Spontaneous conversion in patients with non-valvular atrial fibrillation planned for electrical cardioversion:

Cohen, Ariel; Heidbuchel, Hein; Le Heuzey, Jean-Yves; De Caterina, Raffaele; Merino, Jose L.; Jin, James; Melino, Michael; Winters, Shannon M.; Goette, Andreas; Lip, Gregory Y. H.

DOI:
10.1016/j.ahj.2018.10.008

Spontaneous conversion in patients with non-valvular atrial fibrillation planned for electrical cardioversion: A subanalysis of the ENSURE-AF trial

Ariel A. Cohen, Hein Heidbuchel, Jean-Yves Le Heuzey, Raffaele De Caterina, Jose L. Merino, James Jin, Michael Melino, Shannon M. Winters, Andreas Goette, Gregory Y.H. Lip

PII: S0002-8703(18)30304-1
DOI: https://doi.org/10.1016/j.ahj.2018.10.008
Reference: YMHJ 5796

To appear in: *American Heart Journal*

Received date: 17 April 2018
Accepted date: 28 October 2018

Please cite this article as: Ariel A. Cohen, Hein Heidbuchel, Jean-Yves Le Heuzey, Raffaele De Caterina, Jose L. Merino, James Jin, Michael Melino, Shannon M. Winters, Andreas Goette, Gregory Y.H. Lip , Spontaneous conversion in patients with non-valvular atrial fibrillation planned for electrical cardioversion: A subanalysis of the ENSURE-AF trial. Ymhj (2018), https://doi.org/10.1016/j.ahj.2018.10.008

Spontaneous conversion in patients with non-valvular atrial fibrillation planned for electrical cardioversion: a subanalysis of the ENSURE-AF trial

Ariel A. Cohen[a], Hein Heidbuchel[b], Jean-Yves Le Heuzey[c], Raffaele De Caterina[d], Jose L. Merino[e], James Jin[f], Michael Melino[f], Shannon M. Winters[g], Andreas Goette[h], Gregory Y.H. Lip[i]

[a] *Hôpital Saint Antoine, Hôpital Tenon; Université Pierre et Marie Curie (Paris VI), Paris, France*

[b] *Antwerp University and University Hospital, Cardiology, Antwerp, Belgium*

[c] *Georges Pompidou Hospital, René Descartes University, Cardiology and Arrhythmology, Paris, France*

[d] *G. d'Annunzio University, Institute of Cardiology, Chieti, Italy*

[e] *Hospital Universitario La Paz, Universidad Europea, Madrid, Spain*

[f] *Daiichi Sankyo Pharma Development, Edison, USA*

[g] *Daiichi Sankyo, Inc., Parsippany, USA*

[h] *St. Vincenz Hospital, Paderborn, Germany*

[l] *Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK*

Short title: Spontaneous conversion in non-valvular atrial fibrillation and planned electrical cardioversion

Correspondence: Professor Ariel A. Cohen, Service de Cardiologie, AP-HP – Hôpital Saint-Antoine, 184, rue du faubourg saint Antoine, Paris Cedex 12, and UPMC Université Paris Sorbonne, Paris, France, France. Tel: +33 1 49 28 28 86; Fax: +33 1 49 28 28 84.
E-mail address: ariel.cohen@aphp.fr (A.A. Cohen).

Keywords atrial fibrillation; cardioversion; anticoagulant; predictors

SHORT ABSTRACT

We investigated the characteristics of patients who underwent spontaneous conversion before scheduled cardioversion in the ENSURE-AF study, a prospective randomized clinical trial of anticoagulation in patients undergoing electrical cardioversion of non-valvular atrial fibrillation. The study demonstrated similar efficacy and safety of the oral factor Xa inhibitor edoxaban versus enoxaparin–warfarin. Spontaneous conversion occurred in 7.6% of patients, and was associated with a history of paroxysmal atrial fibrillation but not with thromboembolic or bleeding events.

Strategies for urgent restoration of sinus rhythm in patients presenting with atrial fibrillation (AF) include heart-rate control, immediate direct-current cardioversion, and pharmacological cardioversion.[1] However, cardioversion is associated with periprocedural thromboembolic events. Furthermore, AF symptoms can resolve spontaneously within 24 hours in many patients with new-onset AF.[2-4]

Rates of spontaneous conversion range from 50%[4] to 71%[3] in recent-onset AF, and shorter duration of symptoms is a significant predictor of spontaneous conversion.[5, 6] The ability to identify patients with a high probability of spontaneous conversion is important, and could be used in the decision to postpone cardioversion and avoid the risks associated with the procedure.

EdoxabaN versus warfarin in subjectS UndeRgoing cardiovErsion Of Atrial Fibrillation (ENSURE-AF) is the largest prospective randomized clinical trial of anticoagulation in patients undergoing electrical cardioversion of non-valvular AF; the study demonstrated similar efficacy and safety of the oral factor Xa inhibitor edoxaban versus enoxaparin–warfarin.[7] We performed an ancillary analysis using the ENSURE-AF data to determine the incidence of spontaneous conversion. Our aim was, first, to compare the data from patients with spontaneous conversion to those with non-spontaneous conversion; second, to describe the characteristics and outcomes of patients with spontaneous conversion; and third, to identify independent predictors of spontaneous conversion, to more accurately identify patients who are likely to undergo spontaneous conversion to sinus rhythm.

Methods

The design of the ENSURE-AF study (ClinicalTrials.gov, number NCT02072434) has been described elsewhere.[7, 8] The study design, and the distribution of spontaneous conversion in the 2 groups and according to use of transesophageal echocardiography (TEE), is illustrated in Figure 1.

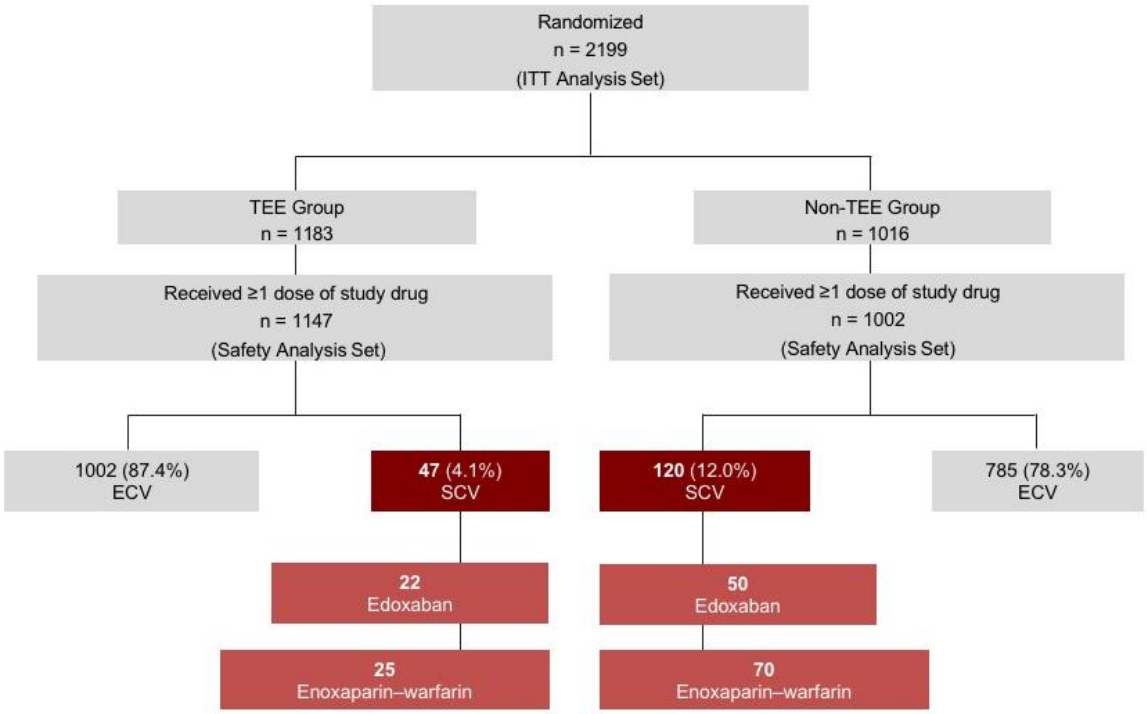

Figure 1. Patient disposition.

ECV, electrical cardioversion; ITT, intention to treat; SCV, spontaneous conversion, TEE, transesophageal echocardiography.

In both treatment groups, cardioversion had to be performed within 3 days of randomization (TEE and cardioversion could be performed on the same day). All patients were followed for safety for 30 days after completing or discontinuing the treatment.

Patients with spontaneous conversion in the preprocedural period (confirmed by an electrocardiogram recording of sinus rhythm, assessed by the investigator) needed to complete 28 days of treatment from the day that spontaneous conversion was noted, and completed 30 days of follow-up.

The primary efficacy endpoint was the composite of stroke, systemic embolic event, myocardial infarction, or cardiovascular mortality occurring from randomization to the end of follow-up. The primary safety endpoint was the composite endpoint of major and clinically relevant non-major bleeding from the first administration of study drug to the end of treatment.

The primary efficacy analysis was done in the intention-to-treat population (defined as all patients enrolled in the study and randomly assigned.[7, 8] The primary safety analysis included all patients who took at least one dose of study drug (safety population). Efficacy and safety outcomes were compared between patients with spontaneous conversion and patients with non-spontaneous conversion.

Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are presented as numbers and percentages of patients in each category. Data were compared using one-way analysis of variance for numerical data and Fisher's exact test for categorical data.

Logistic regression was used to determine clinical and demographic characteristics (age, creatinine clearance, hemoglobin value, CHA_2DS_2-VASc score and its components, congestive heart failure, hypertension, diabetes mellitus, prior stroke or transient ischemic attack, coronary artery disease, edoxaban dose-reduction factor, use of TEE) and prior treatment (calcium-channel blockers, beta-blockers, antiarrhythmic drugs, digoxin, renin−angiotensin system blockers, cardioversion procedure) associated with spontaneous conversion. Odds ratios and 95% confidence intervals were calculated.

Statistical analysis was performed using SAS® software (SAS Institute, Cary, NC, USA).

Results

Between 25 March 2014 and 28 October 2015, 2199 patients were enrolled and randomly assigned to receive edoxaban (n=1095) or enoxaparin–warfarin (n=1104). Of these patients, 167 (7.6%) underwent spontaneous conversion before scheduled electrical cardioversion, 72 patients (6.6%) in the edoxaban arm and 95 (8.6%) in the enoxaparin–warfarin arm. The baseline characteristics of the patients with spontaneous conversion or non-spontaneous conversion are detailed in Table I. Mean age was 63.9 ± 10.3 years in patients with spontaneous conversion and 64.3 ± 10.6 years in patients with non-spontaneous conversion. Mean CHA_2DS_2-VASc scores were 2.6 ± 1.5 and 2.6 ± 1.4, respectively. History of paroxysmal AF was more frequent in the spontaneous conversion group (P<.001), whereas use of beta-blockers was more frequent in the non-spontaneous conversion group (P=.037). The TEE group was less prevalent in the spontaneous conversion group (P<.001).

	Spontaneous conversion n = 167	**Non-spontaneous conversion n = 2032**	***P****
Age (years)	63.9 ± 10.3	64.3 ± 10.6	.66
CHA_2DS_2-VASc score	2.6±1.5	2.6±1.4	.94
Congestive heart failure, n (%)	67 (40.1)	893 (43.9)	0.34
Hypertension, n (%)	131 (78.4)	1583 (77.9)	0.87
Age ≥75y, n (%)	25 (15.0)	334 (16.4)	0.62
Previous stroke or transient ischemic attack, n (%)	7 (4.2)	127 (6.3)	.29
Vascular intervention, n (%)	15 (9.0)	160 (7.9)	0.61
Age 65-74y, n (%)	54 (32.3)	722 (35.5)	0.41
Female, n (%)	76 (45.5)	680 (33.5)	0.0016
History of paroxysmal AF (≤7 days), n (%)	63 (37.7)	352 (17.4)	<.001
Previous cardioversion, n (%)	36 (21.6)	559 (27.6)	.096
Persistent AF, n (%)	104 (62.3)	1673 (82.3)	<.001
Prior treatment, n (%)			
Beta-blockers	119 (71.3)	1590 (78.2)	.037*
Calcium-channel blockers	34 (20.4)	464 (22.8)	.46
Renin-angiotensin system blockers	101 (60.5)	1279 (62.9)	.53
Antiarrhythmic drug (class I/III)	57 (34.1)	607 (29.9)	.25
Amiodarone, n (%)	41(24.6)	498(24.5)	0.990
Propafenone, n (%)	9(5.4)	9(5.4)	9(5.4)
Flecainide, n (%)	5(3.0)	34(1.7)	0.214

Others, n (%)	3(1.8)	18(0.9)	0.245
Digoxin	24 (14.4)	278 (13.7)	.80
Use of TEE	47 (28.1)	1136 (55.9)	<.001

Table I

Characteristics and treatment of patients with and without spontaneous conversion

AF, atrial fibrillation; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, and prior Stroke or transient ischemic attack or thromboembolism, Vascular disease, Age 65–74 years, Sex category; SD, standard deviation; TEE, transesophageal echocardiography. *One-way analysis of variance for numerical data and Fisher's exact test for categorical data.

Forty-seven of 1147 (4.0%) patients underwent spontaneous conversion in the TEE-guided group versus 120 of 1002 (11.8%) patients in the non-TEE-guided group. In a multivariable logistic regression analysis, history of paroxysmal AF (*P*<.001) was associated with spontaneous conversion, whereas advancing age (*P*=.001), baseline creatinine clearance (*P*=.0027), and use of TEE (*P*<.0001) were associated with a reduced likelihood of spontaneous conversion (Table II).

Parameter	**OR (95% CI)**	***P***
History of paroxysmal AF	3.78 (2.58, 5.55)	<.0001
TEE group (vs. non-TEE group)	0.27 (0.18, 0.40)	<.0001
Age (per year increase in age)	0.96 (0.93, 0.98)	.0012
Baseline CrCl (per unit increase in CrCl)	0.99 (0.98, 1.00)	.0027
Paroxysmal AF	3.78 (2.58, 5.55)	<.0001

Table II

Multivariable logistic regression analysis of spontaneous cardioversion

AF, atrial fibrillation; CrCl, creatinine clearance; TEE, transesophageal echocardiography.

None of the patients with spontaneous conversion had a stroke, systemic embolic event, myocardial infarction or cardiovascular death, or had an episode of on-treatment major or major and clinically relevant non-major bleeding.

Discussion

ENSURE-AF is the largest prospective, multicenter, randomized study in patients with AF undergoing planned electrical cardioversion. In this post-hoc analysis from ENSURE-AF, 7.6% of patients underwent spontaneous conversion, with a higher rate among the non−TEE-guided group. History of paroxysmal AF was the only independent predictor of spontaneous conversion. Spontaneous conversion was not associated with thromboembolic or bleeding events.

An ancillary analysis of the multicenter, prospective Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) trial, in which TEE-guided treatment was compared with conventional anticoagulation treatment for the management of AF, reported that 167 of 1041 (16%) patients with AF of >2 days' duration underwent spontaneous conversion, with twice as many of those who converted in the conventional versus the TEE-guided group (21% vs. 11%; *P*<.001).[9] The ACUTE II[10] pilot trial, which compared the safety and efficacy of enoxaparin with unfractionated heparin (and was interrupted prematurely because of low enrollment and event rates) reported that 7 of 76 (9.2%) patients in the enoxaparin group and 13 of 79 (16.5%) in the unfractionated heparin group experienced spontaneous conversion. Similar to our study, the rate of spontaneous conversion in the X-VeRT study, which compared rivaroxaban with vitamin K antagonists for cardioversion in AF in patients with AF of >48 hours' or unknown duration, was 7.7%.[11] These differences in reported rates of spontaneous cardioversion are likely to reflect the duration of AF, which was shorter in ACUTE.

Given the periprocedural risks of thromboembolism, identifying predictors of spontaneous conversion is important for the management of patients being considered for electrical cardioversion. The ongoing ACWAS trial,[12] an investigator-initiated randomized non-inferiority trial, will compare a watch-and-wait approach with the standard of care cardioversion in patients with recent-onset symptomatic AF in the emergency department without urgent need for cardioversion.

Limitations

Despite the large size of the trial, our analysis did not consider some of the predictors of spontaneous conversion reported in the ACUTE trial,[3] such as New York Heart Association class, left-atrial size, and left-atrial spontaneous echo contrast. Stunning and functional recovery of the left atrium and its appendage are strongly determined by the duration of AF, and we could not assess

delay between occurrence of AF and spontaneous conversion, or the TEE parameters in the TEE group. This study was limited to patients with AF of least 48 hours' and <12 months' duration and may not be applicable to patients with a shorter or longer history of AF.

Conclusions

In this contemporary study of patients with AF planned for electrical cardioversion, 7.6% of our population underwent spontaneous conversion, with a higher rate among the non−TEE-guided group. History of paroxysmal AF was the only independent predictor of spontaneous conversion. Spontaneous conversion to sinus rhythm was not associated with thromboembolic or bleeding events.

Acknowledgements

The first draft of the manuscript was written by the authors. Additional writing support was provided by Sophie Rushton-Smith, PhD (MedLink Healthcare Communications Ltd.) and was funded by the authors.

Funding

The ENSURE-AF study was sponsored by Daiichi Sankyo Pharma Development and Daiichi Sankyo Development, Ltd.

Contributors

A.A.C proposed and designed the substudy, analyzed and interpreted full sets of data, and wrote the first draft of the manuscript. A.A.C had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. H.H, J.Y.L.H., R.D.C., J.L.M. participated in the analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. J.J. and M.M. participated in the statistical analysis. S.M.W. participated in administrative, technical, and material support and critical revision of the manuscript. A.G. and G.Y.L. participated in the study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. All authors contributed to the manuscript and approved the final version.

Disclosures

A.A. Cohen: Research Grant; Modest; RESICARD. Consultant/Advisory Board; Modest; Amgen, Astra-Zeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Novartis, Pfizer.

H. Heidbuchel: Research Grant; Modest; Biotronik. Consultant/ Advisory Board; Modest; Boehringer Ingelheim, Bayer, Bristol-Myers-Squibb, Pfizer, Daiichi-Sankyo, Cardiome.

J.Y. Le Heuzey: Consultant/Advisory Board; Modest; Sanofi, Bristol-Myers Squibb/Pfizer, Meda, Daiichi-Sankyo, Boehringer Ingelheim, Bayer, Servier.

R. De Caterina: Research Grant; Modest; Pfizer, Daiichi-Sankyo, Novartis, Merck Sharp & Dohme. Honoraria; Modest; Sanofi, Boehringer Ingelheim, Bayer, Bristol-Myers Squibb.

J.L. Merino: Speakers Bureau; Modest; Cardiome, Daiichi-Sankyo, Medtronic, St. Jude Medical. Consultant/Advisory Board; Modest; Bayer, Biotronik, Boston Scientific, Bristol-Myers Squibb, Cardiome, Daiichi-Sankyo, LivaNova, Medtronic, Pfizer, Sanofi, St. Jude Medical.

J. Jin: Employment; Significant; Daiichi- Sankyo.

M. Melino: Employment; Significant; Daiichi-Sankyo.

S.M. Winters: Employed by Daiichi Sankyo during the conduction of the study; Significant.

A. Goette: Speakers Bureau; Modest; Astra Zeneca, Bayer, Berlin Chemie, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Pfizer, Sanofi-Aventis. Consultant/Advisory Board; Modest; Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer.

G.Y. Lip: Speakers Bureau; Modest; Bayer, Bristol-Myers Squibb, Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, Daiichi Sankyo. Consultant/Advisory Board; Modest; Bayer, Janssen, Bristol-Myers Squibb, Pfizer.

References

1. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37(38):2893-2962.
2. Doyle B, Reeves M. "Wait and see" approach to the emergency department cardioversion of acute atrial fibrillation. Emerg Med Int 2011;2011:545023.
3. Geleris P, Stavrati A, Afthonidis D, Kirpizidis H, Boudoulas H. Spontaneous conversion to sinus rhythm of recent (within 24 hours) atrial fibrillation. J Cardiol 2001;37(2):103-7.
4. Dell'Orfano JT, Patel H, Wolbrette DL, Luck JC, Naccarelli GV. Acute treatment of atrial fibrillation: spontaneous conversion rates and cost of care. Am J Cardiol 1999;83(5):788-90, A10.
5. Lindberg S, Hansen S, Nielsen T. Spontaneous conversion of first onset atrial fibrillation. Intern Med J 2012;42(11):1195-9.
6. Danias PG, Caulfield TA, Weigner MJ, Silverman DI, Manning WJ. Likelihood of spontaneous conversion of atrial fibrillation to sinus rhythm. J Am Coll Cardiol 1998;31(3):588-92.
7. Goette A, Merino JL, Ezekowitz MD, Zamoryakhin D, Melino M, Jin J, et al. Edoxaban versus enoxaparin–warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. The Lancet 2016;388(10055):1995-2003.
8. Lip GYH, Al-Saady N, Jin J, Sun M, Melino M, Winters SM, et al. Anticoagulation Control in Warfarin-Treated Patients Undergoing Cardioversion of Atrial Fibrillation (from the Edoxaban Versus Enoxaparin-Warfarin in Patients Undergoing Cardioversion of Atrial Fibrillation Trial). Am J Cardiol 2017;120(5):792-796.
9. Tejan-Sie SA, Murray RD, Black IW, Jasper SE, Apperson-Hansen C, Li J, et al. Spontaneous conversion of patients with atrial fibrillation scheduled for electrical cardioversion: an ACUTE trial ancillary study. J Am Coll Cardiol 2003;42(9):1638-43.
10. Klein AL, Jasper SE, Katz WE, Malouf JF, Pape LA, Stoddard MF, et al. The use of enoxaparin compared with unfractionated heparin for short-term antithrombotic therapy in atrial fibrillation patients undergoing transoesophageal echocardiography-guided cardioversion: assessment of Cardioversion Using Transoesophageal Echocardiography (ACUTE) II randomized multicentre study. Eur Heart J 2006;27(23):2858-65.

11. Cappato R, Ezekowitz MD, Klein AL, Camm AJ, Ma CS, Le Heuzey JY, et al. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. Eur Heart J 2014;35(47):3346-55.

12. Dudink E, Essers B, Holvoet W, Weijs B, Luermans J, Ramanna H, et al. Acute cardioversion vs a wait-and-see approach for recent-onset symptomatic atrial fibrillation in the emergency department: Rationale and design of the randomized ACWAS trial. Am Heart J 2017;183:49-53.