Atrial fibrillation and chronic heart failure: systematic review suggests digoxin is not associated with increased mortality

A large systematic review and meta-analysis included 52 studies in more than 600,000 people with atrial fibrillation (AF), heart failure, or a combination of these. Analysis of observational studies suggested an increased risk of all-cause mortality with digoxin, but there was no statistically significant effect on the risk of all-cause mortality when only randomised controlled trials were analysed. A statistically significant reduction was seen with digoxin in the secondary outcome, hospital admissions, in all study types. Despite a number of limitations, this study supports the NICE clinical guideline on chronic heart failure which recommends the use of digoxin after other treatments and is consistent with the NICE clinical guideline on AF, which recommends a limited place for digoxin.

Overview and current advice

The NICE clinical guideline on the management of atrial fibrillation (AF) recommends offering either a standard beta-blocker (that is, a beta-blocker other than sotalol) or a rate-limiting calcium-channel blocker as initial monotherapy to people with AF who need drug treatment as part of a rate-control strategy. The choice of drug should be based on the person's symptoms, heart rate, comorbidities and preferences. Digoxin monotherapy may be considered for people with non-paroxysmal AF only if they are sedentary (do no or very little physical exercise). If monotherapy does not control symptoms, and if continuing symptoms are thought to be due to poor ventricular rate control, combination therapy with any 2 of the following should be considered: a beta-blocker, diltiazem or digoxin. Amiodarone should not be considered for long-term rate control.

In the NICE clinical guideline on chronic heart failure (being updated, anticipated publication March 2018) digoxin is recommended for worsening or severe heart failure due to left ventricular systolic dysfunction (LVSD) despite first- and second-line treatment for heart failure.

The largest randomised controlled trial (RCT), the DIG study (n=6800), of digoxin in people with heart failure and LVSD (in normal sinus rhythm) found that, while digoxin did not reduce overall mortality, it did reduce the rate of overall hospitalisation and hospitalisation for worsening heart failure. However, post-hoc analysis of the DIG study suggested that higher serum digoxin concentrations were associated with increased mortality. Since then, an observational study and several retrospective analyses of RCTs, including a large systematic review and meta-analysis, have also suggested an association between digoxin and increased mortality in both AF and heart failure. However, data on this association are conflicting. See the NICE Medicines Evidence Commentary from July 2015 for more detail on the systematic review that considers this issue and the NICE Medicines Evidence Commentary.
Commentaries from April 2013 and July 2013 for further information on digoxin and associated mortality outcomes.

The NICE pathways on chronic heart failure and atrial fibrillation bring together all related NICE guidance and associated products on the conditions in sets of interactive topic-based diagrams. See the Clinical knowledge summaries information on atrial fibrillation and chronic heart failure for a general overview of prescribing considerations.

New evidence

A large systematic review and meta-analysis of 52 studies (observational and RCTs) in 621,845 people considered the effect of digoxin on all-cause mortality and other clinical outcomes. Studies comparing digoxin with control in any population that were published between 1960 and July 2014 were included. The data represented 2,248,775 patient years of follow-up. Of the 42 studies that were included in the quantitative synthesis of outcomes, 7 were RCTs, 9 were post hoc analyses of RCTs and 26 were retrospective or prospective cohort studies. Follow-up ranged from 0.25 to 8.2 years (weighted average 3.7 years). Several statistically significant differences were found between digoxin and control groups at baseline. People in the digoxin groups were slightly older (by 2.4 years), more likely to have diabetes, AF or heart failure and more likely to be taking diuretics or antiarrhythmic drugs.

A total of 41 studies looked at all-cause mortality. This included 7 RCTs in 8406 people. When the authors analysed the different types of data, they found that studies with higher bias reported a greater association between digoxin and increased all-cause mortality (p<0.001). When digoxin was compared with control, the pooled relative risk (RR) of all-cause mortality was 1.76 in unadjusted analyses of observational studies (95% confidence interval [CI] 1.57 to 1.97; 33 analyses, n=331,935), 1.61 in adjusted analyses of observational studies (95% CI 1.31 to 1.97; 22 analyses, n=245,049) and 1.18 in propensity-matched observational studies (95% CI 1.09 to 1.26; 13 analyses, n=414,604). However, no statistically significant difference in the risk of all-cause mortality was found between digoxin and control in RCTs (RR 0.99, 95% CI 0.93 to 1.05; 7 RCTs, n=8406). All 7 of these RCTs were in people who had heart failure.

The authors considered the risk of digoxin on mortality in people who had both heart failure and AF, but no statistically significant effect was found in this group. This was not based on any RCTs, but on 2 analyses of crude observational data, 2 adjusted observational analyses and 2 propensity matched cohorts (total n=46,274 and 139,769 patient years of follow-up).

Meta-regression analyses of observational studies found that baseline differences between treatment groups (such as diabetes and use of diuretics) and other factors (such as date of publication and age) had a statistically significant effect on the association between digoxin and mortality.

For other outcomes, no statistically significant association between digoxin and cardiovascular mortality was found in 5 RCTs (n=8068) in people with heart failure, AF or both, but pooled data from 1 adjusted and 2 unadjusted observational studies in other populations reported an increased risk. A statistically significant reduction in hospital admission was found amongst all study types (when grouped together or analysed by study type). Meta-analysis of all studies (including the DIG trials) found a RR of hospital admission of 0.92 (95% CI 0.89 to 0.95, p<0.001). There was only limited information on digoxin concentrations; this suggested that lower serum digoxin concentrations between 0.5 and 0.9 ng/ml were associated with improved prognosis.

Commentary

Commentary provided by the Medicines and Prescribing Centre

This large systematic review and meta-analysis adds substantially to evidence from previous studies that have looked at the effects of digoxin on mortality. The association between digoxin use and increased mortality reported in observational studies was no longer statistically significant when RCTs were added to the analysis. However, for the secondary outcome of hospital admissions, a statistically
significant reduction was observed with digoxin in all study types. This suggests that digoxin has a neutral effect on all-cause mortality, but reduces hospital admission.

These conclusions are supported by the fact that, in the observational studies, differences were found in the baseline characteristics of participants in the digoxin and control groups, and these had a statistically significant impact on mortality associated with digoxin. In addition, the authors suggested that in observational studies, there is likely to be confounding by indication. This means that sicker people are more likely to be prescribed digoxin, which then leads to a false association between digoxin use and death. The editorial to this paper highlights the limitations of using observational data to guide clinical recommendations and issues the following caution: “An observational study cannot be mutated into a randomised trial by statistical adjustment or propensity matching; the randomisation is a crucial part of trial design.”

A previous large systematic review and meta-analysis of 19 studies in more than 300,000 people by Vamos et al. reported an association between digoxin use and increased mortality, particularly in people who had AF (see the NICE Medicines Evidence Commentary from July 2015). However, all study types (including observational studies and RCTs) were analysed together and only 1 RCT, the DIG study, provided most of the randomised data (6800 people out of 8406 people in all RCTs). In addition, heart failure and AF can have a wide clinical spectrum, but details of severities of these were lacking for all participants. Furthermore, there was limited information on digoxin concentrations and it is not known how this might have affected the risk of mortality reported.

When applying the results of this study to clinical practice, it is important to note that all of the RCTs analysed were in people with heart failure (with or without AF). There is currently a lack of randomised data in people who have AF without heart failure and the findings from this study cannot be generalised to these people. This study supports the use of digoxin after other treatments as outlined in the NICE clinical guideline on chronic heart failure. The lack of RCT data available in people who have AF without heart failure is consistent with the limited placebo of digoxin in the NICE clinical guideline on AF. Results from further RCTs, which are currently underway in people with AF (RATE-AF) and heart failure (DIGIT-HF), may help to inform the future use of digoxin.

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**References**


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