European Review for Medical and Pharmacological Sciences 2013; 17: 3132-3147

Management of atrial fibrillation in the Emergency Department: current approach and future expectations

V. RUSSO[1], S. NAVARIN[1], G. ZAMPINI[1], L. MAGRINI[1], C. MANN[2], M.L. MUIESAN[3], R. DE CATERINA[4], M.B. YILMAZ[5], O. BETON[6], V. MONZANI[7], J. KUBICA[8], C. MÜLLER[9], S. DI SOMMA[1], ON BEHALF OF GREAT NETWORK

[1]Emergency Medicine Department, Sant'Andrea Hospital, School of Medicine and Psychology, "Sapienza" University Rome, Rome, Italy
[2]Emergency Medicine at Taunton & Somerset Hospital, School for Emergency Medicine, London, UK
[3]Division of Internal and Emergency Medicine, University of Brescia, Brescia, Italy
[4]Institute of Cardiology and Center of Excellence on Aging, "G. d'Annunzio" University, Chieti, Italy
[5]Departments of Cardiology, Cumhuriyet University, Sivas, Turkey
[6]Cardiology Clinic, Sivas State Hospital, Sivas, Turkey
[7]Emergency Medicine Unit, Fondazione IRCCS Ca' Granda, Maggiore Policlinico Hospital, Milan, Italy
[8]Department of Cardiology and Internal Medicine, Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[9]Division of Cardiology, University Hospital Basel, Basel, Switzerland

Abstract. – Atrial fibrillation (AF) is the most common cardiac dysrhythmia and occurs in 3.3%-10% of emergency admissions. It is frequently quoted for people over the age of 75, but the cases of AF in young subjects without structural heart disease are also increasing, therefore, leading to the evaluation of "lonely atrial fibrillation" as a new challenge for the clinician. The first diagnosis and treatment often occur in the emergency room and the emergency physician has therefore to evaluate the initial step towards the therapeutic decisions. Although international standard guidelines are available, AF treatment in the Emergency Department (ED) is still heterogeneous in terms of the management strategy chosen. There are two main strategies for the management of AF: rate and rhythm control. Moreover, antithrombotic treatment is pivotal in AF to prevent cardioembolic stroke and it is considered a primary objective after an accurate assessment of antithrombotic treatment risks and benefits. The introduction of innovative echocardiographic approach, directly in ED, seems to improve the management and risk stratification of patients with AF.

This review aims to provide an overview about the current approach and the future expectations in the management of AF in ED. This manuscript represents a synopsis of the lectures on AF management in the ED of the Third Italian GREAT Network Congress, that was hold in Rome, 15-19 October 2012. We decided to use only the most relevant references for each contribution as suggested by each participant at this review.

Key Words:
Atrial fibrillation, Rhytm and rate control, Cardioversion, Antithrombotic therapy.

Introduction

Atrial fibrillation (AF) is the most common cardiac dysrhythmia; it is an age related condition and as the populations of Europe and other developed nations experience longer life expectancies so the prevalence of AF rises. Rates of 5% are frequently quoted for people over the age of 75. AF may manifest itself as an acute or chronic condition and may be asymptomatic or be sufficiently disabling as to restrict the activities of daily living.

AF is also associated with an increasing number of comorbidities, including arterial hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, heart failure and valvular diseases. All these conditions may favor the development of AF altering cardiac structure and function[1].

AF occurs in 3.3%-10% of emergency admissions[2,3]; in some of these cases, it is longstanding and/or incidental to clinical management, but more often AF has developed acutely as either the primary clinical problem or as a complication of another acute (pneumonia, myocardial infarc-

Corresponding Author: Veronica Russo, MD; e-mail: veryo85@hotmail.it

tion, septicaemia, pulmonary emboli, exacerbations of chronic obstructive pulmonary disease etc) or chronic (valvular heart disease, hypertension, heart failure, cardiomyopathies, etc) diseases. One-third of hospitalizations for cardiac rhythm disturbances are attributed to AF, with increasing rates in the last decade. Significant morbidity and mortality, including 15% to 20% of all ischemic strokes and 20% of all strokes, result from AF. The overall mortality rate for patients with AF is approximately double than that for patients in normal sinus rhythm. AF has increasing prevalence and negative impact on quality of life and health care expenses and it is associated with many causes and comorbidities[4,5].

The scientific community has been involved more and more frequently in the study of epidemiological features related to the prolongation of life expectancy and to the resulting comorbidities, leading to an increasing number of cases of AF with the age of patients, especially when considering the permanent form in the context of coronary artery disease and chronic heart failure. Moreover, the cases of AF in young subjects without structural heart disease are also increasing, therefore leading to the evaluation of "lonely atrial fibrillation" as a new challenge for the clinician who needs to consider different anti-arrhytmic, anti-thrombotic and interventional options, as in the case of trans-catheter ablation. The first diagnosis and treatment often occur in the Emergency Room and the emergency physician has therefore to value the initial step towards the therapeutic decisions, including rhythm or rate control.

AF Management: Two Different Strategies

Although international standard guidelines are available, AF treatment in the Emergency Department (ED) is still heterogeneous in terms of the management strategy chosen[6-12]. However, every emergency physician has to immediately provide supplementary oxygen, establishment of an intravenous line, continuous electrocardiographic monitoring, blood pressure and 12 lead ECG. The initial step towards the therapeutic decisions is the determination of AF duration, classification, onset date, date of discovery of AF, frequency, precipitating factors and symptoms. Special attention should also be paid to identify the signs of left ventricular hypertrophy, pre-excitation, bundle branch block, prior myocardial infarction or other structural heart diseases or pulmonary diseases and to measure QRS, QT/Qtc interval[13,14]. The clinical presentation of acute AF depends on a number of factors, so the resulting spectrum of symptoms is broad. Some patients are completely asymptomatic, more often they complain of palpitation, dyspnoea, or weakness, possibly associated with chest discomfort or lightheadedness, but the attack is still reasonably well tolerated. In a minority of cases AF is poorly tolerated due to severe angina or hemodynamic decompensation, i.e. pulmonary oedema, hypotension, or rarely, circulatory collapse with syncope. It would be unusual for acute AF to cause significant hemodynamic instability in the absence of structural heart disease. However, the treatment of precipitating or reversible causes of AF is first recommended. Goals of AF treatment are to alleviate symptoms, improve functional capacity and quality of life and reduce morbidity/mortality associated with AF by preventing tachycardia-induced cardiomyopathy and reduce hospitalization/admission rates[15-18].

Two different strategies exist for the management of cardiac rhythm in patients with AF: rate and rhythm control. While in clinical practice the first strategy is more practical and easy for physicians[6,7], current guidelines recommend rhythm control as a first line strategy for patients presenting to the ED within 48 hours of the onset of AF or if transesophageal echocardiography (TEE) has excluded left atrial thrombus[5,16]. Although it is intuitive that sinus rhythm is better than atrial fibrillation the largest studies of rate versus rhythm strategies (AFFIRM and AF-CHF clinical trials) demonstrated no mortality difference when comparing these strategies[19,20]. However the DIAMOND study demonstrated a reduced mortality in patients in sinus rhythm but this was not applicable to patients on a rhythm control strategy[21] (Figure 1).

Rate Control Strategy

Heart rate control strategy aims to maintain a ventricular rate that protects the patient from consequences of tachycardia. Target ventricular rate control in the absence of accessory pathway (pre-excitation syndrome) can be obtained by atrioventricular nodal conduction slowing drugs (Table I). Initial target ventricular rate is < 100 bpm at rest (lenient rate). If complaints persist despite lenient rate achievement, strict rate control (< 80 bpm at rest and < 110 bpm during moderate exercise) should be substituted. In case of failure to obtain target ventricular heart rate with drug therapy, atrioventricular node ablation

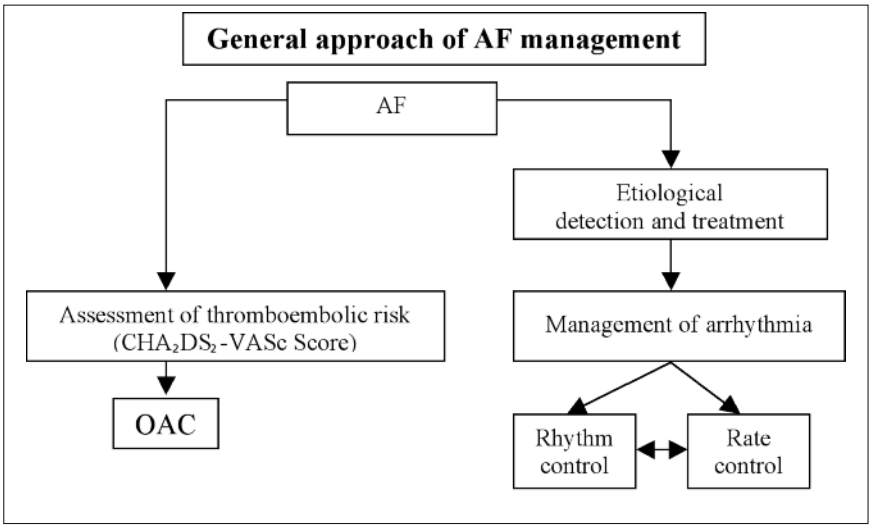

Figure 1. Overview of AF management. If a strategy of rate or rhythm control is not successful, crossover to the alternate strategy may be required. AF, atrial fibrillation; OAC, oral anticoagulation.

Table I. Intravenous administered pharmacological drugs for ventricular rate control with AF patients in acute setting[4,5,22,23].

Drug	Loading dose	Onset	Maintenance dose	Side effects
Heart rate control in patients without accessory pathway[a]				
Esmolol	500 mcg/kg over 1 min	5 min	0.05-0.2 mg/kg/min	Hypotensions, bronchospasm, bradycardia, AV block, heart failure
Metoprolol	2.5-5 mg/kg in 2 min to a maximum of 3 doses	5 mins	NA	Hypotension, bronchospasm, bradycardia, AV block, heart failure
Propranolol	0.15 mg/kg	5 mins	NA	Hypotension, bronchospasm, bradycardia, AV block, heart failure
Diltiazem[b]	0.25 mg/kg over 2 min	2-7 mins	5 to 15 mg/h	Hypotension, AV block, heart failure, bradicardia
Verapamil	0.75-0.15 mg/kg in 2 min	3-5 mins	NA	Hypotension, AV block, heart failure, bradycardia, interaction with digoxin
Digoxin[c]	0.50 mg initially, then 0.25mg/6 h to max 1,5 mg	2 hrs	0.125-0.25 mg/day	AV block, bradycardia, digitalis intoxication (gastrointestinal, ocular, neurological, proarrhythmia)
Heart rate control in patients with accessory				
Amiodarone	150 mg over 10 min (Repeat in 10-30 min if necessary)	< 30 min[e]	0.5 to 1 mg/min IV Then 200 mg daily, orally	Hypotension, bradycardia, pulmonary toxicity, hepatotoxicity, photosensitivity, corneal deposits, skin discoloration, hypo/ hyperthyroidism, polyneuropathy, optic neuropathy, interaction with acenocoumarol/warfarin, bradycardia, QT/QTc prolongation, torsades de pointes (rare)

[a]In the presence of preexitation administration of these drugs can cause torsades de pointes while bloking AV node and enhancing antioventricular conduction over accessory pathway. [b]Diltiazem (iv) could be used in acute setting of heart failure for ventricular control of AF. But routine oral administration of diltiazem/verapamil increases mortality in heart failure patients. [c]According to current guidelines digoxin iv use for heart rate control can be given to heart failure patients. Caution should be taken to give long-time therapy because a recent analysis of the AFFIRM trial showed an overall 41% increase in all-cause mortality in patients taking digoxin vs those not taking digoxin. The increase in all-cause mortality was consistently observed in men and women and in patients with and without underlying heart failure[24]. [d]A caution should be taken for administration of amiodarone in heart failure patients for heart rate control if duration of AF and effective thromboprophylaxis situation is not known. Because it can cardiovert rhythm to sinus ryhthm. It is generally recommended for critically ill patients. [e]Onset of effect of amiodarone is < 30 min if administered iv route and 1-3 weeks for oral route[25]. AV, atrioventricular; NA, not applicable.

and pacemaker implantation can be considered or sinus rhythm restoration (rhythm control) can be attempted in the presence of supportive clinical and echocardiographic factors[5,16,26].

Rhythm Control Strategy

Rhythm control strategy targets sinus rhythm restoration by pharmacological cardioversion (CV) (antiarrhythmic drugs) ± electrical cardioversion and maintenance by antiarrhythmic drugs. This strategy is usually considered for patients with paroxsymal or persistant AF in the presence of favourable clinical and echocardiographic parameters[16-18,22]. These parameters predict high possibility of staying in sinus rhythm after CV. CV may be achieved by means of drugs or electrical shocks. Drugs were commonly used before electrical CV became a standard procedure[4].

Indications and contraindications of both electrical and pharmacological CV are given in Tables II and III, respectively[4,5,27,28].

Electrical Cardioversion

Electrical CV or direct-current CV involves delivery of an electrical shock synchronized with the intrinsic activity of the heart by sensing the R wave of the ECG to ensure that electrical stimulation does not occur during the vulnerable phase of the cardiac cycle. Electrical CV success rates vary from 75 to 93%. They are inversely related to AF duration, chest wall impedance, and left atrial size[29-33]. Immediate electrical CV should be considered in AF causing hemodynamically instability without considering its duration and classification, supportive clinical or echocardiographic parameters, antiarrhythmic drugs and also patient's anticoagulation status[4,18]. But, in the meanwhile thromboprophylaxis should be initiated. Immediate electrical CV is also recommended for AF involving pre-exitation when antegrade conduction via accessory pathway is very fast, because this situation carries very high risk of rapid progression to ventricular tachycardia/fibrillation and abrupt hemodynamic compromise[34].

Table II. Indications and controindications of electrical CV of recent-onset AF in ED.

Indications
1. *Emergent electrical CV;* for patients with recent-onset AF and rapid ventricular rate who has hemodynamic instability (ongoing myocardial ischemia, symptomatic hypotension, heart failure) that does not respond promptly to pharmacological drugs
2. *Emergent electrical CV;* for patients with recent-onset AF involving preexcitation when very rapid tachycardia or hemodynamic instability occurs
3. *Urgent electrical CV;* for patients without hemodynamic instability when symptoms of AF are unacceptable to the patient. In case of early relapse of AF after CV, repeated electrical CV may be made following administration of antiarrhythmic medication
4. Elective electrical CV as an initial treatment may be considered in order to initiate a long-term rhythm control management strategy for patients with recent-onset AF within 48 h of onset by patient/physician choice
5. Elective electrical CV as an initial treatment may be considered in order to initiate a long-term rhythm control management strategy for patients with recent-onset AF over 48 h of onset when TOE has excluded left atrial appendage thrombus by patient/physician choice
6. Enhanced/facilitated elective electrical CV which is electrical CV after pretreatment with antiarrhythmic drugs (amiodarone, flecainide, propafenone or ibutilide) in order to enhance success of electrical CV and prevent recurrent AF, should be considered for patients with recent-onset AF within 48 h of onset or over 48 h if thrombus exluded at TOE
7. Electice electrical CV should be considered in order to to initiate a long-term rhythm control management strategy after antiarrhythmic drug failure to restore sinus rhythm in patients with recent-onset AF within 48 h of onset or over 48 h if thrombus exluded at TOE
Contraindications
1. Known atrial thrombus and no emergent indication for CV
2. In the presence of digitalis toxicity
3. Severe electrolyte imbalance (e.g. hypokalemia) or hyperthyroidism and no emergent indication for CV
4. Frequent repetition of direct-current cardioversion is not recommended for patients who have relatively short periods of sinus rhythm between relapses of AF after multiple CV procedures despite prophylactic antiarrhythmic drug therapy
5. In the presence of doubt about underlying rhythm (e.g multifocal atrial tachycardia) and no emergent indication for CV R43-45
6. Elective electrical CV without anticoagulation
7. Elective electrical CV in patients who can not be safely sedated

Table III. Indications and controindications of pharmacological CV of recent-onset AF in ED.

Indications
1. *Pharmacological CV*; as an initial treatment may be considered in order to initiate a long-term rhythm control management strategy for patients with recent-onset AF within 48 h of onset by patient/physician choice **2.** *Pharmacological CV*; as an initial treatment may be considered in order to initiate a long-term rhythm control management strategy for patients with recent-onset AF over 48 h of onset when TOE has excluded left atrial appendage thrombus by patient/physician choice **3.** *Pharmacological CV*; should be considered in order to to initiate a long-term rhythm control management strategy after electrical CV failure to restore sinus rhythm in patients with recent-onset AF within 48 h of onset or over 48 h if thrombus exluded at TOE **4.** Pretreatment with antiarrhythmic drugs (amiodarone, flecainide, propafenone or ibutilide) in order to enhance success of electrical CV (*enhanced/facilitated elective electrical CV*) and prevent recurrent AF, in patients patients with recent-onset AF within 48 h of onset or over 48 h if thrombus excluded at TOE
Contraindications
1. Known atrial thrombus **2.** Severe electrolyte imbalance (e.g. hypokalemia) or hyperthyroidism

Electrical CV should be performed with the patient in a fasting state under adequate sedation for elective cases. Drugs chosen for sedation should have short acting effect. Oxygen saturation and electrolytes should be normal and anticoagulation status monitored. External pacing pads may be used for both CV and for prophylaxis of asystole or bradycardia if ensue after electrical CV or if sick sinus syndrome is suspected[35]. Currently, two conventional positions (anterolateral and anteroposterior) are commonly used for electrode placement. Several studies have shown that anteroposterior electrode placement is more effective than anterolateral placement. In the presence of pacemaker or implantable cardioverter defibrillator, the electrode paddle should be at least 8 cm from the pacemaker battery, and the anteroposterior paddle positioning is recommended. In pacemaker-dependent patients an increase in pacing threshold should be anticipated. These patients should be monitored carefully and after CV, the device should be interrogated and evaluated to ensure normal function[4].

Success of electrical CV depends on adequacy of delivered current flow through the heart and the major determinants are: the nature of the shock waveform (mono or biphasic) and the level of delivered energy[36-38]. Currently, most evidence favors the use of biphasic external defibrillators due to their categorically lower energy requirements and greater efficacy[39]. A lower prevalence of skin burns and less skeletal muscle damage have also been reported. Additionally, biphasic waveforms result in fewer post-shock arrhythmias, and a shorter period of myocardial stunning[40]. Initial energy requirements are usually ≥ 200 joules for monophasic waveform and ≥ 100 joules for biphasic waveform, with possibly more being required in obese patients and in long-standing AF patients the hemodynamic instability condition, electrical CV should be performed with maximal energy of the present defibrillator[36-38]. Biphasic waveforms may be of special interest in patients who have failed to revert with the use of monophasic waveforms[41].

The risks and complications of electrical CV are associated primarily with thromboembolic events, post-cardioversion arrhythmias, and the risks of general anaesthesia. Thromboembolic events have been reported in about 3% to 5% of patients who did not receive anticoagulation before CV, whereas it is only 0% to 1% by adequate anticoagulation or by exclusion of left atrium thrombi before the procedure[42,43]. Skin burns are a common complication. In patients with sinus node dysfunction, especially in elderly patients with structural heart disease, prolonged sinus arrest without an adequate escape rhythm may occur. Dangerous arrhythmias, such as ventricular tachycardia and fibrillation, may arise in the presence of hypokalaemia, digitalis intoxication, or improper synchronization (R on T phenomenon). The patient may become hypoxic or hypoventilated from sedation, but hypotension and pulmonary oedema are rare[4,5]. However, over-the-night stay is generally recommended.

Pharmacological Cardioversion

Pharmacological CV should be considered to hemodynamically stable patients. Most patients

who undergo pharmacological CV require continuous medical supervision and ECG monitoring during the drug infusion and for a period afterwards (usually about half the drug elimination half-life)[4,5]. Antiarrhythmic drug choice is based on patients' characteristics, presence or absence of structural heart disease and antiarrhythmic drug features, side effects, success rates, and adverse effects (Table IV).

Future Directions

Current practice in the pharmacological management of AFis moving to a more pro-active paradigm. It is to be hoped that the costs of newer

Table IV. Recommended dosage and adverse effects of the drugs most commonly used for the restoration of sinus rhythm[16,44-46].

Drug	Initial dose	Maintenance dose	Adverse effects	Contraindication and precautions
Amiodarone[a]	5 mg/kg i.v. over 1 h	50 mg/h	Phlebitis, hypotension, bradycardia, pulmonary toxicity, hepatotoxicity, photosensitivity, corneal deposits, skin discoloration, hypo/hyper -thyroidism, polyneuropathy, optic neuropathy, interaction with acenocoumarol/ warfarin, bradycardia, QT/QTc prolongation, torsades de pointes (rare)	Hypo or hyper thyroidism, QTc interval > 500 msec, when using concomitant therapy with QT-prolonging drugs, dose og VKAs and of digitoxin/digoxin should be reduced
Flecainide b	2 mg/kg i.v. over 10 min, or 200-300 mg p.o. (pill in the pocket)[c]	100-150 mg/ 12 h	Decrease in BP, may prolong QRS duration, and hence the QT interval; and may inadvertently increase the ventricular rate due to CV to AFL and 1:1 conduction to the ventricles	Not suitable for patients with marked structural heart disease; branch block or wide QRS complex, postinfarction scar, heart failure
Ibutilide	1 mg i.v. over 10 min	1 mg i.v. over 10 min after waiting for 10 min (If AF persists)	Can cause prolongation of the QT interval and torsades de pointes; watch for abnormal T-U waves or QT prolongation. Will slow the ventricular rate, AV block	LV hypertrophy (WT ≥ 1.4 cm), Severe LV systolic dysfunction (EF < 20%), ACS, Concurrent use of Class IA or III antiarrhythmics within 4 hours after ibutilide, QTc interval > 440 msec.
Propafenone b	2 mg/kg i.v. over 10 min or 450-600 mg (oral) (pill in the pocket)[c]	150-300 mg/ 8 h p.o.	Decrease in BP, not suitable for patients with marked structural heart disease; may prolong QRS duration; will slightly slow the ventricular rate, but may inadvertently increase the ventricular rate due to CV to AFL and 1:1 conduction to the ventricles	Contraindicated in coronary artery disease, reduced LV ejection fraction and heart failure, LV hypertrophy (WT ≥ 1.4 cm), Caution in the presence of conduction system Disease (branch block or wide QRS complex) and renal impairment.
Vernakalant	3 mg/kg i.v. over 10 min	Second infusion of 2 mg/kg i.v. over 10 min after 15 min first infusion (If AF persists)	Sneezing, dysgeusia, paraesthesia, nausea, cough, pruritus, dizziness, hyperhidrosis, hypotension or decrease in BP (R39)	Contraindicated in moderate or severe HF, severe AS, ACS (in the last 30 days) or hypotension (SBP < 100 mmHg) Caution in mild HF

[a]Amiodarone administration dose scheme in Table VI can be used for the restoration of sinus rhythm. [b]Flecainide and propafenone can increase QRS duration. An increase > 25% from baseline indicates discontiuation or dose reduction of these drugs. [c]Pill-in-the-pocket' technique – preliminary assessment in a medically safe environment and then used by the patient in the ambulatory setting. ACS: acute coronary syndromes; AF: atrial fibrillation; AFL: atrial flutter; AS: aortic stenosis; BP: blood pressure; CV: cardioversion; EF: ejection fraction; HF: heart failure; LV: left ventricular; SBP: systolic blood pressure; VKAs: vitamin K antagonists; WT: wall thickness.

therapies will be offset by reduced hospitalizations which account for 50% of AF related health costs.

Recent interest has focused on newer agents for rapid CV of acute AF, including Vernakalant. This multi-channel blocker has achieved almost 90% CV rates in routine clinical practice. The effectiveness and safety profile make vernakalant an ideal ED drug.

Moreover, the introduction of newer anticoagulation agents such as Dabigitran ride over the challenge to maintain stable INRs in patients on Warfarin because Dabigatran offers a more predictable dose response and require no regular monitoring of coagulation status; however, concerns remain regarding the reversibility of these non-coumarins.

Vernakalant

Vernakalant is a novel agent, which acts preferentially in the atria by blocking several ion channels, resulting in prolongation of atrial refractoriness and rate-dependent slowing of atrial conduction, but has little impact on currents involved in ventricular repolarization[24,46]. Vernakalant is not classified in Vaughan-Williams class and has a rapid onset of action and a mean elimination half-life of 3-5 hours. Its most common side effects were taste alterations (30%), sneezing (16%), paraesthesiae (10%), and nausea (9%), which usually resolved within 5-15 minutes. Serious adverse events were reported at similar rates for vernakalant and placebo (4.1% vs. 3.9%). Transient hypotension occurred in about 5-7% of patients treated with vernakalant, with the blood pressure returning to baseline after approximately 15-20 minutes. Vernakalant is effective in cardioversion of patients with AF ≤ 7 days or AF ≤ 3 days after cardiac surgery and provides a rapid antiarrhythmic effect with approximately 50% of patients converting within 90 minutes after the start of treatment and a median time to conversion of 8-14 minutes. Vernakalant is administered as a 10 minute infusion of 3 mg/kg and, if AF persists after 15 minutes, a second infusion of 2 mg/ kg can be given[16,46].

Vernakalant has a satisfactory safety profile in patients with minimal-to-moderate heart disease, including ischaemic heart disease, but should be used with caution in hemodynamically stable patients with NYHA class I and II heart failure, because of increased risk of hypotension and non-sustained ventricular arrhythmias in these patients. Vernakalant is contraindicated in patients with hypotension, 100 mmHg, recent (within 30 days) acute coronary syndrome, NYHA class III and IV heart failure, severe aortic stenosis, and QT interval prolongation (uncorrected QT .440 ms). In direct comparison, vernakalant was significantly superior to intravenous amiodarone in restoration of sinus rhythm within 90 min (51.7% vs. 5.2%; $p < 0.0001$) and within 4 hours after infusion (54.4% vs. 22.6%; $p < 0.0001$). Meta-analysis of the efficacy of vernakalant showed that patients were 8.4 times more likely to convert to sinus rhythm within 90 minutes after vernakalant infusion, than on placebo or amiodarone (95% CI 4.4-16.3), without excess risk of serious adverse events (risk ratio 0.91; 95% CI 0.6-1.36)[24,46]. Clinical trials accessing efficacy of vernakalant are summarized in Table V[46], Figure 2).

Table V. Clinical trials assessing efficacy of vernakalant.

Clinical trial	Type of trial	N	Clinical setting	Control group	Primary endpoint	Vernakalant (i.v) vs control (*p*-Value)	Median time to CV (min)
CRAFT	RCT/ phase II	56	AF duration 3-72 h	Plasebo	AF termination within 30 min	56% vs. 5% ($p < 0.001$)	14
ACT I	RCT/ phase III	220	AF duration 3h-7d	Placebo	AF termination within 90 min	51.7% vs. 4% ($p < 0.001$)	11
ACT II	RCT/ phase III	150	AF postcardiac surgery	Placebo	AF termination within 90 min	47% vs. 14%\ ($p < 0.001$)	12.4
ACT III	RCT/ phase III	265	AF duration 3h-7d	Placebo	AF termination within 90 min	51.2% vs. 3.6% ($p < 0.0001$)	8
ACT IV	Open label	167	AF duration 3h-7d	–	AF termination within 90 min	Vernakalant: 50.9%	14
AVRO	RCT	232	AF duration 3-48h	Amiodarone	AF termination within 90 min	53.4% vs. 5.2% ($p < 0.0001$)	11

AF: atrial fibrillation; CV: cardioversion; N: number of patients included; RCT: randomized clinical trial.

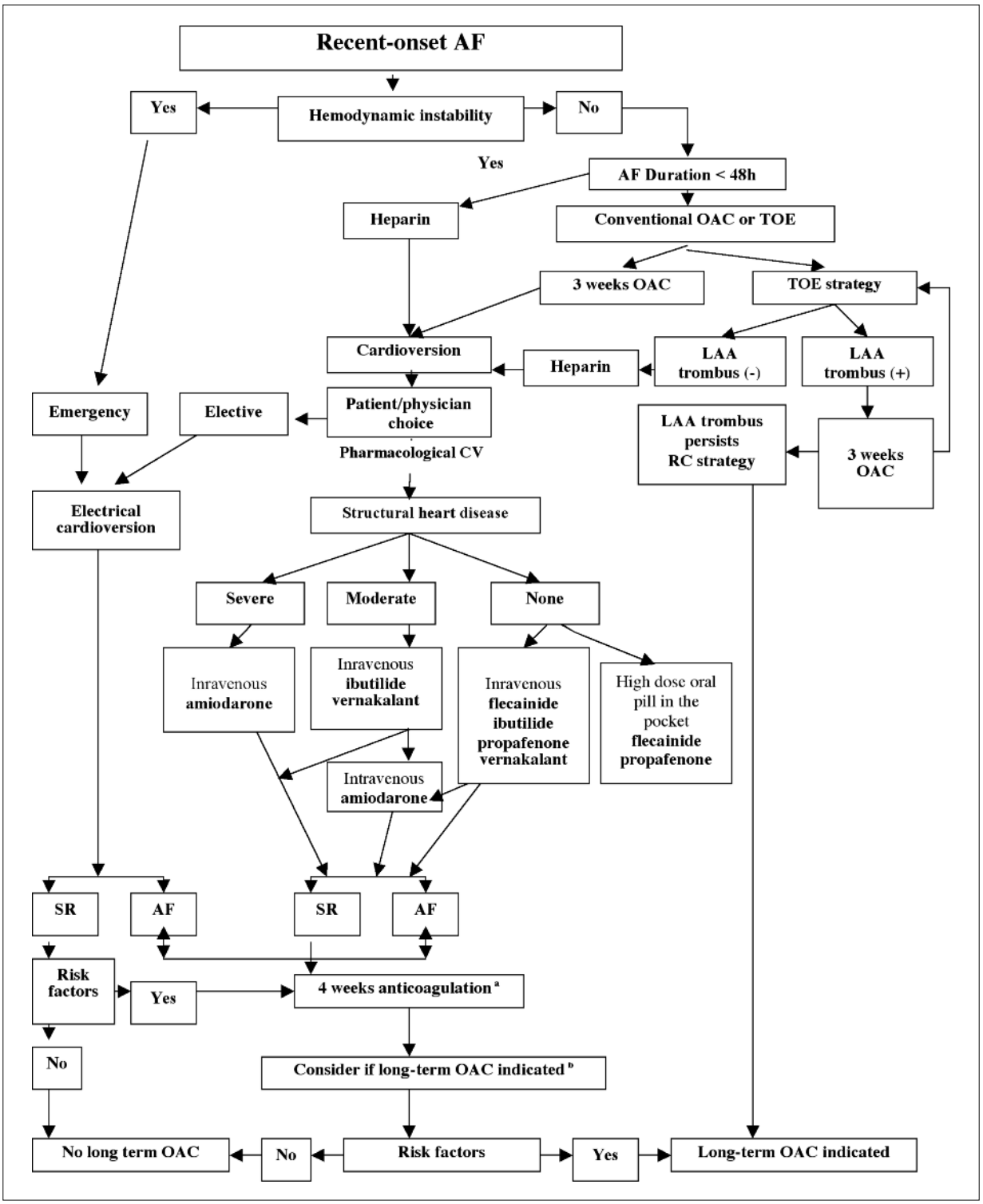

Figure 2. Indications for electrical and pharmacological cardioversion, and choice of antiarrhythmic drugs for pharmacological cardioversion in patients with recent-onset AF4,16. [a]Anticoagulation should normally be continued for 4 weeks after a cardioversion attempt except when AF is recent onset and no risk factors are present. [b]Long-term OAC if stroke risk factors and/or risk of AF recurrence/presence of thrombus. AF: atrial fibrillation; CV: cardioversion; LAA: left atrial appendage; OAC: oral anticoagulant; RC: rate control; SR: sinus rhythm; TOE: transoesophageal echocardiography.

Antithrombotic Prophylaxis Treatment in AF

Issues related to antithrombotic treatment are pivotal in AF to prevent cardioembolic stroke, and are considered a primary objective of treatment in this condition, preceding – in relevance and logical considerations – issues related to rhythm or rate control, or of "upstream therapies"[5,16]. Antithrombotic treatment of atrial fibrillation mostly revolves around anticoagulation, since the role of antiplatelet therapy is now confined to the minority of patients in whom antithrombotic treatment is warranted and in whom anticoagulation is contraindicated[16].

AF favors the formation of intra-atrial thrombi, which can break off and cause thromboembolism, the most serious and frequent being cerebral embolism causing stroke. The risk of stroke in AF is much higher when associated with valve diseases (rheumatic, prosthetic) and increases particularly after CV, whether spontaneous, pharmacological or electrical especially when AF is prolonged before CV. Prophylactic antithrombotic agents substantially decrease the risk of stroke in AF. There are three different clinical situations: Non-valvular AF, AF associated with a prosthetic valve or rheumatic/degenerative/myxomatous (especially mitral) valve disease, and CVof AF regarding individual recommendations for antithrombotic prophylaxis[5,16-18,22].

The incidence of stroke in non-valvular AF is 4-5% globally per year, but varies greatly with the thromboembolic risk factors involved. Thromboembolic risk score CHA_2DS_2-VASc is the best known and practical and recommended by guidelines (Table VI)[16]. Of these risk factors, the most important is a history of stroke, TIA or systemic arterial embolism, with a relative risk of 2.5 to 2.9 and an annual incidence of stroke of 12%. Advanced age is second in importance. If total CHA_2DS_2-VASc risk score is calculated as 9, there is 15,2% annual adjusted stroke rate risk. Antithrombotic therapy according to CHA_2DS_2-VASc risk score is recommended by updated 2012 ESC guideline[16]. Decision-making for thromboprophylaxis needs to balance the risk of stroke against the risk of major bleeding, especially intracranial hemmorrhage, which is the most feared complication of anticoagulation therapy and confers a high risk of death and disability. HAS-BLED score which is a formal bleeding risk assessment (Table VII) is recommended for all patients with AF, and in patients with a HAS-BLED score ≥ 3, caution and regular review are appropriate, as well as efforts to correct the potentially reversible risk factors for bleeding. HAS-BLED score should not be used to exclude patients from oral anticoagulant (OAC) therapy but allows clinicians to make an informed assessment of bleeding risk and, importantly, makes them think of the correctable risk factors for bleeding[5,16]. Target International Normalized Ratio (INR) is between 2.0 to 3.0 in non-valvular AF patients anticoagulated with vitamin K antagonists (VKAs)[16].

Table VI. CHA2DS2-VASc thromboembolic risk scoring scheme.

Risk factors	Score
C: Cardiac failure, left ventricular dysfunction (< 40%)	1
H: Hypertension	1
A: Age ≥ 75	2
D: Diabetes mellitus	1
S: Stroke or TIA or systemic thromboembolism	2
V: Vascular artery disease: myocardial infarction, peripheral arterial diease or complicated aortic plaque	1
A: Age ≥ 65-< 75	1
Sc: Sex category: Female	1

TIA: transient ischemic attack.

Table VII. Clinical characteristics comprising the HAS-BLED bleeding risk score[6].

Clinical characteristics[a]	Score
H: Hypertension (Uncontrolled)	1
A: Abnormal liver or renal funtions (1 point each)	1 or 2
S: Stroke	1
B: Bleeding	1
L: Labile INRs	1
E: Elderly (Age > 65)	1
D: Drugs (aspirin, clopidogrel, NSAIs, etc) or alcohol (point each)	1 or 2

[a]"Hypertension" is defined as systolic blood pressure 160 mmHg. "Abnormal kidney function" is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥ 200 mmol/L or ≥ 2.2 mg/dl. "Abnormal liver function" is defined as chronic hepatic disease (e.g cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin > 2 × upper limit of normal, in association with aspartate aminotransferase/ alanine aminotransferase/ alkaline phosphatase > 3 × upper limit normal, etc.). "Bleeding" refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc. "Labile INRs" refers to unstable/high INRs or poor time in therapeutic range (e.g. < 60%). "Drugs/alcohol" use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc. INR, international normalized ratio[6].

In the peri-cardioversion period, prolonged and effective anticoagulation is considered necessary if the duration of AF is 48 hours or more ["*For patients with AF of ≥ 48 h duration, or when the duration of AF is unknown, oral anticoagulant (OAC) therapy is recommended for ≥ 3 weeks prior to and for ≥ 4 weeks after cardioversion, regardless of the method (electrical or oral/i.v. pharmacological*" (Class of Recommendation I, level of evidence B)][5,16].

In patients with risk factors for stroke or AF recurrence, OAC therapy should then be continued lifelong, irrespective of the apparent maintenance of sinus rhythm following CV[5,16]. An alternative to the ≥ 3 weeks anticoagulation prior to CV is a trans-esophageal echo (TEE)-guided strategy, whereby, for AF lasting ≥ 48 hours or of unknown duration the finding of absent left atrium (LA) thrombi at TEE may allow immediate CV without the cumbersome pre-CV prolonged anticoagulation with OAC, therefore, shortening hospital stay and considerably increasing the efficiency of the overall treatment of acute AF.

If – on the other hand – LA thrombi are found at TEE, current guidelines recommend not to proceed to CV, to anticoagulate the patient for at least 3 weeks with vitamin K antagonists at therapeutic INR, and, possibly, in such cases, reschedule a TEE before the subsequent attempt of CV[5,16].

The peri-CV period is always considered a delicate time because of multiple reports showing increased risk of stroke around CV, due to the dislodgement of previously formed thrombi or the actual occurrence of thrombosis even after resumption of sinus rhythm, due to the phenomenon of "atrial stunning", prompting the recommendation to anticoagulation independent of the risk profile, of the type of AF and of the CV modality. The pro-embolic tendency increases markedly after CV, be it spontaneous, pharmacological or electrical, especially when the period of AF before CV is prolonged[47,48]. After CV, risk of thrombo-embolism due to post CV left atrial dysfunction (so-called 'atrial stunning') persists up to 3 months. Therefore, even in cases where risk factors for stroke are absent and for AF duration of < 48 hours, or for duration ≥ 48 hours with evidence of no thrombi in the LA at TEE, heparin coverage is considered opportune.

For patients with definite AF lasting 48 h or less who have undergone successful CV, we also recommend[3], in keeping with the ESC Guidelines[5,16] continued long-term anticoagulation after the procedure if there are risk factors for thromboembolism [I B]. In such patients we recommend initiation of a VKA and continuation of unfractionated heparin (UFH) or a low-molecular-weight heparin (LMWH) until a therapeutic INR (2-3 in most cases) is achieved[49].

For patients with definite AF lasting 48 hours or less who have undergone successful cardioversion and who have no risk factors for thromboembolism (i.e., CHA_2DS_2-VASc score = 0), we allow for the discontinuation of anticoagulant therapy immediately after cardioversion (IIa B)[49], but we still underline that heparin anticoagulation is recommended around cardioversion even without risk factors for stroke (I C), against some different local practices.

Special notes concerning patients with AF and mechanical prosthetic valves or valvular heart diseases [rheumatic/degenerative/myxomatous (especially mitral valve diseases)] in which incidence of stroke is about 17%. Thereby, AF requires life-long anticoagulation therapy in patients with valvular heart disease. VKAs (Acenocoumarol, warfarin, phenprocoumon) are the only drugs approved for thromboprophylaxis in these patients[23,50]. Target INR is between 2.0-3.0 in patients valvular heart (except prosthesis) disease with AF[23,50].

Recommended level of anticoagulation (INR level) in patients with prosthetic valves in the presence of AF is summarized in Table VIII[23,50]. In ESC/EACTS guideline, the addition of aspirin 75 to 100 mg once daily to therapeutic warfarin is recommended for all patients with mechanical heart valves and those patients with biological valves (e.g. bioprosthesis) who have risk factors (atrial fibrillation, previous thromboembolism, left ventricular (LV) dysfunction, ejection fraction (EF) < 35% and hypercoagulable condition)[23].

Antithrombotic Prophylaxis Treatment in AF: Innovation and Research

The advent of novel oral anticoagulants (NOACs) for stroke prevention in AF, including the oral direct thrombin inhibitor dabigatran etexilate (DE) and the Factor Xa inhibitors rivaroxaban, apixaban and – possibly in the near future – edoxaban –[51] is posing new problems and questions for the peri-CV time in the limited condition of non-valvular AF (since such drugs are not and will likely not be for long time recommended outside of this indication). For NOACs there is limited experience in the peri-

Table VIII. Recommended level of anticoagulation (INR level) in patients with prosthetic valves in the presence of AF23,49.

	Recommended levels in ESC/EACTS guidelines	Recommended levels in ACC/AHA guidelines
Mechanical aortic valve		
Low prosthesis thrombogenicity	3.0	2.5-3.5
Medium prosthesis thrombogenicity	3.5	2.5-3.5
High prosthesis thrombogenicity	4.0	2.5-3.5
Bioprosthesis aortic valve	2.0-3.0	2.0-3.0
Mechanical mitral valve		
Low prosthesis thrombogenicity	3.0	2.5-3.5
Medium prosthesis thrombogenicity	3.5	2.5-3.5
High prosthesis thrombogenicity	4.0	2.5-3.5
Bioprosthesis mitral valve	2.0-3.0	2.0-3.0

Prosthesis thrombogenicity: Low = Carbomedics, Medtronic Hall, St Jude Medical, ON-X; Medium = other bileaflet valves; High = Lillehei-Kaster, Omniscience, Starr-Edwards, Bjork-Shiley and other tilting-disc valves. ACC: American College of Cardiology; AHA: American Heart Association; EACTS: European Association for Cardio-Thoracic Surgery; ESC: European Society of Cardiology.

CV time, and mostly in patients already treated with NOACs and needing CV, with almost no experience with newly occurring AF. The only fully published experience for NOACs at the time of this writing is for DE.

An analysis of outcomes was performed in patients who underwent CV during the RE-LY trial, testing DE 150 mg b.i.d. (DE150), vs DE 110 mg b.i.d. (DE110) vs INR-adjusted warfarin for stroke prevention in AF[52]. Here 1983 CVs were performed in 1270 patients. Efficacy (rate of stroke and systemic embolism) and safety (rate of major bleeding) within 30 days following CV were assessed[53]. For patients undergoing TEE, there was no difference across the three treatment arms in the incidences of LA spontaneous echo contrast or left atrium appendage (LAA) thrombus. The incidence of stroke and systemic embolism was low in all three treatment arms (always < 1%), and with no significant differences [DE110 vs warfarin RR 1.28 (95% CI 0.35-4.76); DE150 vs warfarin RR 0.49 (95% CI 0.09-2.69)]. Rates were also similar in both the TEE-guided and the non TEE-guided CV groups. Major bleeding within 30 days after CV was infrequent (< 2%) in all groups, and with similar incidence [RR 2.82 (95% CI: 0.90-8.82) for DE110 vs warfarin; RR 0.99 (95% CI: 0.25-3.93) for DE150 vs warfarin]. A separate analysis was performed for first CVs of each patient. Results were consistent with all CVs. Here rates for stroke/systemic embolic events and major bleeding were both low[53].

Such experience in the RE-LY subgroups has limitations in that it was a retrospective analysis of patients undergoing CV in a trial not powered to show a difference in stroke and systemic embolism among its three treatment arms in the setting of CV. Low event rates precluded a rigorous statistical analysis between groups (one has, on the other hand, to remark that a definitive superiority study is unlikely to be possible). In addition, case report forms were not prospectively designed to collect complete echocardiographic details. In summary, however, rates of stroke and systemic embolism within 30 days of CV were low for both DE and warfarin, and there were no significant differences for all CVs and first CVs between study groups; outcomes were similar in patients with and without TEE before CV; major bleeding within 30 days was infrequent in all groups. Therefore, in short: efficacy and safety of DE in a large cohort of patients undergoing CV was comparable to that of warfarin regardless of the use of TEE. As a consequence, one may conclude that DE is a reasonable alternative to warfarin in patients requiring CV. This analysis provides at the moment the largest CV experience with a NOAC in this setting. It is likely that similar data will be available soon for rivaroxaban and apixaban.

One additional final remark should be done in the light of the data from the RE-LY subanalysis and of the forthcoming data with other NOACs. Since in non-valvular AF long-term anticoagulation with a direct thrombin inhibitor or with a direct factor Xa inhibitor, instead of a VKA, should be considered [IIa B in the most recent ESC Guidelines update[16]], we have argued that, due to the faster onset of action of NOACs, in such cas-

es no bridging with UFH or a LMWH would be necessary (IIa C), which is an additional non-trivial advantage for the NOACs vs warfarin[49].

Assessment of Heart Disease in AF: Ultimate Echocardiographic Approach

Echocardiography provides a large number of parameters that can be used for improving risk stratification in patients with AF, and play a key role in risk stratification and management of patients with AF[54].

Echocardiography may: (1) give information on the conditions associated with AF, and risk for recurrent AF following CV; (2) identify patients at increased risk for thromboembolic complications of AF before CV and in patients with chronic AF.

TTE should be performed for the initial workup of all patients with acute AF. In a more selected group of patients with paroxysmal or persistent AF or in patients with chronic AF TEE provides accurate information about the presence of a thrombus in the atria and thromboembolic risk.

Transthoracic Echocardiography (TTE)

TTE should be, therefore, performed in almost all patients with a first episode of AF. TTE has the advantages of a bed-side and wide availability and low cost.

Informations about LA and LV size and function, right atrium (RA) and RV size and function, in addition to the presence of valvular, myocardial, pericardial and congenital heart disease which may predispose to AF, may be easily and rapidly acquired by two-dimensional (2D) and Doppler study using TTE. These information may be helpful not only in determining the conditions associated with AF, but also and risk for recurrent AF following CV.

The assessment of mitral valve function can influence the risk of thrombus formation. According to ESC guidelines, TTE usually provides all the information necessary for a routine management, ie the severity, morphology and consequences of mitral stenosis, as well as the extent of other concomitant valve anatomic lesions. Mitral regurgitation is a common finding in patients with AF. When mitral regurgitation is moderate to severe it seems to exert a protection against clinical thromboembolism in chronic AF[55].

A high prevalence of arterial hypertension has been reported in patients with AF and the occurence of AF is greater among hypertensive individuals. In hypertensive patients left ventricle hypertrophy (LVH) is associated with a higher appearance of AF during the follow-up, independently of blood pressure values[56,57]. Accordingly in the LIFE study in patients with absence or regression of echocardiographic LVH the prevalence of atrial dilation was lower. In the presence of LVH (and/or heart failure or other structural heat disease) TTE assessment of global LV systolic function helps to guide the choice of pharmacologic therapy for ventricular rate control in chronic AF. LV dysfunction, as determined from the TTE, independently predicts an increased risk of a stroke in patients with AF. Despite the predictive value of LV dysfunction for thromboembolic risk has been confirmed in many other investigations, it was shown very recently that in "real world" patients with heart failure and atrial fibrillation there are no differences in rates of stroke and stroke/TE between patients with heart failure (HF) with preserved ejection fraction (PEF) and those with HF and reduced EF[58] possibly because AF patients with HF reduced EF (HFREF) were more likely to be on HF medications than patients with HFPEF.

TTE is useful in the assessment of LA size in AF. The normal LA antero-posterior diameter from M-mode echocardiography, measured in the parasternal long-axis or short-axis window, in adults is less than 4.0 cm (or < 2.0 cm/m^2 body surface area (BSA). Hence, 2D derived LA volume assessment using the biplane area-length method or the Simpson's method provides more accurate measures of LA size. A LA volume index of 29 mL/m^2 BSA is usually considered the upper limits of the normal value[59]. LA enlargement is common in AF, particularly in patients with mitral valve disease, LV dilation, annular calcification, or hypertension. In addition, sustained AF may determine itself a further increase in LA size[60], while after CV and maintenance of sinus rhythm the increase in LA size is reversible.

LA enlargement is prognostically important, since it decreases the probability of a long-term maintenance of sinus rhythm after CV[61]. Patients with a severe enlargement of the LA, AF duration greater than one year, rheumatic mitral valve disease, are at greatest risk for recurrent AF[62]. However, when the AF duration is brief, it is worthwhile to attempt a CV, regardless of absolute left atrial size.

In patients with AF, LA volume indexed by BSA (body surface area) and measured before CV, is a more accurate measure of LA remodeling than LA diameter, and is strongly and inde-

pendently associated with higher risks of AF recurrence, with a 90% AF relapse in patients with a LA indexed volume greater than 40 ml/m^2.

As far as risk stratification with respect to recurrent stroke, LA volume is a more robust marker of cardiovascular events than LA area or diameter in subjects with sinus rhythm and in patients with AF. The annual risk of stroke is 1.5% in cases with a normal LA diameter, but raises significantly in patients with an enlarged atrium. TEE is preferred when looking for LA thrombi or when evaluating left and right atrial appendages.

Two systematic reviews have evaluated the stroke risk factors in patients with AF[63,64] and identified age, hypertension, diabetes mellitus, prior stroke/TIA/thrombo-embolism and structural heart disease as the most important risk factors. The presence of moderate to severe LV systolic dysfunction on 2D TTE resulted the only independent echocardiographic risk factor for stroke on multivariable analysis.

Transesophageal Echocardiography (TEE)

Risk of stroke and systemic embolism in patients with AF is linked to a number of underlying pathophysiological mechanisms. 'Flow abnormalities' in AF are evidenced by stasis within the left atrium, with reduced LAA (left atrial appendage) flow velocities, and visualized as spontaneous echo-contrast on TEE[54,65]. In addition progressive atrial dilatation and oedematous/fibroelastic infiltration of the extracellular matrix (ECM) may favour the thrombus formation. The LAA is the dominant source of embolism (90%) in non-valvular AF.

The main advantage of TEE is its ability to detect left and right atrial thrombi, spontaneous echo contrast or reduced LA appendage blood flow velocity, thereby identifying patients at risk for emboli.

The main clinical use of TEE is in the management of anticoagulation in patients with AF of more than 48 hours or high-risk patients with AF of shorter duration who are candidates for CV[54,65]. Standard therapy in such patients consists of four weeks of therapeutic oral anticoagulant therapy before CV, which will cause resolution of most thrombi in patients with non rheumatic AF with a low likelihood for formation of new thrombi.

Alternatively, therapy may be guided by the results of TEE: if no thrombi are seen at TEE, CV can be performed with intravenous heparin, followed by oral anticoagulant therapy for a month, in order to prevent new thrombus formation after CV; if thrombi (or spontaneous echocontrast or low flow velocities in the LAA) are seen, CV should be delayed, after an adequate period of oral anticoagulant therapy.

In patients who have been adequately anticoagulated with oral anticoagulants for at least four weeks prior to CV, there is no indication for TEE. TEE immediately prior to elective CV should be considered only for those patients at increased risk for LA thrombi (e.g., rheumatic mitral valve disease, recent/prior thromboembolism, severe LV systolic dysfunction).

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010; 31: 2369-2429.
2) Zarifis J, Beevers G, Lip GY. Acute admissions with atrial fibrillation in a British multiracial hospital population. Br J Clin Pract 1997; 51: 91-96.
3) Laguna P, Martín A, Del Arco, Gargantilla P, on behalf of the GEFAUR-1 Investigators. Risk factors for stroke and thromboprophylaxis in atrial fibrillation: what happens in daily clinical practice? The GEFAUR-1 study. Ann Emerg Med 2004; 44: 3-11.
4) Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Zamorano JL. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. J Am Coll Card 2006; 48: 149-246.
5) Camm AJ, Kirchhof P, Lip GYP, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. ESC

2010 guidelines for the management of patients with atrial fibrillation. Eur Heart J 2010; 31: 2369-2429.

6) Buccelletti F, Di Somma S, Galante A, Pugliese F, Alegiani F, Bertazzoni G, Gentiloni Silveri N, Legramante JM, Franceschi F. Disparities in management of new-onset atrial fibrillation in the emergency department despite adherence to the current guidelines: Data from a large metropolitan area. Intern Emerg Med 2011; 6: 149-156.

7) Rogenstein C, Kelly AM, Mason S, Schneider S, Lang E, Clement CM, Stiell IG. An International View of How Recent-onset Atrial Fibrillation Is Treated in the Emergency Department. Acad Emerg Med 2012; 19: 1255-1260.

8) Stiell IG, Clement CM, Brison RJ, Rowe BH, Borgundvaag B, Langhan T, Lang E, Magee K, Stenstrom R, Perry JJ, Birnie D, Wells GA. Variation in management of recent-onset atrial fibrillation and flutter among academic hospital emergency departments. Ann Emerg Med 2011; 57: 13-21.

9) delArco C, Martín A, Laguna P, Gargantilla P; Investigators in the Spanish Atrial Fibrillation in Emergency Medicine Study Group (GEFAUR). Investigators in the Spanish Atrial Fibrillation in Emergency Medicine Study Group (GEFAUR). Analysis of current management of atrial fibrillation in the acute setting: GEFAUR-1 study. Ann Emerg Med 2005; 46: 424-430.

10) Zimetbaum P, Ho KK, Olshansky B, Gargantilla P; Investigators in the Spanish Atrial Fibrillation in Emergency Medicine Study Group (GEFAUR). Variation in the utilization of antiarrhythmic drugs in patients with new-onset atrial fibrillation. Am J Cardiol 2003; 91: 81-83.

11) Laguna P, Martín A, Del Arco C, Millán I, Gargantilla P; Spanish Atrial Fibrillation in Emergency Medicine Study Group (GEFAUR-2). Spanish Atrial Fibrillation in Emergency Medicine Study Group (GEFAUR-2). Differences among clinical classification schemes for predicting stroke in atrial fibrillation: implications for therapy in daily practice. Acad Emerg Med 2005; 12: 828-834.

12) Arendts G, Krishnaraj M, Paull G, Rees D. Management of atrial fibrillation in the acute setting--findings from an Australasian survey. Heart Lung Circ 2010; 19: 423-427.

13) Wakai A, O'Neill JO. Emergency management of atrial fibrillation. Postgrad Med J 2003; 79: 313-319.

14) Fuster V, Rydén LE, Asinger RW, Cannom DS, Crijns HJ, Frye RL, Halperin JL, Kay GN, Klein WW, Lévy S, McNamara RL, Prystowsky EN, Wann LS, Wyse DG; American College of Cardiology; American Heart Association; European Society of Cardiology; North American Society of Pacing and Electrophysiology. ACC/AHA/ESCguidelines for the management of patients with atrial fibrillation. Eur Heart J 2001; 22: 1852-1923.

15) Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Zamorano JL. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). J Am Coll Card 2006; 48: 854-906.

16) Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines (CPG), Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S; Document Reviewers, Vardas P, Al-Attar N, Alfieri O, Angelini A, Blömstrom-Lundqvist C, Colonna P, De Sutter J, Ernst S, Goette A, Gorenek B, Hatala R, Heidbüchel H, Heldal M, Kristensen SD, Kolh P, Le Heuzey JY, Mavrakis H, Mont L, Filardi PP, Ponikowski P, Prendergast B, Rutten FH, Schotten U, Van Gelder IC, Verheugt FW. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Eur Heart J 2012; 33: 2719-2747.

17) Gillis AM, Verma A, Talajic M, Nattel S, Dorian P; CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society Atrial fibrillation Guidelines 2010: Rate and Rhythm Management. Can J Cardiol 2011; 27: 47-59.

18) The National Collaborating Centre for Chronic Conditions. Atrial fibrillation: national clinical guideline for management in primary and secondary care. June 2006.

19) Suman-Horduna I, Roy D, Frasure-Smith N, Talajic M, Lespérance F, Blondeau L, Dorian P, Khairy P; AF-CHF Trial Investigators. Quality of life and functional capacity in patients with atrial fibrillation and congestive heart failure. J Am Coll Cardiol 2013; 61: 455-460.

20) Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002; 347: 1825-1833.

21) Pedersen OD, Søndergaard P, Nielsen T, Nielsen SJ, Nielsen ES, Falstie-Jensen N, Nielsen I, Køber L, Burchardt H, Seibaek M, Torp-Pedersen C; DIAMOND study group investigators. Atrial fibrillation, ischaemic heart disease, and the risk of death in patients with heart failure. Eur Heart J 2006; 27: 2866-2870.

22) Martinez AM, Lozano IF, Puig BCV, Sanchez LT, Del Arco Galan C, Ynsaurriaga FA, Mendez CS, Girbau LM. Consensus document. Atrial fibrillation management in the hospital emergency department: 2012 update. Emergencias 2012; 24: 300-324.

23) Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012): Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC); European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2012; 33: 2451-2496.

24) Whitbeck MG, Charnigo RJ, Khairy P, Ziada K, Bailey AL, Zegarra MM, Shah J, Morales G, Macaulay T, Sorrell VL, Campbell CL, Gurley J, Anaya P, Nasr H, Bai R, Di Biase L, Booth DC, Jondeau G, Natale A, Roy D, Smyth S, Moliterno DJ, Elayi CS. Increased mortality among patients taking digoxin-analysis from the AFFIRM study. Eur Heart J 2013; 34: 1481-1488.

25) Siddoway LA. Amiodarone: Guidelines for use and monitoring. Am Fam Physician 2003; 68: 2189-2197.

26) Stiell IG, Macle L; CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: management of recent-onset atrial fibrillation and flutter in the emergency department. Can J Cardiol 2011; 27: 38-46.

27) Mittal S, Stein KM, Markowitz SM, Iwai S, Guttigoli A, Lerman BB. An update on electrical cardioversion of atrial fibrillation. Card Electrophysiol Rev 2003; 7: 285-289.

28) Gall NP, Murgatroyd FD. Electrical cardioversion for AF-the state of the art. Pacing Clin Electrophysiol 2007; 30: 554-567.

29) Gallagher MM, Guo XH, Poloniecki JD, Guan Yap Y, Ward D, Camm AJ. Initial energy sitting, outcome and efficiency in direct current cardioversion of atrial fibrillation. J Am Coll Cardiol 2001; 38: 1498-1504.

30) Lundstrom T, Ryden L. Chronic atrial fibrillation: long term results of direct current cardioversion. Acta Med Scand 1988; 223: 53-59.

31) Lown B. Electrical reversion of cardiac arrhythmias. Br Heart J 1967; 29: 469-489.

32) Dalzell GW, Anderson J, Adgey AA. Factors determining success and energy requirement for cardioversion of atrial fibrillation. Q J Med 1990; 76: 903-913.

33) Dittrich HC, Erikson JS, Schneideman T, Blacky AR, Savides T, Nicod PH. Echocardiographic and clinical predictors for outcome of elective cardioversion of atrial fibrillation. Am J Cardiol 1989; 63: 193-197.

34) Pitcher D, Perkins G. Peri-arrest arrhythmias. In: Nolan JP, ed. Resuscitation guidelines 2010.1st ed. London: Resuscitation Council (UK), 2010; pp. 81-89.

35) Lesser MF. Safety and efficacy of in-office cardioversion for treatment of supraventriculararrhythmias. Am J Cardiol 1990; 66: 1267-1268.

36) Charles DD, Nolan JP, Soar J, Sunde K, Koster RW, Smith GB, Perkins GD. European resuscitation council guidelines for resuscitation 2010, Section 4: Adult advanced life support. Resuscitation 2010; 81: 1305-1352.

37) Nolan JP, Soar J, Zideman DA, Biarent D, Bossaert LL, Deakin C, Koster RW, Wyllie J, Böttiger B; ERC Guidelines Writing Group. European resuscitation council guidelines for resuscitation 2010, Section 1: Executive summary. Resuscitation 2010; 81: 1219-1276.

38) Morrison LJ, Deakin CD, Morley PT, Callaway CW, Kerber RE, Kronick SL, Lavonas EJ, Link MS, Neumar RW, Otto CW, Parr M, Shuster M, Sunde K, Peberdy MA, Tang W, Hoek TL, Böttiger BW, Drajer S, Lim SH, Nolan JP; Advanced Life Support Chapter Collaborators. Part 8: Advanced life support: 2010 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Circulation 2010; 122: 345-421.

39) Khaykin Y, Newman D, Kowalewski M, Korley V, Dorian P. Biphasic versus onophasic cardioversion in shock-resistant atrial fibrillation. J Cardiovasc Electrophysiol 2003; 14: 868-872.

40) Deakin CD, Ambler JJ. Post-shock myocardial stunning: a prospective randomiseddouble-blind comparison of monophasic and biphasic waveforms. Resuscitation 2006; 68: 329-333.

41) Khaykin Y, Newman D, Kowalewski M, Korley V, Dorian P. Biphasic versus monophasic cardioversion in shock-resistant atrial fibrillation. Cardiovasc Electrophysiol 2003; 14: 868-872.

42) Bjerkeland CI, Orning OM. The efficacy of anticoagulant therapy in preventing embolism related to DC electrical conversion of atrial fibrillation. Am J Cardiol 1969; 23: 208-216.

43) Arnold AZ, Mick MJ, Mazurck RP, Loop FD, Trohman RG. Role of prophylactic anticoagulation for direct current cardioversion in patients with atrial fibrillation or atrial flutter. J Am Coll Cardiol 1992; 19: 851-855.

44) Lucà F, LaMeir M, Rao CM, Parise O, Vasquez L, Carella R, Lorusso R, Daniela B, Maessen J, Gensini GF, Gelsomino S. Pharmacological management of atrial fibrillation: one, none, one hundred thousand. Cardiol Res Pract 2011; 2011: 874802.

45) Nair M, George LK, Kosby SKG. Safety and efficacy of ibutilide in cardioversion of atrial flutter and fibrillation. J Am Board Fam Med 2011; 24: 86-92.

46) Bronis K, Metaxa S, Koulouris S, Manolis AS. Vernakalant: Review of a novel atrial selective antiarrhythmic agent and its place in current treatment of atrial fibrillation. Hospital Cronicles 2012; 7: 171-181.

47) Sohara H, Amitani S, Kurose M, Miyahara K. Atrial fibrillation activates platelets and coagulation in a time-dependent manner: A study in patients with paroxismal atrial fibrillation. J Am Coll Cardiol 1997; 29: 106-112.

48) Sparks PB, Jayaprakash S, Mond HG, Vohra JK, Grigg LE, Kalman JM. Left atrial mechanical function after brief duration atrial fibrillation. J Am Coll Cardiol 1999; 33: 342-349.

49) De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, Baigent C, Huber K, Jespersen J, Kristensen SD, Lip GY, Morais J, Rasmussen LH, Siegbahn A, Verheugt FW, Weitz JI. Position paper: parenteral anticoagulants in heart disease: current Status and perspectives (Section II). Position paper of the ESC working group on thrombosis-task force on anticoagulants in heart disease. Thromb Haemost 2013; 109: 769-786.

50) Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS; 2006 Writing Committee Members; American College of Cardiology/American Heart Association Task Force. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2008; 118: e523-661.

51) De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, Baigent C, Huber K, Jespersen J, Kristensen SD, Lip GY, Morais J, Rasmussen LH, Siegbahn A, Verheugt FW, Weitz JI; Coordinating Committee. New oral anticoagulants in atrial fibrillation and acute coronary syndromes: ESC Working Group on Thrombosis-Task force on Anticoagulants in Heart Disease Position Paper. J Am Coll Cardiol 2012; 59: 1413-1425.

52) Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139-1151.

53) Nagarakanti R, Ezekowitz MD, Oldgren J, Yang S, Chernick M, Aikens TH, Flaker G, Brugada J, Kamensky G, Parekh A, Reilly PA, Yusuf S, Connolly SJ. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. Circulation 2011; 123: 131-136.

54) Pepi M, Evangelista A, Nihoyannopoulos P, Flachskampf F, Athanassopoulos G, Colonna P, Habib G, Ringelstein B, Sicari R, Zamorano JL on behalf of the European Association of Echocardiography. Recommendations for echocardiography use in the diagnosis and management of cardiac sources of embolism European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur J Echocardiogr 2010; 11: 461-476.

55) Goldsmith IR, Blann AD, Patel RL, Lip GY. Reduced indexes of left atrial hypercoagulability in patients with severe mitral regurgitation. J Cardiol 2000; 86: 234-236.

56) Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. Circulation 1994; 89: 724-730.

57) Verdecchia P, Reboldi G, Gattobigio R, Bentivoglio M, Borgioni C, Angeli F, Carluccio E, Sardone MG, Porcellati C. Atrial fibrillation in hypertension: predictors and outcome. Hypertension 2003; 41: 218-223.

58) Banerjee A, Taillandier S, Olesen JB, Lane DA, Lallemand B, Lip GYH, Fauchier L. Ejection fraction and outcomes in patients with atrial fibrillation and heart failure: the Loire Valley Atrial Fibrillation Project. Eur J Heart Fail 2012; 14: 295-301.

59) Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John Sutton M, Stewart W; American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on ChamberQuantification; American College of Cardiology Echocardiography Committee; American Heart Association; European Association of Echocardiography, European Society of Cardiology. Reccommendations for chamberquantification. Eur J Echocardiogr 2006; 7: 79-108.

60) Sanfilippo AJ, Abascal VM, Sheehan M, Oertel LB, Harrigan P, Hughes RA, Weyman AE. Atrial enlargement as a consequence of atrial fibrillation. A prospective echocardiographic study. Circulation 1990; 82: 792-797.

61) Kerr CR, Humphries KH, Talajic M, Klein GJ, Connolly SJ, Green M, Boone J, Sheldon R, Dorian P, Newman D. Am Heart J 2005; 149: 489-496.

62) Parkash R, Green MS, Kerr CR, Connolly SJ, Klein GJ, Sheldon R, Talajic M, Dorian P, Humphries KH; Canadian Registry of Atrial Fibrillation. Am Heart J 2004; 148: 649-654.

63) Hughes M, Lip GY. Stroke and thromboembolism in atrial fibrillation: a systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. Thromb Haemost 2008; 99: 295-304.

64) Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. Neurology 2007; 69: 546-554.

65) Grewal GK, Klosterman TB, Shrestha K, Yarmohammadi H, Zurick AO, Varr BC, Tang WH, Lindsay BD, Klein AL. Indications for TEE before cardioversion for atrial fibrillation: implications for appropriateness criteria. JACC Cardiovasc Imaging 2012; 5: 641-648.