

# Digoxin's roles in heart failure patients

## An overview

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### Summary

Digitalis, particularly digoxin, have played an important role in the treatment of heart failure (HF) for over 200 years. In the past three decades, with the greatest knowledge of the pathophysiology of the disease, neurohumoral blockers were more effective in reducing morbidity and mortality and gained greater prominence. In addition, studies have suggested that digoxin does not reduce the risk of death and, in some cases, may even increase it. Thus, its use has been questioned and discouraged. This review aims to look at the pharmacology of digoxin, studies on its benefits and risks in patients with moderate to severe systolic HF and diastolic HF also. This review looks forward to answering the following question: Is there still room for the use of digitalis in HF?

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### Introduction

Cardiac glycosides, or digitalis, have played a prominent role in the treatment of Heart Failure (HF) since William Withering codified their use in his classic monograph on the efficacy of the leaves of the common foxglove plant (*Digitalis purpurea*), to treat dropsy<sup>1</sup>. Nevertheless, throughout the last century and decades, controversies have existed about whether the risks of digitalis preparations outweigh their benefits, particularly in heart failure patients with sinus rhythm. By far, the most prescribed digitalis all over the world is digoxin, and in this text, the terms may be used in similar manners<sup>2,3</sup>. In this review we will initiate with a brief overview of the basic and clinical pharmacology of digitalis. Then, we will examine the clinical trials that have studied the use of digoxin in patients with moderate to severe heart failure, what do the recent guidelines to the treatment of heart failure recommend about its use and some data about cardiac glycosides use in diastolic heart failure.

### Mechanisms of action

#### Inotropic effects

Certainly, the most known actions of cardiac glycosides are their ability to increase the velocity and extent of shortening of cardiac muscle, thereby resulting in an upward and leftward shift of the ventricular function curve (Frank-Starling), relating cardiac performance to filling volume or pressure and increasing ejection fraction. This is so, because these drugs are potent and highly specific inhibitors of the intrinsic membrane protein Na<sup>+</sup>K<sup>+</sup>-ATPase<sup>2,3</sup>.

#### Patients with heart failure

In patients with heart failure (HF), digoxin slows the ventricular rate in sinus rhythm (SR) because of sympathetic stimulation withdrawal and in atrial fibrillation (AF) by increasing parasympathetic tone. These drugs also

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produce an increase of blood flow, a decrease of vascular resistance, venodilation and a decrease of central venous pressure and heart rate. The vasodilation is a result of an increase in cardiac output (CO) and direct baroreflex-mediated withdrawal of sympathetic vasoconstriction. On the coronary circulation, intravenous (IV) administration of digoxin can produce vasoconstriction and transient myocardial ischemia in those with severely obstructed coronary arteries<sup>3</sup>.

Digitalis normalizes the blunted baroreflex mechanisms present in HF. Also, there may be a reduction in plasma norepinephrine levels, serum aldosterone and plasma renin activity. Digoxin induces diuresis in patients with HF and fluid retention, by increasing CO and renal hemodynamics, inhibiting the tubular reabsorption of sodium and increasing secretion of atrial natriuretic peptides<sup>3</sup>.

### Pharmacology

Since digoxin is the most prescribed digitalis all around the world, we will focus on a few pharmacologic characteristics of this drug. It is excreted exponentially, with an elimination half-life of 36-48 hours, in patients with normal renal function, resulting in a loss of about one third of body stores per day. Renal excretion of digoxin is proportional to the glomerular filtration rate, and thus, to creatinine clearance. With daily maintenance therapy, a steady state is reached when daily losses are matched by daily intake. This may take 5-7 half-lives or 7-10 days, in patients with normal renal function, who are starting on the drug. A patient's estimated lean body mass should be used to calculate the maintenance dose. Also, the doses should be adjusted in patients with chronic renal failure. A large number of concomitant drugs may alter digoxin pharmacologic characteristics and lead to intoxication<sup>2</sup>.

Digoxin has extremely low therapeutic index, and its use should be carefully monitored by serum blood levels. The optimal trough serum level is 0.5 to 1.0 ng/mL<sup>2</sup>. This is achieved with a prescribing dose of 0.125 mg to 0.25 mg/day orally taken dose. In the geriatric population and in those with renal dysfunction, the dose might be even lower, such as 0.125 mg in alternate days.<sup>4</sup> Blood samples for measurement of serum digoxin should be taken at least 6 to 8 hours following the last dose<sup>2</sup>.

Generally, overt clinical toxicity tends to emerge at serum concentrations greater than 2.0 ng/mL. Digitalis toxicity should be suspected whenever patients using the drug present with gastrointestinal disturbances (nausea, vomiting, diarrhea), neurological symptoms (mental confusion, tremors of the extremities) or cardiovascular (atrial-ventricular -AV- blocks, ventricular premature beats, atrial tachycardia with variable AV blocks). These individuals must have the drug withdrawn and serum digoxin levels measured<sup>4</sup>. The enhanced automaticity of cardiac tissue in response to digitalis is increased in hypokalemia and some advocate the administration of oral

potassium for atrial, AV junctional or ventricular ectopic rhythms. The widespread availability of Fab fragments of high-affinity, polyclonal, digoxin-specific antibodies could save patients with life-threatening arrhythmias due to digitalis toxicity<sup>2,4</sup>.

### Clinical benefits in heart failure

Several clinical trials have documented symptomatic improvement in HF patients using digitalis. They also improve HF scores, increase exercise capacity and VO<sub>2</sub>, improve hemodynamics at rest and on exercise, increase left ventricular ejection fraction (LVEF) at rest and on exercise, and reduce heart rate (HR). Those benefits occurred independently of the cardiac rhythm or the etiology of HF<sup>5,6,7</sup>.

### PROVED and RADIANCE Trials

Both of these were multicenter, prospective, randomized, placebo-controlled trials to examine digoxin discontinuation in patients with mild-to-moderate HF (ie, in New York Heart Association -NYHA- functional classes II to III and systolic dysfunction - LVEF≤0.35). All patients studied were in sinus rhythm: target serum digoxin concentration in both studies during the baseline run-in phase was 0.9 to 2.0 ng/mL. All individuals received diuretics. RADIANCE (*Randomized Assessment of Digoxin on Inhibitors of Angiotensin-Converting Enzyme*) patients also received concurrent therapy with an angiotensin-converting-enzyme (ACE) inhibitor. When patients were randomly assigned either to continue active digoxin therapy or to withdraw from active drug and receive a matched placebo, 40% of patients in PROVED (*Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin*) and 28% of patients in RADIANCE who received placebo noted a significant worsening of HF symptoms, compared with 20% and 6%, respectively, of patients who continued to receive digoxin. This absolute risk reduction of 20% in digoxin-treated patients constituted a substantial treatment effect. However, neither of these trials had the statistical power to detect an effect of digoxin therapy on the survival of patients with HF, nor the endpoint for which efficacy had already been established for the use of selected vasodilators in this disease. In PROVED trial there was also a reduction in hospitalization for HF, lower blood urea nitrogen (BUN) and serum creatinine levels, a higher LVEF, and better exercise capacity. In RADIANCE, the digoxin group had a better LVEF, quality of life and exercise capacity<sup>5,6</sup>.

Further analysis of these trials have shown some other important additional information: 1) use of digoxin therapy in patients with HF would result in net annual savings of \$406 million<sup>8</sup> and 2) the efficacy of 3 levels of serum digoxin concentrations (0.5 to 0.9 ng/mL, >0.9 to ≤1.2 ng/mL and >1.2 ng/mL) were evaluated with regard

to LVEF and patients outcomes. There was no relation between serum digoxin levels and changes in LVEF, treadmill times and worsening HF. The incidence of worsening HF in the placebo group was 30% and in the 3 digoxin subgroups was 6%, 9% and 12%, respectively ( $P<0.02$ , for no digoxin versus the digoxin subgroups)<sup>9</sup> (Figure 1).

### The Digitalis Investigation Group (DIG)

The DIG trial is the largest trial on digitalis, consisting of two studies (the main trial and the ancillary trial) in a total of 302 centers in United States and Canada. In the main trial 6800 patients with LVEF  $\leq 0.45$  were randomly assigned to digoxin or placebo. The placebo group received diuretics (82%) and ACE inhibitors (95%), and the digoxin group received digoxin, diuretics (81%) and ACE inhibitors (94%). The primary endpoint was all-cause mortality and secondary endpoints were mortality due to cardiovascular causes, mortality due to worsening HF and hospitalizations due to worsening HF or other causes. After a mean follow-up of 37 months, the main findings were that digoxin had no effect on mortality (cardiovascular or all-cause) rates; reduced the incidence of hospitalization caused by worsening HF ( $P<0.001$ ), and incidence of death caused by worsening HF ( $P=0.06$ ). The reduction was greater in those with LVEF  $\leq 0.25$  and for patients with more advanced symptoms. The HF survival and hospitalizations curves appear to separate early, specially in the patient subgroup in which digoxin was withdrawn<sup>7</sup>, supporting the conclusions reached in PROVED<sup>5</sup> and RADIANCE<sup>6</sup>. Benefits were incremental to the use of diuretics and ACE inhibitors. Patients with recorded digoxin levels, >88% were within the prescribed therapeutic range of 0.5 to 2.0 ng/mL at one month. Overall, there were nearly 10% fewer total cardiovascular hospitalizations for each digoxin-treated patient. Despite these encouraging results, an increase in deaths from other cardiac causes (presumed to result from tachyarrhythmias or bradyarrhythmias, low output states and cardiac surgery) was noted in the group randomized to receive digoxin<sup>7</sup>.

In the ancillary trial, 988 patients with LVEF  $>0.45$  (median

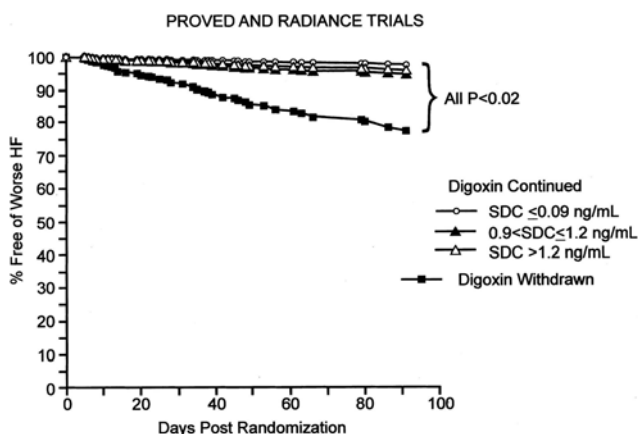
53%) and normal sinus rhythm, receiving ACE inhibitors (>85%) and diuretics (>80%) were randomly assigned to receive placebo or four different daily doses of digoxin (0.125, 0.25, 0.375 and 0.5 mg). The primary outcome was the combined endpoint of HF hospitalization or HF mortality. Also, all-cause mortality and cardiovascular hospitalization were evaluated, as well as the combined outcome of HF hospitalization or cardiovascular mortality<sup>7,10</sup>. During the mean follow-up period of 37 months, 102 (21%) patients in the digoxin group and 119 patients (24%) in the placebo group experienced the primary combined outcome of HF hospitalization or HF mortality ( $P=0.136$ ; HR 0.82; 95% CI 0.63 to 1.07), which is consistent with the main DIG report. During the first 2 years of follow-up after randomization, 67 patients (14%) in the digoxin group and 90 patients (18%) in the placebo group experienced the primary combined outcome ( $P=0.034$ ; HR, 0.71; 95% CI 0.52 to 0.98)<sup>10</sup>.

Hospitalizations from HF or deaths from cardiovascular causes occurred in 142 patients (29%) in the digoxin group and in 154 patients (31%) of those taking placebo ( $P=0.269$ ; HR 0.88; 95% CI 0.70 to 1.11). At 2 years after randomization 89 patients (18%) in the digoxin group as compared to 113 patients (23%) in the placebo group experienced HF hospitalization or cardiovascular mortality (HR 0.75; 95% CI 0.57 to 0.99;  $P=0.044$ ). There were 115 deaths from all causes in the digoxin group (23%) and 116 in the placebo group (23%) (HR 0.99; 95% CI 0.76 to 1.28;  $P=0.925$ ). There was also no significant difference in mortality resulting from HF or from cardiovascular causes. Hospitalizations from worsening HF and for cardiovascular causes were similar in both groups, except for the first 2 years of follow-up, where 59 (12%) of the patients randomized to digoxin and 86 (17%) patients of the placebo group were hospitalized as a result of worsening HF (HR 0.66; 95% CI 0.47 to 0.91;  $P=0.012$ ). There were no differences in all-cause hospitalizations between the 2 groups<sup>10</sup>.

These results show that digoxin has no favorable effect on the natural history of ambulatory patients with chronic mild to moderate diastolic HF and normal sinus rhythm. This is an important fact, since up to 50% of HF patients have diastolic HF. An unanticipated finding in this last study was that digoxin use was associated with increased risk of hospitalization for unstable angina, although this did not result in an elevation of the risk of myocardial infarction. This may be related to reported, but not well-studied, effects of digoxin on platelet and endothelial cell activation<sup>10,11</sup>.

### Subgroup analysis

A *post hoc* subgroup analysis showed that, at the end of 5 years, there was an absolute difference of 5.8% (95% CI 0.5 to 11.1) between men and women in the effect of digoxin on the rate of death from any cause ( $P=0.034$  for the interaction). Specifically, women who were randomly assigned to digoxin had a higher rate of death than women who were randomly assigned to placebo (33.1% x 28.9%;



**Figure 1.** Freedom from worsening heart failure in the Digoxin-withdrawn group and the digoxin group at 3 levels of serum digoxin concentration. Adapted from Rahimtoola 2004<sup>3</sup>.

absolute difference 4.2%; 95% CI -0.5 to 8.8). In contrast, the rate was similar among men randomly assigned to digoxin and placebo (35.2% x 36.9%; absolute difference -1.6; 95% CI -4.2 to 1.0). In the multivariable analysis, digoxin was associated with a significantly higher risk of death among women (adjusted HR for the comparison with placebo 1.23; 95% CI 1.02 to 1.47), but it had no significant effect among men (HR 0.93; 95% CI 0.85 to 1.02;  $P=0.014$ ). Although the mean daily dose of medication prescribed was similar (0.25 mg in men and 0.22 mg in women;  $P=0.28$ ), when the dose was standardized according to the body-mass index, men received a higher dose than women (0.0093 mg x 0.0084 mg per unit of body-mass index;  $P<0.001$ ). However, the medium serum digoxin level was slightly higher in women than in men one month after study entry (0.9 ng/mL x 0.8 ng/mL  $P=0.007$ ). This raises the possibility of sex-associated differences in the pharmacokinetics of digoxin. Also, this may have association with the use of hormone-replacement therapy and digoxin. The medium serum digoxin level was the same 12 months after randomization among women than in men (0.6 ng/mL x 0.6 ng/mL;  $P=0.46$ ). Hospitalizations for suspected digoxin-related toxicity was similar among men and women ( $P=0.97$ ). This study, then, shows an increased risk of death among women with HF treated with digoxin. Since the benefit of digoxin in the previous trials was a small reduction in the secondary endpoint of hospitalization, the authors suggest that women may not consider the potential increased risk of death associated with digoxin therapy worth the small reduction in the risk of hospitalization. In other words, they recommend that digoxin be used very cautiously, if at all, in women with HF<sup>12</sup>.

The incidence of digoxin-induced arrhythmia at a level of 1.7 ng/dL is 10% and at 2.5 ng/mL is 50%, which increases with increasing blood levels<sup>13</sup>. In the DIG trial, serum digoxin concentration  $\geq 2.0$  ng/mL was present in 2.3% of men and in 3.4% of women 1 month after random. Thus, digoxin toxicity may have accounted for excess deaths in women and for deaths ascribed as not caused by HF in the DIG trial<sup>12</sup>.

### Digitalis and other drugs that reduce mortality in HF

It is widely known that most digitalis trials were performed before trials of beta-blockers and angiotensin-receptor blockers (ARBs). ACE inhibitors have been shown to improve survival when combined with diuretics and digitalis<sup>14-16</sup>. Also, beta-blockers have been shown to improve survival when combined with diuretics, digitalis and ACE inhibitors<sup>17-19</sup>. Spironolactone has been shown to improve survival when combined with diuretics, digitalis and ACE inhibitors. Its beneficial effects if patients are already been treated with these drugs and beta-blockers is not known<sup>20</sup>. Besides drug therapy, several devices have improved survival in HF

patients, such as cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillators (ICDs)<sup>4</sup>.

### Digitalis in the contemporary era of medical therapy for HF

Beyond safety and efficacy, another important issue is the impact of therapy in determining HF prognosis. A recently published multimarker tool for HF prognosis determination, the Seattle Heart Failure Score (SHFS), incorporates the effect of ACE inhibitors, beta-blockers and devices in determining HF prognosis. But the utility of digoxin therapy as a potential variable for HF risk prediction could not be ascertained in that study<sup>21</sup>.

In 2009, Georgiopoulou et al. studied the utility of digoxin therapy in a cohort of patients with advanced HF referred for cardiac transplantation evaluation, which were on optimal contemporary medical therapy<sup>22</sup>. They retrospectively reviewed data of 455 advanced HF patients (LVEF  $\leq 30\%$ , NYHA class II to IV symptoms) referred to transplant evaluation (age  $52 \pm 12$  years). Two hundred twenty seven (49.9%) patients underwent digoxin therapy and 228 not. Primary outcome was death ( $n=101$ ), urgent transplantation ( $n=14$ ) or left ventricular assist device (LVAD) implantation ( $n=4$ ). Secondary outcomes included HF and all-cause hospitalization. Digoxin levels were assessed in 115 (50%) of the 227 patients in the digoxin group. Mean daily digoxin dose was 0.13 mg/day (25% to 75%: 0.13 to 0.19). Medium digoxin level was 0.75 ng/dL (25% to 75%: 0.5 to 1.4 ng/mL). Among 43 patients who were started on digoxin after baseline, 32 had the reasons documented, which included worsening HF symptoms leading to hospitalization in 29 and inadequate control of HR in atrial fibrillation (AF) in 3. Among 72 patients who discontinued digoxin after baseline visit, the reasons were documented in 47 and included improved symptoms in 29, gastrointestinal side effects (nausea, anorexia) in 7, worsening renal function and/or difficulty to maintain therapeutic levels in 7, and chronotropic incompetence in 4 patients. Medium follow-up time was 27 months. Overall, 101 of the 455 (20.7%) died (annual mortality of 9.4%), 14 underwent heart transplantation and 4 LVAD implantation. Therefore, the primary outcome was met in 119 patients (26.2%). There were 1098 all-cause hospitalizations (93 per 100 patient-years); of these, 573 (52.2%) were related to HF (48 per 100 patients-years)<sup>22</sup>.

Digoxin use was evaluated: 1) in the original cohort; 2) in a propensity score-matched subset ( $n=322$ ); 3) as a time dependent variant and 4) after adjustment for SHFS. Patients were on optimal therapy: angiotensin-II modulation (92.5%); beta-blockers (91.2%); aldosterone antagonists 45.6% and devices 71%. Two hundred and twenty seven (49.9%) patients were receiving digoxin at baseline. The primary outcome was met in 83 of 277 patients (36.6%) treated with digoxin, versus 36 of 228 (15.8%) patients without (OR 2.28; 95% CI 1.51 to 3.43;  $P<0.001$ ). The composite of primary outcome and HF

hospitalization was met in 63% of patients on digoxin versus 40.4% in those not receiving the drug (OD 1.71; 95% CI 1.32 to 2.23;  $P < 0.001$ ). Both all-cause and HF hospitalization rates were higher in patients taking digoxin<sup>22</sup>. After adjusting for HF severity, with the SHFS, digoxin use was still a significant predictor of primary outcome (HR 1.99; 95% CI 1.31 to 3.02;  $P = 0.001$ ). When baseline renal function (serum creatinine and blood urea nitrogen) was included along with SHFS, digoxin use was still associated with a higher risk for primary outcome (HR 2.03; 95% CI 1.33 to 3.09;  $P = 0.001$ ). This risk was also present for those in sinus rhythm ( $n = 293$ ; HR 3.19; 95% CI 1.78 to 5.72;  $P < 0.001$ ) compared with those in AF ( $n = 162$ ; HR 1.29; 95% CI 0.69 to 2.43;  $P = 0.421$ ;  $P = 0.033$  for the interaction). This risk persisted in the matched subset (HR 1.73; 95% CI 1.09 to 2.75;  $P = 0.021$ ) and with time-varying digoxin use (HR 2.05; 95% CI 1.23 to 3.41;  $P = 0.01$ ). Digoxin was not associated with improvement in either all-cause or HF hospitalization rates. These results were similar across sex and race. In summary, this study suggests that digoxin therapy may be of no benefit in patients with advanced HF referred for cardiac transplantation who received optimal medical therapy. The authors' opinions are that digoxin should be used cautiously in such patients, because of the risk for adverse outcomes<sup>22</sup>.

Francis<sup>23</sup>, in 2008, affirms that, since AF can be the cause of worsening HF symptoms in 20% to 30% of cases, and that slowing the ventricular rate rather than correcting the underlying rhythm disturbance is the preferred therapeutic pathway, small doses of digoxin (0.125 mg/day) should be used in such patients. The author also suggests that one should never thoughtlessly change therapy in those who are doing well. That is, in patients who are using digoxin and are doing well, the drug's concentration should be measured and the dose adjusted accordingly, specially when  $\geq 1.2$  ng/dL, but it might not be a good idea to withdraw digoxin from a clinically stable patient. According to Francis, there is still a role for digoxin in selected patients with chronic HF, although less expansive as it once was<sup>23</sup>.

According to Gheorghade and Braunwald, digoxin use has decreased from 80% to  $< 30\%$  in the past 10 years. However, since mortality and rehospitalization rates for acute HF 90 days after discharge are as high as 15% and 30%, respectively, and that every new agent tested to date known to improve hemodynamics in acute HF syndromes (which include both vasodilators and inotropic agents) has not been shown to be either efficacious or safe, the role of digoxin in these conditions should be reexamined. The authors argument that digoxin: (1) improves hemodynamics acutely, both at rest and at exercise; (2) has beneficial neurohormonal actions, does not impair renal function and has a neutral or beneficial effect on heart rate and blood pressure; (3) is available both orally and intravenously; (4) is inexpensive and therapeutic serum concentrations can be monitored; (5) in relatively low doses resulting in serum concentrations

less than 1 ng/mL it appears to reduce hospitalization and cardiovascular mortality, particularly in patients with severe signs and symptoms or a very depressed ejection fraction; (6) although the drug has relatively narrow toxic-therapeutic ratio, it has been shown that low-dose digoxin is both safe and effective<sup>24</sup>.

### Recommendations of the international guidelines for chronic heart failure

The European Society of Cardiology (ESC) recommends digoxin use (Class I, level of evidence C) in patients in sinus rhythm with symptomatic HF and LVEF  $\leq 40\%$ . It also recommends, as Class IIa and level of evidence B, for the initial control of ventricular rate in a patient with rapid AF in decompensate HF patients, prior to the use of beta-blocker. The Guidelines affirm that serial monitoring of serum electrolytes and renal function is mandatory. The ESC contraindicates digoxin in patients with second and third degree heart block, in pre-excitation syndromes and if there is previous evidence of digoxin intolerance. The digoxin concentration should be checked early during chronic therapy in those with normal renal function<sup>25</sup>.

The American College of Cardiology (ACC) and the American Heart Association (AHA) say that physicians may consider adding digoxin in patients with persistent symptoms of HF, during therapy with diuretics, and ACE inhibitor or ARB and a beta-blocker. If the patient is taking digoxin and not an ACE inhibitor or a beta-blocker, treatment with the digitalis should not be withdrawn, but appropriate therapy with the neurohormonal antagonists should be instituted. Digoxin is prescribed routinely in patients with HF and chronic AF, but beta-blockers are usually more effective when added to digoxin in controlling the ventricular response, particularly during exercise. According to these guidelines, digoxin is not indicated as primary therapy for the stabilization of patients with an acute exacerbation of HF symptoms, including fluid retention or hypotension. The recommendations for digitalis use, in these guidelines, is now IIa<sup>26,27</sup>.

The Brazilian Society of Cardiology has recently published its III Guidelines for chronic HF treatment. According to this society, digoxin is indicated in symptomatic patients in HF with systolic dysfunction (LVEF  $\leq 45\%$ ) in sinus rhythm or in AF, already using optimized therapy (Class I, level of evidence B). In patients with LVEF  $\leq 45\%$  e AF, who are asymptomatic, digoxin may be used to control heart rate (Class IIa, level of evidence B). It should never be prescribed to asymptomatic patients in sinus rhythm and to patients with preserved ejection fraction.<sup>4</sup> For the management of acute HF patients, the Brazilian Society of Cardiology recommends digoxin for patients with LVEF  $\leq 40\%$  and AF, who are admitted with a ventricular response of  $\geq 100$  bpm, with or without beta-blockers. (Class I, level

of evidence B). In patients with acute HF, with LVEF  $\leq$  40% and sinus rhythm, the recommendations for its use is Iib, level of evidence B<sup>28</sup>.

## Conclusions

Digitalis, especially digoxin, have been used for the treatment of heart failure patients for more than 200 years. Although data from clinical trials in the past two decades have shown that there are others classes of drugs that are more effective than digitalis in terms of morbidity and mortality, what we showed in this review is that there is still a role for digoxin in the management of heart failure patients. The rational tendency nowadays, regarding its use, is to adequate the dose to age and the specific population being treated. We conclude that Digitalis are not as good as once was thought, but certainly are not as bad as it recently appeared to be.

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## Conflicts of interest

The authors have no conflict of interest to declare.

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