A retrospective, post-hoc analysis of the AFFIRM randomised controlled trial found taking digoxin was not associated with a statistically significant increase in mortality in people with atrial fibrillation. This challenges the conclusions of previous retrospective studies of AFFIRM that found digoxin was associated with an increase in all-cause mortality. However, these are observational studies and have several limitations. This Medicines Evidence Commentary discusses the differences between this retrospective analysis and a previous retrospective analysis that was considered in a NICE Medicines Evidence Commentary in April 2013. Both retrospective analyses are consistent with the limited place in therapy of digoxin outlined in NICE guidance on the management of atrial fibrillation (currently being updated).

Overview and current advice

The NICE clinical guideline on the management of atrial fibrillation (AF) (currently being updated) recommends beta-blockers or rate-limiting calcium channel blockers as the preferred initial monotherapy to control heart rate in people with permanent AF and those with persistent AF who have been selected for a rate-control treatment strategy. Digoxin should only be considered as monotherapy in predominantly sedentary people. Where monotherapy is inadequate, beta-blockers or rate-limiting calcium channel blockers with digoxin are recommended to control heart rate during normal activities. Rate-limiting calcium channel blockers with digoxin are recommended to control heart rate during exercise.

Digoxin is also recommended in the NICE clinical guideline on chronic heart failure for worsening or severe heart failure due to left ventricular systolic dysfunction (LVSD) despite first- and second-line treatment for heart failure (not specifically in AF).

The largest randomised controlled trial (RCT), the DIG study, 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. Furthermore, an observational study and retrospective analyses
of RCTs have also suggested an association between digoxin and increased mortality in both AF\textsuperscript{3,4} and heart failure\textsuperscript{5}.

In the large AFFIRM RCT (n=4060, mean follow-up 3.5 years) people aged 65 years or older with paroxysmal or persistent AF were randomised to a rate control strategy or a rhythm control strategy (with drug choice at the discretion of the clinician)\textsuperscript{6}. The study did not find any benefit on survival with rhythm-control drugs (such as amiodarone, flecainide and sotalol) over rate-control drugs (digoxin, beta-blockers or rate-limiting calcium channel blockers).\textsuperscript{6} The investigators conducted a retrospective (post hoc) analysis of AFFIRM and suggested that digoxin use was associated with an increase in all cause mortality (adjusted hazard ratio [HR] 1.42, 95% confidence interval [CI] 1.09 to 1.86, \(p=0.0007\)). Furthermore, a recent retrospective analysis of the AFFIRM RCT (Whitbeck et al. 2012)\textsuperscript{8} found that taking digoxin was associated with a statistically significant increase in all-cause mortality (estimated HR 1.41, 95% CI 1.19 to 1.67, \(p=0.001\)) and cardiovascular mortality (estimated HR 1.35, 95% CI 1.06 to 1.71, \(p=0.016\)) in people with AF, with or without heart failure. Digoxin was also associated with an increase in deaths from arrhythmias (estimated HR 1.61, 95% CI 1.12 to 2.30, \(p=0.009\)). However, such observational studies have limitations (see the NICE Medicines Evidence Commentary on Whitbeck et al. [2012]).

See the NICE Evidence topic page on atrial fibrillation for a general overview of the condition. See the Clinical Knowledge Summaries information on atrial fibrillation for a general overview of prescribing considerations.

New evidence

A further retrospective (post-hoc) analysis of the AFFIRM RCT (Gheorghiade et al. 2013)\textsuperscript{9} has also attempted to estimate the effect of digoxin on mortality in AF. It specifically considered 1377 people who were taking digoxin at baseline and compared them with 1329 people who received no digoxin at baseline. The authors attempted to adjust for other variables (confounding factors) that might also affect participants’ risks by propensity score matching. This involved matching 878 individual patients from the digoxin group with 878 individual patients from the control group (not on digoxin), who were estimated to be similar in terms of 59 baseline characteristics (confounding factors). Matched patients had a mean age of 70 years, 40% were women, 11% were described as being of non-white ethnicity and 40% had previously been in hospital because of arrhythmias.

At follow-up (mean 3.5 years), there was no statistically significant difference in all-cause mortality between matched patients taking digoxin as an initial treatment and those who did not take digoxin as an initial treatment (14% versus 13%; HR 1.06, 95% CI 0.83 to 1.37, \(p=0.640\)). This result did not differ when matching was accounted for, nor when various sub-groups of matched patients were considered (including people with and without heart failure; people with left ventricular ejection fraction less than or at least 50%; and male or female). Neither was initial treatment with digoxin associated with an increase in all-cause mortality when its use as monotherapy, or in combination with other rate-controlling drugs, was considered. When the larger cohort before propensity matching (2706 patients) was considered, initial digoxin use was associated with a statistically significant increase in all-cause mortality (HR 1.26, 95% CI 1.04 to 1.54, \(p=0.022\)). However this was no longer significant when adjusted for confounding factors (by both multivariable adjustment and propensity-score adjustment).

In the matched cohort (1756 patients), digoxin was not associated with an increase in cardiovascular mortality (HR 1.13, 95% CI 0.79 to 1.63, \(p=0.494\)), non-cardiovascular mortality (HR 1.08, 95% CI 0.73 to 1.60, \(p=0.709\)), non-fatal-arrhythmias (HR 0.90, 95% CI 0.37 to 2.23, \(p=0.827\)) or all-cause hospitalisation (HR 0.96, 95% CI 0.85 to 1.09, \(p=0.510\)).
Commentary

The methodology of the retrospective analyses of the AFFIRM RCT by Gheorghiade et al. (2013) and Whitbeck et al. (2012) differ in a number of ways: the methods used to adjust for confounding factors; the patients analysed; and the definition used for digoxin use.

This retrospective analysis of the AFFIRM RCT by Gheorghiade et al. (2013) appears to contradict the findings of the retrospective analysis conducted by the AFFIRM investigators and the conclusions of the recent retrospective analysis (Whitbeck et al. 2012). It suggests that digoxin does not increase the risk of mortality or hospital admission in people with AF. However, it still found a statistically significant increase in mortality associated with initial digoxin treatment in the larger cohort, before propensity matching. However, the authors report this can be explained by the fact that, in this larger cohort, more people in the digoxin group had heart failure than in the group not receiving digoxin. This may have led to bias by indication. Therefore, no statistically significant difference was seen when other factors that may have affected the outcomes such as medical history (confounding factors) were adjusted for in the smaller propensity-matched cohort.

An editorial accompanying Gheorghiade et al. (2013) considers why the conclusions of Gheorghiade et al. (2013) and Whitbeck et al. (2012) are so different. In particular, the definition of ‘digoxin use’ was different between studies. Gheorghiade et al. (2013) assessed digoxin use at a fixed time point as treatment at randomisation, whereas Whitbeck et al. (2012) considered use of digoxin over time throughout the study. This time-dependent approach can introduce indication bias due to greater sickness in the digoxin group. For example, it is possible that digoxin might be continued in people who are sicker, or it might be started because people develop heart failure, which in itself can increase mortality. Another difference between the retrospective analyses is that Whitbeck et al. (2012) assessed the full cohort of patients from AFFIRM (n=4058), whereas Gheorghiade et al. (2013) was in a smaller group of selected patients (n=1756) who had data available at a single time-point (at randomisation). It is possible that such missing data may have introduced selection bias in the study by Gheorghiade et al. (2013).

Both retrospective analyses used different methods to adjust for confounding factors, each of which have limitations. The particular method (propensity adjustment) used by Whitbeck et al. (2012) is often subject to incorrect assumptions about the relationship of propensity scores and outcome and can lead to biased estimates of treatment effect. The method (propensity matching) used by Gheorghiade et al. (2013) limits the analysis because it reduces the size of the cohort. Despite attempts to minimise biases, it is possible that the authors of both retrospective analyses did not fully account for the imbalances, and also that other confounders existed which were not known and, therefore, not adjusted for.

These retrospective analyses share several other limitations, including lack of data on adherence, digoxin dose and digoxin plasma concentration (although high serum concentrations [above 1.0 nanogram/ml] were encouraged in AFFIRM; see the NICE Medicines Evidence Commentary on Whitbeck et al. [2012]). There are no double-blind prospective RCTs that have investigated the effect of digoxin on outcomes in people with AF (with or without heart failure). Such studies are needed in order to fully interpret any relationship between digoxin and mortality on a widespread level.

As outlined above, NICE guidance on the management of AF (currently being updated) recommends that beta blockers or rate-limiting calcium channel blockers are the preferred monotherapy in patients with permanent AF who need treatment for rate control. Digoxin should only be considered as monotherapy for AF in patients who are predominantly sedentary.

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References


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