

Cardioversion of atrial fibrillation and atrial flutter revisited: current evidence and practical guidance for a common procedure

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Received 30 October 2019; editorial decision 19 February 2020; accepted 25 February 2020; online publish-ahead-of-print 26 April 2020

Cardioversion is widely used in patients with atrial fibrillation (AF) and atrial flutter when a rhythm control strategy is pursued. We sought to summarize the current evidence on this important area of clinical management of patients with AF including electrical and pharmacological cardioversion, peri-procedural anticoagulation and thromboembolic complications, success rate, and risk factors for recurrence to give practical guidance.

Keywords

Atrial fibrillation • Atrial flutter • Electrical cardioversion • Pharmacological cardioversion • Anticoagulation • Thromboembolism

Introduction

Cardioversion, either by a synchronized direct current (DC) electrical shock (electrical cardioversion, ECV) or by the application of antiarrhythmic drugs (AADs; pharmacological cardioversion, PCV), is an integral part of the management of atrial fibrillation (AF) and atrial flutter (AFL) in symptomatic patients who require a rhythm control strategy.¹ Electrical cardioversion may also be appropriate as a one-time diagnostic shock in supposedly asymptomatic patients with persistent AF to evaluate, whether they nevertheless show improved exercise tolerance during sinus rhythm.² The first reports on PCV of AF using quinidine were published in the late 1940s, while ECV of AF by synchronized DC shock was introduced in the early 1960s.^{3,4} These procedures are readily available and easy to perform with a high overall success rate. Nevertheless, several important points must be considered before embarking on this treatment, among others the need for cardioversion,⁵ the mode (ECV or PCV) and timing of cardioversion, assessment of the individual peri-procedural thrombo-

embolic risk of the patient, anticoagulant therapy, and peri-procedural or subsequent long-term therapy with AADs.

This review summarizes the current scientific evidence for undertaking ECV and PCV, the occurrence of thromboembolic events with cardioversion, image-guiding of cardioversion, and antithrombotic therapy when performing cardioversion. We also give some practical advice for this widely used therapy.

Electrical and pharmacological cardioversion

Electrical cardioversion terminates AF in over 90% of cases and is the treatment of choice in severely haemodynamically compromised patients with new-onset AF or AFL.¹ Pharmacological cardioversion mainly converts recent-onset or paroxysmal (i.e. in principle self-terminating) AF to sinus rhythm in 50–70% of cases within a few hours, when sodium channel blockers (mainly propafenone or

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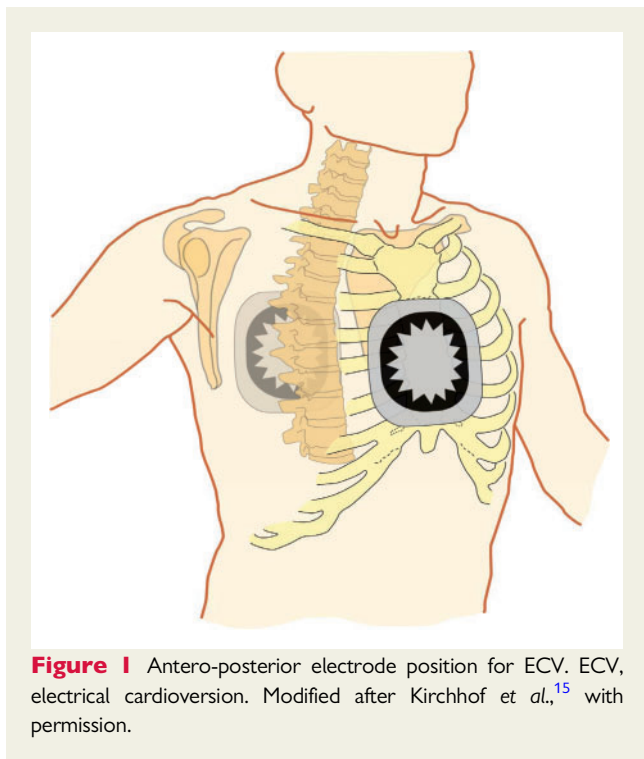


Figure 1 Antero-posterior electrode position for ECV. ECV, electrical cardioversion. Modified after Kirchhof et al.,¹⁵ with permission.

flecainide) or vernakalant are used, while these drugs rarely convert AF of longer duration.^{1,6} Compared to AF, ECV is more effective in AFL, also requiring less energy.^{7,8}

Electrical cardioversion can be performed safely under short sedation with i.v. midazolam and/or propofol and continuous blood pressure monitoring and oximetry during the procedure.⁹ Electrical cardioversion is more effective when using a biphasic defibrillator, and around 40% of patients are pre-treated with an AAD at their ECV.¹⁰ An antero-posterior electrode position (Figure 1) restores sinus rhythm better compared to antero-apical.¹¹ Starting with the maximum shock energy available seems more effective than escalating shock energies.¹² In patients with an implanted pacemaker or implantable cardioverter-defibrillator (ICD), damage to the system can be avoided by biphasic ECV in the antero-posterior paddle position.¹³ Even in patients with implanted defibrillators, ECV seems preferable to internal cardioversion performed with the ICD.¹⁴

Complications of rhythm control with ECV include sedation-related complications, hypotension, ventricular fibrillation due to inappropriate shock synchronization, bradycardias (frequently diagnostic, i.e. unmasking sick sinus or sick atrioventricular node syndrome), tachycardias, such as AFL with 1:1 conduction or torsade de pointes. Cardiac biomarker release and transient ST-segment elevation seen after ECV are self-limiting and may relate to previous cardiac surgery.¹⁶ Real-world data from a contemporary cohort of 1801 patients undergoing ECV or PCV show that complications, in general, are rare (Table 1).¹⁷

Key points

- Electrical cardioversion terminates AF in over 90% of cases and is the treatment of choice in haemodynamically compromised patients.
- Pharmacological cardioversion mainly converts recent-onset AF of <48 h duration.
- Electrical cardioversion with an antero-posterior electrode position restores sinus rhythm better than with an antero-apical position.
- Complications of ECV and PCV are generally rare.

Timing of electrical cardioversion

The RACE 7 ACWAS trial (Rate Control vs. Electrical Cardioversion Trial 7—Acute Cardioversion vs. Wait and See) showed that a wait-and-see approach (with initial rate control and delayed cardioversion only if needed) allowed almost 70% of patients with recent-onset AF reporting at the emergency department to regain sinus rhythm spontaneously vs. only 16% under immediate cardioversion. At 48 h and 4 weeks after index AF, the number of patients in sinus rhythm was similar, i.e. over 90% in both groups. Atrial fibrillation found at 30 days was incidental recurrences or persistent AF. Notably, up to 30% had a recurrence of self-terminating paroxysmal AF after the index conversion, which was also similar between groups.⁵

Key points

- In most patients with recent-onset AF, immediate cardioversion may be replaced by a wait-and-see approach as the default approach with delayed cardioversion as needed.

Timing of recurrences after cardioversion of persistent atrial fibrillation

The response to ECV of persistent (i.e. clinically non-self-terminating) AF is represented by the 1-1-1-1-1 rule (Figure 2). Immediately after the shock, it may be apparent that no single sinus beat was seen (no conversion and shock failure), which may be due to failure of complete capture of the atria by the DC shock. In the subsequent minute, immediate recurrence of AF (IRAF) may occur, which may relate to instantaneous post-shock hyper-vulnerability.^{18,19} Thereafter, 1 day of uninterrupted sinus rhythm occurs, during which the atria are incapable of fibrillating (the so-called relapse gap), which presumably relates to atrial stunning.¹⁹ Thereafter, sub-acute recurrences are common over a period of 1–2 weeks due to spatially non-uniform electrical reverse remodelling that enhances electrical instability of the atria.²⁰ Once reversed electrical remodelling is complete, the rate of recurrences decreases, which is represented by the subsequent phase of late re-occurrences during which AF recurrences appear at a much lower rate (Figure 2).

Table 1 Major complications of PCV and ECV in 1801 real-world patients from the Euro Heart Survey

	PCV (n = 1089), N (%)	ECV (n = 712), N (%)
Non-sudden cardiac death	1 (0.1)	2 (0.3)
Sick sinus syndrome	5 (0.5)	5 (0.7)
Ventricular tachycardia	2 (0.2)	6 (0.8)
Torsades de pointes	3 (0.3)	1 (0.1)
Ventricular fibrillation	0	3 (0.4)
Asystole	7 (0.7)	2 (0.3)
Cardiac syncope	8 (0.8)	1 (0.1)
Pulmonary embolism	1 (0.1)	0
Myocardial infarction	4 (0.4)	0
Transient ischaemic attack	13 (1.3)	2 (0.3)
Non-haemorrhagic stroke	1 (0.1)	2 (0.3)
Heart failure	9 (1.0)	7 (1.1)
Major bleeding	10 (1.0)	9 (1.3)

Modified after Pisters et al.,¹⁷ undefined with permission.
ECV, electrical cardioversion; PCV, Pharmacological cardioversion.

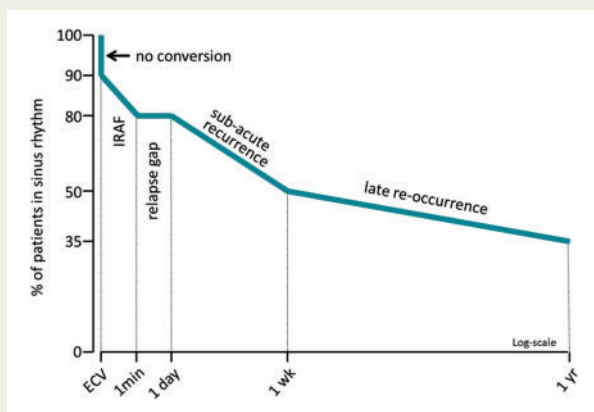


Figure 2 The 1-1-1-1-1 pattern of recurrence after ECV of persistent AF. Modified after Van Gelder et al.,² with permission. AF, atrial fibrillation; ECV, electrical cardioversion; IRAF, immediate recurrence of atrial fibrillation.

Predictors of successful ECV of persistent AF include AF duration, age of the patient, better functional class of the patients, and whether or not pre-treatment with AAD is applied.^{1,21} Drugs affect the various stages differently. First, acute failure of cardioversion can be prevented by pre-treatment with AADs (Table 2).¹ Next, the influence of AADs on recurrences depends on stage-related arrhythmogenic mechanisms and their subsidence during reversed electrical remodeling induced by persistent sinus rhythm after conversion. Immediate recurrences of AF can be prevented by ibutilide but also by sodium channel blockers and probably by sotalol and amiodarone.^{1,22,23} Immediate recurrences of AF may be further reduced by adding verapamil to Class I or III AADs.²⁴ Immediate recurrence of AF-related cardioversion failure can also be ameliorated by reapplying a shock immediately after it appears, since the longer the sinus rhythm episodes last between the consecutive IRAFs, the higher the chance the

relapse gap can be reached. The relapse gap may be lengthened by all AADs but notably also by intracellular calcium-lowering drugs including verapamil and beta-blockers as well as angiotensin receptor blockers.¹⁹ Later (sub-acute) recurrences are prevented by all AADs but even better if combined with an angiotensin receptor blocker or verapamil.^{25,26} Beta-blockers alone may also reduce sub-acute recurrences.²⁷ Presumably, these (add-on) agents control intracellular calcium overflow in atrial cells not used to large calcium transients after having been in AF for months. Late re-occurrences (Figure 2) respond well to AADs and may be managed by season-ticket-ECV, i.e. repeat single ECVs, in patients with low risk of recurrence.^{23,28} However, if recurrence risk is high, catheter ablation is the preferred option.^{1,29}

‘Diagnostic electrical cardioversion’—a possible new indication

In some patients with persistent AF, e.g. those with heart failure both with reduced and with preserved ejection fraction but also others, the relationship between symptoms and arrhythmia may be unclear. In those patients, a ‘diagnostic ECV’ may be performed to show improvement of symptoms (or not) when in stable sinus rhythm. To enhance such assessment, the period in sinus rhythm may be lengthened by using temporary amiodarone or flecainide.^{23,30} Studies are needed in this area to show usefulness of such an approach.

Key points

- Predictors of successful ECV of persistent AF are AF duration, patient age, better function class, and pre-treatment with AADs.

Termination of recent-onset or paroxysmal atrial fibrillation

Successful drug conversion of paroxysmal or recent-onset AF depends on pre-defined time to conversion, previous AF duration, type of AF (persistent AF does not usually respond), type of drug (Class Ic and vernakalant vs. all other AADs), intravenous vs. oral route of administration, and extend of underlying heart disease. Electro-echocardiography may show electrophysiological effects of AADs and predict drug conversion, although the value of these tools needs further assessment.^{31,32}

For immediate restoration of sinus rhythm with PCV, intravenous flecainide, propafenone, or vernakalant are most effective in patients with recent-onset AF. These agents are very safe in patients without significant structural heart disease.^{1,10,23} Flecainide or propafenone may also be given orally using specific dosing schemes, including pill-in-the-pocket.^{33,34} Atrial flutter responds to Class III AAD, while Class Ic agents are not useful since they almost always fail and can actually create a substrate for flutter.^{35,36} If applied for the first time, it is reasonable to perform PCV in-hospital to observe potential adverse effects.^{1,37,38} Also, other agents are used for immediate cardioversion, among them even the typical rhythm control agents amiodarone and sotalol (Figure 3), which mainly control rate rather than rhythm in the initial hours of treatment and, therefore, are ineffective conversion drugs.¹⁰ In persistent AF, *maintaining* the atria in amiodarone or

sotalol administered orally for 1 month is associated with a modest conversion rate around 25%.²⁸ Also, chronic administration of flecainide and propafenone may convert persistent AF but—as a side effect—may cause fast ventricular rates during ongoing AF.^{39,40} Verapamil may enhance chronic drug conversion with amiodarone.⁴¹

Table 2 Drugs affecting cardioversion by lowering ECV threshold or suppressing IRAF

Decrease threshold for cardioversion or suppress IRAF	Suppress sub-acute recurrences
Quinidine	Quinidine
Propafenone	Propafenone
Flecainide	Flecainide
Amiodarone	Amiodarone
Sotalol	Amiodarone + ARBs
Ibutilide	Beta-blockers
Verapamil on top of other AADs	Verapamil on top of other AADs
<i>Uncertain effect</i>	<i>Uncertain effect</i>
Procainamide	Verapamil
Disopyramide	Diltiazem
Dofetilide	Dofetilide
Beta-blockers	
Verapamil	
Diltiazem	

Also, drugs that suppress sub-acute (see Figure 2) recurrences are shown. AAD, antiarrhythmic drug; ARB, angiotensin receptor blocker; ECV, electrical cardioversion; IRAF, immediate recurrence of atrial fibrillation.

Although this pharmacological effect seems modest, it could be useful when temporary AAD therapy prior to ECV is considered.^{23,30}

Notwithstanding the above, recent-onset or paroxysmal AF may terminate spontaneously (Figure 3). Antiarrhythmic drugs foreshorten time to sinus rhythm but at the end of the day, numbers of patients in sinus rhythm are the same.^{5,10}

A risk-based approach to choosing long-term rhythm control therapy after cardioversion (no therapy, AADs, catheter ablation, or combination of these two treatments) is desirable. Prediction models for recurrent AF are being developed and will need to be based on representative, combined data sets.⁴²

Key points

- Intravenous Class Ic AADs or vernakalant are most effective in restoring recent-onset AF.
- When Class Ic AADs are intended to be used as pill-in-the-pocket approach, the very first administration should be performed in-hospital to observe potential adverse effects.
- Atrial flutter is restored by Class III AADs but not Class Ic AADs.

Thromboembolic events with cardioversion

Although cardioversion of AF or AFL is considered safe in general, cardioversion is associated with an increased risk of thromboembolic events.^{1,43} There is no apparent difference in the risk of thromboembolic events of PCV or ECV and no difference between AF and

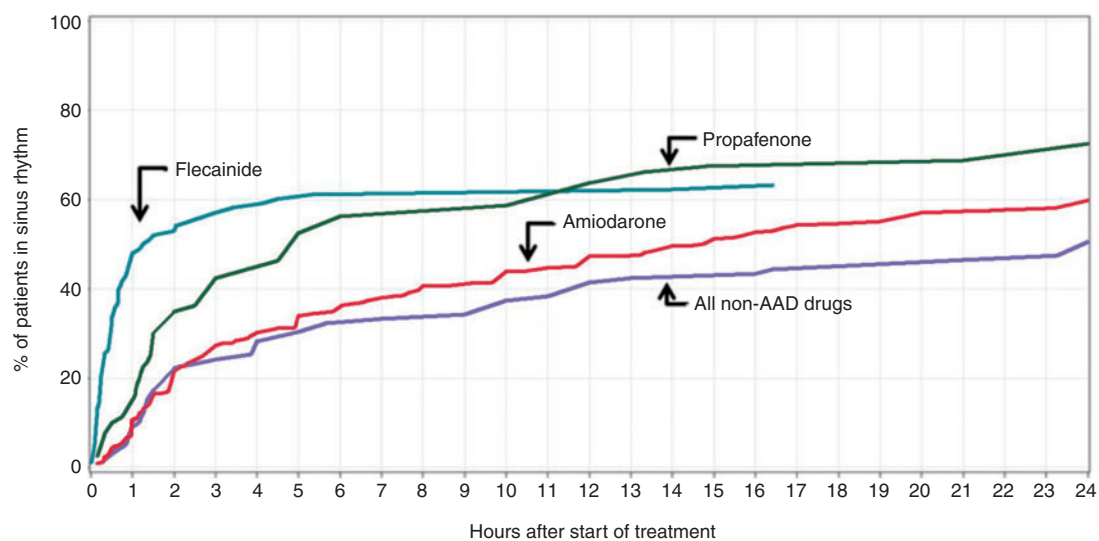


Figure 3 Conversion to sinus rhythm over time after start of drug therapy for recent-onset AF. Class Ic AADs foreshorten time to sinus rhythm significantly. Amiodarone and non-AAD (rate control drugs) are associated with spontaneous conversion, with minimal conversion action of amiodarone discernable from 6 h on. At the end of the day around 60–70% of patients reached sinus rhythm. Modified after Crijns et al.,¹⁰ with permission. AAD, antiarrhythmic drug; AF, atrial fibrillation.

AFL.⁴⁴ Thromboemboli after cardioversion are considered due to embolization of already existing thrombi present in the atrium at the time of cardioversion or to the formation and subsequent embolization of de novo thrombi in the atrium that form while atrial function is still depressed in the weeks after cardioversion.^{45,46}

Key points

- Electrical cardioversion and PCV carry the same thromboembolic risk.
- Cardioversion of AF and AFL carry the same thromboembolic risk.

Thromboembolic events in atrial fibrillation patients without anticoagulant therapy

Historical data showed an incidence of thromboembolic events of 2% in AF patients without anticoagulation and 0.33% in those receiving vitamin K antagonists (VKAs),⁴⁷ while a more recent large retrospective Danish study of 16 274 patients discharged from hospital after a first-time ECV for AF reported a lower thromboembolic event rate during the first 30 days after cardioversion of 1.1% without and 0.28% with VKA treatment.⁴⁸ The different event rates reported may also be due to study design and definitions of thromboembolic events collected. An incidence rate of ~1% was also observed in a retrospective study by Gallagher *et al.*,⁴⁴ who looked at 1950 case records of patients who underwent 2639 ECV. Cardioversion was preceded by VKA treatment for at least 3 weeks in 73% of all cardioversions. Of 756 cases with an international normalized ratio (INR) <2.5 or no measurement before conversion, a thromboembolic event occurred in 1.2%, while in those with an INR >2.5 no thromboembolic events were reported. Patients without anticoagulation and those with inadequate anticoagulation seem to have a comparable thromboembolic event rate of around 1%.

A specific population are patients with AF lasting <48 h. These patients are considered to have a low risk of thromboembolic events post-cardioversion.⁴⁹ The retrospective Finnish CardioVersion (FinCV) study included 7660 cardioversions in 3143 patients.⁵⁰ The 30-day thromboembolic event rate was 0.7%, which was in concordance with six prior small retrospective studies.^{50,51} The FinCV study also demonstrated that in cardioversions of AF <48 h without anticoagulation, the risk of thromboembolic events increased with an increasing CHA₂DS₂-VASc score (from 0.4% in those with a score of 0–2.3% in those with score of ≥5). The incidence of thromboembolic events was significantly lower in cardioversions performed on anticoagulation, and the preventive effect of anticoagulation was significantly greater in patients with a CHA₂DS₂-VASc score of ≥2.⁵² A large retrospective Swedish study in more than 22 000 patients, who were cardioverted with or without oral anticoagulant (OAC) pre-treatment, found similar results.⁵³

Thromboembolic events in atrial fibrillation patients receiving anticoagulant therapy

In anticoagulated patients as included in the European RHYTHM-AF registry, a thromboembolic event rate of 0.51% (15 embolic events in

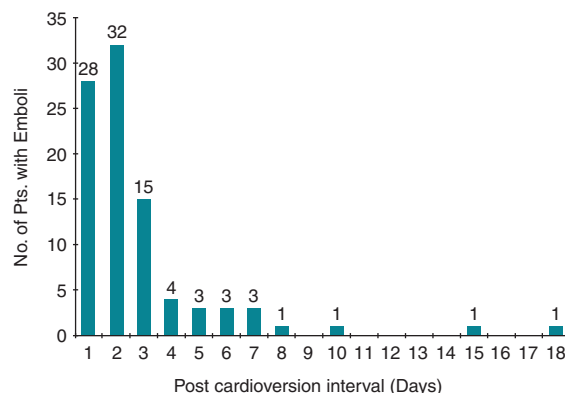


Figure 4 Interval between cardioversion and thromboembolic events in 92 patients. From Berger and Schweitzer⁵⁷ with permission.

2940 patients) was reported with no differences in thromboembolic risk between AF of >48 h or unknown duration compared to AF of <48 h (0.4% vs. 0.3%).⁵⁴ Similar event rates in anticoagulated patients were reported from the Flec-SL (Flecainide Short-Long) trial in 508 patients after ECV and 127 patients after PCV. In total, six patients developed a thromboembolic event (event rate 0.8%) independent of the type of cardioversion, of which three occurred in the first 5 days after cardioversion.⁵⁵ Lastly, a meta-analysis of four randomized controlled trials comparing non-vitamin K antagonist oral anticoagulant (NOAC) therapy with VKAs, including 4517 cardioversions in 3635 patients, found a thromboembolic event rate of 0.41% on NOAC therapy and 0.61% on VKAs.⁵⁶

Key points

- Reported peri-cardioversion thromboembolic event rates are between 1.1% and 2% in patients not or insufficiently anticoagulated and between 0.28% and 0.8% in patients sufficiently anticoagulated.
- In patients with AF lasting <48 h the thromboembolic event rate without anticoagulation is around 0.7% and increases with CHA₂DS₂-VASc score. It is significantly reduced with anticoagulation.

Temporal incidence of thromboembolic events after cardioversion

The timing of thromboembolic events after ECV of AF or AFL was analysed by Berger and Schweitzer,⁵⁷ based on data from 32 studies (published up to 1997) and a total of 4621 patients, including 92 patients with a thromboembolic event post-cardioversion. The interval between cardioversion and thromboembolic episodes ranged from <1 to 18 days (Figure 4). Of the 92 embolic events, 75 (82%) occurred within 3 days, 88 (96%) within 1 week, and 90 (98%) within 10 days of ECV. Current guidelines, therefore, recommend using anticoagulation up to 4 weeks after cardioversion.^{1,43} Factors contributing to peri-procedural thromboembolism include the presence of pre-

existing thrombi, transient atrial stunning after cardioversion, changes in mechanical atrial systolic function, left atrial size, and a prothrombotic state.⁵⁸

Key points

- Almost all thromboembolic events with cardioversion occur within 10 days after the procedure.
- Therefore, anticoagulation up to 4 weeks after cardioversion is recommended.

Image-guided cardioversion

Risk factors for thromboembolism: clinical factors and information from transoesophageal echocardiography

A recent meta-analysis showed that left atrial (LA) thrombus is observed in about 10% of non-valvular AF patients with increased risk in patients with higher age, hypertension, female gender, diabetes, and heart failure.⁵⁹ Patients with LA thrombus have a higher CHADS₂ score (mean difference 0.88, 95% confidence interval: 0.68–1.07) and a 3.5-fold increased risk of stroke/systemic embolism.⁵⁹ A recent *post hoc* analysis from the ENSURE-AF (edoxaban vs. warfarin in subjects undergoing cardioversion of AF) study demonstrated that only age and heart failure were independent risk factors for the detection of LA thrombi.⁶⁰ Thrombus formation is most frequently observed in the left atrial appendage (LAA) but may also occur in the LA cavity,⁶¹ although this is more often associated with mitral valve disease rather than AF or AFL.⁶²

Transoesophageal echocardiography (TOE) enables evaluation of LAA morphology and flow patterns within it, and TOE is the gold standard to rule out thrombus formation,^{1,63} whereas transthoracic echocardiography has limited ability to evaluate the LAA. TOE has a sensitivity of about 92% and a specificity of 98% (with negative and positive predictive values of 100 and 86%) for the identification of LAA thrombosis in patients with AF when compared to intraoperative findings.^{64,65} The sensitivity of TOE can be improved by ultrasound contrast agents that opacify the appendage and facilitate identification of filling defects.⁶⁶ Standard TOE may also be complemented by the use of three-dimensional TOE and tissue-Doppler imaging, including speckle tracking.^{67,68} Three-dimensional TOE allows a more comprehensive LAA assessment by overcoming inadequate imaging planes and other limitations of two-dimensional imaging.⁶³

Because of the multilobed and complex anatomy of the LAA, visualizing the entire LAA to exclude small thrombi is often challenging. Absence of colour flow in the distal part of the LAA or side lobes may indicate a filling defect caused by thrombus formation. Functional evaluation of LAA and the risk of thromboembolism by Doppler echocardiography is recommended.⁶³ Left atrial appendage flow can be assessed upon alignment of the pulsed-wave Doppler signal using colour flow imaging with sampling in the proximal third of the LAA, where maximal flow velocities are obtained. Velocities <40 cm/s are associated with presence of spontaneous echocardiographic contrast (SEC) and, in particular, velocities below 20 cm/s, associate with identification of LAA thrombi and increased risk of thromboembolic events.^{69–72} In fact, SEC, which is promoted by

reduced LAA flow velocities, is the cardiac factor most strongly associated with LAA thrombus and embolic events.⁷⁰ Accordingly, the presence of low flow velocities and/or SEC requires meticulous evaluation of the LAA before cardioversion. In addition to SEC and low LAA flow velocities, TOE may also help identifying other predictors of thromboembolism, e.g. complex aortic plaques. An algorithm detailing echocardiographic evaluation of LAA prior to cardioversion has previously been provided (Figure 5).⁶³

Key points

- A left atrial thrombus is observed in about 10% of non-valvular AF.
- Thrombus formation is most frequently observed in the LAA.
- Transoesophageal echocardiography is the gold standard to rule out left-atrial thrombus formation.
- Low flow in the LAA is associated with SEC, LAA thrombi, and thromboembolic events.

Imaging of the left atrial appendage: new modalities

Excluding *in situ* thrombosis is crucial before cardioversion of AF and AFL, and although TOE is the gold standard,^{1,63} *multidetector computed tomography* (MDCT) and *cardiac magnetic resonance* (CMR), are emerging as new valuable modalities for imaging and assessment of LAA anatomy and function.⁶³ Also, as described above, the number of opportunities for increasing the information gained from echocardiography is growing. Although *transthoracic echocardiography* currently has a limited role in the evaluation on the LAA, the use of harmonic imaging and ultrasound contrast agents have enhanced the sensitivity for detection of LAA thrombi.⁷³ During planned interventional cardiac procedures, *intracardiac echocardiography* (ICE) provides an alternative imaging method, when TOE is not feasible. Intracardiac echocardiography reliably diagnoses LAA thrombi⁷⁴ but is less sensitive than TOE.⁷⁵

Multidetector computed tomography provides three-dimensional volumetric data of the entire heart, including the LAA, with high spatial (0.24–0.4 mm) and temporal (66–100 ms) resolution enabling identification of LAA thrombi (Figure 6) and spontaneous contrast formation similar to the SEC observed by TOE.^{76–78} The sensitivity of MDCT to detect LAA thrombus is up to 100% compared to TOE,⁷⁹ whereas the positive predictive value is between 41% and 92% depending on the type of data acquisition.⁸⁰ The performance of MDCT is enhanced when delayed imaging is used to differentiate between reduced LAA filling and SEC or thrombus.⁸⁰ Cardiac magnetic resonance has high temporal resolution (30–50 ms) and visualizes LAA size and function, and CMR may be used for detection of thrombus in patients with AF. Also, LAA blood flow can be measured by velocity-encoded techniques.⁸¹ The lack of need for radiation is an advantage, whereas limitations of CMR include a lower spatial resolution (1–2 mm), lengthy scanning procedures and inability to be performed in the majority of patients with implanted cardiac devices.

A recent systematic review and meta-analysis of 22 MDCT and 4 CMR studies compared the diagnostic performance of MDCT and CMR with TOE for identification of LAA thrombi.⁸² Multidetector computed tomography demonstrated sensitivity and specificity of

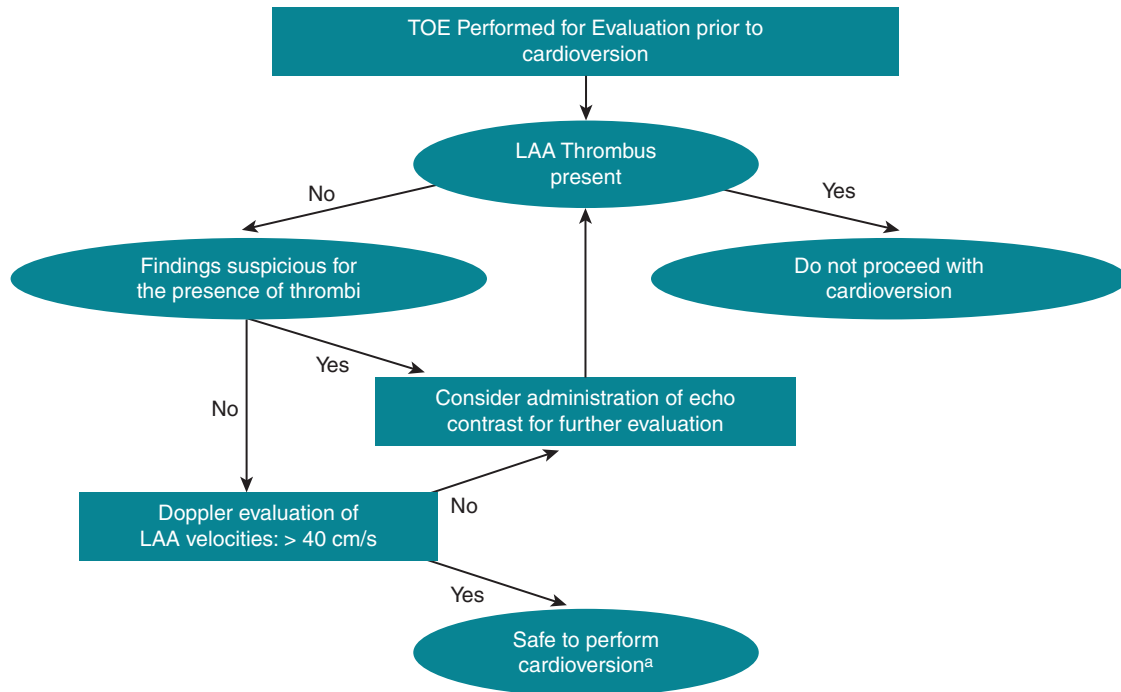


Figure 5 Schematic approach for the TOE evaluation of the LAA before cardioversion. From Beigel *et al.*,⁶³ with permission. ^aSafe if no other contraindications exist for the patient. TOE refers to 2D TOE, but 3D TOE should be used, if available, to increase sensitivity and specificity of findings. 2D, 2-dimensional; 3D, 3-dimensional; LAA, left atrial appendage; TOE, transoesophageal echocardiography.

0.99 and 0.94 vs. TOE with significantly improved specificity of the delayed imaging protocols. Cardiac magnetic resonance demonstrated sensitivity and specificity of 0.80 and 0.98 when compared with TOE. There was no significant difference in the sensitivity or specificity between MDCT and CMR.

Transoesophageal echocardiography-guided cardioversion

Current guidelines recommend TOE to exclude intra-cardiac thrombi, if a strategy of early cardioversion without being therapeutically anticoagulated the preceding 3 weeks is pursued in patients who have been in AF for >48 h.^{1,83} Oral anticoagulation treatment should be initiated immediately in all patients scheduled for cardioversion and maintained for at least 4 weeks. Long-term OAC treatment is based on the thromboembolic risk profile of the individual patient and should be assessed using the CHA₂DS₂-VASc score.^{1,83} Cardioversion can be performed safely, if no LA thrombus is identified, provided that sufficient anticoagulation is achieved before TOE.⁸³ Thus, timing of cardioversion in relation to initiation of anticoagulant therapy is crucial and should depend on the pharmacokinetics of the drug chosen, as the procedure should be performed under therapeutic anticoagulation. If a thrombus is identified on TOE, appropriate anticoagulation is recommended for at least 3 weeks, before a repeat TOE is done to ensure thrombus resolution.⁸⁴

Several randomized and observational studies investigating both low-molecular-weight heparin (LMWH)/warfarin and different NOACs have demonstrated that TOE-guided cardioversion is as safe

as a conventional cardioversion strategy with at least 3 weeks of OAC pre-treatment in terms of thromboembolic events and bleeding.⁸⁵⁻⁸⁸ In the ACUTE (Assessment of Cardioversion Using Transesophageal Echocardiography) Study, the rate of haemorrhagic events was even significantly lower in the TOE-guided cardioversion group. On the other hand, the TOE-group showed a numerical trend towards more deaths.⁸⁵ While some studies show greater rates of successful restoration of sinus rhythm with TOE-guided cardioversion,^{85,86} inconsistent results exist as to long-term maintenance of sinus rhythm.^{85,89}

Key points

- When no LA thrombus is identified on TOE, cardioversion can be performed safely, provided that sufficient anticoagulation is achieved before TOE.

Studies comparing cardioversion on non-vitamin K oral anticoagulant vs. vitamin K antagonist and special subgroups

Since the first NOAC became available for stroke prevention in AF in Europe in 2011, their use has been rapidly increasing.⁹⁰⁻⁹² A similar

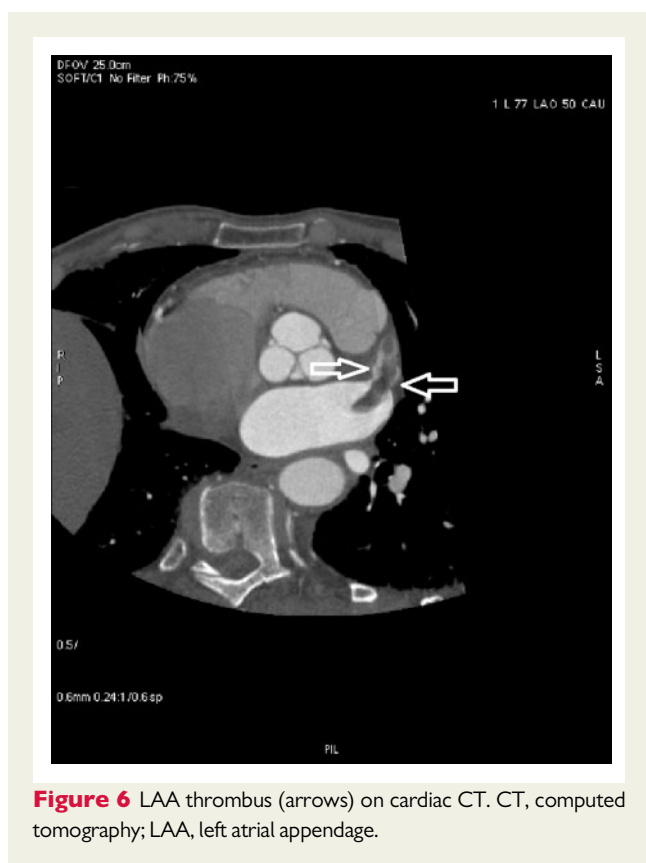


Figure 6 LAA thrombus (arrows) on cardiac CT. CT, computed tomography; LAA, left atrial appendage.

trend has been observed in patients undergoing cardioversion.^{93–95} Nevertheless, registry data from 2015 still showed a relatively high proportion of cardioversions performed on VKAs.⁹³

There is growing evidence that NOACs can safely be used for stroke prevention in patients undergoing cardioversion of AF. The first data came from *post hoc* analyses of the pivotal Phase III studies comparing NOACs with warfarin. In the RE-LY trial, 1983 cardioversions were performed in 7% of the 18 113 patients included, equally distributed across the three treatment arms (dabigatran 150 mg b.i.d., dabigatran 110 mg b.i.d., and dose-adjusted warfarin). Most patients were treated with the study drug for ≥ 3 weeks before cardioversion. Rates of thromboembolic events and major bleeding were low across all treatment arms (Table 3) suggesting that treatment with both doses dabigatran was as safe and effective as with warfarin.⁹⁶ Three minor *post hoc* analyses from the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), and ENGAGE AF-TIMI 48 [Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48 (edoxaban)] showed comparable results.^{97–99}

Prospective trials with the factor-Xa inhibitors rivaroxaban (X-VeRT, Explore the Efficacy and Safety of Once-Daily Oral Rivaroxaban for the Prevention of Cardiovascular Events in Subjects with Non-Valvular Atrial Fibrillation Scheduled for Cardioversion),

edoxaban (Edoxaban vs. Enoxaparin–Warfarin in Patients Undergoing Cardioversion of Atrial Fibrillation, ENSURE-AF), and apixaban (Eliquis Evaluated in Acute Cardioversion Compared to Usual Treatments for Anticoagulation in Subjects with Atrial Fibrillation, EMANATE), which markedly differed in design, confirmed the generally low peri-cardioversion rates of stroke, systemic embolism, death, and serious bleeding events during treatment with NOACs compared with heparin/VKA (Table 3), regardless of whether a standard care approach with ≥ 3 weeks OAC pre-treatment or an early TOE-guided approach was pursued, although these trials were not adequately powered statistically to demonstrate non-inferiority of NOAC treatment.^{87,88,100}

While patients in X-VeRT and ENSURE-AF only initiated OAC treatment with standard doses of rivaroxaban and edoxaban, respectively, before early cardioversion,^{87,88} early cardioversion in EMANATE was performed either after initiating treatment with standard doses apixaban or after a single loading dose [10 mg or 5 mg, if patients fulfilled two of the following criteria: age ≥ 80 years, weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 $\mu\text{mol/L}$)] given at least 2 h before the procedure, the latter mainly in patients with new-onset AF.¹⁰⁰

The comparable efficacy and safety of NOACs and VKA in patients undergoing cardioversion of AF were also confirmed in several recent meta-analyses.^{101–103} Similar to the results of the prospective studies and meta-analyses, several cohort studies with different post-procedural follow-up times and settings also demonstrated very low rates of thromboembolic events (0.15–1.62%) and major bleeding (0.4–1.7%) in patients with AF undergoing cardioversion during NOAC treatment suggesting that NOACs are associated with an acceptable benefit-risk profile in this setting.^{94,95,104–108} Moreover, a pre-specified *post hoc* analysis of the ENSURE-AF study found that patients receiving edoxaban were more satisfied with their treatment than patients on warfarin.¹⁰⁹ Of note, the use of NOACs also lead to faster cardioversion compared to warfarin use when pursuing a standard care approach.^{87,95,100,107,110} Finally, a meta-analysis of the warfarin vs. NOAC cardioversion trials found a lower stroke rate in patients randomized to NOAC therapy.¹¹¹

A major concern when performing cardioversion on NOAC treatment is how to ensure compliance, because unlike VKAs there is currently no test to monitor the quality of peri-procedural NOAC treatment, and observational data in patients on VKA treatment have also shown more frequent complications in patients with suboptimal anticoagulation intensity at the time of cardioversion.⁴⁴ Therefore, patient education on importance of a strict intake schedule, information about adherence aids, and the utilization of telemonitoring systems are crucial and can improve treatment adherence.¹¹² Verbal confirmation of NOAC intake and retrospective pill counting can help to ensure that anticoagulation was taken.

Key points

- The peri-cardioversion rates of stroke, systemic embolism, and bleeding are low with NOACs.
- Non-vitamin K oral anticoagulants can safely be used for stroke prevention in patients undergoing cardioversion of AF.
- Measures to ensure treatment adherence are crucial.

Table 3 Large studies investigating NOACs vs. VKA in the cardioversion setting

Study (year)	RE-LY (2011) ⁹⁶ undefined	X-VerT (2014) ⁸⁷ undefined	ENSURE-AF (2016) ⁸⁸ undefined	EMANATE (2018) ¹⁰⁰ undefined
Study type	Multicentre, international, <i>post hoc</i> analysis	Multinational, randomized, open-label, parallel-group Phase IIIb study	Multicentre, prospective, randomized, open-label, parallel-group with blinded endpoint	Multinational, prospective, randomized, open-label with blinded endpoint adjudication
NOAC	Dabigatran	Rivaroxaban	Edoxaban	Apixaban
Total number of patients (NOAC/warfarin) (N)	1270 (1319/664) ^a	1504 (1002/502)	2199 (1095/1104)	1500 (753/747)
Follow-up	30 days	30 days	58 days	30 days (90 days in patients not converted)
NOAC dosing	110 mg b.i.d. and 150 mg b.i.d.	20 mg o.d. ^b	60 mg o.d. ^c	5 mg b.i.d. ^d
Outcomes	Primary: stroke, systemic embolism and major bleeding	Primary efficacy outcome: composite of stroke, TIA, peripheral embolism, MI, and cardiovascular death Primary safety outcome: major bleeding	Primary efficacy endpoint: composite of stroke, systemic embolic event, MI, and cardiovascular mortality Primary safety endpoint: major and clinically relevant non-major bleeding	Primary efficacy endpoint: stroke, systemic embolism, and all-cause death Primary safety endpoint: major bleeding and clinically relevant non-major bleeding
Age (years)	71.5 ± 8.8 (dabigatran 150 mg), 71.4 ± 8.6 (dabigatran 110 mg), 71.6 ± 8.6 (warfarin) ^e	64.9 ± 10.6 (rivaroxaban), 64.7 ± 10.5 (VKA)	64.3 ± 10.3 (edoxa), 64.2 ± 10.8 (enoxaparin + warfarin)	64.7 ± 12.2 (apixaban), 64.5 ± 12.8 (heparin/warfarin)
CHA ₂ DS ₂ -VASc score ≥2	N/R	959/1504 (63.76%)	1707/2199 (77.63%)	mean 2.4 ± 1.7
TTR in warfarin-treated patients (%)	N/R	N/R	70.8 ± 27.4	65% (beyond first 2 weeks of treatment)
TOE-guided cardioversion, n (%)	Dabigatran 150 mg: 162 (24.11%) Dabigatran 110 mg: 165 (25.5%) Warfarin: 88 (13.25%)	Rivaroxaban: 410 (40.92%) VKA: 218 (43.42%)	Edoxaban: 589/1095 (53.8%) Warfarin: 594/1104 (53.8%)	Apixaban: 418/753 (55.5%) Heparin/warfarin: 437/747 (58.1%)
Patients with primary efficacy outcome, n (%)	Dabigatran 150 mg: 2 (0.3%) Dabigatran 110 mg: 5 (0.77%) Warfarin: 4 (0.6%)	Rivaroxaban: 5/978 (0.51%) VKA: 5/492 (1.02%)	Edoxaban: 5/1095 (0.5%) Warfarin: 11/1104 (1%)	Apixaban: 0 strokes and 2 death Heparin/warfarin: 6 strokes and 1 death
Patients with primary safety outcome, n (%)	Dabigatran 150 mg: 4 (0.6%) Dabigatran 110 mg: 11 (1.7%) Warfarin: 4 (0.6%)	Rivaroxaban: 6/988 (0.61%) VKA: 4/499 (0.8%)	Edoxaban: 16/1067 (1.5%) Warfarin: 11/1082 (1%)	Apixaban: 3 major bleeds and 11 CRNM bleeds Heparin/warfarin: 6 major bleeds and 13 CRNM bleeds

b.i.d., twice a day; CHA₂DS₂-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female); CRNM bleeds, clinically relevant non-major bleeds; EMANATE, Eliquis evaluated in acute cardioversion compared to usual treatments for anticoagulation in subjects with atrial fibrillation; ENSURE-AF, edoxaban vs. warfarin in subjects undergoing cardioversion of atrial fibrillation; MI, myocardial infarction; N/R, not reported; NOAC, non-vitamin K oral anticoagulant; o.d., once daily; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; TIA, transient ischaemic attack; TOE, transoesophageal echocardiography; TTR, time in therapeutic range; VKA, vitamin K antagonist; X-VerT, 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.

^aTotal number of cardioversions.

^b15 mg o.d. in patients with CrCl of 30–49 mL/min.

^c30 mg o.d., if CrCl 15–50 mL/min, body weight ≤60 kg or use of P-gp inhibitors.

^d2.5 mg b.i.d., if at least two of the following: age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL (≥133 μmol/L). Cardioversion could be performed 2 h after a loading dose of 10 mg (5 mg, if at least two of the following: age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL [≥133 μmol/L]).

^eFrom main study.

Cardioversion in patients with atrial fibrillation after acute coronary syndrome and/or percutaneous coronary intervention

Atrial fibrillation and coronary artery disease commonly coexist,¹¹³ and ~5–10% of patients undergoing percutaneous coronary intervention (PCI) also have AF.¹¹⁴ Therefore, the vast majority of these patients require combination therapy with OACs and antiplatelet drugs for a limited period of time after the procedure.¹¹⁵ Acute cardioversion can be justified in patients who are haemodynamically unstable, but usually cardioversion can be deferred. If a cardioversion is planned during the chronic phase after PCI, while patients are on combination therapy with a NOAC and an antiplatelet drug, attention must be paid to the appropriate NOAC dosage as used in the pivotal cardioversion trials.

Cardioversion in patients with atrial fibrillation after left atrial appendage occlusion

Left atrial appendage occlusion (LAAO) is an alternative to OAC treatment if the bleeding risk is high or if OAC treatment is contraindicated. There are currently no data suggesting the optimal management of these patients, if they require a cardioversion, because LAAO and contraindications to OAC were exclusion criteria in the randomized trials.^{116–118} A pre-procedural TOE should be performed in these patients and a short duration of OAC should be considered in patients with concomitant antiplatelet therapy.

In summary, cardioversion under peri-procedural treatment with NOACs appears as safe and effective as under treatment with heparin/VKA regardless of whether pursuing a standard care approach with ≥ 3 weeks pre-treatment or an early approach with a TOE performed immediately before the procedure. The latter is more convenient for patients and healthcare professionals. Immediate cardioversion at least 2 h after a single loading dose of apixaban is feasible and, therefore, might become a more convenient alternative to heparin pre-treatment. Ensuring adherence to NOAC is important, as patients undergoing cardioversion are at increased risk of stroke.

A personalized cardioversion approach to patients after PCI or LAAO is preferred.

Conclusion

Cardioversion is widely used as part of a rhythm control strategy in patients with AF. Nevertheless, a wait-and-see approach is reasonable in patients with recent-onset AF, as the majority will convert spontaneously within 48 h. Recurrences after ECV of persistent AF show a specific pattern which may help guide rhythm control. Although complications of cardioversion overall are rare, it is of utmost importance to assess thromboembolic risk before the procedure, initiate timely OAC and continue life-long in patients with increased stroke risk. The advent of NOACs facilitates the streamlining of the peri-procedural anticoagulation management and, thus, performing cardioversion without major delays, provided that patients have been adequately counselled about the necessity for compliance to NOAC treatment. After the procedure, a close

structured clinical follow-up is mandatory to recognize AF recurrences, to ensure appropriate and effective rhythm control therapy, to evaluate symptoms, and to optimize treatment of underlying cardiovascular conditions.

Conflict of interest: A.B. has received lecture fees from Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, MSD; and research support from Gilead, the Region of Southern Denmark, and the Zealand Region. E.L.G. has received speaker honoraria or consultancy fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, MSD, Portola Pharmaceuticals, and Roche. He is an investigator in the THEMIS, SATELLITE, and FLAVOUR studies (AstraZeneca) and has received research grants from Boehringer Ingelheim. P.K. receives research support for basic, translational, and clinical research projects from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and German Centre for Cardiovascular Research, from several drug and device companies active in atrial fibrillation, and has received honoraria from several such companies in the past. P.K. is listed as inventor on two patents held by University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783). All other authors have no conflict of interest to declare.

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