Edoxaban vs Enoxaparin/Warfarin in Subjects Undergoing Cardioversion of Atrial Fibrillation – The Randomized ENSURE-AF Study

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Declaration of interest

- **AG** has served as a consultant for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and Pfizer; and as a speaker for AstraZeneca, Bayer, Berlin-Chemie, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Pfizer, and Sanofi-Aventis

Background

- In AF patients undergoing cardioversion, current guidelines recommend ≥3 weeks of therapeutic anticoagulation prior to cardioversion and a continuation of anticoagulation for ≥4 weeks post-cardioversion and longer in patients at risk of AF recurrence or if stroke risk factors are present[1,2]
- VKAs have traditionally been used as oral anticoagulation pericardioversion,[1,2] but VKAs are associated with inter- and intrapatient variability, requiring regular monitoring to ensure a target INR range of 2.0 to 3.0
- Current data from post hoc analyses of the phase 3 NOAC studies[3-6] and 1 randomized trial (X-VeRT)[7] suggest NOACs could be a safe alternative to VKAs for pericardioversion anticoagulation

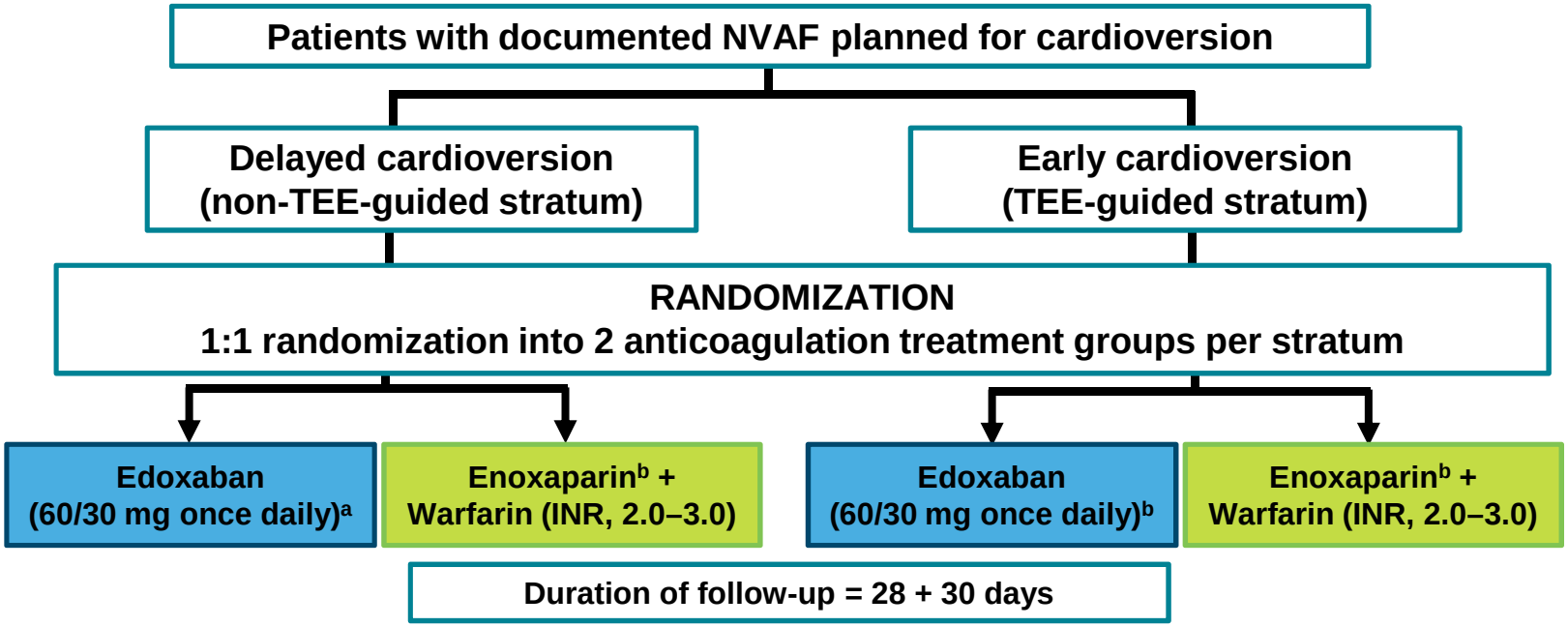
AF = atrial fibrillation; INR = international normalized ratio; NOAC = nonvitamin K antagonist oral anticoagulant; VKA = vitamin K antagonist

1. January CT, et al. *Circulation*. 2014;130:e199-e267 2. Klein AL, et al. *N Engl J Med*. 2001;344:1411-20 3. Nagarakanti R, et al. *Circulation.* 2011;123:131-6 4. Piccini JP, et al. *J Am Coll Cardiol*. 2013;61:1998-2006 5. Flaker G, et al. *J Am Coll Cardiol.* 2014;63:1082-7 6. Plitt A, et al. *Clin Cardiol.* 2016;39:345-6 7. Cappato R, et al. *Eur Heart J.* 2014;35:3346-55

Purpose and key points about methods

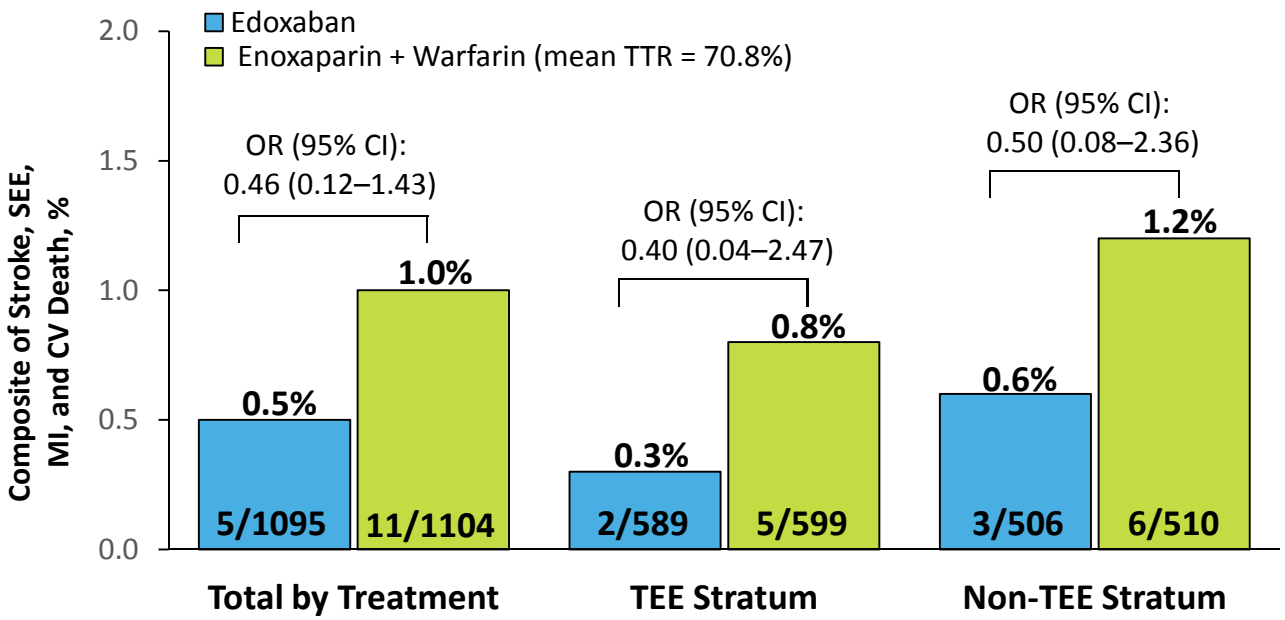
A prospective randomized trial, assessing the efficacy and safety of edoxaban compared to the best possible conventional therapy (enoxaparin/warfarin) in patients with NVAF undergoing cardioversion.

The ENSURE-AF study aimed to demonstrate that once-daily edoxaban is a treatment option for patients undergoing cardioversion.



[a] Patients meeting ≥1 of the following criteria: CrCl ≥15 mL/min and ≤50 mL/min; low body weight (≤60 kg); or concomitant use of P-gp inhibitors (with the exception of amiodarone)
[b] Patients with INR at randomization ≥2 did not require enoxaparin
CrCl = creatinine clearance; INR = international normalized ratio; NVAF = nonvalvular atrial fibrillation; TEE = transesophageal echocardiography
Lip GY, et al. *Am Heart J.* 2015;169:597-604

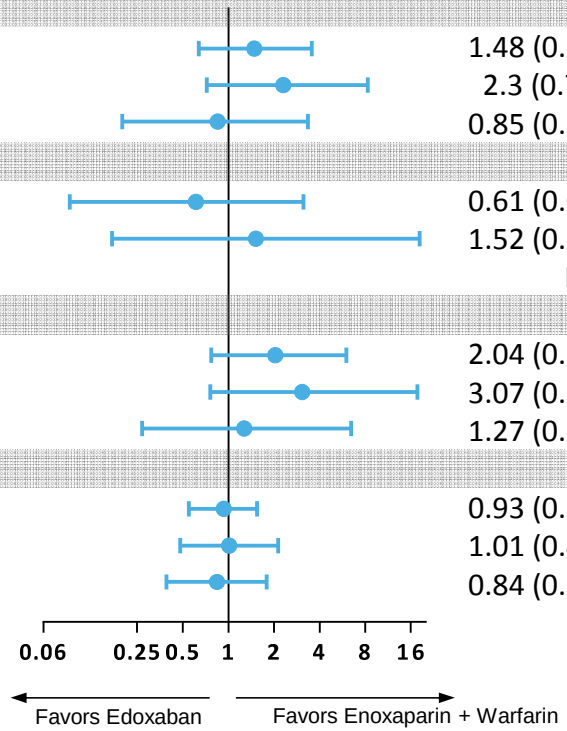
Results – Primary efficacy outcomes[a]



[a] Composite of stroke, SEE, MI, and CV mortality assessed in the ITT population during overall period
CI = confidence interval; CV = cardiovascular; ITT = intent-to-treat; MI = myocardial infarction; OR = odds ratio; SEE = systemic embolic event; TEE = transesophageal echocardiography; TTR = time in therapeutic range

Results – Adjusted safety outcomes[a]

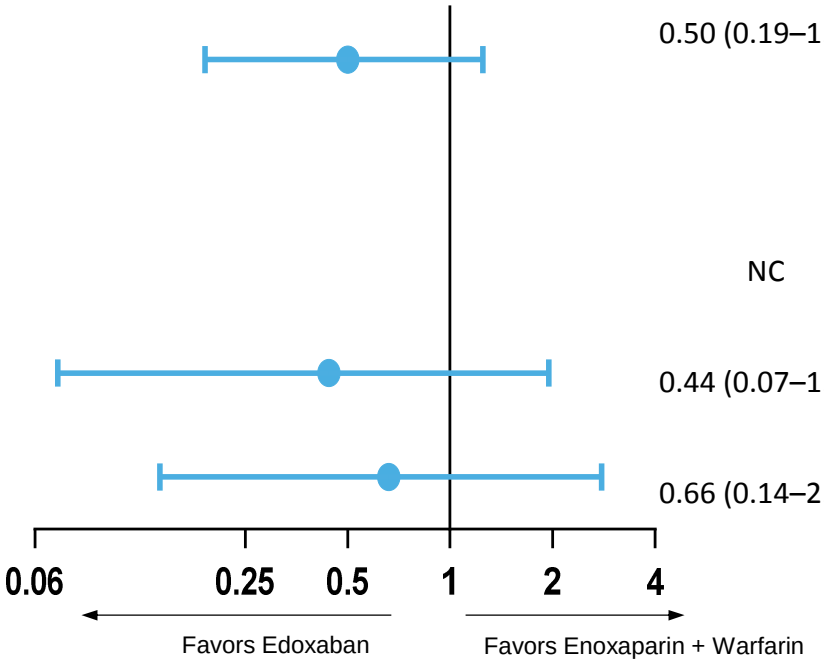
	Event Rate, % (n/N)		OR (95% CI)
	Edoxaban	Enoxaparin + Warfarin	
First Major or CRNM Bleeding			
Total by Treatment	1.5 (16/1067)	1.0 (11/1082)	1.48 (0.64–3.55)
TEE Stratum	1.9 (11/570)	0.9 (5/577)	2.3 (0.72–8.31)
Non-TEE Stratum	1.0 (5/497)	1.2 (6/505)	0.85 (0.20–3.35)
Major Bleeding			
Total by Treatment	0.3 (3/1067)	0.5 (5/1082)	0.61 (0.09–3.13)
TEE Stratum	0.5 (3/570)	0.3 (2/577)	1.52 (0.17–18.27)
Non-TEE Stratum	0	0.6 (3/505)	NC
CRNM Bleeding			
Total by Treatment	1.3 (14/1067)	0.6 (7/1082)	2.04 (0.77–6.00)
TEE Stratum	1.6 (9/570)	0.5 (3/577)	3.07 (0.76–17.70)
Non-TEE Stratum	1.0 (5/497)	0.8 (4/505)	1.27 (0.27–6.45)
Any Bleeding			
Total by Treatment	3.0 (32/1067)	3.2 (35/1082)	0.93 (0.55–1.55)
TEE Stratum	3.0 (17/570)	2.9 (17/577)	1.01 (0.48–2.13)
Non-TEE Stratum	3.0 (15/497)	3.6 (18/505)	0.84 (0.39–1.79)



[a] In the safety population assessed during the on-treatment period
CI = confidence interval; CRNM = clinically relevant nonmajor; NC = not calculated; OR = odds ratio; TEE = transesophageal echocardiography

Results – Net clinical outcome[a]

	Event Rate, % (n/N)		Edoxaban vs Enoxaparin + Warfarin
	Edoxaban	Enoxaparin + Warfarin	OR (95% CI)
Overall	0.7 (8/1095)	1.4 (16/1104)	0.50 (0.19–1.25)
By CrCl, mL/min			
≤50	0 (0/83)	2.63 (2/76)	NC
>50–<80	0.99 (3/304)	2.22 (7/315)	0.44 (0.07–1.95)
≥80	0.62 (4/643)	0.94 (6/636)	0.66 (0.14–2.79)



[a] Composite of stroke, SEE, MI, CV mortality, major bleeding assessed in the ITT population during the entire study duration
CI = confidence interval; CrCl = creatinine clearance; CV = cardiovascular; ITT = intent-to-treat; MI = myocardial infarction; NC = not calculated; OR = odds ratio; SEE = systemic embolic event

Conclusions

ENSURE-AF study is the largest prospective randomized clinical trial to date of anticoagulation for electrical cardioversion in NVAF

- Overall, the rates of the composite primary efficacy endpoint and of major or CRNM bleeding were similarly low in both treatment arms, irrespective of a TEE-guided strategy
- The net clinical outcome was numerically lower but not statistically different in the edoxaban arm vs enoxaparin/warfarin arm
- Edoxaban is an effective and safe alternative to treatment with enoxaparin/VKA strategy for patients undergoing electrical cardioversion of nonvalvular AF and may allow prompt cardioversion to be performed following the start of anticoagulation (≥2 hours for TEE-guided strategy; ≥3 weeks for non-TEE)

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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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Additional slide: Embolic events in AF

- In AF, random electrical pulses are generated in the atrium that override the normal pacemaker and cause the atria to beat in a rapid and uncoordinated way (fibrillation).[1]
- The main complication of AF is an increased risk of stroke, with one in five of all strokes occurring as a result of AF.[2] The risk of stroke also increases with age and strokes in those with AF are nearly twice as likely to be fatal than strokes in those without AF.[2,3]

ESC AF Guidelines

- Updated on 27 August 2016
- Due to the risk of thromboembolic events in the peri-procedural period, clinical guidelines recommend anticoagulation before and after cardioversion in patients with AF.[4,5]
  - Anticoagulation with heparin or a NOAC should be initiated as soon as possible before every cardioversion of AF. For cardioversion of AF, effective anticoagulation is recommended for a minimum of 3 weeks before cardioversion.[4]
  - In patients at risk for stroke, anticoagulant therapy should be continued long-term after cardioversion according to the long-term anticoagulation recommendations, irrespective of the method of cardioversion or the apparent maintenance of sinus rhythm. In patients without stroke risk factors, anticoagulation is recommended for 4 weeks after cardioversion.[4]

1. Patient.co.uk. Atrial Fibrillation. http://www.patient.co.uk/pdf/4198.pdf (2012). Last accessed July 2016. 2. Camm, A. et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *European Heart Journal*. 2010;31:2369–429. 3. Lin, H., Wolf, P. A., Kelly-Hayes, M. & Benjamin, E. J. Stroke Severity in Atrial Fibrillation. *Stroke*. 1996;27:1760–1764. 4. Kirchhof P, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European Heart Journal.* doi:10.1093/eurheartj/ehw210. 5. January CT, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. *J Am Coll Cardiol*. 2014;64:e1-76.