Pharmacologic Cardioversion of Recent-Onset Atrial Fibrillation and Flutter in the Emergency Department: A Systematic Review and Network Meta-analysis

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Study objective: We conduct a systematic review and Bayesian network meta-analysis to indirectly compare and rank antidysrhythmic drugs for pharmacologic cardioversion of recent-onset atrial fibrillation and atrial flutter in the emergency department (ED).

Methods: 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 We also searched for unpublished data.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 recent-onset atrial fibrillation or atrial flutter and compared antidysrhythmic agents, placebo, or control. We determined these outcomes before data extraction: rate of conversion to sinus rhythm within 4 hours, time to cardioversion, rate of significant adverse events, and rate of thromboembolism within 30 days. We extracted data according to Preferred Reporting Items for Systematic Reviews and Meta-analyses network meta-analysis and appraised selected trials with the Cochrane review handbook.

Results: The systematic review initially identified 640 studies; 19 met inclusion criteria. Eighteen trials that randomized 2,069 atrial fibrillation patients provided data for atrial fibrillation conversion rate outcome. Bayesian network meta-analysis using a random-effects model demonstrated that antazoline (odds ratio [OR] 24.9; 95% credible interval [CrI] 7.4 to 107.8), tedisamil (OR 12.0; 95% CrI 4.3 to 43.8), vernakalant (OR 7.5; 95% CrI 3.1 to 18.6), propafenone (OR 6.8; 95% CrI 3.6 to 13.8), flecainide (OR 6.1; 95% CrI 2.9 to 13.2), and ibutilide (OR 4.1; 95% CrI 1.8 to 9.6) were associated with increased likelihood of conversion within 4 hours compared with placebo or control. Overall quality was low, and the network exhibited inconsistency.

Conclusion: For pharmacologic cardioversion of recent-onset atrial fibrillation within a 4-hour ED visit, there is insufficient evidence to determine which treatment is superior. Several agents are associated with increased likelihood of conversion within 4 hours compared with placebo or control. Limited data preclude any recommendation for cardioversion of recent-onset atrial flutter. Further high-quality study is necessary. [Ann Emerg Med. 2020;76:14-30.]

Please see page 15 for the Editor's Capsule Summary of this article.

A **podcast** for this article is available at www.annemergmed.com.

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INTRODUCTION

Background

Atrial fibrillation 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 atrial fibrillation afflicts 1% to 2% of the adult population in the United States.[3] It has been estimated that as the population ages, the incidence and prevalence of atrial fibrillation in the United States will double by 2030.[1,2] Patients with atrial fibrillation have twice the risk of death and are twice as likely to be hospitalized than those without it.[1] Hospital admissions make up the greatest proportion of the annual health care cost of atrial fibrillation,[4] which is estimated to be $26 billion.[1,5] Emergency department (ED) cardioversion of recent-onset atrial fibrillation has been independently shown to significantly reduce hospitalizations[6] and costs.[7] Although the Rate Control Versus Electrical Cardioversion Trial 7–Acute Cardioversion Versus Wait and See (RACE7-ACWAS) trial[8] has determined that a "wait-and-see approach" may be noninferior to immediate

Editor's Capsule Summary

What is already known on this topic

Multiple trials have evaluated the effectiveness of pharmacologic agents for cardioversion of recent-onset atrial fibrillation or flutter in the emergency department. Network meta-analysis can provide indirect comparisons between agents even when direct comparisons have not been undertaken.

What question this study addressed

Which drug is most effective for pharmacologic cardioversion within 4 hours of recent-onset atrial fibrillation or flutter?

What this study adds to our knowledge

Six agents were associated with conversion within 4 hours compared with placebo or control, but limitations of the available data meant that network meta-analysis could not reliably identify the most effective agent or agents.

How this is relevant to clinical practice

There is insufficient evidence to guide practice. Further research is required, perhaps involving a multistage multiarm design to allow robust comparison of multiple agents.

cardioversion for the short term, pharmacologic cardioversion may be less effective (data not shown), and thromboembolic risk may be greater with a delayed approach.[9,10]

Atrial flutter is a supraventricular tachydysrhythmia that is less prevalent than atrial fibrillation,[11] and although the 2 have different underlying mechanisms, atrial flutter often transitions to and from atrial fibrillation.[12,13] Early cardioversion of atrial fibrillation or atrial flutter with duration shorter than 48 hours (recent-onset atrial fibrillation/atrial flutter) is supported by the American Heart Association (AHA),[14] European Society of Cardiology,[15] and the Canadian Cardiovascular Society.[16] Pharmacologic cardioversion is established within ED protocols[17-19] as an alternative to electrocardioversion that avoids the risks of sedation. However, its success rates are relatively lower[20,21] and may vary with respect to antidysrhythmic agent.

Importance

Considering the risks and benefits, ideally, within a shared decisionmaking paradigm,[22,23] clinicians and patients may decide to attempt pharmacologic cardioversion of recent-onset atrial fibrillation or atrial flutter within an ED visit. Current guidelines[14-16] do not uniformly agree on the recommendation of antidysrhythmic agents for atrial fibrillation or atrial flutter cardioversion, and drug preference in clinical practice also varies internationally.[24,25] Previous systematic reviews and meta-analyses[26-33] are limited by heterogeneous samples that included patients with variable atrial fibrillation duration exceeding 48 hours, a duration for which early cardioversion without previous anticoagulation is contrary to current guidelines; and by insufficient head-to-head drug comparisons.

Goals of This Investigation

We performed a systematic review and network meta-analysis to indirectly compare and rank antidysrhythmic agents tested in adults with recent-onset atrial fibrillation or atrial flutter to identify which is most effective for pharmacologic cardioversion in the ED.

MATERIALS AND METHODS

Study Design

We performed our systematic review and network meta-analysis of randomized controlled trials according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[34] (The completed PRISMA-network meta-analysis checklist is shown in Appendix E1, available online at http://www.annemergmed.com.) In contrast to primary studies and conventional meta-analyses that examine only a few interventions through direct head-to-head (pairwise) comparison, network meta-analysis 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, 4 investigators (I.S.d., T.S., R.B., 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 previous pertinent systematic and narrative reviews for additional studies that were not found in our database search. We searched for unpublished data from 2013 to 2018 at opengrey.eu, ntis.gov, and ClinicalTrials.gov and manually reviewed the abstracts of

major emergency medicine and cardiovascular medicine conferences. Last, we contacted experts in the field to help us identify any currently ongoing or unpublished studies that our search may have overlooked. Further search strategy details are shown in Appendix E1, available online at http://www.annemergmed.com.

Study Selection

Four authors (I.S.d., T.S., R.B., and G.C.) independently reviewed abstracts from the combined MEDLINE, EMBASE, and Web of Science search and selected articles for full-text review according to prespecified inclusion and exclusion criteria. The same authors then independently reviewed the full texts. We limited studies to randomized controlled trials and used a patients-intervention-comparison-outcomes format to determine the eligibility of studies for inclusion:

- Patients: Adult patients (≥18 years) with recent-onset atrial fibrillation or atrial flutter, defined in the study as an atrial fibrillation or atrial flutter episode whose onset was within 48 hours before enrollment
- Intervention: One of the predetermined antidysrhythmic drugs, including procainamide, amiodarone, flecainide, propafenone, sotalol, dofetilide, dronedarone, ibutilide, vernakalant, and magnesium
- Comparison: Another antidysrhythmic agent, a different formulation of the same agent, placebo, or control. Digoxin[15,28,31,35] and verapamil[31,32] are not known to convert atrial fibrillation or atrial flutter to sinus rhythm and were therefore considered nonantidysrhythmic controls.
- Outcomes: (1) Rate of conversion to sinus rhythm within 4 hours, a time frame suitable for cardioversion within an ED visit (quantitative); (2) time to cardioversion to sinus rhythm; (3) rate of significant adverse events as reported by the individual trials: cardiac arrest, ventricular dysrhythmia, atrial flutter with 1:1 atrioventricular conduction, hypotension, and bradycardia; and (4) rate of thromboembolism within 30 days

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

Quality Assessment

Four authors (I.S.d., T.S., R.B., and G.C.) independently assessed the risk of bias (study level) within all included studies according to the Cochrane review handbook.[36] The Risk of Bias Tool covers 6 domains of bias: selection, performance, detection, attrition, reporting, and "other." The method of individual study quality assessment is shown in Appendix E1, available online at http://www.annemergmed.com. 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 particular 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 4 hours, we extracted data from rhythm assessment at 4 hours after drug administration. If assessment was reported only before 4 hours, we extracted data from the time closest to 4 hours. In trials that included crossover to the other treatment arm, we extracted only precrossover data. We separated data from atrial fibrillation and atrial flutter patients except for the outcome of adverse event rate. When hypotension and bradycardia occurred simultaneously, we recorded the event as hypotension. When data were unavailable or unclear, we attempted to contact the corresponding authors through e-mail and inspected previous systematic reviews for the trial data of interest. Any issues with data extraction were discussed and resolved by consensus.

Primary Data Analysis

We performed conventional pairwise meta-analyses for the outcome of conversion to sinus rhythm, provided that at least 2 studies were available, to assess the between-study heterogeneity for direct comparisons. 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 network meta-analysis using a Markov chain Monte Carlo method with an unconstrained, random-effects model. The analysis involved 10,000 burn-in iterations and 100,000 simulations using a noninformative prior. We report pairwise comparisons with a league table, with each pairwise comparison reported as an odds ratio with 95% credible interval. A credible interval is one in which a parameter (unobserved) has a given probability. For a 95% credible interval, the value of interest (ie, treatment effect size) lies within the interval with a 95% probability.

We also performed probabilistic analysis and report the results with a surface under the cumulative ranking curve, a numeric presentation of the overall ranking based on the probability that a treatment was most effective for the outcome of interest. For example, a 75% probability of a

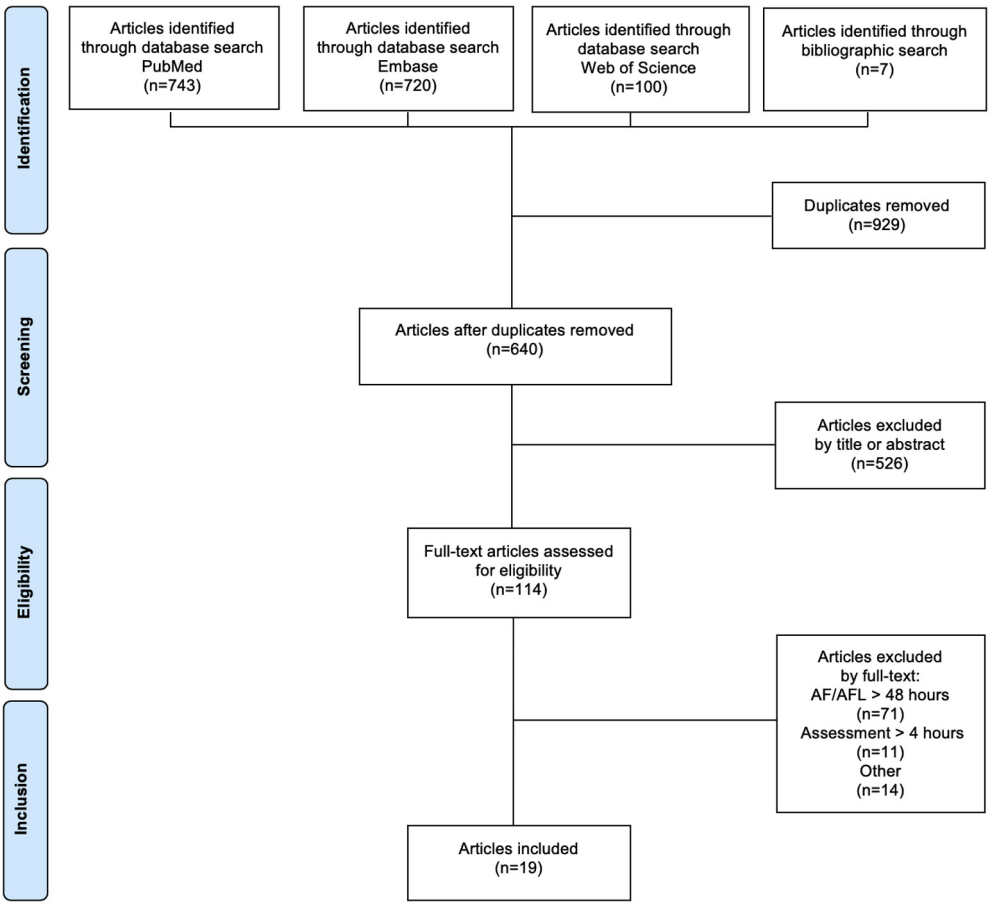

Figure 1. Study selection process.

drug's being ranked first represents a 75% chance that that drug is the superior treatment. In our network meta-analysis, this is the probability that one treatment is most effective for cardioversion to sinus rhythm within 4 hours. The surface under the cumulative ranking curve 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 low, unweighted, pooled cardioversion rate. We also present the cumulative rankograms that underlie the surface under the cumulative ranking curve. Further explanation of network meta-analysis concepts is shown in Appendix E1, available online at http://www.annemergmed.com.

We attempted to analyze all treatment arms, including those from trials with multiple arms. In cases in which the model would not converge because of insufficient data, we either merged those arms with intravenous and oral formulations of the same drug or excluded the node entirely. To increase the feasibility of the network meta-analysis and strengthen the evidence network, we analyzed data from all studies that reported rhythm assessment at 4 hours after drug administration or earlier. We assessed the posterior mean deviance to assess network 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. This did not greatly vary the results, and thus we report only the random-effects model results. The statistical analysis was completed with NetMetaXL (version 1.6.1; CADTH, Ottawa, Canada)[37] and WinBUGS (version 1.4.3; MRC Biostatistics Unit, Cambridge, UK).[38]

RESULTS

Selection of the Included Studies

The study selection process is presented in Figure 1. Nineteen studies[39-57] met inclusion criteria and randomized 2,153 patients across 44 treatment arms. Sixteen treatments were available for comparison, and intravenous amiodarone (5 trials), intravenous flecainide (4 trials), and intravenous ibutilide (4 trials) were the most frequently investigated drugs.

Table 1. Description of included randomized controlled trials.

Trial	Patient Characteristics*	Setting	Investigated Treatments	Rhythm Monitoring/Time of Analysis	Extracted Outcomes
Alp et al[39] 2000	AF <48 h Sample size: 79 Mean age (y): 64.3 Sex: 58% men Heart failure: NR LA diameter: NR	CCU	Flecainide 2 mg/kg IV (maximum 150 mg) Flecainide 4 mg/kg PO (maximum 300 mg)	Continuous 2 h, 8 h	Conversion within 4 h Adverse events
Balla et al[40] 2011	AF <48 h Sample size: 160 Mean age (y): 58.1 (SD 10.3) Sex: 63.1% men Heart failure: NR LA diameter (mm): 42.3 (SD 4.3) (arm 1) 36.1 (SD 3.2) (arm 2) 34.4 (SD 5.3) (arm 3) 32.9 (SD 6.3) (arm 4)	CCU	Amiodarone 30 mg/kg PO Flecainide 3 mg/kg PO Propafenone 8.5 mg/kg PO Placebo	Continuous+serial 3 h, 6 h, 12 h, 24 h	Conversion within 4 h Adverse events
Camm et al[41] 2011	AF 3–48 h Sample size: 232 Mean age (y): 62.7 (SD 11.2) Sex: 63% men Heart failure: 19.8% LA diameter (mm): 40.8 (SD 6.4)	NR	Vernakalant 3 mg/kg IV×10 min; then 2 mg/kg×10 min after 15 min prn Amiodarone 5 mg/kg IV×1 h, then 50 mg IV×1 h	Continuous 1.5 h, 4 h	Conversion within 4 h Median time to conversion (vernakalant only) Adverse events Short-term follow-up
Capucci et al[42] 1999	AF <48 h Sample size: 246 Mean age (y): 58.9 Sex: 51% men Heart failure: NR LA diameter (mm): 39.1 (SD 6.9) (arm 1) 39.6 (SD 5.0) (arm 2) 38.3 (SD 5.8) (arm 3) 38.9 (SD 6.0) (arm 4)	NR	Digoxin IV+quinidine 275 mg PO q2 h×4 Propafenone 450 mg (<60 kg) or 600 mg (>60 kg) PO; then 300 mg PO after 6 h prn Digoxin IV+propafenone 450 mg (<60 kg) or 600 mg (>60 kg) PO; then 300 mg PO after 6 h prn Placebo	Continuous 3 h, 6 h, 12 h, 24 h	Conversion within 4 h Adverse events
Chu et al[43] 2009	AF <48 h Sample size: 44 Mean age (y): 46.9 (SD 14.9) (arm 1) 58.4 (SD 17.7) (arm 2) Sex: 75% men Heart failure: 0% LA diameter: NR	ED	Magnesium 2.5 g IV Placebo	Serial 2 h	Conversion within 4 h Adverse events
Halinen et al[44] 1995	AF <48 h Sample size: 61 Mean age (y): 54.9 (SD 12.7) (arm 1) 53.2 (SD 15.3) (arm 2) Sex: 65.6% men Heart failure: NR LA diameter: NR	ED	Digoxin IV prn+quinidine 200 mg PO q2 h×3 Sotalol 80 mg PO, then 80 mg PO after 2 h; then 80 mg PO q4 h×2 prn	Continuous 3 h, 8 h, 12 h	Conversion within 4 h Adverse events

Table 1. Continued.

Trial	Patient Characteristics*	Setting	Investigated Treatments	Rhythm Monitoring/Time of Analysis	Extracted Outcomes
Hohnloser et al[45] 2004	AF/AFL 3–48 h Sample size: 173 Mean age (y): 63.6 (SD 13.7) Sex: 61.7% men Heart failure (NYHA I–II): 98.3% LA diameter: NR	NR	Tedisamil 0.4 mg/kg IV, then 0.6 mg/kg IV Placebo	Continuous 2.5 h, 24 h	Conversion within 4 h Adverse events Short-term follow-up
Joseph and Ward[46] 2000	AF/AFL <24 h Sample size: 115 Mean age (y): 64.9 (SD 2.0) (arm 1) 61.3 (SD 2.6) (arm 2) 62.8 (SD 2.4) (arm 3) Sex: 53.3% men Heart failure: NR LA diameter (mm): 39.7 (SD 1.1) (arm 1) 38.4 (SD 1.0) (arm 2) 39.5 (SD 1.0) (arm 3)	ED	Amiodarone 5 mg/kg IV×30 min, then 400 mg PO q8 h×6 Sotalol 1.5 mg/kg IV×30 min, then 80 mg PO q8 h×6 Digoxin IV/PO	Continuous 4 h, 24 h, 48 h	Adverse events
Kafkas et al[47] 2007	AF/AFL 3–48 h Sample size: 152 Mean age (y): 62 (SD 16) (arm 1) 64 (SD 18) (arm 2) Sex: 67.8% men Heart failure: NR LA diameter (mm): 43.0 (SD 5.0) (arm 1) 45.0 (SD 6.0) (arm 2)	Inpatient cardiology	Ibutilide 1 mg IV×10 min; then 1 mg IV×10 min after 10 min prn Amiodarone 5 mg/kg IV×30 min, then 1,200 mg IV×24 h	Continuous+serial 4 h	Conversion within 4 h Adverse events
Maciag et al[48] 2017	AF <43 h Sample size: 74 Mean age (y): 68 (SD 12) Sex: 53.3% men Heart failure: NR LA diameter: NR	ED Inpatient medicine	Antazoline 50 mg IV q5 min prn (maximum 250 mg) Placebo	Continuous 1.5 h	Conversion within 4 h Median time to conversion Adverse events
Madonia et al[49] 2000	AF ≤48 h Sample size: 97 Median age (y): 62 (range 22–95) Sex: 46.1% men Heart failure: NR LA diameter: NR	ED	Propafenone 2 mg/kg IV×10 min, then 1 mg/kg IV×2 h; then 300 mg PO q8 h×3 prn Propafenone 600 mg PO, then 300 mg PO after 6 h; then 300 mg PO q8 h×2 prn	IV arm: continuous PO arm: serial 1 h, 3 h, 6 h, 12 h, 24 h	Conversion within 4 h Adverse events
Madrid et al[50] 1993	AF <24 h Sample size: 80 Mean age (y): 55 (SD 14) Sex: 62.5% men Heart failure: NR LA diameter (mm): 38.0 (SD 40.0) (arm 1) 40.0 (SD 15.0) (arm 2)	Inpatient cardiology	Flecainide 1.5 mg/kg IV×15 min, then 1.5 mg/kg IV×1 h Procainamide 1 g IV×30 min, then 2 mg/min IV×1 h	Continuous 1–2 h	Conversion within 4 h Mean time to conversion Adverse events

Table 1. Continued.

Trial	Patient Characteristics*	Setting	Investigated Treatments	Rhythm Monitoring/Time of Analysis	Extracted Outcomes
Martinez-Marcos et al[51] 2000	AF ≤48 h Sample size: 150 Mean age (y): 60 (SD 13) Sex: 46.7% men Heart failure: NR LA diameter (mm): 40.0 (SD 5.0) (arm 1) 40.0 (SD 3.0) (arm 2) 39.0 (SD 5.0) (arm 3)	ED	Amiodarone 5 mg/kg IV×20 min, then 50 mg/h IV Propafenone 2 mg/kg IV×20 min; then 1 mg/kg IV×20 min after 8 h prn 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 4 h Adverse events
Noc et al[52] 1990	AF ≤48 h Sample size: 24 Mean age (y): 71 (SD 9.6) Sex: 62.5% men Heart failure: NR LA diameter: NR	NR	Amiodarone 5 mg/kg IV×3 min Verapamil IV	Continuous 3 h	Conversion within 4 h Adverse events
Reisinger et al[53] 2004	AF 1–48 h Sample size: 207 Mean age (y): 63 (SD 15) (arm 1) 63 (SD 13) (arm 2) Sex: 61.8% men Heart failure: NR LA diameter (mm): 52.0 (SD 8.0) (arm 1) 50.0 (SD 9.0) (arm 2)	NR	Flecainide 2 mg/kg IV×20 min (maximum 200 mg) Ibutilide 1 mg IV×10 min (0.01 mg/kg if <60 kg); then 1 mg IV×10 min (0.01 mg/kg if <60 kg) after 10 min prn	NR 1.5 h	Conversion within 4 h Adverse events
Simon et al[54] 2017	AF ≤48 h Sample size: 100 Mean age (y): 56.5 (SD 15) Sex: 68% men Heart failure (NYHA I–II): 99% LA diameter: NR	ED	Vernakalant 3 mg/kg IV; then 2 mg/kg IV after 15 min prn Ibutilide 1 mg IV×10 min; then 1 mg IV×10 min after 10 min prn	Continuous 1.5 h, 4 h	Conversion within 4 h Median time to conversion Adverse events
Toivonen et al[55] 1986	AF ≤48 h Sample size: 40 Mean age: NR Sex: NR Heart failure: NR LA diameter: NR	ED	Pirmenol 50 mg IV×2 min; then 50 mg IV×2 min after 10 min prn Placebo	Continuous 1 h	Conversion within 4 h Adverse events
Vogiatzis et al[56] 2017	AF 1–48 h Sample size: 78 Mean age (y): 62.4 (SD 7.2) (arm 1) 64.8 (SD 6.1) (arm 2) Sex: 71.8% men Heart failure (EF<50%): 7.7% LA diameter (mm): 42.6 (SD 7.3) (arm 1) 41.8 (SD 6.4) (arm 2)	ED	Vernakalant 3 mg/kg IV; then 2 mg/kg IV after 15 min prn Ibutilide 1 mg IV×10 min; then 1 mg IV×10 min after 10 min prn	NR 1.5 h	Conversion within 4 h Mean time to conversion Adverse events

Table 1. Continued.

Trial	Patient Characteristics*	Setting	Investigated Treatments	Rhythm Monitoring/Time of Analysis	Extracted Outcomes
Walker et al[57] 1996	AF/AFL <48 h Sample size: 41 Mean age: NR Sex: NR Heart failure: NR LA diameter: NR	ED	Magnesium 5 g (20 mmol) IV×30 min Placebo	Serial 4 h	Conversion within 4 h Mean time to conversion Adverse events

AF, Atrial fibrillation; *NR*, not reported; *LA*, left atrium; *CCU*, coronary care unit; *IV*, intravenous; *PO*, oral; *SD*, standard deviation; *prn*, as needed; *q*, every; *AFL*, atrial flutter; *NYHA*, New York Heart Association Class; *EF*, ejection fraction.

**The most common exclusion criteria were current or previous use of study drug or antidysrhythmic (89%), recent acute coronary syndrome (89%), reduced ejection fraction (73%), sinus node disease (58%), renal dysfunction (53%), hemodynamic instability (53%), hepatic dysfunction (47%), metabolic derangement (47%), contraindications to trial drug (47%), pregnancy (42%), thyroid dysfunction (37%), long-QTc interval (37%), and pre-excitation syndrome (32%)

Description of Included Studies

There was variation among the trials, particularly in exclusion criteria, proportion of male subjects (46.1%[49] to 75%[43]), and available data points (1 hour[51,55] to 4 hours[41,46,47,54,57]). Among the treatment arms, there was variation in mean age (46.9 years[43] to 71 years[52]) and left atrial diameter (32.9 mm[40] to 52.0 mm[53]). Drug regimens differed particularly for amiodarone, propafenone, and flecainide, but those for ibutilide and vernakalant were consistent. Two trials[41,45] performed short-term follow-up (28 days[45] and 30 days[41]). Four studies[45-47,57] enrolled a total of 84 patients with recent-onset atrial flutter. The description of included studies is summarized in Table 1 and detailed comprehensively in Table 1 in Appendix E1, available online at http://www.annemergmed.com.

Quality Assessment

The risk of bias assessments within each of the 19 studies at the study level are summarized in Figure 1 in Appendix E1, available online at http://www.annemergmed.com. We rated 75% to be at high risk of bias and 25% to be low risk at the outcome (conversion to sinus rhythm) level.

Quantitative Data Synthesis

Conversion to sinus rhythm within 4 hours. Eighteen trials[39-45,47-57] that randomized 2,069 atrial fibrillation patients provided efficacy data for the outcome of atrial fibrillation conversion within 4 hours. The atrial flutter patient data were insufficient for a separate network meta-analysis of drugs for conversion of atrial flutter within 4 hours. We obtained the raw data for Walker et al[57] through contact with the corresponding author and the data from Capucci et al[42] only through inspection of a previous systematic review.[26] We were unable to separate data for atrial fibrillation and atrial flutter patients from Joseph and Ward.[46] We merged data for intravenous and oral formulations of flecainide[40,50,51,53] and propafenone[40,51] to improve the performance of the models. This method may be justified because as a group, the current guidelines[14-16] do not favor one formulation of flecainide or propafenone over the other; therefore, the intravenous and oral formulations of flecainide and propafenone may be considered clinically interchangeable. Consequently, as a result of merging intravenous and oral data for flecainide and propafenone, Alp et al[39] and Madonia et al[49] did not have any comparator arms to connect to the network and were excluded from network meta-analysis. We did not include the amiodarone oral group because the only arm that included amiodarone oral had zero events. The between-study heterogeneity for the direct comparisons that were informed by 2 or more trials are shown in Table 2 in Appendix E1, available online at http://www.annemergmed.com.

Sixteen trials [40-45,47,48,50-57] that randomized 1,741 patients among 12 treatment groups remained for network meta-analysis. 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 2 to 3 connections apart, and these comparisons demonstrated treatment effect estimates with the widest credible intervals. The evidence network configuration is presented in Figure 2. Six drugs demonstrated with sufficient certainty an association with an increased likelihood of conversion compared with placebo or control: intravenous antazoline, intravenous tedisamil, intravenous vernakalant, intravenous and oral propafenone, intravenous and oral flecainide, and intravenous ibutilide. The network meta-analysis estimates

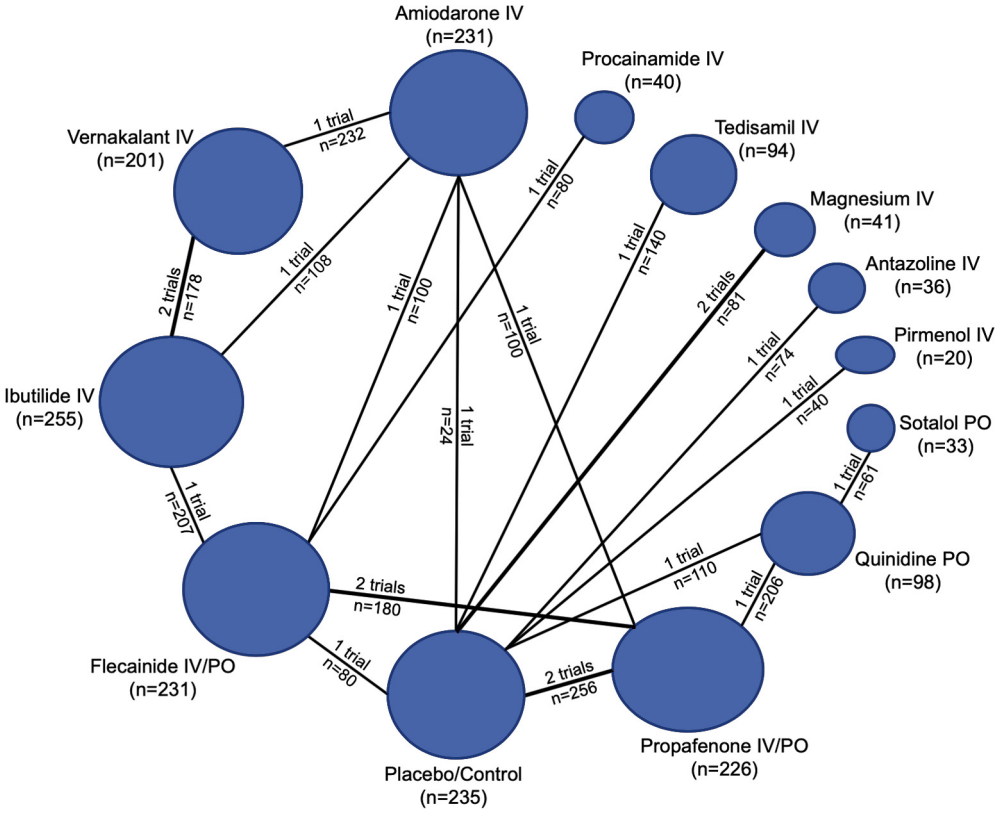

Figure 2. Network configuration of treatments for the outcome of conversion within 4 hours (16 trials; n=1,741). The area of the circles is based on the total number of patients for each treatment among all trials. The thickness of the lines is based on the total number of studies comparing the 2 treatments. Amiodarone IV, flecainide IV/PO, propafenone IV/PO, and ibutilide IV are the most connected nodes (most direct comparisons) with the most direct evidence (largest pooled sample sizes), so their treatment effect estimates would be expected to be least subject to bias and most reliable. Pirmenol IV, sotalol PO, antazoline IV, and procainamide IV are the least connected, with the smallest amount of direct evidence, so their treatment effect estimates would be expected to be most prone to bias and least reliable.

of all pairwise comparisons are shown in Figure 3. There was moderate heterogeneity in the network (1.18; 95% credible interval 0.47 to 1.93), and because of its sparsity, some of its components exhibited inconsistency. The network inconsistency is presented in Figure 2 in Appendix E1, available online at http://www.annemergmed.com. 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 network meta-analysis is illustrated in Figure 3 in Appendix E1, available online at http://www.annemergmed.com.

The results of probabilistic analysis (surface under the cumulative ranking curve) are listed in Table 2, and its underlying rankograms are presented in Figure 4. The unweighted, pooled conversion rate within 4 hours among placebo and control groups was 17.0%, which may be considered the spontaneous 4-hour conversion rate. The complete listing of unweighted, pooled cardioversion rates for this outcome is shown in Table 3. To reiterate, these pooled cardioversion rates are distinct from the surface under the cumulative ranking curve probabilities. The complete trial data (raw) for conversion to sinus rhythm are shown in Table 3 in Appendix E1, available online at http://www.annemergmed.com.

Qualitative Analysis

Time to cardioversion. Six studies[41,48,50,54,56,57] that randomized 485 atrial fibrillation patients and monitored them for a maximum of 4 hours provided data for unweighted mean or median times to atrial fibrillation cardioversion. The times to cardioversion are listed in Table 3. The complete trial data are in Table 4 in Appendix E1, available online at http://www.annemergmed.com.

Rate of Significant Adverse Events. All 19 trials,[39-57] with a total of 2,153 atrial fibrillation and atrial flutter patients, provided data for significant adverse event rate. We were unable to obtain specific data for hypotension and bradycardia from Halinen et al.[44] The selected studies

Antazoline IV												
2.06 (0.35 – 12.36)	**Tedisamil IV**											
3.33 (0.73 – 18.04)	1.61 (0.40 – 7.59)	**Vernakalant IV**										
3.64 (0.90 – 17.87)	1.76 (0.51 – 7.43)	1.10 (0.52 – 2.29)	**Propafenone IV/PO**									
4.11 (0.98 – 20.83)	1.99 (0.54 – 8.76)	1.24 (0.67 – 2.30)	1.13 (0.65 – 1.97)	**Flecainide IV/PO**								
6.14 (1.39 – 32.33)	2.97 (0.77 – 13.62)	1.84 (1.13 – 3.05)	1.69 (0.87 – 3.30)	1.49 (0.92 – 2.42)	**Ibutilide IV**							
13.57 (3.10 – 70.72)	6.55 (1.72 – 29.69)	4.07 (2.54 – 6.61)	3.71 (1.95 – 7.17)	3.29 (1.89 – 5.79)	2.21 (1.33 – 3.68)	**Amiodarone IV**						
16.96 (3.72 – 91.34)	8.19 (2.07 – 38.77)	5.08 (1.91 – 13.82)	4.62 (2.41 – 9.35)	4.11 (1.76 – 9.86)	2.75 (1.09 – 7.10)	1.25 (0.50 – 3.18)	**Quinidine PO**					
25.44 (2.62 – 267.81)	12.29 (1.40 – 115.61)	7.53 (0.95 – 60.46)	6.87 (0.94 – 51.12)	6.10 (0.80 – 46.66)	4.08 (0.52 – 32.15)	1.85 (0.24 – 14.49)	1.48 (0.19 – 11.87)	**Pirmenol IV**				
24.84 (7.39 – 107.80)	11.99 (4.30 – 43.80)	7.52 (3.13 – 18.61)	6.84 (3.60 – 13.77)	6.09 (2.89 – 13.18)	4.07 (1.78 – 9.56)	1.85 (0.83 – 4.23)	1.48 (0.61 – 3.62)	1.00 (0.15 – 6.60)	**Placebo/Control**			
34.87 (4.91 – 325.52)	16.87 (2.64 – 141.28)	10.27 (2.48 – 56.27)	9.33 (2.32 – 50.33)	8.22 (2.32 – 40.77)	5.53 (1.42 – 29.03)	2.51 (0.62 – 13.50)	2.02 (0.43 – 12.18)	1.39 (0.12 – 17.54)	1.36 (0.31 – 7.85)	**Procainamide IV**		
74.36 (9.91 – 665.40)	35.97 (5.33 – 292.70)	22.03 (4.38 – 125.60)	20.03 (4.75 – 98.81)	17.77 (3.82 – 95.06)	11.93 (2.45 – 66.48)	5.41 (1.11 – 29.88)	4.30 (1.21 – 18.30)	2.94 (0.25 – 35.99)	2.91 (0.61 – 15.86)	2.13 (0.24 – 17.65)	**Sotalol PO**	
84.22 (16.07 – 535.30)	40.74 (8.81 – 228.60)	25.11 (6.10 – 110.84)	22.87 (6.36 – 90.33)	20.32 (5.35 – 83.40)	13.59 (3.41 – 58.46)	6.17 (1.57 – 26.10)	4.94 (1.19 – 21.84)	3.35 (0.38 – 30.71)	3.31 (1.11 – 10.96)	2.43 (0.31 – 16.52)	1.15 (0.15 – 8.15)	**Magnesium IV**

IV: intravenous; PO: oral; CrI: credible interval

The treatment effect estimate is derived from direct and indirect comparisons and presented as odds ratio (95% CrI). An odds ratio in red represents an association with increased likelihood of conversion within four hours. A CrI that crosses 1.0 (the null effect) signifies uncertainty in the treatment effect estimate.

Figure 3. Network meta-analysis estimates of pairwise comparisons for the outcome of conversion within 4 hours.

Table 2. Probabilistic analysis (surface under the cumulative ranking curve) for the outcome of conversion within 4 hours.

Rank	Treatment	SUCRA
1	Antazoline IV	0.972
2	Tedisamil IV	0.877
3	Vernakalant IV	0.802
4	Propafenone IV/PO	0.767
5	Flecainide IV/PO	0.723
6	Ibutilide IV	0.590
7	Amiodarone IV	0.435
8	Quinidine PO	0.381
9	Pirmenol IV	0.300
10	Placebo/Control	0.276
11	Procainamide IV	0.218
12	Sotalol PO	0.093
13	Magnesium IV	0.067

SUCRA, Surface under the cumulative ranking curve; IV, intravenous; PO, oral. The SUCRA is a numeric presentation of the overall ranking based on 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.

varied in definition and thoroughness of reported safety outcomes, and significant adverse events were rare, precluding network meta-analysis for this outcome. There was large variation in the intervals during which adverse events were recorded, with periods ranging from 1 hour[51,55] to 48 hours[46] after drug administration. The unweighted, pooled, significant adverse event rates associated with all agents are listed in Table 4. The complete trial data (raw) for significant adverse event rates are shown in Table 4 in Appendix E1, available online at http://www.annemergmed.com. Two studies[41,53] provided limited data from patients with systolic dysfunction. There were no adverse events associated with intravenous ibutilide (n=21), intravenous flecainide (n=17), intravenous vernakalant (n=12), and intravenous amiodarone (n=4).

Rate of Thromboembolism Within 30 Days. The 2 trials[41,45] that performed short-term follow-up reported no thromboembolic events.

LIMITATIONS

We excluded all studies in languages other than English; however, language restriction in systematic reviews and meta-analyses in medicine has not been shown to result in bias.[58] Data were unavailable from one trial[46] because we could not contact the investigators. Only 4 studies[45-47,57] included small samples of atrial flutter patients, and we are unable to draw any conclusions in regard to ED cardioversion of recent-onset atrial flutter. We combined data for intravenous and oral flecainide and propafenone and therefore cannot make distinct recommendations in regard to cardioversion efficacy for intravenous and oral formulations of those agents. However, Alp et al[39] directly compared intravenous and oral formulations of flecainide and reported similar cardioversion rates at 2 hours. Madonia et al[49] directly compared intravenous and oral formulations of propafenone and reported greater efficacy of intravenous propafenone at 3 hours. From the International Registry on Cardioversion of Atrial Fibrillation (RHYTHM-AF), Crijns et al[59] reported cardioversion efficacy of flecainide and propafenone that was consistent with that reported by Alp et al[39] and Madonia et al.[49] Therefore, presumably only the efficacy of the intravenous formulation of propafenone may be greater than what we report for propafenone intravenously and orally in combination. Our analysis of data points earlier than 4 hours in 6 studies[40,42,50-53] may somewhat diminish the treatment effect estimates for flecainide,[40,50,51,53] propafenone,[40,42,51] and intravenous amiodarone,[51,52] all of which have demonstrated a relatively more durable or delayed antidysrhythmic effect in RHYTHM-AF.[59] The trials selected in our systematic review differed in their definitions of adverse events and safety endpoints and had almost exclusively short observation periods (24 hours or shorter) without follow-up; therefore, we cannot comment on longer-term cardioversion efficacy or adverse event rates.

Because no more than 2 trials contributed to a direct comparison, the measurement of between-study heterogeneity may fail to statistically detect potential heterogeneity and will therefore not be informative. The evidence network was made up of a small number of studies, and pooled sample sizes varied greatly. Imbalance in the amount of evidence for each treatment may affect the power and reliability of the overall analysis.[60,61] Across the studies in the network meta-analysis, the risk of bias was mainly unclear in patient selection and high in regard to predetermination and adequacy of sample size. Overall, the study quality was low. The network meta-analysis 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 atrial fibrillation duration, left atrial size, drug dosing regimen, and timing of rhythm assessment) and our merging of intravenous and oral treatment arms for flecainide[40,50,51,53] and propafenone[40,42,51] likely contributed to inconsistency and may affect the generalizability of results. Study sample sizes were too small to control for significant effect

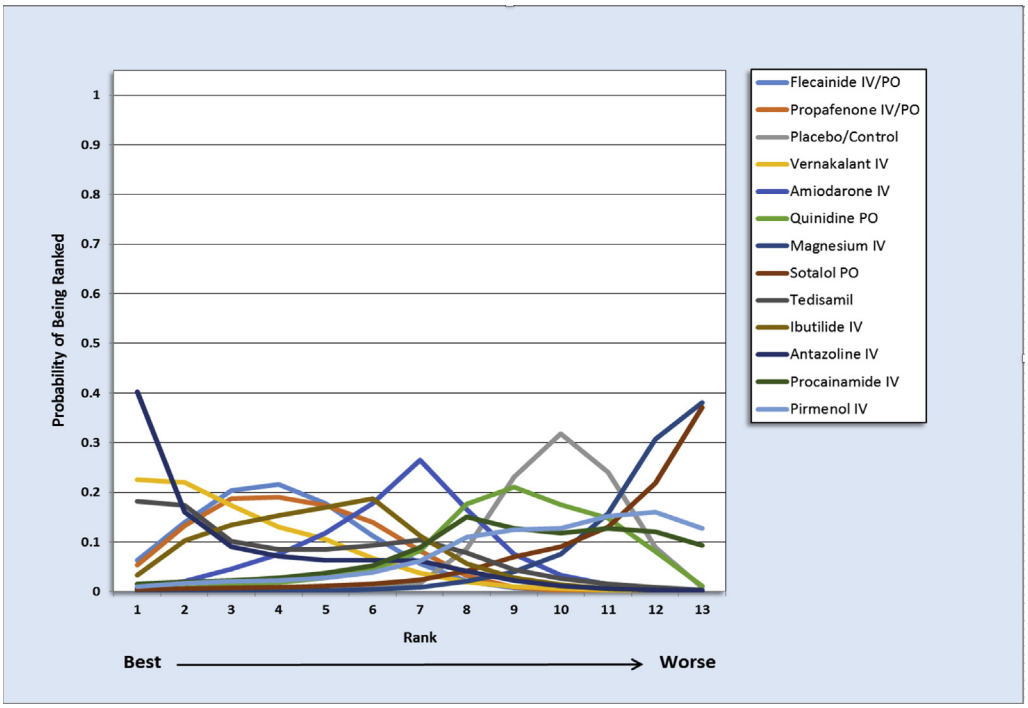

Figure 4. Cumulative rankograms of treatments for the outcome of conversion within 4 hours. A cumulative rankogram presents on the vertical axis the probability for the treatment to assume each of the possible ranks presented on the horizontal axis. The surface under the cumulative ranking curve is between 0 and 1 and can be re-expressed as a percentage. For example, flecainide IV/PO has a 21% probability of being ranked number 4, and amiodarone IV has a 26% probability of being ranked number 7. An uncertain ranking of a group of treatments is illustrated by rankograms with similar distributions and overlap of probabilities across the ranks.

modifiers; however, if more evidence becomes available, 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 effect of inconsistency and found that it did not vary our conclusions. Last, the use of data points across 4 hours may have contributed to indirectness and intransitivity within the network. Consequently, as a result of limitations in the body of studies, bias, imprecision, inconsistency, and indirectness, the probabilistic analysis (surface under the cumulative ranking curve) may be subject to misinterpretation.

DISCUSSION

Through systematic review, we found very limited high-level evidence in regard to pharmacologic cardioversion of recent-onset atrial fibrillation and atrial flutter within 4 hours. On network meta-analysis of the available evidence, 6 antidysrhythmic agents were associated with increased likelihood of atrial fibrillation cardioversion within 4 hours compared with placebo or control. When the probabilistic analysis (surface under the cumulative ranking curve) may be misleading, greater emphasis should be placed on the individual treatment effect estimates and their precision.[62,63] Among the 6 drugs, vernakalant (3 trials, n=201), flecainide (4 trials, n=231), propafenone (3 trials, n=226), and ibutilide (3 trials, n=255) were each well connected in the network, with a moderate amount of direct evidence (pooled sample size). One high-quality, placebo-controlled study[40] with both flecainide and propafenone contributed to their comparisons with placebo or control, suggesting confidence in their treatment effect estimates. Vernakalant was also found to be marginally more effective than ibutilide (moderate amount of low-quality direct evidence[54,56]). The remaining 2 agents, antazoline (1 trial, n=36) and tedisamil (1 trial, n=94), were poorly connected to the network, with small quantities of direct evidence, so their treatment effect estimates should be interpreted with caution.[62] Therefore, although there is insufficient evidence to determine which drug is superior, our network meta-analysis results suggest that vernakalant, flecainide, propafenone, and ibutilide may be effective for atrial fibrillation cardioversion within a 4-hour ED visit. Treatment effect differences among these agents were small and potentially not clinically meaningful, so factors other than efficacy, such as adverse

Table 3. Unweighted pooled cardioversion rate and time to cardioversion.

	Pooled Cardioversion Rate				Time to Cardioversion*	
Treatment	**Trials**	**Events**	**N**	**Rate (95% CI) (%)**	**Trials**	**Mean/Median/Range (Hours)**
Antazoline IV	1	26	36	72.2 (55.9–84.3)	1	0.3
Procainamide IV	1	25	40	62.5 (47.0–75.8)	1	0.5
Flecainide IV/PO	5	193	310	62.3 (56.7–67.5)	1	IV: 0.6
Pirmenol IV	1	12	20	60.0 (38.6–78.2)	1	NR
Vernakalant IV	3	118	201	58.7 (51.8–65.3)	3	0.2
Ibutilide IV	4	143	255	56.1 (49.9–62.0)	2	0.4–0.6
Tedisamil IV	1	48	94	51.1 (41.1–60.9)	0	–†
Propafenone IV/PO	4	163	323	50.5 (45.0–55.9)	0	–
Amiodarone IV	4	79	231	34.2 (28.4–40.5)	1	NR
Quinidine PO	2	24	98	24.5 (17.0–33.9)	0	–
Placebo/Control	8	40	235	17.0 (12.7–22.4)	2	1.2–2.5
Magnesium IV	2	6	41	14.6 (6.5–28.8)	1	1.5
Sotalol PO	1	4	33	12.1 (4.2–27.9)	0	–
Amiodarone PO	1	0	40	0.0 (0.0–10.4)	0	–

CI, Confidence interval; *IV*, intravenous; *PO*, oral; *NR*, Not reported
*During maximum of 4 hoursof observation.
†Dashes indicate no data.

effects, cost, and patient preferences, may be more important in drug selection.

Intravenous amiodarone (4 trials, n=231) was well connected with moderate quantities of direct evidence and found to be only marginally more effective than placebo or control for atrial fibrillation cardioversion within 4 hours; however, the credible interval spanned 1.0 (the null effect), meaning that we cannot be certain of its efficacy. This uncertainty may be at least partially explained by a lack of direct comparisons with placebo or control within a sparseevidence network. Our network meta-analysis results also suggest that amiodarone intravenously may be less effective than vernakalant, flecainide, propafenone, and ibutilide. The treatment effect estimates for the comparisons with vernakalant,[41] flecainide,[51] and propafenone[51] were based on 2 high-quality, direct-comparison trials.[41,51] The estimate for the comparison with ibutilide was derived from one low-quality, direct-comparison trial.[47] The finding that intravenous amiodarone may be relatively less effective for atrial fibrillation cardioversion within a 4-hour ED visit is not surprising. Intravenous amiodarone has a known delayed antidysrhythmic action,[15,16,59,64] presumably because of the time needed to attain a threshold concentration of its active metabolite.[65]

Our network meta-analysis results are somewhat consistent with current guideline recommendations for cardioversion of recent-onset atrial fibrillation. Only 3 of the 12 studies[41,53,54] that are cited in the European Society of Cardiology guidelines[15] met our inclusion criteria. None of the 7 references in the AHA guidelines[14] or 11 references in the Canadian Cardiovascular Society guidelines[16] met our criteria. Furthermore, the AHA[14] and European Society of Cardiology guidelines[15] refer to meta-analyses[27,29,66] that included patients with atrial fibrillation duration longer than 48 hours. Therefore, the current guidelines[14-16] for cardioversion of recent-onset atrial fibrillation or atrial flutter are largely based on trials and meta-analyses whose results may not be applicable to patients with recent-onset atrial fibrillation or atrial flutter, in which "recent onset" is strictly defined by the same guidelines as atrial fibrillation or atrial flutter with duration less than 48 hours.

Our findings support the guideline recommendations for vernakalant,[15,16] flecainide,[14-16] propafenone,[14-16] and ibutilide[14-16] for ED cardioversion of recent-onset atrial fibrillation. Our results for intravenous amiodarone are also compatible with European Society of Cardiology[15] and Canadian Cardiovascular Society guidelines,[16] which discourage its routine use for this indication. Limited randomized controlled trial data for oral amiodarone precluded its analysis. The AHA does not consider time to cardioversion in their recommendations, stating that use of amiodarone oral may be "reasonable."[14] Our network meta-analysis results do not support procainamide,[16] again likely because of a fundamental lack of existing placebo-

Table 4. Unweighted, pooled, significant adverse event rates.

			Adverse Events (%)				
Treatment	**Trials**	**N**	**VD**	**AFL 1:1**	**Hypotension**	**Bradycardia**	**Total**
Sotalol PO	1	33	4 (12.1)	0	U	U	4 (12.1)
Ibutilide IV*	4	278	26 (9.4)	0	2 (0.7)	3 (1.1)	26 (11.2)
Tedisamil IV†	1	114	2 (1.8)	0	0	9 (7.9)	11 (9.7)
Quinidine PO	2	98	8 (8.2)	0	1 (1.0)	0	9 (9.2)
Antazoline IV	1	36	0	0	1 (2.8)	2 (5.6)	3 (8.4)
Flecainide IV	4	230	1 (0.4)	2 (0.9)	7 (3.0)	2 (0.9)	12 (5.2)
Sotalol IV	1	40	0	0	2 (5.0)	0	2 (5.0)
Propafenone PO	3	224	0	0	7 (3.1)	0	7 (3.1)
Amiodarone IV‡	5	291	2 (0.7)	0	5 (1.7)	1 (0.3)	8 (2.7)
Procainamide IV	1	40	0	0	1 (2.5)	0	1 (2.5)
Propafenone IV	2	99	0	0	2 (2.0)	0	2 (2.0)
Placebo/Control	9	285	1 (0.3)	0	4 (1.4)	0	5 (1.7)
Vernakalant IV§	3	201	1 (0.5)	0	2 (1.0)	0	3 (1.5)
Pirmenol IV	1	20	0	0	0	0	0
Amiodarone PO	1	40	0	0	0	0	0
Magnesium IV	2	44	0	0	0	0	0
Flecainide PO	2	80	0	0	0	0	0

VD, Ventricular dysrhythmia; *AFL 1:1*, AFL with 1:1 atrioventricular conduction; PO, oral; *U*, unable to obtain; IV, intravenous.
There were no reported thromboembolic events associated with intravenous amiodarone, intravenous vernakalant, and intravenous tedisamil among the 2 trials[41,45] that performed short-term follow-up.
*7 torsades de pointes.
†1 torsades de pointes; 1 ventricular tachycardia.
‡1 additional event of asystole.
§1 ventricular tachycardia.

controlled study of this agent. We did not find any randomized controlled trial evidence to support the AHA recommendation of dofetilide.[14] Finally, we found limited randomized controlled trial safety data for intravenous amiodarone or any other antidysrhythmic agent in patients with systolic dysfunction. Notwithstanding, intravenous amiodarone remains the recommended primary agent for atrial fibrillation cardioversion in this subpopulation.[15,16] In their 2018 checklist, Stiell et al[18] recommended procainamide for ED cardioversion according to multidisciplinary committee consensus. In our network, procainamide (1 trial, n=40) was poorly connected with a small quantity of direct evidence; therefore, we cannot draw any meaningful conclusions about its relative cardioversion efficacy. However, our findings do agree with those of Stiell et al[18] that discourage intravenous amiodarone for ED cardioversion.

The duration of atrial fibrillation or atrial flutter that constitutes recent onset may need redefinition with objective criteria. Symptom-based definitions may underestimate atrial fibrillation episodes,[67] and occult episodes may yet add to overall atrial fibrillation burden and progression of disease. Studies of electronic monitoring devices or smartphones to detect atrial fibrillation or atrial flutter and guide out-of-hospital treatment with a "pill in the pocket"[68,69] or device-triggered, faster-acting aerosolized antidysrhythmic agent[70] may demonstrate reduced cardiovascular morbidity and hospital costs[71] and improved quality of life. Our network meta-analysis may serve to stimulate randomized controlled trials that directly compare vernakalant, flecainide, propafenone, and ibutilide with placebo, as well as other well-established, fast-acting agents such as procainamide, to definitively determine which drug is most effective and safe for ED cardioversion. A multiarm, multistage design may allow evaluation of several treatments while avoiding prolonged study of treatments that fail to demonstrate efficacy. We found limited randomized controlled trial data for sotalol, antazoline, pirmenol, and tedisamil and no randomized controlled trial data for dofetilide. These agents may also deserve further randomized, placebo-controlled, and head-to-head study. One randomized controlled trial[47] suggested that ibutilide may be effective for cardioversion of recent-onset atrial flutter, a finding also observed in recent,

retrospective studies.[72,73] However, further randomized controlled trials are required to identify which antidysrhythmic, ibutilide or another, may be most effective for recent-onset atrial flutter cardioversion. All future trials should perform rhythm analysis within an appropriate ED visit time frame and then regularly with short intervals during a 24-hour observation period to measure both immediate cardioversion efficacy and its durability. Future studies should also predefine adverse events and safety endpoints to establish reliable drug safety profiles and perform longer-term (eg, 7-day, 30-day) follow-up to determine longitudinal cardioversion efficacy and thromboembolism risk. Our network meta-analysis focused on the outcome of conversion within 4 hours to identify the most effective drug for atrial fibrillation cardioversion during an ED visit. However, clinicians may decide to manage high-risk patients in an observation unit.[9,18] Further analysis for the outcome of conversion within 24 hours may determine that different agents have relatively greater efficacy during an observation unit stay. Last, whether early cardioversion of recent-onset atrial fibrillation improves long-term cardiovascular outcomes remains to be seen. Early cardioversion in the ED 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.[74]

In conclusion, there is a paucity of high-level evidence to inform the pharmacologic cardioversion of recent-onset atrial fibrillation and atrial flutter within a 4-hour ED visit. Although we cannot determine which is superior, several agents are associated with increased likelihood of conversion within 4 hours compared with placebo or control. Our evidence network was limited, and its analysis should be considered primarily hypothesis generating. We are unable to offer any conclusions in regard to cardioversion of recent-onset atrial flutter. Further high-quality, placebo-controlled, and head-to-head studies are necessary to make definitive recommendations for the pharmacologic cardioversion of recent-onset atrial fibrillation and atrial flutter in the ED.

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