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CLINICAL RESEARCH

SAfety of Fondaparinux in transoesophageal echocardiography-guided Electric cardioversion of Atrial Fibrillation (SAFE-AF) study: A pilot study☆

Sécurité du fondaparinux dans la cardioversion électrique de la fibrillation atriale (étude SAFE-AF) : une étude clinique et échocardiographique

Ariel Cohen[a,*], Christoph Stellbrink[b], Jean-Yves Le Heuzey[c], Thomas Faber[d], Etienne Aliot[e], Norbert Banik[f], Stefan Kropff[g], Heyder Omran[h,*], on behalf of the SAFE-AF investigators

[a] *Saint-Antoine university and medical school, université Pierre et Marie Curie, CHU Saint-Antoine, department of cardiology, 184, rue du Faubourg Saint-Antoine, 75571 Paris cedex 12, France*
[b] *Hospital Bielefeld centre, department of cardiology and internal intensive care, Bielefeld, Germany*
[c] *René-Descartes university, Georges-Pompidou European hospital, arrhythmia department, Paris, France*
[d] *Heart centre, Freiburg university, cardiology and angiology I, Freiburg, Germany*
[e] *Institute of heart and vessels Louis-Mathieu, department of cardiology, Vandœuvre-les-Nancy, France*
[f] *Winicker Norimed GmbH, Nuremberg, Germany*
[g] *GlaxoSmithKline, Germany*
[h] *St-Marien hospital Bonn Venusberg, department of internal medicine, Bonn, Germany*

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Abbreviations: ACE, Anticoagulation in cardioversion using enoxaparin; ACUTE, Assessment of cardioversion using transoesophageal echocardiography; AF, Atrial fibrillation; CI, Confidence interval; INR, International normalized ratio; LAA, Left atrial appendage; LMWH, Low-molecular-weight heparin; mITT, modified intention-to-treat; SAFE-AF, SAfety of Fondaparinux in transoesophageal echocardiography-guided Electric cardioversion of Atrial Fibrillation; TIMI, Thrombolysis in Myocardial Infarction; TEE, Transoesophageal echocardiography; UFH, Unfractionated heparin; VKA, Vitamin K antagonist.

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* Corresponding authors.
E-mail addresses: ariel.cohen@sat.aphp.fr (A. Cohen), heyder.omran@marien-hospital-bonn.de (H. Omran).

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KEYWORDS
Anticoagulant;
Atrial fibrillation;
Cardioversion;
Thrombosis

Summary
Background. — Current guidelines recommend unfractionated heparin (UFH) or low-molecular-weight heparin plus an oral anticoagulant for the prevention of thromboembolism in patients undergoing electric cardioversion of atrial fibrillation (AF). Selective factor Xa inhibitors, such as fondaparinux, which has a favourable benefit-risk profile in the prevention and treatment of venous thromboembolism and the management of acute coronary syndromes, have not been systematically evaluated in this setting.
Aim. — To evaluate the efficacy and safety of fondaparinux versus standard treatment in patients undergoing echocardiographically-guided cardioversion of AF.
Methods. — In this multicentre, randomized, open-label, controlled, two-parallel-group, phase II pilot study, patients with AF undergoing electric cardioversion following transoesophageal echocardiography (TEE) were randomized to fondaparinux or standard therapy (UFH plus vitamin K antagonist [VKA]). Patients showing an atrial thrombus in the first TEE (clot-positive) were randomized to treatment with fondaparinux or standard care for 4 weeks before cardioversion.
Results. — The primary endpoint (combined rate of cerebral neurological events, systemic thromboembolism, all-cause death and major bleeding events) occurred in 3 of 174 (1.7%) patients on fondaparinux and 2 of 170 (1.2%) patients on UFH + VKA. The rate of thrombus disappearance among clot-positive patients was higher in the fondaparinux arm (11 of 14; 78.6%) than in the UFH + VKA arm (7 of 14; 50.0%). Incidences of adverse events were similar (45.4% with fondaparinux and 46.5% with UFH + VKA).
Conclusion. — In this pilot study in patients with TEE-guided cardioversion, the use of fondaparinux appeared to be well tolerated, with similar efficacy to UFH + VKA. Furthermore, a trend to greater thrombus resolution was observed.

MOTS CLÉS
Cardioversion électrique ;
Fibrillation atriale ;
Échocardiographie transœsophagienne ;
Fondaparinux

Résumé
Justification. — Les recommandations actuelles suggèrent la prescription d'une héparine non fractionnée ou une héparine de bas poids moléculaire et un traitement anticoagulant oral au décours afin de prévenir le risque thromboembolique artériel des patients en fibrillation atriale avec une indication à une cardioversion électrique. Les inhibiteurs sélectifs du facteur Xa, tels le fondaparinux, ont un profil bénéfice-risque favorable dans la prévention et le traitement de la thrombose veineuse périphérique et dans la prise en charge des syndromes coronaires aigus, mais n'ont pas été évalués dans la fibrillation atriale.
Objectifs. — Évaluer l'efficacité et la sécurité du fondaparinux versus un traitement standard chez les patients ayant une indication à une cardioversion électrique d'une fibrillation atriale guidée par échocardiographie transœsophagienne.
Méthode. — Cette étude randomisée, multicentrique, ouverte, contrôlée avec deux groupes parallèles est une étude pilote de phase II, incluant des patients en fibrillation atriale, ayant une indication à une cardioversion électrique au décours d'une échographie transœsophagienne. Ces patients ont été randomisés entre un groupe fondaparinux et un groupe traitement standard (héparine non fractionnée + AVK). Les patients ayant un thrombus dans l'oreillette ou l'auricule gauche lors de la première échocardiographie transœsophagienne (groupe clot positive) ont été randomisés pour un traitement par fondaparinux ou un traitement standard 4 semaines au décours de la cardioversion.
Résultats. — Le critère de jugement principal (critère combiné événements neurologiques cérébrovasculaires, embolie artérielle systémique, décès de toute cause et saignement majeur) est survenu chez 3 des 174 patients, (1,7 %) du groupe fondaparinux et 2 des 170 patients (1,2 % à des patients sous héparine non fractionnée + AVK). Le taux de disparition de la thrombose atriale gauche dans le groupe clot positive était plus élevé dans le fondaparinux (11/14, 78,6 %) versus 7/14, 50 % dans le groupe héparine non fractionnée + AVK. L'incidence des événements indésirables était similaire dans les deux groupes (45,4 % dans le groupe fondaparinux, 45 % dans le groupe héparine non fractionnée + AVK).
Conclusion. — Dans cette étude pilote de cardioversion guidée par ETO, l'utilisation de fondaparinux apparaît comme bien tolérée avec une efficacité similaire au traitement conventionnel héparine non fractionnée + AVK. Une tendance à un taux de réduction accru de la thrombose auriculaire gauche a été observée.

Background

Electrical cardioversion to restore sinus rhythm is a common procedure for patients with persistent atrial fibrillation (AF). In patients with AF lasting > 2 days, thromboembolic events have been reported in 5—7% of those who undergo cardioversion in the absence of anticoagulation [1—3]. The occurrence of thromboembolism is related to both dislodgement of atrial thrombi and post-cardioversion left atrial stunning [4]. Transoesophageal echocardiography (TEE) offers optimal imaging of the atria and allows for accurate identification and exclusion of thrombi [5]. Furthermore, a TEE-guided approach to early cardioversion of AF in conjunction with periprocedural therapeutic anticoagulation with either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) has a similar safety profile to conventional anticoagulant therapy (i.e. 1 month of effective oral anticoagulation before cardioversion) [6,7]. Hence, current guidelines for the management of AF of > 48 hours' duration recommend ≥ 3 weeks of efficient anticoagulation with an oral anticoagulant (international normalized ratio [INR] 2.0—3.0) before cardioversion followed by ≥ 4 weeks of treatment afterwards, i.e. the ''conventional strategy'' [8]. Alternatively, a TEE-guided strategy can be followed, in which the 3-week period of anticoagulation can be shortened if TEE reveals no left atrial or left atrial appendage (LAA) thrombus or sludge [9—11].

The use of UFH requires frequent monitoring and dose adjustment of anticoagulation [7] whereas LMWH rapidly achieves adequate anticoagulation levels and does not require regular anticoagulation monitoring. However, enoxaparin, which has been shown to be non-inferior to UFH in patients undergoing TEE-guided cardioversion [7], needs to be administered twice daily. In contrast, the antithrombotic fondaparinux sodium has the advantage of once-daily application. This selective factor Xa inhibitor has shown a favourable benefit-risk profile in trials in the prevention and treatment of venous thromboembolism and in the management of acute coronary syndromes, and its use is now recommended in evidence-based guidelines as an alternative to heparin [12—14]. Furthermore, fondaparinux carries a very low risk of thrombocytopoenia [15].

The aim of the SAfety of Fondaparinux in transoesophageal echocardiography-guided Electric cardioversion of Atrial Fibrillation (SAFE-AF) study was to evaluate the efficacy and safety of fondaparinux versus standard therapy (UFH + vitamin K antagonist [VKA]) for the prevention of thromboembolic complications, death and major bleeding events in patients undergoing cardioversion of non-valvular AF.

Methods

Study design

SAFE-AF was an international, multicentre, randomized, open-label, controlled, two-parallel-group, phase II pilot study to evaluate the efficacy and safety of fondaparinux for anticoagulation of patients with AF undergoing electrical cardioversion following TEE (Fig. 1). After stratification into clot-positive and clot-negative patients according to the presence or absence of thrombus in the left atrial cavity or LAA on TEE, patients were randomized to receive either fondaparinux or UFH followed by VKA. The TEE scans were assessed by the treating physicians.

In the fondaparinux arm, clot-negative patients received fondaparinux 7.5 mg once daily subcutaneously (body weight < 100 kg) or 10 mg once daily (body weight > 100 kg) for the first 7—10 days after randomization, followed by 3 weeks of fondaparinux 2.5 mg once daily until day 28 ± 4. Clot-positive patients were given fondaparinux 5—10 mg, depending on weight and renal function, for 28 ± 4 days. In patients whose second TEE showed that the thrombi had disappeared, cardioversion was performed and the patients were treated in the same manner as clot-negative patients.

In the UFH + VKA arm, both clot-negative and clot-positive patients received an initial intravenous bolus injection of 70 IU/kg (≥ 5000 IU) of UFH followed by a continuous infusion with an initial rate of 15 IU/kg per hour. The infusion dose was adjusted to maintain an activated partial thromboplastin time at 1.5—2 times the reference control value and was continued for ≥ 72 hours. VKA treatment was started as soon as possible and adjusted to achieve a target INR of 2—3. In clot-positive patients, TEE was repeated after 28 days and cardioversion was performed if the thrombi had disappeared. Post-cardioversion VKA treatment was continued for 28 days.

Clot-positive patients with persistent thrombi at the second TEE from both groups were excluded from the study except for follow-up on day 90 ± 7.

Patients

Male and female patients aged ≥ 18 years were eligible to participate in this study if they qualified for cardioversion and had AF meeting at least one of the following criteria: acute clinical symptoms (e.g. palpitations, chest pain, dyspnoea, fatigue, light-headedness, syncope) for ≥ 48 hours and < 1 year and AF recorded on a baseline electrocardiogram; newly discovered AF persisting for ≥ 7 days; or recurrent AF persisting for ≥ 7 days and < 1 year. Key exclusion criteria were: duration of current episode of AF > 1 year; acute neurological deficit; treatment with antithrombotic agents (including low-dose anticoagulation > 96 hours before randomization); treatment with oral non-steroidal anti-inflammatory drugs or aspirin > 325 mg/day for > 72 hours before randomization; treatment with two antiplatelet drugs; active and clinically significant bleeding within the past month; major surgery within the past 3 months; uncontrolled arterial hypertension; bacterial endocarditis; calculated creatinine clearance < 30 mL/min; body weight < 50 kg, and planned surgery or intervention within the next 65 days.

The study was conducted in accordance with all applicable regulatory requirements, with the principles of Good Clinical Practice, all applicable patient privacy requirements and the guiding principles of the Declaration of Helsinki, including, but not limited to: institutional review board/independent ethics committee review and favourable opinion/approval of study protocol and any subsequent amendments; patient written informed consent, and investigator reporting requirements. All patients were free to withdraw from the study at any point.

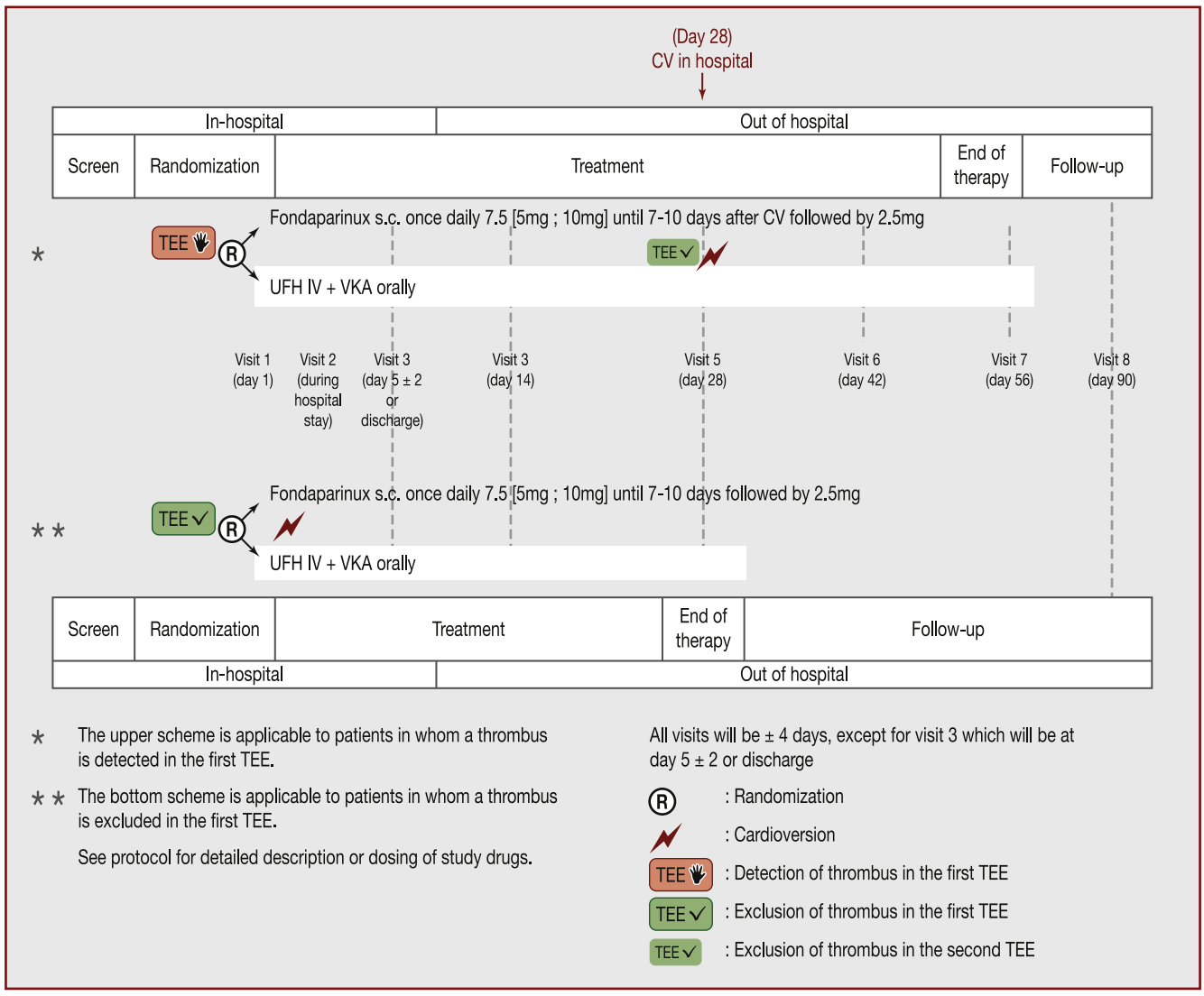

Figure 1. Study design. CV: cardioversion; IV: intravenous; s.c.: subcutaneous; TEE: transoesophageal echocardiography; UFH: unfractionated heparin; VKA: vitamin K antagonist.

Study endpoints

The primary objective of the study was to compare subcutaneous fondaparinux with UFH + VKA with respect to the occurrence of the primary combined endpoint of cerebral neurological events, systemic thromboembolism, all-cause death and major bleeding events occurring during the whole treatment period, i.e. from randomization to 4 days after the last administration of study drug. The secondary objectives of the study were to compare, up to day 90 ± 7, the effects of fondaparinux versus UFH + VKA on the components of the combined endpoint, thrombus resolution, alternative bleeding definitions (please see below), success of electrical cardioversion and hospitalizations.

Major bleeding was defined as a bleed that was clinically overt and at least one of the following: fatal; symptomatic intracranial, retroperitoneal, intraocular; led to a decrease in haemoglobin of ≥ 3.0 g/dL (with each blood transfusion unit counting for 1.0 g/dL of haemoglobin) or required transfusion of ≥ 2 units of red blood cells. Other clinically overt bleeding events that did not meet the criteria for major bleeding were categorized as minor bleeding. Bleeding events were also analysed using other criteria, as defined in the following studies: Thrombolysis in Myocardial Infarction (TIMI) [16] and Anticoagulation in Cardioversion using Enoxaparin (ACE) [7].

All events were reviewed by an independent and blinded adjudication committee (see the Appendix A for details).

Statistical analysis

This was a pilot study and as such was not powered to enable formal statistical comparisons between randomized treatment therapies but did not preclude the analysis of data as observed. The aim was to randomize approximately 350 patients (175 per treatment group) into the study. With this sample size, the half-width of the 95% confidence interval (CI) for the estimated event rate (e.g. for the primary endpoint of efficacy) was at most 3.3 percentage points (absolute width) for an anticipated event rate of 5%. This

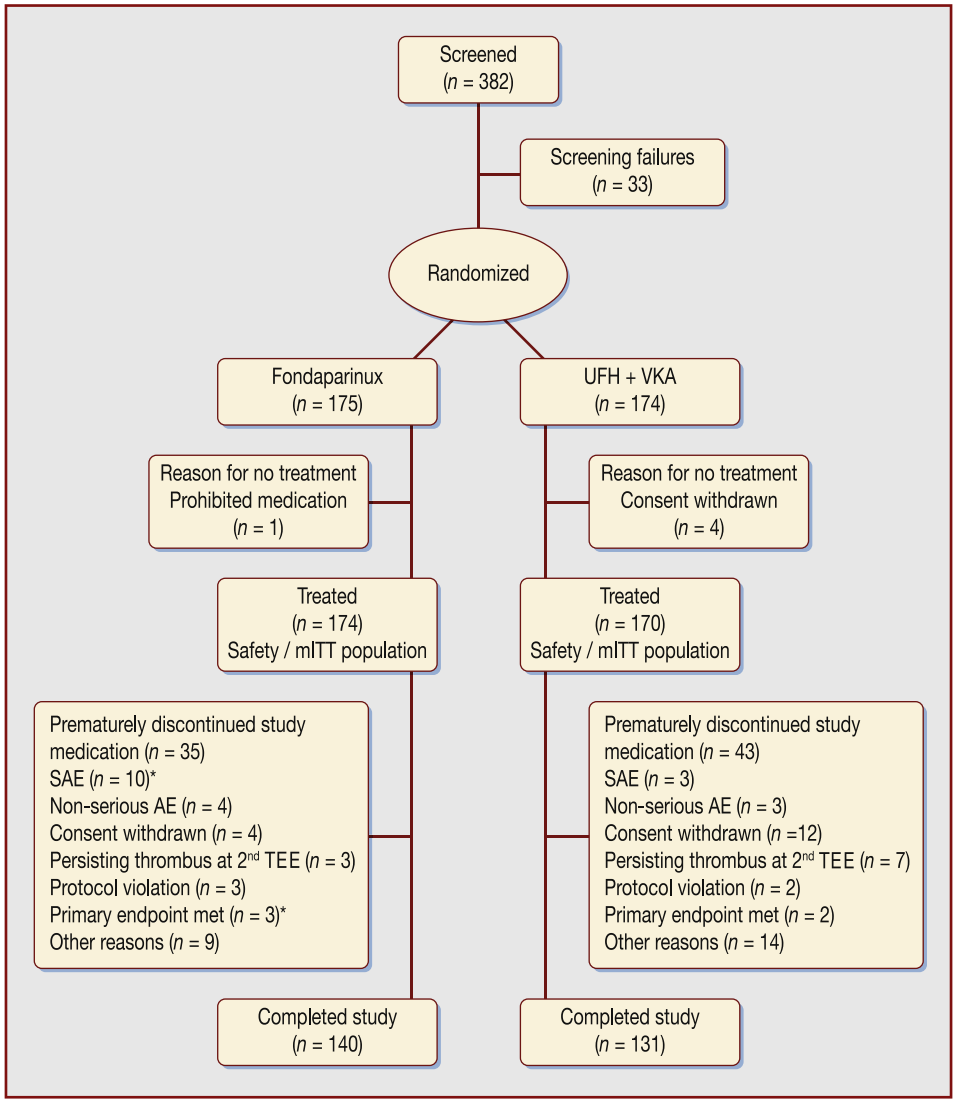

Figure 2. Patient flow chart. AE: adverse event; mITT: modified intention-to-treat; SAE: serious adverse event; TEE: transoesophageal echocardiography; UFH: unfractionated heparin; VKA: vitamin K antagonist. [a] One patient in the fondaparinux arm who met the primary endpoint discontinued due to an SAE.

sample size was expected to provide sufficient accuracy to describe the primary endpoint event rate, allowing for descriptive between-group comparisons and comparisons with historical data.

A generalized linear model stratified according to the absence or presence of a thrombus during first TEE was planned to provide an adjusted estimate of the primary endpoint. However, the adjusted estimates could not be calculated due to the low event rate. Thus, the unadjusted event rates (percentages of patients with an event in each treatment group), including their two-sided 95% CIs and the difference between the treatment groups with the associated two-sided 95% CIs are presented.

Results

Patient disposition

The study was conducted in 34 European study centres (see the Appendix A for locations). A total of 349 patients were enrolled, 175 of whom were randomized to fondaparinux and 174 to standard care with UFH + VKA. One patient in the fondaparinux group did not receive treatment because of a prohibited medication, and four patients in the UFH + VKA group withdrew consent. The safety/modified intention-to-treat (mITT) population therefore comprised 174 patients in the fondaparinux group (14 clot-positive and 160 clot-negative at first TEE) and 170 in the UFH + VKA group (14 clot-positive and 156 clot-negative at first TEE). The patient flow diagram is given in Fig. 2. Baseline characteristics and echocardiographic variables were similar in the two treatment groups and are summarized in Tables 1—3.

Study outcomes

In the mITT analysis, the primary endpoint occurred in three patients (1.7%, 95% CI 0.4—5.0) in the fondaparinux arm and in two patients (1.2%, 95% CI 0.1—4.2) in the UFH + VKA arm. Table 4 provides information on the occurrence of

Table 1 Patient baseline characteristics.

	Fondaparinux ($n = 174$)	UFH + VKA ($n = 170$)
Male	105 (60.3)	110 (64.7)
Age (years)	68.2 ± 11.1	66.8 ± 11.9
Body mass index (kg/m²)	29.3 ± 5.7	28.7 ± 5.8
Underlying heart disease		
Arterial hypertension	135 (77.6)	121 (71.2)
Heart failure	30 (17.2)	43 (25.3)
Coronary artery disease	24 (13.8)	26 (15.3)
Duration of current AF episode (days)	23.3 ± 53.3	18.4 ± 38.0
Most frequent symptoms of current episode		
Dyspnoea	100 (57.5)	108 (63.5)
Palpitations	88 (50.6)	84 (49.4)
Pattern of atrial fibrillation		
Newly discovered	138 (79.3)	124 (72.9)
Recurrent	36 (20.7)	46 (27.1)
Time since first AF episode (months)	52.0 ± 60.4	53.6 ± 76.4
Total number of AF episodes[a]	1 (1—100)	1 (1—105)
$CHADS_2$ score[b]	1.6 ± 1.1	1.5 ± 1.1
CHA_2DS_2-VASc score[c]	2.4 ± 1.3	2.2 ± 1.3
Concomitant antiarrhythmics	160 (92.0)	156 (91.8)
Concomitant amiodarone	51 (29.3)	38 (22.4)

Data are mean ± standard deviation or number (%), unless otherwise stated. AF: atrial fibrillation; UFH: unfractionated heparin; VKA: vitamin K antagonist.
[a] Median (range).
[b] $CHADS_2$ score = one point for each of C (congestive heart failure), H (hypertension), A (age ≥ 75 years), D (diabetes mellitus); two points for S (history of stroke/transient ischaemic attack/thromboembolism).
[c] CHA_2DS_2-VASc score = 1 point for each of C (congestive heart failure), H (hypertension), D (diabetes mellitus), V (vascular disease), A (age 65—74 years), Sc (sex category = female); two points for each of A (age ≥ 75 years) and S (history of stroke/transient ischaemic attack/thromboembolism).

Table 2 Transthoracic echocardiography.

	Fondaparinux ($n = 174$)	UFH + VKA ($n = 170$)	*P*
LVEF (%)[a]	54.9 ± 12.6	54.1 ± 13.0	0.60
Left atrial diameter (mm)[b]	46.1 ± 8.3	45.2 ± 8.4	0.30
Any mitral valve regurgitation[c]	110 (65.5)	95 (57.9)	0.18

Data are mean ± standard deviation or number (%). LVEF: left ventricular ejection fraction; UFH: unfractionated heparin; VKA: vitamin K antagonist.
[a] Data available in 167 fondaparinux and 165 UFH + VKA patients.
[b] Data available in 165 fondaparinux and 161 UFH + VKA patients.
[c] Data available in 168 fondaparinux and 164 UFH + VKA patients.

the primary endpoints. All of the events were in clot-negative patients; all three events in the fondaparinux arm were major bleedings, one of which was a fatal intracranial bleed. In this patient, post-treatment cerebral imaging revealed a large cerebral tumour. No cases of major bleeding were observed in clot-positive patients treated with fondaparinux. In the UFH + VKA arm, one major bleed and one cerebrovascular event occurred.

Table 5 details the results of the components of the composite outcome at the end of treatment + 4 days and follow-up (90 ± 7 days). The number of major bleedings remained the same when the ACE study criteria [7] for major bleeding were applied. However, when major bleeding was classified according to the stricter TIMI criteria [17], there were fewer major bleedings in both arms: one in the fondaparinux arm and none in the UFH + VKA arm. Minor bleeding occurred in three patients in the fondaparinux arm and in four patients in the UFH + VKA arm during the treatment period.

Cardioversion was performed in 151 of 174 (86.8%) patients in the fondaparinux arm and 148 of 170 (87.1%) patients in the UFH + VKA arm. Fifteen patients in the fondaparinux arm and 10 patients in the UFH + VKA arm were in sinus rhythm before the planned cardioversion, so this procedure was not performed. Cardioversion was deferred due to the presence of thrombi in 28 patients. The

Table 3 Transoesophageal echocardiography.

	Fondaparinux ($n = 174$)	UFH + VKA ($n = 170$)
Thrombus in LAA or LA	14 (8.0)	14 (8.2)
LA spontaneous echocardiographic contrast		
Moderate	11 (6.3)	15 (8.8)
Severe	6 (3.4)	7 (4.1)
LAA spontaneous echocardiographic contrast		
Moderate	18 (10.3)	12 (7.1)
Severe	4 (2.3)	9 (5.3)
Sludge	2 (1.1)	2 (1.2)
Thrombus size (LAA), maximum diameter (cm)[a]	1.1 ± 0.6	1.5 ± 0.5

Data are mean ± standard deviation or number (%). LA: left atrium; LAA: left atrial appendage; UFH: unfractionated heparin; VKA: vitamin K antagonist.
[a] Data available in 10 fondaparinux and 9 UFH + VKA patients.

Table 4 Details of patients who met the primary endpoint.

Treatment group	Clot status	Age (years)	Event
Fondaparinux	Negative	87	Major bleeding (rectus sheath/abdominal wall haematoma)
Fondaparinux	Negative	50	Major bleeding (intracranial)
Fondaparinux	Negative	86	Major bleeding (retroperitoneal)
UFH + VKA	Negative	93	Cerebral event: massive stroke
UFH + VKA	Negative	81	Major bleeding (gastrointestinal)

UFH: unfractionated heparin; VKA: vitamin K antagonist.

primary success rate of electrical cardioversion was similar between fondaparinux-treated and UFH + VKA-treated patients (90.7% vs 89.9%; $P = 0.85$, two-sided Fisher's exact test, Table 6). Sinus rhythm persisted at the end of follow-up (90 ± 7 days) in 109 patients in the fondaparinux arm and in 111 patients in the UFH + VKA arm (Table 6).

At the second TEE, left atrial thrombi had disappeared in 11 of 14 (78.6%) cases in the fondaparinux arm and in 7 of

Table 5 Primary and secondary endpoints (modified intention-to-treat/safety population).

	Until end of treatment + 4 days			Until follow-up (90 ± 7 days)		
	Fondaparinux ($n = 174$)	UFH/VKA ($n = 170$)	% difference (95% CI)	Fondaparinux ($n = 174$)	UFH/VKA ($n = 170$)	% difference (95% CI)
Primary endpoint[a]	3 (1.7)	2 (1.2)	0.5 (−2.0–3.1)[b]	6 (3.4)	2 (1.2)	2.3 (−0.9–5.4)
Cerebral neurological events	0	1 (0.6)	−0.6 (−1.7–0.6)	1 (0.6)	1 (0.6)	0 (−.6–1.6)
Systemic thromboembolism	0	0	0	0	0	0
All-cause death	1 (0.6)	0	0.6 (−0.5–1.7)	3 (1.7)	0	1.7 (−0.2–3.7)
Major bleeding events	3 (1.7)	1 (0.6)	1.1 (−1.1–3.4)	4 (2.3)	1 (0.6)	1.7 (−0.8–4.2)
Minor bleeding events	3 (1.7)	4 (2.4)	−0.6 (−3.6–2.4)	4 (2.3)	5 (2.9)	−0.6 (−4.0–2.7)
Major or minor bleeding events	6 (3.4)	5 (2.9)	0.5 (−3.2–4.2)	8 (4.6)	6 (3.5)	1.1 (−3.1–5.2)

Data are number (%) unless otherwise stated. CI: confidence interval; UFH: unfractionated heparin; VKA: vitamin K antagonist.
[a] Combined rate of cerebral neurological events, systemic thromboembolism, all-cause death and major bleeding events.
[b] $P = 1.0$ (Fisher's exact test).

Table 6 Secondary endpoints (modified intention-to-treat/safety population).

	Fondaparinux ($n = 174$)	UFH/VKA ($n = 170$)
Primary successful electrical cardioversion[a]	137 (90.7)	133 (89.9)
Thrombus in LA/LAA at second TEE[b]	3 (21.4)	7 (50.0)
Sinus rhythm		
At end of treatment	114 (65.5)	119 (70.0)
At follow-up[c]	109 (71.2)	111 (77.6)
Rehospitalization		
Until end of treatment + 4 days	14 (8.0)	7 (4.1)
Until follow-up	18 (10.3)	11 (6.5)

Data are number (%). LA: left atrium; LAA: left atrial appendage; TEE: transoesophageal echocardiography; UFH: unfractionated heparin; VKA: svitamin K antagonist.
[a] Data available in 151 fondaparinux and 148 UFH + VKA patients.
[b] Among the 14 fondaparinux and 14 UFH + VKA patients with a clot at the first TEE.
[c] Data available in 153 fondaparinux and 143 UFH + VKA patients.

14 (50.0%) cases in the UFH + VKA arm (odds ratio 3.67, 95% CI 0.70—19.12; $P = 0.24$, Fisher's exact test).

The mean duration of hospital stay was 5.9 ± 5.9 days in the fondaparinux arm and 8.1 ± 4.1 days in the UFH + VKA arm ($P < 0.001$, t test). Rehospitalization occurred in 18 (10.3%) patients treated with fondaparinux and in 11 (6.5%) patients treated with UFH + VKA until the end of follow-up ($P = 0.24$, Fisher's exact test).

Safety results

The incidences of treatment-emergent adverse events were similar in both treatment groups (79 of 174 [45.4%] in the fondaparinux group vs 79 of 170 [46.5%] in the UFH + VKA group), with recurrent AF being the most frequently reported. Three patients (all clot-negative at baseline and all treated with fondaparinux) died, one during the treatment phase (haemorrhagic shock following abdominal wall haematoma) and two during follow-up (one reported as ''sudden death, natural'' and one intracranial bleeding in the presence of a previously undiagnosed brain tumour).

Discussion

The results of our pilot study show that TEE-guided cardioversion of AF using the selective factor Xa inhibitor fondaparinux is associated with low rates of thromboembolism and major bleeding and resulted in numerically similar efficacy/safety event rates compared with the UFH + VKA treatment arm. Of interest, the current study demonstrates, for the first time, that fondaparinux is effective for dissolving atrial thrombi before cardioversion in patients with AF.

TEE-guided direct electrical cardioversion is often performed to restore sinus rhythm quickly and relieve patients' symptoms; it is considered a safe procedure if appropriate anticoagulation is initiated beforehand [18]. Hence, TEE-guided cardioversion in conjunction with anticoagulation is recommended in guidelines for the treatment of persistent AF [11,13].

The ACE study compared the LMWH enoxaparin with UFH + VKA during TEE-guided or conventional cardioversion and demonstrated non-inferiority of enoxaparin to standard care with UFH + VKA for preventing thromboembolism and bleeding [7]. Because LMWH is easier to administer and does not need frequent monitoring, currently it is often used in TEE-guided cardioversion. However, enoxaparin has to be given twice daily and carries a small but potential risk of thrombocytopoenia.

The results of our study showed a very low combined efficacy/safety event rate in both the fondaparinux (1.7%) and UFH + VKA (1.2%) arms, about one-third of the expected rate based on the rate in the control arm of the ACE study [7]. Our finding of a low event rate is similar to that in other studies investigating the value of TEE-guided cardioversion. The Assessment of Cardioversion Using Transoesophageal Echocardiography (ACUTE II) study, which included 155 patients randomized to either enoxaparin or UFH + VKA [6], reported no cases of embolism or major bleeding. The Ludwigshafen Observation Cardioversion Study comprised 1076 consecutive non-randomized patients, of whom 719 underwent TEE-guided cardioversion [19]. The rate of thromboembolic complications was very low (6/719; 0.8%), as was major bleeding (2/719; 0.3%). The AFFECT study, which treated 162 patients with the LMWH certoparin, only reported one embolic event and three major bleedings [20].

Interestingly, embolism and bleeding rates were much higher in the UFH + VKA arm in the ACE study, at 4.8% [7]. A potential explanation for this difference in event rates is the fact that the ACE study included patients who underwent TEE-guided cardioversion as well as patients who received conventional longer-term treatment with anticoagulation. Another possible explanation could be the strict anticoagulation control in our study.

Importantly, our study underlines the safety of TEE-guided cardioversion in the setting of effective anticoagulation. A further relevant finding in our study was that we did not observe major bleedings in clot-positive patients with prolonged treatment of therapeutic doses of fondaparinux (≥ 4 weeks of therapeutic doses of fondaparinux).

The mean duration of hospitalization was shorter in fondaparinux-treated patients than in the conventionally-treated patients. This was mainly due to the need for more and prolonged anticoagulation monitoring in the UFH + VKA arm. Similar results were reported in the ACUTE II study of enoxaparin versus UFH [6].

The most important limitation of our study is the low event rate. Hence, direct comparison between fondaparinux and standard care is not statistically feasible. Nevertheless, we used hard endpoints and all events were reviewed by an independent and blinded adjudication committee. A central laboratory for TEE assessments was involved in the study but the results obtained did not influence investigators' treatment decisions. In addition, completeness and readability of the TEEs were limited and thus were not described in detail.

Conclusions

In patients with TEE-guided cardioversion, the use of fondaparinux appeared to be well tolerated, with similar efficacy to UFH + VKA. Furthermore, a trend towards greater thrombus resolution with fondaparinux was observed.

Disclosure of interest

Ariel Cohen: research grant from RESICARD (research nurses); consultant and lecture fees from AstraZeneca, Bayer Pharma, Boehringer-Ingelheim, Daiichi Sankyo, GlaxoSmithKline and sanofi-aventis.

Christoph Stellbrink: consultant fees from Boehringer-Ingelheim.

Jean-Yves Le Heuzey: consultant and lecture fees from sanofi-aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, GlaxoSmithKline, MSD, Servier and Meda.

Norbert Banik: was an employee of GlaxoSmithKline Germany at the time of conduct of the trial and is now an employee of Winicker Norimed GmbH, Nuremberg.

Stefan Kropff: is an employee of GlaxoSmithKline Germany.

Heyder Omran: consultant and lecture fees from Bayer Pharma, Boehringer-Ingelheim, GlaxoSmithKline and sanofi-aventis.

Thomas Faber and Etienne Aliot declare that they have no conflicts of interest concerning this article.

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Appendix A

Participating centres (principal investigators)

France

Paris (Ariel Cohen, Richard Isnard), Tours (Gérard Doll), Evecquemont (Michel Barboteu), Antony (Didier Villemant), Albi, (Daniel Galley), Toulouse (Olivier Fondard, Michel Galinier), Pessac (Raymond Roudaut), Rennes (Christophe Leclercq), Creteil (Nicolas Lellouche), Brest (Jacques Mansourati), Montpellier (Jean-Marc Davy), Pau (Nicolas Delarche), Poitiers (Bruno Degand).

Germany

Pirna (Christoph Axthelm), Freiburg (Thomas Faber), Magdeburg (Samir Said), Bonn (Lars Lickfett, Heyder Omran), Berlin (Martin Moeckel, Philipp Herold, Stefan Hoffmann), Kassel (Joerg Neuzner, Karl-Friedrich Appel), Wesel (Christiane Tiefenbacher), Duisburg (Gisbert Vossbeck), Frankfurt (Gerhard Cieslinski), Hagenow (Ralph Zimmermann), Unna (Mehmet Kandil), Bielefeld (Christoph Stellbrink), Simbach (Johann Auer), Potsdam (Andreas Ruttloff), Bad Tölz (Hans-Ulrich Kreider-Stempfle).

Independent boards and committees

Steering committee

Ariel Cohen (Paris, France), Heyder Omran (Bonn, Germany), Etienne Aliot (Vandœuvre-les-Nancy, France), Thomas Faber (Freiburg, Germany), Christoph Stellbrink (Bielefeld, Germany), Jean-Yves Le-Heuzey (Paris, France).

Independent data monitoring committee

Gilles Montalescot (Paris, France), Peter Hanrath (Aachen, Germany), Hartmut Stützer (Cologne, Germany).

Clinical event adjudication committee

Hans Christoph Diener (Essen, Germany), Jean-Claude Deharo (Marseille, France).

Central echo-laboratory

Andreas Hagendorff (Leipzig, Germany).

Data management, statistical analysis, medical writing

Winicker Norimed GmbH, Clinical Research, Deutschherrnstraße 15—19, D-90429 Nuremberg, Germany.

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