Meta-analysis of cardiovascular outcomes with dronedarone in patients with atrial fibrillation or heart failure

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CRD summary
This review concluded that, compared to controls, pooled analysis showed increased all-cause and cardiovascular mortality and increased heart failure exacerbations with dronedarone in a wide spectrum of populations; therefore, it should be used with caution especially in those with cardiovascular risk factors. As the authors conclusions depend on questionable sensitivity analyses they should be treated with some caution.

Authors' objectives
To evaluate the cardiovascular safety profile of dronedarone across the populations in which it has been tested.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1966 to December 2010. Search terms were reported. The reference lists of reviews and included studies were checked for additional studies. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) of more than 100 adults (18 years or older) that compared dronedarone to comparator were eligible for inclusion. Studies where dronedarone was used as an adjunctive treatment were excluded. Primary outcomes of interest were all-cause mortality and cardiovascular mortality at longest follow-up. Secondary outcomes were ventricular tachyarrhythmia, stroke and systemic embolism, acute coronary syndrome, heart failure exacerbations and rehospitalisation.

Trials included people with permanent, paroxysmal or persistent atrial fibrillation, and in one study heart failure. Most studies excluded those with high-degree atrioventricular blocks, bradycardia, prolonged corrected QT interval and implantable cardioverter–defibrillators. Mean ages ranged from 62 to 75 years, and between 51 and 79% were men. In most studies dronedarone dosage was 400mg twice daily; in one study doses ranged up to 1,600mg daily. Most were placebo controlled, but in one study the comparator was amiodarone (600mg/day then 200mg/day).

One reviewer assessed studies for inclusion. Results were checked by other authors. Disagreements were resolved by consensus.

Assessment of study quality
Quality was assessed according to methods of randomisation, concealment, blinding, intention-to-treat, baseline comparisons, concomitant interventions and completeness of follow-up.

The authors did not state how many of them assessed quality.

Data extraction
Data were extracted to calculate risk ratio (RR) and 95% confidence intervals (CI).

One reviewer extracted data. Results were checked by other authors. Disagreements were resolved by consensus.

Methods of synthesis
A random-effects model was used to calculate pooled risk ratio and 95% confidence intervals. Heterogeneity was assessed using X² test and I². Low heterogeneity was defined as I² less than 25%. Sensitivity analysis explored the effect of removing one study that contributed to heterogeneity, and the study with an active comparator. Subgroup analyses investigated removal of those studies in people with heart failure, and with permanent atrial fibrillation. Publication bias was assessed using funnel plots and Egger's test.
Results of the review

Seven RCTs (10,676 participants) were included. Study size ranged from 174 to 4,628 participants. Follow-up ranged from three to 26 months.

All studies were considered high quality. No details were reported.

There were more deaths in the dronedarone groups than in the control groups, but pooled data showed no statistically significant difference for all-cause mortality ($\chi^2$=53%, seven trials) and cardiovascular mortality ($\chi^2$=75%). Removal of one large study removed heterogeneity for both outcomes, and led to statistically significant worse effects with dronedarone. Removal of a further study on people with heart failure, led to no statistically significant effect on total mortality, but maintained the statistically significant worse effect on cardiovascular mortality (five trials). The effect of removing the study on people with permanent atrial fibrillation had similar results.

The effects on risk of heart failure exacerbations were not statistically significant ($\chi^2$=52%, six trials) until the removal of the same large study that contributed to heterogeneity, resulting in dronedarone being associated with a statistically significant worsening in heart failure exacerbations.

In subgroup analysis dronedarone decreased rehospitalisation rates in people with paroxysmal or persistent atrial fibrillation (two trials). All other secondary outcomes (apart from acute coronary syndrome) showed trends towards worse outcomes with dronedarone, but none were statistically significant.

Sensitivity analyses showed that removing the study that used an active comparator did not change results.

Authors' conclusions

Pooled analysis showed increased all-cause and cardiovascular mortality and increased heart failure exacerbations with dronedarone in a wide spectrum of populations.

CRD commentary

The aims of this review were clearly stated in terms of the inclusion criteria. Search terms reported appeared inadequate for finding studies in populations other than in those with atrial fibrillation (such as with heart failure or other arrhythmias). It was possible that studies were missed. Methods of study selection and data extraction were aimed at reducing possible reviewer error or bias, those for quality assessment weren't clear. Quality was assessed, but details of assessment results weren't clearly reported, so it was not possible to comment on any possible bias in individual studies.

Overall, the methods of synthesis appeared appropriate and heterogeneity was assessed. Little information was presented about the included participants, especially concerning severity of disease or any concomitant medications, and this could affect the generalisability of the results. The main analyses were generally inconclusive and only removal of the largest study (contributing around three quarters of the review's mortality events), with the longest follow-up, resulted in statistically significant results. The authors made no attempt to explain why this study may have have been clinically or methodologically different from other studies.

As the conclusions depend on sensitivity analyses, and because study quality results were not clearly presented, they should be treated with some caution.

Implications of the review for practice and research

Practise: The authors stated that caution should be exercised in using dronedarone, especially in people with cardiovascular risk factors.

Research: The authors did not state any implications for research.

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None stated.

Bibliographic details

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.