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

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Short title: Cardioversion of recent-onset atrial fibrillation

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ABSTRACT

Atrial fibrillation (AF) represents the most common arrhythmia and it is associated with increased morbidity and mortality carrying high social costs. Because of its high prevalence, AF is usually managed not only by cardiologists, but also by general practitioners or in the emergency departments. Conventional classification of AF includes “recent-onset AF” defined as an arrhythmia episode of < 48 hours (h) in duration. In patients with a definite duration of AF of less than 24 h and with a very low-risk profile (CHA₂DS₂VASC 0 in male, 1 in female) the thromboembolic risk seems low and the standard 4-weeks anticoagulation is now considered an optional treatment. Cardioversion (electrical or pharmacological) in recent-onset AF represents a valid rhythm approach strategy. Electrical CV is usually reserved for hemodynamically unstable patient and performed with biphasic waveform shocks. Pharmacological CV is preferred in hemodynamically stable patients. Several antiarrhythmics drugs have been studied but some questions still remain unresolved mainly due to the lack of randomized clinical trials and prospective studies. Current guidelines do not uniformly agree on which drug to use for pharmacological CV, and drug preference varies widely in clinical practice. The aim of this narrative review is to sum up and critically evaluate the last evidence about recent-onset AF, giving some practical consideration with a focus in particular on rhythm control with pharmacological CV.

KEY WORDS: Anticoagulation; Atrial fibrillation; Cardioversion; Pharmacological Cardioversion; Stroke.
INTRODUCTION

Atrial fibrillation (AF) is the most common and prevalent arrhythmia, affecting 33.5 million people worldwide [1,2]. Reported epidemiologic numbers estimate it will double cases from 2010 to 2030, and the prospected AF prevalence in Europe will be around 17 million people [3,4]. AF patients have twice the risk of death and hospitalization compared to those without AF (e.g.: AF is a major risk factor for new-onset heart failure) [5]. Hospital admissions represent the most important part of the total healthcare AF related costs, which consist of 1% of the total healthcare expenditure in the United Kingdom and $26 billion/year in the USA [3,6]. Considering this background, it’s necessary to stress the public awareness on the screening and treatment of AF and on modifiable risk factors (e.g. hypertension, obesity, alcohol use, etc.), leading to cost containment and improving patients outcomes [7,8]. The classical definition of AF identifies four categories: i) paroxysmal (self-terminating or cardioverted within 7 days), ii) persistent (self-terminating or cardioverted over 7 days), iii) long-standing persistent (lasting for 1 year after rhythm strategy adoption), or iv) permanent (accepted by patient and physician) [9].

Besides this definition, international guidelines identify the recent-onset AF clinical entity, defined by an arrhythmia episode duration lower than 48 hours (h) [9,10]. Early AF detection poses two important clinical concerns about anticoagulation regimens and rhythm control strategy. When the onset of AF can be precisely defined as being < 48 h, the thromboembolic risk is low but CV per se may imply some risk. This justifies that anticoagulation has to be started as soon as possible and continued 4 weeks after cardioversion (CV) (or sine-die, according to CHA2DS2-VASc score) in most of the patients, except in those with a very low-risk profile [9]. According to the famous quote “atrial fibrillation begets atrial fibrillation” [11], a progression of AF is associated with structural heart changes developing along with time, leading to an 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, an early CV approach may be a valid strategy.
also to reverse the alterations that favour AF persistence. Cardioversion may also improve cardiac function, reduce many of the AF related symptoms and improve the quality of life [16-19]. Moreover, early CV in the emergency department has been shown to be safe and effective and significantly reduces healthcare costs. Both electrical and pharmacological CV can be effective in restoring SR [20]. Nevertheless, current guidelines do not uniformly agree on which drug to use for pharmacological CV, and drug preference varies widely in clinical practice. These different approaches in the pharmacological intervention are due to a lack of RCTs and prospective studies. The actual clinical practice is based on weak evidence, including studies in which recent-onset AF definition was not often clear (> and/or < 48 h) and insufficient drug comparisons are presented.

The purpose of this review is to sum up and critically evaluate the last evidence about recent-onset AF, giving some practical considerations with a focus in particular on rhythm control with pharmacological CV.

**DEFINITION OF RECENT-ONSET ATRIAL FIBRILLATION**

The term “recent-onset AF” refers to the time between the onset of symptoms and the detection of the arrhythmia. The most widely accepted cut-off value to define “recent onset” is < 48h [9,10,21]. Despite this, several studies actually considered a broad spectrum of durations ranging between 12 h, 7 days or < 24 h [22-27].

Besides the formal issue of the terminology that should be standardized to achieve a better comparison between studies, it is important to use an operative definition of “recent-onset”, in order to discriminate, for example, the need of anticoagulation before the CV. Nowadays, it seems reasonable to define “recent-onset” AF with the cut-off of < 48h as recommended by both North-American and European guidelines [9,10]. However, we have to consider that it is not always easy for the patient to identify the exact amount of time that has passed from the onset of symptoms. Moreover, not always the onset of symptoms corresponds to the real onset of the arrhythmia. If the
patient is not sure about the precise time of onset, applying the caution principle, it is mandatory to consider AF lasting > 48 h.

CARDIOVERSION AND THROMBOEMBOLIC RISK

Patients undergoing CV 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 CHA₂DS₂VASc if AF has been present for 48 or more hours [28]. If there is uncertainty over the exact duration of AF, the patient should be anticoagulated as if their prior AF is > 48 hours [28,29]. Transesophageal echocardiography (TOE) before cardioversion is not indicated in recent onset AF (< 48), regardless of the patient’s anticoagulant status. It is accepted as a precautionary measure in case of dubious therapy adherence, recent stroke, rheumatic valve disease or mitral valve stenosis (moderate/severe) and mechanical valve prosthesis [9]. The presence of pre-existing thrombus (especially if non-anticoagulated), the reduced mechanical function, named atrial stunning, occurring in the first period after post-CV and a transient prothrombotic state are the factors involved in the risk of thromboembolism associated with AF lasting 48 hours or more or of uncertain duration [28]. No randomized controlled trials (RCTs) evaluated the practice of anticoagulation vs. no anticoagulation in patients with AF with a duration of AF <48 hours. Observational data suggest that the risk of stroke/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 (CHA₂DS₂VASc 0 in male, 1 in female) [30-32]. As stated in the European Society of Cardiology (ESC) 2020 guidelines in patients at very low risk (CHA₂DS₂VASc 0 in male, 1 in female) with new-onset AF <24 hours, 4 weeks of anticoagulation after CV could be omitted [9,28,29]. For patients with a CHA₂DS₂VASc profile at risk of stroke (score ≥ 2 in female and ≥ 1 in male) anticoagulation should be prescribed at long term (class I recommendation for CHA₂DS₂VASc ≥ 3 in female and ≥ 2 in male, class IIa recommendation for CHA₂DS₂VASc=2 in female and =1 in male) even after the first episode of AF, independently of restoration of SR with effective CV. Cardioversion on
anticoagulant is generally safer than CV without anticoagulation in terms of thromboembolic incidence rate, especially with CHA2DS2-VASc ≥ 2 and AF duration > 12 h. Low-molecular-weight heparin (LMWH) is the most used drug in this setting and a single dose is generally considered to be safe. Given the similar pharmacodynamic and -kinetic, a single dose of Non-Vitamin K Oral Anticoagulants (NOACs) may be a reasonable alternative. In recent years, 3 RCTs have shown a low rate of thromboembolic events following CV with LMWH or vitamin K antagonist (VKA), as well as with NOAC anticoagulation regimens, but none of those provided specific information on patients with AF duration of < 48h [9,29].

RECENT ONSET AF WITH HEMODYNAMIC INSTABILITY

The first step in the evaluation of recent-onset AF is to assess patient’s hemodynamic status. In patients presenting with hemodynamic instability or with high-risk clinical features such as ventricular rate > 150 bpm, ongoing chest pain and/or critical perfusion, urgent electrical CV is recommended [9,33]. Several studies in the Emergency Department (ED) showed that this approach is safe and effective [34].

SPONTANEOUS CARDIOVERSION TO SINUS RHYTHM: PROS AND CONS OF A “WAIT AND SEE” APPROACH

The “wait-and-see” approach is an interesting option studied in several trials for recent-onset AF patients. In 1999 Cotter G. et al. [35] found that spontaneous conversion to SR in 100 ED patients was high and reached 90% in specific subgroups. These findings were later confirmed by P. Geleris et al.[36] who observed spontaneous conversion to SR in 73.4% of patients with recent-onset AF, especially in the first 12h. Similarly, Doyle et al. [37] underlined that acute AF spontaneously resolved with a “wait-and-see” protocol in almost two-thirds of the study patients, who reported a high degree of satisfaction. Recently, new evidence supporting a “wait-and-see” approach in recent-onset AF came from the RACE 7 ACWAS trial (Rate Control versus Electrical Cardioversion Trial
Acute Cardioversion versus Wait and See) [25]. Four hundred and twenty-seven patients with recent-onset AF (< 36 h) were randomized in the ED to a “wait-and-see” approach (delayed CV group, in which rate-control strategy was initiated first) or to early CV. Most of the of patients in the delayed CV group and in the early CV group were in SR at 4 weeks (91 vs 94%, respectively). The Authors concluded that a “wait-and-see” approach was non-inferior to early CV in achieving a conversion to SR at 4 weeks, in particular when AF duration was < 24 h [25]. Nevertheless, as already highlighted, the “wait-and-see” strategy should be considered in a careful balance between pros and cons of its application [38,39]. This strategy is determined by three factors: physician, patient and Health and Care System organization, and all these three ones condition daily practice of recent-onset AF management, in which an individualized approach is mandatory [40].

CARDIOVERSION OF RECENT-ONSET AF

Cardioversion in AF represents a valid approach for rhythm control strategy. The choice between electrical or pharmacological CV should encompass a careful evaluation of the patient’s profile (i.e. hemodynamic status, presence of structural heart disease, symptoms, fluid and electrolyte balance, etc.) and hospital setting (need for anesthesiologist, experience, etc.).

For example, Kaliemia and Magnesemia imbalance could act as triggers for AF. Moreover, the correction of electrolyte imbalances could avoid possible anti-arrhythmic drugs (AADs) side effects, such as exacerbation of a QT prolongation or digitalis intoxication. No data are available on cost-effectiveness of routinary determination of serum electrolytes, but it seems reasonable to perform it.

Electrical cardioversion

Electrical CV is generally reserved to hemodynamically unstable patients but it is widely performed also in recent-onset AF episodes in stable patients, especially if young with no associated structural-heart disease [41]. Biphasic waveform shock had higher success rates with lower provided energies
than monophasic waveform CV [42]. Anteroposterior pads placement is generally considered to be superior to the anterolateral position, even if a recent trial has not confirmed these findings [20,43]. Electrical CV can be preceded by intravenous (IV) or per os pharmacological facilitation [44,45]. Vice-versa, electrical attempt to restore SR often follows a pharmacological CV failure [20,46]. There are few evidence-based comparisons between “pure” pharmacological versus “pure” electrical CV in recent-onset AF and it is still a matter of debate which is the best approach in terms of feasibility, cost, risks and effectiveness. In the recent RAFF2 trial (Electrical versus pharmacological cardioversion for emergency department patients with acute atrial fibrillation), both drug-shock and shock-only strategies were highly effective and safe as CV strategies indeed [20].

**Pharmacological cardioversion**

Pharmacological CV is a reasonable and effective approach. Potential benefits of pharmaco-induced CV are avoiding sedation drugs and testing oral antiarrhythmic agents’ tolerance if a pill-in-the-pocket strategy is applied. However, pharmacological side effects, prolonged telemetric monitoring and in ED/hospital structure stay represent not negligible limitations. We were reviewed the main data from literature related to clinical use of AADs, even in risk benefits perspective, as summarized in Table 1 and Table 2.

**Oral Quinidine**

In 1918, Walter von Frey reported in a Viennese medical journal the antiarrhythmic properties of quinidine, a quinine related compound [47]. Throughout the 19th century, it has been one of the milestones of AF pharmacological CV [48]. It was the standard of care against which the most of new AADs have been tested and its use has been 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 reported efficacy ranges between 30% and 90%
In a meta-analysis by Miller et al. [56], quinidine showed moderate efficacy in restoring SR when compared to 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 co-administration of an atrioventricular node blocker is required. The main concerns about quinidine are the great burden of side effects and the narrow therapeutic window. A consistent number of patients suffer from gastrointestinal intolerance, which could affect long-term adherence to the drug. In the context of acute CV, the potential arrhythmogenicity of quinidine is the most relevant issue. The most dangerous effect following quinidine administration is torsade de pointes due to excess QT interval prolongation which may even be idiosyncratic. The reported incidence of this life-threatening arrhythmia ranges from 1% to 8% in treated patients [57,58]. Due to these safety concerns and with the introduction of newer effective AADs, quinidine is no longer considered as an actual therapeutic option for pharmacological CV of AF in the latest guidelines [9,59].

**Intravenous procainamide**

Procainamide is another class IA agent which is not currently recommended for AF pharmacological CV [9,59]. It is a 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 has been stressed that procainamide (with flecainide, propafenone and ibutilide) is the recommended drug in hemodynamically stable pre-excited AF patients [61]. In non-pre-excited AF, procainamide has limited efficacy in restoring SR when compared to other available drugs [62,63]. In a blinded study comparing procainamide and ibutilide, effective CV was reported in 15-20% of patients [64]. Procainamide is available only for IV administration because of short half-life and serious adverse effects of oral administration (rash, fever, lupoid reaction). The most common adverse effect of IV administration is hypotension due to the depression of
systolic function. Torsade de pointes is a consequence of excessive QT prolongation but is less frequent than in quinidine CV.

**Flecainide and propafenone intravenous regimen and 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 instead maintains mild beta- and calcium-blocking properties [65]. Propafenone and flecainide are both reported in the ESC guidelines as evidence IA class agents for restoring SR [9]. Considering recent-onset AF, available data suggest that in patients with no underlying heart disease, flecainide or propafenone can be used either IV or orally (“pill-in-the-pocket strategy”) with a success rate of 65–96% and 43–89% for IV administration, respectively and of 78–95% and 45-78% for the oral loading regimens. Intravenous and “pill-in-the-pocket” approaches differ with regard to mean time to restoration SR (0.4–0.9h for flecainide IV, 0.5–8.0h IV for propafenone IV and 1.8h and 2.8–5.0h for oral loading administrations, respectively) [58,66].

When not contraindicated, a beta-blocker, verapamil or diltiazem should be given before these drugs in order to reduce the risk of rhythm conversion to atrial flutter with 1:1 A-V conduction. Accurate 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 must be avoided in patients with sinus node dysfunction or AV conduction defects. First administration should always be done in-hospital to assess efficacy and safety, with self-administration by the patient at home, after careful education, provided that symptoms are typical of AF and the patient ensures to stay at rest in the hours that follow oral loading. Notably, i.v. administration of flecainide or propafenone does not predict adverse events during out-of-hospital self-administration [67].
Compared to placebo and other AADs (e.g.: amiodarone, propafenone, quinidine, sotalol) flecainide, have been found safe and effective in restoring SR in recent-onset AF [51,68-71]. Oral propafenone is well absorbed and achieves peak blood levels in 2–3 hours but hepatic first-passage metabolism produces a metabolite (5-hydroxy-propafenone) which contributes to increase drug total effectiveness both for oral and IV formulations. Similarly to flecainide, IV and oral propafenone has been found safe and effective in recent-onset AF CV versus placebo and versus other AADs [55,72-75].

Although time to CV is shorter with IV medications, a relevant benefit in oral administration is the subsequent possibility of a “pill-in-the-pocket” strategy [76-78]. Selected patients with infrequent, symptomatic paroxysmal AF, could self-administrate per os a single dose of 200-300 mg flecainide or 450-600 mg propafenone (based on weight < or > 70 kg). This represents a valid therapeutic option with an efficacy marginally lower vs in-hospital CV [79]. This regimen is proposed only in patients previously treated under clinical and instrumental monitorization, to exclude drugs-related adverse events. Although a modest number of drug side effects (e.g.: flecainide: GI and optical) are known, numerous drug interactions, especially for propafenone, have been reported. As well as their interactions, a particular caveat is necessary for patients with underlying structural or arrhythmical heart disease, such as Brugada syndrome or ventricular pre-excitation, in which intrinsic proarrhythmic properties of these drugs contribute to increase mortality, especially for AF degeneration in atrial flutter (AFL) with 1:1 AV conduction [80]. Common manifestations on ECG for these drugs are: progressive prolongation of PR and QRS intervals, minor effects on QT interval and bradycardia.

**Intravenous and oral amiodarone**

Class III antiarrhythmic drug amiodarone has class I, II, III and IV activity, blocking Na+, L-type Ca2+, and many K+ currents. It lengthens the duration of the action potential, prolonging refractoriness thus decreasing the excitability of the cardiac tissue. Through a non-competitive
inhibition of $\alpha$- and $\beta$-adrenergic receptors it produces also a vasodilator effect. The use of amiodarone for AF CV is very common in particular in the setting of patients with structural heart disease or contraindications to class IC drugs. Rate of conversions to SR at 24 h with amiodarone in recent-onset AF ranges from 58% [81] to 92% [35], with lower rates for AFL (29% reported by Kafkas et al., [82]). However, it is important to stress that IV amiodarone has a relatively long time to CV, 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 comparing the efficacy and the safety of amiodarone with other AADs in the setting of recent-onset AF. Despite the not favorable pharmacokinetic profile, amiodarone has also been tested for CV with acute oral loading [84]. Balla et al. [69] analyzed 160 patients and found a conversion rate at 24 h of 85% with amiodarone, 87.5% with flecainide, 85% with propafenone and 17.5% with placebo. Similar results were reported by Peuhkurinen et al. [85], in 62 patients with 87% conversion rate at 24 h with amiodarone (35% with placebo). Intravenous amiodarone has been compared with many different classes of AADs or placebo. Cotter et al. [35] compared amiodarone (125 mg/h for a total of 3 g) versus placebo (with IV Digoxin if heart rate > 100 bpm) resulting in high conversion rate at 24 h (92% vs 64%, respectively). Similar results were reported in another study by Kochiadakis et al. [72] The effect of the addition of oral loading dose of ranolazine to IV amiodarone demonstrated higher efficacy compared with amiodarone alone. In two studies the oral loading dose of ranolazine was 1500 mg, with a conversion rate of 88% [86] and 87% [87] compared with 65% and 70% of amiodarone alone, respectively. A different oral loading dose of 1000 mg was studied by Tsanaxidis et al. [81] getting a 98% conversion rate with the combination compared with 58% of amiodarone alone at 24 h. The combination has also the advantage of a more rapid effect. No statistically significant difference was observed comparing CV rate at 24 h of amiodarone to ibutilide in AF (69% to 77%) [82]. Trials comparing amiodarone with propafenone and flecainide reported 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]. Comparison with procainamide showed conflicting results. Amiodarone was superior to procainamide [72] in conversion rate at 24 h, whereas another study found a similar conversion rate (81.4% amiodarone and 82.7% procainamide) with faster action of procainamide [89]. A comparison with vernakalant showed lower efficacy of amiodarone at 90 min (5a vs 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. Usual IV formulation uses Polysorbate 80 as a solvent, known to be associated with clinically-relevant adverse events. Other formulations of IV amiodarone developed to improve safety profile have been reported with success [91,92]. The potential risk of phlebitis of peripheral vein must always be taken into account. When a central vein cannot be used, reduction of this risk can be obtained using low infusion concentrations (1.2 mg/mL), lower total doses (less than 0.45 mg), and using bolus administration instead of longer infusions.[93]

**Intravenous vernakalant**

Vernakalant is a relatively atrial-selective AAD with sodium and potassium channels blocking properties [94]. Vernakalant is approved in Europe, Canada and many other countries for the pharmacological CV of recent-onset AF [95,96] and for post-operative AF lasting less than 3 days in duration [97]. Since its first presentation in 2004 under the investigational product name of RSD1235, this drug proved effective and safe for acute restoration of SR in several RCTs with reported success rates up to 69% and a median time to conversion of 8-14 minutes [90,97-100]. Currently, vernakalant is recommended for pharmacological CV of new-onset AF in patients with no history of ischemic or structural heart disease and may be considered as an alternative to amiodarone in patients with mild heart failure (NYHA class I or II), including those with ischemic heart disease but without hypotension, severe aortic stenosis, acute coronary syndromes, high-grade atrioventricular block /sick sinus syndrome (not backed up by pacemaker) and long QT interval [9]. Infusion protocol consists of a first dose of 3 mg/kg i.v. over 10 minutes followed by a second dose
of 2 mg/kg i.v. over 10 minutes, 15 minutes later if AF persists (max 5mg/kg/24h) [9]. Dysgeusia, sneezing and paresthesia are the most common side effects. Hypotension and conversion of AF into 1:1 AV conduction AFL are rarer but serious potential side effects [101]. In many setting, the cost of vernakalant, as compared to other options, constitutes a potential limitation to its standard use.

**Intravenous ibutilide and intravenous sotalol**

Ibutilide is a “pure” class III drug specifically designed and approved in the US to overcome the limitations of the other available agents for pharmacological CV [102,103]. It is approved in many countries, but it is underprescribed due to its high cost. Ibutilide has a sort half-life and can be administered only intravenously due to high hepatic first-pass effect. Intravenous ibutilide (1mg/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 in restoring SR in AF ranged from 24 to 50%, while with AFL the success rate was higher (30-76%) [64,103-105]. When compared to procainamide or racemic sotalol, ibutilide appeared to be more effective in restoring SR [64,103,104]. In a randomized controlled comparison with flecainide, the two drugs showed a similar efficacy and safety profile.[105] The most consistent advantages of ibutilide are the rapid onset of action and the neutral effect on myocardial contractile performance even in patients with depressed ejection fraction. The most common adverse effects are hypotension and bradycardia while the most dangerous event is polymorphic ventricular tachycardia or torsade de pointes [102,103]. The reported incidence of non-sustained and sustained ventricular arrhythmias ranges from 1.7 to 3.6% [102,103]. Therefore, patients treated with ibutilide should be ECG monitored for at least 4 hours with focused monitoring on QT interval prolongation.

According to the latest guidelines, ibutilide is the first choice for AFL CV [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 IV administration to acutely terminate AF is not supported by solid evidence and therefore its
use is not currently recommended [9,59]. When directly compared to quinidine or flecainide, it appeared to be less effective and compared to placebo showed a non-significant superiority [49,71,106]. Sotalol shares the most common side effects with other beta-blockers (fatigue, bronchoconstriction, bradycardia, hypotension), but also prolongs QT interval and can predispose to torsade de pointes. Therefore, the QT interval should always be checked after sotalol therapy introduction.

**Drugs with no proven efficacy for conversion of atrial fibrillation: beta-blockers, calcium-channel blockers and digoxin**

In AADs classification system, beta-blockers are listed as class II agents, non-dihydropyridine-Calcium Channel Blockers (non-DHP-CCB; Verapamil and Diltiazem) as class IV and digoxin as class V. All these drugs have no proven efficacy in AF rhythm control, and they have to be prescribed only as rate control strategy [9]. Currently, beta-blockers play no role in the management of recent-onset AF pharmacological CV [107], although limited, controversial and low-quality evidence with bisoprolol [108], landiolo [109] and esmolol [110] has been reported. Both beta-blockers and non DHP-CCP can have a role in the pill-in-the-pocket strategy of recent onset AF, specifically 30 minutes before taking the AADs. This approach could prevent a degeneration of AF into AFL with 1:1 AV conduction, although this it has not been definitely proven [10]

Digoxin is a cardiac glycoside. It is well absorbed per os, with a half-life of 1.7 days. In AF, it has no role in rhythm control [111], and it remains a choice for rate control, on top of non-DHB-CCB or beta-blockers [112]. It is considered a positive inotropic agent, generally used in AF patients with heart failure and, due to its parasympathetic-mimetic property, a negative chronotropic and dromotropic drug [113]. During its administration, toxic levels have to be avoided and it is extremely important to check electrolyte imbalances (e.g.: hypokalemia). If symptomatic toxic levels are accidentally achieved, digoxin-specific antibodies should be considered. In clinical
practice, it is also necessary to evaluate its numerous drug-drug interactions (e.g.: amiodarone, verapamil, etc.).

**PRACTICAL CONSIDERATIONS FOR RECENT-ONSET AF**

Table 3 summarizes the principal indications for the AAD choice in the context of different clinical scenarios, as reported in literature and in clinical experience. Practical management of recent onset AF should always encompass three fundamental issues: (1) assessment of the patient's hemodynamic status, (2) appropriate selection of the best AAD according to patient’s profile and (3) stroke prevention with OAC after restoration of SR according to the time of AF onset and stroke/bleeding patient’s risk profile (Figure 1).

In daily clinical practice, our drugs of choice, in hemodynamically stable patients, are amiodarone and flecainide, respectively in patients with or without structural heart disease. After sinus rhythm restoration, an observation period of 4-6 hours is considered reasonable to detect early AF recurrence and to monitor sedation side effects and AAD-related arrhythmic events. There is no consensus on long-term AF recurrence monitoring. In our practice, after AF CV, patients are regularly followed up in AF outpatient clinic with recurrence monitoring strategies (e.g. ECG Holter) mainly based on patients’ symptoms. In current digital era, handheld devices (e.g. single-lead ECG devices, smartwatches, photoplethysmographic apps or smartphone handheld ECG recorders) which have been developed for AF screening purpose may be an effective tool for extensive monitoring of AF recurrences [7,9].

**CONCLUSIONS**

Cardioversion in AF patients remains a safe and effective therapeutic option. Prevention of thromboembolic risk remains a fundamental step in management of AF also in the setting of recent onset AF. Four weeks of OAC is required after CV, either occurring spontaneously or as a result of pharmacological/electrical interventions, in most of the patients, except if AF onset is < 24 hours with CHA2DS2VASc = 0 (male) or = 1 (female). In hemodynamic compromised settings, electrical CV strategy plays a key role. Pharmacological CV is a safe and effective option, also for non-
responders to electrical CV, but given the potential side effects of the ADDs, a careful clinical
evaluation is always necessary. However, beyond the choice between electrical or pharmacological
CV, a holistic evaluation of the patient based on medical judgment is still of paramount importance
to provide each patient with the best treatment in each clinical setting.
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Table 1. Effects of different agents in the cardioversion of recent-onset AF

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Route</th>
<th>Standard dose</th>
<th>Time to CV * (h)</th>
<th>Efficacy (%)</th>
<th>Adverse events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>PO</td>
<td>400 mg/dose every 6 h</td>
<td>3.1-6.1</td>
<td>30-90</td>
<td>3-46</td>
</tr>
<tr>
<td>Procainamide</td>
<td>IV</td>
<td>5–15 mg/kg (max dose 1000 mg) at 0.2–0.4 mg/kg/min over 10–15 min.</td>
<td>&lt;1.5</td>
<td>15-20</td>
<td>2-12</td>
</tr>
<tr>
<td>Flecainide</td>
<td>IV/PO</td>
<td>IV: 1.5–2 mg/kg in 10 min. PO: 300mg, 200 mg, if b.w.&lt;70Kg.</td>
<td>IV: 0.4-0.9</td>
<td>IV: 65–96</td>
<td>IV: 3.4-31</td>
</tr>
<tr>
<td>Propafenone</td>
<td>IV/PO</td>
<td>IV: 1.5–2 mg/kg in 10 min. PO: 600mg, 450 mg, if b.w.&lt;70Kg.</td>
<td>IV: 0.5-8.0</td>
<td>PO: 78–95</td>
<td>PO: 0.23</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>IV/PO</td>
<td>IV: 5-7 mg/kg bolus followed by 50 mg-1g/hour in 24 h. PO: 30 mg/kg</td>
<td>IV: 5.6-19.4</td>
<td>IV: 58-92</td>
<td>IV: 0-7.7</td>
</tr>
<tr>
<td>Vernakalant</td>
<td>IV</td>
<td>3 mg/kg in 10 min (max 1st dose: 339 mg); 2 mg/kg in 10 min, after waiting 15 min. (max 2nd dose: 226 mg).</td>
<td>0.2</td>
<td>47-93</td>
<td>0-2.6</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>IV</td>
<td>1 mg in 10 min (0.01 mg/kg if b.w. &lt; 60 Kg); 1 mg in 10 min, after waiting for 10 min.</td>
<td>0.4-0.9</td>
<td>24-50</td>
<td>1.7-3.6</td>
</tr>
<tr>
<td>Sotalol</td>
<td>IV</td>
<td>1.5 mg/kg in 10 min.</td>
<td>&lt;4</td>
<td>11-85</td>
<td>10-23</td>
</tr>
<tr>
<td>Placebo</td>
<td>---</td>
<td>--</td>
<td>2.5-17.0</td>
<td>46.2-56.7</td>
<td>2.3</td>
</tr>
</tbody>
</table>

CV: cardioversion; IV: intravenous; PO: per os; b.w.: body weight; AF: Atrial fibrillation; *: During minimum of 4 h and maximum of 24 h observation, reported as mean/median; Adverse events: AFL 1:1 (Class I agent), bradycardia, hypotension, ventricular dysrhythmia (ventricular tachycardia/ventricular fibrillation).
Table 2. Major side effects and warnings of different antiarrhythmic agents

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Class</th>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>IA</td>
<td>AF to AFL 1:1 (rare), TdP (1-8%), high-grade AV block (rare). Avoid in HF or ischemic patients.</td>
</tr>
<tr>
<td>Procainamide</td>
<td>IA</td>
<td>AF to AFL 1:1 (rare), high-grade AV block (rare), QRS-QT prolongation, Hypotension. Drug-induced lupus. Avoid in HF or ischemic patients.</td>
</tr>
<tr>
<td>Fleca...</td>
<td>IC/IVB</td>
<td>AF to AFL 1:1 (3.5-5%), high-grade AV block (rare), QT prolongation. Avoid in HF or ischemic patients.</td>
</tr>
<tr>
<td>Propafenone</td>
<td>IC/IVB</td>
<td>AF to AFL 1:1 (3.5-5%), high-grade AV block (rare), QRS prolongation. Avoid in HF or ischemic patients.</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>IIA</td>
<td>TdP (0.7%), Hypotension (IV 5.1%; OS 0.6%), Bradycardia (0.8%), AV blocks. Phlebitis. Use in HF or ischemic patients</td>
</tr>
<tr>
<td>Vernakalant</td>
<td>IIA</td>
<td>Hypotension, AF to ALF 1:1 (rare), NSVT, QT and QRS prolongation. Avoid in HF or ischemic patients, severe aortic stenosis and in body weight &gt; 113 kg.</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>IIA</td>
<td>NSVT (1.7-3.8%), TdP (up to 8%), QT prolongation, Hypotension, Bradycardia, AV blocks.</td>
</tr>
<tr>
<td>Sotalol</td>
<td>IIA</td>
<td>TdP (up to 8%), QT and PR prolongation, Bradycardia, AV blocks.</td>
</tr>
</tbody>
</table>

AF: Atrial fibrillation; AFL: Atrial flutter; AV: atrio-ventricular; HF: heart failure; TdP: Torsade des pointes; NSVT: non sustained ventricular tachycardia.
**Table 3.** Treatment choice for recent-onset AF in different clinical settings

<table>
<thead>
<tr>
<th>Patients clinical situation</th>
<th>Treatment of choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamic unstable or shock</td>
<td>Electrical cardioversion</td>
</tr>
</tbody>
</table>
| No HF and/or LV dysfunction | Flecainide IV/PO  
Propafenone IV/PO  
Vernakalant IV  
Sotalol IV |
| LV dysfunction and/or HF | Amiodarone IV (with caution)  
Ibutilide IV (with caution) |
| Intraventricular conduction disturbances | Amiodarone IV |
| Pre-excited AF | Procainamide IV  
Flecainide IV  
Propafenone IV |
| ACS or ongoing ischemia setting | Amiodarone IV |
| Post-operative setting | Amiodarone IV  
Ibutilide IV |

AF: atrial fibrillation; HF: heart failure; LV: left ventricular; ACS: acute coronary syndrome; IV: intravenous; PO: per os.
**Figure 1.** Practical consideration for the management of recent onset AF

AF: atrial fibrillation; CV: cardioversion, AADs: antiarrhythmics drugs, OAC: oral anticoagulant; m: male; f: female

**Recent Onset AF**

### Hemodynamic Assessment
- Urgent Electrical CV in case of acute hemodynamic instability
- Pharmacological CV or Electrical CV in case of no hemodynamic instability according to patient’s profile and hospital setting (need for anesthesiologist, experience, etc.)
- “Wait and See” approach in selected cases if electrolyte disturbances, recent AADs assumption and/or 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 side effects and drug interactions

### Stroke Prevention after CV
- OAC for at least 4 weeks (optional if AF onset < 24 hours) with CHA2DS2-VASc = 0 (m) or = 1 (f)
- OAC life-long if CHA2DS2-VASc ≥ 1 (m) or ≥ 2 (f)