Pharmacologic Cardioversion of Recent-Onset Atrial Fibrillation: A Systematic Review and Network Meta-analysis

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ABSTRACT

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

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 We also searched for unpublished data.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 AF ≤ 48 hours and compared antidysrhythmic agents, placebo, or control. We determined these outcomes prior to data extraction: 1) Rate of conversion to sinus rhythm within 24 hours, 2) Time to cardioversion to sinus rhythm, 3) Rate of significant adverse events, and 4) Rate of thromboembolism within 30 days. We extracted data according to PRISMA-NMA and appraised selected trials using the Cochrane review handbook.

Results: The systematic review initially identified 640 studies; 30 met inclusion criteria. Twenty-one trials that randomized 2,785 patients provided efficacy data for the conversion rate outcome. Bayesian network meta-analysis using a random effects model demonstrated that ranolazine + amiodarone 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 PO (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 hours 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.

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

Keywords: Antidysrhythmic, Antiarrhythmic, Atrial Fibrillation, Cardioversion, Network Meta-Analysis

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 United Kingdom[4] and as much as $26 billion annually in the United States[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 ischemic stroke,[11] systemic thromboembolism, and cardiovascular death.[12-14] "Further Background" is Supplementary Appendix 1.

Cardioversion of AF with duration shorter than 48 hours (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 1) heterogeneous samples that included patients with variable AF duration exceeding 48 hours, a duration for which early cardioversion

without prior anticoagulation is contrary to guidelines, and 2) 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 Supplement.) 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., 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, 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 Appendix 2.

Study Selection

Four authors (I.d., R.B., T.S., 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.

Patients: 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 hours prior to enrollment

Intervention: One of the predetermined antidysrhythmic drugs: Procainamide, Amiodarone, Flecainide, Propafenone, Sotalol, Dofetilide, Dronedarone, Ibutilide, Vernakalant, Magnesium Sulfate

Comparison: 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

Outcomes: 1) Rate of conversion to sinus rhythm within 24 hours, a time frame suitable for cardioversion within an observation stay or short-term admission (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 upon the final group of included articles.

Quality Assessment

Four authors (I.d., R.B., T.S., G.C.) independently assessed the risk of bias within all included studies at the study level according to the 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 Appendix 3. 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.d., T.S.) extracted the data from each article for each of the outcomes. For the outcome of conversion within 24 hours, we extracted data from rhythm assessment at 24 hours after drug administration. If assessment was only reported prior to 24 hours, we extracted data from the time point closest to 24 hours. 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 IV and 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 was 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 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 hours. Importantly, the SUCRA is distinct from the unweighted, pooled cardioversion and adverse event rates that we report as secondary outcomes 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 Appendix 4.

We attempted to analyze 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 analyzed data from all studies that reported rhythm assessment between four and 24 hours 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 four hours. Twenty-three studies[37-59] that randomized 3,009 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 hours[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 detailed comprehensively in Supplementary 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 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 hours

Twenty-one trials[37-44,46,48-59] that randomized 2,785 AF patients provided efficacy data for the outcome of AF conversion within 24 hours. The AFL patient data were insufficient for a separate NMA of drugs for conversion of AFL within 24 hours. 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 favor 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 hours 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 2,456 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 to 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 hours among placebo and control groups was 51.5%, which may be considered the spontaneous 24-hour 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 Supplementary Table S2.

Qualitative Analysis

Time to cardioversion

Seventeen trials[37,39,40,43,44,46,48-52,54-59] that randomized 2,154 AF patients and monitored patients for a maximum of 24 hours 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 Supplementary Table S3.

Rate of significant adverse events

All 23 trials[37-59] that randomized 3,009 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 hours[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 Supplementary 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 thromboembolic events.

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 hours. 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-hour 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 etiology, 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 transesophageal 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-hour cardioversion window and subsequent commitment to several weeks of anticoagulation, either following early transesophageal 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 hours. 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 hours.

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 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 ED/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 analyze 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 was 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 eight hours, and Madonia et al[53] directly compared the two formulations of propafenone and reported similar efficacy at 24 hours. Furthermore, Crijns et al[60] describe similar effectiveness for flecainide IV and PO at 16 hours and propafenone IV and PO at 24 hours. 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 hours 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 hours after drug initiation. Cardioversion rates may vary with duration of rhythm monitoring. Therefore, our analysis of data points earlier than 24 hours 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 hours 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 Appendix 5.

In conclusion, there is insufficient high-level evidence to determine which treatment is superior for pharmacologic cardioversion of recent-onset atrial fibrillation within 24 hours. 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.

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Legends

Figure 1. Study selection process

AF: atrial fibrillation; AFL: atrial flutter

Figure 2. Network configuration of treatments for the outcome of conversion within 24 hours (18 trials; n=2,456)

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

Figure 3. Network Inconsistency between direct and indirect estimates for the outcome of conversion within 24 hours

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.

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

Figure 5. Cumulative rankograms of treatments for the outcome of conversion within 24 hours

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