Chronic atrial fibrillation: a systematic review of medical heart rate control management

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CRD summary
The authors concluded that available limited data supported use of digoxin in combination with a β-blocker or rate-limiting calcium antagonist as a first-line treatment for chronic atrial fibrillation. The lack of numerical and statistical data and the unjustified exclusion of studies rated as poor quality made it difficult to determine the reliability of this conclusion.

Authors' objectives
To assess the effectiveness of digoxin, β-blockers and calcium antagonists in controlling heart rate and improving symptoms and exercise tolerance in patients with chronic atrial fibrillation.

Searching
MEDLINE, EMBASE and unspecified Cochrane databases were searched. Search dates were not reported. Limited details on search terms were reported. Key journals, conference proceedings and bibliographies of relevant articles were handsearched.

Study selection
Randomised controlled trials (RCTs) and observational studies that evaluated oral digoxin, β-blockers or calcium antagonists (at least one in the treatment arm) alone or in combination for rate control in patients with chronic atrial fibrillation were eligible for inclusion.

The included studies evaluated varied combinations of digoxin and β-blockers or calcium antagonists (diltiazem, verapamil). Treatment durations ranged from one day to one year. The mean age of patients ranged from 48 to 74 years. Varied protocols were used to assess response to treatments (for example, 24 hour heart rate recordings, varied exercise protocols). Outcomes evaluated included: change in exercise or resting heart rates; exercise tolerance; and adverse drug events.

Two reviewers independently screened identified articles for eligibility.

Assessment of study quality
The quality of RCTs was assessed on the basis of the Delphi list according to the following criteria: adequacy of randomisation; allocation concealment; blinding; reporting of eligibility criteria; intention-to-treat analysis; reporting of side effects; and loss to follow-up. For observational studies, quality was assessed according to the adequacy of eligibility criteria, sample selection, outcome measurement criteria and duration of follow-up. Quality was rated as good, fair or poor. It was unclear how the ratings were achieved.

Two reviewers independently assessed study quality.

Data extraction
Data on the number of patients on digoxin, regimens of β-blockers or calcium antagonists and effects on outcomes (such as resting and exercise heart rates) were extracted and entered into a predefined form.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Studies were grouped into tables according to intervention category (β-blockers, diltiazem, verapamil) and results summarised in a narrative synthesis. Nine studies rated as poor quality were excluded.
Results of the review
Overall 46 studies (n=1,062 patients) were included: 36 RCTs (n=867); one cross-over non-randomised trial (n=52); one case-control (n=23), and eight observational time series studies (n=120). Quality of included studies varied from fair to good.

β-blockers alone (10 studies): One study reported improved heart rate control at rest compared with digoxin. Four studies reported that exercise heart rate was better controlled compared with digoxin. Two studies found that β-blockers (sotalol and xamoterol) improved exercise tolerance compared with no treatment (one study) and digoxin (one study); six studies reported no improvement in exercise capacity. β-blockers were associated with significant dose-related side-effects.

Combination of β-blockers with digoxin (17 studies): Combination therapy compared with digoxin resulted in better control of resting (13 studies) and exercise heart rates (19 studies). The effect of the combination therapy on exercise tolerance was mixed: five studies reported deterioration in exercise capacity; three studies reported some improvement; and 10 reported no change.

Calcium antagonists alone (10 studies): Monotherapy with diltiazem compared to digoxin resulted in improved exercise heart rate control, but not exercise capacity (five studies). Monotherapy with verapamil compared to digoxin resulted in improved exercise heart rate (three studies) and exercise capacity (two studies). No effect on exercise tolerance was found in two studies.

Combination of diltiazem with digoxin (11 studies): Combination therapy compared to digoxin resulted in improved resting and exercise heart rates in 11 studies. Exercise tolerance was found to improve in only two out of eight studies.

Combination of verapamil with digoxin (12 studies): Combination therapy compared with digoxin alone resulted in improved resting and exercise heart rates (nine studies) and ambulatory heart rate (four studies). The effect on exercise tolerance was mixed: improvement was reported in three studies and no change was found in four studies. Diltiazem and verapamil were associated with significant dose-related side-effects.

Authors' conclusions
Available limited data supported use of digoxin in combination with a β-blocker or rate-limiting calcium antagonist as a first-line treatment for chronic atrial fibrillation.

CRD commentary
The review question and inclusion criteria were clearly stated. Three databases were searched and efforts were made to find published and unpublished studies without language restriction, hence the possibility of publication and language biases was minimised. Steps were taken to minimise reviewer error and bias in study selection and quality assessment, but not explicitly with data extraction. Quality assessment was performed using appropriate criteria, but it was unclear how the reported quality ratings were achieved. The decision to summarise results narratively was supported by the small sample sizes and differences in study methods (designs, outcomes). The statistical and clinical significance of the reported results was unclear as no numerical data was reported. The authors acknowledged limitations due to the small number of studies and patients reviewed. It is difficult to determine the reliability of the authors' conclusion given the lack of numerical and statistical data, and the unjustified exclusion of studies rated as poor quality.

Implications of the review for practice and research
Practice: The authors stated that digoxin in combination with a β-blocker or rate-limiting calcium antagonist should be the first line management for chronic atrial fibrillation.

Research: The authors stated that further large RCTs of the effectiveness and safety of digoxin alone or in combination with β-blockers or calcium antagonists for heart rate control in patients with chronic atrial fibrillation were needed. Future studies should also assess the effects of different treatment options on exercise capacity and quality of life outcomes in patients with chronic atrial fibrillation.
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