

The Use of Digitalis: A Reflection of Medicine as the Science of Provisional Truths

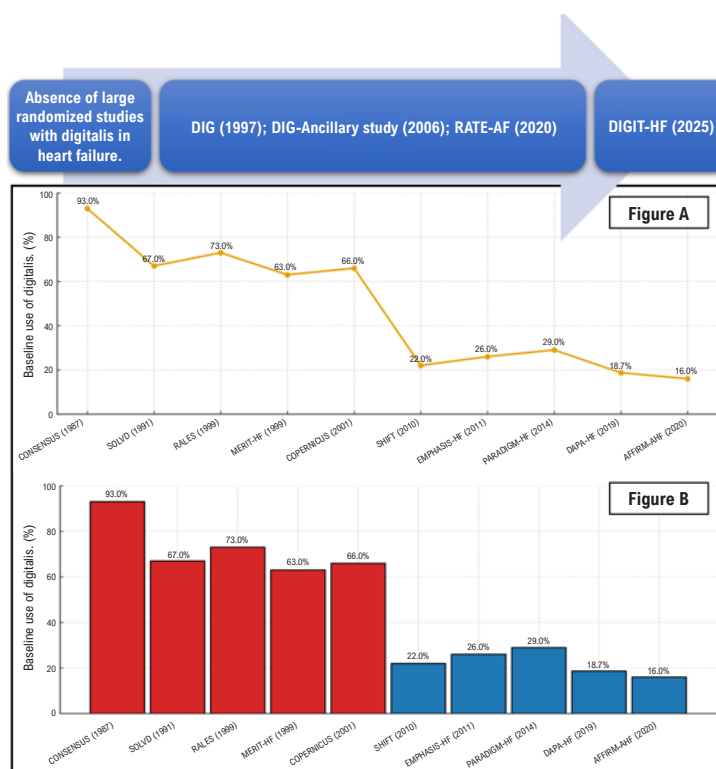
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Central Illustration: The Use of Digitalis: A Reflection of Medicine as the Science of Provisional Truths



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Prevalence of digitalis in large heart failure studies in parallel with digitalis studies. Prior to 2010: high prevalence of digitalis (red). After 2010: lower prevalence of digitalis (blue).

Keywords

Digoxin; Digitoxin; Heart Failure.

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Introduction

According to current guidelines (class I recommendation), the treatment of heart failure with reduced ejection fraction (HFrEF) – defined as left ventricular ejection fraction (LVEF) $\leq 40\%$ – should be based on the quadruple therapy scheme aimed at reducing cardiovascular outcomes. This regimen consists of beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), renin–angiotensin–aldosterone system blockers (including angiotensin-converting enzyme inhibitors [ACEIs], Angiotensin II Receptor Blockers [ARBs], or Angiotensin

Receptor–Neprilysin Inhibitors [ARNIs]), and Sodium–Glucose Cotransporter-2 Inhibitors (SGLT2i).^{1,2}

In recent decades, with the therapeutic evolution of HFrEF, some medications such as digitalis,¹ once widely recommended, have been relegated to the role of adjuvants for refractory patients. These drugs lost prominence due to their adverse effects and the unequivocal benefits of the “Fantastic Four,” especially from the late 1990s onward (Central Illustration). However, in light of recent evidence,³ digitalis appear to be regaining relevance as an additional treatment option for Heart Failure (HF), reflecting that, given the constant nuances in the use of digitalis over the years, medicine is indeed the science of provisional truths.

Digitalis and mechanism of action

Digitalis exert positive inotropic and negative chronotropic effects. Their mechanisms are primarily based on inhibition of the intrinsic membrane protein Na^+/K^+ -ATPase (enhancing myocardial contractility). In parallel, they exert sympatholytic effects, increasing vagal tone (inhibiting efferent sympathetic nerve activity, reducing epinephrine and renin concentrations), and reducing heart rate (HR), including in the context of atrial fibrillation (AF), thereby contributing to improvement in HF.^{4,5}

However, the boundary between therapeutic effects and adverse effects is narrow. Notable adverse events include arrhythmias (bradyarrhythmias or tachyarrhythmias), gastrointestinal symptoms, and visual disturbances (xanthopsia and blurred vision), particularly in the presence of risk factors for intoxication such as advanced age, female sex, chronic kidney disease, electrolyte disorders, and drug interactions.⁵

The oral representatives of digitalis are digoxin and digitoxin. The former has lower plasma protein binding (10–40%), a shorter half-life (36–48 hours), greater renal excretion, and an earlier and faster peak of action. In contrast, digitoxin exhibits higher serum protein binding (>90%), a longer half-life (4–6 days), predominantly hepatic excretion, and a slower, more sustained effect. Therefore, particularly in patients with chronic kidney disease, digitoxin presents a safer profile and more gradual action, with a lower incidence of rapid peaks of activity.⁶

History of digitalis use

From the 18th to the 20th century, digitalis was one of the few therapeutic options available for HF. In the 1980s and 1990s, these drugs were still widely recommended, as demonstrated in landmark studies with ACE inhibitors in patients with HFrEF: CONSENSUS (1987) and SOLVD (1991), in which 93% and 66.5% of participants, respectively, were using digitalis.^{7,8}

The first robust study evaluating digoxin in HF was the DIG trial (1997),⁹ a randomized, multicenter, double-blind, placebo-controlled study. It assessed the efficacy of digoxin in symptomatic patients with LVEF <45% in sinus rhythm. A total of 6,800 patients were included, followed for a mean period of 37 months, and evaluated for the primary endpoint of all-cause mortality. The sample consisted of severe patients, with a mean LVEF of 28%; 32% were in New York Heart Association (NYHA) functional class III/IV, optimized with contemporary therapy (94% on ACE inhibitors, 80% on diuretics, and 42% on nitrates). The study concluded that digoxin did not provide benefit in reducing all-cause mortality. Although it reduced HF hospitalizations by

28% (secondary endpoint), the DIG trial removed digitalis from its former central role in HF therapy.⁹

Moreover, there is evidence of a lack of benefit from digitalis in other scenarios, such as in patients with LVEF >45%,¹⁰ and in AF control when compared with BB.¹¹ A progressive decline in its use has also been observed in contemporary trials with new therapies for HFrEF, such as ARNI (PARADIGM-HF, 2014, 30% of patients using digitalis)¹² and SGLT2 inhibitors (DAPA-HF, 2019, 18.7% using digitalis).¹³

Currently, guidelines assign a low level of recommendation for digitalis (class IIb) in symptomatic HFrEF, despite optimized quadruple therapy.^{1,2} In patients with AF who are refractory or have contraindications to BB, its use remains a possibility (class IIa), albeit with caution.²

In light of new evidence

In 2025, an important study on the use of digitalis in HFrEF (in this case, digitoxin), the DIGIT-HF trial,³ was published, reigniting the relevance of these drugs in the management of HF. This was also a randomized, placebo-controlled, double-blind, multicenter study, including symptomatic HFrEF patients (LVEF <40% with NYHA ≥III or LVEF <30% with NYHA ≥II) under optimized therapy for at least six months. A total of 1,212 patients were randomized, with a mean age of 66 years, 20% of whom were women. Over 36 months, the primary endpoint of all-cause mortality and HF hospitalization was reduced by 18% (Hazard Ratio [HR] 0.82; 95% Confidence Interval [CI]: 0.69–0.98; $p = 0.03$), corresponding to a number needed to treat of 22. Despite a trend, there was no statistically significant reduction in the individual components of the endpoint.³

Compared with the DIG trial, DIGIT-HF³ had a smaller sample size (17.8% of DIG), included 30% of patients with atrial fibrillation (versus none in DIG), and recruited more symptomatic patients under contemporary, better-optimized therapy. Evidently, the study presented important limitations. The most significant was the sample size, which was smaller than the target (2,190 patients), requiring extensions and amendments, with a consequent loss of statistical power. It is possible that the reduced sample size limited the ability to detect differences in the individual endpoints (mortality/hospitalization). There were also instances of unblinding (82 patients), loss to follow-up (25 patients), and low use of SGLT2 inhibitors (20%).

Nevertheless, DIGIT-HF highlighted relevant aspects.³ First, the reduction in the composite endpoint of death/HF hospitalization occurred in more severely ill patients (mean LVEF of 28% and nearly 70% in NYHA class ≥III/IV) compared with other studies, such as PARADIGM-HF (approximately 25% in NYHA class ≥III/IV).¹² Second, the positive impact occurred in a setting of optimized therapy (use of beta-blockers, renin–angiotensin–aldosterone system blockers, and MRAs in approximately 96%, 94%, and 75% of patients, respectively). In other words, these were patients refractory to the initial recommended treatment. Such a situation is common and difficult to manage in practice, and in this context, a reduction in outcomes was observed in addition to standard HF therapy (and not as a replacement). Thus, considering the high residual risk in HF – on the order of 15.8 events (cardiovascular death/HF hospitalization) per 100 patients per year in optimized patients¹⁴ – digitalis emerge as a therapeutic alternative.

Table 1 – Randomized studies evaluating the benefit of digitalis in heart failure and/or atrial fibrillation

Study	Year of publication	Inclusion criteria	Assessment	Sample/follow-up	Primary outcome: RR or HR (95%CI)	Secondary outcomes: RR or HR 95% CI)
DIG	1997	LVEF<45% + sinus + symptomatic HF	Digoxin x placebo	6,800/mean 37 months	Overall mortality: 0.99 (0.91-1.7); p=0.80	Hospitalization for worsening HF: 0.72 (0.66-0.79); p<0.001; hospitalization for CV causes: 0.87 (0.81-0.93); p<0.001
DIG-Ancillary study	2006	LVEF>45% + sinus + chronic HF	Digoxin x placebo	988/mean 37 months	Death from HF/hospitalization for HF: 0.82 .63-1.07; p=0.136	Overall mortality: 0.99 (0.76-1.28); p=0.925; Death from HF/hospitalization for HF 2 years): 0.71 (0.52-0.98); p=0.034
RATE-AF	2020	Permanent AF + NYHA≥II + age≥60 years	Digoxin x bisoprolol	160/mean 12 months	Quality of life (PCS score): 1.03 (-1.2 – 3.9)/p=0.3*	Less adverse events with dogoxin (25%) x bisoprolol (64%); p=0.001
DIGIT-HF	2025	LVEF<40% + NYHA≥II or LVEF<30% and NYHA≥II + therapy optimization > 6 months	Digoxin x placebo	1212 /mean at 36 months	Overall mortality/hospitalization for HF: 0.82 (0.69-0.98); p=0.03	Overall mortality: 0.860.69-1.07; first hospitalization for HF: 0.85 (0.69-1.05)

*Mean adjusted difference; HF: heart failure; CI: confidence interval; AF: atrial fibrillation; CV: cardiovascular; LVEF: left ventricular ejection fraction; HR: hazard ratio; NYHA: New York Heart Association; PCS: Physical Component Summary; RR: risk ratio.

Furthermore, the study suggests greater benefit in patients with lower Systolic Blood Pressure (SBP ≤120 mmHg, HR 0.61; 95% CI: 0.48–0.79) and higher HR (HR ≥75 bpm, HR 0.63; 95% CI: 0.48–0.83),³ that is, in patients who were more severely ill and more difficult to optimize pharmacologically.

Finally, the safety observed with digitoxin use in DIGIT-HF is of utmost relevance, considering the toxicity and potential adverse events associated with elevated serum levels of digitalis.^{5,15} No significant differences in adverse effects or discontinuation were found between digitoxin and placebo,³ demonstrating the drug's safety when appropriately monitored. Notably, 43% of the sample had an estimated glomerular filtration rate below 60 mL/min/1.73 m². Even in this subgroup, the benefit was present (HR 0.73; 95% CI: 0.56–0.94),³ precisely among patients with chronic kidney disease, a comorbidity affecting 45% of individuals with HFrEF¹⁶ who are at increased risk of digoxin intoxication.⁵

These findings add to previous evidence that, when serum levels of digitalis are monitored, safety is maintained alongside outcome reduction, such as attenuation of mortality with digoxinemia between 0.5–0.8 ng/mL, in contrast to increased mortality at serum digoxin levels above 1.2 ng/mL.¹⁵

Thus, the DIGIT-HF study³ reopened discussions regarding the use of digitalis. In light of the nuances in HF treatment over the years, digitalis has proven to be an excellent example of medicine

as the science of transient truths, reaffirming – after centuries of use – the statement of the renowned Dutch physician K. F. Wenckebach: “A long life is too short to learn enough about this wonderful drug.”⁶

Conclusion

For all these reasons, digitalis remain as an additional treatment option for HF – maintaining the same indication as in current guidelines – and never as a substitute for the initial standard quadruple therapy.^{1,2} Nevertheless, it is expected that the current apprehension, and even stigma, surrounding the use of digitalis will be progressively attenuated, with recognition of their true therapeutic indication, provided that careful monitoring of toxicity is ensured.

Author Contributions

Conception and design of the research, Statistical analysis and Writing of the manuscript: Wolf PJ; Acquisition of data: Wolf PJ, Mattos VBM, Rossi RM, Vasconcellos M, Bruscky L, Assad H, Fortuna F; Analysis and interpretation of the data: Wolf PJ, Santos CC, Rossi J, Finger MAA, Correia EB, Valdigem B; Critical revision of the manuscript for content: Wolf PJ, Santos CC, Rossi J, Finger MAA, Correia EB.

Potential conflict of interest

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Study association

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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