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META-ANALYSIS OF OBSERVE STUDIES IN EPIDEMIOLOGY

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Increased All-Cause Mortality Associated With Digoxin Therapy in Patients With Atrial Fibrillation

An Updated Meta-Analysis

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Abstract: Digoxin is still commonly used in atrial fibrillation (AF) patients with and without heart failure (HF) for heart rate control. Studies concerning the detrimental effects of digoxin therapy in AF patients are inconsistent. This updated meta-analysis examined the association of digoxin therapy with all-cause mortality in AF patients, stratified by heart function status. We included observational studies with multivariate-adjusted data on digoxin and all-cause mortality in the analysis. The relative risks (RRs) of all-cause mortality were calculated and reported with 95% confidence intervals (95% CIs). Seventeen studies comprising 408,660 patients were included. Overall, in AF patients, digoxin treatment was associated with a significant increase in all-cause mortality after multivariate-adjustment (RR = 1.22; 95% CI 1.15–1.30). When stratified by heart function status, digoxin treatment was associated with a 14% increase in all-cause mortality in AF patients with HF (RR = 1.14, 95% CI 1.04–1.24), and a 36% increase in those without HF (RR = 1.36, 95% CI 1.18–1.56). The increased risk of all-cause mortality was significantly higher in AF patients without HF compared with those with HF (*P* for interaction = 0.04). This meta-analysis demonstrates that digoxin therapy was associated with a significant increase in all-cause mortality in AF patients, especially in those without HF. Given other available options, digoxin should be avoided as a first-line agent for heart rate control in AF patients.

(*Medicine* 94(52):e2409)

Abbreviations: AF = atrial fibrillation, CI = confidence interval, DIG = Digitalis Investigation Group, HF = heart failure, RCT = randomized control trial, RR = relative risk, SDC = serum digoxin concentration, SE = standard errors.

Editor: Patrick Wall.
Received: October 4, 2015; revised: December 7, 2015; accepted: December 9, 2015.
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Supplemental Digital Content is available for this article.
YC and XC contributed equally to this work.
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002409

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting more than 33 million individuals worldwide.[1] The burden of AF also seems to be an important factor for heart failure (HF). Indeed, the Euro Heart Survey on AF showed that HF is present in more than 30% of AF patients.[2]

Digoxin, a pharmaceutical derivative of digitalis, which has been used in clinical practice for decades, is still commonly used in AF patients with and without HF for heart rate control, owing to its negative chronotropic activity.[3] The Digitalis Investigation Group (DIG) trial is the only large-sample randomized control trial (RCT) that showed that digoxin had a neutral effect on all-cause mortality, although it had beneficial effects on death caused by worsening HF and HF hospitalizations.[4] However, the DIG trial only included HF patients with sinus rhythm, and these results cannot be extended to patients with AF. Recently, some observational studies have shown that digoxin was associated with increased mortality in AF patients,[5–8] but this was not supported by other studies.[9–11] Some recently published meta-analyses also reported conflicting conclusions.[12–15] These inconsistent conclusions maybe caused by the following.

(1) All AF patients were included, but not stratified by heart function status at baseline. The biological effects and clinical rationale for digoxin treatment in AF patients may be different among patients with or without HF.
(2) There was a difference in statistical analysis methods used, such as multivariate Cox regression or propensity score matching.
(3) There were different definitions of digoxin exposure (eg, baseline treatment when enrolled or incident treatment during follow-up).

Given these inconsistent results, we performed an updated systematic review and meta-analysis to examine the association of digoxin with all-cause mortality in AF patients, stratified by heart function status.

METHODS

Ethics Statement

This study is a meta-analysis of published studies, and ethical approval was not required.

Search Strategy and Selection Criteria

We performed the search according to the recommendations of the Meta-Analysis of Observational Studies in Epidemiology Group.[16] The electronic databases, including

PubMed, EMBASE, and the Cochrane Library, were searched for studies to August 31, 2015, using a combined text and MeSH heading search strategy with the terms "digitalis" or "digoxin" or "digitoxin" or "cardiac glycosides" and "mortality," "death," "deaths" or "fatal," and "atrial fibrillation." We further manually reviewed the reference lists of identified studies. The search was restricted to human studies, but there were no language or publication form restrictions.

The inclusion criteria of studies for analysis were: inclusion of AF patients aged ≥18 years; adjusted relative risks (RRs) and 95% confidence intervals (CIs) reported for all-cause mortality associated with digoxin treatment; AND follow-up duration ≥1 year.

Studies were excluded if: the RR was only adjusted for age and sex; data were reported as composite endpoints, but not specified for all-cause mortality; and data were derived from the same study.

Data Extraction, Synthesis, and Analysis

Two investigators (YC and XC) independently conducted literature searches, reviewed the potentially articles, and abstracted data from eligible studies. Discrepancies were resolved by discussion with other investigators (YulH and YunH).

The primary analysis was the RRs of all-cause mortality associated with digoxin treatment. The secondary analysis was whether the risk of mortality was affected by heart function status. Adjusted RRs from the multivariate Cox regression models from each study were extracted and logarithmically transformed. The corresponding standard errors (SEs) were calculated to stabilize the variance and normalize the distribution.[17,18] If more rigorous analytic methodology, such as propensity score-matched analysis, was reported in the included studies, these data were used for analysis. We used inverse variance method to combine the calculated log RRs and SEs. I^2 statistics were used to test the heterogeneity among studies. If values of I^2 were >50%, we considered there was significant heterogeneity among the included studies and the results were pooled using random-effects models. Alternatively, fixed-effects models were used.

Subgroup analyses of the primary analysis were performed by sex (women vs men), definition of digoxin exposure (baseline treatment when enrolled versus incident treatment during follow-up), study design (prospective registry study vs retrospective cohort study vs post-hoc analysis of RCT), follow-up duration (<2 years vs ≥2 years), and analytic model (multivariate Cox regression model vs propensity score-matched analysis). Sensitivity analyses were conducted by omitting 1 study at a time and recalculating the pooled RRs. Publication bias was assessed by inspecting funnel plots in which the natural log of RR was plotted against its SE, and further tested by Egger test and Begg test. *P* values were 2-tailed, and statistical significance was set at 0.05. All analyses were conducted using RevMan (Version 5.3; The Cochrane Collaboration, Copenhagen, Denmark) and Stata software (Version 12.0; Stata Corp LP, College Station, TX).

RESULTS

Studies Retrieved and Characteristics

Overall, 2082 manuscripts were initially retrieved. After screening titles and abstracts, we found that 31 qualified for full review. Finally, 17 articles comprising 408,660 patients were included in this study (Figure 1).[5–11,19–28] There were 3 reports from the Atrial Fibrillation Follow-Up Investigation of Rhythm Management study.[26,29,30] We only included the report by Whitbeck et al[26] for the primary analysis, as it employed more rigorous analytic methodology, including defined digoxin treatment as baseline treatment, time-dependent covariates, and propensity score-matched analysis.

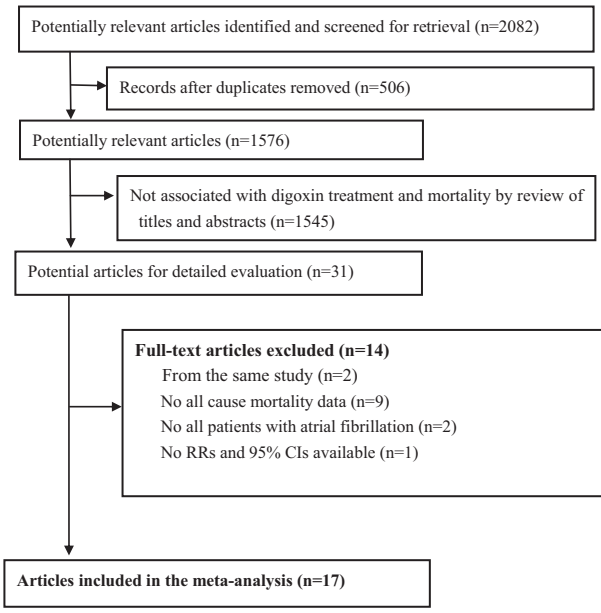

FIGURE 1. Flow of papers through review. CIs = confidence intervals, RRs = relative risks.

Table 1 summarizes the key characteristics of all included studies. Seven studies reported data from prospective registry studies,[6,9,10,23,25,27,28] 5 studies were retrospective cohort studies,[5,7,19–21] and 5 studies were post-hoc analyses of RCTs.[8,11,22,24,26] One study only included AF patients with HF,[20] another study only included those without HF,[7] and all other studies included both AF patients with and without HF. The sample size ranged from 608 to 140,111, and the ratio of digoxin treatment was from 17.3% to 53.4%. Most studies defined digoxin treatment at enrollment, 5 studies also reported the risk of mortality with digoxin treatment defined as a time-varying covariate,[6–9,26] and 1 study only used digoxin treatment as a time-varying covariate for analysis.[11] The follow-up duration ranged from 1 to 4.7 years.

Association Between Digoxin Treatment and Risk of All-Cause Mortality

There was significant heterogeneity among the included studies ($I^2 = 82\%$), therefore we used random-effects models in analyses. Overall, in AF patients, digoxin treatment was associated with a significant increase in all-cause mortality after multivariate-adjustment (RR = 1.22; 95% CI 1.15–1.30, $P < 0.001$, Figure 2). No evidence of publication bias was observed based on visual inspection of the funnel plot (Supplemental Figure 1, http://links.lww.com/MD/A587), and according to Begg test and Egger test (both >0.05).

In the subgroup analyses conducted according to sex, definition of digoxin exposure, study design, follow-up duration and analytic model, and digoxin treatment were significantly associated with higher risk of all-cause mortality across subgroups (Table 2). We found no significant differences among these subgroups.

TABLE 1. Characteristics of Included Studies

Study	Country	Study Design	Heart Function	Sample (Women, %)	Digoxin Treatment	Age, years (Range or SD)	Follow-Up, years	Statistical Method
Hallberg et al 2007 (RIKS-HIA)[23]	Sweden	Prospective registry study	With/without HF	60764 (43.2%)	27.0%	67 (5.8)	1	Multivariate Cox regression with propensity score matching
Gjesdal et al 2008 (SPORTIF III and V)[22]	USA	Post-hoc analysis of RCT	With/without HF	7329 (30.8%)	53.4%	71 (9.0)	1.5	Multivariate Cox regression
Fauchier et al 2009[20]	France	Retrospective study	All with HF	1269 (39%)	32%	74 (13)	2.4	Multivariate Cox regression
Friberg et al 2010 (SCAF) [10]	Sweden	Prospective registry study	With/without HF	2824 (45.3%)	28.4%	74 (NA)	4.6	Multivariate Cox regression with propensity score matching
Whitbeck et al 2013 (AFFIRM trial)[26]	USA	Post-hoc analysis of RCT	With/without HF	4060 (39.3%)	46.9%	69.7 (9)	3.5	Multivariate Cox regression with propensity score matching
Chao 2014 (NHIRD) [19]	Taiwan, China	Retrospective study	With/without HF	4781 (45.6%)	17.3%	67.8 (15.7)	4.26	Multivariate Cox regression
Rodriguez-Manero et al 2014 (AFBAR)[25]	Spain	Prospective registry study	With/without HF	777 (47.0)	27.3%	74.9 (9.3)	2.9	Multivariate Cox regression
Gamst et al 2014[21]	Denmark	Retrospective study	With/without HF	8880 (42.1%)	40.8%	80 (73.3–85.4)	1	Multivariate Cox regression
Mulder et al 2014 (RACE II)[24]	Netherlands	Post-hoc analysis of RCT	With/without HF	608 (34.5%)	46.7%	68 (8)	2.9	Multivariate Cox regression
Shah et al 2014[5]	Canada	Retrospective study	With/without HF	140111(52.4%)	27.4%	79.6 (7.3)	3.5	Multivariate Cox regression with propensity score matching
Turakhia et al 2014 (TREAT-AF)[6]	USA	Prospective registry study	With/without HF	122465 (1.6%)	23.4%	72.1 (10.3)	2.9	Multivariate Cox regression and propensity score matching
Allen et al 2015 (ORBIT-AF)[9]	USA	Prospective registry study	With/without HF	9,619 (43%)	30.6%	75 (67–82)	1.8	Multivariate Cox regression with propensity score matching
Al-Zakwani et al 2015 (Gulf SAFE)[27]	Middle East	Prospective registry study	With/without HF	1962 (48%)	36%	56 (16)	1	Multivariate Cox regression
Freeman et al 2015 (ATRIA-CVRN Study)[7]	USA	Retrospective study	All without HF	27288 (47.8%)	17.8%	70.7 (12.9)	1.17	High-Dimensional Propensity Score Matching
Okin et al 2015 (LIFE trial)[11]	USA	Post-hoc analysis of RCT	With/without HF	937 (47.5%)	39.7%	70 (6)	4.7	Multivariate Cox regression with propensity score matching
Pastori et al 2015[28]	Italy	Prospective registry study	With/without HF	815 (42.6)	21%	73 (8.5)	2.8	Multivariate Cox regression with propensity score matching
Washam et al 2015 (ROCKET AF)[8]	Multi center	Post-hoc analysis of RCT	With/without HF	14171 (40%)	37%	73 (65–78)	1.94	Multivariate Cox regression with propensity score matching

AF = atrial fibrillation, AFBAR = Atrial Fibrillation in the BARrbanza area, AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management study, ATRIA-CVRN = AnTicoagulation and Risk factors In Atrial fibrillation-Cardiovascular Research Network, Gulf SAFE = Gulf Survey of Atrial Fibrillation Events, HF = heart failure, LIFE = Losartan Intervention For Endpoint Reduction in hypertension, NHIRD = National Health Insurance Research Database, ORBIT-AF = Outcomes Registry for Better Informed Treatment of Atrial Fibrillation, RACEII = Rate control drugs in the Rate Control Efficacy in Permanent AF: A Comparison between Lenient versus Strict Rate Control II trial, RIKS-HIA = Registry of Information and Knowledge about Swedish Heart Intensive care Admissions, ROCKET AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation, SCAF = Stockholm Cohort study on Atrial Fibrillation, SPORTIF = Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation, TREAT-AF = The Retrospective Evaluation and Assessment of Therapies in AF study.

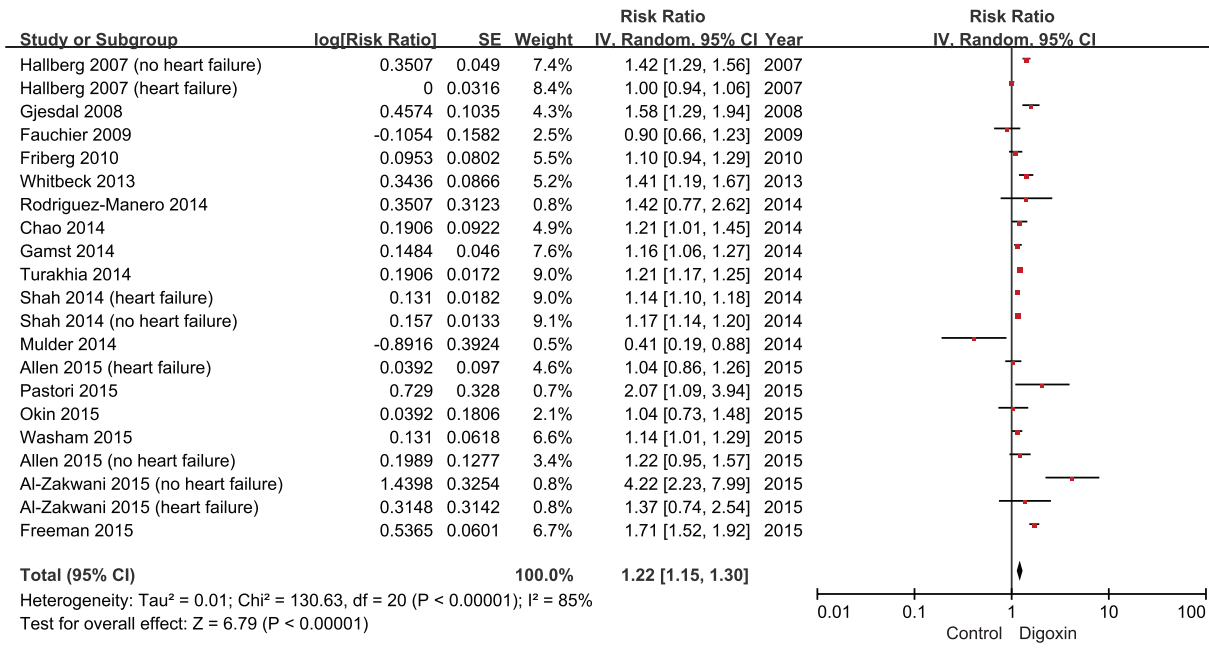

FIGURE 2. Forest plot of the comparison: digoxin therapy versus no digoxin therapy, outcome: all-cause mortality in atrial fibrillation (AF) patients.

Sensitivity analysis showed that the primary results were not influenced by omitting 1 study at a time, or by using data from 2 other reports[29,30] from the Atrial Fibrillation Follow-Up Investigation of Rhythm Management study study to replace data from the report by Whitbeck et al.[26]

All-Cause Mortality in Digoxin Treatment Was Modified by Heart Function

Eight studies reported the risk of all-cause mortality in AF patients with or without HF,[5,8,9,19,23,25–27] and 2 studies reported data for AF patients with HF, but did not include data for those without HF,[6,20] while 2 other studies only supplied data for AF patients without HF.[7,11] Pooled data from these studies showed that digoxin treatment was associated with a 14% increase of all-cause mortality in AF patients with HF (RR = 1.14, 95% CI 1.04–1.24, $P < 0.001$) and a 36% increase in those without HF (RR = 1.36, 95% CI 1.18–1.56, $P < 0.001$). There was a significant difference of risk in AF patients with and without HF (Figure 3, P for interaction = 0.04).

Sensitivity analysis was performed by only including those studies reported both data in AF patients with or without HF, respectively. Meta-analysis of these studies also showed that the

TABLE 2. Subgroup Analyses of the Association Between Digoxin Treatment and All-Cause Mortality

Subgroup	Number of Studies	Risk Ratio (95% CI)	*P* Value Between Subgroups
Sex			
Men	7	1.30 (1.18, 1.45)	0.55
Women	7	1.24 (1.11, 1.40)	
Definition of digoxin exposure			
Baseline treatment	16	1.23 (1.16, 1.30)	0.49
Incident treatment during follow-up	6	1.28 (1.15, 1.42)	
Study design			
Prospective registry study	7	1.24 (1.10, 1.40)	0.96
Retrospective cohort study	5	1.22 (1.12, 1.33)	
Post-hoc analysis of RCT	5	1.20 (0.96, 1.49)	
Follow-up duration			
<2 years	8	1.32 (1.14, 1.54)	0.13
≥2 years	9	1.17 (1.12, 1.23)	
Analytic model			
Multivariate Cox regression	9	1.26 (1.06, 1.50)	0.63
Propensity score matched	8	1.21 (1.13, 1.29)	

CI = confidence interval, RCT = randomized control trial.

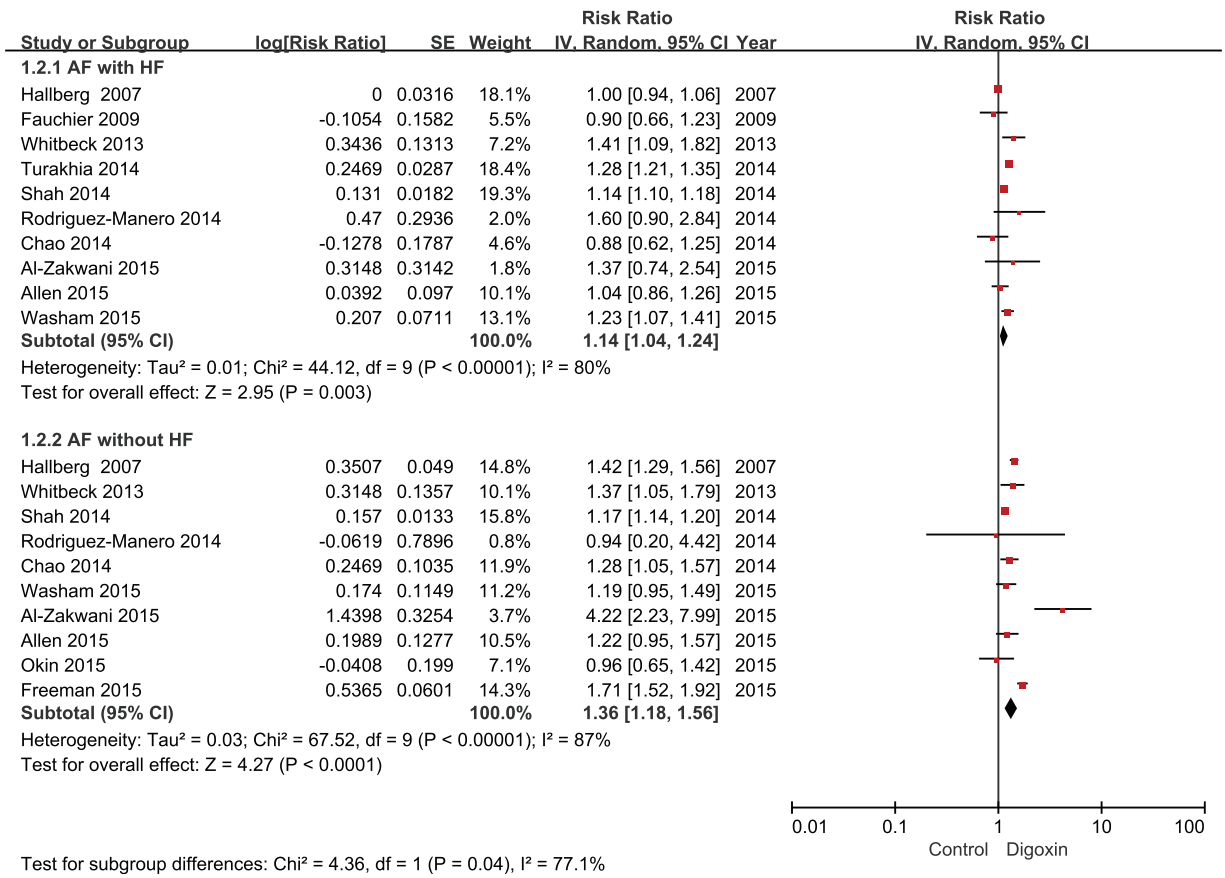

FIGURE 3. Forest plot of the comparison: digoxin therapy versus no digoxin therapy, outcome: all-cause mortality in AF patients with HF and without HF. AF = atrial fibrillation, HF = heart failure.

risk of all-cause mortality was significantly higher in AF patients without HF compared with those with HF (RR = 1.32, 95% CI 1.16–1.50 in AF patients without HF; RR = 1.12, 95% CI 1.03–1.23 in AF patients with HF, *P* for interaction = .04) (Supplemental Figure 2, http://links.lww.com/MD/A587).

DISCUSSION

To our knowledge, this is the most comprehensive meta-analysis examining the risk of all-cause mortality associated with digoxin treatment in AF patients, stratified by baseline heart function status. We found that, in AF patients, digoxin treatment was associated with a 22% increase in all-cause mortality. The risk was mildly increased in AF patients with HF, but much more pronounced in those without HF.

Ziff et al[14] performed a meta-analysis concerning the safety of digoxin treatment in observational and controlled trial data, and reported that in data from RCTs, digoxin had a neutral effect on mortality. It should be noted that data from RCTs included in this study were based on HF patients with sinus rhythm and largely driven by the DIG trial. However, the biological or clinical rationale for digoxin treatment may be different in AF patients compared with those with sinus rhythm. Therefore, conclusions from patients with sinus rhythm cannot be extended to AF patients.

Several mechanisms may be involved in the association between the risk of mortality and digoxin treatment in AF patients. First, it is known that digoxin has a narrow therapeutic window. A post-hoc analysis of the DIG trial showed that digoxin treatment was associated with a reduction of mortality when the serum digoxin concentration (SDC) was between 0.5 and 0.9 ng/mL, but an increase in mortality when SDC was >1.2 ng/mL.[31] Higher SDC is associated with life-threatening cardiac arrhythmias. The dose of digoxin may be increased to target ventricular rate control in real-world practice or in observational studies, but monitoring of SDC is lacking. For example, it was reported in the AnTicoagulation and Risk factors In Atrial fibrillation-Cardiovascular Research Network study that SDC was never measured in 31% of digoxin users.[7] Second, susceptibility to some detrimental effects of digoxin therapy, including reduced AV-node conduction and interaction with other antiarrhythmic drugs, may be greater in AF patients.[32] This could be a potential explanation for the heterogeneity of mortality associated with digoxin in HF with AF compared with those with sinus rhythm. Third, other putative mechanisms, including increased endothelial and platelet activation,[33] and activation of baroreceptor function[34] may also be associated with the risk of digoxin therapy in AF patients.

Similar to our study, the risk of all-cause mortality associated with digoxin treatment has been analyzed in 3 previously published meta-analyses.[12,13,15] However, none reported that the risk of all-cause mortality was different between AF patients with HF compared with those without HF. In contrast, our study first reported that the risk of mortality associated with digoxin therapy was much more pronounced in AF patients without HF

compared with those with HF. The effects of digoxin on hemodynamics and neurohumoral mechanisms[35] may be beneficial in HF patients, while such effects are not involved in the treatment of AF without HF. This maybe an underlying explanation for the different effect sizes for mortality associated with digoxin in AF patients with and without HF. Compared with prior meta-analyses, our study had several strengths.

(1) We updated the search strategy and included more recently published studies, with a larger sample of patients (more than 408,000 patients) for analysis. The large sample of patients have sufficient power to detect the significant heterogeneity of digoxin safety in patients with and without HF.
(2) Multiple subgroup analyses (according to sex, trial characteristics, analytic model, etc.) and sensitivity analyses were performed, and consistent results were found in these analyses.

It should be noted that our study was based on data from observational studies. A criticism is that observational studies are inherently not experimental and could not draw firm conclusions from such studies.[36] We agree that RCTs are needed to further evaluate the role of digoxin in AF patients.[37] However, it seems that such RCTs are unlikely to be performed. Large-sample observational studies can provide valuable information and are critical to answer relevant questions in real-world practice and to help choose treatment strategies.[38] In this study, we documented that in real-world practice, digoxin treatment was associated with increased mortality in AF patients, especially in those without HF. In these patients, digoxin was mainly used for heart rate control. Given other available drugs for heart rate control, such as nondihydropyridine calcium channel antagonists and beta-blockers, digoxin should be used with caution in the management of AF, especially in those without HF.

Several limitations of the current meta-analysis should be considered. First, we had no individual patient-level data for analysis. However, the large sample size of our study, strict adjustment for potential confounders (including propensity score-matched analysis) of the included studies, and consistent results in multiple subgroup analyses may have reduced the likelihood that other confounders influenced the association between mortality and digoxin. Second, we did not perform analysis of SDC and risk of mortality, as SDC values were not available in most of the included studies. However, the AnTicoagulation and Risk factors In Atrial fibrillation-Cardiovascular Research Network study reported that in AF patients the mean SDC was higher in patients who died compared with survivors (1.15 vs 0.94 ng/mL; $P < 0.001$).[7] These results strongly suggested that the detrimental effects of digoxin in AF patients might be driven by higher SDC.

In conclusion, our study showed that digoxin therapy was associated with a significant increase in all-cause mortality in AF patients, especially in those without HF. Given other available treatment options, clinicians should avoid using digoxin as a first-line agent for heart rate control in AF patients. Furthermore, if used as an additional therapy, dosing should be adjusted to maintain the SDC with an upper limit of 1.0 ng/mL.[39]

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