

Digoxin for patients with atrial fibrillation and heart failure: paradise lost or not?[†]

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This editorial refers to ‘Increased mortality among patients taking digoxin—analysis from the AFFIRM study’[‡], by M.G. Whitbeck et al., on page 1481; and ‘Lack of evidence of increased mortality among patients with atrial fibrillation taking digoxin: findings from post hoc propensity-matched analysis of the AFFIRM trial’[#], by M. Gheorghiade et al., on page 1489

Digoxin is one of the oldest drugs in cardiovascular medicine, and it was traditionally used in patients with atrial fibrillation (AF) and heart failure (HF).¹ In the last 20 years, the use of this drug has markedly declined, and in the most recent 2012 European Society of Cardiology (ESC) HF Guidelines,² it is stated that for patients with HF and a left ventricular ejection fraction (LVEF) $\leq 40\%$, who are in sinus rhythm ‘digoxin may be used’. This recommendation is based on the Digitalis Investigation Group (DIG) trial,³ in which the effect of digoxin on outcome was examined in 6800 patients with HF. For HF patients with AF, other drugs (in particular beta-blockers) should be preferred,² since they provide better rate control. In the 2010 ESC AF Guidelines,⁴ it is stated that digoxin is effective for long-term rate control at rest, but not during exercise. Prospective, randomized, placebo-controlled outcome studies examining the effect of digoxin in patients with AF (with or without HF) are not available.

Digoxin in heart failure

In the past, it was assumed that the beneficial effect of digoxin in HF was due to its (positive) inotropic properties, which were more pronounced at higher doses of the drug.^{1,5} However, a large number of studies in patients with HF has shown that positive inotropic drugs lead to an unfavourable effect on outcome, and these drugs are now contraindicated in patients with (chronic) HF. In contrast to this inotropic effect, digoxin also exerts potentially

favourable autonomic- or neurohormonal-inhibiting properties,^{6,7} which primarily occur at lower serum digoxin concentrations (SDCs).^{1,5–7} This has been increasingly recognized in the last 25 years, and a *post hoc* analysis of the DIG trial⁸ showed that, in patients who received digoxin, low SDC (0.5–0.9 ng/mL) was associated with a lower all-cause mortality than in patients in the placebo group [29.3% vs. 32.9%, crude hazard ratio (HR) 0.78, adjusted HR 0.77, both $P < 0.001$; -6.3% , $P = 0.005$], while all-cause mortality in patients with $SDC \geq 1.0$ was 41.7% (crude HR 1.23, $P = 0.002$ vs. placebo, $P = NS$ for adjusted HR) (Figure 1). In another analysis, in which other cut-off levels were used, a serum SDC of ≥ 1.2 was associated with a crude mortality of 48.0% (crude HR 1.34, $P < 0.001$ vs. placebo, adjusted HR 1.16, $P = NS$).⁹ However, no well-designed, prospective trials have been conducted to confirm these findings.

Digoxin in atrial fibrillation

In patients with AF, the primary effect of digoxin is slowing down atrioventricular (AV) conduction, leading to a reduction in ventricular response at rest, but much less so during exercise.^{2,4} This effect of digoxin is due to enhancement of vagal tone, and is less prominent during increased sympathetic activity, such as exercise.¹⁰ Given the fact that higher digoxin doses (leading to higher SDCs) have far less neurohormonal-inhibiting properties than lower doses, it can be assumed that such higher doses are also less efficient in slowing down the ventricular rate, although this has not been investigated. In this respect, beta-blockers are more effective than digoxin in slowing heart rate during exercise in patients with AF, and beta-blockers now have a prominent place in AF patients, both with and without HF,^{2,4} and seem to have replaced digoxin in many patients. There are no double-blind, prospective, randomized studies that have investigated the effect of digoxin on outcome in AF patients (with or without HF). Although

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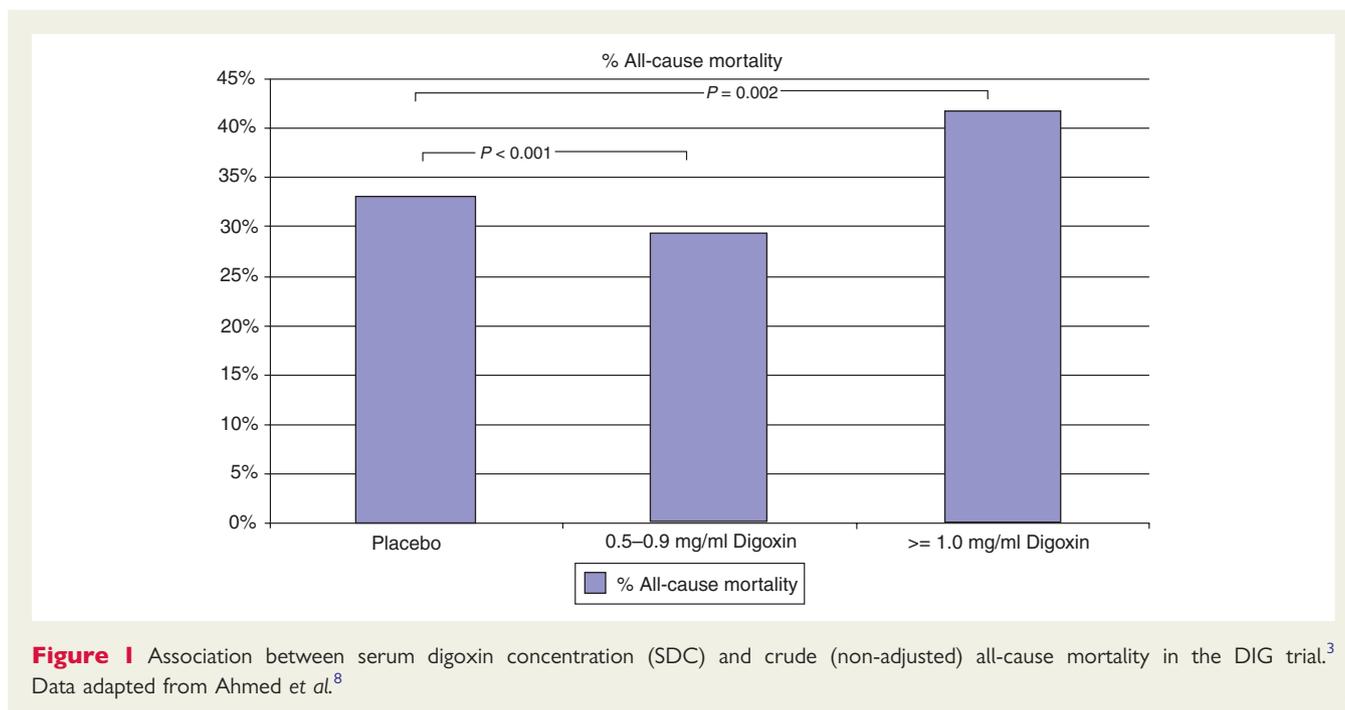
[†] Adapted from Jay N. Cohn.²⁰

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observational data suggest that its use is associated with an increased mortality in AF patients with or without HF, its effect becomes neutral when differences in baseline characteristics are taken into account.¹¹

Digoxin in the AFFIRM study

Whitbeck *et al.* have now presented data on the effect of digoxin on outcome in patients with AF (with or without HF)¹² who had been enrolled in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial.¹³ The AFFIRM study was a trial of 4060 patients with AF (and a high risk of stroke) who were randomized to rate control vs. rhythm control, and who had a mean follow-up of 3.5 years. At baseline, 26.5% of patients ($n = 1076$) had HF as defined by a history of HF and/or a LVEF $< 40\%$. Of the 4060 patients, 69.4% ($n = 2816$) received digoxin within 6 months of randomization and/or during the study, but this treatment was clearly not randomized. Digoxin was one of the four drugs used in the rate control strategy group and, of the 2027 patients in that group, 949 used digoxin for initial therapy and 1432 patients received it at any time. Of the 2033 patients in the rhythm control group, 417 used digoxin for initial therapy and 1106 received it at any time.¹² Baseline descriptions of many important clinical characteristics, such as age, sex, race, and renal function, were not provided. Among those presented, prognostically important baseline characteristics such as history of cardiomyopathy, symptoms of AF, and failure of antiarrhythmic drugs prior to randomization were different for digoxin (their table 1). However, of a large number of other variables (reported in their table 2), it is unclear whether these were different between patients on digoxin vs. those not on digoxin. During follow-up, 666 of the 4060 patients died (16%), and half of them died from a cardiovascular cause. Digoxin was associated with an increase

in all-cause mortality [HR 1.41, 95% confidence interval (CI) 1.19–1.67, $P < 0.001$] and this was true both in patients with HF (HR 1.41) and in those without HF (HR 1.37) (both $P < 0.05$). Digoxin was also associated with cardiovascular mortality and arrhythmic mortality. In a stepwise examination of the multivariate Cox regression model for all-cause mortality, the HR for the association between digoxin and all-cause mortality ranged between 1.36 and 1.66, and the greatest effect was seen after adding NYHA functional class.¹² In their Discussion, the authors also mention that high serum levels were encouraged in the AFFIRM protocol (≥ 1.0 ng/mL),¹² but data on SDCs or on the dose of digoxin used in the study are not reported. The authors conclude by saying that digoxin is associated with an increase in all-cause mortality, and that these findings call into question the widespread use of digoxin in patients with AF.

Discussion

Although the findings of Whitbeck *et al.*¹² are important and intriguing, there are two major issues that need to be discussed, which may cause serious concern. First, this was a *post hoc* analysis, not performed by the AFFIRM investigators themselves, and a previous study by the AFFIRM investigators, in which data on digoxin had already been reported, albeit less detailed, was published in 2004.¹⁴ Patients in the present analysis were obviously not randomized for digoxin. Moreover, despite the fact that the authors report that they have conducted propensity-adjusted analyses, that controlled for multiple co-morbidities, these analyses leave a lot of doubts. It is unclear what is corrected for, and important clinical parameters, such as renal function, but also severity of HF, do not seem to have been taken into account. The investigators used three different ways to examine the effect of digoxin on mortality, but all have significant limitations, as acknowledged

by the authors, and, thus, conclusions are subject to significant uncertainty.¹⁵ The second, and probably even more important issue is that patients in AFFIRM were receiving high doses of digoxin, since they were encouraged to have an SDC ≥ 1.0 ng/mL. This strategy may have been successful for achievement of the (strict) heart rate target in AFFIRM (alone, or in combination with another rate control drug), but may also have led to one of the first signs of digoxin toxicity, the induction of AV block with an accelerated junctional rhythm. This may have been missed by the attending physician but may ultimately have contributed to the observed increased mortality. The occurrence of digoxin toxicity contributing to the present outcome is even more likely since elderly frail patients were enrolled in AFFIRM and in such patients renal dysfunction, and digoxin toxicity, may develop more frequently. Overall, it is very likely that digoxin acted as an inotrope in most AFFIRM patients, and did not have a significant vagal effect, which is the most important (beneficial) effect of the drug in AF.

What can we learn from the study by Whitbeck *et al.*¹² and what—if any—is the place of digoxin in AF patients with or without HF? In AF, rate control is now the treatment of choice for many patients,⁴ so, for that reason, digoxin could still be of value in patients. However, a recent randomized trial in AF patients with and without HF showed that lenient rate control (resting heart rate ≤ 110 b.p.m.) was not inferior to strict rate control (resting heart rate ≤ 80 b.p.m.).¹⁶ Furthermore, and somewhat in line with this, is a recent meta-analysis of four large placebo-controlled, randomized HF trials of the effect of beta-blockers in 1677 patients with AF (and HF)¹⁷ which showed that although beta-blockers significantly reduced heart rate, they did not affect outcome. These data together therefore question the influence of the effect of lowering heart rate on outcome in patients with AF (with or without HF). With regard to the place of digoxin in AF, it is likely that this will further diminish in the future, because of its inefficacy to reduce heart rate during exercise on the one hand, and the outcome of studies such as the study of Whitbeck *et al.*,¹² albeit that it was a *post hoc* study and non-randomized, on the other hand. Furthermore, achieving an SDC ≥ 1.0 ng/mL should no longer be recommended. With regard to the place of digoxin in HF, this may be more positive for several reasons. First, as indicated above, if lower SDCs can be reached and maintained, digoxin could still be of use in HF.^{8,9,18} Secondly, in a recently published study,¹⁹ the effects of the sinus node inhibitor ivabradine in the Systolic Heart failure treatment with the If inhibitor Ivabradine Trial (SHIFT) were compared with the effect of digoxin in the DIG trial, and they showed a remarkable similarity. The composite morbidity–mortality outcome of cardiovascular death and HF hospitalization (which is the most common endpoint in current HF trials)² was reduced by 18% in SHIFT, and by 15% in the DIG trial. In both trials, the main effect was on HF hospitalizations, which was –26% in SHIFT and –28% in DIG.¹⁹ However, it must be pointed out of course that in SHIFT, this effect was against a background of other drugs, in particular beta-blockers, while in DIG no beta-blockers were used. Therefore, digoxin in patients with HF may still have a place, not as an inotropic drug, because for these drugs paradise is ‘lost’,²⁰ but as a neurohormonal modulator, when given in low doses. Indeed, low-dose digoxin may still be useful, but trials examining this question are urgently needed.

Conflict of interest: none declared.

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