Meta-Analysis of Effects of Digoxin on Survival in Patients with Atrial Fibrillation or Heart Failure: An Update

Mate Vamos, MD, PhD[a,1], Julia Wiebke Erath, MD[a,1], Alexander Philipp Benz, MD[a], Renato Delascio Lopes, MD, PhD[b], and Stefan Hans Hohnloser, MD[a,*]

In 2015, 3 independent meta-analyses raised concerns about digoxin therapy being associated with an increased mortality risk in patients with atrial fibrillation (AF) and with heart failure (HF). Although several other studies have been published since then fostering these safety issues, the most recent 2016 European guidelines for AF still recommend this therapy as a class I indication. We performed an updated systematic review and random-effect meta-analysis on publications up to March 2018 reporting data on digoxin associated mortality in subjects with AF or HF. Based on the adjusted survival data of all identified 37 trials comprising a total of 825,061 patients, digoxin use was associated with an increased relative risk of all-cause mortality (hazard ratio [HR] 1.17, 95% confidence interval [CI] 1.05 to 1.29, $p < 0.01$). Treatment with digoxin was associated with an increased mortality risk in the subgroup of patients with AF (n = 627,620, HR 1.23, 95% CI, 1.17 to 1.30, $p < 0.01$), and in the subgroup of patients with HF (n = 197,441, HR 1.11, 95% CI, 1.06 to 1.16, $p < 0.01$). A sensitivity analysis of studies reporting data on new digoxin users (n = 41,687) demonstrated an even higher risk for all-cause mortality compared with patients not receiving cardiac glycosides (HR 1.47, 95% CI, 1.15 to 1.88, $p < 0.01$). In conclusion, this updated meta-analysis confirms that digoxin use is associated with increased mortality in patients with AF or HF. **(Am J Cardiol 2019;123:69−74)**

In 2015 we have demonstrated in a systematic review and meta-analysis comprising data from more than 300,000 patients that digoxin therapy is associated with an increased mortality risk in patients with atrial fibrillation (AF) and with heart failure (HF).[1] Two independent working groups have confirmed our results in their meta-analyses.[2−3] Since these publications, a series of new studies has been published, many of them in large patient populations[4−9] and/or based on retrospective analyses of randomized controlled clinical trials.[5−6,8,10−12] In addition, some studies provide additional data on digoxin daily dosing and/or plasma concentrations.[8,12] In the light of the fact that the most recent guidelines for AF continue to recommend digoxin therapy as a class I indication,[13−14] an updated meta-analysis of all available digoxin studies appears to be a timely issue.

Methods

This is an updated meta-analysis utilizing the same review protocol and methodology as published previously[1] including study reports up to March 2018. Briefly a MEDLINE and a COCHRANE search of the English literature dealing with the effects of digoxin on all-cause-mortality in subjects with AF or HF was performed. Only full-sized articles published in peer-reviewed journals were considered for inclusion, if the following requirements were met: (1) inclusion of AF or HF patient populations; (2) report of adjusted results of effects of digoxin on all-cause-mortality; (3) effect sizes provided as hazard ratios (HR) with 95% confidence intervals (CI). Eighteen new publications[4−12,15−23] were selected and added to the originally included 19 studies (complete listing of all references provided in Supplementary Table 1; flow-chart of study selection provided in Supplementary Figure 1). Studies were categorized as AF or HF studies according to the primary focus and inclusion criterion of each publication.

HR (with 95% upper and lower CI) as available in the selected nonrandomized studies had been adjusted for important baseline clinical variables with different types of statistical methods (i.e., multivariate Cox proportional hazards model, propensity-score matching, and inverse probability weighting; Supplementary Table 1). The random-effect model was used to calculate HR for the overall effect and for the 2 subgroups (AF, HF). A forest plot was constructed showing the individual trials with the pooled estimates. Heterogeneity between individual trial estimates was assessed using the Q statistic and I^2 statistic. Publication bias was assessed using the funnel plot, and the adjusted rank-correlation test according to Begg and Mazumdar. Three sensitivity analyses were conducted: (1) comprising studies providing data on the daily digoxin dose and/or digoxin plasma levels, (2) comprising studies reporting data on new digoxin users, and (3) comprising studies

[a]University Hospital Frankfurt, Goethe University, Frankfurt, Germany; and [b]Duke University Medical Center, Duke University School of Medicine, Durham, North Carolina. Manuscript received July 11, 2018; revised manuscript received and accepted September 27, 2018.

[1]Dr. Vamos and Dr. Erath equally contributed.

See page 73 for disclosure information.

*Corresponding author: Tel: +49-69-6301-7404; fax. +49-69-6301-7017.

E-mail address: hohnloser@em.uni-frankfurt.de (S.H. Hohnloser).

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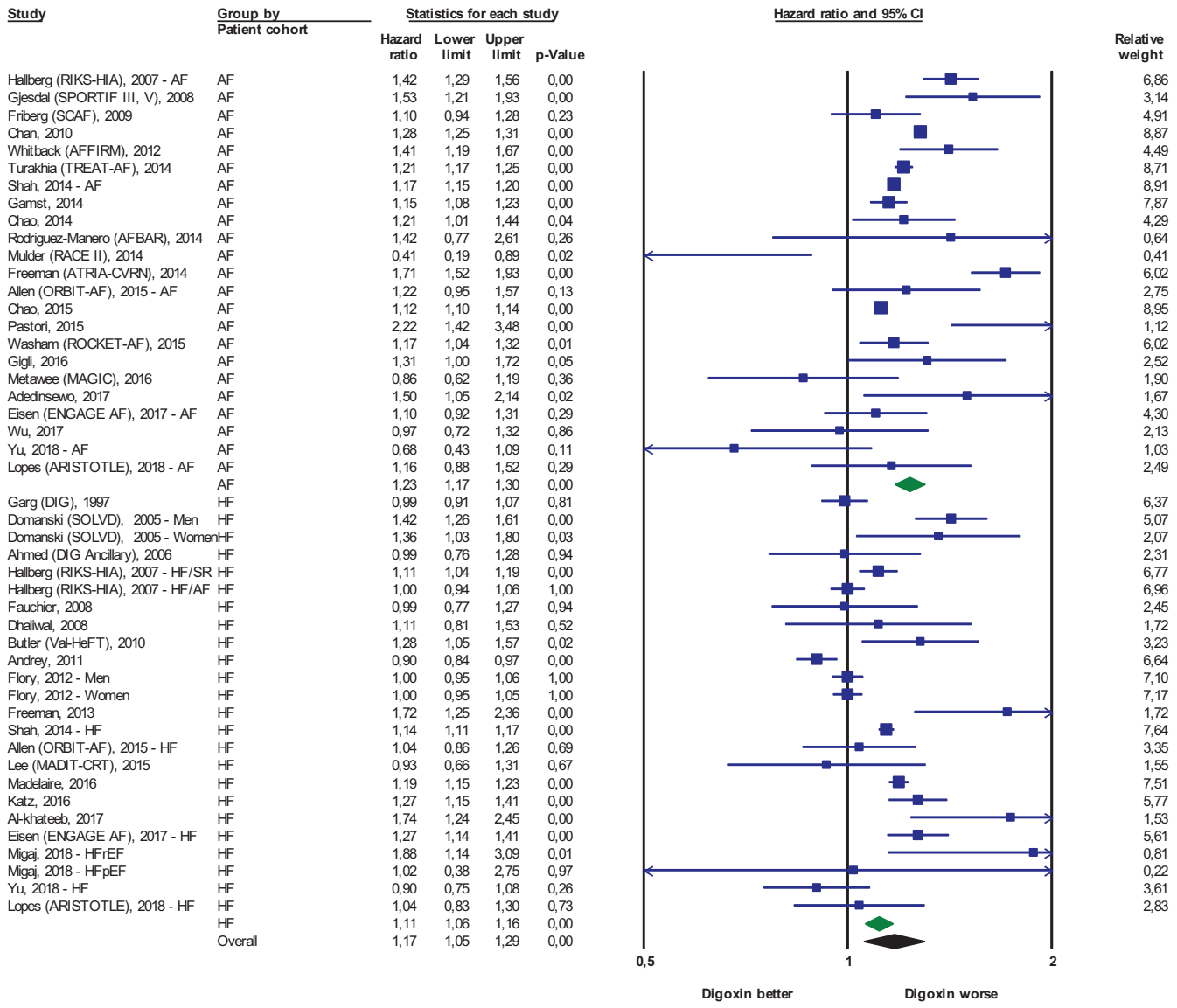

Figure 1. Forest plot of studies describing the effects of digoxin on mortality, both for studies in atrial fibrillation and heart failure. Data had been adjusted for potential confounders in the various studies.

published since our initial meta-analysis. All statistical analyses were conducted utilizing Comprehensive Meta-Analysis 3.3 (Biostat, Inc.).

Results

A total of 37 trials comprising 825,061 patients provided adjusted survival data and form the basis of this meta-analysis. Statistical methods used for adjustment are listed in Supplementary Table 1, and the most important clinical parameters used for adjustment in the various multivariate models are summarized in Supplementary Table 2.

Digoxin use was associated with an overall 17% increased relative risk of all-cause mortality compared with patients not receiving this medication (HR 1.17, 95% CI 1.05 to 1.29, $p < 0.01$, $I^2 = 88.1\%$; Figure 1). Treatment with digoxin was associated with an increased mortality risk in the subgroup of patients with AF (n = 627,620, HR 1.23, 95% CI 1.17 to 1.30, $p < 0.01$), and in the subgroup of patients with HF (n = 197,441, HR 1.11, 95% CI 1.06 to 1.16, $p < 0.01$; Figure 1). According to the rank correlation test of Begg and Mazumdar, there was no evidence of significant publication bias ($t = 0.035$, $p = 0.73$; Supplementary Figure 2).

Ten of the 37 studies reported data on mean daily digoxin dose (range 0.062 to 0.250 mg) and/or data on mean or median digoxin plasma levels (range 0.55 to 1.02 ng/ml; Table 1). A sensitivity analysis of these studies (n = 224,699) revealed a similar HR for mortality (1.17, 95% CI 1.00 to 1.37, $p = 0.05$, $I^2 = 94.6\%$; Figure 2, Supplementary Figure 3).

The meta-analysis of the 3 studies[5,8,10] reporting data on subsets of new digoxin users (n = 41,687) demonstrated an elevated risk for all-cause mortality in incident users of digoxin (HR 1.47, 95% CI 1.15 to 1.88, $p < 0.01$, $I^2 = 61{,}8\%$; Figure 3, Supplementary Figure 4).

The sensitivity analysis of studies published after 2015 (date of our initial meta-analysis) revealed a similar HR for

Table 1
Publications with data on digoxin doses and serum concentrations

Study, Year	Patient cohort	Patient number	Mean digoxin dose (mg)	Mean serum digoxin concentration (ng/ml)
Chan, 2010	AF	120864	0.0625	0.8 (median 1.0)
Mulder (RACE II), 2014	AF	608	0.250	no data
Freeman (ATRIA-CVRN), 2014	AF	14787	0.164	0.96 (available for 69% of all pts)
Pastori, 2015	AF	815	0.126	no data
Lopes (ARISTOTLE), 2018	AF	11204	no data	0.55-0.62 (median, available for 76% of all pts)
Garg (DIG), 1997	HF (SR)	6800	0.244	0.8
Ahmed (DIG Ancillary), 2006	HF (SR)	988	0.235	no data
Flory, 2012 - Men	HF (SR/AF)	27194	0.159	1.2 (available for 20% of all pts)
Flory, 2012 - Women	HF (SR/AF)	30035	0.136	1.3 (available for 20% of all pts)
Freeman, 2013	HF (SR/AF)	2891	0.150	1.02 (availble for 70% of all pts)
Lee (MADIT-CRT), 2015	HF (SR/AF)	1820	0.125-0.250	no data

AF = atrial fibrillation; HF = heart failure; SR = sinus rhythm.

mortality as the main analysis (1.16, 95% CI 1.09 to 1.23, p < 0.01, I^2 = 65.4%; Figure 4, Supplementary Figure 5).

Discussion

In this updated systematic review and meta-analysis including the most recent publications, our previous observations[1] were corroborated in more than 810,000 patients. Digoxin use was associated with increased mortality in patients suffering from both, AF or HF, who were otherwise treated with contemporary medications.

These results are also in line with the observations from Wang et al and Ouyang et al.[2–3] There is only one other meta-analysis[24] reporting partially different results. Although Ziff et al found the pooled risk ratio for death with digoxin in Cox adjusted analyses 1.61 (1.57 to 1.97) and 1.18 (1.09 to 1.26) in studies with propensity-score matching, the investigators concluded that digoxin is associated with a neutral mortality effect in "randomized controlled trials" (risk ratio 0.99, 0.93 to 1.05). This subgroup analysis, however, included only 5 very small studies (mean number of included patients 240) along with the DIG trial and its ancillary publication (Supplementary Table 3). Of note, the primary endpoint of these studies was improvement in exercise tolerance, all were conducted before the times of modern HF therapy (1988 to 1990), and all had only very short follow-up periods (3 to 6 months). Furthermore, the observed effect was dominated by 1 single study, namely the DIG trial (6800 of 8406 patients). Due to these shortcomings, this meta-analysis is not able to resolve the safety concerns regarding digoxin therapy.

The 2013 ACCF/AHA Guidelines for the Management of Heart Failure recommended digoxin in patients with HFrEF as a class IIb indication (level B).[25] Of note, none of the updates of this guideline released in 2016 and 2017 dealt with digoxin therapy. The 2014 AHA/ACC/HRS guideline for the management of AF also recommends digoxin use as a class I indication (level C) for rate-control of AF in patients with HFrEF.[13] Although the 2016 European heart failure guidelines have emphasized the safety concerns of digoxin therapy and restricted the indication for digoxin use in patients with HF and sinus rhythm as a IIb class (level B),[26] the most recent European guidelines for AF continue to recommend digoxin therapy in AF

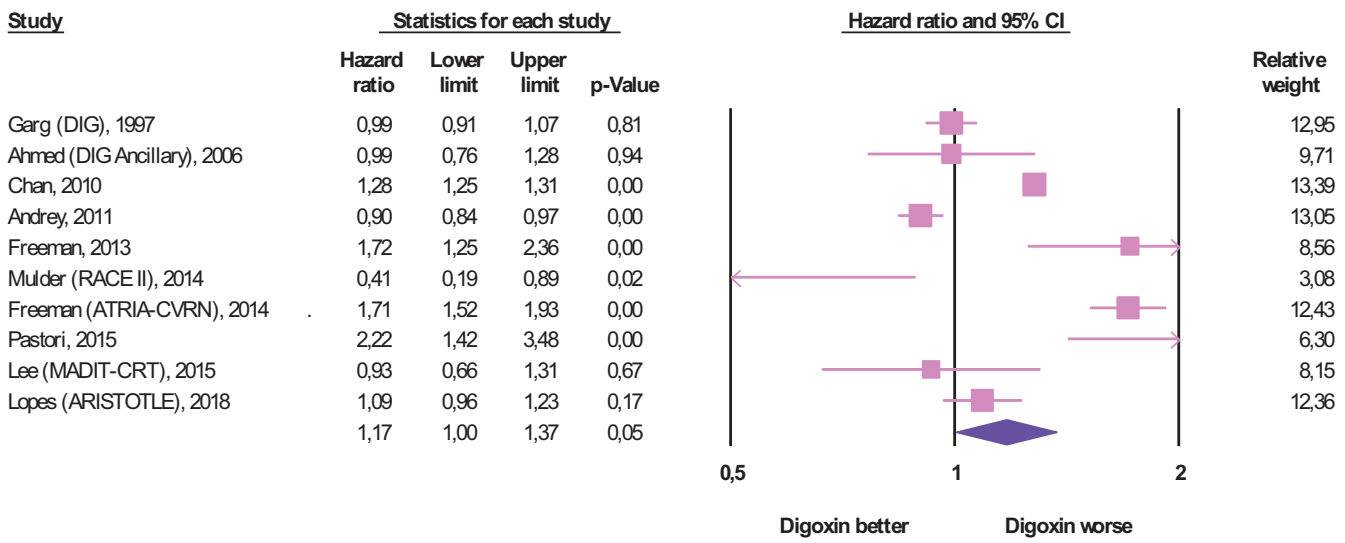

Figure 2. Sensitivity analysis of studies which provided data on digoxin dosing and/or serum levels: Forest-plot.

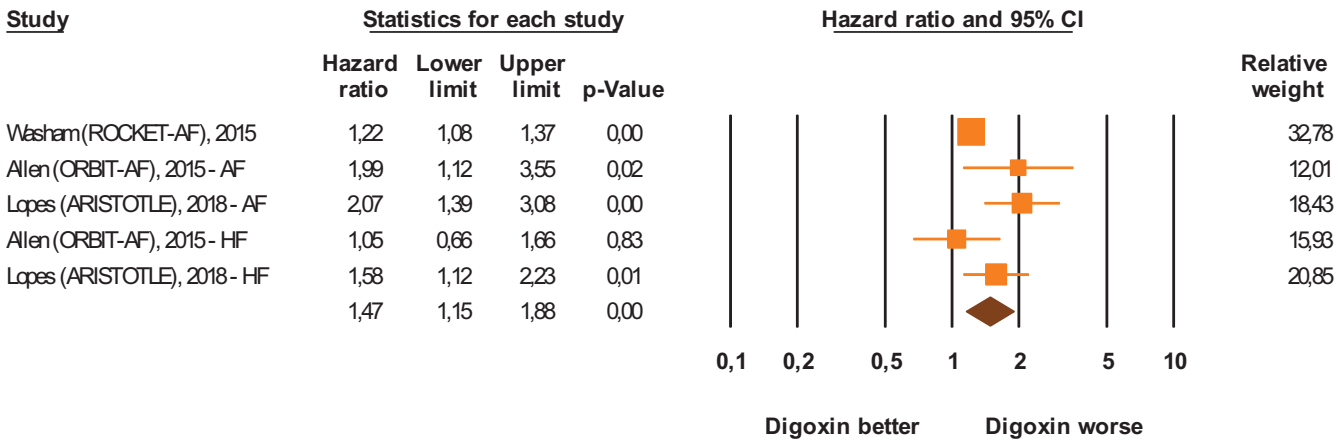

Figure 3. Sensitivity analysis of new digoxin users: Forest-plot.

patients with or without HF again as a class I indication (level B).[14]

In the sensitivity analysis of the studies reporting data on digoxin dose and/or plasma levels, a similar HR for mortality was found. In a recently published post hoc analysis of the ARISTOTLE trial, the risk of death was independently related to the digoxin serum concentration in AF patients.[8] Each 0.5 ng/ml increase in baseline serum digoxin concentration was associated with an increase in death (adjusted HR 1.19, 1.07 to 1.32), which was consistently observed in patients with or without HF. Previously, Chan et al reported in end stage renal disease that each 1.0 ng/ml increase in serum digoxin level significantly increased the risk for mortality by 19%.[15]

Three studies reported survival data specifically in incident digoxin users. This type of analysis is particularly important since it removes the survival bias that is present in most of the observational studies. In this subgroup, the present meta-analysis demonstrated an even higher risk for all-cause mortality (HR 1.47, 1.15 to 1.88).

The most important limitation of the present study is that of all of the identified studies only 1 was a randomized controlled clinical trial, whereas the remaining were observational studies using different statistical adjustments. Generally, digoxin is more likely to be prescribed when a patient has advanced HF, has more difficult to control ventricular rate in AF, is intolerant of β-blockers or calcium channel blockers, and/or has persistent/permanent rather than paroxysmal AF. In such patients, mortality risk is likely to be higher independent of digoxin use. As summarized in Supplementary Table 2, demographics, presence of structural heart disease, chronic kidney disease, or other relevant co-morbidities were used for adjustment in most of the studies. However, other potentially relevant covariates

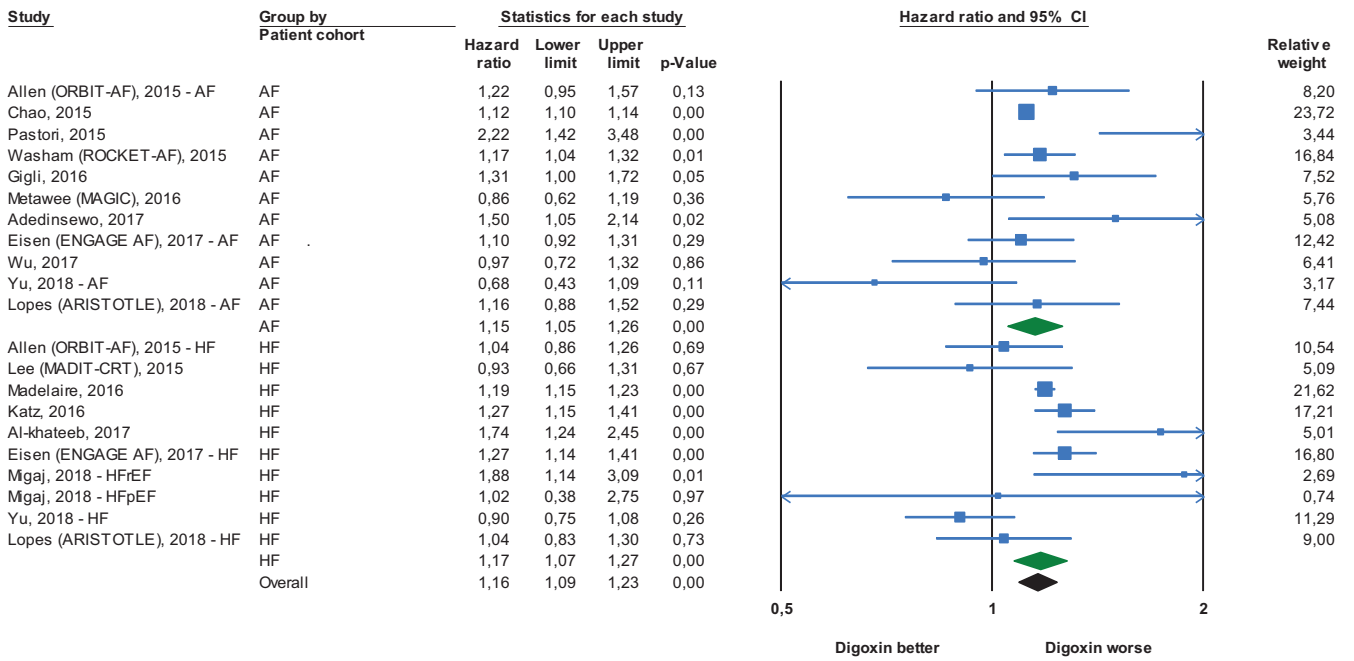

Figure 4. Sensitivity analysis of studies published after 2015: Forest-plot.

were included only in some studies. Thus, residual confounding cannot be excluded. The significant methodologic and statistical heterogeneity, such as different studies including baseline and time-varying digoxin use, should be also acknowledged.

Two randomized controlled digoxin trials are currently enrolling patients. The RATE-AF study is a small prospective, randomized, feasibility study (estimated enrollment: 160 participants), and aims to detect a difference in quality of life, exercise capacity, echocardiographic parameters, and biomarkers comparing digoxin with β-blockers as initial rate control therapy in permanent AF (ClinicalTrials.gov identifier: NCT02391337). The DIGIT-HF is a prospective, randomized, double-blind, clinical trial (estimated enrollment: 2,200 participants) investigating the hypothesis that digitoxin—at serum concentrations in the lower therapeutic range—reduces mortality and morbidity in patients with advanced chronic systolic HF with or without AF (EudraCT number: 2013-005326-38).

The present comprehensive meta-analysis confirmed that digoxin use is associated with an increased mortality risk in AF and in HF patients treated according to contemporary guidelines. Until results of randomized placebo-controlled studies become available, digoxin should be used with great caution.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2018.09.036.

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