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Edoxaban versus enoxaparin–warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial

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Summary

Background Edoxaban, an oral factor Xa inhibitor, is non-inferior for prevention of stroke and systemic embolism in patients with atrial fibrillation and is associated with less bleeding than well controlled enoxaparin–warfarin therapy. Few safety data about edoxaban in patients undergoing electrical cardioversion are available.

Methods We did a multicentre, prospective, randomised, open-label, blinded-endpoint evaluation trial in 19 countries with 239 sites comparing edoxaban 60 mg per day with enoxaparin–warfarin in patients undergoing electrical cardioversion of non-valvular atrial fibrillation. The dose of edoxaban was reduced to 30 mg per day if one or more factors (creatinine clearance 15–50 mL/min, low bodyweight [≤60 kg], or concomitant use of P-glycoprotein inhibitors) were present. Block randomisation (block size four)—stratified by cardioversion approach (transoesophageal echocardiography [TEE] or not), anticoagulant experience, selected edoxaban dose, and region—was done through a voice-web system. The primary efficacy endpoint was a composite of stroke, systemic embolic event, myocardial infarction, and cardiovascular mortality, analysed by intention to treat. The primary safety endpoint was major and clinically relevant non-major (CRNM) bleeding in patients who received at least one dose of study drug. Follow-up was 28 days on study drug after cardioversion plus 30 days to assess safety. This trial is registered with ClinicalTrials.gov, number NCT02072434.

Findings Between March 25, 2014, and Oct 28, 2015, 2199 patients were enrolled and randomly assigned to receive edoxaban (n=1095) or enoxaparin–warfarin (n=1104). The mean age was 64 years (SD 10·54) and mean CHA_2DS_2-VASc score was 2·6 (SD 1·4). Mean time in therapeutic range on warfarin was 70·8% (SD 27·4). The primary efficacy endpoint occurred in five (<1%) patients in the edoxaban group versus 11 (1%) in the enoxaparin–warfarin group (odds ratio [OR] 0·46, 95% CI 0·12–1·43). The primary safety endpoint occurred in 16 (1%) of 1067 patients given edoxaban versus 11 (1%) of 1082 patients given enoxaparin–warfarin (OR 1·48, 95% CI 0·64–3·55). The results were independent of the TEE-guided strategy and anticoagulation status.

Interpretation ENSURE-AF is the largest prospective randomised clinical trial of anticoagulation for cardioversion of patients with non-valvular atrial fibrillation. Rates of major and CRNM bleeding and thromboembolism were low in the two treatment groups.

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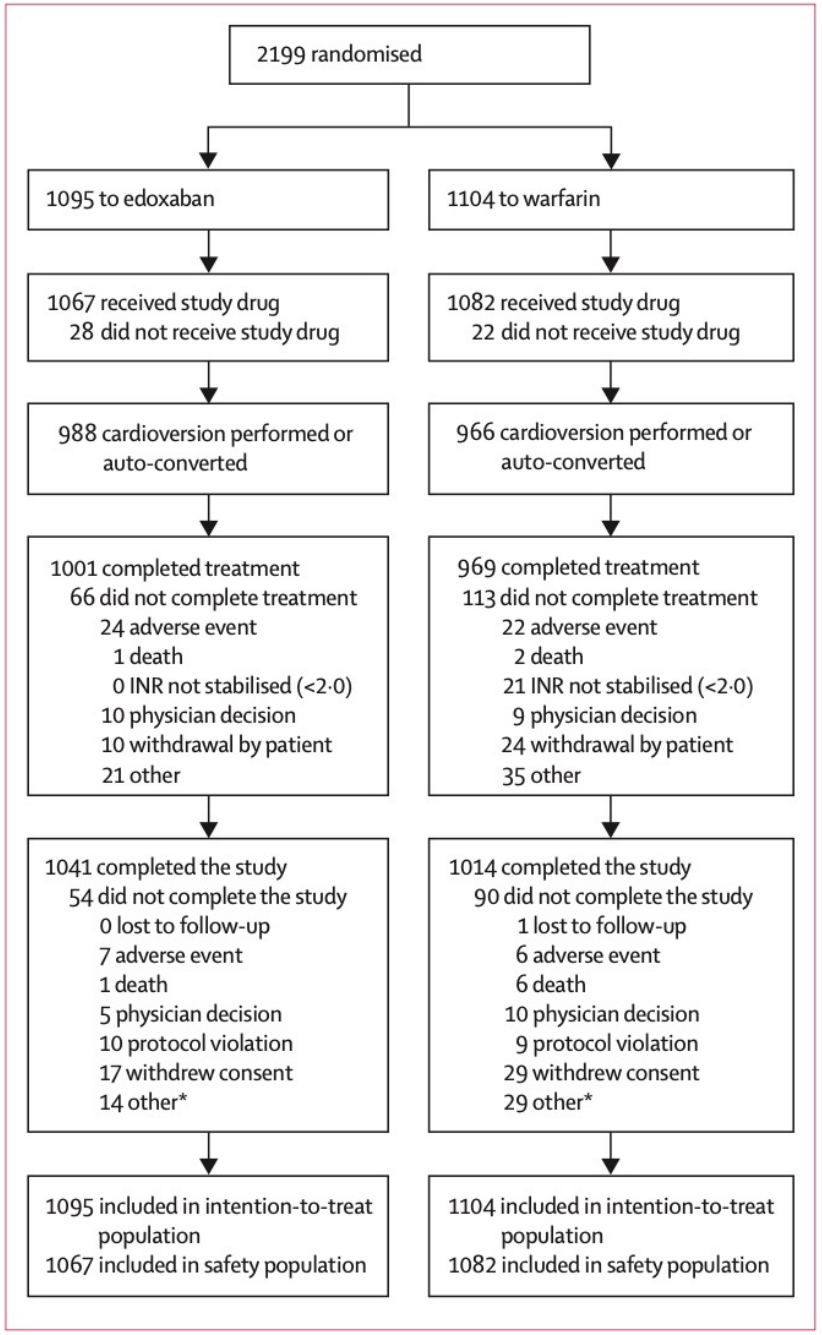

Figure: **Study design**
*Multiple reasons, mainly due to exclusion criteria, technical issues with TEE performance, or non-stabilised INR. TEE=transoesophageal echocardiography. INR=international normalised ratio.

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	Total by treatment		Transoesophageal echocardiography stratum		Non-transoesophageal echocardiography stratum	
	Edoxaban (n=1095)	Enoxaparin–warfarin (n=1104)	Edoxaban (n=589)	Enoxaparin–warfarin (n=594)	Edoxaban (n=506)	Enoxaparin–warfarin (n=510)
Age						
Mean age, years	64·3 (10·3)	64·2 (10·8)	64·9 (10·5)	64·5 (11·2)	63·6 (10·1)	63·8 (10·3)
<75 years	923 (84%)	917 (83%)	482 (82%)	479 (81%)	441 (87%)	438 (86%)
≥75 years	172 (16%)	187 (17%)	107 (18%)	115 (19%)	65 (13%)	72 (14%)
Sex						
Men	721 (66%)	722 (65%)	385 (65%)	389 (65%)	336 (66%)	333 (65%)
Women	374 (34%)	382 (35%)	204 (35%)	205 (35%)	170 (34%)	177 (35%)
Race (proportion white)	1062 (97%)	1086 (98%)	570 (97%)	581 (98%)	492 (97%)	505 (99%)
Region						
Eastern Europe	650 (59%)	649 (59%)	397 (67%)	398 (67%)	253 (50%)	251 (49%)
Middle East or Africa	39 (4%)	43 (4%)	15 (3%)	16 (3%)	24 (5%)	27 (5%)
North America	46 (4%)	49 (4%)	22 (4%)	24 (4%)	24 (5%)	25 (5%)
Western Europe	360 (33%)	363 (33%)	155 (26%)	156 (26%)	205 (41%)	207 (41%)
Bodyweight						
Mean weight, kg	90·9 (18·3)	91·2 (19·0)	90·3 (18·6)	90·3 (17·2)	91·6 (18·1)	92·2 (20·9)
≤60 kg	21 (2%)	33 (3%)	12 (2%)	16 (3%)	9 (2%)	17 (3%)
Body-mass index						
Mean body-mass index, kg/m²	30·6 (5·7)	30·7 (5·8)	30·4 (5·6)	30·4 (5·4)	31·0 (5·7)	31·0 (6·3)
<30 kg/m²	560 (51%)	559 (51%)	322 (55%)	307 (52%)	238 (47%)	252 (49%)
Edoxaban dose 30 mg*	94 (9%)	91 (8%)	51 (9%)	51 (9%)	43 (8%)	40 (8%)
Creatinine clearance	94·0 (35·7)	94·1 (34·7)	91·9 (35·8)	91·8 (32·0)	96·3 (35·6)	96·8 (37·4)
Mean creatinine clearance						
≤50 mL/min	83 (8%)	76 (7%)	47 (8%)	43 (7%)	36 (7%)	33 (6%)
>50 and <80 mL/min	304 (28%)	315 (29%)	175 (30%)	171 (29%)	129 (25%)	144 (28%)
≥80 mL/min	643 (59%)	636 (58%)	328 (56%)	332 (56%)	315 (62%)	304 (60%)
Anticoagulant experienced	791 (72%)	808 (73%)	426 (72%)	440 (74%)	365 (72%)	368 (72%)
Current user of vitamin K antagonist†	513 (47%)	558 (51%)	251 (43%)	294 (49%)	262 (52%)	264 (52%)
Current user of non-vitamin K antagonist oral anticoagulant†	157 (14%)	148 (13%)	103 (17%)	101 (17%)	54 (11%)	47 (9%)
CHA_2DS_2-VASc score (mean)	2·6 (1·4)	2·6 (1·4)	2·7 (1·5)	2·7 (1·5)	2·5 (1·5)	2·5 (1·3)
0–1	252 (23%)	232 (21%)	132 (22%)	121 (20%)	120 (24%)	111 (22%)
2	305 (28%)	306 (28%)	161 (27%)	160 (27%)	144 (28%)	146 (29%)
>2	536 (49%)	560 (51%)	295 (50%)	309 (52%)	241 (48%)	251 (49%)
Atrial fibrillation history						
Paroxysmal (≤7 days)	208 (19%)	207 (19%)	138 (23%)	132 (22%)	70 (14%)	75 (15%)
Persistent (>7 days, <1 year)	887 (81%)	890 (81%)	451 (77%)	458 (77%)	436 (86%)	432 (85%)
Medical history						
Congestive heart failure	476 (43%)	484 (44%)	258 (44%)	259 (44%)	218 (43%)	225 (44%)
Coronary artery disease	181 (17%)	197 (18%)	89 (15%)	111 (19%)	92 (18%)	86 (17%)
Hypertension	850 (78%)	864 (78%)	471 (80%)	474 (80%)	379 (75%)	390 (76%)
Diabetes	218 (20%)	197 (18%)	115 (20%)	105 (18%)	103 (20%)	92 (18%)
Ischaemic heart disease	2 (<1%)	3 (<1%)	2 (<1%)	1 (<1%)	0	2 (<1%)
Ischaemic stroke or transient ischaemic attack	68 (6%)	66 (6%)	42 (7%)	45 (8%)	26 (5%)	21 (4%)
Life-threatening bleed	3 (<1%)	3 (<1%)	3 (1%)	1 (<1%)	0	2 (<1%)

*Dose reduction factors were: creatinine clearance 15–50 mL/min, low bodyweight (≤60 kg), or concomitant use of P-glycoprotein inhibitors (excluding amiodarone).
†Current defined as using vitamin K antagonist or non-vitamin K antagonist oral anticoagulant at randomisation or within 30 days before randomisation. Percentages are based on the numbers of anticoagulant experienced.

Table 1: **Demographics and baseline characteristics (intention-to-treat population)**

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	Total by treatment			Transoesophageal echocardiography stratum			Non-transoesophageal echocardiography stratum		
	Edoxaban (n=1095)	Warfarin plus enoxaparin (n=1104)	OR (95% CI)	Edoxaban (n=589)	Warfarin plus enoxaparin (n=594)	OR (95% CI)	Edoxaban (n=506)	Warfarin plus enoxaparin (n=510)	OR (95% CI)
Primary endpoint*	5 (<1%)	11 (1%)	0·46 (0·12–1·43)	2 (<1%)	5 (1%)	0·40 (0·04–2·47)	3 (1%)	6 (1%)	0·50 (0·08–2·36)
Stroke	2 (<1%)	3 (<1%)	0·67 (0·06–5·88)	0	2 (<1%)	..	2 (<1%)	1 (<1%)	..
Intracranial haemorrhage	0	0	..	0	0	..	0	0	..
Systemic embolic event	1 (<1%)	1 (<1%)	..	1 (<1%)	1 (<1%)	..	0	0	..
Myocardial infarction	2 (<1%)	3 (<1%)	0·67 (0·06–5·88)	0	2 (<1%)	..	2 (<1%)	1 (<1%)	..
Cardiovascular death	1 (<1%)	5 (<1%)	0·20 (0–1·80)	1 (<1%)	0	..	0	5 (1%)	..

OR=odds ratio. *Primary endpoint was composite of stroke, systemic embolic event, myocardial infarction, and cardiovascular mortality.

Table 2: **Primary efficacy results in the intention-to-treat population for the overall study period**

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	Total by treatment			Transoesophageal echocardiography stratum			Non-transoesophageal echocardiography stratum		
	Edoxaban (n=1067)	Warfarin plus enoxaparin (n=1082)	OR (95% CI)	Edoxaban (n=570)	Warfarin plus enoxaparin (n=577)	OR (95% CI)	Edoxaban (n=497)	Warfarin plus enoxaparin (n=505)	OR (95% CI)
First major or clinically relevant non-major bleeding	16 (1%)	11 (1%)	1·48 (0·64–3·55)	11 (2%)	5 (1%)	2·25 (0·72–8·31)	5 (1%)	6 (1%)	0·85 (0·20–3·35)
Major bleed	3 (<1%)	5 (<1%)	0·61 (0·09–3·13)	3 (1%)	2 (<1%)	1·52 (0·17–18·27)	0	3 (1%)	..
Intracranial haemorrhage	0	0	..	0	0	..	0	0	..
Gastrointestinal bleed	1 (<1%)	1 (<1%)	..	1 (<1%)	0	..	0	1 (<1%)	..
Fatal non-intracerebral haemorrhage	0	1 (<1%)	..	0	0	..	0	1 (<1%)	..
Life-threatening bleed	1 (<1%)	1 (<1%)	..	1 (<1%)	1 (<1%)	..	0	0	..
Other*	1 (<1%)	2 (<1%)	..	1 (<1%)	1 (<1%)	..	0	1 (<1%)	..
Clinically relevant non-major bleeding	14 (1%)	7 (1%)	2·04 (0·77–6·00)	9 (2%)	3 (1%)	3·07 (0·76–17·70)	5 (1%)	4 (1%)	1·27 (0·27–6·45)
All bleeding	32 (3%)	35 (3%)	0·93 (0·55–1·55)	17 (3%)	17 (3%)	1·01 (0·48–2·13)	15 (3%)	18 (4%)	0·84 (0·39–1·79)

*Other included haematuria in the edoxaban group and intra-articular bleeding in the warfarin–enoxaparin group.

***Table* 3: Safety outcomes as adjudicated bleeding events (safety population, on-treatment period)**

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	Edoxaban (n=1030)*	Warfarin plus enoxaparin (n=1027)*	OR (95% CI)
Number of events (%)	8 (1%)	16 (1%)	0·50 (0·19–1·25)
Creatinine clearance ≤50 mL/min	0/83 (0%)	2/76 (3%)	0·50 (0·00–3·17)
Creatinine clearance >50 to <80 mL/min	3/304 (1%)	7/315 (2%)	0·44 (0·07–1·95)
Creatinine clearance ≥80 mL/min	4/643 (1%)	6/636 (1%)	0·66 (0·14–2·79)

Net clinical benefit is a composite of stroke, systemic embolic event, myocardial infarction, cardiovascular mortality, and major bleedings. OR=odds ratio. *Some patients did not have baseline creatinine clearance measurements.

Table 4: **Net clinical benefit in the intention-to-treat population for the overall period, by creatinine clearance strata**

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	Total by treatment		Transoesophageal echocardiography stratum		Non-transoesophageal echocardiography stratum	
	Edoxaban (n=1067)	Warfarin plus enoxaparin (n=1082)	Edoxaban (n=570)	Warfarin plus enoxaparin (n=577)	Edoxaban (n=497)	Warfarin plus enoxaparin (n=505)
Any adverse events	320 (30%)	357 (33%)	152 (27%)	181 (31%)	168 (34%)	176 (35%)
Related adverse events	54 (5%)	69 (6%)	29 (5%)	44 (8%)	25 (5%)	25 (5%)
Serious adverse events	85 (8%)	83 (8%)	48 (8%)	48 (8%)	37 (7%)	35 (7%)
Related serious adverse events	11 (1%)	15 (1%)	7 (1%)	13 (2%)	4 (1%)	2 (<1%)
Severe adverse events	29 (3%)	25 (2%)	16 (3%)	11 (2%)	13 (3%)	14 (3%)
Related severe adverse events	4 (<1%)	5 (<1%)	3 (1%)	5 (1%)	1 (<1%)	0
Adverse events leading to death	1 (<1%)	5 (<1%)	1 (<1%)	0	0	5 (1%)
Adverse events leading to study drug interruption or discontinuation	49 (5%)	53 (5%)	25 (4%)	28 (5%)	24 (5%)	25 (5%)

Table 5: **Treatment-emergent adverse events in the safety population for the overall study period**

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Research in context

Evidence before this study

Post-hoc studies of cardioversion, although limited because of lengthy anticoagulation before the cardioversion, have shown a good safety profile for non-vitamin K antagonist oral anticoagulants (NOACs). One prospective study evaluating rivaroxaban against non-optimised vitamin K antagonist management suggested a good safety profile of this agent. All of these studies are limited by small numbers. Data about the use of NOACs for peri-cardioversion have been provided by post-hoc subgroup analyses from large phase 3 stroke prevention trials and one randomised trial. There are limited data with edoxaban in the setting of electrical cardioversion of non-valvular atrial fibrillation.

Added value of this study

The ENSURE-AF study is the largest randomised clinical trial of anticoagulation for cardioversion in patients with atrial fibrillation, with findings showing very low event rates against exceptionally well controlled warfarin. This trial also provides the largest prospective trial data for an NOAC (ie, edoxaban) in this clinical setting. Edoxaban was also compared against optimised standard care (warfarin with enoxaparin bridging), with the time in the therapeutic range on warfarin being more than 70%, and excellent adherence to edoxaban therapy with more than 99% compliance.

Implications of all the available evidence

The NOACs seem to be safe and user friendly, and provide rapid onset of oral anticoagulation; they provide an alternative to heparin plus warfarin.

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