



## Atrial fibrillation

# Digoxin-associated mortality: a systematic review and meta-analysis of the literature

Mate Vamos, Julia W. Erath, and Stefan H. Hohnloser\*

Department of Cardiology, Division of Clinical Electrophysiology, J.W. Goethe University, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany

Received 22 January 2015; revised 16 March 2015; accepted 8 April 2015

There are conflicting data regarding the effect of digoxin use on mortality in patients with atrial fibrillation (AF) or with congestive heart failure (CHF). The aim of this meta-analysis was to provide detailed analysis of the currently available study reports. We performed a MEDLINE and a COCHRANE search (1993–2014) of the English literature dealing with the effects of digoxin on all-cause-mortality in subjects with AF or CHF. Only full-sized articles published in peer-reviewed journals were considered for this meta-analysis. A total of 19 reports were identified. Nine reports dealt with AF patients, seven with patients suffering from CHF, and three with both clinical conditions. Based on the analysis of adjusted mortality results of all 19 studies comprising 326 426 patients, digoxin use was associated with an increased relative risk of all-cause mortality [Hazard ratio (HR) 1.21, 95% confidence interval (CI), 1.07 to 1.38,  $P < 0.01$ ]. Compared with subjects not receiving glycosides, digoxin was associated with a 29% increased mortality risk (HR 1.29; 95% CI, 1.21 to 1.39) in the subgroup of publications comprising 235 047 AF patients. Among 91.379 heart failure patients, digoxin-associated mortality risk increased by 14% (HR 1.14, 95% CI, 1.06 to 1.22). The present systematic review and meta-analysis of all available data sources suggest that digoxin use is associated with an increased mortality risk, particularly among patients suffering from AF.

**Keywords** Digoxin • Mortality • Atrial fibrillation • Congestive heart failure

### Clinical perspective

This systematic review and meta-analysis of the current literature indicates that digoxin therapy is associated with increased mortality in patients treated for atrial fibrillation or for heart failure. Our data call for randomized trials of dose-adjusted digoxin therapy in these two clinical entities under contemporary conditions.

## Introduction

Digoxin has been introduced in clinical practice more than 200 years ago. The two main indications for its use are the treatment of symptomatic heart failure in patients with impaired left-ventricular function and rate control in patients with atrial fibrillation (AF). The scientific evidence with respect to digoxin's effects on heart failure is mainly based on two withdrawal studies<sup>1,2</sup> and one large randomized placebo-controlled trial (DIG<sup>3,4</sup>). With regards to the second indication, rate control in AF, there is not a randomized placebo-controlled study yielding supportive data. Nevertheless, both indications are endorsed by recent guideline recommendations.<sup>5–7</sup> However, it is well appreciated that digoxin has a narrow therapeutic window in part related to significant drug–drug interactions and may cause harm if not carefully administered including

regular measurements of serum digoxin levels. A series of recent studies have cast serious doubt on the benefit of digoxin when added to contemporary heart failure treatment.<sup>8–13</sup> In fact, some observations have indicated that digoxin may have a negative effect on mortality.<sup>8,12–22</sup> In the light of such conflicting data, a systematic review of published data appears to be timely and may provide the best way to estimate the effectiveness and safety of digoxin therapy and to identify patient populations which are less likely to benefit.

## Methods

### Study selection

A comprehensive MEDLINE and COCHRANE search was conducted from 1993 (the publication year of the digoxin withdrawal trials<sup>1,2</sup>) to

\* Corresponding author. Tel: +49 69 6301 7404, Fax: +49 69 6301 7017, Email: [hohnloser@em.uni-frankfurt.de](mailto:hohnloser@em.uni-frankfurt.de)

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November 2014 of the English literature dealing with the effects of digoxin on all-cause-mortality in patients with AF or congestive heart failure (CHF). In order to identify and retrieve all potentially relevant articles regarding this topic, the search was performed utilizing the terms 'digoxin', 'mortality', 'chronic heart failure', and 'atrial fibrillation'. An additional search was also performed using the names of the 10 authors most frequently cited in narrative reviews on this subject and bibliographies of the most recent narrative review articles.

Potentially relevant articles were evaluated by two experienced, independent reviewers, and additional manuscripts were retrieved that either reviewer felt were potentially relevant. Any disagreement was subsequently resolved by all authors of this meta-analysis. Additional publications were identified using the reference lists of selected manuscripts. Only full-size articles of English language published in peer-reviewed journals were considered for this meta-analysis. Randomized controlled trials, case-control studies, or cohort studies were eligible for this meta-analysis if the following requirements, prospectively defined by our review protocol,<sup>23,24</sup> were met:

- (i) inclusion of AF or heart failure patient populations;
- (ii) report of adjusted results of effects of digoxin on all-cause-mortality (as the primary or secondary study outcome measure);
- (iii) effect sizes provided as hazard ratios (HR).

Studies reporting only composite endpoints but no specific data on all-cause mortality or dealing with different patient populations were not considered.

Methodological quality of all studies was assessed using the Methodological Index for Non-Randomized Studies (MINORS).<sup>25</sup> A score system with a maximum value of 24 points (each item to be scored from 0 to 2) was used regarding the following aspects: aim of the study, inclusion of consecutive patients, prospective data collection, appropriate endpoint to the aim of the study, unbiased evaluation of endpoints, follow-up period appropriate to the endpoint, loss to follow-up no more than 5%, comparable control group, contemporary groups, baseline equivalence of groups, prospective calculation of the sample size, use of adequate statistical analysis. After both reviewers independently scored the selected publications, the average MINORS score was used for final assessment. Studies were defined to be low-quality and high-quality studies based on their MINORS scores of  $< 16$  and  $\geq 16$  points.<sup>25,26</sup>

## Statistical analysis

All statistical analyses were conducted utilizing Comprehensive Meta-Analysis 3.3 (Biostat, Inc., USA). Heterogeneity between individual trial estimates was assessed using the  $Q$  statistic and  $I^2$  statistic.<sup>27</sup> The principal measurement of effect size (i.e. all-cause mortality) was the HR along with the 95% upper and lower confidence intervals (CI). All selected non-randomized studies provided risk assessments which had been adjusted for important baseline clinical variables with different types of statistical methods (mostly Cox regression analysis or propensity-matched analysis). The random-effect model,<sup>28,29</sup> was used to calculate HR for the overall effect and for the two subgroups (AF, heart failure) in this meta-analysis. A forest plot was constructed showing the individual trials with the pooled estimates. Publication bias was assessed using the funnel plot, the trim and fill method of Duval and Tweedie,<sup>29</sup> and an adjusted rank-correlation test according to Begg and Mazumdar.<sup>30</sup> Sensitivity analyses including only publications reporting separate data for patient subsets suffering from AF or CHF, respectively, and studies providing data on the daily digoxin dose and/or the mean digoxin plasma levels were performed.

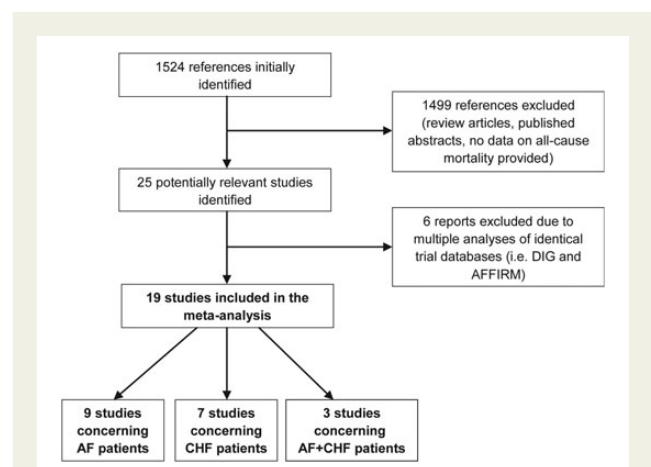
## Results

### Selection of studies

From a total of 1524 studies initially identified, 25 matched our search criteria. Additional six trials were excluded because they consisted of reports based on the same original trial database (i.e. *post-hoc* analyses of DIG<sup>31-34</sup> and AFFIRM<sup>35,36</sup> studies). This yielded a total of 19 studies which were selected for the present analysis (Figure 1). The individual trial characteristics are given in Table 1. Digoxin use was defined as use at baseline or as a time varying covariate.<sup>37</sup> Nine studies comprised patients with AF<sup>9,14-16,18,20,21,38,39</sup> and seven comprised patients with CHF (in sinus rhythm or in AF).<sup>3,4,10-13,22</sup> The remaining three studies reported separate data for patients suffering from both conditions.<sup>8,17,19</sup> The primary inclusion criterion for the study by Chao *et al.*<sup>19</sup> consisted of the diagnosis of AF. Hence, this study was initially included in the meta-analysis as an AF study although end-point results were available for the overall patient group as well as for the patient subset with AF only and heart failure only.

Accordingly, this meta-analysis comprises data from 235 047 AF patients and 91 379 patients with heart failure. Patients were followed between 0.83 and 4.7 years (average observation period  $2.57 \pm 1.13$  years) in the individual studies. Of all identified studies, only one (and its ancillary publication) was a randomized controlled clinical trial,<sup>3,4</sup> whereas the remainder of studies was retrospective or prospective observational studies (Table 1). All included reports were assessed as high-quality publications (average MINORS score:  $19.7 \pm 1.6$ )

There were significant differences in treatment effects between individual studies indicated by the statistical test for heterogeneity ( $Q = 153.5$ ,  $P < 0.01$ ,  $T^2 = 0.008$ ,  $I^2 = 85.7\%$ ).<sup>27</sup> According to the rank correlation test of Begg and Mazumdar,<sup>30</sup> there was no evidence of significant publication bias ( $Tau = 0.087$ ,  $P = 0.28$ ). Furthermore, corresponding to the Duval and Tweedie's trim and fill input method,<sup>29</sup> there was no evidence that publication bias would impact on the overall effect size observed (HR 1.214 vs. HR 1.208) (Figure 2).



**Figure 1** Flow diagram of the literature search and study selection.

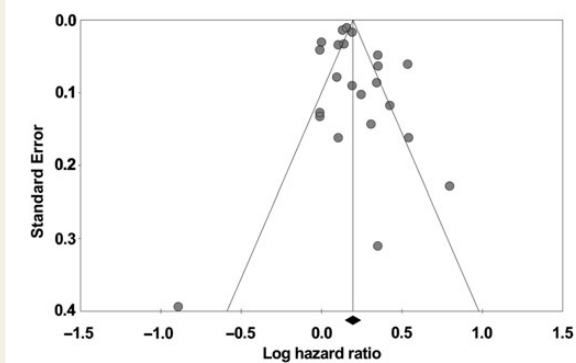
**Table 1** Publications included in the meta-analysis

Study, Year	Subgroup	Patient cohort	Design	Digoxin use defined as	Subjects		Follow-up (years)	Quality (MINORS score)	
					Total	Digoxin			
Hallberg (RIKS-HIA), 2007 <sup>8</sup>	AF	AF	Prospective registry study	Baseline use	21 459	4872	1	High (17.5)	
Gjesdal (SPORTIF III, V), 2008 <sup>14</sup>		AF	<i>Post-hoc</i> analysis of RCT	Baseline use	7329	3911	1.55–1.64	High (20)	
Friberg (SCAF), 2010 <sup>9</sup>		AF	Prospective registry study	Baseline use	2824	802	4.7	High (19)	
Whitback (AFFIRM), 2012 <sup>15</sup>		AF	<i>Post-hoc</i> analysis of RCT	Time-varying covariate	4060	2816	3.5	High (20.5)	
Turakhia (TREAT-AF), 2014 <sup>16</sup>		AF	Analysis of administrative database	Baseline use and time-varying covariate	122 465	28 679	2.9	High (19)	
Shah, 2014 <sup>17</sup>	AF	AF	Retrospective population-based cohort study	Baseline use	46 262	23 131	3.0–4.2	High (18.5)	
Gamst, 2014 <sup>18</sup>		AF	Retrospective population-based cohort study	Baseline use	8880	3622	1	High (18)	
Chao, 2014 <sup>19</sup>		AF	Analysis of administrative database	Baseline use	4781	829	4.26	High (18)	
Rodriguez-Manero (AFBAR), 2014 <sup>38</sup>		AF	Prospective registry study	Baseline use	777	270	2.9	High (19.5)	
Mulder (RACE II), 2014 <sup>39</sup>		AF	<i>Post-hoc</i> analysis of RCT	Baseline use	608	284	2.9	High (21)	
Freeman (ATRIA-CVRN), 2014 <sup>20</sup>		AF	Retrospective population-based cohort study	Baseline use and time-varying covariate	14 787	4231	1.17	High (20)	
Pastori, 2015 <sup>21</sup>		AF	Prospective observational study	Baseline use	815	171	2.73	High (19.5)	
Garg (DIG), 1997 <sup>3</sup>	Men	CHF (SR)	RCT	Baseline use	6800	3397	3.04	High (23.5)	
Domanski (SOLVD), 2005 <sup>22</sup>		CHF (SR/AF)	<i>Post-hoc</i> analysis of RCT	Baseline use	6797	2244	3.4	High (20)	
Domanski (SOLVD), 2005 <sup>22</sup>		Women	CHF (SR/AF)	Baseline use					
Ahmed (DIG Ancillary), 2006 <sup>4</sup>		CHF (SR)	RCT	Baseline use	988	492	3.0	High (23)	
Hallberg (RIKS-HIA), 2007 <sup>8</sup>		CHF - SR	CHF (SR)	Prospective registry study	Baseline use	22 345	3796	1	High (17.5)
Hallberg (RIKS-HIA), 2007 <sup>8</sup>		CHF - AF	CHF (AF)	Baseline use	16 960	7758			
Fauchier, 2008 <sup>10</sup>		CHF (AF)	Prospective registry study	Baseline use	1269	591	2.4	High (19)	
Dhaliwal, 2008 <sup>11</sup>		CHF (SR/AF)	Retrospective population-based cohort study	Baseline use	347	155	0.83	High (17)	
Butler (Val-HeFT), 2010 <sup>12</sup>		CHF (SR/AF)	<i>Post-hoc</i> analysis of RCT	Baseline use	5010	3374	1.9	High (20.5)	
Freeman, 2013 <sup>13</sup>		CHF (SR/AF)	Analysis of administrative database	Baseline use and time-varying covariate	2891	529	2.5	High (18.5)	
Shah, 2014 <sup>17</sup>		CHF	CHF (AF)	Retrospective population-based cohort study	Baseline use	27 972	13 986	3.0–4.3	High (18.5)

AF, atrial fibrillation; CHF, congestive heart failure.

### Effects of digoxin on all-cause mortality

Mortality risks were reported in all selected studies after adjustment for important baseline variables for a total of 326,426 patients. Based on the analysis of all 19 trials, digoxin use was associated with an overall 21% increased relative risk of all-cause mortality compared with patients not receiving this medication (HR 1.21, 95% CI, 1.07 to 1.38,  $P < 0.01$ ) (Figure 3).



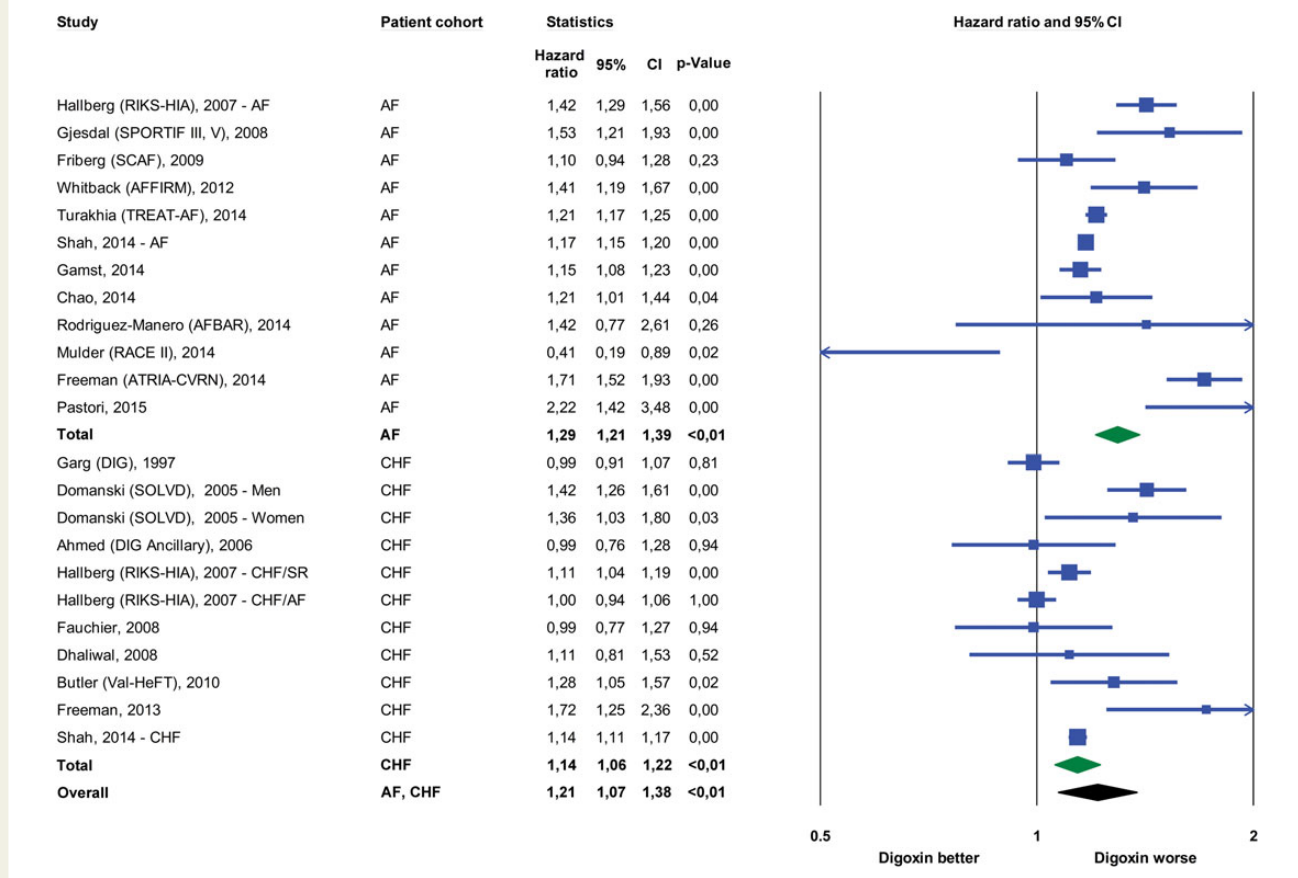
**Figure 2** Funnel plot of publications included in the meta-analysis.

A total of 235 047 AF patients were included in 12 studies with a range between 608 and 122 465 patients per study. For this subgroup of patients, treatment with digoxin was associated with an increased mortality risk of 29% when compared with AF patients not receiving digoxin (HR 1.29, 95% CI, 1.21 to 1.39,  $P < 0.01$ ) (Figure 3). We included the AFFIRM *post-hoc* analysis by Whitback<sup>15</sup> in this set of studies; however, we repeated the analysis after substituting this study by the one of Gheorgiade *et al.*<sup>35</sup> which used the same database but a different analysis methodology.<sup>37</sup> The HR for digoxin-associated mortality risk remained similarly elevated (HR 1.27, 95% CI 1.18 to 1.36,  $P < 0.01$ ) (see Supplementary material online, Figure S1).

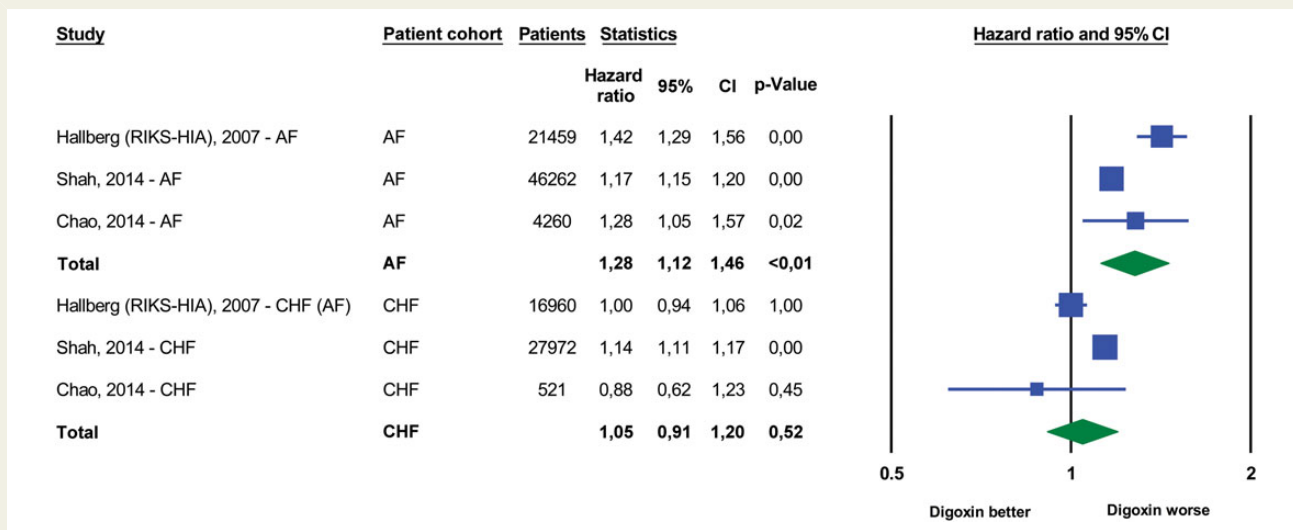
Nine studies comprised 91 379 subjects with heart failure. In this patient population, digoxin use was again associated with a higher risk for all-cause mortality compared with individuals not treated by cardiac glycosides (HR 1.14, 95% CI, 1.06 to 1.22,  $P < 0.01$ ) (Figure 3).

### Analysis of studies comprising subsets of patients with atrial fibrillation and congestive heart failure

Three large studies comprising a total of 117 434 patients reported all-cause mortality data for subsets of patients with AF and with



**Figure 3** Forest plot of studies describing the effects of digoxin on mortality, both for studies in atrial fibrillation and congestive heart failure. Data had been adjusted for potential confounders in the various studies.



**Figure 4** Forest plot of three large studies reporting data on patient populations with atrial fibrillation (upper half) and congestive heart failure (lower half) relying on the same databases and applying identical analytic methodology.

**Table 2** Publications reporting data on digoxin dosing and/or plasma levels

Study, Year	Patient cohort	Patient number	Mean digoxin dose (mg)	Mean serum digoxin concentration (ng/mL)
Mulder (RACE II), 2014 <sup>39</sup>	AF	608	0.250	No data
Freeman (ATRIA-CVRN), 2014 <sup>20</sup>	AF	14 787	0.164	0.96 (available for 69% of all patients)
Pastori, 2015 <sup>21</sup>	AF	815	0.126	No data
Garg (DIG), 1997 <sup>3</sup>	CHF (SR)	6800	0.244	0.8
Ahmed (DIG Ancillary), 2006 <sup>4</sup>	CHF (SR)	988	0.235	No data
Freeman, 2013 <sup>13</sup>	CHF (SR/AF)	2891	0.150	1.02 (available for 70% of all patients)

AF, atrial fibrillation; CHF, congestive heart failure.

CHF.<sup>8,17,19</sup> In the respective studies, data sources were identical for the two patient subsets and the same analysis methodology was applied. As shown in *Figure 4*, there was a substantial increase in the digoxin-associated risk of death in all three studies for patients with AF (HR 1.28, 95% CI, 1.12 to 1.46,  $P < 0.01$ ). The estimated pooled mortality risk for all three patient samples with CHF revealed no significant increase in those subjects who were receiving digoxin (HR 1.05, 95% CI, 0.91 to 1.20,  $P = 0.52$ ).

### Analysis of studies providing data on digoxin dosing and/or plasma levels

Six of the 19 studies<sup>3,4,13,20,39</sup> reported data on the daily digoxin dose and/or the mean digoxin plasma levels (*Table 2*). A sensitivity analysis of these studies revealed a similar HR (1.26, 95% CI, 0.91 to 1.74; *Figure 5*) as the analysis of all 19 studies, although this was no more statistically significant despite the inclusion of almost 27 000 patients. Only three studies<sup>3,13,20</sup> reported data on digoxin plasma levels (*Table 2*).

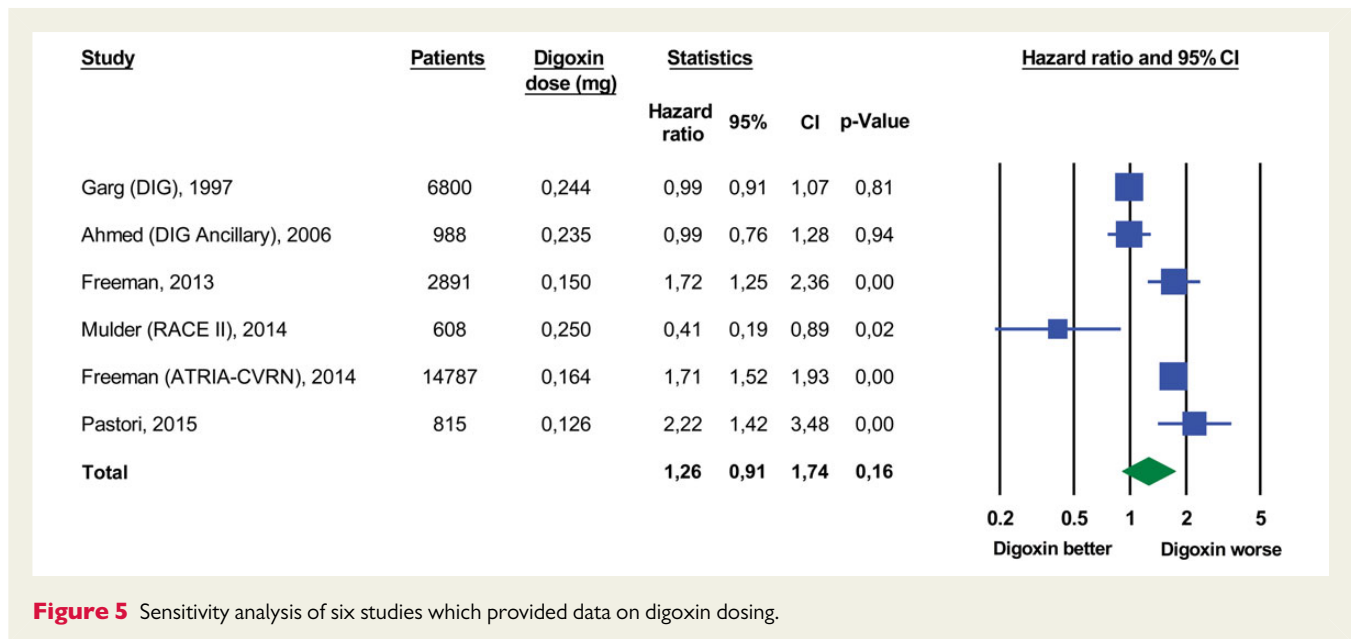
## Discussion

### Main findings

The present meta-analysis on the effects of digoxin on all-cause mortality is to the best of our knowledge the largest one published today. It is based on 19 published studies comprising data from more than 300 000 patients suffering from AF or CHF. Our results indicate that digoxin therapy is associated with an increased mortality risk in these patients, particularly in those treated for AF.

### Prior studies

There is only one randomized controlled trial of digoxin in patients with a left-ventricular ejection fraction of  $< 0.45$  and sinus rhythm, the so-called DIG-trial.<sup>3</sup> Digoxin was administered in 3397 patients and matching placebo in 3403 in addition to diuretics and ACE-inhibitors. After an average follow-up of 37 months, digoxin did not reduce mortality in comparison to placebo (34.8 vs. 35.1%) but reduced the rate for hospitalization due to heart failure. For



**Figure 5** Sensitivity analysis of six studies which provided data on digoxin dosing.

the indication of rate control in AF, there is a complete lack of controlled randomized studies. Based on the DIG trial, digoxin is currently recommended in the ESC and the US guidelines on heart failure as a class IIb, level B, or class IIa, level B, for consideration in patients with reduced LVEF in sinus rhythm to reduce the risk of hospitalization.<sup>5,7</sup> The ESC guidelines on AF recommend digoxin for rate control in patients with heart failure and LV dysfunction (IIa, level C).<sup>6</sup> In essence, these recommendations reflect the highly unsatisfactory data basis on which to judge the supposed benefits of digoxin.<sup>40</sup>

Since the publication of the DIG trial, several uncontrolled retrospective<sup>12–20,22</sup> and prospective<sup>8,21,38</sup> observational studies have raised serious concerns as to the safety of digoxin therapy for AF or for CHF. For instance, the largest of all studies, the retrospective TREAT-AF study, reported data from 122 465 patients with newly diagnosed non-valvular AF.<sup>16</sup> Digoxin use was independently associated with mortality after multivariate adjustment and after careful propensity matching. Others have reported similar findings from studies conducted in patients with CHF.<sup>13,17</sup>

The present meta-analysis provides further evidence for a harmful effect of digoxin on mortality. Utilizing data from all studies published over the last two decades and reporting data on all-cause mortality, it demonstrates an increase in the relative risk of dying of 21% in subjects treated with cardiac glycosides compared with patients not receiving digoxin. Importantly, all studies reported data which were carefully adjusted for potential confounders. The increase in risk seemed to be more pronounced in patients who were treated with digoxin for rate control in AF (HR 1.29, 95% CI 1.21 to 1.39) than in patients treated for CHF (HR 1.14, 95% CI 1.06 to 1.22). This differential effect was similarly evident when the three large studies reporting on AF and on heart failure populations based on identical methodology were examined separately. Digoxin therapy in AF carried a HR of 1.28 (95% CI, 1.12 to 1.46) compared with a HR of 1.05 (95% CI, 0.91 to 1.20) in heart failure. As to potential explanations for these seemingly disparate effect sizes, positive effects of glycosides on haemodynamics (increased cardiac output, decreased

pulmonary wedge pressure) or neurohumoral mechanisms (vagomimetic action, improved baroreceptor sensitivity, decreased activation of the renin–angiotensin system, etc.)<sup>41</sup> may yield some overall positive effects in heart failure patients while such effects are unlikely to play a role in the treatment of AF. In this clinical condition, unwanted electrophysiological effects resulting in the occurrence of brady- or tachyarrhythmias may be operational without any beneficial haemodynamic digoxin effects.

### Potential mechanisms of digoxin-associated mortality increase

It is well appreciated that digoxin has a narrow therapeutic window. Maintaining strict serum levels is therefore essential. In fact, Rathore *et al.*<sup>33</sup> could demonstrate in a *post-hoc* analysis of the DIG trial that higher serum digoxin levels (defined as  $\geq 1.2$  ng/mL) were significantly associated with increased mortality whereas at lower plasma concentrations there seemed to be clinical benefit. Other potentially detrimental digoxin effects, particularly in AF, include digoxin-mediated increase in vagal tone, reduced AV-node conduction, and shortening of atrial refractory periods; all of these effects may render the atrium more susceptible to AF. Digoxin has been found to be associated with doubling of relapses of AF following cardioversion.<sup>42</sup> Finally, digoxin may provoke paroxysmal atrial tachycardias, ventricular tachyarrhythmias including fascicular or bi-directional ventricular tachycardia or torsade de pointes tachycardia, and serious bradyarrhythmias including high-degree AV block, particularly when electrolyte disorders are present.<sup>43</sup> These proarrhythmic effects of glycosides may be caused or further accentuated by significant drug–drug interactions, for instance with antiarrhythmic drugs such as amiodarone or quinidine.<sup>44</sup> This is exemplified in a recent randomized trial of dronedarone in patients with AF.<sup>45</sup> This trial was stopped prematurely because of excess mortality in the dronedarone compared with the control arm. In a *post-hoc* analysis, it could be demonstrated that 11 out of 13 arrhythmic deaths in the

dronedarone arm occurred in patients who simultaneously received digoxin. The most likely explanation for this is the drug–drug interaction between dronedarone and digoxin at the level of the P-glycoprotein transport system which resulted in significantly elevated serum digoxin levels in patients who died.

## Limitations

This meta-analysis is subject to all potential limitations of this kind of analysis. We did not have access to individual patient data from all studies reviewed and had to rely on published information. All identified studies used contemporary sophisticated statistical adjustments to counteract potential confounding but residual confounding cannot be completely excluded.<sup>46</sup> However, the large number of data sets obtained in more than 300 000 patients and the internal consistency of findings emphasize the validity of this meta-analysis. Finally, only a few studies provided data on digoxin dose or plasma levels but no relationship of mortality and such data was reported except in the publication of Rathore *et al.*<sup>33</sup> However, the majority of the articles on digoxin therapy are based on data from contemporary studies during which the importance of daily digoxin dose and low target plasma levels was already appreciated.

## Conclusions

This meta-analysis of the contemporary literature indicates that digoxin therapy particularly without proper serum level control is associated with an increased mortality risk in patients with AF and with CHF. Our sensitivity analysis, however, suggests negative effects of digoxin particularly in the AF population but somewhat less unfavourable effects in the CHF population. Coupled with the notion emphasized by Rathore *et al.*,<sup>33</sup> this calls for randomized trials of dose-adjusted digoxin therapy at least in CHF patients. Until such proper randomized controlled trials are being completed, digoxin should be used with great caution (including monitoring plasma levels), particularly when administered for rate control in AF.

## Supplementary material

Supplementary Material is available at *European Heart Journal* online.

**Conflict of interest:** J.W.E. has nothing to disclose. S.H.H. reports receiving consulting fees from Bayer Healthcare, Boehringer Ingelheim, Gilead, J&J, Medtronic, Pfizer, St Jude Medical, Sanofi-Aventis; and lecture fees from Boehringer Ingelheim, Bayer Healthcare, Bristol-Myers Squibb, Pfizer, St Jude Medical, Sanofi-Aventis, and Cardiome, outside the submitted work. M.V. reports non-financial support from Twinmed Kft./ Boston Scientific and from Medtronic Hungaria Kft., outside the submitted work.

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