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

ABSTRACT

Objective: We conducted a systematic review and Bayesian network meta-analysis (NMA) to indirectly compare and rank antidysrhythmic drugs for pharmacologic cardioversion of recent-onset atrial fibrillation (AF) and atrial flutter (AFL) 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 We also searched for unpublished data.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 AF or AFL and compared antidysrhythmic agents, placebo, or control. We determined these outcomes before data extraction: 1) Rate of conversion to sinus rhythm within four hours, 2) Time to cardioversion 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; 19 met inclusion criteria. Eighteen trials that randomized 2,069 AF patients provided data for AF conversion rate outcome. Bayesian network meta-analysis using random effects model demonstrated that antazoline (odds ratio [OR] 24.9; 95% credible interval [CrI], 7.4-107.8), tedisamil (OR 12.0; 95% CrI, 4.3-43.8), vernakalant (OR 7.5; 95% CrI, 3.1-18.6), propafenone (OR 6.8; 95% CrI, 3.6-13.8), flecainide (OR 6.1; 95% CrI, 2.9-13.2), and ibutilide (OR 4.1; 95% CrI, 1.8-9.6) were associated with increased likelihood of conversion within four hours when compared to placebo/control. Overall quality was low, and the network exhibited inconsistency.

Conclusions: For pharmacologic cardioversion of recent-onset AF 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 four hours when compared to placebo/control. Limited data precludes any recommendation for cardioversion of recent-onset AFL. Further high-quality study is necessary.

INTRODUCTION

Background

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 AF afflicts one to two percent of the adult population in the United States (U.S.).[3] As the population ages, it has been estimated that the incidence and prevalence of AF in the U.S. will double by 2030.[1,2] Patients with AF have twice the risk of death and are twice as likely to be hospitalized than those without AF.[1] Hospital admissions make up the greatest proportion of the annual healthcare cost of AF,[4] which is estimated to be $26 billion.[1,5] Emergency department cardioversion of recent-onset AF 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 (RACE 7 ACWAS) trial[8] has determined that a "wait-and-see approach" may be non-inferior to immediate cardioversion for the short term, pharmacologic cardioversion may be less effective (I. S. deSouza, MD; unpublished analysis of ACWAS trial[8] data), and thromboembolic risk may be greater with a delayed approach.[9,10]

Atrial Flutter (AFL) is a supraventricular tachydysrhythmia that is less prevalent than AF[11] and although the two have different underlying mechanisms, AFL often transitions to and from AF.[12,13] Early cardioversion of AF/AFL with duration shorter than 48 hours (recent-onset AF/AFL) is supported by the American Heart Association (AHA),[14] European Society of Cardiology (ESC),[15] and the Canadian Cardiovascular Society (CCS).[16] Pharmacologic cardioversion is established within ED protocols[17,18,19] 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 decision-making paradigm,[22 23] clinicians and patients may decide to attempt pharmacologic cardioversion of recent-onset AF/AFL within an ED visit. Current guidelines[14 15 16] do not uniformly agree upon the recommendation of antidysrhythmic agents for AF/AFL cardioversion, and drug preference in clinical practice also varies internationally.[24 25] Prior systematic reviews and meta-analyses[26 27 28 29 30 31 32 33] 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 current guidelines and 2) insufficient head-to-head drug comparisons.

Goals of This Investigation

We performed a systematic review and network meta-analysis (NMA) to indirectly compare and rank antidysrhythmic agents tested in adults with recent-onset AF/AFL in order to identify which is most effective for pharmacologic cardioversion in the ED.

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 Meta-Analysis

statement.[34] (The completed "PRISMA-NMA Checklist" is in the Appendix.) 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 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. Lastly, 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" is in the Appendix.

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 the eligibility of studies for inclusion.

Patients: Adult patients (age 18 years and older) with recent-onset AF or AFL, defined in the study as an 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
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 AF or AFL to sinus rhythm and were therefore considered non-antidysrhythmic controls
Outcomes: 1) Rate of conversion to sinus rhythm within four 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 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 (study level) within all included studies according to the Cochrane review handbook.[36] The risk of bias

tool covers six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and "other" bias. "Method of Individual Study Quality Assessment" is in the Appendix. 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 of 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 four hours, we extracted data from rhythm assessment at four hours after drug administration. If assessment was only reported prior to four hours, we extracted data from the time point closest to four hours. In trials that included crossover to the other treatment arm, we extracted only pre-crossover data. 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 data extraction were discussed and resolved by consensus.

Data Analysis

We performed conventional pairwise meta-analyses for the outcome of conversion to sinus rhythm, provided that at least two 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 NMA 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 non-informative prior. We report pairwise comparisons using a league table with each pairwise comparison reported as an odds ratio (OR) with 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 report 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. 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 one treatment is most effective for cardioversion to sinus rhythm within four hours. 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 low, unweighted, pooled cardioversion rate. We also present the cumulative rankograms that underly the SUCRA. Further explanation of "Network Meta-Analysis Concepts" is in the Appendix.

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 at four 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. Importantly, this did not greatly vary the results, and thus we only report the random effects model results. The statistical analysis was completed using NetMetaXL 1.6.1 (CADTH, Ottawa, Canada) [37] and WinBUGS 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 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57] met inclusion criteria and randomized 2,153 patients across 44 treatment arms. Sixteen treatments were available for comparison, and amiodarone IV (5 trials), flecainide IV (4 trials), and ibutilide 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 (46.1%[49] to 75%[43]), and available data points (1[51 55] to 4 hours[41 46 47 54 57]). Among the treatment arms, there was variation in mean age (46.9[43] to 71 years[52]) and left atrial diameter (32.9[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[45] and 30 days[41]). Four studies[45 46 47 57] enrolled a total of 84 patients with recent-onset AFL. The description of included studies is summarized in Table 1 and detailed comprehensively in Supplementary Table 1 in the Appendix.

Quality Assessment

The risk of bias assessments within each of the 19 studies at the study level are summarized in Supplementary Figure 1 in the Appendix. We rated 75% to be high risk and 25% to be low risk of bias at the outcome (conversion to sinus rhythm) level.

Quantitative Data Synthesis

Conversion to Sinus Rhythm within 4 hours

Eighteen trials[39 40 41 42 43 44 45 47 48 49 50 51 52 53 54 55 56 57] that randomized 2,069 AF patients provided efficacy data for the outcome of AF conversion within four hours. The AFL patient data were insufficient for a separate NMA of drugs for conversion of AFL within four 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 prior systematic review.[26] We were unable to separate data for AF and AFL patients from

Joseph and Ward.[46] We merged data for IV and PO 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 15 16] do not favor 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. Consequently, as a result of merging IV and PO 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 NMA. We did not include the amiodarone PO group because the only arm that included amiodarone PO had zero events. The between-study heterogeneity for the direct comparisons that were informed by two or more trials are in Supplementary Table 2 in the Appendix.

Sixteen trials [40 41 42 43 44 45 47 48 50 51 52 53 54 55 56 57] that randomized 1,741 patients among 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. Six drugs demonstrated with sufficient certainty an association with an increased likelihood of conversion when compared to placebo/control: antazoline IV, tedisamil IV, vernakalant IV, propafenone IV/PO, flecainide IV/PO, and ibutilide IV. The NMA estimates of all pairwise comparisons are in Table 2. There was moderate heterogeneity in the network (1.18; 95% CrI, 0.47 to 1.93), and due to its sparsity, some of its components exhibited inconsistency. The network inconsistency is presented in

Supplementary Figure 2 in the Appendix. 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 Supplementary Figure 3 in the Appendix.

The results of probabilistic analysis (SUCRA) are listed in Table 3, and its underlying rankograms are presented in Figure 3. The unweighted, pooled conversion rate within four 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 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 3 in the Appendix.

Qualitative Analysis

Time to cardioversion

Six studies[41 48 50 54 56 57] that randomized 485 AF patients and monitored them for a maximum of four hours provided data for unweighted, mean or median times to AF cardioversion. The times to cardioversion are listed in Table 4. The complete trial data are in Supplementary Table 4 in the Appendix.

Rate of significant adverse events

All 19 trials[39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57] with a total of 2,153 AF and AFL 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 varied 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 recorded with periods ranging from one[51 55] to 48 hours[46] following drug administration. The unweighted, pooled significant adverse event rates associated with all agents are listed in Table 5. The complete trial data (raw) for significant adverse event rate are in Supplementary Table 4 in the Appendix. Two studies[41 53] provided limited data from patients with systolic dysfunction. There were no adverse events associated with ibutilide IV (n=21), flecainide IV (n=17), vernakalant IV (n=12), and amiodarone IV (n=4).

Rate of Thromboembolism within 30 days

The two 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 was unavailable from one trial,[46] because we could not contact the investigators. Only four studies[45 46 47 57] included small samples of AFL patients, and we are unable to draw any conclusions with regards to ED cardioversion of recent-onset AFL. 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[39] directly compared IV and PO formulations of

flecainide and reported similar cardioversion rates at two hours. Madonia et al[49] directly compared IV and PO formulations of propafenone and reported greater efficacy of propafenone IV at three hours. From the International Registry on Cardioversion of Atrial Fibrillation (RHYTHM-AF),[59] Crijns et al reported cardioversion efficacy of flecainide and propafenone that was consistent with Alp et al[39] and Madonia et al.[49] Therefore, presumably only the efficacy of the IV formulation of propafenone may be greater than what we report for propafenone IV and PO in combination. Our analysis of data points earlier than four hours in six studies[40 42 50 51 52 53] may somewhat diminish the treatment effect estimates for flecainide,[40 50 51 53] propafenone,[40 42 51] and amiodarone IV,[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.

Since no more than two 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 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, and timing of rhythm assessment) and our merging of IV and PO treatment arms for flecainide[40 50 51 53] and propafenone[40 42 51] likely contributed to inconsistency and may impact the generalizability of results. Study sample sizes were too small to control for significant effect modifiers; however, if more 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. Lastly, the use of data points across four 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 (SUCRA ranking) may be subject to misinterpretation.

DISCUSSION

Through systematic review, we found very limited high-level evidence with regard to pharmacologic cardioversion of recent-onset AF and AFL within four hours. Upon NMA of the available evidence, six antidysrhythmic agents were associated with increased likelihood of AF cardioversion within four hours when compared to placebo/control. When the probabilistic analysis (SUCRA ranking) may be misleading, greater emphasis should be placed upon the individual treatment effect estimates and their precision.[62 63] Among the six 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/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 two 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 NMA results suggest that vernakalant, flecainide, propafenone, and ibutilide may all be effective for AF 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 effects, cost, and patient preferences, may be more important in drug selection.

Amiodarone IV (4 trials, n=231) was well-connected with moderate quantities of direct evidence and found to be only marginally more effective than placebo/control for AF cardioversion within four hours; however, the CrI that 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 to placebo/control within a sparse evidence network. Our NMA results also suggest that amiodarone IV 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 upon two 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 amiodarone IV may be relatively less effective for AF cardioversion within a four-hour ED visit is not surprising. Amiodarone IV has a known, delayed anti-dysrhythmic action[15 16 59 64] presumably due to the time needed to attain a threshold concentration of its active metabolite.[65]

Our NMA results are somewhat consistent with current guideline recommendations for cardioversion of recent-onset AF. Only three[41 53 54] 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[14] or 11 references in CCS guidelines[16] met our criteria. Furthermore, the AHA[14] and ESC guidelines[15] refer to meta-analyses[27 29 66] that included patients with AF duration longer than 48 hours. Therefore, the current guidelines[14 15 16] for cardioversion of recent-onset AF/AFL are largely based upon trials and meta-analyses whose results may not be applicable to patients with recent-onset AF/AFL, where "recent-onset" is strictly defined by those same guidelines as AF/AFL with duration less than 48 hours.

Our findings support the guideline recommendations of vernakalant,[15 16] flecainide,[14 15 16] and propafenone,[14 15 16] and ibutilide[14 15 16] for ED cardioversion of recent-onset AF. Our results for amiodarone IV are also compatible with ESC[15] and CCS guidelines[16] which discourage its routine use for this indication. Limited RCT data for amiodarone PO precluded its analysis. The AHA does not consider time to cardioversion in their recommendations, stating that use of amiodarone PO may be "reasonable".[14] Our NMA results do not support procainamide,[16] again likely due to a fundamental lack of existing placebo-controlled study of this agent. Notably, we did not find any RCT

evidence to support the AHA recommendation of dofetilide.[14] Finally, 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 16] In their 2018 checklist, Stiell et al[18] recommended procainamide for ED cardioversion based upon 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 as to its relative cardioversion efficacy. However, our findings do agree with Stiell et al[18] where it discourages amiodarone IV for ED cardioversion.

The duration of AF/AFL that constitutes "recent-onset" may need redefinition with objective criteria. Symptom-based definitions may underestimate AF episodes,[67] and occult episodes may yet add to overall AF burden and progression of disease. Studies of electronic monitoring devices or smartphones to detect AF/AFL 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 NMA may serve to stimulate RCTs 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 multi-arm, multi-stage design may allow evaluation of several treatments while simultaneously avoiding prolonged study of treatments that fail to demonstrate efficacy. We found limited RCT data for sotalol, antazoline, pirmenol, and tedisamil and no RCT data for dofetilide. These agents may also deserve further randomized, placebo-controlled and head-to-head study. One

RCT[47] suggests that ibutilide may be effective for cardioversion of recent-onset AFL, a finding also observed in recent, retrospective studies.[72 73] However, further RCTs are required to identify which antidysrhythmic, ibutilide or other, may be most effective for recent-onset AFL 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 (i.e. 7-day, 30-day) follow-up to determine longitudinal cardioversion efficacy and thromboembolism risk. Our NMA focused on the outcome of conversion within four hours in order to identify the most effective drug for AF 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. Lastly, whether or not early cardioversion of recent-onset AF 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 AF and AFL within a 4-hour ED visit. Although we cannot determine which is superior, several agents are associated with increased likelihood of conversion within four hours when compared to placebo/control.

Our evidence network was limited, and its analysis should be considered primarily hypothesis-generating. We are unable to offer any conclusions with regard to cardioversion of recent-onset AFL. 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 and AFL in the ED.

Acknowledgments: We would like to thank Mr. Christopher Stewart, senior librarian at SUNY Downstate Health Sciences University, for his help with formulating the search strategy. We are also grateful to Drs. Gerard Markey and Lori Bash for their contributions to this study.

REFERENCES

1. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation.* 2019 Mar 5;139(10):e56-e528.
2. Colilla S, Crow A, Petkun W, et al. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol.* 2013;112(8):1142-1147.
3. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation.* 2016;133(4):e38-360.
4. Patel NJ, Deshmukh A, Pant S, et al. Contemporary trends of hospitalization for atrial fibrillation in the United States, 2000 through 2010: implications for healthcare planning. *Circulation.* 2014;129(23):2371-2379.
5. Rozen G, Hosseini SM, Kaadan MI, et al. Emergency Department Visits for Atrial Fibrillation in the United States: Trends in Admission Rates and Economic Burden From 2007 to 2014. *J Am Heart Assoc.* 2018;7(15):e009024.
6. Martin A, Coll-Vinent B, Suero C, et al. Benefits of rhythm control and rate control in recent-onset atrial fibrillation. the hermes-af study. *Acad Emerg Med.* 2019;26(9):1034-1043.
7. Sacchetti A, Williams J, Levi S, et al. Impact of emergency department management of atrial fibrillation on hospital charges. *West J Emerg Med.* 2013;14(1):55-57.
8. Pluymaekers N, Dudink E, Luermans J, et al. Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation. N Engl J Med 2019;380:1499-508.

9. Nuotio I, Hartikainen JE, Gronberg T, et al. Time to cardioversion for acute atrial fibrillation and thromboembolic complications. *JAMA.* 2014;312(6):647-649.
10. Airaksinen KE, Gronberg T, Nuotio I, et al. Thromboembolic complications after cardioversion of acute atrial fibrillation: the FinCV (Finnish CardioVersion) study. *J Am Coll Cardiol.* 2013;62(13):1187-1192.
11. Granada J, Uribe W, Chyou PH, et al. Incidence and predictors of atrial flutter in the general population. *J Am Coll Cardiol.* 2000;36(7):2242-2246.
12. Bertaglia E, Zoppo F, Bonso A, et al. Long term follow up of radiofrequency catheter ablation of atrial flutter: clinical course and predictors of atrial fibrillation occurrence. *Heart.* 2004;90(1):59-63.
13. Brembilla-Perrot B, Girerd N, Sellal JM, et al. Risk of atrial fibrillation after atrial flutter ablation: impact of AF history, gender, and antiarrhythmic drug medication. *J Cardiovasc Electrophysiol.* 2014;25(8):813-820.
14. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2014;64(21):e1-76.
15. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J.* 2016;37(38):2893-2962.
16. Andrade JG, Verma A, Mitchell LB, et al. 2018 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. *Can J Cardiol.* 2018;34(11):1371-1392.
17. Stiell IG, Clement CM, Perry JJ, et al. Association of the Ottawa Aggressive Protocol with rapid discharge of emergency department patients with recent-onset atrial fibrillation or flutter. *CJEM.* 2010;12(3):181-191.
18. Stiell IG, Scheuermeyer FX, Vadeboncoeur A, et al. CAEP Acute Atrial Fibrillation/Flutter Best Practices Checklist. *CJEM.* 2018;20(3):334-342.
19. Baugh CW, Clark CL, Wilson JW, et al. Creation and Implementation of an Outpatient Pathway for Atrial Fibrillation in the Emergency Department Setting: Results of an Expert Panel. *Acad Emerg Med.* 2018;25(9):1065-1075.
20. Michael JA, Stiell IG, Agarwal S, et al. Cardioversion of paroxysmal atrial fibrillation in the emergency department. *Ann Emerg Med.* 1999;33(4):379-387.
21. Bellone A, Etteri M, Vettorello M, et al. Cardioversion of acute atrial fibrillation in the emergency department: a prospective randomised trial. *Emerg Med J.* 2012;29(3):188-191.
22. Flynn D, Knoedler MA, Hess EP, et al. Engaging patients in health care decisions in the emergency department through shared decision-making: a systematic review. *Acad Emerg Med.* 2012;19(8):959-967.
23. Seaburg L, Hess EP, Coylewright M, et al. Shared decision making in atrial fibrillation: where we are and where we should be going. *Circulation.* 2014;129(6):704-710.
24. Stiell IG, Clement CM, Brison RJ, et al. Variation in management of recent-onset atrial fibrillation and flutter among academic hospital emergency departments. *Ann Emerg Med.* 2011;57(1):13-21.

25. Rogenstein C, Kelly AM, Mason S, et al. An international view of how recent-onset atrial fibrillation is treated in the emergency department. *Acad Emerg Med.* 2012;19(11):1255-1260.
26. Slavik RS, Tisdale JE, Borzak S. Pharmacologic conversion of atrial fibrillation: a systematic review of available evidence. *Prog Cardiovasc Dis.* 2001;44(2):121-152.
27. Chevalier P, Durand-Dubief A, Burri H, et al. Amiodarone versus placebo and class Ic drugs for cardioversion of recent-onset atrial fibrillation: a meta-analysis. *J Am Coll Cardiol.* 2003;41(2):255-262.
28. McNamara RL, Tamariz LJ, Segal JB, et al. Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. *Ann Intern Med.* 2003;139(12):1018-1033.
29. Bash LD, Buono JL, Davies GM, et al. Systematic review and meta-analysis of the efficacy of cardioversion by vernakalant and comparators in patients with atrial fibrillation. *Cardiovasc Drugs Ther.* 2012;26(2):167-179.
30. Yan H, Aung TT, Guoqiang Z, et al. Meta-analysis of effect of vernakalant on conversion of atrial fibrillation. *BMC Res Notes.* 2013;6:94.
31. Lip GY, Apostolakis S. Atrial fibrillation (acute onset). *BMJ Clin Evid.* 2014;2014:0210
32. Markey GC, Salter N, Ryan J. Intravenous Flecainide for Emergency Department Management of Acute Atrial Fibrillation. *J Emerg Med.* 2018;54(3):320-327.
33. Akel T, Lafferty J. Efficacy and safety of intravenous vernakalant for the rapid conversion of recent-onset atrial fibrillation: A meta-analysis. *Ann Noninvasive Electrocardiol.* 2018;23(3):e12508.
34. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med.* 2015;162(11):777-784.
35. The Digitalis in Acute Atrial Fibrillation (DAAF) Trial Group. Intravenous digoxin in acute atrial fibrillation: Results of a randomized, placebo-controlled multicentre trial in 239 patients. *Eur Heart J.* 1997;18(4):649-654.
36. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. https://training.cochrane.org/handbook. Accessed February 23, 2019.
37. Brown S, Hutton B, Clifford T, et al. A Microsoft-Excel-based tool for running and critically appraising network meta-analyses--an overview and application of NetMetaXL. *Syst Rev.* 2014;3:110.
38. Lunn DJ, Thomas A, Best N, et al. WinBUGS - a Bayesian modelling framework: concepts, structure, and extensibility. *Statistics and Computing*. 2000;10:325–337.
39. Alp NJ, Bell JA, Shahi M. Randomised double blind trial of oral versus intravenous flecainide for the cardioversion of acute atrial fibrillation. *Heart.* 2000;84(1):37-40.
40. Balla I, Petrela E, Kondili A. Pharmacological conversion of recent atrial fibrillation: a randomized, placebo-controlled study of three antiarrhythmic drugs. *Anadolu Kardiyol Derg.* 2011;11(7):600-606.
41. Camm AJ, Capucci A, Hohnloser SH, et al. A randomized active-controlled study comparing the efficacy and safety of vernakalant to amiodarone in recent-onset atrial fibrillation. *J Am Coll Cardiol.* 2011;57(3):313-321.

42. Capucci A, Villani GQ, Aschieri D, et al. Safety of oral propafenone in the conversion of recent onset atrial fibrillation to sinus rhythm: a prospective parallel placebo-controlled multicentre study. *Int J Cardiol.* 1999;68(2):187-196.
43. Chu K, Evans R, Emerson G, et al. Magnesium sulfate versus placebo for paroxysmal atrial fibrillation: a randomized clinical trial. *Acad Emerg Med.* 2009;16(4):295-300.
44. Halinen MO, Huttunen M, Paakkinen S, et al. Comparison of sotalol with digoxin-quinidine for conversion of acute atrial fibrillation to sinus rhythm (the Sotalol-Digoxin-Quinidine Trial). *Am J Cardiol.* 1995;76(7):495-498.
45. Hohnloser SH, Dorian P, Straub M, et al. Safety and efficacy of intravenously administered tedisamil for rapid conversion of recent-onset atrial fibrillation or atrial flutter. *J Am Coll Cardiol.* 2004;44(1):99-104.
46. Joseph AP, Ward MR. A prospective, randomized controlled trial comparing the efficacy and safety of sotalol, amiodarone, and digoxin for the reversion of new-onset atrial fibrillation. *Ann Emerg Med.* 2000;36(1):1-9.
47. Kafkas NV, Patsilinakos SP, Mertzanos GA, et al. Conversion efficacy of intravenous ibutilide compared with intravenous amiodarone in patients with recent-onset atrial fibrillation and atrial flutter. *Int J Cardiol.* 2007;118(3):321-325.
48. Maciag A, Farkowski MM, Chwyczko T, et al. Efficacy and safety of antazoline in the rapid cardioversion of paroxysmal atrial fibrillation (the AnPAF Study). *Europace.* 2017;19(10):1637-1642.
49. Madonia S, De Simone M, Brai G, et al. Intravenous versus oral initial load of propafenone for conversion of recent-onset atrial fibrillation in the emergency room: a randomized trial. *Ital Heart J.* 2000;1(7):475-479.
50. Madrid AH, Moro C, Marin-Huerta E, et al. Comparison of flecainide and procainamide in cardioversion of atrial fibrillation. *Eur Heart J.* 1993;14(8):1127-1131.
51. Martinez-Marcos FJ, Garcia-Garmendia JL, Ortega-Carpio A, et al. Comparison of intravenous flecainide, propafenone, and amiodarone for conversion of acute atrial fibrillation to sinus rhythm. *Am J Cardiol.* 2000;86(9):950-953.
52. Noc M, Stajer D, Horvat M. Intravenous amiodarone versus verapamil for acute conversion of paroxysmal atrial fibrillation to sinus rhythm. *Am J Cardiol.* 1990;65(9):679-680.
53. Reisinger J, Gatterer E, Lang W, et al. Flecainide versus ibutilide for immediate cardioversion of atrial fibrillation of recent onset. *Eur Heart J.* 2004;25(15):1318-1324.
54. Simon A, Niederdoeckl J, Skyllouriotis E, et al. Vernakalant is superior to ibutilide for achieving sinus rhythm in patients with recent-onset atrial fibrillation: a randomized controlled trial at the emergency department. *Europace.* 2017;19(2):233-240.
55. Toivonen LK, Nieminen MS, Manninen V, et al. Conversion of paroxysmal atrial fibrillation to sinus rhythm by intravenous pirmenol. A placebo controlled study. *Br Heart J.* 1986;55(2):176-180.
56. Vogiatzis I, Papavasiliou E, Dapcevitch I, et al. Vernakalant versus ibutilide for immediate conversion of recent-onset atrial fibrillation. *Hippokratia.* 2017;21:67-73.
57. Walker S, Taylor J, Harrod R. The acute effects of magnesium in atrial fibrillation and flutter with a rapid ventricular rate. *Emergency Medicine.* 1996;8(4):207-213.
58. Morrison A, Polisena J, Husereau D, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. *Int J Technol Assess Health Care.* 2012;28(2):138-144.

59. Crijns HJ, Weijs B, Fairley AM, et al. Contemporary real life cardioversion of atrial fibrillation: Results from the multinational RHYTHM-AF study. *Int J Cardiol*. 2014;172(3):588-594.
60. Mills EJ, Ghement I, O'Regan C, et al. Estimating the power of indirect comparisons: a simulation study. *PLoS One.* 2011;6(1):e16237.
61. Thorlund K, Mills EJ. Sample size and power considerations in network meta-analysis. *Syst Rev.* 2012;1:41.
62. Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. *BMJ.* 2013;346:f2914.
63. Brignardello-Petersen R, Bonner A, Alexander PE, et al. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *J Clin Epidemiol*. 2018;93:36-44.
64. Kulakowski P, Karczmarewicz S, Karpinski G, et al. Effects of intravenous amiodarone on ventricular refractoriness, intraventricular conduction, and ventricular tachycardia induction. *Europace.* 2000;2(3):207-215.
65. Morady F, DiCarlo LA, Jr., Krol RB, et al. Acute and chronic effects of amiodarone on ventricular refractoriness, intraventricular conduction and ventricular tachycardia induction. *J Am Coll Cardiol.* 1986;7(1):148-157.
66. Letelier LM, Udol K, Ena J, et al. Effectiveness of amiodarone for conversion of atrial fibrillation to sinus rhythm: a meta-analysis. *Arch Intern Med.* 2003;163(7):777-785.
67. Strickberger SA, Ip J, Saksena S, et al. Relationship between atrial tachyarrhythmias and symptoms. *Heart Rhythm.* 2005;2(2):125-131.
68. Alboni P, Botto GL, Baldi N, et al. Outpatient treatment of recent-onset atrial fibrillation with the "pill-in-the-pocket" approach. *N Engl J Med.* 2004;351(23):2384-2391.
69. Andrade JG, MacGillivray J, Macle L, et al. Clinical effectiveness of a systematic "pill-in-the-pocket" approach for the management of paroxysmal atrial fibrillation. *Heart Rhythm.* 2018;15(1):9-16.
70. Narasimhan R, Belardinelli L, Schuler CA. Combining Electronic Monitoring With Inhaled Pharmacological Therapy to Manage Cardiac Arrhythmias Including Atrial Fibrillation. In: Google Patents; 2018.
71. Saborido CM, Hockenhull J, Bagust A, et al. Systematic review and cost-effectiveness evaluation of 'pill-in-the-pocket' strategy for paroxysmal atrial fibrillation compared to episodic in-hospital treatment or continuous antiarrhythmic drug therapy. *Health Technol Assess.* 2010;14(31):iii-iv, 1-75.
72. Vinson DR, Lugovskaya N, Warton EM, et al. Ibutilide Effectiveness and Safety in the Cardioversion of Atrial Fibrillation and Flutter in the Community Emergency Department. *Ann Emerg Med.* 2018;71(1):96-108 e102.
73. Nagam MR, Thiel GG, Dutczak O, et al. Abstract 627: Patient Selection, Dosing Patterns, Safety, and Delayed Time to Effect of Intravenous Amiodarone in the Cardioversion of Atrial Fibrillation and Flutter in 13 United States Community Emergency Departments. SAEM Annual Meeting Abstracts. *Acad Emerg Med.* 2018;25(S1):S224.
74. Andrade JG, Champagne J, Deyell MW, et al. A randomized clinical trial of early invasive intervention for atrial fibrillation (EARLY-AF) - methods and rationale. *Am Heart J.* 2018;206:94-104.