REVIEW ARTICLE

Cardioversion of recent-onset atrial fibrillation: current evidence, practical considerations, and controversies in a complex clinical scenario

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ABSTRACT

Atrial fibrillation (AF) represents the most common arrhythmia and is associated with increased morbidity and mortality generating high social costs. Due to its high prevalence, AF is usually managed not only by cardiologists but also by general practitioners or clinicians in emergency departments. The conventional classification of AF includes "recent-onset AF" defined as an arrhythmia episode shorter than 48 hours. In patients with a definite duration of AF of less than 24 hours and a very low–risk profile (CHA$_2$DS$_2$VASc of 0 in men and 1 in women), the thromboembolic risk seems to be low, and the standard 4-week anticoagulation therapy is now regarded as optional treatment. Cardioversion (electrical or pharmacological) in recent-onset AF represents a valid rhythm control strategy. Electrical cardioversion is usually reserved for hemodynamically unstable patients and performed with biphasic waveform shocks. On the other hand, pharmacological cardioversion is preferred in hemodynamically stable patients. Several antiarrhythmic drugs have been studied so far, but some questions still remain unresolved mainly due to lack of randomized clinical trials and prospective studies. The current guidelines do not uniformly agree on which drug to use for pharmacological cardioversion, and drug preference varies widely in clinical practice. The aim of this narrative review is to sum up and critically evaluate novel evidence regarding recent-onset AF as well as to provide some practical considerations particularly focused on rhythm control with pharmacological cardioversion.

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Introduction Atrial fibrillation (AF) is the most common and prevalent arrhythmia, affecting 33.5 million people worldwide.[1,2] Based on epidemiological data, it is estimated that the number of AF cases will double between 2010 and 2030, and the predicted AF prevalence in Europe will reach around 17 million cases.[3,4] Patients with AF are at 2-fold higher risk of death and hospitalization compared with those without AF (eg, AF is a major risk factor for new-onset heart failure).[5] Hospital admissions represent the key part of the total AF-related healthcare costs, which constitute 1% of the total healthcare expenditure in the United Kingdom and 26 billion dollars per year in the United States.[3,6] Considering this background, it is necessary to raise public awareness about

the screening and treatment of AF and modifiable risk factors (eg, hypertension, obesity, and alcohol use), which may lead to cost containment and improve patient outcomes.[7,8] The classic definition identifies 4 types of AF: 1) paroxysmal (self-terminating or cardioverted within 7 days); 2) persistent (self-terminating or cardioverted over 7 days); 3) long-standing persistent (lasting for a year after rhythm strategy implementation); and 4) permanent (accepted by the patient and the physician).[9]

Besides this definition, international guidelines identify the recent-onset AF clinical entity, defined as an arrhythmia episode shorter than 48 hours.[9,10] Early AF detection poses 2 pressing clinical concerns about anticoagulation regimens and the rhythm control strategy. When

the onset of AF can be precisely defined as lasting shorter than 48 hours, the thromboembolic risk is low, but cardioversion per se may imply some risk. This justifies starting anticoagulation as soon as possible and continuing the therapy for 4 weeks following cardioversion (or sine die, according to the CHA_2DS_2VASc score) in most patients, except those with a very low–risk profile.[9] According to the famous quote "atrial fibrillation begets atrial fibrillation",[11] AF progression is associated with structural changes in the heart, which develop with time and lead to increased resistance to sinus rhythm (SR) restoration and an increased risk of stroke, systemic embolism, and cardiovascular death.[12-15] For these reasons, in patients with recent-onset AF, early cardioversion may also be a good strategy to reverse the alterations that favor AF persistence. Cardioversion may also improve cardiac function, reduce many AF-related symptoms, and improve the quality of life.[16-19] Moreover, early cardioversion performed in the emergency department has been shown to be safe and effective and significantly reduces healthcare costs. Both electrical and pharmacological cardioversion can be effective in restoring SR.[20] Nevertheless, the current guidelines do not unanimously agree on which drug to use for pharmacological cardioversion, and drug preference varies widely in clinical practice. Various approaches to the pharmacological intervention are used due to lack of randomized controlled trials (RCTs) and prospective studies. The current clinical practice is based on weak evidence, including studies in which the adopted definition of recent-onset AF was not often clear (duration longer and/or shorter than 48 hours) and insufficient drug comparisons were presented.

This review aims to sum up and critically evaluate novel evidence on recent-onset AF as well as to provide some practical considerations particularly focused on rhythm control using pharmacological cardioversion.

Definition of recent-onset atrial fibrillation

The term "recent-onset AF" refers to the time between the onset of symptoms and the detection of arrhythmia. The most widely accepted cutoff value to define "recent onset" is below 48 hours.[9,10,21] Despite this, several studies actually considered a broad spectrum of time intervals ranging between 12 hours, 7 days, or less than 24 hours.[22-27]

Besides the formal issue regarding terminology, which should be standardized to enable better comparison between studies, it is crucial to use an operative definition of "recent-onset" in order to discriminate, for example, the need for anticoagulation before cardioversion. Nowadays, it seems reasonable to define "recent-onset" AF with the cutoff value of less than 48 hours, as recommended by both the North American and

European guidelines.[9,10] However, it is not always easy for the patient to identify the exact amount of time that has passed from the onset of symptoms. Moreover, the onset of symptoms does not always correspond with the real onset of arrhythmia. If the patient is not sure about the precise time of onset, applying the principle of caution, it is mandatory to consider AF lasting longer than 48 hours.

Cardioversion and thromboembolic risk

Patients undergoing cardioversion of AF, either pharmacological or electrical, are at increased risk of stroke and thromboembolism, especially in the absence of oral anticoagulation (OAC). This risk is well defined and justifies OAC for at least 4 weeks, independently of the CHA_2DS_2VASc score if AF has been present for 48 hours or longer.[28] If there is uncertainty about the exact duration of AF, the patient should be anticoagulated as if their prior AF lasted 48 hours.[28,29] Transesophageal echocardiography before cardioversion is not indicated in recent-onset AF (<48 hours), regardless of the patient's anticoagulation status. However, it is accepted as a precautionary measure in the case of dubious therapy adherence, recent stroke, rheumatic valve disease or mitral valve stenosis (moderate or severe), and mechanical valve prosthesis.[9] The presence of a pre-existing thrombus (especially if nonanticoagulated), reduced mechanical function, called atrial stunning, occurring in the first period of time after cardioversion, and a transient prothrombotic state are factors involved in the risk of thromboembolism associated with AF lasting 48 hours or longer or of uncertain duration.[28] So far, no randomized controlled trials (RCTs) have evaluated the use of anticoagulation versus no anticoagulation in patients with AF lasting shorter than 48 hours. Observational data suggest that the risk of stroke and/or thromboembolism is very low (0–0.2%) in patients with a definite duration of AF less than 12 hours and with a very low–risk profile (CHA_2DS_2VASc of 0 in men and 1 in women).[30-32] As stated in the 2020 European Society of Cardiology (ESC) guidelines, 4 weeks of anticoagulation after cardioversion could be omitted in patients at very low risk (CHA_2DS_2VASc of 0 in men and 1 in women) with new-onset AF lasting shorter than 24 hours.[9,28,20] In patients with a CHA_2DS_2VASc profile indicating the risk of stroke (score ≥2 in women and ≥1 in men), long-term anticoagulation should be prescribed (class I recommendation for CHA_2DS_2VASc ≥3 in women and ≥2 in men; class IIa recommendation for CHA_2DS_2VASc of 2 in women and 1 in men) even after the first episode of AF, independently of SR restoration with effective cardioversion. Cardioversion on anticoagulation is generally safer than without it in terms of the thromboembolism

incidence rate, especially with $CHA_2DS_2VASc \geq 2$ and AF duration above 12 hours. Low-molecular-weight heparin is the most frequently used drug in this setting and a single dose is generally considered safe. Given the similar pharmacodynamic and –kinetic properties, a single dose of non–vitamin K antagonist oral anticoagulants may be a reasonable alternative. In recent years, 3 RCTs have shown a low rate of thromboembolic events following cardioversion with low-molecular-weight heparin or vitamin K antagonist use as well as with non–vitamin K antagonist oral anticoagulation regimens, but none of those provided specific data on patients with AF lasting shorter than 48 hours.[9,29]

Recent-onset atrial fibrillation with hemodynamic instability   The first step in the evaluation of recent-onset AF is to assess the patient's hemodynamic status. Urgent electrical cardioversion is recommended in patients presenting with hemodynamic instability or high-risk clinical features such as a ventricular rate above 150 bpm, ongoing chest pain, and / or critical perfusion.[9,33] Several studies conducted in emergency departments showed that this approach is safe and effective.[34]

Spontaneous cardioversion to sinus rhythm: pros and cons of the wait-and-see approach
The wait-and-see approach is an interesting option for patients with recent-onset AF, which has been studied in several trials. In 1999, Cotter et al[35] showed that the rate of spontaneous conversion to SR in 100 patients in the emergency department was high and reached 90% in specific subgroups. These findings were later confirmed by Geleris et al,[36] who observed spontaneous conversion to SR in 73.4% of patients with recent-onset AF, especially in the first 12 hours. Similarly, Doyle et al[37] underlined that acute AF spontaneously resolved with the wait-and-see protocol in almost 2/3 of the study patients, who reported a high degree of satisfaction. Recently, new evidence supporting the wait-and-see approach in recent-onset AF came from the RACE 7 ACWAS (Rate Control Versus Electrical Cardioversion Trial 7–Acute Cardioversion Versus Wait and See) trial.[25] A total of 427 patients with recent-onset AF (<36 hours) were randomized in the emergency department to the wait-and-see approach (the delayed-cardioversion group in which the rate-control strategy was initiated first) or to early cardioversion. Most patients in the delayed-cardioversion group and in the early-cardioversion group were in SR at 4 weeks (91% vs 94%, respectively). The authors concluded that the wait-and-see approach was noninferior to early cardioversion in achieving the conversion to SR at 4 weeks, in particular when AF lasted shorter than 24 hours.[25] Nevertheless, as already highlighted, the wait-and-see strategy should

be considered based on balancing benefits and harms of its implementation.[38,39] This strategy is determined by 3 factors: the physician, the patient, and healthcare system organization, and all of these influence the management of recent-onset AF in daily practice, in which an individualized approach is mandatory.[40]

Cardioversion of recent-onset atrial fibrillation
Cardioversion in AF represents a valid approach for rhythm control. The choice between electrical and pharmacological cardioversion should encompass a careful evaluation of the patient's profile (eg, hemodynamic status, presence of structural heart disease, symptoms, and fluid and electrolyte balance) and hospital settings (need for anesthesiologist assistance, experience, etc).

For example, potassium and magnesium imbalance could act as a trigger for AF. Moreover, the correction of electrolyte imbalance could help avoid possible adverse effects of antiarrhythmic drug (AAD) use, such as the exacerbation of QT prolongation or digitalis intoxication. No data are available on the cost-effectiveness of the routine determination of serum electrolyte levels, but it seems reasonable to measure them.

Electrical cardioversion   Electrical cardioversion is generally reserved for hemodynamically unstable patients, but it is also widely performed in stable patients with recent-onset AF episodes, especially in those young and without structural heart disease.[41] Biphasic waveform shock is associated with higher success rates with lower energies applied than during monophasic waveform cardioversion.[42] Anteroposterior pad placement is generally considered superior to the anterolateral position, even though a recent trial has not confirmed these findings.[20,43] Electrical cardioversion can be preceded by intravenous or oral pharmacological facilitation.[44,45] An electrical attempt to restore SR often follows the failure of pharmacological cardioversion.[20,46] There are few evidence-based comparisons between "pure" pharmacological versus "pure" electrical cardioversion in recent-onset AF and it is still a matter of debate which approach is the best in terms of feasibility, costs, risks, and effectiveness. Indeed, in the recent RAFF2 (Electrical Versus Pharmacological Cardioversion for Emergency Department Patients with Acute Atrial Fibrillation) trial, both drug-and-shock and shock-only approaches were highly effective and safe as cardioversion strategies.[20]

Pharmacological cardioversion   Pharmacological cardioversion is a reasonable and effective approach. The potential benefits of pharmacologically induced cardioversion include avoiding sedation drugs and testing tolerance to oral AADs if the pill-in-the-pocket strategy is used. However, pharmacological adverse effects, prolonged telemetric monitoring, and stay in an emergency

TABLE 1 Effects of various agents for cardioversion of recent-onset atrial fibrillation

Drug	Route	Standard dose	Time to cardioversion[a], h	Efficacy, %	Adverse events[b], %
Quinidine	Oral	400 mg every 6 hours	3.1–6.1	30–90	3–46
Procainamide	Intravenous	5–15 mg/kg (maximum dose of 1000 mg) at 0.2–0.4 mg/kg/min over 10–15 min	<1.5	15–20	2–12
Flecainide	Intravenous	1.5–2 mg/kg in 10 min	0.4–0.9	65–96	3.4–31
	Oral	300 mg; 200 mg, if BW <70 kg	1.8	78–95	0–23
Propafenone	Intravenous	1.5–2 mg/kg in 10 min	0.5–8	43–89	0–17
	Oral	600 mg; 450 mg, if BW <70 kg	2.8–5	45–78	4.9–14
Amiodarone	Intravenous	5–7 mg/kg in a bolus followed by 50 mg–1 g/h in 24 hours	5.6–19.4	58–92	0–7.7
	Oral	30 mg/kg	7.9–20	85–87	0–3.2
Vernakalant	Intravenous	3 mg/kg in 10 min (maximum first dose, 339 mg); 2 mg/kg in 10 min, after waiting 15 min (maximum second dose, 226 mg)	0.2	47–93	0–2.6
Ibutilide	Intravenous	1 mg in 10 min (0.01 mg/kg if BW <60 kg); 1 mg in 10 min, after waiting for 10 min	0.4–0.9	24–50	1.7–3.6
Sotalol	Intravenous	1.5 mg/kg in 10 min	<4	11–85	10–23
Placebo	–	–	2.5–17	46.2–56.7	2.3

a   During a minimum of 4-hour and a maximum of 24-hour monitoring, reported as mean or median values

b   Adverse events: 1:1 atrial flutter (in patients taking class I agents), bradycardia, hypotension, ventricular dysrhythmia (ventricular tachycardia / ventricular fibrillation)

Abbreviations: BW, body weight

TABLE 2 Major adverse effects and warnings for different antiarrhythmic agents

Drug	Class	Adverse effects and warnings
Quinidine	IA	AF to AFL 1:1 (rare), TdP (1%–8%), high-grade atrioventricular block (rare). Avoid in HF or ischemia.
Procainamide	IA	AF to AFL 1:1 (rare), high-grade AV block (rare), QRS and QT interval prolongation, hypotension. Drug-induced lupus may develop. Avoid in HF or ischemic patients.
Flecainide	IC / IVB	AF to AFL 1:1 (3.5%–5%), high-grade atrioventricular block (rare), QT interval prolongation. Avoid in HF or ischemia.
Propafenone	IC / IVB	AF to AFL 1:1 (3.5%–5%), high-grade atrioventricular block (rare), QRS interval prolongation. Avoid in HF or ischemia.
Amiodarone	IIIA	TdP (0.7%), hypotension (intravenous, 5.1%; oral, 0.6%), bradycardia (0.8%), atrioventricular blocks. Phlebitis may develop. Use in HF or ischemia.
Vernakalant	IIIA	Hypotension, AF to ALF 1:1 (rare), NSVT, QT and QRS interval prolongation. Avoid in HF or ischemia, severe aortic stenosis, and when body weight >113 kg.
Ibutilide	IIIA	NSVT (1.7%–3.8%), TdP (up to 8%), QT interval prolongation, hypotension, bradycardia, atrioventricular blocks
Sotalol	IIIA	TdP (up to 8%), QT and PR interval prolongation, bradycardia, atrioventricular blocks

Abbreviations: AFL, atrial flutter; HF, heart failure; NSVT, nonsustained ventricular tachycardia; TdP, torsade de pointes; others, see TABLE 1

department or a hospital represent significant limitations. The main data on the clinical use of AADs, including risks and benefits, are summarized in TABLES 1 and 2.

Oral quinidine   In 1918, Walter von Frey reported the antiarrhythmic properties of quinidine, a quinine-related compound, in a Viennese medical journal.[47] Throughout the 19th century, it has

been one of the milestones of AF pharmacological cardioversion.[48] It was the standard of care against which the most of new AADs have been tested and its use was endorsed by international guidelines until 2006.[49-53] The evidence supporting the use of quinidine in the acute restoration of SR is limited, since it includes even uncontrolled studies, and the reported efficacy ranges between 30% and 90%.[49,54,55] In a meta-analysis by Miller et al,[56] quinidine showed moderate efficacy in restoring SR as compared with calcium channel blockers, digoxin, and placebo. As a class IA antiarrhythmic drug, quinidine blocks rapid Na⁺ channels prolonging the action potential and the QT interval. Quinidine has also anticholinergic activity and facilitates atrioventricular conduction; therefore, the coadministration of an atrioventricular node blocker is required. A great burden of adverse effects and a narrow therapeutic window raise main concerns about quinidine. A considerable number of patients suffer from gastrointestinal intolerance, which could affect long-term adherence to drug therapy. In the context of acute cardioversion, the potential arrhythmogenicity of quinidine is the most relevant issue. Torsade de pointes due to excessive QT interval prolongation, which may be even idiosyncratic, is the most dangerous effect of quinidine administration. The reported incidence of this life-threatening arrhythmia ranges from 1% to 8% in treated patients.[57,58]

Due to safety concerns and the introduction of newer, effective AADs, quinidine is no longer considered an actual therapeutic option for pharmacological cardioversion of AF in the latest guidelines.[9,59]

Intravenous procainamide   Procainamide is another class IA agent that is not currently recommended for pharmacological AF cardioversion.[9,59] It is the drug of choice for wide-QRS tachycardias caused by antegrade conduction through an accessory pathway.[60] In the latest ESC guidelines for the management of supraventricular tachycardias, it was stressed that procainamide (with flecainide, propafenone, and ibutilide) is the recommended drug in hemodynamically stable pre-excited patients with AF.[61] In non-pre-excited AF, procainamide has limited efficacy in restoring SR compared with other available drugs.[62,63] In a blinded study comparing procainamide and ibutilide, effective cardioversion was reported in 15% to 20% of patients.[64] Procainamide is available only for intravenous administration because of short half-life and serious adverse effects of oral administration (rash, fever, and lupoid reaction). The most common adverse effect of intravenous administration is hypotension due to lower systolic function. Torsade de pointes is a consequence of excessive QT prolongation, but it is less frequently observed than in quinidine cardioversion.

The intravenous regimen of flecainide and propafenone and the pill-in-the-pocket strategy   Flecainide and propafenone are class IC AADs. They affect myocardial electric potential phase 0 with slow sodium channel binding kinetics. They have a negative inotropic effect, more pronounced in flecainide than propafenone, which maintains mild β- and calcium-blocking properties instead.[65] Propafenone and flecainide are both reported in the ESC guidelines as level of evidence IA agents for restoring SR.[9] Considering recent-onset AF, available data suggest that flecainide or propafenone can be used in patients without underlying cardiac disease either intravenously or orally (the pill-in-the-pocket strategy) at success rates of 65% to 96% and 43% to 89%, respectively, for intravenous administration, and of 78% to 95% and 45% to 78%, respectively, for oral loading regimens. Intravenous and "pill-in-the-pocket" approaches differ with regard to mean time to SR restoration (0.4–0.9 hours for intravenous flecainide, 0.5–8 hours for intravenous propafenone, and 1.8 hours and 2.8–5 hours for oral loading doses of flecainide and propafenone, respectively).[58,66]

If not contraindicated, a β-blocker, verapamil, or diltiazem should be administered before these drugs in order to reduce the risk of rhythm conversion to atrial flutter (AFL) with 1:1 atrioventricular conduction. The proper selection of patients is essential for a successful "pill-in-the-pocket" strategy. This approach can be used in symptomatic patients with infrequent recurrences of AF. It should be avoided in those with sinus node dysfunction or atrioventricular conduction defects. The first administration should always be performed in the hospital to assess efficacy and safety, and self-administration by the patient at home, after careful education, can be implemented provided that symptoms are typical of AF and the patient agrees to rest in the hours following oral loading doses. Notably, the intravenous administration of flecainide or propafenone does not predict adverse events during out-of-hospital self-administration.[67]

Compared with placebo and other AADs (eg, amiodarone, propafenone, quinidine, and sotalol), flecainide has been considered safe and effective in restoring SR in recent-onset AF.[51,68-71]

Oral propafenone is well absorbed and achieves peak blood levels in 2 to 3 hours, but hepatic first-passage metabolism produces a metabolite (5-hydroxy-propafenone) that contributes to increased total drug effectiveness both for oral and intravenous formulations. Similarly to flecainide, intravenous and oral propafenone has been reported to be safe and effective in recent-onset AF cardioversion compared with placebo and other AADs.[55,72-75]

Although time to cardioversion is shorter with intravenous medications, the possibility to subsequently implement the "pill-in-the-pocket"

strategy is a relevant benefit of oral administration.[76-78] Selected patients with infrequent, symptomatic paroxysmal AF could take a single dose of 200 to 300 mg flecainide or 450 to 600 mg propafenone on their own (depending on body weight below or above 70 kg). This represents a valid therapeutic option with an efficacy marginally lower than in the case of in-hospital cardioversion.[79] This regimen is proposed only in patients previously treated under clinical and device-supported surveillance to exclude drug-related adverse events. Although a low number of drug-induced adverse effects (eg, gastrointestinal and ocular for flecainide use) is known, multiple drug interactions, especially for propafenone, have been reported. Besides considering drug-drug intearctions, a particular caution is needed in patients with underlying structural heart disease or arrhythmia, such as Brugada syndrome or ventricular pre-excitation, in which the intrinsic proarrhythmic properties of these drugs increase mortality, especially due to AF degeneration in atrial flutter with 1:1 atrioventricular conduction.[80] Common manifestations resulting from the use of these drugs seen on electrocardiography include: the progressive prolongation of PR and QRS intervals, minor effects on the QT interval, and bradycardia.

Intravenous and oral amiodarone Amiodarone, a class III antiarrhythmic drug, has class I, II, III, and IV activity blocking Na$^+$, L-type Ca^{2+}, and numerous K$^+$ currents. It prolongs the duration of the action potential and, as a result, refractoriness, thus decreasing the excitability of the cardiac tissue. Through the noncompetitive inhibition of α- and β-adrenergic receptors, it also has a vasodilating effect. The use of amiodarone for AF cardioversion is very common, particularly in patients with structural heart disease or contraindications to class IC drugs. The rate of conversions to SR with amiodarone at 24 hours in recent-onset AF ranges from 58%[81] to 92%,[35] with lower rates for AFL (29% reported by Kafkas et al[82]). However, intravenous amiodarone is characterized by a relatively long time to cardioversion, usually not shorter than 6 hours.[83] Indeed, a common feature that distinguishes amiodarone from other AADs is the late onset of effect, probably due to its pharmacokinetics. Several studies have been conducted to compare the efficacy and safety of amiodarone and other AADs in recent-onset AF. Despite the unfavorable pharmacokinetic profile, amiodarone has also been tested in cardioversion with acute oral loading.[84] Balla et al[69] analyzed 160 patients and observed a conversion rate at 24 hours of 85% for amiodarone, 87.5% for flecainide, 85% for propafenone, and 17.5% for placebo. Similar results were reported by Peuhkurinen et al[85] in 62 patients with

the 87% conversion rate at 24 hours with amiodarone (35% with placebo). Intravenous amiodarone has been compared with numerous different classes of AADs or placebo. Cotter et al[35] compared amiodarone (125 mg/h for a total of 3 g) and placebo (with intravenous digoxin if heart rate exceeded 100 bpm) and demonstrated a high conversion rate at 24 hours (92% versus 64%, respectively). Similar results were reported in another study by Kochiadakis et al.[72] The effect of the addition of an oral loading dose of ranolazine to intravenous amiodarone showed higher efficacy compared with amiodarone alone. In 2 studies, the oral loading dose of ranolazine was 1500 mg, with conversion rates of 88%[86] and 87%[87] compared with 65% and 70% for amiodarone alone, respectively. A different oral loading dose of 1000 mg was studied by Tsanaxidis et al,[81] who observed the 98% conversion rate with drug combination compared with 58% for amiodarone alone at 24 hours. The combination has also the advantage of producing a more rapid effect. No significant difference was observed for the cardioversion rate at 24 hours for amiodarone and ibutilide in AF (69%–77%).[82] Trials comparing amiodarone with propafenone and flecainide reported the higher efficacy of flecainide and similar conversion rates between amiodarone and propafenone, with the advantage of lower time to conversion with class IC drugs.[72,73,88] A comparison with procainamide yielded conflicting results. Amiodarone was superior to procainamide[72] regarding the conversion rate at 24 hours, whereas another study reported a similar conversion rate (81.4% for amiodarone and 82.7% for procainamide) and faster action of procainamide.[89] A comparison with vernakalant showed lower efficacy of amiodarone at 90 minutes (5% versus 51%).[90] Overall, amiodarone has a good efficacy and safety profile. Intravenous use can be associated with hypotension or hemodynamic deterioration especially in patients with known left ventricular dysfunction. The standard intravenous formulation uses polysorbate 80 as a solvent, known to be associated with clinically relevant adverse events. Other formulations of intravenous amiodarone developed to improve its safety profile have been successfully used.[91,92] A potential risk of phlebitis involving peripheral veins should always be considered. When a central vein cannot be used, the risk can be reduced by using low infusion concentrations (1.2 mg/ml), lower total doses (less than 0.45 mg), and bolus administration instead of long infusions.[93]

Intravenous vernakalant Vernakalant is a relatively atrial-selective AAD with sodium and potassium channel blocking properties.[94] It is approved in Europe, Canada, and many other countries for pharmacological cardioversion of recent-onset AF[95,96] and postoperative AF lasting

less than 3 days.[97] Since its first presentation in 2004 under the investigational product name of RSD1235, this drug proved to be effective and safe for the acute restoration of SR in several RCTs, with reported success rates of up to 69% and a median time to conversion of 8 to 14 minutes.[90,97-100] Currently, vernakalant is recommended for pharmacological cardioversion of new-onset AF in patients with no history of ischemic or structural heart disease and may be considered an alternative to amiodarone in patients with mild heart failure (New York Heart Association functional class I or II), including those with ischemic heart disease but without hypotension, severe aortic stenosis, acute coronary syndromes, high-grade atrioventricular block and/or sick sinus syndrome (not treated with a pacemaker), and a long QT interval.[9] As per the infusion protocol, the first intravenous dose of 3 mg/kg over 10 minutes should be followed by the second intravenous dose of 2 mg/kg over 10 minutes, 15 minutes later if AF persists (maximally 5 mg/kg/24 h).[9] Dysgeusia, sneezing, and paresthesia are the most common adverse effects. Hypotension and conversion of AF into 1:1 atrioventricular conduction AFL are rarer yet serious potential adverse effects.[101] In many settings, the cost of vernakalant, as compared with other options, constitutes a potential limitation to its standard use.

Intravenous ibutilide and sotalol   Ibutilide is a "pure" class III drug specifically designed and approved in the United States to overcome the limitations of other available agents for pharmacological cardioversion.[102,103] It is approved in numerous countries yet underprescribed due to its high price. Ibutilide has a short half-life and can be administered only intravenously owing to the strong hepatic first-pass effect. Intravenous ibutilide (1 mg/10 min and a repeated dose after 10 minutes if SR restoration is not observed) has been used for conversion of AF and AFL. The efficacy of restoring SR in AF ranged from 24% to 50%, while the success rate was higher in AFL (30%–76%).[64,103-105] Compared with procainamide or racemic sotalol, ibutilide appeared to be more effective in restoring SR.[64,103,104] In a randomized controlled comparison with flecainide, the 2 drugs showed a similar efficacy and safety profile.[105] The most consistent advantages of ibutilide include the rapid onset of action and the neutral effect on myocardial contractile performance even in patients with decreased left ventricular ejection fraction. Hypotension and bradycardia are the most common adverse effects, whereas polymorphic ventricular tachycardia or torsade de pointes are the most dangerous events.[102,103] The reported incidence of nonsustained and sustained ventricular arrhythmias ranges from 1.7% to 3.6%.[102,103] Therefore, patients treated with ibutilide should be monitored by electrocardiography for at least 4 hours with a focus on QT interval prolongation.

According to the latest guidelines, ibutilide is the first-choice drug for AFL cardioversion [61] and one of the possible agents for AF conversion.[9,59]

Oral sotalol is widely used and currently reported in the guidelines as a prophylactic agent in AF. Its intravenous administration to acutely terminate AF is not supported by firm evidence and, therefore, its use is currently not recommended.[9,59] When directly compared with quinidine or flecainide, it appeared to be less effective, and, compared with placebo, it showed a nonsignificant superiority.[49,71,106] Sotalol shares the most common adverse effects with other β-blockers (fatigue, bronchoconstriction, bradycardia, and hypotension), but also prolongs the QT interval and can predispose to torsade de pointes. Therefore, the QT interval should always be checked after sotalol therapy initiation.
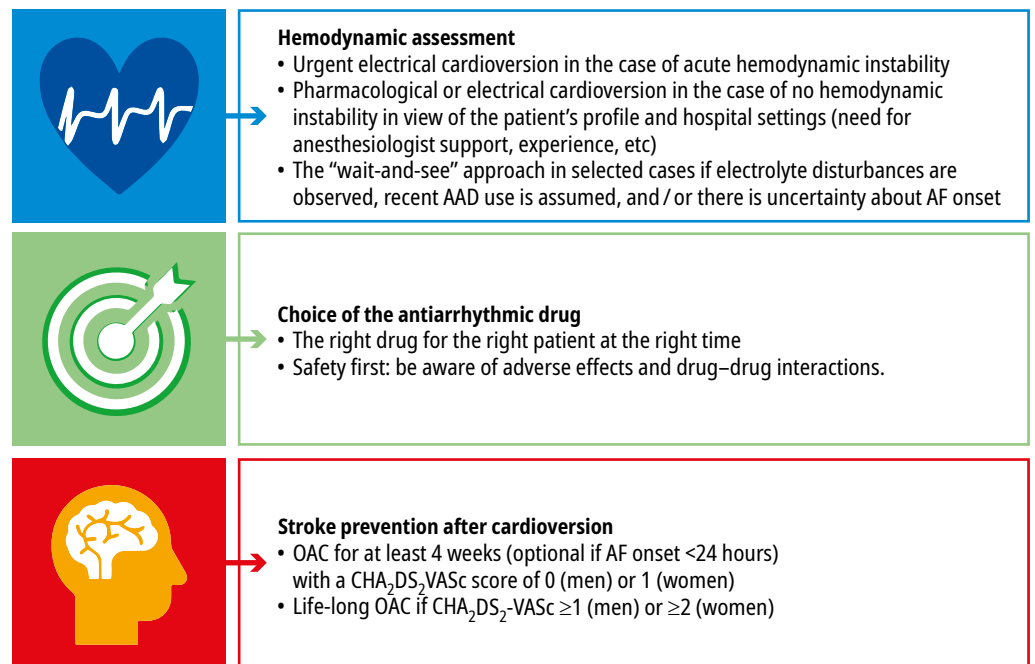
Drugs with no proven efficacy for conversion of atrial fibrillation: β-blockers, calcium channel blockers, and digoxin   In the AAD classification system, β-blockers are listed as class II, nondihydropyridine calcium channel blockers (verapamil and diltiazem) as class IV, and digoxin as class V agents. All these drugs have no proven efficacy in AF rhythm control and they have to be prescribed only as a rate control strategy.[9] Currently, β-blockers do not play any role in the management of recent-onset AF using pharmacological cardioversion,[107] although limited, controversial, and low-quality evidence has been reported for bisoprolol,[108] landiolol,[109] and esmolol.[110] Both β-blockers and nondihydropyridine calcium channel blockers can play a role in the pill-in-the-pocket strategy for recent-onset AF, especially 30 minutes before taking AADs. This approach could prevent the deterioration of AF into AFL with 1:1 atrioventricular conduction, although it has not been definitely proven yet.[10]

Digoxin is a cardiac glycoside. It is well absorbed when administered orally, with a half-life of 1.7 days. In AF, it plays no role in rhythm control[111] and it remains the drug of choice for rate control, on top of nondihydropyridine calcium channel blockers or β-blockers.[112] It is regarded as a positive inotropic agent, generally used in AF patients with heart failure and, due to its parasympathomimetic properties, as a negative chronotropic and dromotropic drug.[113] During its administration, toxic levels should be avoided and it is extremely important to check electrolyte imbalances (eg, hypokalemia). If symptomatic toxic levels are accidentally achieved, digoxin-specific antibodies should be considered. In clinical practice, it is also necessary to evaluate numerous drug–drug interactions (eg, with amiodarone and verapamil).

TABLE 3 Treatment choice for recent-onset atrial fibrillation in various clinical settings

Patient's clinical status	Treatment of choice
Hemodynamic instability or shock	Electrical cardioversion
No HF and / or LV dysfunction	Intravenous / oral flecainide Intravenous / oral propafenone Intravenous vernakalant Intravenous sotalol
LV dysfunction and / or HF	Intravenous amiodarone (with caution) Intravenous ibutilide (with caution)
Intraventricular conduction disturbances	Intravenous amiodarone
Pre-excited AF	Intravenous procainamide Intravenous flecainide Intravenous propafenone
ACS or ongoing ischemia	Intravenous amiodarone
Postoperative setting	Intravenous amiodarone Intravenous ibutilide

Abbreviations: ACS, acute coronary syndrome; LV, left ventricular; others, see TABLES 1 and 2

Hemodynamic assessment
- Urgent electrical cardioversion in the case of acute hemodynamic instability
- Pharmacological or electrical cardioversion in the case of no hemodynamic instability in view of the patient's profile and hospital settings (need for anesthesiologist support, experience, etc)
- The "wait-and-see" approach in selected cases if electrolyte disturbances are observed, recent AAD use is assumed, and / or there is uncertainty about AF onset

Choice of the antiarrhythmic drug
- The right drug for the right patient at the right time
- Safety first: be aware of adverse effects and drug–drug interactions.

Stroke prevention after cardioversion
- OAC for at least 4 weeks (optional if AF onset <24 hours) with a CHA_2DS_2VASc score of 0 (men) or 1 (women)
- Life-long OAC if CHA_2DS_2-VASc ≥ 1 (men) or ≥ 2 (women)

FIGURE 1 Practical considerations for the management of recent-onset atrial fibrillation
Abbreviations: AAD, antiarrhythmic drug; OAC, oral anticoagulation; others, see TABLE 1

Practical considerations for recent-onset atrial fibrillation Principal indications for AAD use in various clinical scenarios, as reported in the literature and clinical experience, are summarized in TABLE 3. The practical management of recent-onset AF should always encompass 3 fundamental issues: 1) the assessment of the patient's hemodynamic status; 2) the appropriate selection of the best AAD according to the patient's profile, and 3) stroke prevention with OAC after restoring SR, based on the time of AF onset and the patient's stroke and bleeding risk profile (FIGURE 1).

In daily clinical practice, amiodarone and flecainide are the drugs of choice in hemodynamically stable patients with or without structural heart disease, respectively.

After sinus rhythm restoration, 4–6-hour surveillance is considered reasonable to detect early AF recurrence and to monitor sedation-induced adverse effects and AAD-related arrhythmic events. There is no consensus on long-term AF recurrence monitoring. In our practice, patients after AF cardioversion are regularly followed up in an AF outpatient clinic, using

recurrence monitoring strategies (eg, electro-cardiography Holter recording) mainly based on patients' symptoms. In the current digital era, handheld devices (eg, single-lead electrocardiography devices, smartwatches, photoplethysmographic apps, or smartphone handheld electrocardiography recorders), which have been developed for AF screening, may be effective tools for extensive monitoring of AF recurrences.[7,9]

Conclusions Cardioversion in patients with AF remains a safe and effective therapeutic option. Prevention of thromboembolic risk remains a fundamental step in the management of AF, also in recent-onset AF. Four-week OAC is required after cardioversion, either occurring spontaneously or as a result of pharmacological or electrical interventions, in most patients, except if AF onset is shorter than 24 hours with a CHA_2DS_2VASc score of 0 (men) or 1 (women). In hemodynamically compromised settings, electrical cardioversion plays a key role. Pharmacological cardioversion is a safe and effective option, also for patients who do not respond to electrical cardioversion, but, given the potential adverse effects of ADDs, a careful clinical evaluation is always necessary. However, beyond the choice between electrical or pharmacological cardioversion, a holistic evaluation of the patient based on clinical judgment is still of paramount importance to provide each patient with the best treatment in all clinical settings.

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