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DIGOXIN AND MORTALITY IN PATIENT WITH ATRIAL FABRILATION

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ABSTRACT

Background:Digoxin is recommended for long-term rate control in paroxysmal, persistent, and permanent atrial fibrillation (AF). While some analyses suggest an association of digoxin with a higher mortality in AF, the intrinsic nature of this association has not been examined in propensity-matched cohorts, which is the objective of the current study

Objectives: The goal of this paper was to explore whether digoxin use was independently associated with increased mortality in patients with AF and if the association was modified by heart failure and/or serum digoxin concentration**.**

Methods: The association between digoxin use and mortality was assessed in 17,897 patients by using a propensity score–adjusted analysis and in new digoxin users during the trial versus propensity score–matched control participants. The authors investigated the independent association between serum digoxin concentration and mortality after multivariable adjustment**.**

RESULTS: A total of 29 studies with a total of 621,478 patients were included. Digoxin use was associated with an increased risk of all-cause mortality in all patients with atrial fibrillation (HR 1.17, 95% CI 1.13-1.22, p<0.001), especially in patients without heart failure (HR 1.28, 95% CI 1.11-1.47 , P<0.001). There was no significant association between digoxin and mortality in patients with atrial fibrillation and heart failure (HR 1.06, 95% CI 0.99-1.14, p=0.110). Digoxin use was associated with sudden cardiac death (SCD) (HR 1.40, 95% CI 1.23-1.60, P<0.001) and cardiovascular (CV) mortality in all patients with atrial fibrillation, with or without heart failure Associated with increased risk (HR 1.27, 95% CI 1.08-1.50, P<0.001) and digoxin use was not significantly associated with all-cause hospitalization(HR1.13, 95% CI 0, 92-1.39, P=0.230) .
Conclusions: We concluded that digoxin use was associated with an increased risk of all-cause mortality, cardiovascular mortality, and SCD, and did not reduce readmission rates for atrial fibrillation, with or without heart failure. Digoxin may have a neutral effect on all-cause mortality in patients with atrial fibrillation and heart failure.

INTRODUCTION

Digoxin is an cardiac glycoside derived from Digitalis lanata. Since the 1960 , digoxin has played an major role as a therapeutic agent for heart rate control in patients with Atrial fibrillation or heart failure[6] Atrial fibrillation is one of the amonges types of arrhythmias world wide in clinical practice . The presently expected occurrence of AF in adults is among two-four percent[1]. The prevalence of atrial fabrillation continue to increase , owing to aging of the general population [2]. and intensified screening for undiagnosed Atrial fibrillation using various detection devices[3]. Atrial. Digoxin exert chronotropic effect by parasympathetic stimulation and inotropic effects through suppression of the sodium-–potassium ATPase , activity boosting of the sodium–-calcium exchange and increasing intracellular calcium concentration , which increases contraction [6][7] . Owing to its negative chronotropic activity , digoxin is still commonly used for heart rate control in patients with atrial fabrilation or heart failure , especially in those who don't reach their heart rate target or who are unable to tolerate β-blocker medications . During previouse years , data on the safety of digoxin treatment in patients with Atrial fibrillation continue to emerge . Many observational studies indicate that digoxin has potentially dangerous acts effects in patients with atrial fabrilation [8][10] . Furthermore , many meta-analyses suggest that digoxin is associated with increased risk of mortality in patients with Atrial fibrillation[11][13] . Nevertheless , neutral effects on mortality in patients with atrial fabrilation receiving digoxin therapy were also reported [14][15]. up to the latest meta-analysis showed there is no evidence of difference in all cause mortality in patients with Atrial fibrillation receiving digoxin therapy compared with those receiving the control intervention [16] . Furthermore , 2020 European Society of Cardiology guidelines for Atrial fibrillation management recommend digoxin in patients with heart failure with decreased ejection fraction as a class I indication (level B) [3] . A series of new and conflicting studies have been published , and it is still controversial as to whether digoxin is associated with increased mortality in patients with Atrial fibrillation . It is also still not clear whether, if digoxin use is associated with reduced hospitalization in patients with Atrial fibrillation [15][17] . however , few meta-analyses have focused on serious adverse events , such as systemic embolic event , myocardial infarction , cardiovascular mortality and sudden cardiac death . Therefore, we performed a meta-analysis to evaluate the risk of mortality and readmission with digoxin in patients withAtrial fibrillation with or without heart failure . We also compared the risk of serious adverse events in patients taking digoxin with those not taking digoxin.

METHODS

This meta-analysis was conducted according to the Preferred Reporting Item for the Guidelines for Systematic Reviews and Meta-Analysis (PRISMA)[18]. This project has been prospectively registered in the PROSPERO database (CRD42020222258). Literature searches were carried out in PubMed, Embase and Cochrane Libraries to identify and retrieve all articles potentially relevant to the topic. Searches conducted as of September 2020 using the following keywords: "digoxin" or "digitalis" or "digoxin" and "atrial fibrillation". See the appendix for more details on search strategies. Searches are limited to human studies, study designs are limited to retrospective analyses of observational studies or randomized controlled trials (RCTs), and language is limited to English. Manual searches were also performed by checking the reference lists of included studies.

RESULTS

Between January 2006 and June 2009,The AFFIRM trial randomized 4060 patients to rhythm control (2033 patients) vs. rate control patients). The study included 1594 females representing 39.3% of the study cohort. Overall, 2816 patients (69.4%) received digoxin within 6 months of randomization and/or during the study. In addition, 1647 patients (58.5%) and 1898 (67.4%) among the 2816 on digoxin received beta-blockers and ACE inhibitors at some point during the study, respectively, compared with the 718 patients (57.7%, P = 0.65) and 734 (59%, P < 0.001) not on digoxin (1244 patients). Figure 1 summarizes the number of patients on digoxin vs. not on digoxin at baseline, through 8-month visit, last follow-up, and death. Moreover, among the 2441 patients on digoxin at one or more follow-up visit (1389 rate control group; 1052 rhythm control), the median duration of therapy was 32 [16, 46] months. Corresponding times for patients randomized to rate and rhythm control were 32 [16, 46] months and 28 [8, 44]months, respectively. Figure 2 shows all-cause mortality for patients always vs. never on digoxin during the course of the study.

Figure 1 Number of patients on digoxin vs. not on digoxin at critical times of the study.

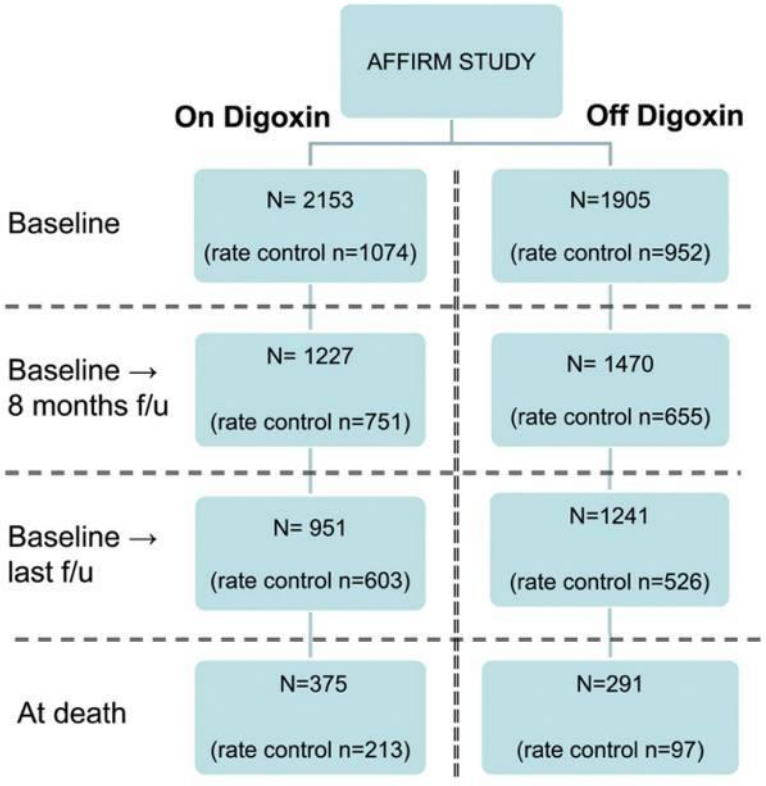
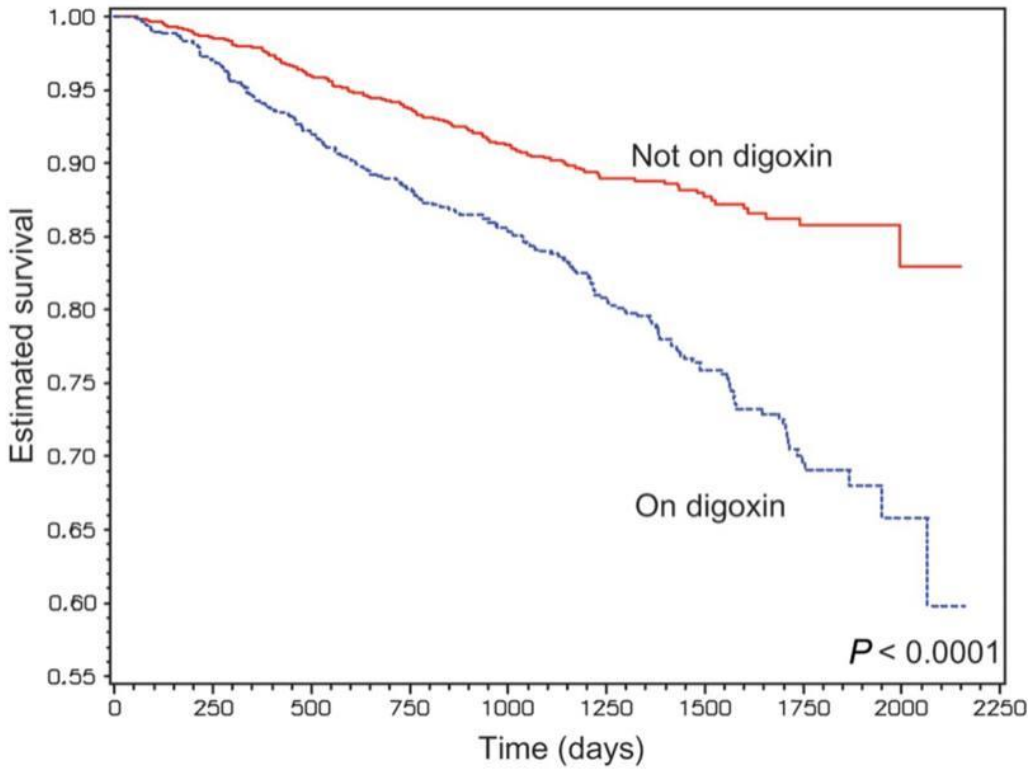


Figure 2 Kaplan–Meier curves for all-cause mortality based on digoxin use during the study. Shown are Kaplan–Meier ...



Number of patients on digoxin vs. not on digoxin at critical times of the study.

In September 2007 and March 2014, 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[31–34] and AFFIRM[35,36] 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.[37] Nine studies comprised patients with AF[9,14–16,18,20,21,38,39] . The primary inclusion criterion for the study by Chao *et al.*[19] consisted of the diagnosis of AF. Hence, this study was initially included in the meta-analysis as an AF study although endpoint results were available for the overall patient group as well as for the patient subset with AF only and heart failure only.

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[8]	AF	AF	Prospective registry study	Baseline use	21 459	4872	1	High (17.5)
Gjesdal (SPORTIF III, V), 2008[14]		AF	*Post-hoc* analysis of RCT	Baseline use	7329	3911	1.55–1.64	High (20)
Friberg (SCAF), 2010[9]		AF	Prospective registry study	Baseline use	2824	802	4.7	High (19)
Whitback (AFFIRM), 2012[15]		AF	*Post-hoc* analysis of RCT	Time-varying covariate	4060	2816	3.5	High (20.5)
Turakhia (TREAT-AF), 2014[16]		AF	Analysis of administrative database	Baseline use and time-varying covariate	122 465	28 679	2.9	High (19)
Shah, 2014[17]	AF	AF	Retrospective population-based cohort study	Baseline use	46 262	23 131	3.0–4.2	High (18.5)
Gamst, 2014[18]		AF	Retrospective population-based cohort	Baseline use	8880	3622	1	High (18)

		study					
Chao, 201419	AF	Analysis of administrative database	Baseline use	4781	829	4.26	High (18)
Rodriguez-Manero (AFBAR), 201438	AF	Prospective registry study	Baseline use	777	270	2.9	High (19.5)
Mulder (RACE II), 201439	AF	*Post-hoc* analysis of RCT	Baseline use	608	284	2.9	High (21)
Freeman (ATRIA-CVRN), 201420	AF	Retrospective population-based cohort study	Baseline use and time-varying covariate	14 787	4231	1.17	High (20)
Pastori, 201521	AF	Prospective observational study	Baseline use	815	171	2.73	High (19.5)

DISCUSSION

This meta-analysis pooled data comparing the effects of digoxin therapy with no digoxin therapy or other heart rate-controlling drugs in patients with atrial fibrillation. The analysis confirmed that digoxin use in patients with atrial fibrillation was associated with an increased risk of all-cause mortality, with or without concomitant heart failure. Patients with atrial fibrillation who were taking digoxin had a 17% higher risk of all-cause death than those who were not taking digoxin. In the subgroup of patients with atrial fibrillation without heart failure, those taking digoxin had a 28% higher risk of all-cause mortality than those not taking digoxin. Interestingly, in the subgroup of AF patients with heart failure, digoxin was not significantly associated with all-cause mortality. Digoxin has also been associated with an increased risk of SCD and cardiovascular death. Digoxin did not reduce readmission rates for atrial fibrillation, regardless of the presence of heart failure. We demonstrated that digoxin use was associated with an increased risk of all-cause mortality in patients with atrial fibrillation, similar to previous meta-analyses[11-13][43] .

The underlying mechanisms of how digoxin increases mortality in atrial fibrillation are not fully understood. However, multiple mechanisms may be involved. First, digoxin is potentially cardiotoxic. Cardiac glycosides can cause cardiovascular damage by regulating sodium-potassium ATPase, which is involved in reactive oxygen species production, cardiac remodeling, and arrhythmias [44].

Second, digoxin may exacerbate platelet activation in patients with atrial fibrillation, which is associated with an increased incidence of cardiovascular disease [45].

Pastori et al. [46] found a significant in vivo correlation between serum digoxin concentration and platelet activation. In particular, supratherapeutic digoxin concentrations increased platelet aggregation. Third, digoxin is eliminated by the kidneys, with a narrow therapeutic window. Digoxin interacts with many other drugs, resulting in increased serum digoxin concentrations and increased risk of cardiac arrhythmias [47]. Many older and more ill patients have renal insufficiency and may be taking drugs that may increase serum digoxin concentrations. Elevated serum digoxin can lead to side effects and toxicity. When all enrolled patients with atrial fibrillation were stratified by cardiac functional status at baseline, we found that digoxin was still associated with an increased risk of all-cause mortality in patients with atrial fibrillation without heart failure, but there was no evidence that all-cause death. lead to death in heart failure patients with atrial fibrillation, unlike several previous meta-analyses [11, 43, 48-50]. We included more studies in our study than previous meta-analyses that provided data on the use of digoxin in patients with atrial

fibrillation and heart failure. Most of these studies reported no significant association between digoxin and mortality in patients with atrial fibrillation and heart failure[10, 15, 23, 25, 31, 35, 37-39, 41]. Even a recent randomized controlled trial comparing the clinical effect of low-dose digoxin with bisoprolol in patients with atrial fibrillation with symptoms of heart failure found that digoxin was more effective in symptom control of atrial fibrillation and heart failure-related symptoms, which Consistent with lower N-terminal natriuretic peptide concentrations and fewer adverse events of the Pro-B type [50]. Digoxin has positive inotropic, negative chronotropic, and anti-adrenergic effects[7] . These effects are thought to be beneficial in patients with atrial fibrillation and heart failure, which may explain conflicting results in patients with atrial fibrillation without heart failure. However, according to the AFFIRM study [52], beta-blockers are the most effective heart rate control drugs, and digoxin is usually the second-line option or in combination with beta-blockers, perhaps not with neutral mortality The effect of digoxin is used in patients with heart failure with atrial fibrillation, but other heart rate control drugs such as beta-blockers may improve survival. Therefore, we performed a subgroup analysis of patients not receiving beta-blockers. Five studies reported data on digoxin alone versus no other rate control therapy in patients with atrial fibrillation with or without heart failure, where all heart rates were fitted by nonpropensity score-matched models, which also Added treatment with digoxin. It should be noted that our meta-analysis was based on data from observational studies or post hoc analyses of randomized controlled trials. Because most RCTs limit follow-up to days to weeks, and do not assess long-term mortality or hospitalization. More recently, Sethi et al. [16] A meta-analysis of digoxin-controlled heart rate in patients with atrial fibrillation based on data from randomized controlled trials. They noted that based on current knowledge, the clinical impact of digoxin on all-cause mortality and serious adverse events is unclear, as none of the studies included in this meta-analysis reported long-term follow-up data. More information from large observational studies is currently needed to help us learn more about the long-term effects of digoxin. It is known that digoxin is more commonly used in patients with a higher comorbidity burden and who require additional heart rate control therapy; in other words, patients who receive digoxin are generally more ill than those who do not require digoxin, leading to selection bias. Therefore, initiation of digoxin during follow-up avoids potential selection bias caused by baseline digoxin use. When we summarized studies reporting on the initiation of digoxin therapy in patients with atrial fibrillation during follow-up, digoxin remained associated with an increased risk of all-cause mortality.To reduce potential confounding factors, some studies often used Cox regression or logistic regression models to adjust for clinical variables in observational studies, and some studies performed propensity score-matched cohorts

to select digoxin and non-diagnostics with various patient-related baseline characteristics. The digoxin treatment group was well balanced. In our subgroup analysis, a pooled analysis of the unadjusted HR for mortality in patients with atrial fibrillation showed that patients taking digoxin had a 42% higher risk of all-cause mortality than those not taking digoxin.

However, after adjustment for baseline differences, the risk of all-cause mortality was lower in the subgroups with HR adjusted by statistical models. The results of these subgroup analyses still suggest that digoxin treatment is associated with an increased risk of all-cause mortality in patients with atrial fibrillation. Zift people. [53]Recommended use of digoxin is associated with a reduction in hospital admissions. Singer et al. [15]has also shown that digoxin is associated with a reduced risk of heart failure recurrence. In our study, however, we found no evidence of an overall reduction in readmission rates in patients with atrial fibrillation. Regarding serious adverse events during follow-up, we found that digoxin use was not significantly associated with SEE/stroke, MI, and non-cardiovascular mortality, but the risks of SCD and cardiovascular mortality were 40% and 27%, respectively. The incidence of digoxin in patients with atrial fibrillation was higher than in patients not taking digoxin. SCD events account for a portion of cardiovascular deaths. Eisen et al. [36] examined the relationship between baseline characteristics and SCD in patients with atrial fibrillation. They found that digoxin use was a significant predictor of SCD in patients with atrial fibrillation. Based on the mechanism of action of digoxin, the increase in SCD is attributable to arrhythmic death [10] .

This may be a fundamental explanation for the increased risk of SCD associated with digoxin.

CONCLUSION

Digoxin use in patients with atrial fibrillation increases the risk of all-cause mortality, especially in patients without concomitant heart failure. Digoxin use is also associated with an increased risk of SCD and cardiovascular death, and digoxin does not appear to reduce readmission rates for atrial fibrillation, with or without heart failure. However, digoxin may have a neutral effect on all-cause mortality in patients with atrial fibrillation and heart failure. Therefore, digoxin may be an additional option for heart rate control in patients with atrial fibrillation and heart failure, especially in patients with beta-blocker intolerance or inability to achieve target heart rates. However, we recommend that digoxin should be used with caution and with appropriate concentration monitoring to avoid toxicity.

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