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The ENSURE-AF trial

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Comparing TEE vs Non-TEE guided cardioversion of atrial fibrillation: the ENSURE-AF trial

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Running Head: TEE-Guided Strategy versus Conventional Anticoagulation for Cardioversion

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Abstract

Background ENSURE-AF (NCT 02072434) assessed therapy with edoxaban versus enoxaparin–warfarin in patients with nonvalvular atrial fibrillation (AF) undergoing elective electrical cardioversion (ECV).

Objectives To evaluate clinical features and primary efficacy (composite of stroke, systemic embolic events, myocardial infarction and cardiovascular mortality during study period) and safety endpoints (composite of major and clinically relevant nonmajor bleeding during on-treatment period) in patients awaiting ECV of AF with a transesophageal echocardiography (TEE)-guided versus a non-TEE guided strategy.

Methods In this prospective randomized open-label blinded endpoint study, 2199 patients were randomized to edoxaban 60 mg once daily (30 mg for creatinine clearance 15–50 mL/min, weight ≤60 kg, and/or concomitant use of P-glycoprotein inhibitor) or enoxaparin–warfarin. Primary efficacy endpoint and safety endpoint were reported. Associates of TEE use, efficacy endpoint and safety endpoint were explored using multivariable logistic regression.

Results In total, 589 patients from the edoxaban stratum and 594 from the enoxaparin-warfarin stratum were allocated to the TEE-guided strategy. Primary efficacy was similar regardless of TEE approach ($p = 0.575$). There were no significant differences in bleeding rates, regardless of TEE approach ($p = 0.677$). Independent predictors of TEE use were: history of ischaemic stroke/ transient ischaemic attack, hypertension and valvular heart disease. Mean CHA_2DS_2VASc and HAS-BLED score were independent predictors of the efficacy endpoint whilst mean age was an independent predictor of the safety endpoint.

Conclusions Thromboembolic and bleeding events were not different between patients undergoing TEE-guided strategy and in those undergoing an optimized conventional anticoagulation approach for ECV of AF.

Keywords: atrial fibrillation, cardioversion, edoxaban, oral anticoagulants, transesophageal echocardiography

Introduction

Oral anticoagulants (OAC) substantially decrease an inherent risk of stroke associated with electrical cardioversion (1, 2). According to the guidelines, patients without indications for long-term anticoagulation who have atrial fibrillation (AF) longer than 48 hours should be treated with OAC at least 3 weeks before cardioversion and 4 weeks after it (3). In case of high CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/transient ischaemic attack (TIA), vascular disease, age 65 to 74 years, sex category), this "window of opportunity" might be shorter. The presence of multiple stroke risk factors make the risk of thromboembolic complications unacceptably high (approximately 10%) when compared to patients without risk factors (1). The conversion of AF to sinus rhythm may result in thromboembolism even after short episodes (< 48 h) of the arrhythmia (4). Moreover, left atrial thrombi have been found on transesophageal echocardiography (TEE) in 4% of AF patients within the first 48 h of AF (5).

In case of the necessity of early cardioversion, a TEE-guided strategy with abbreviated anticoagulation seems to be a viable alternative to conventional 3-week anticoagulation (6-8). TEE enables physicians to precisely diagnose or exclude thrombus in the left atrial appendage or in the other cardiac chambers. This strategy is particularly beneficial in very symptomatic AF patients because cardioversion can be performed quickly where there is a thrombus-negative TEE. If thrombus in either the atrial appendage or the atrium is identified by the TEE, cardioversion should be delayed due to high risk of thromboembolism. OAC should be implemented for another 4-12 weeks to allow thrombus resolution. Another TEE after prolonged anticoagulation should be considered in such cases to evaluate thrombus presence (8). Cardioversion may be safely performed in case of absence of thrombus (6).

Current data support the use of rivaroxaban, dabigatran, apixaban or edoxaban or anticoagulation with optimally-managed vitamin K antagonists (VKA) [with International Normalised Ratio (INR) within range 2.0-3.0] in patients scheduled for cardioversion (7, 9, 10). The benefits of non-vitamin K antagonist oral anticoagulants (NOACs) include a faster onset of action than VKA; also, there is no need for bridging during treatment, and no delay associated with waiting for a therapeutic INR because of no need of serial analysis of hemostatic parameters. However, strict adherence to the NOACs is of critical importance (8).

The EdoxabaN versus warfarin in subjectS UndeRgoing cardiovErsion Of Atrial Fibrillation (ENSURE-AF) trial (NCT 02072434) was the largest prospective study of anticoagulation for patients with non-valvular AF scheduled for electrical cardioversion. The aim of this ancillary analysis from the ENSURE-AF trial was to evaluate the primary efficacy and safety endpoints in patients awaiting elective electrical cardioversion of AF with a TEE-guided versus a non-TEE guided strategy.

Methods

The design of the ENSURE-AF trial (NCT 02072434) have been described previously (11, 12). It was a multicenter, prospective, randomized, open-label, blinded endpoint evaluation trial where patients with non-valvular AF (of duration from 48 hours to 12 months) undergoing elective electrical cardioversion were randomized (1:1) to receive either edoxaban 60 mg once-daily (QD; 30 mg QD for creatinine clearance [CrCl] of 15–50 mL/min, weight ≤60 kg, and/or concomitant use of P-glycoprotein inhibitor) or enoxaparin-warfarin within each stratum (ie, stratification according to cardioversion approach to TEE-guided or non–TEE-guided group). The intention of the enrolment was to achieve the balance of therapy assignment within each group. Patients were stratified to TEE-guided group or non-TEE-guided group, as determined by the local investigator and local standard clinical practice (at the discretion of individual investigators at local centres). There was no mandated standardised protocol.

Study investigators, statisticians and patients were not masked to the treatment allocation while the adjudication committee was.

In the TEE-guided group, TEE and cardioversion had to be done within 3 days of randomization, but could be performed on the same day. Enoxaparin and warfarin (minimum of 1 dose each) had to be continued before cardioversion in patients in the enoxaparin-warfarin group until INR of 2.0 or greater was achieved. The treatment with warfarin was adjusted to maintain the therapeutic INR level of 2.0-3.0 with INR measurements once every 2-3 days until reaching the therapeutic range. A special algorithm for the management of patients with labile INR was designed and implemented. In the enoxaparin-warfarin group, warfarin was continued from the time of obtaining INR within therapeutic range to day 28 after cardioversion.

In patients allocated to the edoxaban group, the anticoagulation had to be started at least 2 hours before cardioversion. The next dose of edoxaban was planned for the day after cardioversion and then every 24 hours up to day 28 after electrical cardioversion.

In all subjects, cardioversion was planned at a minimum of 21 days from the start of treatment. In the edoxaban group, patients were treated with edoxaban for a minimum of 21 days before cardioversion followed by the procedure and an additional 28 days of treatment. In case of spontaneous cardioversion (defined as confirmation of sinus rhythm in 12 lead electrocardiogram) in the preprocedural time patients have to complete 28 days of management from the day of spontaneous cardioversion appeared and 30 days of follow-up.

In case of thrombi on TEE, patients had the opportunity to complete 28 days of study medication. All patients were followed-up for safety for 30 days after finishing or discontinuing the therapy.

All patients with a CHA_2DS_2-VASc score ≥ 2 and male subjects with CHA_2DS_2-VASc score $=1$ (where the use of OAC is preferred over aspirin) will require to be transitioned at the end of the study treatment to a standard-of-care anticoagulant consistent with current guidelines on stroke prevention in patients with AF (8, 13). These subjects will receive the treatment chosen by the investigator.

The primary efficacy endpoint was defined as a composite of stroke, systemic embolic event (SEE), myocardial infarction (MI), and cardiovascular death analysed during the overall study period, 28 days on study drug after cardioversion and then follow-up was performed for safety for another 30 days after finishing or discontinuing the medication. The primary safety endpoint was defined as the composite of major and clinically relevant nonmajor bleeding (CRNM) analysed during the on-treatment period from the time of first dose to last dose of study drug taken + 3 days. The primary safety endpoint was evaluated in patients who received ≥ 1 dose of the study drug.

The study protocol was compliant with the Declaration of Helsinki and the International Conference on Harmonization consolidated guideline E6 for Good Clinical Practice (CPMP/ICH/135/95). A signed patient informed consent form was obtained before participation in the study.

Statistical analysis

The primary efficacy analysis was performed on the intention-to-treat population . Efficacy outcomes were analyzed during the overall study period . All patients who took at least one dose of study drug were included in primary safety analysis. Safety outcomes were analyzed during the on-treatment period, defined as the time period the subject was taking study medication plus up to 3 days after their last dose for that time period. Demographic and clinical characteristics were summarized by TEE- and non–TEE-guided ECV. Sensitivity analyses were calculated in the per-protocol population of all randomly assigned patients without any predefined major protocol deviations. The association of baseline characteristics variables with the TEE use was evaluated using univariate logistic regression analyses. The variables with statistically significant association on univariate logistic regression analysis were entered into multivariable logistic regression models to identify multivariable predictors of TEE use. The selected variables were included as predictors of efficacy endpoint or safety endpoint in a stepwise logistic regression analysis. A significance level of 0.1 is required to allow a variable into the model and for a variable to stay in the model. Odds ratios and 95% confidence intervals are shown to evaluate the difference between treatment arms.

Results

In this study, 2,199 patients were enrolled from 2014 to 2015, from 239 centers in 19 countries in Europe and the United States of America: 1,095 patients were randomized to edoxaban and 1,067 of them received study drug whilst 1,104 patients were randomized to enoxaparin-warfarin group and 1,082 subjects received study drug. From the TEE-guided stratum, 589 patients were randomized to edoxaban and 594 to enoxaparin-warfarin.

Patients in the TEE-guided group were more likely to be older (p=0.0358) and to have a higher mean CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/transient ischaemic attack (TIA), vascular disease, age 65 to 74 years, sex category) score (p=0.0046), CHA_2DS_2-VASc score ≥ 5 (p=0.0165), hypertension (p=0.0181), ischaemic stroke / transient ischaemic attack (TIA) (p=0.0077) and valvular heart disease (defined as aortic stenosis, aortic regurgitation, mitral regurgitation or mitral valve prolapse) (p < 0.0001) than those in non-TEE guided group, Table 1. There were no significant differences in mean HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalised Ratio, elderly (age > 65 years), drugs or alcohol concomitantly) score (Table 1).

There were 89 (47 in edoxaban and 42 in warfarin) patients who had a thrombus seen during the TEE. No patients with thrombus had stroke, SEE, MI or CV mortality (the composite of Stroke, SEE, MI and CV Mortality is the primary efficacy endpoint).

Patients in Austria, Belgium, Bulgaria, Czech Republic, Germany, France, Hungary, Poland and Russia were more likely to be stratified to TEE-guided group whilst patients in Denmark, Spain, United Kingdom, Israel, Italy, Netherlands and Sweden were more likely to be stratified to non-TEE approach (Table 2). None of the patients included from the UK were entered into the TEE-guided stratum.

Stroke, systemic embolic events (SEE), myocardial infarction (MI) or cardiovascular mortality occurred in 7 (0.59%) patients in the TEE-guided group and in 9 (0.89%) patients in the non-TEE-guided group [odd ratio (OR) 0.67, 95% confidence interval (CI) 0.21-2.02, p=0.575) (Table 3).

Major or clinically relevant non-major bleeding (CRNM) appeared in 16 (1.39%) patients in the TEE-guided group and in 11 (1.10%) patients in the non-TEE-guided group (OR 1.27, 95% CI

0.55-3.05, p=0.677) (Table 3). Major bleeding events occurred in 5 (0.44%) patients in the TEE-guided group and in 3 (0.30%) patients in the non-TEE-guided group (OR 1.46, 95% CI 0.28-9.41, p=0.878) (Table 3).

Factors associated with TEE use were history of ischaemic stroke / TIA, hypertension and valvular heart disease (Table 4). Associates of the efficacy endpoint were mean HAS-BLED and CHA_2DS_2VASc scores, whereas the main associate of the safety endpoint was age (see Table 5).

Discussion

In this large, prospectively collected dataset of anticoagulation for patients with nonvalvular AF scheduled for electrical cardioversion, overall rates of major cardiovascular and bleeding events were low. Second, there were no significant differences in safety and efficacy outcomes between TEE-guided and non-TEE-guided group scheduled for electrical cardioversion of nonvalvular AF. This large multinational trial also provides insights into country practice differences with regard to the popularity of TEE-guided cardioversion, and the clinical predictors of TEE use for cardioversion.

Patients stratification according to cardioversion approach (TEE or non-TEE) reflected country-specific routine standards of care and preferences. As an example, all patients in the UK were stratified to non-TEE approach whilst all patients in Belgium and approximately all patients in Germany and Hungary were stratified to TEE approach. A similar percentage of patients were qualified to TEE and non-TEE strategy in Ukraine and the United States of America.

In the Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) Multicenter Study (6), a conventional stroke prevention strategy with warfarin for 3 weeks was compared to TEE-guided strategy with short-term anticoagulation (unfractioned heparin intravenous or warfarin). There were no significant differences between the two strata in the rate of embolic events. There was no significant difference between groups in terms of death from cardiac causes. TEE-guided group had fewer total haemorrhagic events than the non-TEE guided group. Unfortunately, the ACUTE study was stopped early and was underpowered to report convincingly the outcomes of the two strategies (low rates of embolic events and major hemorrhagic events).

Data on the primary outcome (defined as ischaemic stroke and systemic embolism) in patients with TEE-guided cardioversion and with cardioversion without TEE were provided in the post-hoc analysis of data from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) (14). There was no ischaemic stroke and systemic embolism in both groups. Of note, the prevalence of congestive heart failure was lower than in the ENSURE-AF.

In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study the number of patients medicated in each arm according to TEE approach was not available and some patients had more than one cardioversion (15, 16). In one systematic review and meta-analysis (17), the subgroup analysis of the primary outcomes (defined as ischaemic stroke and systemic embolism) according to the use of TEE was performed. Results from ARISTOTLE (14), RE-LY (15) and EXplore the efficacy and safety of once-daily oral riVaroxaban for the prEvention of caRdiovascular events in patients with non-valvular aTrial fibrillation scheduled for cardioversion (X-VERT) (7) trials were analysed. RE-LY reported 2 primary outcomes in the TEE-guided group (1 of which in VKA arm and 1 in NOAC arm, risk ratio (RR) 0.27, 95% confidence interval (CI) 0.02-4.21) and 9 primary outcomes in non-TEE-guided group (6 of which in NOAC arm and 3 in VKAs arm, RR 1.16, 95% CI 0.29-4.63), whilst X-VERT reported 2 primary outcomes in TEE-guided group (0 in NOAC arm and 2 in VKA arm, RR 0.11, 95% CI 0.01-2.21) and 1 event in non-TEE-guided group (in the VKA arm, RR 0.16, 95% CI 0.01-3.94). In this meta-analysis, patients medicated with NOACs with TEE-guided cardioversion had a non-significant RR 0.18 [95% CI 0.02-1.35). This estimate did not differ from pooled analysis of NOACs versus VKA in subjects with non-TEE guided cardioversion (RR 0.75, 95% CI 0.15-3.76).

In our analysis, electrical cardioversion preceded by TEE-guided approach was comparably safe to non-TEE guided strategy with strict adherence to OAC therapy. In the above mentioned meta-analysis there was a trend towards higher safety of TEE-guided strategy which could be related to underpowered comparisons.

Similarly to our study, in the Flecainide Short-Long Trial (18) the type of treatment prior to planned elective cardioversion of persistent AF (TEE-guided approach versus anticoagulation before and after the procedure) did not affected stroke rate. Unfortunately, bleeding events before cardioversion were not counted. Moreover, the use of TEE was non-randomized what might have induced bias.

Thromboembolic and bleeding events were similar in both groups in our study probably because of optimal use of enoxaparin-warfarin therapy with acceptable time in therapeutic range and high compliance (of more than 99%) associated with management with edoxaban. The very good quality of anticoagulation therapy is one of the strengths of our study. Another strength of the trial is its prospective design which is the largest dataset comparing a NOAC (edoxaban) to warfarin in terms of efficacy and safety in the peri-cardioversion period.

Our study shows that factors associated with TEE use were history of ischaemic stroke / TIA, hypertension and valvular heart disease. TEE enables the visualization of thrombus in cardiac chambers. All forms of valvular heart diseases accompanying AF, except of mitral stenosis, do not seem to elevate the risk of thrombo-embolism beyond the level entailed by AF alone, and do not seem to be additional risk factors (19). Ischaemic stroke / TIA and hypertension are thromboembolic factors. Left atrial thrombus is present in approximately 10% of patients with nonvalvular AF and its presence is associated with a higher mean age, and greater prevalence of female gender, hypertension, diabetes mellitus and chronic heart failure (20).

For the efficacy endpoint, mean HAS-BLED and mean CHA_2DS_2VASc score were associates of outcome. Thus, the need for strict adherence to the OAC therapy has to be emphasized to patients, particularly to those with high HAS-BLED and mean CHA_2DS_2VASc score. Those patients should have been regularly reminded by physicians about the significance of OACs in stroke prevention. Regular re-assessment should be a part of a comprehensive and holistic approach to the management of high risk patients with AF which is The Atrial fibrillation Better Care (21).

In our study age was the predictor of safety endpoint. Patients aged ≥ 75 years have elevated risk for stroke and major bleeding, but the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) (22), a randomized controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with AF (WASPO) (23) and some other randomized controlled trials support the use of VKAs or NOACs in AF patients aged ≥ 75 years (24).

Limitations

This study has some limitations that should be described. The main limitation of the study is the non-randomized allocation to either of the two strategies (TEE-guided approach, non-TEE guided approach). The above mentioned two groups are not directly comparable. Therefore, this analysis

is informative, but far from conclusive. Country-specific stratification may express routine standards of care. There was no mandated standardised protocol.

Possibly, patients with greater probability of thrombus in left atrium may have been stratified to TEE-approach. Furthermore, the ENSURE-AF study was underpowered to show statistically significant differences for efficacy or safety endpoints. Moreover, the open-label study design might be related with bias in reporting outcome. Limited follow-up period appears to be also one of the study limitations.

Conclusions

There are country practice differences with regard to the popularity of TEE-guided cardioversion, and the clinical predictors of using this strategy. Major cardiovascular events and bleeding outcomes were similar in patients undergoing TEE-guided strategy relative to those undergoing an optimized conventional anticoagulation approach for electrical cardioversion of AF, despite a higher CHA_2DS_2-VASc score and more prevalent valvular heart disease and prior stroke in the former.

Declaration of Interests

Jose Merino received personal fees from Abbott, Bayer, Biotronic, Boston Scientific, Bristol-Myers Squibb, Cardiome, Daiichi Sankyo, LivaNova, Medtronic, Pfizer, and Sanofi outside the submitted work.

Raffaele De Caterina reports Steering Committee membership and National Coordination for Italy of several studies on NOACs in cardiovascular disease, including APPRAISE-2, ARISTOTLE, AVERROES, ENGAGE AF-TIMI 38, Re-DUAL PCI; as well as fees, honoraria and research funding from Sanofi- Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Novartis, Merck, Portola.

James Jin is an employee of Daiichi Sankyo.

Kurt Huber received personal fees from Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, and Pfizer outside the submitted work

Michael Melino are: Employees of Daiichi Sankyo at the time of writing.

Andreas Goette, has 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, Pfizer, and Sanofi-Aventis.

Gregory Y.H. Lip was consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally.

Monika Kozieł reported no conflict of interest.

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Table 1. Baseline demographics according to electrical cardioversion approach

Variable	TEE-guided group n = 1183	Non-TEE-guided group n = 1016	p-value
Age, mean ± SD	64.7±10.8	63.7±10.2	0.0358
Age ≥ 75 years, n (%)	222 (18.8)	137 (13.5)	0.0008
Male sex, n (%)	774 (65.4)	669 (65.8)	0.8364
CHA2DS2-VASc, mean ± SD	2.7±1.5	2.5±1.4	0.0046
CHA2DS2-VASc ≥ 5, n (%)	42 (3.6)	19 (1.9)	0.0165
Ischaemic stroke/TIA, n (%)	87 (7.4)	47 (4.6)	0.0077
Hypertension, n (%)	945 (79.9)	769 (75.7)	0.0181
Diabetes, n (%)	220 (18.6)	195 (19.2)	0.7217
Congestive heart failure, n (%)	517 (43.7)	443 (43.6)	0.9624
Myocardial infarction, n (%)	73 (6.2)	74 (7.3)	0.2976
Valvular heart disease	339 (28.7)	151 (14.9)	<0.0001
HAS-BLED, mean ± SD	0.9±0.80	0.9±0.77	0.2471

TEE, transesophageal echocardiography, CHA2DS2-VASc; congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke/transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category, HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalised Ratio, elderly (age > 65 years), drugs or alcohol concomitantly

Table 2. Country-specific stratification of patients according to electrical cardioversion approach

Country, n (%)	Non-TEE	TEE	Total
Austria	6 (18.8)	26 (81.3)	32
Belgium	0 (0.0)	41 (100.0)	41
Bulgaria	42 (33.6)	83 (66.4)	125
Czech Republic	80 (46.2)	93 (53.8)	173
Germany	4 (3.3)	119 (96.8)	123
Denmark	43 (75.4)	14 (24.6)	57
Spain	92 (64.8)	50 (35.2)	142
France	10 (25.6)	29 (74.4)	39
United Kingdom	159 (100.0)	0 (0.0)	159
Hungary	1 (0.6)	178 (99.4)	179
Israel	51 (62.2)	31 (37.8)	82
Italy	47 (68.1)	22 (31.9)	69
Netherlands	42 (89.4)	5 (10.6)	47
Poland	12 (22.2)	42 (77.8)	54
Russia	48 (39.3)	74 (60.7)	122
Sweden	9 (64.3)	5 (35.7)	14
Ukraine	220 (51.2)	210 (48.8)	430
United States of America	49 (51.6)	46 (48.4)	95

TEE, transesophageal echocardiography.

Table 3. Efficacy and safety outcomes rates according to electrical cardioversion approach

	TEE-guided group n = 1183	**Non-TEE-guided group n = 1016**	**p-value**
First stroke, SEE, MI or cardiovascular mortality			
N	1183	1016	
n (%)	7 (0.59)	9 (0.89)	
OR (95% CI)	0.67 (0.21-2.02)		0.575
Major or CRNM bleeding events			
N	1147	1002	
n (%)	16 (1.39)	11 (1.10)	
OR (95% CI)	1.27 (0.55-3.05)		0.677
Major bleeding events			
N	1147	1002	
n (%)	5 (0.44)	3 (0.30)	
OR (95% CI)	1.46 (0.28-9.41)		0.878

CRNM, clinically relevant non-major bleeding, MI, myocardial infarction, OR, odds ratio, CI, confidence interval, SEE, systemic embolic events, TEE, transesophageal echocardiography

Table 4. Independent predictors of the use of TEE

	Multivariate analysis		
	OR	**95% CI**	**p-value**
History of ischaemic stroke/ transient ischaemic attack (no versus yes)	0.66	0.45-0.95	0.027
Hypertension (no versus yes)	0.80	0.65-0.98	0.031
Valvular heart disease (no versus yes)	0.44	0.35-0.54	<0.001

CI, confidence interval, OR, odds ratio

Table 5. Independent predictors of safety or efficacy endpoints

	Multivariate analysis		
	OR	**95% CI**	**p-value**
Predictors of safety endpoints			
Age	1.05	1.01-1.09	0.022
Predictors of efficacy endpoints			
Mean CHA_2DS_2VASc score	1.47	1.01-2.12	0.042
Mean HAS-BLED score	1.78	0.95-3.33	0.073

CHA2DS2-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke/transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category CI, confidence interval, HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalised Ratio, elderly (age > 65 years), drugs or alcohol concomitantly OR, odds ratio