Meta-Analysis of *Digoxin* Use and Risk of Mortality in Patients With Atrial Fibrillation

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There is an ongoing debate on the safety of digoxin use in patients with atrial fibrillation (AF). To address this issue, the investigators assembled a synthesis of the available evidence on the relation between digoxin and all-cause mortality in patients with AF. PubMed and the Embase database were systematically searched to identify all eligible studies examining the association between digoxin use and the mortality risk in AF. Overall hazard ratios and 95% confidence intervals were calculated using the random-effects model. Eleven observational studies were identified that met the inclusion criteria, 5 of which additionally used propensity score matching for statistical adjustment. In total, 318,191 patients were followed up for a mean of 2.8 years. Overall, digoxin use was associated with a 21% increased risk for mortality (hazard ratio 1.21, 95% confidence interval 1.12 to 1.30). Sensitivity analyses found the results to be robust. In the propensity score−matched AF patients, digoxin use was associated with a 17% greater risk for mortality (hazard ratio 1.17, 95% confidence interval 1.13 to 1.22). When the AF cohort was grouped into patients with and without heart failure, the use of digoxin was associated with an increase in mortality in patients with and those without heart failure, and no significant heterogeneity was seen between the groups (p >0.10). In conclusion, the results suggest that digoxin use was associated with a greater risk for mortality in patients with AF, regardless of concomitant heart failure. A well-powered randomized trial is necessary to reveal the true effect of digoxin. **(Am J Cardiol 2015;115:901−906)**

Digoxin has been used worldwide for decades to achieve rate control in patients with atrial fibrillation (AF), particularly in those with heart failure (HF). Clinical guidelines currently endorse the use of digoxin in AF,[1,2] despite the lack of randomized trials of digoxin in AF patients. In the largest study, the Digitalis Investigation Group (DIG) study, digoxin was reported to have a neutral effect on mortality in patients with HF,[3] but elevated serum levels of digoxin were found to be correlated with increased mortality in multiple patient population.[4,5] Therefore, the safety of digoxin in patients with AF should be adequately addressed. Recently, a number of observational studies have focused on the safety of digoxin in patients with AF and generated mixed results.[6−16] Therefore, we aimed to quantify the association between the use of digoxin and risk for mortality in AF and to discern whether the mortality risk differs between patients with and without HF.

Methods

Our systematic review was conducted according to the Meta-Analysis of Observational Studies in Epidemiology guidelines.[17] Each investigator independently conducted a systematic search of PubMed and Embase from their inception to December 29, 2014, using the following key words: "digitalis" OR "digoxin" AND "atrial fibrillation" AND "mortality" OR "death." The search was limited to human research, with no restrictions on language. In addition, a manual search of the reference lists of all identified studies and review articles was performed to identify relevant studies.

Abstracts of identified reports were screened to exclude studies that clearly did not meet the eligibility criteria. The full text of those selected for further review was obtained and evaluated. Studies were considered for inclusion if they fulfilled the following criteria: (1) prospective or retrospective studies assessing the association between digoxin use and risk for all-cause mortality in patients with AF, (2) follow-up $\geq$1 year, (3) described adjustment for potential confounding, and (4) reported effect estimates with confidence intervals (CIs), standard errors, or sufficient information to calculate these.

Two investigators independently extracted data from each study. Discrepancies were discussed and resolved by agreement. The following data were extracted from each study: study name, year of publication, setting, study design, number of participants, mean age, study duration, methods for confounding adjustment and variables adjusted for, effect estimates, and CIs or standard errors (or information required to compute these). When multiple effect estimates were reported, maximally adjusted estimates were extracted.

The quality of each study was assessed independently by 2 investigators (A.-J.O., Y.-N.L.) using the Newcastle-Ottawa Scale (NOS).[18] The NOS consists of 3 parameters of quality: selection, comparability, and outcome. The NOS assigns

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See page 905 for disclosure information.

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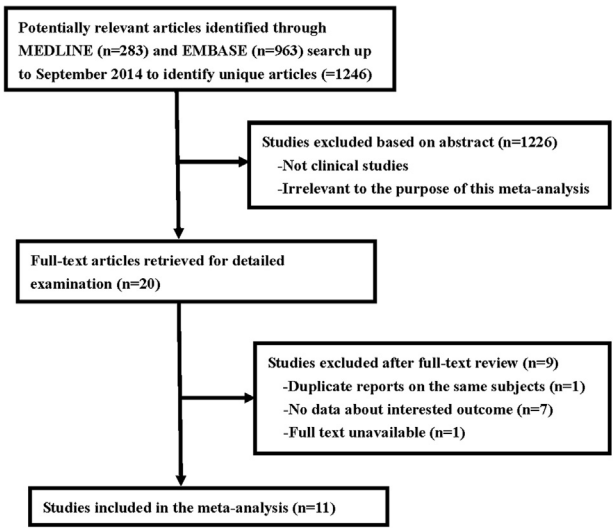

Figure 1. Search strategy and flowchart for studies included in the meta-analysis.

a maximum of 4 points for selection, 2 points for comparability, and 3 points for exposure or outcome. Therefore, a score of 9 points indicates the highest quality, 6 to 8 points indicates medium quality, and <6 points indicates low quality. Any discrepancies were resolved by consensus.

Our meta-analysis and statistical analyses were performed by using Stata 12.0 (StataCorp LP, College Station, Texas). A p value <0.05 was considered to indicate statistical significance, unless otherwise specified. Publication bias was assessed with funnel plots and Egger's regression asymmetry test. Heterogeneity was measured using Cochran's Q and the I^2 statistic; for the Q statistic, a p value <0.10 was considered to indicate statistical significance for heterogeneity, while for I^2, a value >50% was considered to indicate significant heterogeneity.[19] The primary measurement was the pooled hazard ratios (HR) of mortality from individual studies calculated using the random-effects model (DerSimonian and Laird method), which accounts for heterogeneity among studies.

We obtained the pooled risk estimate from studies using a Cox regression survival model to evaluate the association between digoxin use and mortality risk. Furthermore, because observational study designs are limited by an inherent imbalance of both known and unknown confounders, an additional pooled survival analysis was performed on the basis of the propensity score−matching method, which can balance all measured baseline characteristics across treatment groups. We also explored whether the association between digoxin and mortality risk was related to HF status (HF vs no HF).

To test the robustness of the results, we performed a 1-way sensitivity analysis. The scope of this analysis was to evaluate the influence of individual studies by estimating the average HR in the absence of each study.

Results

We retrieved 1,203 citations from database searches. After title and abstract screening, 1,184 were found not to be relevant to this meta-analysis and were excluded. After detailed evaluation of the remaining 20 full-text reports, 9 were excluded for reasons described in Figure 1. Thus, 11 studies[6−16] were included in the primary analyses.

Study and patient characteristics are summarized in Table 1. A total of 318,191 patients were involved. The participants were monitored for 1 to 4.6 years, and the studies were published from 2007 to 2014. Ten studies reported the association between digoxin use and mortality risk on the basis of Cox regression modeling and 5 studies[6,7,11,12,16] additionally on the basis of propensity score matching. On the basis of the NOS, 6 studies[6,7,10−12,15] were of high quality and 5 of medium quality.[8,9,13,14,16]

The pooled analysis on the basis of Cox survival regression modeling showed that digoxin use was associated with a 21% increased risk for mortality (95% CI 1.12 to 1.30; Figure 2), and significant heterogeneity was detected for this outcome ($I^2 = 83.6\%$, $p < 0.001$). Sensitivity analysis showed that the HRs for mortality were similar, without great fluctuation (data not shown). Subgroup analysis showed that both prospective and retrospective studies exhibited significant findings. On the basis of propensity score matching, digoxin use was associated with a 17% increased risk for mortality (95% CI 1.13 to 1.22), but no significant heterogeneity was detected ($I^2 = 40.0\%$, $p = 0.154$).

An additional analysis was performed to determine whether the risk for mortality differed between patients with and without HF. As shown in Figure 3, we found that digoxin use was associated with a 15% increased mortality risk among AF patients with HF (95% CI 1.12 to 1.17) and an 18% increased risk among patients without HF (95% CI 1.15 to 1.21). There was no significant heterogeneity between groups ($p = 0.125$).

Funnel plots and Egger's tests indicated no significant publication bias in the meta-analyses (Egger's test = 0.921). A fail-safe N test indicated that it would take 421 unpublished null-result studies to bring the combined p to a nonsignificant level.

Discussion

This meta-analysis suggests that in patients with AF, digoxin is associated with increased risk for mortality after controlling for confounders and propensity scores. In addition, digoxin use in patients with AF was associated with 15% and 18% greater risk for mortality in the group of patients with HF compared with those without HF, respectively.

The DIG trial, which randomized patients with HF to digoxin, demonstrated a neutral effect on mortality compared with placebo.[3] However, a post hoc analysis of the DIG trial showed that patients with serum digoxin concentrations ≥1.2 ng/ml had an 11.8% higher absolute mortality rate than patients receiving placebo.[4] Because digoxin is widely prescribed to control heart rate in the AF population, the safety of digoxin in patients with AF should be adequately addressed. In the present analysis, increased mortality risk after digoxin use was observed in patients with AF. We hypothesize that arrhythmias, including ventricular arrhythmias and worsened sinus node dysfunction, are a potential source of mortality. The incidence of digoxin-induced arrhythmia was reported to be dose related: 10% at a level of 1.7 ng/ml and 50% at 2.5 ng/ml.[20]