

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 STATA 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 | | |
| 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 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 | paroxysmal atrial arrhythmias including tachycardia/AF, nor reacting to standard treatment | avoid in patients with history of seizures, concurrently 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 x1 if ≥ 70 kg or 200 mg PO x1 if < 70 kg | 200–300 mg x1** | 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 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 | 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 | | |
| 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 | 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 | 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 | 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 and New Zealand; NYHA – New York Heart Association; po – per os (orally); SBP – systolic blood pressure WPW – Wolff–Parkinson–White syndrome.

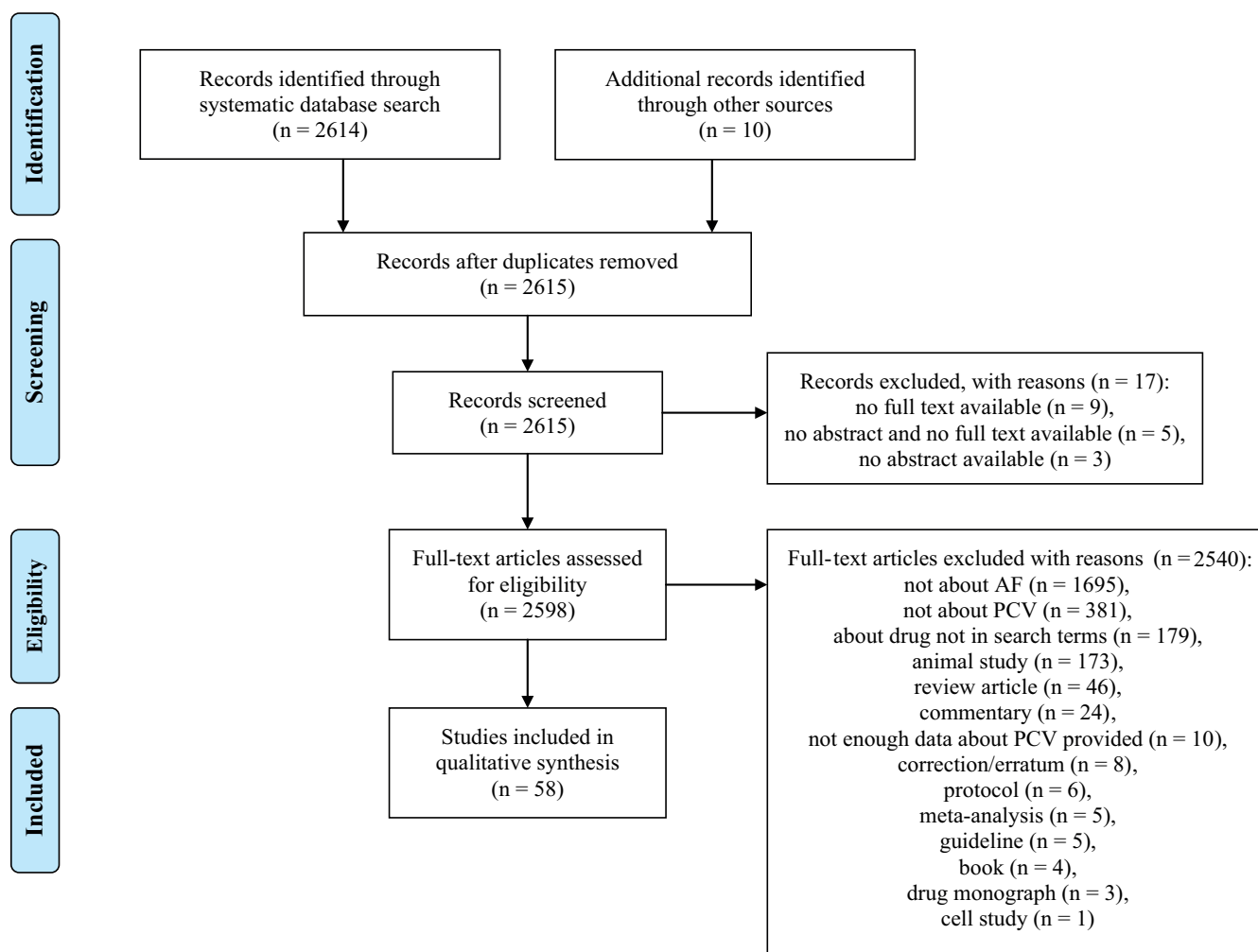


Fig. 1. Flowchart of the literature search strategy

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).

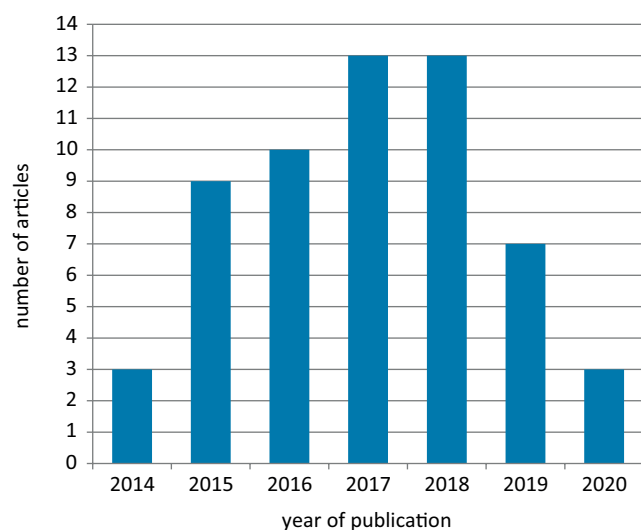


Fig. 3. Number of analyzed articles published in a given year

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 → 2 nd 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 |
| Balík 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 1 st infusion → vernakalant 2 mg/kg iv over 10 min; if AF 2 h after 1 st 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 1 st infusion → 2 mg/kg iv over 10 min; if AF 2 h after 1 st 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 |
| Carbaljosa 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 2 nd dose → 34 (22–62) | if AF 15 min after 1 st 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 | 2 nd 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 | 2 nd 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 2 nd 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 + 1 mg iv; 1 mg iv | I = 51.3% (20/39), A + I = 71.8% (28/39) | 175–120; 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 |
| Karaveloglou 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: 2 nd dose after 10 min, V: 2 nd 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 (1 st 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) | 2 nd 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) | 2 nd 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; PRO-P: 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 |
|------------------------------------|---------------------|--|------------------|--------------------|------------------------------------|---|---------------|--|--|--|--|---|---|------------------------|
| Pohjantah- ti-Maaroos et al. | III 2019 | single-center non-random- ized retrospective | Finland | 200 | F 55.3 ±13.0; V 59.3 ±12.5 | F 65, V 66 | ED | flecainide 100, ver- nakalant 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 → 2 nd 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 | Switzer- land | 32 | 74 (36–86) | 10 F, 22 M | ICU | vernaka- lant | 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 | vernaka- lant | 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 | amioda- rone | 150 mg over 30 min, followed by 20–50 mg/h | 10 | 150 | administration of a 2 nd 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 | vernaka- lant 49, ibutilide 51 | V: 3 mg/kg in 100 mL normal saline iv infu- sion over 10 min; I: 1 mg in 100 mL nor- mal saline iv infusion over 10 min | vernakalant: 34/49 (29 converted after 1 st infu- sion); ibutilide: 22/51 (14 converted after 1 st infu- sion) | V 10, I 26 | if AF 15 min after vernaka- lant infusion → 2 nd infusion (10 min) of vernakalant (2 mg/kg); if AF 10 min after ibutilide infusion → 2 nd infusion of ibutilide (10 min, 1 mg); if AF 2 h after 1 st 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 |
| Simopo- ulos 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 | amioda- rone 255; amio- darone + 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 | amioda- rone | 2 × 150 mg iv + 3 × 400 mg po | 1 | not stated ("by the next day") | not stated | bipolar-type schizoaffective dis- order, 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 |
|-------------------|---------------------|--|---------|--------------------|-------------------------|-----------------|-------------|-------------------------------|---|-------------------|--|--|--|------------------------|
| Striell 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 | procaïnamide | 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% | 88 (2–30), 9 required 2 nd infusion | 2 nd 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%) | 2 nd 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), sotalolol (46 M, 34 F) | not stated | D (n = 298), S (n = 80) | dofetilide, sotalolol | 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 |
| Zerjoun et al. | V 2014 | observational | Germany | 24 | 69.6 ±6.3 | F 26.1% | not stated | verapamil ± 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 1 st week and then 0.4 g/day (0.2 g bid) in the 2 nd week followed by 0.2 g/day (0.2 g qd) in the 3 rd 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 contraindicated 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 constraints (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, Heiddbuchel 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 \pm SD) | 124.0 \pm 147.8 | 184.6 \pm 155.7 | p = 0.059 |
| Age [years] (mean \pm SD) | 60.7 \pm 11.8 | 62.1 \pm 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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