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CLINICAL RESEARCH
Atrial fibrillation

Pharmacologic cardioversion of recent-onset atrial fibrillation: a systematic review and network meta-analysis

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Aims We sought to identify the most effective antidysrhythmic drug for pharmacologic cardioversion of recent-onset atrial fibrillation (AF).

Methods and results We searched MEDLINE, Embase, and Web of Science from inception to March 2019, limited to human subjects and English language. We also searched for unpublished data. We limited studies to randomized controlled trials that enrolled adult patients with AF ≤ 48 h and compared antidysrhythmic agents, placebo, or control. We determined these outcomes prior to data extraction: (i) rate of conversion to sinus rhythm within 24 h, (ii) time to cardioversion to sinus rhythm, (iii) rate of significant adverse events, and (iv) rate of thromboembolism within 30 days. We extracted data according to PRISMA-NMA and appraised selected trials using the Cochrane review handbook. The systematic review initially identified 640 studies; 30 met inclusion criteria. Twenty-one trials that randomized 2785 patients provided efficacy data for the conversion rate outcome. Bayesian network meta-analysis using a random-effects model demonstrated that ranolazine + amiodarone intravenous (IV) [odds ratio (OR) 39.8, 95% credible interval (CrI) 8.3–203.1], vernakalant (OR 22.9, 95% CrI 3.7–146.3), flecainide (OR 16.9, 95% CrI 4.1–73.3), amiodarone oral (OR 10.2, 95% CrI 3.1–36.0), ibutilide (OR 7.9, 95% CrI 1.2–52.5), amiodarone IV (OR 5.4, 95% CrI 2.1–14.6), and propafenone (OR 4.1, 95% CrI 1.7–10.5) were associated with significantly increased likelihood of conversion within 24 h when compared to placebo/control. Overall quality was low, and the network exhibited inconsistency. Probabilistic analysis ranked vernakalant and flecainide high and propafenone and amiodarone IV low.

Conclusion For pharmacologic cardioversion of recent-onset AF within 24 h, there is insufficient evidence to determine which treatment is superior. Vernakalant and flecainide may be relatively more efficacious agents. Propafenone and IV amiodarone may be relatively less efficacious. Further high-quality study is necessary.

Keywords Antidysrhythmic • Antiarrhythmic • Atrial fibrillation • Cardioversion • Network meta-analysis

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What's new?

- Systematic review of the literature identified 21 randomized controlled trials with 2,785 adult patients who were given antidysrhythmic drug, placebo, or control for cardioversion of atrial fibrillation with duration up to 48 hours (recent-onset atrial fibrillation).
- Bayesian network meta-analysis limited by study quality and inconsistency demonstrates that there is insufficient evidence to determine which antidysrhythmic drug is superior for cardioversion of recent-onset atrial fibrillation within 24 hours.
- Vernakalant and flecainide may be relatively more efficacious, and propafenone and intravenous amiodarone may be relatively less efficacious than other agents for cardioversion of recent-onset atrial fibrillation within 24 hours

Introduction

Atrial fibrillation (AF) is the most common clinically significant dysrhythmia with a global prevalence of 33.5 million.[1] Reported numbers are highest in developed nations,[2] and as the population ages, it is estimated that the prevalence of AF in Europe will increase to 17 million by 2030.[2,3] Patients with AF have twice the risk of death and are twice as likely to be hospitalized than those without AF.[1] One percent of the total healthcare expenditure in the UK[4] and as much as $26 billion annually in the USA[1,5] are related to AF, with the greatest proportion attributed to hospital admissions.[6] Early cardioversion of AF in the emergency department has been independently shown to significantly reduce hospital admissions[7] and costs.[8] Early cardioversion of recent-onset AF may also prevent the progression to sustained AF[9,10] and its associated greater risks of ischaemic stroke,[11] systemic thromboembolism, and cardiovascular death.[12–14] 'Further Background' is Supplementary material online, *Appendix S1*.

Cardioversion of AF with duration shorter than 48 h (recent-onset AF) is supported by the European Society of Cardiology (ESC),[15] American Heart Association (AHA),[16] and Canadian Cardiovascular Society (CCS).[17] Pharmacologic cardioversion is established within protocols[18–21] as an alternative to electrocardioversion that avoids the risks of sedation. However, its success rate is relatively lower[22] and may vary with respect to antidysrhythmic agent. Current guidelines[15–17] do not uniformly agree upon the recommendation of antidysrhythmic agents for AF cardioversion, and drug preference in clinical practice also varies internationally.[22] Prior systematic reviews and meta-analyses[23–30] are limited by (i) heterogeneous samples that included patients with variable AF duration exceeding 48 h, a duration for which early cardioversion without prior anticoagulation is contrary to guidelines and (ii) insufficient head-to-head drug comparisons. Therefore, we performed a network meta-analysis (NMA) to indirectly compare and rank antidysrhythmic agents tested in adults with recent-onset AF in order to identify which is most effective for pharmacologic cardioversion.

Methods

Study design

We performed our systematic review and NMA of randomized controlled trials (RCT) according to the Preferred Reporting Items for Systematic Reviews and Network Meta-Analysis statement.[31] (The completed 'PRISMA-NMA Checklist' is in the Supplementary material online.) In contrast to primary studies and conventional meta-analyses that only examine a few interventions through direct, head-to-head (pairwise) comparison, NMA provides estimates of relative efficacy among all interventions even when direct comparisons among them have not been investigated. The protocol for this systematic review was registered in PROSPERO with number CRD42018083781.

Data sources and search strategy

In conjunction with a medical librarian, four investigators (I.d., R.B., T.S., and G.C.) independently searched the medical literature in MEDLINE (through PubMed), Embase, and Web of Science from inception to March 2019. The MEDLINE, Embase, and Web of Science searches were combined and limited by human subject and English language. Additionally, we searched bibliographies of the included articles and prior pertinent systematic and narrative reviews for additional studies that were not found in our database search. We also searched for unpublished data from 2013 to 2018 at opengrey.eu, ntis.gov, and clinicaltrials.gov and manually reviewed the abstracts of the major cardiovascular and emergency medicine conferences: American Heart Association, European Society of Cardiology, Heart Rhythm Society (formerly North American Society of Pacing and Electrophysiology), Europace Cardiostim, World Congress on Cardiac Pacing and Electrophysiology, Asian-Pacific Symposium on Cardiac Pacing and Electrophysiology, Society of Academic Emergency Medicine, American Academy of Emergency Physicians, and American College of Emergency Physicians. Lastly, we contacted experts in the field to help us identify any currently ongoing or unpublished studies that our search may have overlooked. 'Database Search Strategy' is Supplementary material online, *Appendix S2*.

Study selection

Four authors (I.S.d., R.B., T.S., and G.C.) independently reviewed abstracts from the combined MEDLINE, Embase, and Web of Science search and selected articles for full-text review based upon pre-specified inclusion and exclusion criteria. The same authors then independently reviewed the full-texts. We limited studies to RCTs and used a PICO format to determine eligibility of studies for inclusion.

*P*atients: Adult patients (age 18 years and older) with recent-onset AF or atrial flutter (AFL), defined in the study as AF or AFL episode whose onset was within 48 h prior to enrolment.

*I*ntervention: One of the predetermined antidysrhythmic drugs: Procainamide, Amiodarone, Flecainide, Propafenone, Sotalol, Dofetilide, Dronedarone, Ibutilide, Vernakalant, and Magnesium Sulfate.

*C*omparison: Another antidysrhythmic agent, a different formulation of the same agent, placebo, or control—Digoxin,[15,25,28,32] Verapamil,[28,29] and Diltiazem[33] are not known to convert AF to sinus rhythm and were therefore considered non-antidysrhythmic controls.

*O*utcomes: (i) Rate of conversion to sinus rhythm within 24 h, a time frame suitable for cardioversion within an observation stay or short-term admission (quantitative), (ii) time to cardioversion to sinus rhythm, (ii) rate of significant adverse events as reported by the individual trials—cardiac arrest, ventricular dysrhythmia, AFL with 1:1 atrioventricular conduction, hypotension, and bradycardia, and (iv) rate of thromboembolism within 30 days.

Differences were resolved by consensus, and all authors agreed upon the final group of included articles.

Quality assessment

Four authors (I.S.d., R.B., T.S., and G.C.) independently assessed the risk of bias within all included studies at the study level according to the

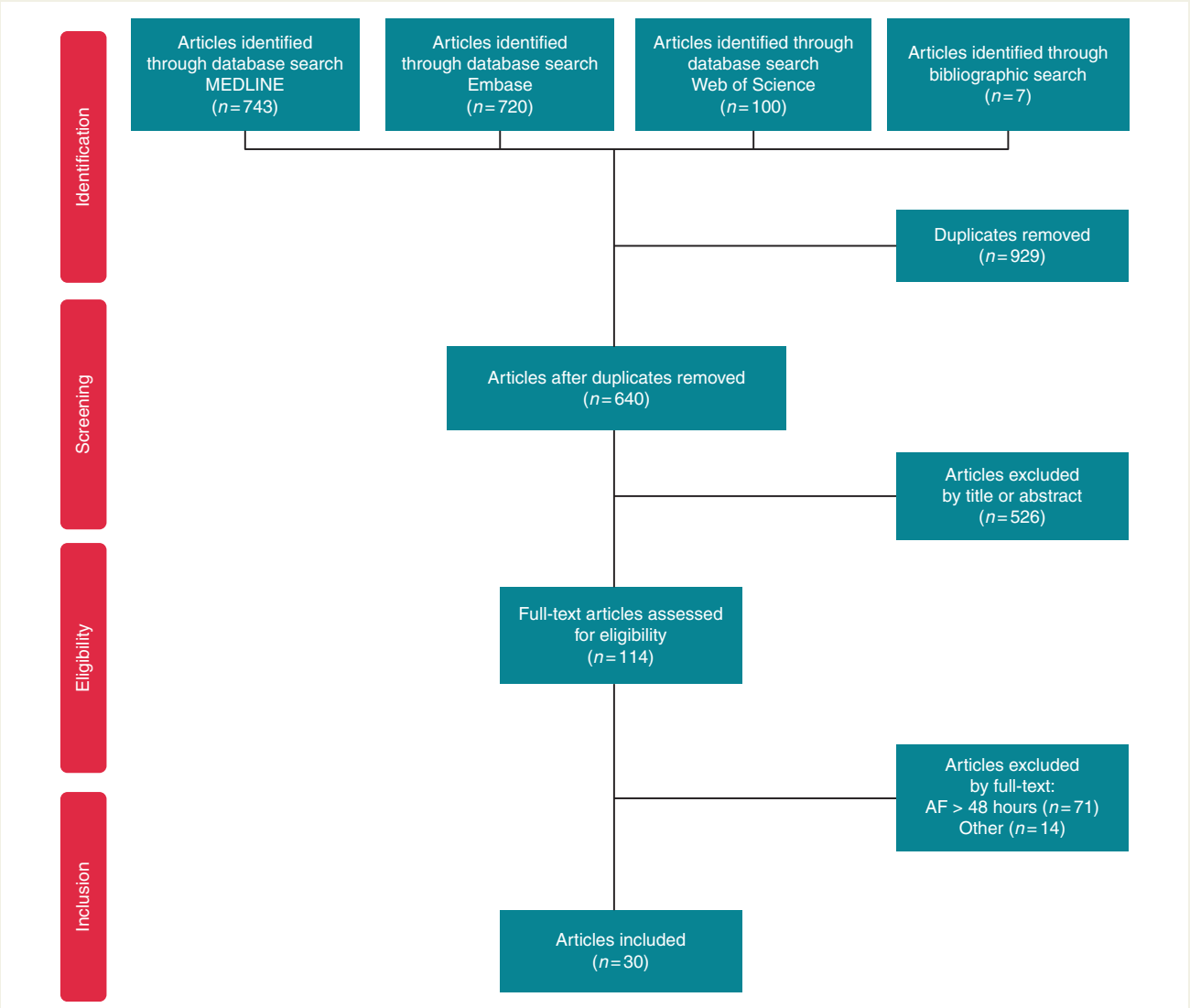

Figure 1 Study selection process. AF, atrial fibrillation.

Cochrane review handbook.[34] The risk of bias tool covers six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and 'other' bias. Our 'Method of Individual Study Quality Assessment' is Supplementary material online, *Appendix S3*. All divergences were resolved by consensus. Each study was classified as high or low risk within each of the domains at the study level and also individually at the outcome (conversion to sinus rhythm) level. When discussing the confidence in a specific treatment effect estimate, we considered the quality (risk of bias at outcome level) of the direct evidence contributing to that estimate.

Data extraction

Two authors (I.S.d. and T.S.) extracted the data from each article for each of the outcomes. For the outcome of conversion within 24 h, we extracted data from rhythm assessment at 24 h after drug administration. If assessment was only reported prior to 24 h, we extracted data from the time point closest to 24 h. In trials that included crossover to the other treatment arm, we extracted only pre-crossover data. We assigned data from treatment arms that included both intravenous (IV) and oral (PO) formulations of the same drug to the IV group. We separated data from AF and AFL patients except for the outcome of adverse event rate. When hypotension occurred simultaneously with bradycardia, we recorded the event as hypotension. When data were unavailable or unclear, we attempted to contact the corresponding authors through electronic mail and inspected prior systematic reviews for the trial data of interest. Any issues with extraction were discussed and resolved by consensus.

Data analysis

Using the extracted data for conversion to sinus rhythm, we created a network diagram to illustrate which of the considered treatments (nodes) were compared (connected) directly and which were compared indirectly through one or more common comparators. We conducted a Bayesian NMA using a Markov Chain Monte Carlo method with an unconstrained, random-effects model. We conducted the analysis with 10 000 burn-in iterations and 100 000 simulations using a non-informative prior. We report pairwise comparisons (NMA estimates) using a league table with each pairwise comparison reported as an odds ratio (OR) with a 95% credible interval (CrI). A CrI is an interval in which

Table 1 Description of included randomized controlled trials

Trial	Patient characteristics[a]	Setting	Investigated treatments	Rhythm monitoring/time points of analysis	Extracted outcomes
Alp *et al.*[37]	AF < 48 h Sample size: 79 Mean age (yrs): 64.3 Sex: 58% male Heart failure: NR LA diameter: NR	CCU	(1) Flecainide 2 mg/kg IV (maximum 150 mg) (2) Flecainide 4 mg/kg PO (maximum 300 mg)	Continuous 2 h, 8 h	Conversion within 24 h Mean time to conversion Adverse events
Balla *et al.*[38]	AF ≤ 48 h Sample size: 160 Mean age (yrs): 58.1 ± 10.3 Sex: 63.1% male Heart failure: NR LA diameter (mm): 42.3 ± 4.3 (arm 1) 36.1 ± 3.2 (arm 2) 34.4 ± 5.3 (arm 3) 32.9 ± 6.3 (arm 4)	CCU	(1) Amiodarone 30 mg/kg PO (2) Flecainide 3 mg/kg PO (3) Propafenone 8.5 mg/kg PO (4) Placebo	Continuous + Serial 3 h, 6 h, 12 h, 24 h	Conversion within 24 h Adverse events
Camm *et al.*[9]	AF 3–48 h Sample size: 232 Mean age (yrs): 62.7 ± 11.2 Sex: 63% male Heart failure: 19.8% LA diameter (mm): 40.8 ± 6.4	NR	(1) Vernakalant 3 mg/kg IV × 10 min, then 2 mg/kg × 10 min after 15 min prn (2) Amiodarone 5 mg/kg IV × 1 h, then 50 mg IV × 1 h	Continuous 1.5 h, 4 h	Conversion within 24 h Median time to conversion (vernakalant only) Adverse events Short-term follow-up
Capucci *et al.*[40]	AF < 48 h Sample size: 246 Mean age (yrs): 58.9 Sex: 51% male Heart failure: NR LA diameter (mm): 39.1 ± 6.9 (arm 1) 39.6 ± 5.0 (arm 2) 38.3 ± 5.8 (arm 3) 38.9 ± 6.0 (arm 4)	NR	(1) Digoxin IV + Quinidine 275 mg PO q2h × 4 (2) Propafenone 450 mg (< 60 kg) or 600 mg (> 60 kg) PO, then 300 mg PO after 6 h prn (3) Digoxin IV + Propafenone 450 mg or 600 mg PO, then 300 mg PO after 6 h prn (4) Placebo	Continuous 3 h, 6 h, 12 h, 24 h	Conversion within 24 h Mean time to conversion Adverse events
Chiladakis *et al.*[41]	AF < 12 h Sample size: 46 Mean age (yrs): 62.5 Sex: 54% male Heart failure (NYHA I–II): 91% LA diameter (mm): 37.0 ± 6.0 (arm 1) 38.0 5.0 (arm 2)	NR	(1) Magnesium 2.5 g IV (2) Diltiazem IV	Continuous 6 h	Conversion within 24 h Adverse events
Cotter *et al.*[42]	AF < 48 h Sample size: 100 Mean age (yrs): 66 Sex: 43% male Heart failure:	Inpatient medicine	(1) Digoxin IV prn + Amiodarone 125 mg/h IV (3 g total) (2) Digoxin IV prn + Placebo	Continuous 8 h, 24 h	Conversion within 24 h Adverse events

Continued

Table I *Continued*

Trial	Patient characteristics[a]	Setting	Investigated treatments	Rhythm monitoring/time points of analysis	Extracted outcomes
	4% (arm 1) 8% (arm 2) LA diameter > 45 mm: 28% (arm 1) 30% (arm 2)				
Fragakis *et al.*[43]	AF < 48 h Sample size: 51 Mean age (yrs): 62 ± 8 (arm 1) 64 ± 7 (arm 2) Sex: 64.7% male Heart failure: NR LA diameter (mm): 43.0 ± 5.0 (arm 1) 45.0 ± 5.0 (arm 2)	CCU	(1) Amiodarone 5 mg/kg IV × 1 h, then 50 mg/h IV × 24 h (2) Ranolazine 1500 mg PO then Amiodarone 5 mg/kg IV × 1 h, then 50 mg/h IV × 24 h	Continuous 24 h	Conversion within 24 h Mean/median time to conversion Adverse events
Halinen *et al.*[44]	AF < 48 h Sample size: 61 Mean age (yrs): 54.9 ± 12.7 (arm 1) 53.2 ± 15.3 (arm 2) Sex: 65.6% male Heart failure: NR LA diameter: NR	ED	(1) Digoxin IV prn + Quinidine 200 mg PO q2h × 3 (2) Sotalol 80 mg PO, then 80 mg PO after 2 h, then 80 mg PO q4h × 2 prn	Continuous 3 h, 8 h, 12 h	Conversion within 24 h Mean/median time to conversion Adverse events
Hohnloser *et al.*[45]	AF/AFL 3–48 h Sample size: 173 Mean age (yrs): 63.6 ± 13.7 Sex: 61.7% male Heart failure (NYHA I–II): 98.3% LA diameter: NR	NR	(1) Tedisamil 0.4 mg/kg IV, then 0.6 mg/kg IV (2) Placebo	Continuous 2.5 h, 24 h	Adverse events Short-term follow-up
Innes *et al.*[46]	AF < 48 h Sample size: 41 Mean age (yrs): 58 ± 11 (arm 1) 62 ± 10 (arm 2) Sex: 61% male Heart failure: 4.9% LA diameter: NR	ED	(1) Digoxin IV + Quinidine 200 mg PO q2h (maximum 1 g) (2) Verapamil IV + Quinidine 200 mg PO q2h (maximum 1 g)	NR 6 h, 24 h	Conversion within 24 h Mean time to conversion Adverse events
Joseph and Ward[47]	AF/AFL < 24 h Sample size: 115 Mean age (yrs): 64.9 ± 2.0 (arm 1) 61.3 ± 2.6 (arm 2) 62.8 ± 2.4 (arm 3) Sex: 53.3% male Heart failure: NR LA diameter (mm): 39.7 ± 1.1 (arm 1)	ED	(1) Amiodarone 5 mg/kg IV × 30 min, then 400 mg PO q8h × 6 (2) Sotalol 1.5 mg/kg IV × 30 min, then 80 mg PO q8h × 6 (3) Digoxin IV/PO	Continuous 4 h, 24 h, 48 h	Adverse events

Continued

Table I *Continued*

Trial	Patient characteristics[a]	Setting	Investigated treatments	Rhythm monitoring/time points of analysis	Extracted outcomes
	38.4 ± 1.0 (arm 2) 39.5 ± 1.0 (arm 3)				
Kafkas *et al.*[48]	AF/AFL 3–48 h Sample size: 152 Mean age (yrs): 62 ± 16 (arm 1) 64 ± 18 (arm 2) Sex: 67.8% male Heart failure: NR LA diameter (mm): 43.0 ± 5.0 (arm 1) 45.0 ± 6.0 (arm 2)	Inpatient cardiology	(1) Ibutilide 1 mg IV × 10 min, then 1 mg IV × 10 min after 10 min prn (2) Amiodarone 5 mg/kg IV × 30 min, then 1200 mg IV × 24 h	Continuous + Serial 4 h	Conversion within 24 h Mean time to conversion Adverse events
Kochiadakis *et al.*[49]	AF < 48 h Sample size: 143 Mean age (yrs): 63 ± 12 Sex: 53.8% male Heart failure: NR LA diameter (mm): 43.0 ± 6.0 (arm 1) 43.0 ± 5.0 (arm 2) 41.0 ± 6.0 (arm 3)	CCU	(1) Digoxin IV + Propafenone 2 mg/kg IV × 15 min, then 10 mg/kg IV × 24 h (2) Digoxin IV + Amiodarone 300 mg IV × 1 h, then 20 mg/kg IV and 600 mg PO q8h × 24 h (3) Digoxin IV + Placebo	Continuous 24 h	Conversion within 24 h Mean time to conversion Adverse events
Kochiadakis *et al.*[50]	AF ≤ 48 h Sample size: 362 Mean age (yrs): 65 ± 10 Sex: 50% male Heart failure: NR LA diameter (mm): 40.8 ± 5.5 (arm 1) 41.6 ± 6.1 (arm 2) 42.2 ± 5.4 (arm 3) 41.3 ± 6.2 (arm 4)	CCU	(1) Digoxin IV + Procainamide 1 g IV × 30 min, then 2 mg/min IV × 24 h (2) Digoxin IV + Propafenone 2 mg/kg IV × 15 min, then 10 mg/kg IV × 24 h (3) Digoxin IV + Amiodarone 300 mg IV × 60 min, then 20 mg/kg IV × 24 h (4) Digoxin IV + Placebo	Continuous 24 h	Conversion within 24 h Mean/median time to conversion Adverse events
Kosior *et al.*[51]	AF < 48 h Sample size: 81 Mean age (yrs): 64.0 ± 11.6 Sex: 43.2% male Heart failure: NR LA diameter (mm): 43.9 ± 5.0 (arm 1) 40.0 ± 3.0 (arm 2)	Inpatient cardiology	(1) Propafenone 600 mg PO, then 300 mg PO after 8 h prn (2) Digoxin IV + Quinidine 400 mg PO, then Quinidine 200 mg PO q2h (maximum 1400 mg)	Continuous 8 h, 24 h	Conversion within 24 h Median time to conversion Adverse events
Koskinas *et al.*[52]	AF ≤ 48 h Sample size: 121 Mean age (yrs): 64 ± 9 (arm 1) 66 ± 11 (arm 2) Sex: 44.6% male	CCU	(1) Amiodarone 5 mg/kg IV × 60 min, then 50 mg/h IV × 24 h (2) Ranolazine 1500 mg PO once, then Amiodarone	Continuous 12 h, 24 h	Conversion within 24 h Mean time to conversion Adverse events

Continued

Table I *Continued*

Trial	Patient characteristics[a]	Setting	Investigated treatments	Rhythm monitoring/time points of analysis	Extracted outcomes
	Heart failure: NR LA diameter (mm): 46.0 ± 6.0 (arm 1) 49.0 ± 8.0 (arm 2)		5 mg/kg IV × 60 min, then 50 mg/h IV × 24 h		
Madonia *et al.*[53]	AF ≤ 48 h Sample size: 97 Median age (yrs): 62 (range 22–95) Sex: 46.1% male Heart failure: NR LA diameter: NR	ED	(1) Propafenone 2 mg/kg IV × 10 min, then 1 mg/kg IV × 2 h, then 300 mg PO q8h × 3 prn (2) Propafenone 600 mg PO, then 300 mg PO after 6 h, then 300 mg PO q8h × 2 or prn	IV Arm: Continuous PO Arm: Serial 1 h, 3 h, 6 h, 12 h, 24 h	Conversion within 24 h Adverse events
Martinez-Marcos *et al.*[54]	AF ≤ 48 h Sample size: 150 Mean age (yrs): 60 ± 13 Sex: 46.7% male Heart failure: NR LA diameter (mm): 40.0 ± 5.0 (arm 1) 40.0 ± 3.0 (arm 2) 39.0 ± 5.0 (arm 3)	ED	(1) Amiodarone 5 mg/kg IV × 20 min, then 50 mg/h IV (2) Propafenone 2 mg/kg IV × 20 min, then 1 mg/kg IV × 20 min after 8 h prn (3) Flecainide 2 mg/kg IV × 20 min, then 1 mg/kg IV × 20 min after 8 h prn	Continuous + Serial 1 h, 8 h, 12 h	Conversion within 24 h Median time to conversion Adverse events
Peuhkurinen *et al.*[55]	AF 3–48 h Sample size: 62 Mean age (yrs): 56 ± 13 (arm 1) 62 ± 12 (arm 2) Sex: 72.6% male Heart failure: NR LA diameter (mm): 39.0 ± 6.0 (arm 1) 38.0 ± 5.0 (arm 2)	NR	(1) Amiodarone 30 mg/kg PO (2) Placebo	Continuous 24 h	Conversion within 24 h Median time to conversion Adverse events
Simon *et al.*[56]	AF ≤ 48 h Sample size: 100 Mean age (yrs): 56.5 ± 15 Sex: 68% male Heart failure (NYHA I–II): 99% LA diameter: NR	ED	(1) Vernakalant 3 mg/kg IV, then 2 mg/kg IV after 15 min prn (2) Ibutilide 1 mg IV × 10 min, then 1 mg IV × 10 min after 10 min prn	Continuous 1.5 h, 4 h	Conversion within 24 h Median time to conversion Adverse events
Tsanaxidis *et al.*[57]	AF < 48 h Sample size: 173 Mean age (yrs): 70 ± 10 (arm 1) 67 ± 11 (arm 2) Sex: 45.7% male Heart failure: NR LA diameter (mm): 42.0 ± 5.0 (arm 1) 41.0 ± 4.0 (arm 2)	CCU	(1) Amiodarone 5 mg/kg IV × 1 h, then 50 mg/h IV × 24 h (2) Ranolazine 1 g PO, then Amiodarone 5 mg/kg IV × 1 h, then 50 mg/h IV × 24 h	NR 24 h	Conversion within 24 h Mean time to conversion Adverse events

Continued

Table 1 *Continued*

Trial	Patient characteristics[a]	Setting	Investigated treatments	Rhythm monitoring/time points of analysis	Extracted outcomes
Walker *et al.*[58]	AF/AFL < 48 h Sample size: 41 Mean age: NR Sex: NR Heart failure: NR LA diameter: NR	ED	(1) Magnesium 5 g (20 mmol) IV × 30 min (2) Placebo	Serial 4 h	Conversion within 24 h Mean time to conversion Adverse events
Xanthos *et al.*[59]	AF < 48 h Sample size: 223 Mean age (yrs): 65 ± 12 (arm 1) 64 ± 13 (arm 2) Sex: 51.6% male Heart failure: NR LA diameter (mm): 42.0 ± 7.0 (arm 1) 42.0 ± 5.0 (arm 2)	NR	(1) Digoxin IV + Amiodarone 200 mg PO q8h (2) Digoxin IV + Amiodarone 5 mg/kg IV × 30 min then 1000 mg IV × 24 h prn	Continuous 24 h	Conversion within 24 h Mean time to conversion

AF, atrial fibrillation; AFL, atrial flutter; CCU, coronary care unit; ED, emergency department; h, hours; IV, intravenous; LA, left atrium; min, minutes; NR, not reported; NYHA, New York Heart Association Class; PO, oral; prn, as needed; q, every; yrs, years.
[a]The most common exclusion criteria were: current or previous use of study drug or antidysrhythmic (96%), recent acute coronary syndrome (74%), hemodynamic instability (70%), thyroid dysfunction (70%), renal dysfunction (65%), hepatic dysfunction (65%), reduced ejection fraction (57%), sinus node disease (52%), contraindications to trial drug (48%), chronic lung disease (43%), metabolic derangement 42%), pregnancy (42%), long QTc (39%), and pre-excitation syndrome (26%).

an (unobserved) parameter has a given probability. For a 95% CrI, the value of interest (i.e. treatment effect size) lies within the interval with a 95% probability.

We also performed probabilistic analysis and reported the results using Surface Under the Cumulative Ranking Curve (SUCRA), a numeric presentation of the overall ranking based upon the probability that a treatment was most effective for the outcome of interest. The probability is the percentage of times that the simulations conducted within the NMA showed a treatment to be superior to the others. For example, a 75% probability of a drug being ranked first represents a 75% chance of that drug being the superior treatment. In our NMA, this is the probability that a treatment is most effective for AF cardioversion to sinus rhythm within 24 h. Importantly, the SUCRA is distinct from the unweighted, pooled cardioversion and adverse event rates that we report in the qualitative analysis. It is possible for a treatment to be ranked relatively high and also to have demonstrated a relatively lower unweighted, pooled cardioversion rate. We also present the cumulative rankograms that underly the SUCRA. A rankogram visually presents the probability for a treatment to assume each of the possible ranks. Further explanation of 'Network Meta-Analysis Concepts' is Supplementary material online, *Appendix S4*.

We attempted to analyse all treatment arms including those from trials with multiple arms. In cases where the model would not converge due to insufficient data, we either merged those arms with IV and PO formulations of the same drug or excluded the node entirely. To increase the feasibility of the NMA and strengthen the evidence network, we analysed data from all studies that reported rhythm assessment between 4 and 24 h after drug administration. We assessed the posterior mean deviance to assess inconsistency between direct and indirect estimates in each loop. We ran separate models to control for inconsistency if present. Finally, we conducted sensitivity tests by performing random- and fixed-effects models. Importantly, these did not greatly vary the results, and thus we report only the random-effects model. We completed the analysis using NetMetaXL 1.6.1 (CADTH, Ottawa, Canada)[35] and WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).[36]

Results

Selection of included studies

The study selection process is presented in *Figure 1*. Thirty studies initially met inclusion criteria, however, seven had endpoints earlier than 4 h. Twenty-three studies[37–59] that randomized 3009 AF and AFL patients across 55 study arms remained eligible. Eighteen treatments were available for comparison, and amiodarone IV (11 trials), propafenone PO (4 trials), and propafenone IV (4 trials) were the most frequently investigated drugs.

Description of included studies

There was variation among the trials, particularly in exclusion criteria, proportion of male subjects (43.0%[42] to 72.6%[55]), and available data points (4[39,48,56,58] to 24 h[38,40,42,43,45–47,49–53,55,57,59]). Among the treatment arms, there was variation in mean age (54.9[44] to 70[57] years) and left atrial diameter (32.9[38] to 49.0 mm[52]). Drug regimens differed particularly for amiodarone IV, propafenone, and flecainide, but those for ibutilide and vernakalant were consistent. Two trials[39,45] performed short-term follow-up (28[45] and 30 days[39]). Four studies[45,47,48,58] enrolled a total of 81 patients with recent-onset AFL. The description of included studies is summarized in *Table 1* and

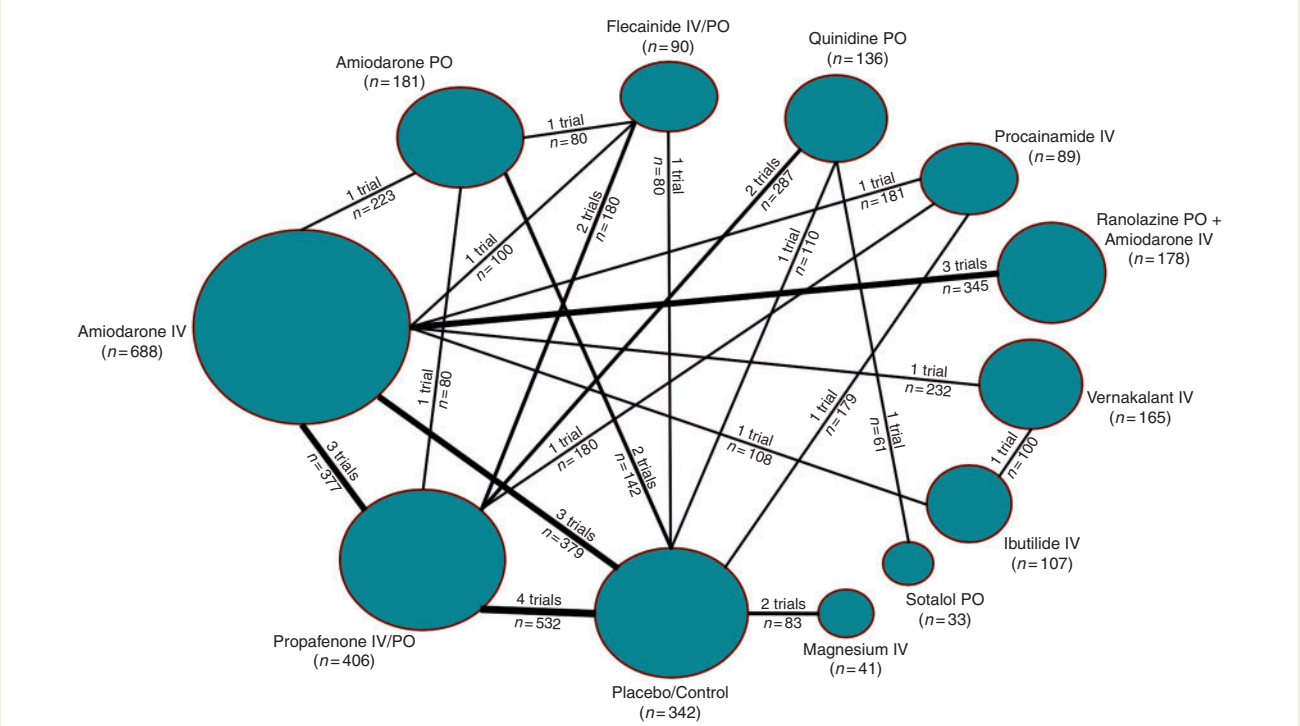

Figure 2 Network configuration of treatments for the outcome of conversion within 24 h (18 trials; $n = 2456$). The area of the circles is based upon the total number of patients for each treatment among all trials. The thickness of the lines is based upon the total number of studies comparing the two treatments. Amiodarone IV and propafenone IV/PO are the most connected nodes (most direct comparisons) with the largest quantity of direct evidence (largest pooled sample sizes), so their treatment effect estimates would be expected to be least subject to bias and most reliable. Sotalol PO and magnesium IV are the least connected nodes with the smallest quantity of direct evidence, so their treatment effect estimates would be expected to be most prone to bias and least reliable. IV, intravenous; PO, oral.

detailed comprehensively in the Supplementary material online, *Table S1*.

Quality assessment

The risk of bias assessments within each of the 23 individual studies at the study level are summarized in the Supplementary material online, *Figure*. We rated 83% to be high risk and 17% to be low risk of bias at the outcome (conversion to sinus rhythm) level.

Quantitative data synthesis

Conversion to sinus rhythm within 24 h

Twenty-one trials[37–44,46,48–59] that randomized 2785 AF patients provided efficacy data for the outcome of AF conversion within 24 h. The AFL patient data were insufficient for a separate NMA of drugs for conversion of AFL within 24 h. We obtained the raw data for Walker *et al.*[58] through contact with the corresponding author and the data from Capucci *et al.*[40] only indirectly through inspection of a prior systematic review.[23] We were unable to separate data for AF and AFL patients in Hohnloser *et al.*[45] and Joseph and Ward.[47] Since our methodology considered the treatment arms in Innes *et al.*[46] to be identical, there were no comparator arms to connect to the network, and Innes *et al.*[46] was excluded from NMA. We merged data for IV and PO preparations of flecainide and propafenone to improve the performance of the models. This may be justified because as a group, the current guidelines[15–17] do not favour one formulation of flecainide or propafenone over the other; therefore, the IV and PO formulations of flecainide and propafenone may be considered clinically interchangeable. Also, from the International Registry on Cardioversion of Atrial Fibrillation (RHYTHM-AF)[60] Crijns *et al.* report similar cardioversion efficacy at 24 h for IV and PO formulations of both flecainide and propafenone. Consequently, as a result of merging IV and PO data for flecainide and propafenone, Alp *et al.*[37] and Madonia *et al.*[53] did not have any comparator arms to connect to the network and were excluded from NMA.

Eighteen trials[38–44,48–52,54–59] that randomized 2456 patients in 12 treatment groups remained for NMA. The evidence network was made up of a limited number of studies that were variable in both connectedness and sample size, and these factors may have limited the strength of the analysis. For example, some comparisons were often two to three connections apart, and these comparisons demonstrated treatment effect estimates with the widest CrIs. The evidence network configuration is presented in *Figure 2*. Seven drug regimens demonstrated with sufficient certainty an association with an increased likelihood of conversion when compared to placebo/control: ranolazine PO plus amiodarone IV, vernakalant IV, flecainide IV/PO, amiodarone PO, ibutilide IV, amiodarone IV, and propafenone IV/PO.

The NMA estimates of all pairwise comparisons are in *Table 2*. There was moderate heterogeneity in the network (0.8, 95% CrI 0.4–1.5), and due to its sparsity, some of its components exhibited inconsistency. The network inconsistency is presented in *Figure 3*. We adjusted for inconsistency at each of the inconsistency nodes and found that the results remained consistent. The risk of bias at the study level across the studies whose data were included in the NMA is illustrated in *Figure 4*.

The results of probabilistic analysis (SUCRA) are listed in *Table 3*, and its underlying rankograms are presented in *Figure 5*. The unweighted, pooled conversion rate within 24 h among placebo and control groups was 51.5%, which may be considered the spontaneous 24-h conversion rate. The complete listing of unweighted, pooled cardioversion rates for this outcome is in *Table 4*. To reiterate, these pooled, cardioversion rates are distinct from the SUCRA probabilities. The complete trial data (raw) for conversion to sinus rhythm are in the Supplementary material online, *Table S2*.

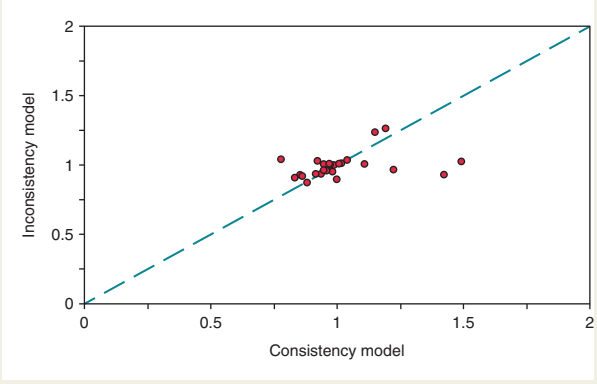

Figure 3 Network Inconsistency between direct and indirect estimates for the outcome of conversion within 24 h. This is a plot of the individual data points' posterior mean deviance contributions for the consistency model (horizontal axis) and the unrelated mean effects model (vertical axis) along with the line of equality. The more the contributions to the deviance are similar and close to 1 for both models, the less evidence of inconsistency there is in the network.

Qualitative analysis

Time to cardioversion

Seventeen trials[37,39,40,43,44,46,48–52,54–59] that randomized 2154 AF patients and monitored patients for a maximum of 24 h reported unweighted mean or median times to AF cardioversion. We were unable to obtain separate time to cardioversion data for AF and AFL patients in Hohnloser *et al.*[45] and Joseph and Ward.[47] The complete listing of unweighted ranges of time or mean/median times to cardioversion are in *Table 4*. The complete trial data for mean or median time to cardioversion are in the Supplementary material online, *Table S3*.

Rate of significant adverse events

All 23 trials[37–59] that randomized 3009 AF and AFL patients provided data for significant adverse event rate. We were unable to obtain specific data for hypotension from Xanthos *et al.*[59] or specific data for hypotension and bradycardia from Halinen *et al.*[44] The selected studies varied widely in definition and thoroughness of reported safety outcomes, and significant adverse events were rare precluding NMA for this outcome. There was large variation in the intervals over which adverse events were collected and reported with periods ranging from four[39,48,56,58] to 48 h[47] following drug administration. The unweighted, pooled significant adverse event rates for all agents are listed in *Table 5*. The complete trial data (raw) for significant adverse event rate are in the Supplementary material online, *Table S3*. Three studies[39,42,52] provided limited data from patients with systolic dysfunction. There were no adverse events associated with amiodarone IV ($n = 22$), ranolazine PO plus IV amiodarone IV ($n = 15$), and vernakalant IV ($n = 12$).

Rate of thromboembolism within 30 days

The two trials[39,45] that performed short-term follow-up reported no thrombo-embolic events.

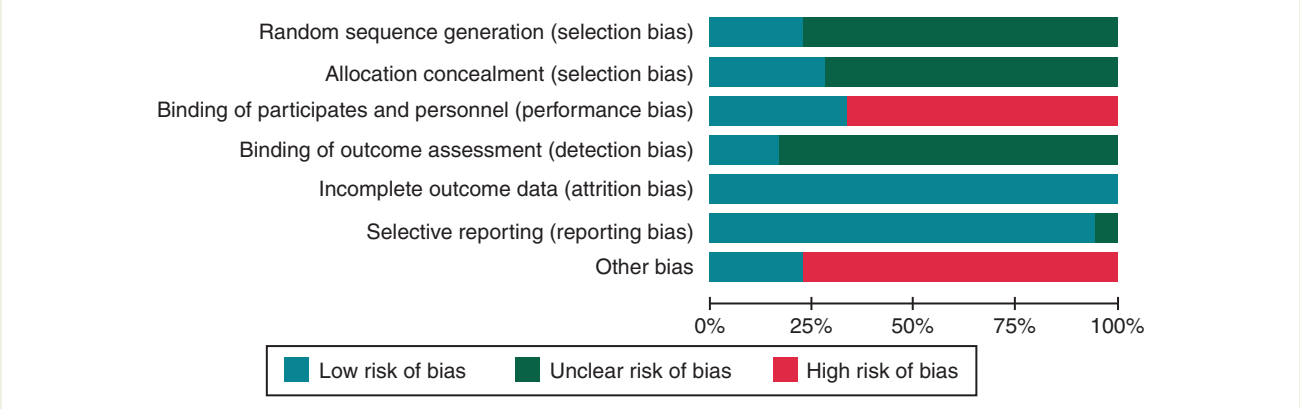

Figure 4 Summary of the risk of bias assessments across the studies in the network meta-analysis (study level).

Table 2 Network meta-analysis estimates of pairwise comparisons for the outcome of conversion within 24 h

Ranolazine PO + Amiodarone IV														
1.74 (0.24–13.31)	Vernakalant IV													
2.36 (0.35–16.17)	1.36 (0.16–11.25)	Flecainide IV/PO												
3.92 (0.65–23.21)	2.26 (0.29–16.45)	1.66 (0.32–8.34)	Amiodarone PO											
5.04 (0.67–39.79)	2.90 (0.58–14.56)	2.14 (0.25–18.85)	1.29 (0.17–10.25)	Ibutilide IV										
7.34 (2.14–26.39)	4.23 (0.88–20.15)	3.11 (0.75–13.32)	1.88 (0.54–6.80)	1.46 (0.29–7.31)	Amiodarone IV									
9.68 (1.94–49.24)	5.58 (0.86–35.37)	**4.10 (1.03–16.54)**	2.47 (0.67–9.36)	1.92 (0.29–12.68)	1.32 (0.48–3.57)	Propafenone IV/PO								
10.95 (1.38–89.76)	6.30 (0.64–61.50)	4.64 (0.67–32.39)	2.80 (0.44–18.14)	2.17 (0.21–21.92)	1.49 (0.28–7.89)	1.13 (0.27–4.72)	Quinidine PO							
24.47 (3.05–205.89)	**14.04 (1.43–142.59)**	**10.36 (1.37–81.17)**	6.25 (0.92–44.92)	4.85 (0.48–50.03)	3.33 (0.63–18.12)	2.53 (0.49–13.55)	2.24 (0.27–19.21)	Procainamide IV						
27.16 (2.97–268.20)	**15.61 (1.42–181.88)**	**11.51 (1.40–100.93)**	6.94 (0.98–53.71)	5.38 (0.46–64.95)	3.69 (0.59–24.24)	2.81 (0.46–18.08)	2.48 (0.28–23.30)	1.11 (0.12–11.26)	Magnesium IV					
39.83 (8.34–203.10)	**22.92 (3.67–146.30)**	**16.86 (4.12–73.31)**	**10.17 (3.08–35.96)**	**7.91 (1.22–52.52)**	**5.41 (2.08–14.57)**	**4.11 (1.67–10.53)**	3.64 (0.79–17.37)	1.63 (0.31–8.57)	1.47 (0.30–7.09)	Placebo/ Control				
68.35 (3.38–1466.71)	**39.20 (1.67–948.77)**	**28.87 (1.56–568.18)**	**17.39 (1.01–324.78)**	13.57 (0.57–336.40)	9.27 (0.60–150.76)	7.03 (0.53–100.80)	6.19 (0.71–59.35)	2.79 (0.13–60.54)	2.52 (0.11–56.40)	1.71 (0.12–25.61)	Sotalol PO			

Treatment effect estimate is derived from direct and indirect comparisons and presented as odds ratio (95% CrI); odds ratio in bold represents an association with increased likelihood of conversion within 24 h. A CrI that crosses 1.0 (the null effect) signifies uncertainty in the treatment effect estimate.
IV, intravenous; PO, oral.

Discussion

Through systematic review and NMA, we identified seven antidysrhythmic agents or regimens that may be effective for conversion of recent-onset AF within 24 h. Of the seven treatments, amiodarone IV and propafenone had the most direct comparisons and strongest direct evidence within the network, so there is relatively more confidence about their efficacy. There is less certainty about the true efficacy of ranolazine plus amiodarone IV, vernakalant, flecainide, amiodarone PO, and ibutilide. Probabilistic analysis identified ranolazine with amiodarone IV as the most likely superior drug regimen; however, ranolazine with amiodarone IV is not yet approved for AF cardioversion. Vernakalant and flecainide are available agents that also ranked high and may be relatively more effective than the other drugs. The treatment effect difference between these agents was small and potentially not clinically meaningful, so factors other than efficacy such as adverse effects, cost, and patient preferences, may be more important in drug selection. In contrast, propafenone and amiodarone IV were both ranked low and may, therefore, be relatively less effective.

Among the studies identified in our review, we found a spontaneous 24-h conversion rate of 51.5%. When measured against pharmacologic cardioversion rates, the spontaneous conversion rate may mitigate the absolute benefit of antidysrhythmic therapy. Clinicians may decide to manage recent-onset AF patients, particularly those with higher risk (i.e. older age, diabetes, systolic dysfunction, initial AF episode),[20,61,62] in an observation unit for symptom/rate control, diagnosis, and treatment of potential underlying AF aetiology, consideration of stroke prophylaxis, and transitioning to outpatient care.[21] Within an observation unit stay, those patients with a sufficient remaining time window for early cardioversion may also be monitored for spontaneous conversion or undergo transoesophageal echocardiography to exclude left atrial thrombus prior to cardioversion.[15–17] Clinicians will need to weigh the likelihood of spontaneous conversion against the risk of missing the 48-h cardioversion window and subsequent commitment to several weeks of anticoagulation, either following early transoesophageal echocardiography-guided cardioversion[16,17] or peri-procedurally prior to cardioversion at a later date.[15–17]

Our NMA results are somewhat consistent with current guideline recommendations for cardioversion of recent-onset AF. Only two[39,56] of the 12 studies that are cited in the ESC guidelines[15] met our inclusion criteria. None of the seven references in the AHA guidelines[16] or 11 references in the CCS guidelines[17] met our criteria. Furthermore, the ESC[15] and AHA guidelines[16] refer to meta-analyses[24,26,63] that included patients with AF duration longer than 48 h. Therefore, the current guidelines[15–17] for cardioversion of recent-onset AF are largely based upon trials and meta-analyses whose results may not be applicable to patients with recent-onset AF, where 'recent-onset' is clinically defined by those same guidelines as AF with duration shorter than 48 h.

Our NMA findings support the guideline recommendations of flecainide[15–17] and vernakalant.[15,17] Our results also support the recommendations of ibutilide,[15–17] amiodarone (IV[15,17] and PO[16]), and propafenone[15–17] but as second-line options. We found limited RCT safety data for amiodarone IV or any other antidysrhythmic agent in patients with systolic dysfunction. Notwithstanding, amiodarone IV

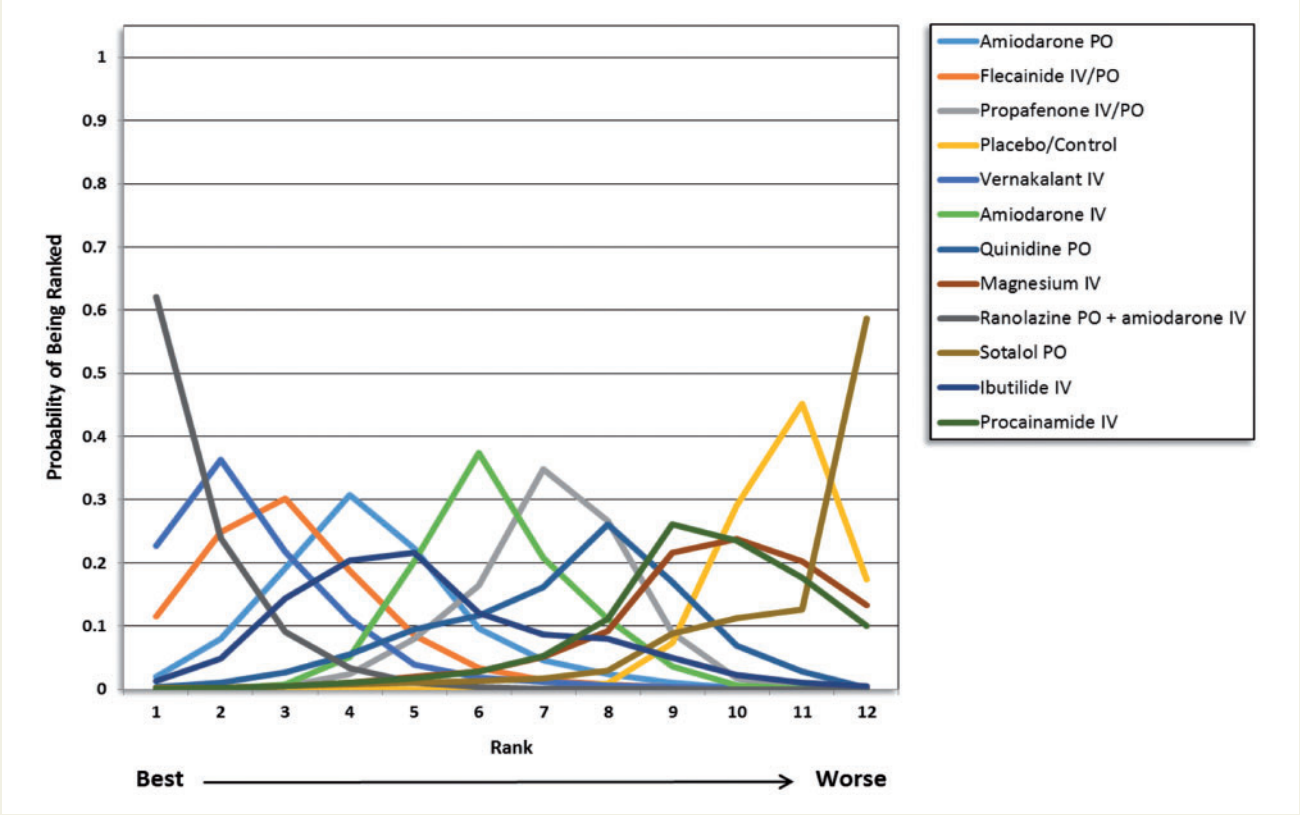

Figure 5 Cumulative rankograms of treatments for the outcome of conversion within 24 h. A cumulative rankogram presents on the vertical axis the probability for the treatment to assume each of the possible ranks that are presented on the horizontal axis. The surface under the cumulative ranking curve (SUCRA) is between 0 and 1 and can be re-expressed as a percentage. For example, vernakalant IV has 36% probability of being #2 and amiodarone IV has 37% probability of being ranked #6. IV, intravenous; PO, oral.

remains the recommended, primary agent for AF cardioversion in this subpopulation.[15,17] In contradiction to guidlelines,[16,17] we did not find sufficient RCT evidence to recommend procainamide[17] or any evidence to support dofetilide.[16] Finally, among published cardioversion protocols,[20,21] our NMA results support Baugh *et al.*'s emergency department/observation unit pathway[21] that uses ibutilide or flecainide and Stiell *et al.*'s Best Practices checklist[20] where it discourages the use of amiodarone IV. However, our NMA found that the efficacy of procainamide is uncertain and therefore, does not definitively agree with Stiell *et al.*'s recommendation[20] of procainamide.

Our systematic review and NMA was not without limitations. We included only RCTs so as to analyse data from studies of the highest quality possible, therefore we cannot comment on the conclusions from non-randomized studies that may contradict our findings. We excluded all studies in languages other than English, which may result in language bias, however, language restriction in systematic reviews and meta-analyses in medicine has not been shown to result in bias.[64] Data were unavailable from two trials,[45,47] because we could not contact the investigators. We combined data for IV and PO flecainide and propafenone and therefore cannot make distinct recommendations regarding cardioversion efficacy for IV and PO formulations of those agents. However, Alp *et al.*[37] directly compared the two formulations of flecainide and reported similar cardioversion rates at 8

Table 3 Probabilistic analysis (SUCRA) for the outcome of conversion within 24 h

Rank	Treatment	SUCRA
1	Ranolazine PO + Amiodarone IV	0.946
2	Vernakalant IV	0.860
3	Flecainide IV/PO	0.809
4	Amiodarone PO	0.699
5	Ibutilide IV	0.614
6	Amiodarone IV	0.524
7	Propafenone IV/PO	0.447
8	Quinidine PO	0.429
9	Procainamide IV	0.234
10	Magnesium IV	0.220
11	Placebo/Control	0.118
12	Sotalol PO	0.102

IV, intravenous; PO, oral; SUCRA, surface under the cumulative ranking curve. The SUCRA is a numeric presentation of the overall ranking based upon the probability that a treatment is most effective for the outcome of interest. The SUCRA rank of an intervention is estimated by calculating the total ranking probabilities of that intervention.

Table 4 Unweighted, pooled cardioversion rates and times to cardioversion

Treatment	Pooled cardioversion rate				Time to cardioversion[a]	
	Trials	Events	N	Rate (95% CI) (%)	Trials	Mean/median/range (h)
Ranolazine PO + Amiodarone IV	3	165	178	92.7 (87.8–95.8)	3	8.6–10.2
Amiodarone PO	3	155	181	85.6 (79.7–90.1)	2	7.9–20.0
Quinidine PO	4	151	177	85.3 (79.3–89.8)	4	3.1–6.1
Propafenone IV/PO	7	424	503	84.3 (80.9–87.2)	5	IV: 0.5–8.0/PO: 2.8–5.0
Flecainide IV/PO	3	138	169	81.7 (75.1–86.8)	2	IV: 0.4–0.9/PO: 1.8
Procainamide IV	1	61	89	68.5 (58.3–77.3)	1	9.0
Amiodarone IV	10	461	688	67.0 (63.4–70.4)	8	5.6–19.4
Ibutilide IV	2	68	107	63.6 (54.1–72.1)	2	0.4–0.9
Vernakalant IV	2	99	165	60.0 (52.4–67.2)	2	0.2
Sotalol PO	1	17	33	51.6 (35.2–68.0)	1	10.2
Placebo/Control	8	176	342	51.5 (46.2–56.7)	5	2.5–17.0
Magnesium IV	2	17	41	41.5 (27.7–56.7)	1	1.5

CI, confidence interval; IV, intravenous; PO, oral.
[a]During minimum of 4 h and maximum of 24 h observation.

Table 5 Unweighted, pooled significant adverse event rates

Treatment	Trials	N	Adverse events (%)				
			VD	AFL 1:1	HypoTN	Brady	Total
Ibutilide IV[a]	2	130	20 (15.4)	0	0	0	20 (15.4)
Ranolazine PO + Amiodarone IV	3	178	0	0	27 (15.2)	0	27 (15.2)
Sotalol PO	1	33	4 (12.1)	0	U	U	4 (12.1)
Tedisamil IV[b]	1	114	2 (1.8)	0	0	9 (7.9)	11 (9.7)
Procainamide IV	1	89	0	0	6 (6.7)	0	6 (6.7)
Quinidine PO	4	177	9 (5.1)	0	2 (1.1)	0	11 (6.2)
Amiodarone IV[c]	11	748	2 (0.3)	0	38 (5.1)	6 (0.8)	46 (6.1)
Sotalol IV	1	40	0	0	2 (5)	0	2 (5)
Propafenone PO	4	267	5 (1.9)	0	7 (2.6)	1 (0.4)	13 (4.9)
Flecainide IV	2	89	1 (1.1)	1 (1.1)	1 (1.1)	0	3 (3.4)
Placebo/Control	10	438	1 (0.2)	0	1 (0.2)	8 (1.8)	10 (2.3)
Propafenone IV	4	236	0	0	2 (0.8)	0	2 (0.8)
Vernakalant IV[d]	2	165	1 (0.6)	0	0	0	1 (0.6)
Amiodarone PO	3	181	0	0	1 (0.6)	0	1 (0.6)
Magnesium IV	2	44	0	0	0	0	0
Flecainide PO	2	80	0	0	0	0	0

There were no reported thrombo-embolic events associated with amiodarone IV, vernakalant IV, and tedisamil IV among the two trials[39,45] that performed short-term follow-up.
AFL 1:1, atrial flutter with 1:1 atrioventricular conduction; Brady, bradycardia; HypoTN, hypotension; IV, intravenous; PO, oral; U, unable to obtain; VD, ventricular dysrhythmia.
[a]Three torsades de pointes.
[b]One torsades de pointes and one ventricular tachycardia.
[c]One additional event of asystole.
[d]One ventricular tachycardia.

h, and Madonia *et al.*[53] directly compared the two formulations of propafenone and reported similar efficacy at 24 h. Furthermore, Crijns *et al.*[60] describe similar effectiveness for flecainide IV and PO at 16 h and propafenone IV and PO at 24 h. Therefore, our results for flecainide and propafenone may be considered representative of the effectiveness of IV and PO formulations of each drug independently.

The trials selected from our systematic review differed in their definitions of adverse events and safety endpoints and had almost exclusively short observation periods (24 h or shorter) without follow-up. Therefore, we cannot comment on longer-term cardioversion efficacy or adverse event rates.

The evidence network was made up of a limited number of studies, and pooled sample sizes varied greatly. Imbalance in the amount of evidence for each treatment group may have affected the power and reliability of the overall analysis.[65,66] Across the studies in the NMA, the risk of bias was mainly unclear in patient selection and high with regard to predetermination and adequacy of sample size. Overall, the study quality was low. The NMA results include treatment effect estimates that vary in precision, therefore, there may be more certainty about the cardioversion efficacy of some agents and less certainty about others. The network inconsistency may be explained by factors beyond the outlier treatment arms. Conceptual heterogeneity in potential effect modifiers (such as AF duration, left atrial size, drug dosing regimen, timing of rhythm assessment) and our merging of IV and PO treatment arms for flecainide[38,54] and propafenone[38,40,49–51,54] likely contributed to network inconsistency and may impact the generalizability of results. Study sample sizes were too small to control for significant effect modifiers; however, if additional evidence becomes available in the future, one could potentially conduct covariate-adjusted analysis to account for some heterogeneity. The scarce evidence base precluded a sensitivity analysis that excluded comparisons for which there is inconsistency. We explored the impact of inconsistency and found that it did not vary our conclusions. The use of data points across several hours may have contributed to indirectness and intransitivity within the network. Seven[39,41,44,48,54,56,58] of the 18 studies provided data for NMA only from time points earlier than 24 h after drug initiation. Cardioversion rates may vary with duration of rhythm monitoring. Therefore, our analysis of data points earlier than 24 h may have diminished the treatment effect estimates, particularly for amiodarone,[39,48] and to a lesser extent, flecainide[54] and propafenone,[54] all of which have demonstrated a relatively more durable or delayed antidysrhythmic effect.[60] However, the spontaneous conversion rate will also increase over time, and our analysis of data points earlier than 24 h from placebo/control groups[41,58] may have inflated the treatment effect estimates of drugs in comparison to placebo/control. Consequently, as a result of limitations in body of studies, bias, imprecision, inconsistency, and indirectness, the probabilistic analysis warrants low confidence. Lastly, whether or not early cardioversion of recent-onset AF improves long-term cardiovascular outcomes remains to be seen. Early cardioversion may serve as a bridge to continued rhythm control with maintenance antidysrhythmic drug therapy or left atrial ablation, treatment strategies that are being investigated in the ongoing Early Aggressive Invasive Intervention for Atrial Fibrillation (EARLY-AF) trial.[67] 'Implications for Future Research' is Supplementary material online, *Appendix S5*.

Conclusion

There is insufficient high-level evidence to determine which treatment is superior for pharmacologic cardioversion of recent-onset AF within 24 h. Vernakalant and flecainide may be relatively more efficacious agents. In comparison, propafenone and amiodarone IV may be relatively less efficacious. Our evidence network was limited, and its analysis should be considered primarily hypothesis-generating. Further high-quality, placebo-controlled, and head-to-head studies are necessary in order to make definitive recommendations for the pharmacologic cardioversion of recent-onset AF.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: none declared.

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Implantation of leadless pacemaker through neo-orifice after tricuspid valve edge-to-edge repair

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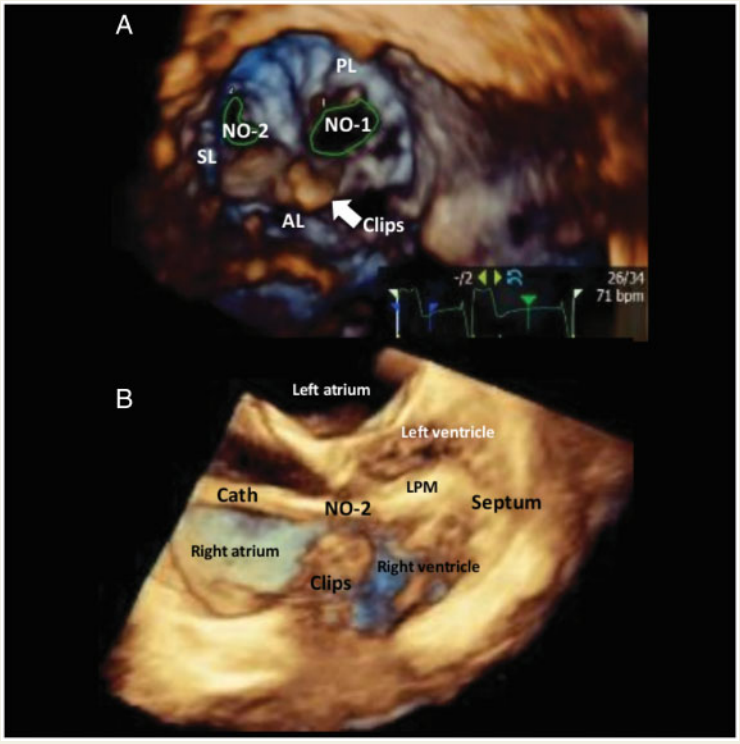

We present a case of a 71-year-old female with dilated cardiomyopathy, bradycardic permanent atrial fibrillation, and complete right bundle branch block, who underwent leadless pacemaker (LPM) implantation (Micra, Medtronic Inc.) after edge-to-edge tricuspid valve repair for severe functional tricuspid regurgitation with three MitraClips XTR (Abbott Inc.) deployed. A possible worsening of tricuspid regurgitation triggered the decision to reject a conventional ventricular lead implantation. Leadless pacemaker implantation was guided using three-dimensional transoesophageal echocardiography (3D TOE) in order not to damage the repaired valve with the large delivery catheter (Cath) (*Panel A*). Two tricuspid valve neo-orifices (NOs) formed after clip implantation were visualized for adequate steering of the delivery catheter. Initially, the delivery catheter was introduced through the larger NO-1 [1.6 cm^2, between posterior and anterior (AL) leaflets]. However, limited steering led to unsuitable LPM positions with high threshold values. Under strict 3D TOE guidance, the delivery catheter was then withdrawn and reintroduced through the smaller NO-2 (0.6 cm^2, between septal leaflet and AL), which led to optimal septal-apical LPM positioning with acceptable threshold value of 0.25 V/0.24 ms (*Panel B*). Severity of pre-existing moderate residual tricuspid regurgitation remained unchanged.

Leadless pacemaker implantation after edge-to-edge tricuspid valve repair is feasible but can be challenging in terms of limited steering of the delivery catheter; however, 3D TOE guidance helps with safe and effective steering through tricuspid valve NOs.

The full-length version of this report can be viewed at: https://www.escardio.org/Education/E-Learning/Clinical-cases/Electrophysiology.