

## Digoxin: A systematic review in atrial fibrillation, congestive heart failure and post myocardial infarction

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### Abstract

**AIM:** To review digoxin use in systolic congestive heart

failure, atrial fibrillation, and after myocardial infarction.

**METHODS:** A comprehensive PubMed search was performed using the key words "digoxin and congestive heart failure", "digoxin and atrial fibrillation", "digoxin, atrial fibrillation and systolic congestive heart failure", and "digoxin and myocardial infarction". Only articles written in English were included in this study. We retained studies originating from randomized controlled trials, registries and included at least 500 patients. The studies included patients with atrial fibrillation or heart failure or myocardial infarction and had a significant proportion of patients (at least 5%) on digoxin. A table reviewing the different hazard ratios was developed based on the articles selected. Our primary endpoint was the overall mortality in the patients on digoxin *vs* those without digoxin, among patients with atrial fibrillation and also among patients with atrial fibrillation and systolic heart failure. We reviewed the most recent international guidelines to discuss current recommendations.

**RESULTS:** A total of 18 studies were found that evaluated digoxin and overall mortality in different clinical settings including systolic congestive heart failure and normal sinus rhythm ( $n = 5$ ), atrial fibrillation with and without systolic congestive heart failure ( $n = 9$ ), and myocardial infarction ( $n = 4$ ). Overall, patients with systolic congestive heart failure with normal sinus rhythm, digoxin appears to have a neutral effect on mortality especially if close digoxin level monitoring is employed. However, most of the observational studies evaluating digoxin use in atrial fibrillation without systolic congestive heart failure showed an increase in overall mortality when taking digoxin. In the studies evaluated in this systematic review, the data among patients with atrial fibrillation and systolic congestive heart failure, as well as post myocardial infarction were more controversial. The extent to which discrepancies among studies are based on statistical methods is currently unclear, as these studies' findings are generated by retrospective analyses that employed

different techniques to address confounding.

**CONCLUSION:** Based on the potential risks and benefits, as well as the presence of alternative drugs, there is a limited role for digoxin in the management of patients with normal sinus rhythm and congestive heart failure. Based on the retrospective studies reviewed there is a growing volume of data showing increased mortality in those with only atrial fibrillation. The proper role of digoxin is, however, less certain in other subgroups of patients, such as those with both atrial fibrillation and systolic congestive heart failure or after a myocardial infarction. Further studies may provide helpful information for such subgroups of patients.

**Key words:** Digoxin; Atrial fibrillation; Heart failure; Myocardial infarction; Mortality

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**Core tip:** This systematic review evaluates mortality with the use of digoxin in congestive heart failure (CHF) with sinus rhythm, atrial fibrillation with and without CHF, and post myocardial infarction. In patients with CHF with sinus rhythm, there continues to be a niche for digoxin use as an adjunctive therapy for symptomatic control with the understanding that there is no effect on mortality. The role for digoxin among patients who only have atrial fibrillation seems very limited; however, those with atrial fibrillation and systolic congestive heart failure or post myocardial infarction need further assessment as many questions remain regarding the benefit of digoxin in this population.

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## INTRODUCTION

Digoxin is one of the oldest drugs used today in cardiovascular medicine in the United States and around the globe. It is used frequently to treat heart failure symptoms and to decrease the ventricular rate in atrial fibrillation (AF). Digoxin was one of the first treatments for heart failure management and was shown to decrease hospitalizations without decreasing mortality in patients with sinus rhythm and left ventricular ejection fraction (LVEF) of less than 45%<sup>[1]</sup>. Nowadays digoxin remains indicated for patients with persistent symptoms despite optimal medical therapy even with the advent of several new classes of cardiovascular medications with proven benefit on symptoms and survival [including beta blockers, angiotensin converting

enzyme inhibitors (ACEI), angiotensin receptor blockers and mineralocorticoid antagonists]. In the setting of AF, digoxin is not mentioned in the 2014 guidelines anymore as an option for rate control, except among patients with AF and heart failure; however, concerns arose regarding its safety even in this subgroup of patients<sup>[2-4]</sup>. No randomized controlled clinical trials have been performed to date to assess the efficacy and safety of digoxin in patients with AF. Most of the current data regarding the safety and efficacy of digoxin are based on observational studies which have had conflicting results. We review the data available regarding the use of digoxin in congestive heart failure (CHF), AF, and after myocardial infarction, as well as the current guidelines indications for digoxin use from the American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC).

## Digoxin mechanisms of action

Digoxin's primary mechanism of action is through inhibition of sodium-potassium adenosine triphosphatase (ATPase). Its role in heart failure patients is based on its inotropic properties, due to inhibition of sodium-potassium ATPase which leads to increased intracellular calcium concentrations through the sodium-calcium exchanger<sup>[5-8]</sup>. This causes the cardiac action potential to lengthen which causes lower heart rates as well as increases myocardial contractility due to the increased calcium for sarcomeric excitation-contraction coupling<sup>[8]</sup>. Digoxin also has neurohormonal effects and causes improved baroreceptor sensitivity, decreases norepinephrine concentration, and decreases activation of the renin-angiotensin system<sup>[5,6,9]</sup>.

From the electrophysiologic standpoint, digoxin has a parasympathetic effect on the sinoatrial node, by decreasing the automaticity as well as on the atrioventricular conduction system by decreasing conduction and increasing the effective refractory periods<sup>[6]</sup>.

## MATERIALS AND METHODS

### Literature search

A comprehensive PubMed search was performed using the key words "digoxin and congestive heart failure", "digoxin and AF", "digoxin, AF and systolic congestive heart failure", and "digoxin and myocardial infarction". Only articles written in English were included in this study. We retained studies originating from randomized controlled trials, registries and included at least 500 patients. The studies included patients with AF or heart failure or myocardial infarction and had a significant proportion of patients (at least 5%) on digoxin. A table reviewing the different hazard ratios was developed based on the articles selected. Our primary endpoint was the overall mortality in the patients on digoxin vs those without digoxin, among patients with AF and also among patients with AF and systolic heart failure. We reviewed the most recent international guidelines to

discuss current recommendations.

## RESULTS

### Literature review

A total of 18 studies were found that evaluated digoxin and overall mortality in the different clinical settings including systolic heart failure and sinus rhythm ( $n = 5$ ), AF with and without heart failure ( $n = 9$ ), and myocardial infarction ( $n = 4$ ).

### Congestive heart failure with sinus rhythm

For over 200 years, digoxin has been used to treat patients with systolic heart failure in normal sinus rhythm, but over the past several decades digoxin has been scrutinized regarding its therapeutic benefit and risk. As studies began to show the benefits of ACEI in reducing mortality, clinicians began to question the role of digoxin. This led physicians to inquire whether discontinuing digoxin from patients' medical regimens had any effect, especially if patients were also taking ACEI, since no long term benefit had been shown with digoxin.

The Randomized Assessment of Digoxin on Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) study randomized 178 patients with New York Heart Association (NYHA) Class II-III heart failure, LVEF of  $< 35\%$ , and normal sinus rhythm to evaluate whether removing digoxin had any clinical significance. This study found that stable patients on digoxin, ACEI, and diuretics had an increased risk of clinical decline when digoxin was removed from their medication regimen with a 5.9 estimated relative risk (95%CI: 2.1-17.2) of worsening heart failure compared to those continuing digoxin. In addition, patients' no longer taking digoxin had lower quality-of-life scores, decreased ejection fraction and increased heart rate and body weight<sup>[10]</sup>. The RADIANCE study established the short term benefit of digoxin in preventing worsening functional decline, exercise capacity and LV ejection fraction in patients with heart failure and normal sinus rhythm<sup>[10]</sup>. Furthermore, the Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED) trial also demonstrated the efficacy of digoxin in patients with mild to moderate systolic heart failure on diuretic therapy<sup>[11]</sup>. Both studies however had a short term follow up (12 wk for RADIANCE and 20 wk for PROVED)<sup>[10,11]</sup>. It remained unknown whether the results would be similar with longer follow-up. This led the Digitalis Investigation Group to perform a randomized, double-blinded placebo-controlled trial to evaluate the effects of digoxin on mortality and hospitalizations in patients with heart failure and normal sinus rhythm<sup>[1]</sup>.

The DIG study enrolled 6800 patients with LVEF of 45% or less and they were randomized to receive digoxin (3397 patients) or placebo (3403 patients) in addition to diuretics and ACEI. The DIG study failed to demonstrate a beneficial effect of digoxin on overall mortality with 1181 deaths in the digoxin group

(34.8%) and 1194 deaths in the placebo group (35.1%) giving an estimated risk ratio (RR) of 0.99 (95%CI: 0.91-1.07,  $P = 0.80$ )<sup>[1]</sup>. Also, no difference was seen in cardiovascular deaths with 1016 in the digoxin group (29.9 %) vs 1004 in the placebo group (29.5%) with RR = 1.01 (95%CI: 0.93-1.10,  $P = 0.78$ )<sup>[1]</sup>.

However, there was a trend towards a lower risk of mortality secondary to heart failure with 394 deaths in the digoxin group compared to 449 in the placebo group with a RR of 0.88 (95%CI: 0.77-1.01,  $P = 0.06$ ). Overall, the number of hospitalizations attributed to worsening heart failure was lower in the digoxin group compared to placebo with a RR of 0.72 (95%CI: 0.66-0.79,  $P < 0.001$ )<sup>[1]</sup>. When combining death from any cause or hospitalization due to worsening heart failure, the digoxin group had fewer events (RR = 0.85; 95%CI: 0.79-0.91,  $P < 0.001$ ). This was also seen when combining heart failure deaths or hospitalizations due to worsening heart failure (1041 vs 1291, RR = 0.75; 95%CI: 0.69-0.82,  $P < 0.001$ ). In addition, a subgroup analysis of the prior outcome, digoxin appeared to have the greatest beneficial effect among those at highest risk, especially those with lower ejection fraction, enlarged hearts, and those in NYHA functional class III or IV<sup>[1]</sup>.

A post-hoc analysis evaluated men in the DIG study according to serum digoxin concentrations to assess if drug concentration had an association with mortality and hospitalizations. In this analysis, there was a reduction in all-cause mortality in patients with lower serum digoxin levels (0.5-0.8 ng/mL) with a 6.3% (95%CI: 2.1%-10.5%,  $P = 0.005$ ) absolute lower mortality rate compared with patients receiving placebo. As the serum digoxin concentration increased, the absolute risk in mortality increased to the point that those with levels greater than 1.2 ng/mL had an 11.8% (95%CI: 5.7%-18.0%,  $P < 0.001$ ) higher absolute mortality rate than patients receiving placebo. Similar conclusions persisted even with multivariable adjustments<sup>[12]</sup>.

Finally, a recent meta-analysis by Hood *et al.*<sup>[13]</sup> reviewed 13 randomized controlled trials where patients were randomized to digoxin and focused on mortality, hospitalization, and clinical status. This meta-analysis showed that digoxin had no effect on mortality which was mostly driven by the data from the DIG study. This meta-analysis also found that in the four studies that provided data on hospitalizations for worsening heart failure, digoxin had significantly fewer hospitalizations due to worsening heart failure with an overall relative risk reduction of 23.4% and number needed to treat ranging from 13-17<sup>[13]</sup>.

### Current guidelines

The most current ACC/AHA and ESC guidelines recommendation on the use of digoxin in heart failure with reduced ejection fraction and normal sinus rhythm are based on the prior studies. The ACC/AHA guidelines in 2013 (class IIa, level of evidence B) as well as the

ESC guidelines in 2012 (class IIb, level of evidence B) recommended digoxin for symptomatic improvement and improved quality of life as well as to decrease hospitalizations for heart failure exacerbations<sup>[14,15]</sup>. The guidelines emphasize the importance of initiating goal-directed medical therapy as the primary treatment for heart failure due to its known mortality benefit. However, the guidelines continue to allow physicians discretion regarding digoxin and emphasize the importance of close monitoring for digoxin toxicity<sup>[14,15]</sup>.

### ***Atrial fibrillation with and without congestive heart failure***

In the general population, AF is the most common sustained cardiac arrhythmia. For many years, the primary approach to treatment was to maintain normal sinus rhythm with anti-arrhythmic medications and cardioversion, as a rhythm control strategy was thought to decrease morbidity and mortality compared to a rate control strategy. However, after the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial as well as other randomized clinical trials, there was a shift in practice towards maintaining rate control in asymptomatic patients, as these trials exposed no significant improvement in mortality with rhythm control<sup>[16-22]</sup>. Digoxin was one of the four rate control medications used in the AFFIRM trial and remains an option for rate control.

Over the past two decades, controversy regarding the use of digoxin in patients with AF has arisen due to the potential for adverse effects. An initial retrospective analysis of AFFIRM trial data found that digoxin was associated with lower survival<sup>[23]</sup>. Yet, these findings were attributed to the patients' comorbid conditions which placed them at increased risk of death, rather than to an adverse effect of the medication. This observation was confirmed in another retrospective analysis of AFFIRM trial<sup>[24]</sup>.

Subsequently, a Swedish study evaluated one year mortality among patients admitted to the coronary care unit with AF, CHF, or both in relation to digoxin. This study found that long term use of digoxin was associated with lower survival in patients with AF without CHF, with an adjusted estimated hazard ratio (HR) of 1.42 (95%CI: 1.29-1.56)<sup>[25]</sup>. However, no significant increase in mortality risk was seen in patients with CHF alone or in combination with AF.

Two retrospective studies re-evaluated the safety of digoxin use from the AFFIRM database by correcting for potential confounders, but they used different methodologies and found apparently conflicting results<sup>[4,26]</sup>. The first retrospective analysis regarded digoxin as a time dependent covariate in a propensity-adjusted Cox model and found that digoxin was associated with increased all-cause mortality, with a HR of 1.41 (95%CI: 1.19-1.67,  $P < 0.001$ ) as well as increased cardiovascular and arrhythmic mortality<sup>[4]</sup>. The increased all-cause mortality was also seen in patients with (HR = 1.41, 95%CI: 1.09-1.84,  $P = 0.010$ ) and without (HR = 1.37, 95%CI:

1.05-1.79,  $P = 0.019$ ) heart failure<sup>[4]</sup>.

Shortly after, a second retrospective analysis was published using propensity matching to evaluate digoxin use at baseline. This analysis found no significant difference in all-cause mortality (HR = 1.06, 95%CI: 0.83-1.37,  $P = 0.640$ ) or hospitalizations<sup>[26]</sup>. The differences in results between the two retrospective analyses appear to arise from the different statistical methods used, with each analysis carrying some potential bias<sup>[27]</sup>. The study by Whitbeck and colleagues had an indication bias that the authors mitigated using adjustment for covariates and propensity scores<sup>[4]</sup>. Meanwhile, the second study suffered from crossover bias and a depleted sample size associated with matching<sup>[26]</sup>. Although the authors' stated conclusions were not in agreement, it is worth noting that there was some overlap in their 95%CI for all-cause mortality and that the overlapping portion (1.19-1.37) is consistent with a clinically significant, deleterious effect of digoxin in this patient population.

The aforementioned analyses of AFFIRM data have been followed by many other studies. In an observational study using the National Health Insurance Research Database in Taiwan, 4781 patients with AF were studied. In this analysis, digoxin was associated with an increased risk of all-cause mortality, with an adjusted HR of 1.21 (95%CI: 1.01-1.44,  $P = 0.037$ )<sup>[28]</sup>. During subgroup analysis, digoxin portended worse survival among patients without heart failure but not among those with heart failure<sup>[28]</sup>.

In one of the largest retrospective analyses evaluating newly diagnosed AF, the The Retrospective Evaluation and Assessment of Therapies in Atrial Fibrillation study evaluated 122465 patients in the Veterans Affairs health care system. The study found digoxin to be associated with increased mortality after multivariate adjustments (HR = 1.26, 95%CI: 1.23-1.29,  $P < 0.001$ ) and propensity matching (HR = 1.21, 95%CI: 1.17-1.25,  $P < 0.001$ )<sup>[3]</sup>. This conclusion persisted even after accounting for kidney function and history of documented heart failure, heightening the concern that digoxin reduces survival. However, data regarding the degree of left ventricular dysfunction or the NYHA class were not available; it is unknown how accounting for the severity of heart failure would impact this study's findings.

Another large retrospective analysis of the Anticoagulation and Risk Factors In Atrial Fibrillation Cardiovascular Research Network trial evaluated digoxin in patients with new onset AF and no history of CHF. This observational study used patients belonging to the Kaiser Permanente database and living mainly on the west coast of the United States. In this study, digoxin was shown to be associated with a higher risk of death with HR = 1.71 (95%CI: 1.52-1.93,  $P < 0.001$ )<sup>[29]</sup>. This conclusion was robust in distinctions between intention-to-treat and as-treated analyses.

A post-hoc analysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin



K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) evaluating digoxin use and its association with cardiovascular events was performed. The trial enrolled 14171 patients of which 5239 patients were taking digoxin at baseline. In this analysis, baseline digoxin use was associated with an increased all-cause mortality with an adjusted HR of 1.17 (95%CI: 1.04-1.32,  $P = 0.009$ )<sup>[30]</sup>. Similar findings persisted when accounting for covariates using a regression model as well as with a time-dependent model. In subgroup analysis, the all-cause increased mortality was observed among patients with and without heart failure, as judged by left ventricular function or NYHA status<sup>[30]</sup>.

In a population based retrospective analysis evaluating digoxin in patients 65 years or older with and without heart failure, an increased risk of all-cause mortality was detected in analyses based on propensity matching and multivariable Cox regression modeling. In this study, the heart failure group had a 14% greater hazard of all-cause mortality with digoxin (adjusted HR = 1.14, 95%CI: 1.10-1.17,  $P < 0.001$ ), similar to the non-heart failure group which had a 17% greater hazard of all-cause mortality with digoxin (adjusted HR = 1.17, 95%CI: 1.14-1.19,  $P < 0.001$ )<sup>[2]</sup>.

Hazard ratios for total mortality are reported in Table 1 for the main AF studies with digoxin, as well as for patients with or without CHF.

### Current guidelines

The 2014 AHA/ACC/Heart Rhythm Society (HRS) guidelines (Class IIa, level of evidence B) and 2010 ESC guidelines (Class IIa, level of evidence C) do not consider digoxin as a first line therapy for rate control in AF; however, digoxin can be considered in combination with a beta blocker and/or nondihydropyridine calcium channel blocker when the ventricular rate is poorly controlled in patients with underlying left ventricular dysfunction<sup>[36,37]</sup>. Due to controversy and concern regarding increased mortality in many post-hoc analyses, the guidelines continue to stress caution when administering medication and to periodically check digoxin levels, in an attempt to reduce adverse effects especially in the long term setting<sup>[36,37]</sup>.

### Digoxin use in myocardial infarction

The AHA/ACC and ESC guidelines agree that in certain clinical situations digoxin use in patients presenting with ST elevation myocardial infarction is effective; moreover, digoxin use has been deemed appropriate for AF rate control in patients presenting with CHF and ongoing ischemia<sup>[38,39]</sup>. With increased attention toward the risk/benefit tradeoff of digoxin therapy, a recent retrospective analysis evaluated whether patients chronically taking digoxin had increased in-hospital mortality when admitted for acute coronary syndrome. The analysis considered 20331 patients of which 244 were taking digoxin upon admission to the hospital, using multivariate modeling as well as

propensity score matching. Neither statistical method showed significantly increased in-hospital mortality<sup>[40]</sup>. On the other hand, several studies performed in the 1990's evaluated outcomes among patients surviving a myocardial infarction (remotely after the index event) and found increased mortality with digoxin<sup>[40-43]</sup>. For instance, the retrospective study by Køber *et al.*<sup>[41]</sup> found post-MI patients being treated with digoxin at one year and five years to have 38% and 74% mortality respectively vs much lower rates among those not receiving digoxin (8% at one year and 26% at five years), both differences being statistically significant<sup>[41]</sup>. However, many patients in these older studies were not on current standard therapies including beta blockers.

### Current guidelines

Both the AHA/ACC and ESC guidelines address the use of digoxin in the acute management of patients who present with acute ST elevation myocardial infarction. Both sets of guidelines agree that, in patients who present with acute heart failure symptoms due to severe LV dysfunction and AF with rapid ventricular rates and ongoing ischemia, digoxin may be given intravenously to improve rate control without undue concern for negative inotropic effects from beta blockers and calcium channel blockers<sup>[38,39]</sup>. A potential downside of digoxin in this clinical setting though may be an increase oxygen consumption.

## DISCUSSION

This review of the current literature regarding the use of digoxin in CHF with sinus rhythm, AF with and without CHF, and post myocardial infarction highlights the concern regarding mortality risk when using digoxin. In patients with CHF with sinus rhythm, there continues to be a niche for digoxin use as an adjunctive therapy for symptomatic control once goal directed therapy has been optimized, with the understanding that there is no effect on mortality as seen in the DIG study and with a close monitoring of digoxin level.

However, no randomized controlled trial has evaluated the role of digoxin in conjunction with the current mainstay treatment strategy for CHF. It is unknown whether findings from the DIG study or prior studies can be applied to the modern strategy for heart failure<sup>[13,44]</sup>. Recent observational studies have conflicting findings regarding digoxin when evaluating patients on current optimal heart failure therapy. Although the conflicts might be resolved by a contemporary randomized trial, such a trial may not take place<sup>[45-47]</sup>. Furthermore, as novel agents like Ivabradin and the new angiotensin receptor neprilysin inhibitor become more prevalent along with left ventricular assist devices, digoxin may become less relevant in this patient population especially that these new therapies have shown to improve survival<sup>[48,49]</sup>.

Questions remain regarding digoxin as a rate control strategy for those with and without heart failure. A

**Table 1** Hazard ratio estimates from studies describing the effects of digoxin on total mortality in patients with atrial fibrillation

Study	Subjects	Hazard ratio estimates <sup>1</sup>		
		Overall mortality	AF without CHF	AF with CHF
Shah <i>et al</i> <sup>[2]</sup>	140111	NA	<sup>2</sup> 1.17 (95%CI: 1.14-1.19, <i>P</i> < 0.001)	<sup>2</sup> 1.14 (95%CI: 1.10-1.17, <i>P</i> < 0.001)
Turakhia <i>et al</i> <sup>[3]</sup>	122465	<sup>2</sup> 1.26 (95%CI: 1.23-1.29, <i>P</i> < 0.001)	<sup>2</sup> Significant, details not given	1.29 (95%CI: 1.23-1.36, <i>P</i> < 0.001)
TREAT AF		1.21 (95%CI: 1.17-1.25, <i>P</i> < 0.001)		1.28 (95%CI: 1.21-1.36, <i>P</i> < 0.001)
Hallberg <i>et al</i> <sup>[25]</sup>	38419	NA	<sup>2</sup> 1.42 (95%CI: 1.29-1.56, <i>P</i> < 0.001)	1.00 (95%CI: 0.94-1.06)
Freeman <i>et al</i> <sup>[29]</sup>	14787	NA	<sup>2</sup> 1.71 (95%CI: 1.52-1.93, <i>P</i> < 0.001)	NA
ATRIA-CVRN				
Washam <i>et al</i> <sup>[30]</sup>	14171	<sup>2</sup> 1.17 (95%CI: 1.04-1.32, <i>P</i> = 0.0093)	1.18 (95%CI: 0.94-1.46)	1.24 (95%CI: 0.98-1.57)
ROCKET AF		1.14 (95%CI: 1.01-1.29, <i>P</i> = 0.0402)		
Gjesdal <i>et al</i> <sup>[31]</sup>	7329	<sup>2</sup> 1.53 (95%CI: 1.22-1.92, <i>P</i> < 0.001)	NR	<sup>2</sup> Significant, details not given
SPORTIF III and V				
Chao <i>et al</i> <sup>[28]</sup>	4781	<sup>2</sup> 1.21 (95%CI: 1.01-1.44, <i>P</i> = 0.037)	<sup>2</sup> 1.28 (95%CI: 1.05-1.57)	0.88 (95%CI: 0.62-1.23)
Whitbeck <i>et al</i> <sup>[4]</sup>	4058	<sup>2</sup> 1.41 (95%CI: 1.19-1.67, <i>P</i> < 0.001)	<sup>2</sup> 1.37 (95%CI: 1.05-1.79, <i>P</i> = 0.019)	<sup>2</sup> 1.41 (95%CI: 1.09-1.84, <i>P</i> = 0.010)
AFFIRM				
Friberg <i>et al</i> <sup>[32]</sup>	2824	1.10 (95%CI: 0.94-1.28, <i>P</i> = 0.23)	NR	NR
SCAF		1.04 (95%CI: 0.89-1.21)		
Gheorghiad <i>et al</i> <sup>[26]</sup>	1756	1.06 (95%CI: 0.83-1.37, <i>P</i> = 0.640)	1.08 (95%CI: 0.8-1.47, <i>P</i> = 0.609)	1.08 (95%CI: 0.69-1.69, <i>P</i> = 0.743)
AFFIRM				
Pastori <i>et al</i> <sup>[33]</sup>	815	<sup>2</sup> 2.22 (95%CI: 1.42-3.48, <i>P</i> < 0.001)	NR	NR
Rodriguez-Manero <i>et al</i> <sup>[34]</sup>	777	1.42 (95%CI: 0.77-2.60, <i>P</i> = 0.2)	0.94 (95%CI: 0.20-4.41, <i>P</i> = 0.9)	1.6 (95%CI: 0.9-2.9, <i>P</i> = 0.9)
AFBAR				
Mulder <i>et al</i> <sup>[35]</sup>	608	<sup>2</sup> 0.41 (95%CI: 0.19-0.89)	NR	NR
RACE II				

Data also subdivided to those with and without congestive heart failure when applicable. <sup>1</sup>May apply different statistical methods to estimate hazard ratios.

<sup>2</sup>Statistically significant. CHF: Congestive heart failure; AF: Atrial fibrillation; NR: Not recorded; NA: Not applicable; SPORTIF: Stroke prevention using oral thrombin inhibitor in atrial fibrillation.

recent meta-analysis reviewing over 300000 patients with AF, CHF or both found that digoxin was associated with an overall 21% increased relative risk of all-cause mortality (HR = 1.21, 95%CI: 1.07-1.38, *P* < 0.01). The meta-analysis also showed increased risk of all-cause mortality during subgroup analyses of patients with AF (HR = 1.29, 95%CI: 1.21-1.39, *P* < 0.01) and CHF (HR = 1.14, 95%CI: 1.06-1.22, *P* < 0.01) even if the hazard ratio was lower than for the other subgroups included in this analysis (*i.e.*, AF without CHF)<sup>[50]</sup>.

To date, no randomized trial has been performed to evaluate the use of digoxin and its associated risk in AF patients. Such a trial might provide clarity about whether digoxin should be indicated in this population but is unlikely to happen considering the generic nature of the drug, the development of new drugs<sup>[48,49]</sup> and the burden of current healthcare costs. There are also some ethical concerns in enrolling subjects in a trial on a drug where previous studies have shown at best a neutral effect on mortality while many others raise some serious concern on safety. Therefore our understanding of digoxin's adverse effects will likely continue to be driven by retrospective analyses, which have their inherent biases and limitations in trying to evaluate associations corrected for confounders. In many retrospective studies, it is unclear what digoxin dose and/or serum levels patients had during the trials. This may be the driving force for many of the noted adverse outcomes, as prior studies evaluating digoxin in heart failure patients found that those with higher digoxin levels experienced worse outcomes<sup>[12]</sup>. In the absence of more definitive data from a prospective

randomized controlled trial, the widespread adoption of a rate control strategy for AF favoring digoxin as a single first line agent has been appropriately removed from the 2014 ACC/HRS/AHA guidelines; indeed, reasonably safe and inexpensive alternatives such as beta blockers or calcium channel blockers are readily available. The subgroup of patients for which digoxin remains most controversial, in our opinion, consists of those patients with AF and CHF, for whom a benefit for digoxin could potentially extend beyond rate control (*i.e.*, inotropic effect); these patients often have low blood pressure and may be very sensitive to negative inotropic drugs<sup>[51]</sup>. Another potential clinical situation that may warrant the careful use of digoxin is AF with very low blood pressure when beta blockers and calcium channel blockers cannot be utilized.

Finally, digoxin use in patients following a myocardial infarction requires further investigation, especially immediately post MI. In this particular situation, negative inotropic drugs such as beta blockers and calcium blockers can have a deleterious effect by precipitating or worsening CHF, and digoxin may be used to control AF with rapid ventricular response since it lacks negative inotropic properties. Overall, it seems unreasonable at this point of time with the available data to recommend discontinuing patients that are stable on digoxin or to start new patients on digoxin in some indications, provided that digoxin is used cautiously.

The worrisome signal linking digoxin to increased mortality has been identified by various studies employing different designs and/or statistical methods, even though this signal has not been clearly confirmed

by prospective randomized controlled trial data. It is possible that the increased mortality is due to dosages that were inappropriately high for some patients, but this remains impossible to ascertain from existing data. Based on the potential risks and benefits, as well as the presence of alternative drugs, there is little role for digoxin among patients who only have AF. The proper role of digoxin is, however, less certain in other subgroups of patients, such as those with AF and systolic CHF or at the acute phase of a myocardial infarction. Further studies may provide helpful information for such subgroups of patients.

## COMMENTS

### Background

Digoxin is one of the oldest drugs used today in cardiovascular medicine around the world, and was one of the first treatments for heart failure management. Currently, this drug is frequently used to treat heart failure symptoms and to decrease the ventricular rate in atrial fibrillation (AF). In regards to heart failure management, digoxin remains indicated for patients with persistent symptoms despite optimal medical therapy. In the setting of AF, digoxin is no longer mentioned in the 2014 guidelines as an option for rate control, except among patients with AF and heart failure; however, concerns arose regarding its safety even in this subgroup of patients. Current data regarding the safety and efficacy of digoxin is based on observational studies with conflicting results as no randomized controlled clinical trials have been performed. Authors' aim is to review the data available regarding the use of digoxin in congestive heart failure (CHF), AF, or after myocardial infarction, as well as the current guidelines for digoxin use from the American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC).

### Research frontiers

The concern linking digoxin to increased mortality has been shown by various studies; however, this has not been confirmed by prospective randomized controlled trials. If digoxin's role in patients with only AF is limited, its role and safety in certain subgroups of patients such as those with systolic CHF and AF or during the acute phase of a myocardial infarction remain unclear. Further studies may provide helpful.

### Innovations and breakthroughs

Digoxin has been used for centuries to treat systolic congestive heart failure, AF and after myocardial infarctions. Authors' goal was to review manuscripts concerning digoxin and mortality in these populations. The authors discussed the current data available and concisely displayed the data in tabular form to summarize the findings. The authors also reviewed the current recommended guidelines from the ACC/AHA and ESC regarding each subgroup when available.

### Applications

Given the potential risks and benefits of digoxin, as well as the presence of alternative drugs, there is little role for digoxin among patients who only have AF. The proper role of digoxin is, however, less certain in other subgroups of patients, such as those with AF and systolic CHF or at the acute phase of a myocardial infarction. Further studies may provide helpful information for such subgroups of patients.

### Peer-review

In this systematic review, the authors have provided a thorough and critical analysis of the use of digoxin in multiple clinical settings including patients with systolic congestive heart failure, AF or after myocardial infarction.

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