Mixed treatment comparisons for atrial fibrillation: evidence network or bewildering entanglement?

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This editorial refers to ‘Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation’ by N. Freemantle et al., on page 329.

Atrial fibrillation (AF) imparts significant morbidity and mortality, affecting more than 6 million patients in Europe alone. The impairment in quality of life attributable to AF is similar to the deficits associated with myocardial infarction or heart failure.1 Current clinical practice guidelines advocate antiarrhythmic therapy for patients with debilitating symptoms despite adequate rate control.2,3 Although successive generations of antiarrhythmic drugs have broadened the array of therapeutic options, rates of AF recurrence and toxicity remain frustrating.4 In 2009, dronedarone (400 mg b.i.d.) became the first antiarrhythmic drug in nearly 2 decades to be approved in the European Union for the treatment of AF. Direct comparisons between dronedarone and other antiarrhythmic agents are limited, creating uncertainty for clinicians.

Given the paucity of direct, head-to-head data comparing dronedarone and other antiarrhythmic agents for AF, Freemantle et al.5 analysed outcomes from 40 different randomized-controlled trials of currently available guideline recommended class IC and class III agents (amiodarone, dronedarone, flecainide, propafenone, and sotalol).6 In addition to conventional random-effect meta-analysis models that evaluated only the direct comparisons between drugs, the investigators constructed a model that accommodated both the direct and indirect treatment comparisons within the available data.

In direct comparisons, amiodarone had the greatest overall efficacy for the prevention of recurrent AF [odds ratio (OR) 0.15, 95% CI 0.10–0.22] and was superior to both sotalol and dronedarone. In terms of safety, all of the included antiarrhythmic drugs were associated with an increased rate of discontinuation for adverse events compared with placebo, though the risk was lowest with dronedarone (OR 1.63, 95% CI 1.32–2.03). In the mixed-treatment analysis, sotalol was associated with an increased risk of all-cause mortality relative to placebo (OR 3.44, 95% CI 1.02–11.59). When restricting their analysis to trials with more than 100 patients in each arm, there was an increased odds of death among those treated with amiodarone (P = 0.049) and sotalol (P = 0.013). Dronedarone was associated with a lower risk of stroke (OR 0.69, 95% CI 0.57–0.84), while amiodarone and sotalol were not. When comparing the totality of the evidence across all of the selected endpoints, dronedarone was found to have less efficacy than amiodarone (more recurrences) but fewer serious adverse events (amiodarone vs. dronedarone, OR 0.40, 95% CI 0.20–0.80) and suggest that for every 16 patients treated with amiodarone instead of dronedarone, there would be one additional death. Others have estimated one death for every 104 treated.6 The uncertainty around these estimates is considerable and neither achieves statistical significance. Heterogeneous amiodarone doses (including doses >400 mg) also confound interpretation of these findings. While a direct, active-comparator trial of dronedarone and amiodarone in patients with persistent AF was completed and included in these meta-analyses, the DIONYSOS (Double-blind trial to evaluate efficacy and safety of drOnedarone [400 mg b.i.d.] vs. amiodarONe [600 mg q.d. for 28 daYS, then 200 mg q.d. thereafter] for at least 6 mOnths for the maintenance of Sinus rhythm in patients with AF) trial did not reveal a statistically significant safety difference.

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advantage with dronedarone. However, DIONYSOS was small, underpowered, and limited by brief follow-up. The data regarding stroke rates are a novel and important contribution of this meta-analysis. The association between dronedarone and lower odds of stroke is intriguing and raises the possibility that antiarrhythmic drug therapy may lower stroke risk. Prior work has shown that amiodarone therapy for the prevention of postoperative AF is associated with a lower risk of stroke following cardiac surgery. However, as acknowledged by the authors, several factors limit the conclusions drawn from these analyses. Stroke and systemic embolism were not adjudicated, principal endpoints in most (if not all) antiarrhythmic drug trials and are susceptible to reporting bias. Second, stroke prophylaxis and quality of anticoagulation have been variable in antiarrhythmic drug trials. For example, prior studies have shown higher rates of discontinuation of warfarin among patients managed with a rhythm-control strategy. In the more recent ATHENA study (A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg b.i.d. for the prevention of cardiovascular Hospitalization or death from any cause in patients with Atrial fibrillation/atrial flutter), the largest study included in the analysis, only 60% of the patients with a CHADS2 score ≥2 were receiving oral anticoagulant therapy and the time in therapeutic range was only 50%. The Permanent Atrial fibrillation Outcome Study using dronedarone on top of the standard therapy (PALLAS) trial (NCT01151137) should provide important insight into dronedarone therapy, its therapeutic mechanisms, and its effect on stroke risk.

Both direct and indirect meta-analyses present challenges when interpreting and applying the results. There is considerable statistical and clinical heterogeneity present within this collection of trials. For example, the ATHENA trial was largely a trial of the elderly (mean age 72 years), compared with the overall median age of 62 across all 40 studies. Additionally, there was a significant variation in the duration and type of AF enrolled across the trials, variables known to impact both the risk of recurrence and outcomes. Although random-effect models accommodate statistical heterogeneity, their ability to account for clinical heterogeneity may be incomplete. The authors’ decision to pool different dosing strategies could bias estimates of discontinuation and recurrence rates. The brief follow-up in many of these trials highlights the need for long-term outcomes data following antiarrhythmic therapy for AF. Fifteen (38%) of the 40 studies followed patients for 6 months or less. Long-term outcomes are more robust estimates for the tolerability and safety of drug therapy, but would optimally require analysis of hazard ratios rather than ORs.

The findings of Freemantle et al. confirm and extend the findings of prior meta-analyses of dronedarone. While dronedarone maintains sinus rhythm less effectively than other antiarrhythmic drugs, it appears to have important safety advantages. Thus, dronedarone represents an important addition to the antiarrhythmic armamentarium. The analysis by Freemantle et al. provides a broad overview of the relative safety and efficacy trade-offs among the currently available agents, facilitating the selection of treatment plans for individual patients. Establishing effectiveness for regulatory approval of new drugs has typically mandated placebo controls for assay sensitivity, while clinical decision-making is most informed by head-to-head comparisons of efficacy and safety between active drugs. Since 2004, the European Medicines Agency has recommended that both placebo-controlled and active comparator trials should be performed for new drugs. Large, randomized, comparative effectiveness trials with sufficient long-term follow-up are the gold standard for defining optimum clinical practice. In AF, definitive trials should not only examine recurrence rates and safety endpoints, but also hospitalization, thrombo-embolic events, and quality of life. As the therapeutic armamentarium expands, the expense and diversity of patient populations may render this paradigm impracticable due to increasing costs and dwindling resources. Absent these data, comparative efficacy and safety will continue to rely upon a Gordian web of broad-based models, indirect estimates and sticky assumptions.


References