REVIEW ARTICLE

Pharmacological cardioversion of atrial fibrillation: practical considerations

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KEY WORDS

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ABSTRACT

The choice between rhythm and rate control strategy represents one of the most intriguing dilemmas in the management of atrial fibrillation (AF). Although the advantage of rhythm over rate control in terms of outcome has not been unequivocally proven, the initial management of patients with symptomatic episodes of AF frequently involves early cardioversion. As electrical cardioversion (EC) is challenging in terms of fasting status and involvement of an anesthesiologic team, pharmacological cardioversion (PC) is usually selected as the first step toward rhythm conversion. Qualification criteria for PC or EC are similar and should comprise assessment of hemodynamic status, estimation of arrhythmic episode duration, evaluation of anticoagulation regimen, exclusion of other supraventricular arrhythmias, and assessment of the chance of rhythm conversion and persistence of sinus rhythm. Finally, the choice of adequate antiarrhythmic drug (AAD) depends on the presence of structural heart disease (SHD) and local experience. In patients without any SHD, complications occur rarely, hence traditional (propafenone, flecainide) or nonclassical Vaughan–Williams class I (antazoline) or class III (vernakalant, ibutilide, or dofetilide) drugs are preferred. The presence of SHD consistent with any left ventricular hypertrophy, heart failure, myocardial ischemia, or valvular heart disease limits the choice of AAD to amiodarone. Given the risk of ventricular proarrhythmia of AAD, safety should always prevail over the enticing possibility of rhythm conversion. The present review aims to provide a comprehensible summary of proper qualification for PC, selection of suitable AAD, and state-of-the-art periprocedural management of patients with recent-onset AF.

Introduction Clinical significance of atrial fibrillation (AF) is associated not only with an increased risk of systemic embolism and impaired outcome but also with decreased quality of life (QOL).[1,2] The rhythm control strategy, along with optimal rate control, should mainly result in symptomatic relief.[3,4] Also, there are plausible scientific data suggesting improved outcome in patients with early implementation of complex rhythm control strategy, including antiarrhythmic drugs (AADs), electrical cardioversion (EC), and pulmonary vein isolation.[5] The first step of rhythm control strategy is pharmacological cardioversion (PC), which consists in intravenous or oral administration of AADs in order to convert AF to sinus rhythm (SR) under the constant electrocardiographic monitoring.[3,4] This procedure may terminate symptomatic episodes of AF, improve QOL, prevent redundant hospital admissions, and reduce health care costs.[6] According to the current European Society of Cardiology (ESC) guidelines,[7] either PC or EC is recommended as the initial management of patients with new-onset and symptomatic AF, provided there are no contraindications. Although EC is associated with a 90% chance of restoring SR, it requires general anesthesia, and PC frequently serves as an initial attempt at rhythm conversion.[8] The overall efficacy of PC was estimated at around 50%–70%, depending on the patient's profile and AAD applied.[8-10] Available AADs share different limitations, including increased risk of induction of ventricular arrhythmias (Vaughan–Williams class Ic, eg, propafenone) or delayed onset of action (amiodarone), or have limited regional availability (vernakalant, antazoline, and ibutilide), hence

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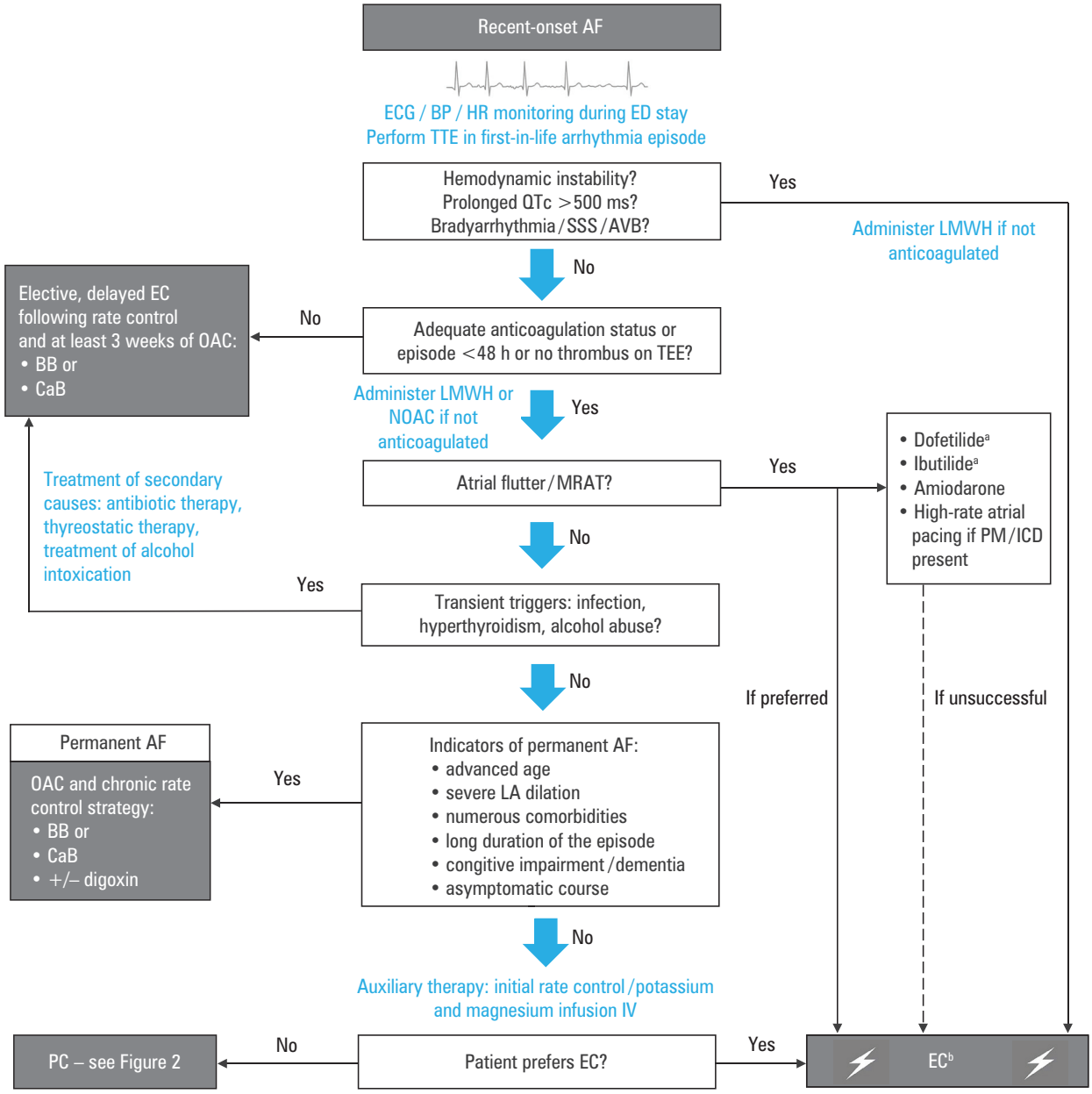

FIGURE 1 Initial considerations prior to an attempt at the management of rhythm control in acute setting

a Dofetilide and ibutilide may cause proarrhythmia due to QTc prolongation and are not available in certain European countries, including Poland

b Electrical cardioversion in atrial flutter / MRAT is performed using low energy of 70–100 J, while in the case of AF higher energy of 150–200 J may be required; the diagnosis of atrial flutter should prompt early referral for catheter ablation

Abbreviations: AF, atrial fibrillation; AVB, atrioventricular block; BB, β-blockers; BP, blood pressure; CaB, nondihydropiridine calcium channel blockers; EC, electrical cardioversion; ECG, electrocardiographic study; ED, emergency department; HR, heart rate; ICD, implantable cardioverter-defibrillation; IV, intravenously; LA, left atrium; LMWH, low-molecular-weight heparin; MRAT, macroreentrant atrial tachycardia; NOAC, non–vitamin-K antagonist oral anticoagulant; OAC, oral anticoagulation; PC, pharmacological cardioversion; PM, pacemaker; SSS, sick sinus syndrome; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography

the AAD selection should be tailored to individual patient's characteristics and clinical settings.[11] Certain nonclassical AADs, including antazoline, seem to be highly effective in restoring SR.[12-15]

Given the annually increasing prevalence of AF,[4] the knowledge regarding state-of-the-art management of new-onset AF seems vital for all practicing clinicians in the field of internal medicine. This review summarizes contemporary knowledge on the qualification for PC, choice of suitable AADs for rhythm conversion, and periprocedural care of AF patients.

Rhythm vs rate control strategy: to convert or not to convert The decision to proceed to restoration of SR in acute setting requires a complex multiple-step approach that should incorporate the evaluation of the patient's hemodynamics, duration of arrhythmia, anticoagulation status, differentiation of AF from other supraventricular arrhythmias, and consideration of futility of the attempted cardioversion (FIGURE 1). The management of patients with newly-diagnosed AF should follow the holistic ABC pathway (A, anticoagulation; B, better symptom management;

C, comorbidity optimization), which was shown to translate into improved survival of patients with AF.[7]

In every patient with new-onset AF, hemodynamic instability should be ruled out upon admission to an emergency department (ED).[7] In the case of hypotension and / or signs of peripheral hypoperfusion, the patients should be urgently submitted to the EC following a single dose of low-molecular-weight heparin, if not previously anticoagulated.[16] Also, the presence of sick sinus syndrome or advanced atrioventricular block or QTc interval above 500 ms favors EC, as PC might lead to excessive bradycardia or malignant ventricular arrhythmia.[7]

The next step should involve an assessment of the thromboembolic risk and the presence of adequate antithrombotic treatment.[7] Both EC and PC should be treated in the same way, as they increase the risk of thromboembolic complications, which may occur early or late after the procedure.[17] The core variable for determining the thromboembolic risk is the estimated duration of an arrhythmic episode. The risk is 4 times lower when the conversion to SR takes place up to 12 hours after the onset, and grows 4-fold between 12 and 48 hours.[3] Therefore, the patients with AF duration of 48 hours or longer or with uncertain duration should be cardioverted after at least 3 weeks of adequate oral anticoagulation (OAC).[18] Patients on long-term OACs may proceed to cardioversion, but clinicians should be aware of the fact that nearly 6% of the patients on non–vitamin K oral anticoagulants (NOACs) and 13% on vitamin K antagonists have thrombus in the left atrial appendage (LAA) on transesophageal echocardiography (TEE).[19] Also, patients with heart failure (HF) and low left ventricular ejection fraction (LVEF) have higher propensity for thrombus formation in the left atrium (LA) despite chronic OAC.[20] Although thrombi in the LAA represent a mechanism responsible for thromboembolic complications, no study has proven that their presence in patients on adequate OAC increases the risk of thromboembolic complications. The exclusion of thrombus within the LAA on TEE obviates the need for prolonged anticoagulation prior to the procedure.[20,21] Detection of a thrombus in the LAA is an indication for repeated TEE prior to planned cardioversion following institution or modification of antithrombotic therapy.[7] Of note, both patients with arrhythmia lasting less than 48 hours and patients without thrombus on TEE should receive heparin or NOAC prior to cardioversion.[22-24] In general, cardioversion is reckoned to be safe despite the lack of anticoagulation, providing that symptoms of arrhythmia persist for less than 48 hours.[7] The procedure is particularly safe in patients without a history of thromboembolism and AF duration below 12 hours or patients with a low CHA_2DS_2-VASc score of 1 or lower for men or 2 or lower for women, and AF duration between 12 and 48 hours.[4] In general, the CHA_2DS_2-VASc score represents a good predictor of thromboembolic complications in anticoagulation-naïve patients undergoing cardioversion after less than 48 hours since the onset of AF episode.[25] Following cardioversion, all patients should be anticoagulated for at least 4 weeks. In those with definite duration of an AF episode below 24 hours and CHA_2DS_2-VASc score of 0 in men and 1 in women, the 4-week anticoagulation may be skipped.[26] Chronic anticoagulation following the 4-week period should be considered in men with a CHA_2DS_2-VASc score of 1 and women with a CHA_2DS_2-VASc score of 2, while it is definitely recommended in the patients with higher values of the CHA_2DS_2-VASc score.[26]

Particular focus should be placed on differentiation of AF from other forms of supraventricular arrhythmia, such as atrial flutter (AFl).[27] AFl may also derive from the conversion from AF, as a result of treatment with class Ic AADs.[28] The diagnosis of AFl should lead to a decision of upfront EC, as PC is related with low likelihood of the rhythm conversion.[29] Following successful restoration of SR, the patients should be referred for catheter ablation, especially in the case of typical AFl.[30]

The core element of care of patients with recent-onset AF is rate control with a β-blocker or a nondihydropyridine calcium channel blocker (diltiazem or verapamil), which should be implemented also in the patients in whom early cardioversion is planned.[31] The most reasonable approach involves careful titration of intravenous β-blocker. Caution is warranted, as overdose of the rate control agents may lead to excessive bradycardia after successful cardioversion. Although digoxin is frequently used as an adjunct drug to β-blockers or calcium channel blockers in the patients with permanent AF, its use in the patients with persistent or paroxysmal AF referred for cardioversion may predispose them to postcardioversion bradycardia and is generally not indicated.[32]

Furthermore, clinicians should be watchful of temporary but not instantaneously removable AF triggers, including infection, hyperthyroidism, and alcohol intoxication.[33] In these clinical scenarios, treatment of the underlying cause, initial rate control, and adequate anticoagulation should be implemented, followed by scheduled elective EC (**FIGURE 1**). Rapid attempt to perform PC or EC poses a high risk of failure. On the other hand, the presence of secondary AF should not be an excuse for not implementing chronic anticoagulation therapy in the patients at risk, as the arrhythmia relapses in the majority of individuals.[34]

Certain transient AF triggers, such as hypokalemia and hypertensive crisis, should be corrected in the acute setting, as their treatment may facilitate successful cardioversion or even cause spontaneous rhythm conversion.[35]

Clinicians should perform a complex analysis of the desired strategy of either rate or rhythm control, as the goal of restoring SR might not be achievable in all patients.[36] Based on firm data,[36] adequate rate control is noninferior to repeated cardioversions in terms of long-term risk of

death, thromboembolic complications, bleeding, or a need for pacemaker implantation. Several factors advocate in favor of the rate control strategy, most notably extensive fibrosis and dilation of LA, consistent with irreversible anatomic substrate for AF persistence. LA diameter of 50–55 mm or higher in parasternal long-axis view represents a proposed threshold above which the rate control strategy should be selected.[37] Patients with structural abnormalities, including severe mitral valve insufficiency or moderate / severe mitral valve stenosis should not be referred for acute rhythm control prior to treatment of the valvular heart disease.[38] Thus, every attempt at PC or EC in the patients with new-onset AF should be preceded by transthoracic echocardiography.[7] Also, long duration of an AF episode, especially above 1 year, asymptomatic course (European Heart Rhythm Classification class 1–2a), older age, female sex, higher CHA_2DS_2-VASc score, and high comorbidity index favor the rate control strategy and no attempt of cardioversion.[38] Contrary to that, young and highly symptomatic patients with first-in-life clinically documented AF episode[21] and no imaging signs of LA remodeling are good candidates for acute rhythm conversion. In addition, any suspicion of tachycardia-induced cardiomyopathy should prompt early rhythm conversion to facilitate LVEF improvement.[39]

The chance of restoring SR may be estimated by the AF-CVS score comprising a set of variables including age, presence of HF, vascular disease, not the first episode of AF, and time from the previous episode.[40] Rhythm conversion may also be predicted with the well-known CHA_2DS_2-VASc score.[38]

Careful discussion with the patient is crucial to understand their preferences in terms of the chosen strategy. All patients should be made aware that regardless of the selected strategy, the long-term outcome is similar, while the attempt of cardioversion offers the benefit of imminent symptom control.[36]

How to convert: pharmacological or electrical cardioversion Assuming that patients are correctly selected, the initial rhythm control strategy may comprise AAD infusion or EC performed in collaboration with the anesthesiologic team or EC facilitated by initial AAD infusion (drug-shock scenario).[41] Existing meta-analyses provide no clear superiority of either strategy for hemodynamically stable AF.[9] The choice of the procedure should regard its pros and cons, patient preferences, and available resources. As EC requires anesthesiologic consult, fasting status, and transient general anesthesia, it generally creates a greater burden for the health care system than a simple drug infusion. The usual approach involves an initial PC, followed by salvage EC in the case of a lack of rhythm conversion. Both procedures require the same adequate anticoagulation in order to minimize the risk of systemic thromboembolic complications. It should be noted that, apart from mere arrhythmia termination by PC or EC, current recommendations allow for the upfront pulmonary vein isolation as the first-line rhythm control therapy prior to administration of AAD, both in paroxysmal and persistent AF.[7]

All in all, PC leads to rhythm conversion in 50%–70% of patients,[9] while subsequent salvage EC increases the overall success rate to 96%.[10] Overall safety of PC is comparable to that of EC, despite the risk of AAD side effects.[8-10] Transient hypotension incidence is significantly higher after PC, but it does not translate into impaired outcomes.[8-10] Such aspects as AF recurrence rate after 4 weeks, ED revisit due to AF, duration of in-hospital stay, readmission rate, and thromboembolic risk are similar for PC and EC strategies.[8-10] Initial PC may lower the health care–associated costs, as EC is a more expensive procedure that requires more staff and monitoring space.[6,8-9] Taking into consideration all the abovementioned factors, the choice of either strategy should be a shared doctor-patient decision.

When to convert: should we hurry? The duration of AF is one of the crucial factors determining whether cardioversion is going to be successful.[42] Surprisingly, while the cardioversion-related thromboembolic risk is the lowest in the first 12 hours of an AF episode, cardioversion at that time is often unsuccessful.[42] It may be caused by heightened sympathetic nervous activity and stress during the onset of AF, either as an underlying cause or as a result of the arrhythmia.[42] On the other hand, the rate of successful cardioversions after 48 hours lowers as well.[3] Prolonged arrhythmia favors structural and electrical remodeling, which results in resistance to cardioversion.[3,18] Early cardioversion can stop the abovementioned changes in the heart, reduce symptoms, and translate into better QOL, while lowering the health care costs.[18] Thus, based on current evidence, cardioversion seems to be the most effective between 12 and 48 hours after the onset of arrhythmia.[3] Unclear AF episode duration and inadequate anticoagulation are indications to perform elective EC with varying efficacy of 66%–95%.[3] In the patients with persistent AF, the chance of restoring SR lowers with time. Moreover, prolonged AF episodes result in a higher rate of AF recurrence. Therefore, elective cardioversions should not be delayed.[3]

The waiting strategy is quite a new approach to AF management. A landmark multicenter trial by Pluymaekers et al[43] randomized patients to either early EC or delayed EC after 48 hours from the arrhythmia onset with initial rate control strategy. The arrhythmia ceased spontaneously within 48 hours in 69% of the patients, while the percentage of patients with SR was comparable both at 48 hours and 4-weeks after the onset

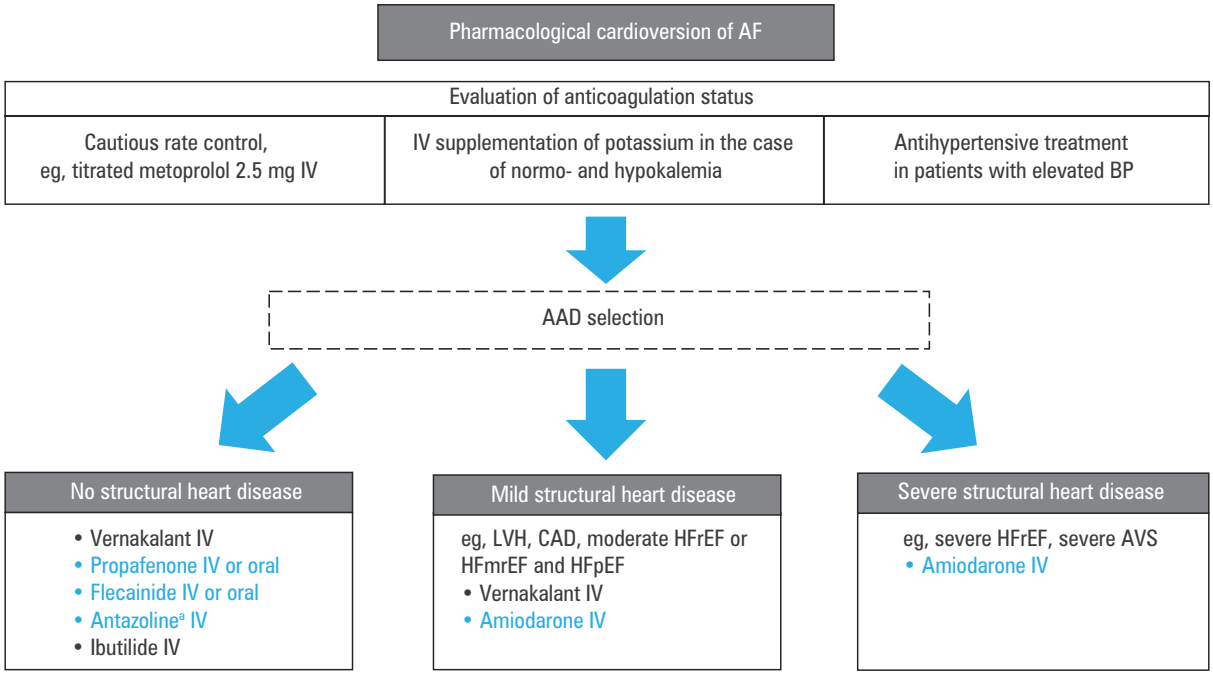

FIGURE 2 Choice of antiarrhythmic drugs for pharmacological cardioversion of atrial fibrillation. Antiarrhythmic drugs available in Poland are marked blue.

a The use of antazoline is not endorsed by the current European Society of Cardiology or American guidelines but its use is reasonable based on data from 1 randomized controlled trial and observational studies; the drug has been approved in Poland for treatment of supraventricular arrhythmias
Abbreviations: AAD, antiarrhythmic drug; AVS, aortic valve stenosis; CAD, coronary artery disease; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly-reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LVH, left ventricular hypertrophy; others, see **FIGURE 1**

of the index arrhythmic event.[3,43,44] Spontaneous SR conversion usually occurs up to 24–48 hours after the AF onset, and can be expected particularly in the patients with the first detected AF episode, no history of HF, or structural heart disease (SHD), and no LA enlargement.[44] The patients characterized by a greater chance of spontaneous rhythm conversion may be identified by means of the ReSinus score,[45] which comprises AF episode duration below 24 hours, heart rate at admission above 125 bpm, potassium replacement at K^+ level of 3.9 mmol/l or lower, N-terminal pro–B-type natriuretic peptide level below 1300 pg/ml, and lactate dehydrogenase level below 200 U/l.[45] Using this score allows for significantly lower utilization of health care resources and a more organized care of patients who often report outside the office hours.[3,43,44] The structured approach targeting comorbidities and arrhythmia precipitating factors has shown benefits in terms of shorter time spent in the ED and higher chances of preserving SR.[45]

After the "golden 48 hours," the chances of spontaneous cardioversion are negatively affected by the duration of AF.[46] Spontaneous conversion to SR after 48 hours occurs in 7% to 17% of individuals, especially if treated with chronic AAD therapy, which is observed predominantly in the patients referred for elective EC.[47,48] Due to a short observation period in most studies focused on spontaneous cardioversion, this phenomenon is not yet well known and its clinical significance is unclear.[47]

Antiarrhythmic drug selection for pharmacological cardioversion The current European and American recommendations advocate in favor of AAD selection for PC based on the presence of SHD[7,49] (**FIGURE 2**). In the patients without SHD, vernakalant, propafenone, flecainide, and ibutilide are viable options.[50-53] In the case of accompanying HF, coronary artery disease, significant valvular heart disease, or left ventricular hypertrophy, amiodarone represents the only pharmaceutical agent suitable for PC.[54] Amiodarone should not be used as an initial AAD for rhythm conversion in healthy individuals due to the risk of perivascular administration and acute organ toxicity.[7] As none of the AADs was linked to improved survival in any clinical scenario, including AF, safety should always be the primary factor underlying the choice of AADs.

Patients undergoing PC should remain under constant electrocardiographic and blood pressure (BP) monitoring, so that possible complications can be immediately managed[55] (**FIGURE 2**). Therefore, the choice of AAD for chronic use, without constant electrocardiographic and hemodynamic supervision is a scenario different from acute use of AADs in the safe milieu of ED. The consensus is that AADs should be administered only to symptomatic patients, and only 1 drug from groups I and III can be used at a time in 1 patient, given the risk of proarrhythmia.[7,49,55] The real-world data contradict the guidelines and raise safety concerns, as 2 and more AADs are used in 25% of all patients undergoing PC. However, this

approach does not lead to greater cardioversion efficacy than the administration of a single AAD.[12]

A scientific debate is ongoing concerning the definition of SHD and the validity of not applying the Vaughan–Williams group I agents in the patients with any form of SHD,[56] based on historical risk of proarrhythmia and sudden cardiac arrest in HF patients enrolled in the CAST (Cardiac Arrhythmia Suppression Trial), which did not pertain to clinical setting of AF.[57] The guidelines do not support the use of certain AADs that were proven useful in everyday practice, including antazoline, which was shown to exhibit high efficacy and relative safety, especially in patients without SHD.[12-15]

According to a recent meta-analysis by Orso et al,[11] involving 7988 patients, the highest chance of successful termination of AF was reported in the individuals treated with quinidine--verapamil (87%), antazoline (86%), vernakalant (85%), tedisamil (80%), amiodarone-ranolazine (80%), lidocaine (78%), dofetilide (77%), and flecainide (71%). However, not all of the abovementioned drugs are routinely used in everyday clinical practice due to safety concerns.

The overview of commonly used AADs for rhythm conversion in AF, along with the supporting evidence, is presented in TABLE 1. General principles and practical considerations concerning PC are included in TABLE 2. This review does not cover certain AADs that are not utilized in daily clinical practice in any part of the world or have been withdrawn as causing proarrhythmia (eg, quinidine[58] or tedisamil[59]).

Vernakalant Vernakalant belongs to the Vaughan––Williams class III AADs, and its efficacy and safety were confirmed in randomized controlled trials (RCTs).[50,60,61] It selectively blocks cardiac transient outward potassium current, being more effective at higher heart rates. It is administered in a 10-minute intravenous infusion, which can be repeated after 10 minutes (TABLE 1). Vernakalant facilitates early AF termination with median time ranging from 8 to 12 minutes. Its efficacy against AFl is much lower.[62] The drug is endorsed by the current ESC guidelines as the first-line pharmacologic agent in AF patients with or without mild SHD. Vernakalant may be utilized in the patients with coronary artery disease barring for 1-month after acute coronary syndrome, HF with mildly--reduced or preserved ejection fraction in the New York Heart Association classes I and II, as well as in the patients with left ventricular hypertrophy. The main limitation of its use is its high cost and unavailability in certain parts of the world, including Poland. The American guidelines do not recommend vernakalant due to flaws in the confirmatory trials, primarily an inadequate comparator in the form of amiodarone and inadequate timeframe for time to conversion of 90 minutes.[50]

Propafenone Propafenone is a sodium channel blocker belonging to class Ic as per the Vaughan–Williams classification. It has a β-blocking and a weak calcium channel blocking activity. Propafenone increases effective refractory period (ERP) of the atria and ventricles in a rate-dependent manner.[63] Propafenone in an intravenous form is available in Europe but not in the United States. Intravenous propafenone is one of the first-line agents recommended for PC of AF in the patients without heart diseases.[53,64,65] On the other hand, propafenone is not recommended in the patients with SHD, such as HF, depressed left ventricular function, atrioventricular (AV) conduction disturbances and bundle branch blocks, or sinus node dysfunction. Propafenone confers the risk of proarrhythmia and has a negative inotropic effect. Possible adverse effects comprise sinus bradycardia (6%), HF deterioration, and conversion of AF to AFl rarely with 1:1 AV conduction that requires rapid EC. It can also widen the QRS complex mimicking ventricular rhythm / ventricular tachycardia and requiring drug discontinuation.[21] The noncardiovascular side effects are rare and include paresthesia and dizziness. Following in--hospital safety confirmation, it may be utilized as a "pill-in-the-pocket."[51,65] It should be preceded (30 min) by a β-blocker or a calcium channel blocker administration in order to avoid rapid AV conduction. In patients weighing less than 70 kg, a lower propafenone dose should be used.[66] Genetic predisposition to slow drug metabolism is present in 7% to 10% of the general population, which may predispose patients to increased risk of side effects.[66]

Flecainide Flecainide belongs to class Ic and it selectively blocks fast inward sodium current and potassium outward current. Flecainide prolongs ERP of the atria, ventricles, accessory pathways, and the AV node, and consequently prolongs QRS duration and QT interval.[63] It exerts a stronger antiarrhythmic effect than propafenone.[63] Intravenous flecainide is one of the first-line agents recommended for PC of recent onset AF.[52,67] The pharmacokinetics of flecainide allows for rapid intravenous infusion (2 mg/kg over 10–30 min) and relatively fast rhythm conversion.[68] However, the use of flecainide should be limited to patients without SHD. Hypotension is present in 2% of patients even without SHD.[69] Flecainide may facilitate conversion of AF to AFl, sometimes with 1:1 conduction. It can also widen the QRS complex requiring drug discontinuation.[70] The noncardiovascular side effects are uncommon and include transient dizziness and paresthesia.[63] Intravenous flecainide is available in many countries, except for the United States and Poland. The use of oral form of flecainide for PC is a possible alternative.[67] However, before the first self-administration, safety of this form of the "pill-in-the-pocket" approach should be tested in hospital conditions. A study evaluating an oral inhalation of flecainide in paroxysmal AF (INSTANT study[71]) has been published

TABLE 1 Summary of randomized controlled trials and high-volume observational studies regarding different antiarrhythmic agents used for acute rhythm control of atrial fibrillation (continued on the next page)

AAD	Class[a]	Route and dose	Time to conversion	Efficacy	Adverse actions/properties/contraindications	Study, design, and number of participants	Comparator
Vernakalant	III	IV, 3 mg/kg/10 min, after 10 min 2 mg/kg/10 min	8–12 min	50%–70%	• Contraindicated in the case of systolic BP <100 mm Hg, recent acute coronary syndrome within 1 month, HF with NYHA III or IV, prolonged QT, or severe aortic stenosis; • May cause hypotension, QT prolongation, QRS widening, or nonsustained ventricular tachycardia; • Not approved in the United States; unavailable in Poland	AVRO[50]; RCT; n = 254	Amiodarone
						ACT-III[60]; RCT; n = 276	Placebo
						SPECTRUM[61]; RCT; n = 1778	Placebo
Propafenone	Ic	Oral, 450–600 mg	30 min	43%–89%	• Propafenone and flecainide share similar properties; • Contraindicated in structural heart disease, including HF, coronary artery disease, LVH, and significant valvular heart disease; • May cause AFl with 1:1 conduction, hence its use should be accompanied by a β-blocker or a calcium channel blocker • Transient QRS widening • Propafenone and flecainide can be utilized as the "pill-in--the-pocket" strategy	Boriani et al[64]; RCT; n = 240	Placebo
		IV, 1.5–2 mg/10 min					
Flecainide	Ic	Oral, 200–300 mg	25 min	46%–90%		Pohjantähti-Maaroos et al[52]; Obs; n = 200	Vernakalant
		IV, 2 mg/kg/10 min					
Amiodarone	III	IV, 5–7 mg/kg/1–2 h; up to 1.2 g/24 h IV, infusion no faster than 50 mg/h	5.5 h	44%–68%	• Delayed onset of action; • May cause skin necrosis and phlebitis, significant organ toxicity, including hyper- and hypothyroidism, liver failure, and lung fibrosis in the case of chronic use; • Safe AAD in structural heart disease; • IV amiodarone may cause hypotension and negative inotropic effect, it has lypophilic properties and high contents of iodine, dissolve in glucose and use a volumetric pump	Galve et al[54]; RCT; n = 100	Placebo
						Letelier et al[73]; Meta; n = 2000	Placebo or rate control agents
Ibutilide	III	IV, 1 mg/10 min after 10 min, repeat 1 mg/10 min	60 min	AF, 31%–51%; AFl, 63%–76%	• Risk of QT prolongation and torsade de pointes; • More effective in AFl than AF; • Monitor for at least 4 h after infusion • Contraindicated in LVH and low LVEF	Stambler et al[53]; RCT; n = 266	Placebo
						Ellenbogen et al[76]; RCT; n = 200	Placebo
						Volgman et al[77]; RCT; n = 127	Procainamide
Dofetilide	III	Oral, 125–500 μg twice daily	–	24 h, 70%; 36 h, 91%	• Dose adjustment to renal function, body size, and age; • Risk of QT prolongation and torsade de pointes induction; • Do not use as "pill-in-the-pocket"; • More effective in AFl than AF; • Not available in Europe	SAFIRE-D[80]; RCT; n = 325	Placebo
		IV, 8 μg/kg/30 min	3 h	AF, 22%–24%; AFl, 64%–75%		Nørgaard et al[81]; RCT; n = 96	Placebo

TABLE 1 Summary of randomized controlled trials and high-volume observational studies regarding different antiarrhythmic agents used for acute rhythm control of atrial fibrillation (continued from the previous page)

AAD	Class[a]	Route and dose	Time to conversion	Efficacy	Adverse actions/properties/contraindications	Study, design, and number of participants	Comparator
Antazoline	Ia	IV, 200 mg +/- after 30–60 min 200 mg IV	16 min	75%–83%	• Atropine-like effect with increased AV conduction and transient tachyarrhythmia, dry mouth, nausea and vomiting, vertigo; • Commonly used as antihistamine drug; • Available only in Poland; • Safety in structural heart disease was not verified	AnPAF[15]; RCT; n = 74	Placebo
						Farkowski et al[14]; Obs; n = 432	Propafenone
						CANT[13]; Obs; n = 450	Propafenone/Amiodarone
						CANT II[12]; Obs; n = 1365	Propafenone/Amiodarone
Procainamide[b]	Ia	IV, 15 mg/kg/30 min	55 min	52.2%	• Risk of QT prolongation; • Drug-induced lupus erythematosus, contraindicated in structural heart disease	RAFF2[86]; RCT; n = 396	EC/placebo
						Stiell et al[87]; Obs; n = 341	–

[a] Vaughan–Williams class

[b] Procainamide is only supported by the AHA/ACC guidelines in patients with pre-excited atrial fibrillation in the Wolfs-Parkinson-White syndrome if no hemodynamic compromise is present.

Abbreviations: ACC, American College of Cardiology; AFl, atrial flutter; AHA, American Heart Association; AV, atrioventricular; HF, heart failure; LVEF, left ventricular ejection fraction; Meta, meta-analysis; NYHA, New York Heart Association classification; Obs, observational study; RCT, randomized controlled trial; others, see FIGURES 1 and 2

recently and confirmed safety and efficacy of this form of treatment.

Amiodarone Amiodarone represents a universally utilized and widely available class III AAD.[72] It is a highly lipophilic benzofuran compound with 37% iodine content. The drug has a very long half-life reaching 100 days, as it is slowly released from lipid-rich tissues (fat and muscles). It exerts its antiarrhythmic effect by blocking the potassium and sodium channels, which leads to prolongation of QT interval and reduction of AV and intraventricular conduction. The intravenous compound is characterized by negative inotropic effect that may lower BP, but it is virtually the only AAD that may be administered in hemodynamically unstable patients.[7] Prior to intravenous administration, the drug should be dissolved in 5% glucose solution and administered initially at a dose of about 300 mg over 2 hours. The daily maximal dose is 1.2 g.[7] Intravenous amiodarone is commonly used as an AAD for AF conversion with moderate efficacy of about 50%.[54,73] It is crucial to expect delayed termination of AF with a median time of 5.5 hours, which is much longer than for the other class I and III AADs. This AAD is recommended primarily in AF patients with SHD, given its proven safety in individuals with HF and acute myocardial infarction.[69] Also, in hemodynamically unstable patients with AF and low LVEF, amiodarone infusion may be used for rapid rate control.[74] Amiodarone should not be used as the first-line drug for PC of AF in the patients without structural heart abnormalities, as this may lead to local infusion-site skin necrosis if the intravenous line is displaced or, rarely, acute organ toxicity, most notably hyperthyroidism.[75]

Ibutilide Ibutilide exerts its class III AAD properties by blocking potassium channels and activating the slow inward sodium channel, which translate into increased duration of action potential and ERP of the atrial and ventricular myocardial cells.[21] Ibutilide is mainly metabolized in the liver, and its plasma half-life is 5 to 6 hours. It is only available in intravenous form due to extensive first-pass metabolism.[82] Reported efficacy rate of restoring SR is 31% to 51% for recent-onset AF, and 63% to 76% for AFl.[53,77,78] Ibutilide may be utilized only in patients without SHD.[7] It is imperative to monitor the patients for 4 hours after the drug infusion, given significant, dose-dependent QT prolongation and the increased risk of torsade de pointes (4%) or monomorphic ventricular tachycardia (4.9%).[79] Regardless of the high efficacy of dofetilide and ibutilide in the rhythm conversion in AFl patients, their real-life use is limited due to increased role of AFl ablation and limited regional availability.

Dofetilide Dofetilide is a representative of class III AADs and its properties include the capability

TABLE 2 Practical considerations and safety measures concerning pharmacological cardioversion of atrial fibrillation

- Patients should be under ECG and noninvasive BP monitoring.
- Initial laboratory tests should be available prior to pharmacological cardioversion: potassium concentration, serum creatinine concentration, complete blood count, and thyroid stimulating hormone level.
- All patients with the first-ever episode of AF should undergo transthoracic echocardiography prior to pharmacological cardioversion focused on left atrial diameter/area/volume, presence of LVH, left ventricular systolic function, and presence of valvular heart disease, especially mitral valve regurgitation or stenosis.
- AF should be confirmed initially on 12-lead ECG, and repeated ECG should be performed after restoration of SR.
- Duration of PQ and QTc intervals and QRS complex should be documented.
- It is not recommended to use overlapping AADs.
- AADs should only be used in symptomatic patients.
- In the case of a lack of AAD efficacy, urgent or delayed EC should be considered.
- Patients should be monitored for at least 2 hours after the end of AAD infusion.
- Transcutaneous/transvenous pacing should be easily available.
- Patients should not drive vehicles and should be supervised on the day of the procedure, especially if they receive antazoline.
- Specific median time to rhythm conversion of different AADs should be taken into consideration.
- Amiodarone often leads to delayed conversion to SR (12–24 hours).

Abbreviations: SR, sinus rhythm; others, see **FIGURES 1** and **2**

to block the rapid component of the delayed potassium channel current. Dofetilide administration leads to prolongation of action potential and ERP of the atria twice more often than of the ventricles.[80] Oral dofetilide was approved by the Food and Drug Administration in 2000 but is not marketed in Europe and Australia, while its intravenous form was withdrawn worldwide. Thus, practical use of dofetilide in PC of AF is limited.[21] Intravenous dofetilide is moderately effective in terminating recent-onset AF and requires strict electrocardiographic monitoring during and after infusion due to the risk of QT prolongation and torsade de pointes (2%–4% of cases). Dofetilide administration should be started in a hospital, and monitoring of the QT interval is obligatory. Similarly to ibutilide, intravenous dofetilide is effective in conversion of AFl to SR.[81] Based on the results of the DIAMOND trial[82] (Danish Investigation on Arrhythmia and Mortality on Dofetilide), oral dofetilide was effective in termination of AF and prevention of its recurrence.

Antazoline Since its first use in the 1960s, antiarrhythmic properties of antazoline have attracted attention of researchers.[83] These properties have been somewhat forgotten, and antazoline served primarily as a traditional, first-generation, parenteral antihistamine drug. In the 1990s, antazoline has been rediscovered as an AAD and its use for rapid conversion of AF to SR in electrophysiology laboratories, and subsequently EDs, has grown exponentially in Poland. Antazoline mesylate belongs to the Vaughan–Williams class Ia, and shows properties similar to quinidine.[83-85] The drug exerts anticholinergic activity, which translates into transient elevation of heart rate.[84-85] It causes moderate prolongation of QTc interval, QRS complex, and LA ERP. Antazoline has a rapid onset of action leading to rhythm conversion within a median time of 16 minutes.[15] The usual dose varies from 200 to 400 mg diluted in saline and administered in a rapid bolus.[12] Thanks to its atropine-like properties, antazoline triggers transient increase of heart rate and QRS widening, which directly precede restoration of SR. For this reason, antazoline is frequently administered together with a β-blocker. Possible adverse effects include temporary xerostomia, nausea, vomiting, hypotension, and postcardioversion bradycardia.[12-15] The efficacy and safety of antazoline were initially proven in a preliminary RCT in 74 patients, where PC efficacy was 72.2% in the antazoline group and 10.5% in the placebo group, while the use of antazoline was not linked to any life-threatening adverse effects.[16] Furthermore, in a retrospective analysis by Farkowski et al,[14] covering 432 patients, antazoline was more effective than propafenone in restoring SR (71.6% vs 55.1%), while the adverse effects were comparable in both groups. The CANT I and CANT II studies (Cardioversion with antazoline in Atrial Fibrillation) provided respectively single- and multicenter data on 1365 patients subjected to PC.[13] The efficacy of antazoline in terms of AF termination (78.3%) was comparable with that of propafenone (72.7%) and superior to amiodarone (66.9%), while the adverse effects were evenly distributed between the subgroups.[12] Antazoline was approved in Poland for PC of supraventricular arrhythmias, however, the widespread use of this drug has not been reflected in the current European guidelines[7]. Given a lack of high-volume RCTs, antazoline use should be limited to patients without SHD, who undergo strict electrocardiographic supervision.

"Pill-in-the-pocket" strategy Chemical conversion of a short-duration AF episode may be performed by the patients themselves. This strategy seems attractive, as it provides patients with the comfort of having the chance to restore SR without a cumbersome visit to the ED. It improves the peace of mind and well-being of patients, and significantly decreases utilization of health care resources. The current European and American guidelines allow a single oral dose of propafenone (450–600 mg) and flecainide (200–300 mg), providing that the safety and efficacy of the Vaughan–Williams class Ic drugs were confirmed in hospital settings.[7,63] This strategy is particularly useful in the patients with recent-onset AF, no SHD, and infrequent arrhythmic episodes. A recent study validated the safety of the "pill-in-the-pocket" strategy, as significant adverse effects occurred in 3% of the patients in a cohort of 273 individuals.[88] Complications consisted of syncope/hypotension and 1:1 AFl.[88] Since the latter complication is probable, a β-blocker or nondihydropyridine calcium channel blocker should be administered 30 minutes prior to AAD intake.

A modification of this approach involves a booster dose of Ic AAD in the patients who are already on chronic maintenance antiarrhythmic therapy. It is contraindicated to use oral dofetilide for this purpose due to a risk of polymorphic ventricular tachycardia. In addition, a single oral amiodarone dose does not offer greater benefit in terms of rhythm conversion, as this lipophilic drug acts by accumulating in the body, and a single oral dose cannot modify its efficacy in the acute setting.[7]

More recently, an inhalation solution of flecainide was proposed, which was documented to be efficient and safe when administered by patients at home.[71] Inhaled flecainide at the highest dose restored SR in 50% of patients within 90 minutes.[71]

Auxiliary management of atrial fibrillation: does it matter? **Potassium and magnesium infusion** Hypokalemia is one of the key precipitating factors of an AF episode.[89] Although not included in the current recommendations, intravenous potassium administration is a common practice.[7] It does not require adequate anticoagulation regimen, as return of SR is regarded as spontaneous termination of arrhythmia. What is not widely known, is the fact that not only hypokalemia but also serum potassium within the reference value should prompt its careful intravenous supplementation, as it promotes rhythm conversion.[35] Serum potassium concentration of 3.8 mol/l or greater is associated with a higher probability of successful EC.[90] According to a recent cohort study, intravenous administration of potassium and magnesium may increase the rate of spontaneous termination of AF, but not AFl.[36] It is suggested that more dynamic increase in the serum potassium level (>0.047 mmol/h) may be associated with a higher PC efficacy, but it does not seem to affect the time to conversion.[91] Potassium infusion can cause pain at the infusion site. This can be minimized by administering a solution of low potassium concentration and at a slow rate.[91]

Hypomagnesemia seems to contribute to AF occurrence, but the beneficial effects of intravenous magnesium administration for management AF are not well established.[35] Potassium and magnesium infusions in AF are often combined, therefore it is impossible to differentiate their contribution to the observed outcomes.[35] Even up to 20% of the patients with AF, as compared with those without AF, can have a significantly lower level of magnesium.[92] According to the randomized LOMAGHI study,[93] low-dose magnesium (single dose of 4.5 g administered over 30 min) was associated with better rate control and greater chance of rhythm conversion at 24 hours than high-dose magnesium (single dose of 9 g administered over 30 min) and placebo.[93]

β-Blockers β-Blockers represent the Vaughan–Williams class II drugs, but they are used primarily for lowering the ventricular response and handling AF-related symptoms. Administration of a β-blocker is not regarded as an attempt at cardioversion and does not require preparation in terms of anticoagulation. Data on the contribution of β-blockers to PC are very limited. Pretreatment with oral metoprolol may lower both the early- and long-term rate of AF recurrence.[94] However, β-blocker administration after conversion to SR is not effective in preventing AF recurrence in the first 5 days after cardioversion.[95] As the authors of this review, we endorse the strategy of administering intravenous or oral metoprolol in patients with mean heart rate above 130 bpm, providing that severe left ventricular dysfunction is excluded. β-Blockers are characterized by a negative inotropic effect, and should not be applied in hemodynamically unstable patients with AF. In these patients, tachyarrhythmia reflects a compensatory reflex to maintain cardiac output.

Summary Acute pharmacological conversion of AF to SR represents the initial attempt at rhythm control in patients with both paroxysmal and persistent AF. Given proper qualification of the patients, PC may deliver rapid relief to symptomatic individuals and obviate the need for hospital admission. Evaluation of anticoagulation status and swift selection of adequate pharmaceutical agent for the procedure are crucial. Still, frequent consults at the ED requring acute rhythm control advocate in favor of prolonged AAD therapy and referral for pulmonary vein isolation. One should remember that in the case of low intensity or lack of symptoms associated with an AF episode, a "wait-and-see" strategy might be a viable option, as the majority of episodes resolve spontaneously within days.

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