For a trial in which both non-inferiority and superiority hypotheses are of interest, both intention-to-treat and on-treatment analyses are relevant.[24,25] The analyses for the primary bleeding outcomes demonstrated consistent findings.

No significant differences were observed for the composite outcome of cardiovascular death, stroke, SEE, myocardial infarction, and definite stent thrombosis or for the individual components between the two treatment groups. The overall annual stroke rate was low and similar to the other NOAC AF PCI trials.[8–10] Of note, relative to the stroke rate, the bleeding risk according to our primary outcome definition was approximately 15 times higher. Our study was underpowered to detect small but potentially clinically meaningful differences among less frequent ischaemic outcomes. However, a very early numerical increase in ischaemic events (myocardial infarction, stent thrombosis, and cardiovascular death) was noted in patients without aspirin. The consistency of the trends among all NOAC AF PCI trials toward numerically more myocardial infarctions and stent thromboses in patients with very early withdrawal of aspirin therapy raises concerns. This finding might be attributed to response variability and efficacy of clopidogrel as a single antiplatelet drug when the carryover effect from the periprocedural antiplatelet therapy (including aspirin) is over.[26,27]

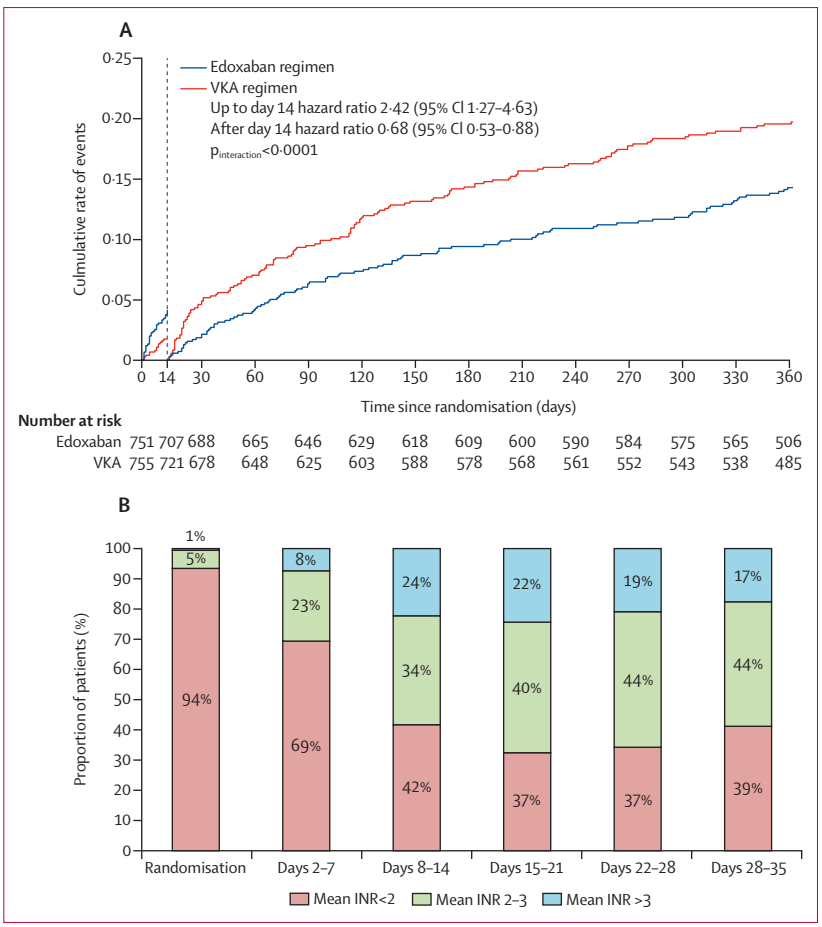

Figure 3: **Landmark analysis for the primary outcome of major or CRNM bleeding with a landmark at the end of day 14 (A) and distribution of INR values over the study period in patients on the VKA regimen (B)**
INR calculations are based on observed INR values. If a patient had multiple INRs within a week, mean INR was used. INR=international normalised ratio. VKA=vitamin K antagonist.

Our trial should be interpreted in light of several limitations: the median time in therapeutic range for the patients who received VKA was modestly lower than in ENGAGE AF-TIMI 48 but similar to other NOAC AF PCI studies.[8–11] However, the observed median time in therapeutic range in NOAC AF PCI trials reflects the challenges with VKA treatment in routine clinical practice. Few patients took a more potent P2Y12 inhibitor; therefore, our trial must primarily be viewed as a comparison of clopidogrel-based antiplatelet therapies, which is consistent with all previous NOAC AF PCI trials. Furthermore, our study was designed as an open-label study, with potential treatment or reporting bias, which might explain why more patients withdrew from the VKA group. 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.

In conclusion, in patients with atrial fibrillation who had PCI, the edoxaban-based dual antithrombotic therapy was non-inferior for bleeding compared with VKA-based triple antithrombotic regimen without significant differences in ischaemic events.

Contributors

PV and AG were co-principal investigators. PV, AG, MV, TL, JT, LE, RS, PL, P-ER, and WZ were collaborators and were involved in the design of the study and its implementation and contributed to all revisions of the manuscript. PV and AG wrote the first draft of the manuscript. GG contributed to all revisions of the manuscript and MV and GG provided expertise on the meta-analysis. PL was the study coordinator. VB, GC, ZL, IV, and KM provided data and contributed to revision of the manuscript. P-ER did the statistical analysis and contributed to all revisions of the manuscript. All authors critically reviewed and revised the manuscript and approved the final version.

Declaration of interests

PV has received personal fees from Daiichi Sankyo during the study; and personal fees from AstraZeneca, Bayer, and Terumo outside the submitted work. AG has received honoraria and speaker fees from AstraZeneca, Bayer Health Care, Berlin-Chemie, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Boston Scientific, Daiichi Sankyo, Medtronic, Novartis, and Omeicos. AG's research has been supported by Josef-Freitag-Stiftung and Deutsche Herzstiftung outside the submitted work. MV reports grants and personal fees from Abbott, Alvimedica, Amgen, Bayer, Bristol-Myers Squibb, Coreflow, Daiichi Sankyo, Vifor, Idorsia, Terumo, and iVascular outside the submitted work; and grants and personal fees from AstraZeneca and Medicure outside the submitted work. LE reports consultant fees, speaking honoraria, and travel expenses from Abbott, Bayer, Biosense Webster, Biotronik, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Daiichi Sankyo, Medtronic, Pfizer, and Sanofi Aventis. LE's research has been supported by the German Research Foundation (DFG) and German Heart Foundation outside the submitted work. TL reports personal fees from Abbott, Boston Scientific, Bayer, Boehringer Ingelheim, Daiichi Sankyo, and Pfizer outside the submitted work. JT reports personal fees from AstraZeneca, Bayer, and Boehringer Ingelheim outside the submitted work. KM reports salary for participation as an investigator in the ENTRUST-AF PCI trial. IV reports personal fees from Daiichi Sankyo during the study. PL, P-ER, RS, and WZ report that they are employees of Daiichi Sankyo Europe and were during the conduct of the study. GG, VB, GC, and ZL declare no competing interests.

Data sharing

The ENTRUST-AF PCI trial is sponsored by Daiichi Sankyo. Multiple substudies are predefined. Internal investigators, who actively participated in the study, and who provide a methodologically sound study proposal will be granted priority access to the study data for 60 months. After 60 months, access is extended to external investigators not affiliated to the trial. Study proposals can be filed at the Vivli website.

For **data access requests** see https://vivli.org/

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