Does the choice of drug in pharmacologic cardioversion correlate with the guidelines? Systematic review

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Abstract

Background. Atrial fibrillation (AF) is the most common sustained arrhythmia, the most common cause of supraventricular tachycardia in the global population and the most common arrhythmia requiring treatment in an emergency department.

Objectives. To systematically review recent literature and quantify the correlation between the choice of pharmacological cardioversion (PCV) drug and the national or international guidelines.

Materials and methods. A systematic review was performed in accordance with the PRISMA statement methodology. The PubMed search engine was used to search for articles regardless of type or language and published in the last 6 years (May 2014–May 2020). In addition, we searched for AF guidelines and recommendations published online by cardiology and emergency medicine societies.

Results. The search strategy returned a total of 2615 abstracts. A total of 2598 full texts were screened; 2540 full texts were excluded with reasons and 58 articles from 32 countries were included in the analysis. In 17 of the 58 articles (29%), we noted discrepancies with the AF guidelines, specifically regarding the PCV drug used, the patients' comorbidities and the contraindications associated with the PCV drug. The most common clinical situation for the use of a contraindicated drug was when ibutilide was administered to patients with heart failure. The analysis did not reveal any statistically significant correlations, although the correlation between the sample size and guideline adherence was close to statistical significance ($p < 0.06$).

Conclusions. Our systematic analysis revealed substantial non-adherence to AF treatment guidelines.

Key words: atrial fibrillation, cardioversion, guideline adherence, antiarrhythmic

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Background

Atrial fibrillation (AF) is the most common sustained arrhythmia and the most common cause of supraventricular tachycardia in the world.[1,2] Furthermore, acute AF is a common complaint among emergency department (ED) patients and is the most common arrhythmia requiring treatment in the ED.[3] It commonly occurs because AF is often caused by common diseases (see Table 1). However, ongoing academic discussions seek to answer whether a patient with AF who does not have any cardio-pulmonary disease should be diagnosed with "lone AF".[4] According to the latest AF guidelines published by the European Society of Cardiology (ESC), the term/diagnosis of "lone AF" should not be used because AF always has an underlying cause.[5]

Table 1. Etiology of atrial fibrillation (AF) (according to Benjamin et al. and Kirchhof et al.)

Ageing
Cardiomyopathies
Chronic obstructive pulmonary disease
Coronary artery disease
Diabetes
Heart failure
Heart valve disease
Hypertension
Obesity
Post-operative
Thyroid disease
Unknown (not yet diagnosed, formerly "lone AF")

There are 2 widely accepted and separate goals of AF treatment: rate control and rhythm control. In the case of paroxysmal AF, a clinician has a choice of 2 methods to restore sinus rhythm (SR): pharmacological (chemical) cardioversion (PCV) or electric cardioversion (ECV). According to a large international emergency physician survey, PCV is the first line of treatment for recent-onset AF.[6] The efficacy of PCV in restoring sinus rhythm varies among published studies and is subject to ongoing debate.

When deciding to perform PCV, clinicians have several antiarrhythmic drugs to choose from, which are listed in national and international guidelines (Table 2). Little is known about adherence to AF guidelines when it comes to PCV, particularly in the ED.

Objectives

The aim of this study was to systematically review the most recent literature in an attempt to answer the following clinical question: Do recently published articles about PCV reveal any correlation between the choice of PCV drug and national or international guidelines?

Materials and methods

A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement methodology.[7] The PubMed search engine was used to find articles regardless of type or language and published in the last 6 years (May 2014–May 2020). The unusual six-year timespan was purposefully chosen because the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) and National Institute for Health and Care Excellence (NICE) guidelines were published in December and August of 2014, respectively.[6,7] The following search terms were applied: atrial fibrillation AND pharmacological cardioversion AND antazoline OR amiodarone OR dronedarone OR flecainide OR ibutilide OR procainamide OR propafenone OR vernakalant.

(((((((("atrial fibrillation"[MeSH Terms] OR ("atrial"[All Fields] AND "fibrillation"[All Fields]) OR "atrial fibrillation"[All Fields]) AND (("pharmacology"[MeSH Terms] OR "pharmacology"[All Fields] OR "pharmacological"[All Fields]) AND ("electric countershock"[MeSH Terms] OR ("electric"[All Fields] AND "countershock"[All Fields]) OR "electric countershock"[All Fields] OR "cardioversion"[All Fields]))) AND ("antazoline"[MeSH Terms] OR "antazoline"[All Fields])) OR ("amiodarone"[MeSH Terms] OR "amiodarone"[All Fields])) OR ("dronedarone"[MeSH Terms] OR "dronedarone"[All Fields])) OR ("flecainide"[MeSH Terms] OR "flecainide"[All Fields])) OR ("ibutilide"[Supplementary Concept] OR "ibutilide"[All Fields])) OR ("propafenone"[MeSH Terms] OR "propafenone"[All Fields])) OR ("procainamide"[MeSH Terms] OR " procainamide"[All Fields])) OR ("vernakalant"[Supplementary Concept] OR "vernakalant"[All Fields]) AND ("2014/05/01"[PDAT] : "2020/05/01"[PDAT])

The search strategy yielded a total of 2615 abstracts. A total of 2598 (full texts) were screened, of which 2540 were excluded with reasons (Fig. 1). Although they included large patient samples, meta-analyses were excluded due to an insufficient amount of detail about PCV and the patients' comorbidities. Articles describing the use of antiarrhythmic drugs as prophylaxis of AF prior to surgery were also excluded. So-called "pre-treatment" studies with an antiarrhythmic drug immediately prior to electric cardioversion did not meet the criteria of PCV and were also excluded. The following data was extracted from the 58 eligible full-text articles: number of patients (n), patient age (or average age), patient sex, etiology of AF (or significant comorbidities), antiarrhythmic drug chosen for PCV, dose, bolus or infusion, success of PCV, time to SR, management after PCV attempt (e.g., Was the dose of PCV drug repeated? Was another antiarrhythmic drug administered? Was ECV performed instead?), and country where the patients were treated.

Data were extracted from the articles and entered into Excel spreadsheets (Microsoft Office 2007; Microsoft Corp., Redmond, USA) and subsequently exported to STATISTICA v. 12.0 (StatSoft Inc., Tulsa, USA) for analysis.

Table 2. Pharmacological cardioversion recommendations published in national and international guidelines

Drug	Route	Dose								Indications (class, source)	Contraindications (class, source)
		ACEP	AHA/ACC/HRS 2014 + 2019 update	CAEP 2018	CCS 2018	ERC 2015	ESC 2016	NHFA/ CSANZ 2018	NICE 2014		
Amiodarone	iv*	not stated	150 mg over 10 min, then 1 mg/min for 6 h, then 0.5 mg/min for 18 h or change to oral dosing	not recommended	150 mg bolus, then 60 mg/h for 6 h, then 30 mg/h for 18 h	300 mg over 20–60 min followed by 900 mg over 24 h. Less effective than flecainide, ibutilide, and propafenone	5–7 mg/kg over 1–2 h; follow-up dose: 50 mg/h to a maximum of 1.0 g over 24 h	recommended	recommended for patients with structural heart disease	newly detected HF in the presence of AF with a rapid ventricular response (AHA), hypertrophic cardiomyopathy + AF (AHA Class IIa), ACS + AF associated with severe LV dysfunction and HF or hemodynamic instability (AHA Class IIb), severely impaired heart function (ERC), HF + AF (ESC), IHD + AF (ESC), structural heart disease (CCS)	hyperthyroidism + AF ("Antiarrhythmic drugs and cardioversion often fail to achieve sustained sinus rhythm while thyrotoxicosis persists; therefore, efforts to restore normal sinus rhythm may be deferred until the patient is euthyroid." – AHA)
Antazoline	iv	not stated	not stated	not stated	not stated	not stated	not stated	not stated	not stated	paroxysmal atrial arrhythmias including tachycardia/ AF, nor reacting to standard treatment	avoid in patients with history of seizures, concurently using MAO inhibitors, anticholinergic drugs, CNS depressants, or alcohol); use carefully in patients with HTN, DM, hyperthyroidism, and prostatic hyperplasia
Flecainide	po	300 mg PO ×1 if ≥70 kg or 200 mg PO ×1 if <70 kg	200–300 mg ×1**	not stated	300 mg (>70 kg), 200 mg (≤70 kg)	recommended; more effective than amiodarone	200–300 mg; iv: 1.5–2 mg/kg over 10 min	recommended; more effective than amiodarone	recommended for patients without ischemic or structural heart disease	no evidence of structural or ischemic heart disease + AF (ACEP, NICE)	known ischemic or structural heart disease + AF (ESC, NICE), LV systolic dysfunction, moderate LV hypertrophy or coronary artery disease (GRADE: Strong, Evidence: Moderate, NHFA)
Ibutilide	iv	1 mg iv over 10 min; may repeat same dose 10 min after first infusion if still in AF; if still in AF at 60 min after last infusion consider electrical cardioversion	1 mg over 10 min; may repeat 1 mg once if necessary (if weight <60 kg, use 0.01 mg/kg)	not stated	1 mg iv over 10 min, may repeat once	recommended; more effective than amiodarone	1 mg over 10 min; follow-up dose: 1 mg over 10 min after waiting for 10 min	not stated	not stated	post-cardiac and thoracic surgery + AF (AHA Class IIa), hemodynamically stable WPW and pre-excitation syndromes + AF (AHA Class IIa), "no need to confirm lack of structural heart disease or occlusive coronary disease" (ACEP)	long QTc, hypokalemia, HF (ACEP, CAEP, ESC), severe LVH (ESC), hypomagnesemia (CCS)

Table 2. Pharmacological cardioversion recommendations published in national and international guidelines – cont.

Drug	Route	Dose								Indications (class, source)	Contraindications (class, source)
		ACEP	AHA/ACC/HRS 2014 + 2019 update	CAEP 2018	CCS 2018	ERC 2015	ESC 2016	NHFA/CSANZ 2018	NICE 2014		
Procainamide	iv	not stated	not stated	15 mg/kg in 500 mL NS over 30–60 min	15–18 mg/kg over 30–60 min	not stated	not stated	not stated	not stated	hemodynamically stable WPW and pre-excitation syndromes + AF (AHA Class I), (CAEP)	Brugada syndrome (CCS), hypotension (SBP < 100 mm Hg) or long QT (QTc > 500 ms) (CAEP)
Propafenone	po	not stated	450–600 mg ×1**	not stated	600 mg (>70 kg), 450 mg (≤70 kg)	recommended; more effective than amiodarone	450–600 mg; iv: 1.5–2 mg/kg over 10 min	not stated	not stated	COPD + AF ("may be considered in patients with obstructive lung disease who develop AF and do not have bronchospasm" – AHA)	COPD + AF ("contraindicated in patients with bronchospasm" – AHA), known ischemic or structural heart disease + AF (ESC, NICE)
Vernakalant	iv	not stated	not stated	not stated	3 mg/kg over 10 min, followed by 2 mg/kg if no conversion	not stated	3 mg/kg over 10 min/follow-up dose: 2 mg/kg over 10 min after waiting for 15 min	not stated	not stated	mild HF (NYHA Class I–II) + AF, IHD + AF (ESC)	avoid in patients with hypotension (SBP < 100 mm Hg), recent (<30 days) ACS, HF (NYHA Class III–IV), QT long QT (uncorrected >440 ms) and severe aortic stenosis (CCS, ESC)

* Use a large peripheral vessel and change to oral amiodarone within 24 h of IV (central line) administration.
** It is recommended to pre-treat with a β-blocker or nondihydropyridine calcium channel antagonist ≥30 min before administering this drug.
ACEP – American College of Emergency Physicians; ACS – acute coronary syndrome; AF – atrial fibrillation; AHA/ACC/HRS – American Heart Association/American College of Cardiology/Heart Rhythm Society; AV – atrio-ventricular; CAD – coronary artery disease; CAEP – Canadian Association of Emergency Physicians; CCS – Canadian Cardiovascular Society; COPD – chronic obstructive pulmonary disease; ERC – European Resuscitation Council; ESC – European Society of Cardiology; GI – gastrointestinal; IHD – ischemic heart disease; iv – intravenous; LV – left ventricular; MAO – monoamine oxidase; NICE – National Institute for Health and Care Excellence; NHFA/CSANZ – National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand; NYHA – New York Heart Association; po – per os (orally); SBP – systolic blood pressure; WPW– Wolff–Parkinson–White syndrome.

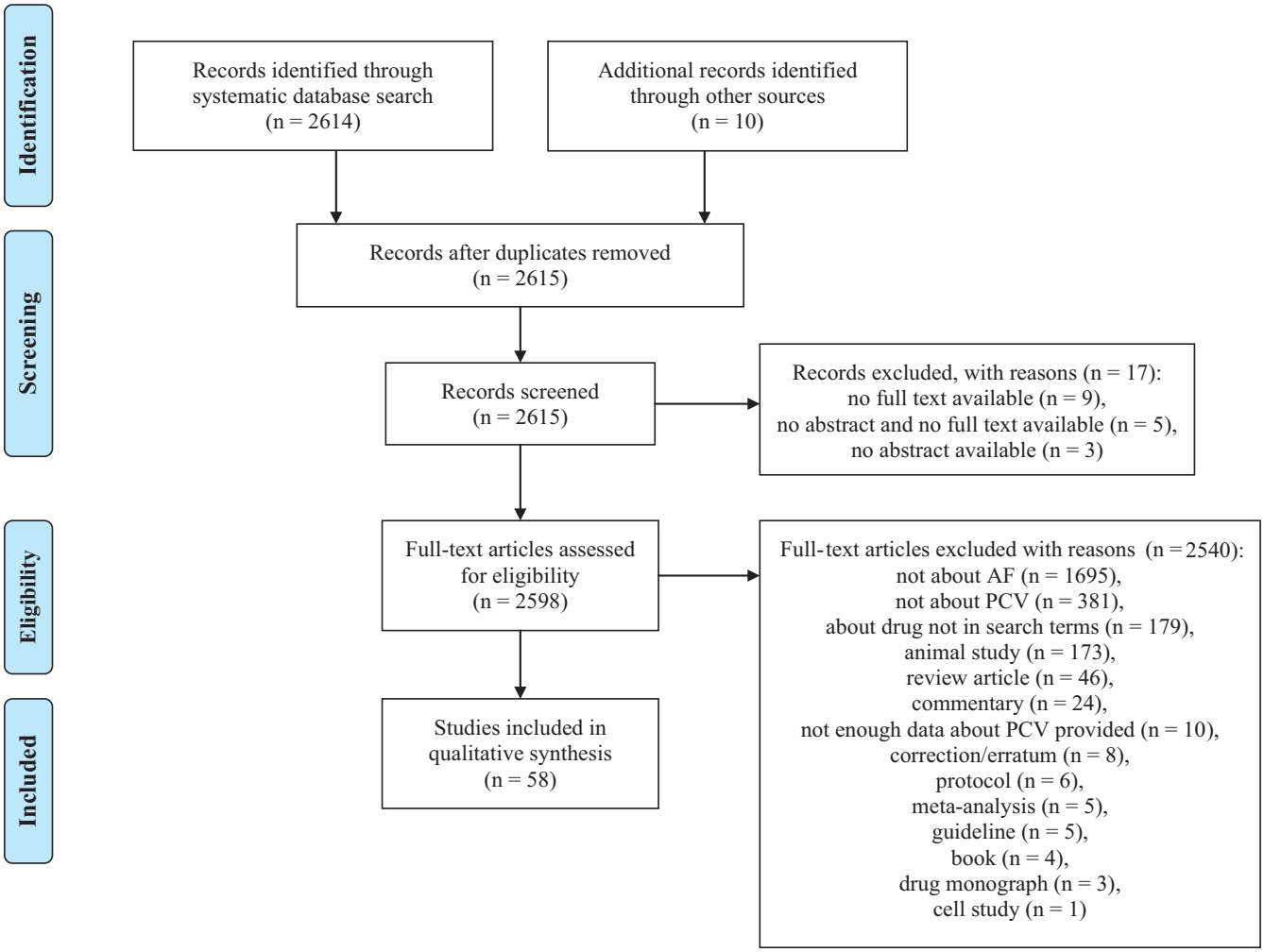

Fig. 1. Flowchart of the literature search strategy

The following statistical tests were performed: Mann–Whitney U test (for continuous variables) and Fisher's two-tailed test (for categorical variables). Values of $p < 0.05$ were considered statistically significant.

In addition, we searched for AF guidelines and recommendations published online by cardiology and emergency medicine societies. Our search returned guidelines from Australia (National Heart Foundation of Australia (NHFA)/Cardiac Society of Australia and New Zealand (CSANZ)),[8] Canada (Canadian Association of Emergency Physicians (CAEP), Canadian Cardiovascular Society (CCS)),[9,10] Europe (European Resuscitation Council (ERC), ESC)[5,11] UK (NICE),[12] and USA (American College of Emergency Physicians (ACEP), AHA/ACC/HRS) (Table 2).[13,14] We used these recommendations as a reference point to answer the research question described earlier.

Results

Our search returned 58 articles from 32 countries; most articles were published in 2017–2018 (Fig. 2,3).[15–71] Unfortunately, not all relevant data was provided by the authors, thus making it impossible to perform a full meta-analysis. Detailed results of the systematic review are summarized in Table 3 (Fig. 2,3).

Despite the incomplete data, the analyzed articles revealed a surprising trend of non-adherence to AF treatment guidelines. In 17 of the 58 articles (29%), we noted discrepancies with AF guidelines, specifically regarding the PCV drug used, the patients' comorbidities and the PCV contraindications (Table 4).[16,18,20–22,26–28,31,32,36,39,41,49,55,60,63] According to the data presented in the articles, it appeared that a total of 239 patients underwent PCV using a drug that was contraindicated given their specific comorbidities. In the described cases, the most common culprit PCV drug was ibutilide, followed by vernakalant, amiodarone, propafenone, and flecainide. The most commonly described clinical situation for the use of contraindicated drug was ibutilide when administered to a patient with HF, which is contraindicated according to the ACEP, CAEP and ESC guidelines (Table 2).[10,12,13,31,39,55,63] In 9 of the 17 articles, using a contraindicated drug during PVC was performed in the ED (Table 4).[21,22,26,27,32,36,39,55,63] Due to incomplete data, it was impossible to assess whether an additional 338 patients were administered a PCV drug that was contraindicated or not.[21,36] (Table 4).

Fig. 2. Number of analyzed articles describing pharmacological cardioversion in the particular country's patient population (illustration by Zu).

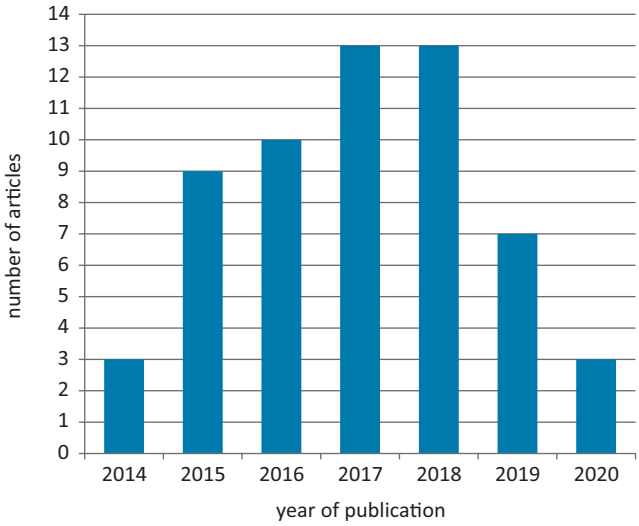

Fig. 3. Number of analyzed articles published in a given year

Analysis using the Mann–Whitney U test and Fisher's test did not reveal any statistically significant correlations between adherence to AF guidelines and demographic variables such as sample size, patient age, and male sex (Table 5). However, it is noteworthy that the correlation between the sample size and guideline adherence was close to statistical significance ($p < 0.059$). It appears that the larger the sample size, the less adherence was observed. The analysis using Fisher's two-tailed tests did not reveal any statistically significant correlations between adherence to AF guidelines and the type of study/article, region/country or department where the PCV was performed (Table 5).

It is noteworthy that our search retrieved a total of 6 articles (in 1612 patients) that included PCV using antazoline mesilate.[19,32–34,42,66] This is an old antihistaminic drug, which, despite its proven antiarrhythmic efficacy, is not currently mentioned in any AF guidelines.[72–74] According to publicly available data, it appears that the intravenous form of antazoline is registered and sold in Poland only; therefore, it is not surprising that majority of the research on antazoline was conducted and published by Polish physicians.[74–78]

Discussion

Although we found articles describing PCV performed on all of the inhabited continents of the world, we are aware that they do not necessarily reflect daily clinical practice. The articles we analyzed did not contain enough data to answer the question why the AF guidelines were not followed. We do not want to speculate about the particular authors' intent or the circumstances during the described PCV. However, given our institutional experience with PCV, we can think of several possible reasons, most of which are rather mundane or perhaps even temporary, e.g., the availability of antiarrhythmic drugs, institutional/personal experience with particular drug(s), and interest in comparing the efficacy of a new drug (e.g., vernakalant) compared to a "tried and tested" drug.

The very same issue of non-adherence with AF guidelines was addressed in the literature, although the answers

Table 3. Detailed results of the systematic review

Author(s)	Date of publication	Study type	Country	Number of patients	Age of patients [years]	Sex of patients	PCV setting	PCV drug	PCV drug dose and route	PCV successful, n	Time to SR [min]	Management after failed PCV attempt	Comorbidities	AF guideline adherence
Albakri et al.	VII 2017	case report	Germany	1	60	M	IMD	flecainide	1 mg/kg	1	30	after 25 min → 2nd infusion of flecainide 0.3 mg/kg	borderline hypertension without LV hypertrophy, obstructive bronchitis, episodic orthostatic intolerance (most probably vasovagal)	Y
Amin et al.	III 2015	prospective single-center observational	Netherlands	112	63 ±1	52 F, 60 M	CER	flecainide	2 mg/kg (maximum dose of 150 mg) iv infusion over 10 min	97	not stated	if AF 6 h after infusion → ECV	CAD 11, HTN 52, DM 8, THY 5	N
Andrade et al.	I 2018	prospective single-center observational	Canada	80	53.0 ±12.6	27 F, 53 M	AF clinic	immediate release AV nodal blocker + AAD Class Ic	diltiazem 30–60 mg po, verapamil 30–60 mg po or metoprolol 25–50 mg po + if <70kg → F: 200 mg po or PROP: 450 mg po; if ≥70kg → F: 300 mg po or P 600 mg po	in 30/43	<6 h	if AF 6 h after infusion → ECV	HVD 2, CAD 4, DM 8, HTN 16	Y
Balik et al.	X 2017	retrospective	Czech Republic	197	67.8 ±11.4 (amiodarone), 66.8 ±11.3 (propafenone)	not stated	ICU	amiodarone; propafenone	AMIO: 1.8–4.6 g iv infusion over 2–6 days; PROP: 460–700 mg/day iv infusion*	amiodarone in 114/197;	not stated	switch drugs, ECV	hyperthyroidism (5 A)	N
Balsam et al.	IX 2015	retrospective, non-randomized, no placebo-controlled observational study	Poland	141 (74 persistent AF, 67 paroxysmal AF)	57 (49–63)	38 F, 103 M	EPL	antazoline	maximum 500 mg iv 30–50 mg/min	in 79/141 (31% of persistent AF patients, 83% of paroxysmal AF patients)	≤20	not stated	HTN 69.3%, lone AF 22.7%, THY 18.4%, DM 12.1%, HVD 2.8%	Y
Beatch et al.	V 2016	RCT	Canada, Chile, Israel, Mexico, Peru, South Africa, USA	129	63.7 (SD 12.7)	53 F, 76 M	not stated	vernakalant	3 mg/kg iv infusion over 10 min	59	25% converted in ≤11; endpoint at 90	if AF 15 min after 1st infusion → vernakalant 2 mg/kg iv over 10 min; if AF 2 h after 1st infusion → ECV	HTN 89, HVD 27, CAD 18, DM 18	Y

Table 3. Detailed results of the systematic review – cont.

Author(s)	Date of publication	Study type	Country	Number of patients	Age of patients [years]	Sex of patients	PCV setting	PCV drug	PCV drug dose and route	PCV successful, n	Time to SR [min]	Management after failed PCV attempt	Comorbidities	AF guideline adherence
Beatch et al.	II 2017	RCT	China, Hong-Kong, India, Korea, Taiwan	55	60.7 ±13.7	18 F, 37 M	not stated	vernakalant	3 mg/kg iv infusion over 10 min	29	median 17, endpoint at 90	if AF 15 min after 1st infusion → 2 mg/kg iv over 10 min; if AF 2 h after 1st infusion → ECV	HF 5, IHD 4, VHD 2	N
Bonora et al.	IX 2017	retrospective propensity matching	Italy	179 (amiodarone), 179 (flecainide, propafenone)	66.2 ±12.8 (amio), 66.4 ±11.6 (flec or prop)	not stated	ED	amiodarone, flecainide, propafenone	AMIO: 5 mg/kg in a 20 min infusion; FLEC or PROP: 2 mg/kg in 15 min rapid infusion	after 12 h → A 95/179 and F or P 130/179; after 48 h → A 139/179 and F or P 154/179	A 420 (331.6–508.3); F or P 55 (44.8–65.1)	a 15 mg/kg dose in 24 h slow maintenance infusion)	IHD 76 (A), 18 (F or P); HTN 290 (A), 223 (F or P); VHD 48 (A), 53 (F or P); THY 23 (A), 67 (F or P)	N
Carbajosa et al.	X 2017	prospective multi-center observational	Spain	165	68 (56–77)	76 F, 89 M	ED	vernakalant	3 mg/kg iv infusion over 10 min	in 128/165	8 (6–12); after 2nd dose → 34 (22–62)	if AF 15 min after 1st infusion → vernakalant 2 mg/kg iv over 10 min	HTN 99, DM 16, HF 15	N
Champion et al.	VI 2018	prospective single-center observational	France	75	not stated	not stated	ICU	amiodarone	median dose of 300 mg (150–600 mg)	51	NS	ECV	not stated	Y
Chauveau et al.	VI 2019	case series	France	1	32	F	ICU	flecainide	100 mg iv	yes	NS	NA	speculation (thyroiditis? left-sided accessory pathway?)	Y
Comelli et al.	XI 2018	case report	Italy	1	56	M	ED	flecainide	100 mg iv infusion over 20 min	yes, spontaneous	~30	not stated	none	Y
Cosin-Sales et al.	VI 2016	prospective single-center observational	Spain	47	66 (24–89)	24 F, 23 M	ED	vernakalant	not stated	45	12.5 (1–115, median 8)	NS	HTN 28, DM 3, IHD 3, HF 1, CMP 1	N
Costabel et al.	II 2015	single-center, retrospective	Brazil	121	58.1 ±13.9	39 F, 82 M	ED	vernakalant	initial dose 3.0 mg/kg iv over 10 min	102	10	2nd dose 2 mg/kg iv	56 HTN, 16 structural heart disease, 6 HF (EF < 55%), 2 COPD, 2 DM	N
Dalyanoglu et al.	V 2018	single-center, retrospective	Germany	129	70.2 ±9.1	39 F, 90 M	CSD	vernakalant	3 mg/kg iv over 10 min	57	13.7 ±14.1	2nd dose 2 mg/kg iv over 10 min	124 CAD, 16 CAD + HVD, 37 DM, 70 hyperlipidemia, 109 HTN, 20 HVD, 21 LVEF < 50%	N

Table 3. Detailed results of the systematic review – cont.

Author(s)	Date of publication	Study type	Country	Number of patients	Age of patients [years]	Sex of patients	PCV setting	PCV drug	PCV drug dose and route	PCV successful, n	Time to SR [min]	Management after failed PCV attempt	Comorbidities	AF guideline adherence
Dasgupta et al.	III 2020	retrospective, single-center	USA	14	15 (14–17)	not stated	PED	ibutilide	if >60 kg: 1 mg iv over 10 min, if <60 kg 0.01 mg/kg iv over 10 min	9	not stated	a 2nd dose of equal amount, at the physician's discretion	not stated	Y
Dilber et al.	XI 2015	case report	Croatia	1	75	M	ED	amiodarone, propafenone	AMIO: 300 mg in 250 mL 5% dextrose solution iv infusion; PROP: 150 mg in 250 mL 5% dextrose solution iv infusion	0	NA	transesophageal echocardiography + ECV	HTN	Y
Dong et al.	VI 2017	prospective single-center observational	China	79	64.6 ±11.2 (40–80)	31 F, 48 M	not stated	ibutilide (39), ibutilide ± amiodarone (40)	AMIO 300 mg + I 1 mg iv; I 1 mg iv	I = 51.3% (20/39), A + I = 71.8% (28/39)	I 75–120; A+I 60–120	additional ibutilide 1 mg	CAD 51.31% (I), 47.11% (A+I); HTN 56.41%, 61.12%; DM 5.11%, 6.24%; HF 29.71%, 28.35%	N
Farkowski et al.	VI 2016	retrospective case-control	Poland	432	68.9 ±9.8	152 F, 280 M	ED	antazoline 334, propafenone 98	ANT: 50 mg every 3–5 min up to max 250–300 mg or SR; PROP: max 2 mg/kg iv slow bolus	A 239, P 54	not stated	other drug, ECV or discharge	CAD (A 138, P 28), DM (A 58, P 15), IHD (A 66, P 14), HTN (A 202, P 55), HVD (A 3, P 2), non-ischemic structural heart disease (A 3, P 0), THY (A 29, P 15)	N
Farkowski et al.	XII 2018	retrospective case-control	Poland	548	CAD(–) 66.9 ±9.9, CAD(+) 71.3 ±9.1	CAD(–) F 84, 112 M; CAD(+) F 27, 111 M	ED	antazoline	50 mg every 3–5 min up to max 250–300 mg or SR	CAD(–) 125, CAD(+) 114	not stated	not stated	HTN 95, 107; DM 10, 48; THY 23, 6; CAD(+): post-PCI 47, post-CABG 53, post-MI 65	Y
Farkowski et al.	V 2019	experimental prospective, control group	Poland	5	63.4 (59.9–66.8)	not stated	EPL	antazoline	257.1 (246.7–267.6) mg	5	8.4 ±6.2	not stated	not stated	Y
Gillinov et al.	IV 2016	multi-center RTC	Canada + USA	261	68.4 ±8.4	62 F, 199 M	CSD	amiodarone	3 g po before hospital discharge, with a maintenance dose of 200 mg/day or less for 60 days if direct-current cardioversion was successful	244 at hospital discharge, 227 from discharge to 60 days	not stated	ECV	all post-cardiac surgery (CABG 100, HVD 43, CABG + HVD 7), DM 79, HF 33, HTN 198, HVD 148, post-MI 48, post-stroke 15	Y

Table 3. Detailed results of the systematic review – cont.

Author(s)	Date of publication	Study type	Country	Number of patients	Age of patients [years]	Sex of patients	PCV setting	PCV drug	PCV drug dose and route	PCV successful, n	Time to SR [min]	Management after failed PCV attempt	Comorbidities	AF guideline adherence
Hamilton et al.	VI 2015	retrospective	UK	564	68 (mean)	257 F, 307 M	ED	flecainide (n = 85), amiodarone (n = 32)	NS	F 69, A 26, F + A 19	not stated	21 received PCV + ECV	COPD 40, DM 51, HF 29, HTN 249, HVD 52, IHD 162, previous congenital heart disease 5, stroke/TIA 37, THY 48	N
Kapelios	VII 2019	case report	Greece	1	55	M	not stated	amiodarone	300 mg in 60 min iv	1	not stated	NA	ibrutinib	Y
Karavelioglu et al.	I 2015	retrospective	Turkey	218	64.1 ±14.6	126 F, 92 M	ED	amiodarone	300 mg in 100 mL 5% dextrose solution (over 1 h) iv + 900 mg AMIO in 500 mL 5% dextrose (over 23 h) iv	not stated	not stated	not stated	CAD 27, DM 37, HF 20, HTN 125	Y
Kriz et al.	VIII 2016	prospective observational, single-centre	Austria	236	66.8 ±1.8	133 F, 103 M	ED	ibutilide 107, vernakalant 68, flecainide 59, amiodarone 2	I: 0.87 mg iv for 10 min; V: 3 mg/kg iv for 10 min; FLEC: 2 mg/kg (max 200 mg) iv for 10–20 min; AMIO: 150 mg iv for a 10 min	I 73, V 54, F 42, A 2	not stated	I: 2nd dose after 10 min, V: 2nd dose 2 mg/kg (max 340 mg) after 15 min	DM (I 17, V 0, F 6, A 1), HF/LV dysfunction (I 3, V 4, F 1, A 0), HTN (I 89, V 46, F 47, A 2), stroke/TIA/TE (I 7, V 7, F 1, A 0), vascular disease* (I 19, V 10, F 8, A 0)	N
Lewis et al.	XII 2015	case report	UK	1	38	M	not stated	flecainide	1.5 mg/kg (120 mg)	1	90	not stated	none	Y
Liberman et al.	VI 2018	retrospective, single-center	USA	13	16 (4.6–20.3)	not stated	PED	flecainide	<40 kg: 4–6 mg/kg, 40–70 kg: 200 mg, >70 kg: 300 mg	13	60 (30–120)	NA	CMP 6, HVD 3, post-heart transplantation 1	N
Maciag et al.	X 2017	single-center, randomized, double-blind, placebo-controlled, superiority clinical trial	Poland	36	68 ±12 (31–90)	35 F, 39 M	"ED or clinical ward"	antazoline	50 mg diluted to 10 cm^3 every 5 min iv (total dose 250 mg/50 cm^3)	26	16 (9–35)	not stated	HTN 52; CAD 13; THY 4	Y
Maimone et al.	IX 2015	case report	Italy	1	73	F	not stated	amiodarone	5 mg/kg (1st h), 50 mg/h (maintenance)	1	not stated	not stated	iodine contrast	Y
Manolis et al.	II 2018	retrospective single-center observational	Greece	23	63 ±12	10 F, 13 M	CD	vernakalant	3 mg/kg over 10 min, and after 15 min	15 (65%)	25 ±31 min (median ¼ 12 min)	2nd infusion of 2 mg/kg over 10 min	HTN 4, "mild CAD" 3, post-AVR normal EF 1, CMP 1, idiopathic 9	Y

Table 3. Detailed results of the systematic review – cont.

Author(s)	Date of publication	Study type	Country	Number of patients	Age of patients [years]	Sex of patients	PCV setting	PCV drug	PCV drug dose and route	PCV successful, n	Time to SR [min]	Management after failed PCV attempt	Comorbidities	AF guideline adherence
Mansoor et al.	XI 2014	retrospective, single-center	South Africa	59	16–82 (mean: 51.9)	26 F, 33 M	CSD	amiodarone	300 mg in 200 mL of 5% dextrose water over 45 min iv, followed by 900 mg in 1 L of 5% dextrose water over 24 h	7 (PCV only), 35 (ECV + PCV), 9 (ECV only), 5 (ECV + other PCV drug), 2 (other PCV drug), 1 spontaneous cardioversion	not stated	PCV was performed after failed ECV	all were immediately post-cardiac surgery (CABG or HVD); 24 DM, 33 CAD, 6 CAD + HVD, 35 HTN, 20 DM + HTN	Y
Milojevic et al.	I 2019	retrospective, single-center	France	200	65.9 ±16	58 F, 142 M	MICU	amiodarone	300 mg iv for 30 min (10 mg/min), if <40 kg: consider 150 mg for 30 min iv (5 mg/min), if >90 kg: consider 450 mg for 30 min iv (15 mg/min)	66	2% @ 20, 18% @ 40, 22% @ 60, 24% @ 90	not stated	not stated	Y
Mitrić et al.	IV 2016	retrospective, single-center	Australia	177	69 (60–75)	64 F, 113 M	ICU	amiodarone	median (IQR) total dose 905 mg (488–1651) (includes boluses and infusions)	86 (91 had recurrence of AF)	not stated (median treatment with amiodarone 24 h (16–40 h))	not stated	COPD 58, DM 25, HF 22, HTN 106, IHD 58, MI 43, HVD 9, PVD 40	Y
Mochalina et al.	III 2015	retrospective	Sweden	113	63 (23–87)	44 F, 69 M	not stated	vernakalant	3 mg/kg over 10 min	75	10 (4–90)	2nd infusion of 2 mg/kg over 10 min	HTN 57, IHD 18, DM 8, CHF 3	Y
Nemati et al.	VI 2016	RCT (2 centers)	Iran	122	A: 68.1 ±9.9, P: 66.7 ±8.7	not stated	ICU	amiodarone 67, propafenone 55	AMIO: 300 mg iv, followed by 600 mg iv over 12–24 h after the occurrence of AF; PROP: 600 mg po and 150 mg every 8 h for 10 days after the onset of AF	A 44, P 38	A 384.1 ±428.4, P 262.5 ±321.5	repeat dose, switch drugs, ECV	all after CABG, HTN P 39 A 52; hyperlipidemia P 38 A 45; DM P 28 A 33; CHF P 0 A 2; COPD P 9 A 21; right atrium enlargement P 0 A 1, intra-aortic balloon pump P 5 A 6; previously diagnosed AF P 5 A 2	N
Pluymaekers et al.	III 2019	multicenter, randomized, open-label, non-inferiority trial	Netherlands	219	65 ±11	89 F, 130 M	CD	not stated ("preferably with flecainide")	not stated	83	not stated	not stated	HTN 133, DM 25, MI 13	Y

Table 3. Detailed results of the systematic review – cont.

Author(s)	Date of publication	Study type	Country	Number of patients	Age of patients [years]	Sex of patients	PCV setting	PCV drug	PCV drug dose and route	PCV successful, n	Time to SR [min]	Management after failed PCV attempt	Comorbidities	AF guideline adherence
Pohjantahti-Maaroos et al.	III 2019	single-center non-randomized retrospective	Finland	200	F 55.3 ±13.0; V 59.3 ±12.5	F 65, V 66	ED	flecainide 100, vernakalant 100	F: 2.0 mg/kg (max 150 mg) during 30 min; V: 3.0 mg/kg (max 339 mg) during 10 min	F 46%, V 67%	120	AF after 15 min → 2nd dose of V 2.0 mg/kg (max 226 mg) during 10 min	DM F 9, V 9; HTN F 37, V 46; Prior AMI F 0, V 3	Y
Rudiger et al.	V 2014	retrospective single-center	Switzerland	32	74 (36–86)	10 F, 22 M	ICU	vernakalant	3 mg/kg over 10 min iv	17	30 (4–355)	2 mg/kg	all post-CS: 13 CABG, 18 HVD, 9 "major vascular", LV EF 35–80%	Y
Schnaubelt et al.	IV 2020	single-center trial	Austria	10	76 (63–79)	4 F, 6 M	ICU	vernakalant	3 mg/kg in 100 mL of normal saline iv	7	8.0 (6.0–9.0)	2 mg/kg in 100 mL of normal saline iv	all after elective cardiac surgery: 7 HVD, 3 HVD + CABG	Y
Shibata et al.	IV 2016	retrospective single-center	Japan	23	68 (60, 76)*	7 F, 16 M	ICU	amiodarone	150 mg over 30 min, followed by 20–50 mg/h	10	150	administration of a 2nd drug (not defined which), ECV	all post-surgery: CABG 8, CABG + HVD 4, HVD 9, vascular 2	Y
Simon et al.	III 2016	RCT	Austria	100	56.5 (SD 15.00)	32 F, 68 M	ED	vernakalant 49, ibutilide 51	V: 3 mg/kg in 100 mL normal saline iv infusion over 10 min; I: 1 mg in 100 mL normal saline iv infusion over 10 min	vernakalant: 34/49 (29 converted after 1st infusion); ibutilide: 22/51 (14 converted after 1st infusion)	V 10, I 26	if AF 15 min after vernakalant infusion → 2nd infusion (10 min) of vernakalant (2 mg/kg); if AF 10 min after ibutilide infusion → 2nd infusion of ibutilide (10 min, 1 mg); if AF 2 h after 1st infusion → ECV	HF (48 V, 51 I); HTN (30 V, 36 I); DM (5 V, 6 I); THY (7 V, 7 I); CAD (3 V, 4 I)	N
Simopoulos et al.	IX 2018	prospective, randomized, allocation-concealed, single-blind, single-site clinical trial	Greece	511	A: 65.5 ±9.6, A+R: 65.3 ±9.5	A: 31 F, 224 M; A+R: 35 F, 221 M	CSD	amiodarone 255; amiodarone + ranolazine 256	AMIO: 300 mg in 30 min + 750 mg in 24 h iv; AMIO + R: 500 mg po + 375 mg after 6 h and 375 mg twice daily thereafter	511	≤24 h: 37 A, 235 A+R > 24 h: 218 A, 21 A+R	A: 375 mg in 12 h	all after CABG surgery, DM (152 A, 146 A+R), HTN (140 in both groups), MI (139 A, 154 A+R)	Y
Stefatos et al.	VI 2018	case report	Canada	1	45	M	not stated	amiodarone	2 × 150 mg iv + 3 × 400 mg po	1	not stated ("by the next day")	not stated	bipolar-type schizoaffective disorder, apiprazole in depot	Y

Table 3. Detailed results of the systematic review – cont.

Author(s)	Date of publication	Study type	Country	Number of patients	Age of patients [years]	Sex of patients	PCV setting	PCV drug	PCV drug dose and route	PCV successful, n	Time to SR [min]	Management after failed PCV attempt	Comorbidities	AF guideline adherence
Stiell et al.	II 2020	multi-center partial factorial trial of 2 protocols (blinded, placebo-controlled RCT + nested, open-label trial)	Canada	204	60 (22–92)	70 F, 134 M	ED	procainamide	15 mg/kg in 500 mL of normal saline solution, over 30 min (max dose 1500 mg)	106	23 (14–35)**	ECV	age ≥75 years 29, CAD 16, CHF 6, COPD or asthma 19, DM type I 18, HVD 17, HTN 75, pacemaker or ICD 3, stroke or TIA 15	Y
Stoneman et al.	XI 2017	prospective, single-center	Ireland	42	57.7 (32–82)	10 F, 32 M	ED	vernakalant	3 mg/kg (max 113 kg) 10 min iv infusion	83%	8.8 (2–30), 9 required 2nd infusion	2nd iv infusion 2 mg/kg (max 113 kg), 10 min	HTN 20	Y
Su et al.	V 2017	retrospective	USA	48	68.9 ±14.0	12 F, 36 M	ICU	amiodarone	150 mg bolus iv followed by 1 mg/min for 6 h, then 0.5 mg/min for 18 h for a total of 1050 mg	not stated	not stated	not stated	AGE 33, reduced LV EF 6, LV hypertrophy 20, pulmonary HTN 14, prior MI 6, DM 13, OBE 11, THY 1	N
Tsanaxidis et al.	IV 2017	RCT	Greece	173	68 ±10	80 F, 93 M	not stated	amiodarone 81 ± ranolazine 92	AMIO: 5 mg/kg in 1 h followed by 50 mg/h; R: 1 g po	90%	10–15 h	not stated	HTN: A 53, A+R 65; IHD: A 13, A+R 29; OBE: A 32, A+R 27; DM: A 9, A+R 7	Y
Urtubia et al.	II 2016	retrospective single-center	Spain	12	56	1 F, 11 M	ED	vernakalant	3 mg/kg in 10 min	10	not stated (8 cardioverted with single dose)	2 mg/kg in 10 min, ECV	DM 2, HTN 6, stroke 2	Y
Vinson et al.	I 2018	retrospective cohort	USA	361	60.9 (14.8)	142 F, 219 M	ED	ibutilide	1 mg iv over 10 min	204	at 90 min was 44% (95% CI 38.9% to 49.3%), at 4 h it was 54.8% (95% CI 49.6% to 60.1%), and at ED discharge it was 56.5% (95% CI 51.2% to 61.7%)	2nd dose or ECV	HTN 202, DM 39, HF 18	N
Vogiatzis et al.	IV 2017	single-center RCT + cost-effectiveness analysis	Greece	78	63.72 ±6.67	22 F, 56 M	CD	vernakalant, ibutilide	V: 3 mg/kg iv over 10 min; I: 1 mg iv over 10 min	V 19, I 22	V 11.8 ±4.3, I 33.9 ±20.25 min	V 2 mg/kg, I 1 mg	HTN: V 27, I 23; CAD: V 18, I 13; HVD: V 5, V 6; lone AF: V 7, I 7	Y

Table 3. Detailed results of the systematic review – cont.

Author(s)	Date of publication	Study type	Country	Number of patients	Age of patients [years]	Sex of patients	PCV setting	PCV drug	PCV drug dose and route	PCV successful, n	Time to SR [min]	Management after failed PCV attempt	Comorbidities	AF guideline adherence
Wu et al.	II 2019	retrospective, single-center	China	181	60.1±8.5	22 F, 159 M	ICU	amiodarone	2 mg/kg in 10 min at 1 mg/kg/h until AF remission or 24 h	42	1584 (1.1 days)	ECV if hemodynamically unstable	all after esophageal or lung surgery, CAD 36, DM 39, HTN 71, OBE 51	Y
Wybraniec et al.	X 2018	retrospective, single-center, observational	Poland	450	65.5 ±11.9	238 F, 212 M	ED	antazoline, amiodarone, propafenone	AMIO: infusion in 5% glucose ± bolus 150 mg iv; PROP: 150 mg po or 70 mg in 100 mL 0.9% NaCl iv over 3 min; ANT: 100–200 mg iv bolus over 3 min or in 100 mL 0.9% NaCl iv over 5–15 min	314/450	not stated	not stated	HTN 328, DM 79), CAD/PAD 144	Y
Yarlagadda et al.	XII 2017	single-center retrospective study of consecutive patients	USA	378	64 ±11	dofetilide (205 M, 93 F), sotalol (46 M, 34 F)	not stated	D (n = 298), S (n = 80)	dofetilide, sotalol	D (125/215, 58%), S (30/48, 62.5%)	not stated	ECV	HTN (D: 252, 84.5%) (S: 67, 83.7%); DM (D: 63, 21.1%) (S: 20, 25%); CAD (D: 93, 31.2%) (S: 41, 51.2%)	Y
Zeemering et al.	VII 2018	retrospective	Netherlands	221	succ 61 ±13; fail 57 ±15	succ (93 M, 64 F); fail (52 M, 12 F)	not stated	flecainide	2 mg/kg (max 150 mg) iv infusion	157/221 (71%)	not stated	not stated	COPD 10, DM 15, HTN 95,	Y
Zeriouh et al.	V 2014	observational	Germany	24	69.6 ±6.3	F 26.1%	not stated	vernakalant ± flecainide	3 mg/kg/min iv infusion over 10 min	14	15–375	V: 2 mg/kg/min over 10 min; F: 300 mg po	DM 17.4%; HTN 78.3%	Y
Zhang et al.	XII 2018	single-center, open-label RCT	China	41	A: 72 ±13, A+W: 71 ±12	A: 11 F, 10 M; A+W: 12 F, 8 M	not stated	amiodarone 21, amiodarone + Wenxin Keli 20	5 mg/kg in 1 h iv followed by 50 mg/h iv ± Wenxin Keli 18 g thrice daily for 24 h	A 17, A+W 14	A 291 ±235, A+W 725 ±475	ECV or radiofrequency ablation	DM (A: 3, A+W: 9), HTN: (A: 14, A+W: 15)	Y
Zheng et al.	VII 2017	retrospective	China	48	63 ±12	A: 27 M	not stated	amiodarone	0.6 g/day (0.2 g tid) in the 1st week and then 0.4 g/day (0.2 g bid) in the 2nd week followed by 0.2 g/day (0.2 g qd) in the 3rd week and lasted for 11.5 months	A 43	A 211 ±126	not stated	CAD (A 36); CMP (A 7); HTN (A 40); HF (A 3)	Y

Table 4. Articles describing PCV performed using a contraidicated drug

Author(s)	Year of publication	Country	PCV setting	PCV drug	AF guideline adherence issue
Amin et al.	2015	Netherlands	CER	flecainide	11 patients had CAD
Balik et al.	2017	Czech Republic	ICU	amiodarone	5 patients had hyperthyroidism
Beatch et al.	2017	China, Hong-Kong, India, Korea, Taiwan	not stated	vernakalant	5 patients had HF (2 had NYHA III), 2 patients had HVD (not specified if aortic stenosis or not)
Bonora et al.	2017	Italy	ED	flecainide or propafenone, amiodarone	18 patients with IHD received flecainide or propafenone, 53 patients with HVD received flecainide or propafenone, 23 patients with THY received amiodarone
Carbajosa et al.	2017	Spain	ED	vernakalant	15 patients had HF (patients with NYHA II–IV HF were excluded)
Cosin-Sales et al.	2016	Spain	ED	vernakalant	1 patient had HF (NYHA not specified)
Costabel et al.	2015	Brazil	ED	vernakalant	"Patients with severe valvular heart disease, restrictive cardiomyopathy, hypertrophic cardiomyopathy, and those with known ejection fraction (EF) <35% were excluded" and yet 5.3% of 121 patients had EF < 55%
Dalyanoglu et al.	2018	Germany	CSD	vernakalant	21 patients had LVEF < 50%
Dong et al.	2017	China	not stated	ibutilide, amiodarone	29.71% of the patients had HF and received ibutilide, 28.35% had HF and received ibutilide + amiodarone (patients with LVEF < 35% were excluded)
Farkowski et al.	2016	Poland	ED	propafenone	14 patients had IHD, 2 patients had HVD
Hamilton et al.	2015	UK	ED	flecainide, amiodarone	52 patients had HVD, 5 had previous congenital heart disease, 162 had IHD (not stated how many of them received flecainide); 48 patients had unspecified THY (not stated how many received amiodarone)
Kriz et al.	2016	Austria	ED	ibutilide, flecainide, vernakalant	1 patient with HF/LV dysfunction received flecainide; 3 patients with HF/LV dysfunction received ibutilide, 4 patients with HF/LV dysfunction received vernakalant (elsewhere in the article it is stated that patients with HF and "severely reduced left ventricular ejection fraction" were excluded)
Lieberman et al.	2018	USA	PED	flecainide	6 patients had CMP + 3 patients had HVD
Nemati et al.	2016	Iran	not stated	propafenone	9 patients had COPD (not stated if patients had bronchospasm or dyspnea at the time of PCV)
Simon et al.	2016	Austria	ED	ibutilide	49 patients had HF (NYHA I) and 2 patients had NYHA II (patients with NYHA III and IV were excluded)
Su et al.	2017	USA	ICU	amiodarone	1 patient had hyperthyroidism
Vinson et al.	2018	USA	ED	ibutilide	18 patients had HF (3 of which had EF < 40%)

CAD – coronary artery disease; CER – cardiac emergency room; CMP – cardiomyopathy; ED – emergency department; EF – ejection fraction; HF – heart failure; HVD – heart valve disease; ICU – intensive care unit; LV – left ventricular; NYHA – New York Heart Association; PED – pediatrics department; THY – thyroid disease.

were not definitive. Authors suggested reasons such as lack of quality evidence (see Table 2 for information about the level of evidence in the analyzed AF guidelines), impossibility to establish AF onset, concerns about thromboembolic events, concerns about negative inotropic or proarrhythmic effect of PCV drugs, time constrains (excluding secondary causes of AF is time-consuming and adds more complexity to decision-making), and the fact that a significant number of ED patients with AF spontaneously revert to SR.[35,45,49,78–81] Finally, patient preference, or perhaps the physician's attitude, towards a given therapeutic option may influence the decisions about adopting a wait and observe approach or rhythm control or rate control, as well as electrical or pharmacological cardioversion.[46]

In a survey of 561 physicians, Heidbuchel et al. found 8 major barriers to AF guidelines implementation that were knowledge-related (e.g., diagnosing AF based on duration instead of etiology, uncertainty during decision-making, use and interpretation of risk assessment scores, difficulties in choosing stroke prevention treatment), skill-related (e.g., difficulties in EKG interpretation/detection of AF, difficulties in discussing with patients their treatment strategy) and systemic (e.g., poor cooperation between specialists and general practitioners, local regulations regarding the use of novel anticoagulants).[82]

Table 5. Correlation of several factors with the adherence to the PCV recommendations as described in AF treatment guidelines

Factor	AF guideline adherence		p-value
	PCV protocol adhered to the guidelines	PCV protocol did not adhere to the guidelines	
Overall guideline adherence (n, %)	47/64, 70.7%	17/64, 29.3%	–
Sample/number of patients in the study (mean ±SD)	124.0 ±147.8	184.6 ±155.7	p = 0.059
Age [years] (mean ±SD)	60.7 ±11.8	62.1 ±12.5	p = 0.345
Sex (n, % of males)	30/43, 66.1%	13/43, 60.7%	p = 0.284
Type of study/article			
RCT (n, %)	5/41, 12.2%	3/17, 17.7%	p = 0.680
case report (n, %)	7/41, 17.1%	0/17, 0%	p = 0.093
other than RCT or case report (n, %)	29/41, 70.7%	14/17, 82.4%	p = 0.514
Region/country where the PCV was performed			
Europe (n, %)	25/41, 61.0%	10/17, 58.8%	p = 1.000
USA (n, %)	3/41, 7.32%	3/17, 17.7%	p = 0.344
Department where PCV was performed			
ICU (n, %)	7/30, 23.3%	3/16, 18.8%	p = 1.000
ED (n, %)	9/30, 30.0%	9/16, 56.3%	p = 0.115
other than ICU or ED (n, %)	14/31, 45.2%	4/16, 25.0%	p = 0.218

AF – atrial fibrillation; ED – emergency department; ICU – intensive care unit; PCV – pharmacological cardioversion; RCT – randomized controlled trial; SD – standard deviation.

Limitations

Our systematic review had several limitations, most notably, the high heterogeneity and incompleteness of the obtained data which did not allow us to perform a meta-analysis. Specifically, we were unable to extract enough data about the patients (e.g., patient age is provided only as an average value, comorbidities listed as totals without mention if any patients had more than 1 comorbidity). Therefore, it was not possible to assess if AF guidelines were followed during PCV of those patients. Furthermore, although reports of single cases are universally defined as weak evidence, we had little data to choose from and decided to include them in the analysis. Had there been more data from large trials available, we would have chosen them over case reports, thus making our statistical analysis and conclusions more robust. Finally, we are aware that there might be national AF guidelines which we were unable to find.

Conclusions

Our review of the published clinical literature about PCV reveals significant non-adherence to AF treatment guidelines. Specifically, the drugs used for PCV in patients with AF and comorbidities such as heart failure and thyroid disease are inconsistent with the guidelines.

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