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Digoxin Impact on Heart Failure Patients with Atrial Fibrillation

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ABSTRACT

Background: Digoxin is a cardiac glycoside, derived from the plant *Digitalis purpurea*. For many years digitalis has been widely used in the treatment of heart failure (HF), owing to its cardiotoxic and neurohormonal effects and atrial fibrillation (AF), due to its parasympathomimetic effect on the AV node. **Objective:** The aim of this paper is to evaluate the available evidence on the safety and efficacy of digoxin in patients with HF and AF, by reviewing the pertinent literature. **Methods:** We conducted a PubMed/MEDLINE and SCOPUS search to evaluate the currently available evidence on the administration of digoxin and its association with all-cause mortality risk in patients with AF and HF. **Results:** Several observational analyses of clinical trials and meta-analyses have shown conflicting results on the safety and efficacy of digoxin administration in patients with AF and HF. According to these results, digoxin should be avoided in patients without HF, as it is associated with worse outcomes. On the other hand, in patients with AF and HF digoxin should be used with caution. **Conclusion:** The impact of digoxin on all-cause mortality and adverse effects in these patients remains unclear based on the current evidence. More trials at low risk of bias evaluating the effects of digoxin are needed.**Keywords:** Digoxin, Atrial fibrillation, Heart failure, Mortality, Hospitalization.

1. BACKGROUND

Digoxin is a cardiac glycoside, derived from the plant *Digitalis purpurea*, that was first described by Sir William Withering in 1785 (1). Digoxin's primary biochemical mechanism of action involves inhibition of the sodium-potassium adenosine triphosphatase ($\text{Na}^+\text{-K}^+$ ATPase), mainly in myocardial tissue, causing an increase on intracellular sodium concentration. Progressively accumulating Na ions lead to an increase of intracellular calcium via the $\text{Na}^+\text{-Ca}^{2+}$ exchange system. Thus, calcium is stored in the sarcoplasmic reticulum and upon release increases contractile force (2). In addition to the direct effects on myocyte function, digoxin has beneficial effects on hemodynamic, neurohormonal and electrophysiological parameters (Table 1) (3).

For many years, digitalis has been widely used in the treatment of heart failure (HF), owing to its cardiotoxic and neurohormonal effects and atrial fibrillation (AF), due to its parasympathomimetic effect on AV node (Table 2) (4). The increased contractility of the heart result in increased cardiac output and a subsequent reduction of ventricular filling pressure, which favors patients with HF. Based on the results of the Digitalis Investigation Group (DIG) trial, digoxin can be used as a second line therapy in patients with heart failure with reduced ejection fraction (HFrEF), as it improves symptoms and reduces hospitalization (RR 0.72; 95% CI 0.66-0.79) (5, 6). Additionally, digoxin can be used for rate control in AF patients, as it slows down the conduction in the AV node, decreases the heart rate and leads to a decreased ventricular response by stimulating the parasympathetic nervous system. Current 2016 ESC guidelines recommend the use of digoxin in symptomatic HFrEF (NYHA II-IV), despite treatment with an ACE-I (or ARB), a beta-blocker and an MRA to lessen the risk of hospitalizations (Class IIb, Level of Evidence B) and also for control of ventricular response in patients with AF and LVEF<40% in combination with beta-blockers or as monotherapy (Class I, Level of Evidence B) (7, 8). The most recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend digoxin for symptomatic HFrEF (Class IIa, Level of Evidence B), to control resting heart rate in patients with HFrEF (Class I, Level of Evidence C) and in combination with a beta-blocker (or a non-dihydropyridine calcium channel blocker in pa-

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tients with heart failure with preserved ejection fraction (HFpEF) as a reasonable strategy to control resting and exercise heart rate in patients with concomitant HF and AF (Class IIa, Level of Evidence B) (9, 10).

2. OBJECTIVE

The aim of this paper is to evaluate the available evidence on the safety and efficacy of digoxin in patients with HF and AF, by reviewing the pertinent literature.

3. PATIENTS AND METHODS

Materials and study design

In order to identify apposite publications of interest, we conducted a PubMed/MEDLINE and SCOPUS search using the terms ‘digoxin’, ‘atrial fibrillation’ and ‘heart failure’ as “Title/Abstract” or as “MeSH Terms”. For the purpose of this review we then limited the search to “Humans”, and we considered full-size articles of English language or publications in languages other than English, provided that they had a detailed abstract in English. The articles retained included patients with AF and/or HF and had a significant proportion of patients on digoxin.

4. RESULTS

Although digoxin is one of the most prescribed drugs for the treatment of HF, not enough randomized controlled trials (RCTs) have been conducted assessing the safety and efficacy of this drug in these patients (11-13). Whereas, ACE inhibitors showed to have beneficial effects on reducing mortality, digoxin started to be scrutinized regarding its impact on patients’ survival.

The first RCTs conducted were the Randomized Assessment of Digoxin on Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) and the Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED) trial. RADIANCE trial was a double-blinded, placebo-controlled, digoxin-withdrawal study. This study enrolled 178 patients with NYHA II or III HF and LVEF<35% in normal sinus rhythm, who were clinically stable while receiving digoxin, diuretics and ACE inhibitors. Digoxin’s discontinuation was associated with an increase in worsening HF (RR 5.9; 95% CI 2.1-17.2) (11). PROVED trial followed a similar protocol and enrolled 88 patients with mild to moderate HFrEF in sinus rhythm and stable symptoms, who received long-term treatment with digoxin and diuretics. Digoxin’s withdrawal was associated with an increase in worsening HF (39%, digoxin withdrawal group vs. 19%, digoxin maintenance group) and worsening exercise capacity (12).

However, there are some limitations in both studies. On the one hand, both studies enrolled a small number of patients (RADIANCE, n=178; PROVED, n=88) and on the other hand they had a short-term follow-up (RADIANCE 12 weeks; PROVED 20 weeks) (11, 12). These limitations prompted the Digitalis Investigation Group (DIG) to conduct a randomized, double-blinded, placebo-controlled trial to assess the association between di-

Hemodynamic effects in heart failure
Increased cardiac output
Decreased PCWP
Increased LVEF
Neurohormonal effects
Vagomimetic action
Improved baroreceptor sensitivity
Decreased norepinephrine serum concentration
Decreased activation of renin-angiotensin system
Direct sympathetic inhibitory effect
Increased sympathetic CNS outflow at high doses
Decreased cytokine concentrations
Increased release of ANP and BNP
Electrophysiological effects
S-A node: slowing of the sinus rate
Atrium: no effect or decreased refractory period
AV node: slowed conduction
Ventricle and Purkinje fibers: practically no electrophysiological effects at low therapeutic doses

Table 1. Effects of Digoxin. PCWP, pulmonary capillary wedge pressure; CNS, central nervous system; ANP, atrial natriuretic peptide; and BNP, brain natriuretic peptide

Heart Failure (HF)	Atrial Fibrillation (AF)
↑ Inotropy	↓ AV nodal conduction (parasympathomimetic effect)
↑ EF	
↓ Preload	↓ Ventricular rate in atrial flutter and fibrillation
↓ Pulmonary congestion/edema	

Table 2. Digoxin mechanisms of action in HF and AF. EF, Ejection Fraction; AV, Atrioventricular

goxin use and mortality in patients with HF and normal sinus rhythm.

The DIG trial was divided into two parts based on the LV systolic function of patients. One evaluating mortality in patients with reduced EF<45% (DIG-Main, 6,800 patients) and the other in patients with preserved EF >45% (DIG-Ancillary, 988 patients). Patients were randomized to receive digoxin or placebo in addition to ACE inhibitors and diuretics with mean follow-up of 3 years (37 months). The DIG-Main study showed that digoxin was associated with fewer hospitalizations (RR 0.72; 95% CI 0.66-0.79; p<0.001), but no effect on overall mortality was observed (RR 0.99; 95% CI 0.91-1.07; p=0.80). However, in the digoxin group there was a trend toward a decreased risk of HF related mortality (RR 0.88; 95% CI 0.77-1.01; P=0.06) (5). In the DIG-Ancillary similar findings observed in patients with HFpEF, where digoxin had a neutral effect on all-cause mortality (RR 0.99; 95% CI 0.76-1.28) and a beneficial effect on HF related deaths or hospitalizations (RR 0.82; 95% CI 0.63-1.07) (5).

A post-hoc analysis of the DIG trial was conducted a few years later. This analysis enrolled 3782 men with LVEF<45% and aimed to assess variations in serum digoxin concentration and their impact on mortality and

Study	N (digoxin)	N(no digoxin)	Adjusted HR (95% CI) overall mortality	Adjusted HR (95% CI) overall mortality in patients with HF	Adjusted (95% CI) overall mortality in patients without HF
AFFIRM[15]	N/A	N/A	1.42 (1.09-1.86)	N/R	N/R
AFFIRM[16]	2.153	1.905	1.41 (1.19-1.67)	1.41 (1.09-1.84)	1.37 (1.05-1.79)
AFFIRM[17]	878	878	1.06 (0.83-1.37)	1.08 (0.69-1.69)	1.08 (0.80-1.47)
AFFIRM[18]	1.027	1.348	1.15 (0.89-1.50)	N/R	N/R
SPORTIF[19]	3.911	3.418	1.53 (1.22-1.92)	N/R	N/R
RACE-II[20]	284	324	0.41 (0.19-0.89)	N/R	N/R
ROCKET-AF[21]	5.239	8932	1.17 (1.04-1.32)	1.23 (1.07-1.41)	1.19 (0.95-1.48)
RIKS-HIA [22]	4.872 (without HF) 7.758 (with HF)	16.587 (without HF) 9.202 (with HF)	N/A	1.00 (0.94-1.06)	1.42 (1.29-1.56)
Chao et al.[23]	38.898	168.678	1.12 (1.10-1.14)	N/R	N/R
TREAT-AF[24]	28.679	93.786	1.26 (1.23-1.29)	1.29 (1.23-1.36)	N/R
SCAF[25]	802	2022	1.10 (0.94-1.28)	N/R	N/R
ORBIT-AF[26]	2.267 (prevalent use) 681 (incident use)	6.671	N/R	1.04 (0.86-1.27) (prevalent use) 1.05 (0.66-1.65) (incident use)	1.22 (0.95-1.58) (prevalent use) 1.99 (1.12-3.56) (incident use)
ATRIA-CVRN[27]	4.231	10.556	N/A	N/A	1.71 (1.52-1.93)
ENGAGE AF-TIMI 48[28]	6.327	14.778	1.22 (1.12-1.34)	1.27 (1.14-1.41)	1.10 (0.92-1.31)
ARISTOTLE[29]	5.824	12.073	1.09 (0.96-1.23)	1.04 (0.83-1.30)	1.16 (0.88-1.52)

AF, atrial fibrillation; HR, hazard ratio; HF, heart failure; N/R, not reported; N/A, not applicable

Table 3. Observational studies evaluating the association between digoxin use and mortality in patients with AF with or without HF

hospitalizations. Patients with lower serum digoxin levels (0.5-0.8ng/ml) had a 6.3% lower mortality rate (95% CI 2.1%-10.5%; $p=0.005$) compared with those received placebo. In contrast, patients with higher serum levels (1.2ng/ml or higher) had an 11.8% higher all-cause mortality rate (95% CI 5.7%-18.0%; $p<0.001$) compared with placebo group (13).

A meta-analysis by Hood *et al.* reviewed 13 trials, comprising a total of 7.896 patients. This meta-analysis showed that patients treated with digoxin had significantly fewer hospitalizations with an overall relative risk reduction (RRR) of 23.4% and no effect on death rate, summarizing the already mentioned data (14).

While RCTs have been conducted assessing the safety and efficacy of digoxin in patients with HF, there are no similar trials evaluating the outcomes of digoxin's use in patients with AF. Thus, a sufficient number of observational studies have been published (Table 3) (15-29).

5. DISCUSSION

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial randomized patients with AF to compare two treatment strategies: rhythm-control and rate-control. An initial post-hoc analysis of the AFFIRM trial showed that digoxin use was associated with an increased risk of death (HR 1.42; 95% CI 1.09-1.86) (15). Three post-hoc analyses of the AFFIRM trial were performed the following years, in order to evaluate digoxin's safety with conflicting results (16-18). More specifically, the first post-hoc analysis demonstrated that patients receiving digoxin had an increase in all-cause (EHR 1.41; 95% CI 1.19-1.67;

$p<0.001$), cardiovascular (EHR 1.35; 95% CI 1.06-1.71; $p=0.016$) and arrhythmic mortality (EHR 1.61; 95% CI 1.12-2.30; $p=0.009$). Same findings observed regardless of the presence or absence of HF (EHR 1.41; 95% CI 1.09-1.84; $p=0.010$ and EHR 1.37; 95% CI 1.05-1.79; $p=0.019$, respectively) (16). The second one showed no association with an increased all-cause mortality (HR 1.06; 95% CI 0.83-1.37; $p=0.640$) and hospitalizations and no difference between patients with or without HF (HR 1.08; 95%CI 0.69-1.69 and HR 1.08; 95% CI 0.80-1.47, respectively) (17). In the last one digoxin use was associated with a decrease in mortality in patients with EF<30% (HR 0.29; 95% CI 0.10-0.87; $p=0.027$) and with a neutral effect on mortality in patients with EF>30% (HR 1.21; 95% CI 0.91-1.60; $p=0.18$) (18).

The Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and IV studies enrolled 7329 patients with AF randomized to receive either warfarin or NOAC ximelagatran. A post-hoc analysis of these studies showed that patients used digoxin had a higher mortality rate compared with non-users (HR 1.58; 95% CI 1.29-1.94) (19).

RACE II was a RCT conducted to investigate the association between digoxin and CV morbidity and mortality in patients with AF. Post-hoc analysis of RACE II showed no increase in mortality in these patients during a follow-up of 3 years (HR 0.41; 95% CI 0.19-0.89) (20).

A retrospective analysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compare with Vitamin K Antagonists for Prevention of Stroke and Embolism (ROCKET-AF) trial was performed and revealed an increased all-cause mortality in patients receiving

digoxin (HR 1.17; 95% CI 1.04-1.32). This increase was noted in both patients with HF (HR 1.23; 95% CI 1.07-1.41; $p=0.79$) and those without HF (HR 1.19; 95% CI 0.95-1.48; $p=0.79$) (21).

A prospective cohort study was performed using data from the Registry of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HA). Patients enrolled in this study were admitted to coronary care units and post hospital discharge, they were followed up for 1 year. The AF patients without HF discharged with digoxin demonstrated a higher mortality rate than those in which digoxin was not administered (RR 1.42; 95% CI 1.29-1.56). There was no such difference between patients with HF with or without AF (22).

A study conducted by *Chao et al.* enrolled patients with AF classified into two groups: rate and no-rate control. Digoxin administration was associated with higher risk of mortality (HR 1.12; 95% CI 1.10-1.14) in both patients with and without HF (23). Similar to *Chao et al.*, an analysis of The Retrospective Evaluating and Assessment of Therapies in AF (TREAT-AF) study showed that digoxin use was correlated with an increased risk of death in patients with AF, regardless of HF status (24). In contrast, a report from Stockholm Cohort study of Atrial Fibrillation (SCAF) comprised patients with AF or atrial flutter and indicated that digoxin did not have a higher risk of mortality (HR 1.10; 95% CI 0.94-1.28) (25).

An analysis from the US Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) did not reveal any significant modification effect of either prevalent or incident digoxin use on mortality in patients with HF (HR 1.04; 95% CI 0.86-1.27 and HR 1.05; 95% CI 0.66-1.65, respectively). However, the analysis did report that patients without HF and with incident digoxin use had an increased risk of mortality (HR 1.99; 95% CI 1.12-3.56) (26). Similar to ORBIT-AF analysis, Anticoagulation and Risk Factors in Atrial Fibrillation Cardiovascular Research Network (ATRIA-CVRN) noted that incident digoxin use was associated with increased mortality (HR 1.63; 95% CI 1.56-1.71) and that serum digoxin concentration was higher in patients who died compared to those who survived (1.15ng/ml vs. 0.94ng/ml; $p<0.001$) (27).

More recently two analyses were published (28, 29). The first one was an analysis of the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial. After propensity matching, a significant increase in risk of all-cause mortality (HR 1.31; 95% CI 1.19-1.43) and sudden cardiac death (HR 1.58; 95% CI 1.36-1.85) was observed in patients with HF receiving digoxin. In patients without HF there wasn't a statistically significant increase in all-cause death (HR 1.16; 95% CI 0.98-1.36). However, in these patients an association between digoxin use and high risk of sudden cardiac death was observed (HR 1.90; 95% CI 1.36-2.65) (28). The second one was an observational study of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. Baseline digoxin use was not independently associated

with higher risk of all-cause mortality (HR 1.09; 95% CI 0.96-1.23; $p=0.19$). This was consistent in patients with and without HF. However, the risk of death was related to serum digoxin concentration and was highest in patients with concentrations ≥ 1.2 ng/ml (HR 1.56; 95% CI 1.20-2.04). Also, initiating digoxin in patients during the conduction of the trial resulted in an increased risk of death and sudden cardiac death (29).

The forenamed studies showed conflicting results, regarding the correlation between digoxin use and mortality in patients with AF. Thus, several meta-analyses were performed to evaluate the safety of digoxin in these patients.

In 2015 six meta-analyses were performed. *Vamos et al.* based on the analysis of 19 studies found that digoxin use was associated with an increased risk of all-cause mortality (HR 1.21; 95% CI 1.07-1.38). These results refer to both AF subgroup (HR 1.29; 95% CI 1.21-1.39) and HF subgroup (HR 1.14; 95% CI 1.06-1.22) (30). *Ziff et al.* reviewing 52 studies showed that the pooled risk ratio for mortality in adjusted analyses was 1.61 (1.31-1.97). However, the authors reported that digoxin had a neutral effect on mortality based on the analysis of the RCTs included (HR 0.99; 95% CI 0.93-1.05; $p=0.75$) (31). In another meta-analysis by *Bavishi et al.* included 10 studies and demonstrated that digoxin use was associated with an increased risk of all-cause mortality in patients with concomitant AF and HF (32). *Chen et al.* reviewed 17 studies comprising 408,660 patients and observed that digoxin therapy was associated with a significant increase in all-cause mortality in patients with AF and HF (RR 1.14; 95% CI 1.04-1.24) and especially in those without HF (RR 1.36; 95% CI 1.18-1.56) (33). *Wang et al.* included 8 studies and 302,738 patients and found that in patients with AF there was a higher risk of death (HR 1.375; 95% CI 1.201-1.574) related with digoxin use, regardless of concomitant HF (HR 1.201; 95% CI 1.074-1.344 with HF, HR 1.172; 95% CI 1.148-1.198 without HF) (34). Last but not least, the meta-analysis by *Ouyang et al.* reported that digoxin was related with a 15% increased risk of death in the HF group (1.12-1.17) and an 18% increased risk of mortality in the no-HF group (1.15-1.21) (35).

Finally, three most recent meta-analyses were performed to evaluate the effects of digoxin on mortality. In 2016, a meta-analysis associated digoxin with all-cause mortality (pooled HR 1.27; 95% CI 1.19-1.36) in patients with AF and especially in those without HF (pooled HR 1.47; 95% CI 1.27-1.73) compared to those with concomitant HF (pooled HR 1.21; 95% CI 1.07-1.36) (36). *Sethi et al.* found no evidence of a difference in all-cause mortality (RR 0.82; TSA-adjusted CI 0.02-31.2; $I^2=0\%$), serious adverse events (RR, 1.65; TSA-adjusted CI 0.24-11.5; $I^2=0\%$), quality of life, heart failure (RR, 1.05; TSA-adjusted CI, 0.00-1141.8; $I^2=51\%$); and stroke (RR, 2.27; TSA-adjusted CI 0.00-7887.3; $I^2=17\%$). Also, they compared digoxin with placebo and reported that digoxin was superior to placebo in controlling the heart rate both within 6 and 6-24 hours, but inferior to beta blockers (37). In 2019, a meta-analysis of 38 trials and 825,061

patients by *Vamos et al.* indicated that digoxin was associated with increased all-cause mortality (HR 1.17; 95% CI 1.05-1.29) both in patients with AF (HR 1.23; 95% CI 1.17-1.30) and with HF (HR 1.11; 95% CI 1.06-1.16) (38).

Over the last 15 years a significant number of observational studies have been published assessing the association between digoxin use and outcomes in patients with AF with or without HF, due to lack of RCTs. Results have been conflicting and several meta-analyses were performed to clarify the safety and efficacy of digoxin use. These meta-analyses and especially the most recent one by *Vamos et al.* (38) included only one RCT designed to evaluate the effect of digoxin on mortality, the DIG trial, that in fact did not include patients with AF. Also, in these analyses patients receiving digoxin were older with significant comorbidities, so there was a non-comparable baseline risk and the results are at a risk for prescription bias.

The use of digoxin as second-line treatment in HF_{rEF} and as rate control treatment in concomitant HF and AF is endorsed by ESC and ACC/AHA and is included in the corresponding guidelines. However, in patients with AF without HF the use of digoxin is controversial based on the results of the observational analyses and meta-analyses, as the risk of all-cause mortality is higher in these patients. Digoxin should generally be used with caution and in low doses in patients with AF and HF, as toxicity may result even with mildly increased levels because of its narrow therapeutic index.

6. CONCLUSION

Given that AF is the most common cardiac arrhythmia and its prevalence is steadily increasing and that HF and AF often coexist, it is imperative to clarify the safety and efficacy of the drugs used in these conditions. However, it remains unclear whether the use of digoxin is associated or not with higher risk of mortality in patients with both AF and HF. The upcoming DECISION trial (NCT03783429), a multicenter, randomized, double-blind placebo controlled clinical trial will report data on effectiveness and safety of digoxin in these patients. This trial will evaluate the effect of digoxin on all-cause mortality, cardiovascular death, HF hospitalizations, heart rate in both AF and sinus rhythm and other outcomes and it may provide further evidence regarding digoxin safety in these patients.

- **Author's Contribution:** A.G. and F.M. gave substantial contributions to the conception or design of the work in acquisition, analysis, or interpretation of data for the work. I.K, E.A., V.M, and M.A-E. had a part in article preparing for drafting or revising it critically for important intellectual content. G.T, N.K., and D.V. gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- **Conflicts of interest:** There are no conflicts of interest.
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