

Digoxin in Heart Failure with Reduced Ejection Fraction: A Proposal for a Practical Precision Medicine-Based Guide

Germano Emílio Conceição-Souza^{1,2} 

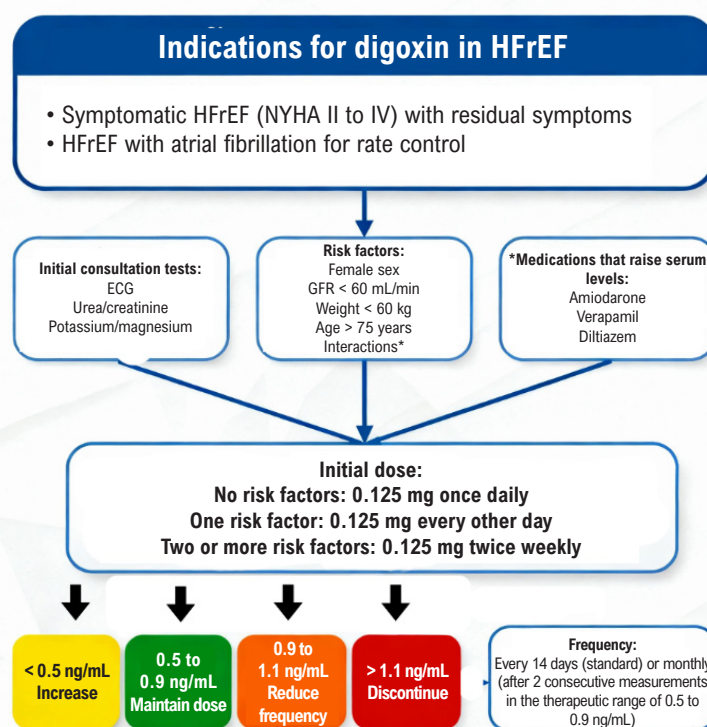
Instituto de Ensino e Pesquisa Clínica São José,¹ São José dos Campos, SP – Brazil

Hospital Regional de São José dos Campos,² São José dos Campos, SP – Brazil

Central Illustration: Digoxin in Heart Failure with Reduced Ejection Fraction: A Proposal for a Practical Precision Medicine-Based Guide



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Decision and management flowchart for digoxin in HFrEF. Proposed algorithm for digoxin management in HFrEF. The flow integrates clinical indication, verification of contraindications, risk stratification for initial dose, and monitoring cycle. Dose adjustment is guided by serum level ranges (colors), targeting the therapeutic target of 0.5 to 0.9 ng/mL. Source: The author. ECG: electrocardiogram; GFR: glomerular filtration rate; HFrEF: heart failure with reduced ejection fraction; NYHA: New York Heart Association functional class.

Keywords

Heart Failure; Digoxin; Precision Medicine; Cardiac Glycosides; Pharmacokinetics.

Mailing Address: Germano Emílio Conceição-Souza •

Instituto de Ensino e Pesquisa Clínica São José - Rua Teopompo de Vasconcelos, 147. Postal Code 12243-830, Vila Adyana, São José dos Campos, SP - Brazil

E-mail: germano.souza@iepsj.com.br

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Introduction: the paradox of digitalis therapy

Digoxin holds a unique position in the history of cardiovascular medicine. Although it is the oldest drug in continuous use for heart failure (HF) treatment, there has been a sharp decline in prescriptions over the past two decades. Overshadowed by the advent of disease-modifying therapies and stigmatized due to concerns regarding toxicity, digoxin was relegated to a Class IIa recommendation in the Brazilian guideline¹ and a third-line recommendation (Class IIb) in the major international guidelines.^{2,3}

Nonetheless, the systematic exclusion of digoxin may represent a historical error based on incomplete interpretations of old data. In a scenario where heart failure with reduced ejection fraction (HFrEF) still imposes high morbidity, mortality, and residual symptoms despite optimized therapy, the premise of this viewpoint is unequivocal: digoxin is not obsolete; what has become obsolete is the empirical fixed-dose prescription model. In light of contemporary evidence, we propose a revival of digitalis therapy guided by precision medicine.

There are significant pharmacokinetic distinctions between different digitalis compounds. Digoxin is eliminated via the urinary system, has a short half-life (26 to 48 hours), is more hydrophilic, and has low protein binding; in contrast, digitoxin is primarily eliminated by the liver, has a long half-life (5 to 7 days), is more lipophilic, and has high protein binding. In this context, the use of digitoxin has been considered safer in patients with concomitant kidney disease.

Building evidence: from the DIG trial to the contemporary era

The negative turning point for digoxin was the Digitalis Investigation Group (DIG) study, published in 1997, which randomized 6,800 patients with HFrEF. Although it demonstrated a significant reduction in hospitalizations for HF, the study was neutral for overall mortality.⁴ This neutral result, however, masked a complex pharmacological reality: higher doses increased mortality, offsetting the benefit of lower doses.

In 2003, a fundamental post hoc analysis conducted by Rathore et al. redefined the understanding of the medication. By stratifying patients from the DIG trial by serum digoxin concentration, the authors identified a narrow therapeutic window. Patients with levels between 0.5 and 0.9 ng/mL showed a significant reduction in mortality. In contrast, levels above 1.2 ng/mL increased the risk of death.⁵ This association was corroborated in the setting of atrial fibrillation by the ARISTOTLE trial substudy, published in 2018 by Lopes et al., confirming that digoxin-associated mortality was driven by supratherapeutic serum levels, regardless of systolic function.⁶

The definitive validation of the “low-level, high-vigilance” concept emerged in 2025 with the publication of the DIGIT-

HF study. This randomized clinical trial included 2,666 patients with advanced HFrEF, testing digitoxin with dose adjustment guided by serum levels. The results demonstrated a robust reduction in the composite outcome of mortality or hospitalization due to worsening HF, validating the safety of therapeutic monitoring.⁷ It is worth noting that digitoxin differs from digoxin in some pharmacokinetic aspects.

Simultaneously, the DECISION study brings a pragmatic perspective. With a planned inclusion of 980 patients, this study innovates by including not only patients with HFrEF but also those with mildly reduced ejection fraction. The DECISION study’s focus on patient-centered outcomes (“days alive and out of hospital”) and the use of low doses of digoxin reinforce the current trend toward therapeutic personalization.⁸

Proposed practical guide: risk stratification

To translate this evidence into clinical practice, especially in the Brazilian context where digitoxin is not available, we propose a structured protocol for digoxin use. The central pillars of this guide are recognition of risk factors for intoxication (Table 1) and proactive dose adjustment.

Dosage and monitoring algorithm

We recommend abolishing the initial dose of 0.25 mg/day for the majority of patients. The dose should be titrated according to the number of risk factors present (Table 1), as follows:

- No risk factors: Begin with 0.125 mg (half tablet) daily.
- One risk factor: Begin with 0.125 mg every other day.
- Two or more risk factors: Begin with 0.125 mg twice a week (for example, Mondays and Thursdays)

The complete management strategy, including monitoring intervals and dose adjustments based on serum levels, is detailed in the Central Illustration.

Follow-up should be intensive. At the first consultation (baseline), electrocardiogram, renal function (urea/creatinine), and electrolytes (sodium, potassium, magnesium) are

Table 1 – Risk factors for digitalis intoxication and mechanisms involved

Risk factor	Definition criteria	Pharmacokinetic mechanism
Female sex	-	Lower apparent muscle volume of distribution for the drug
Kidney disease	Estimated GFR < 60 mL/min/1.73 m ²	Reduced renal clearance of digoxin, prolonging the half-life
Low weight	Body mass < 60 kg	Lower skeletal muscle mass (main tissue reservoir of the drug)
Advanced age	Age > 75 years	Physiological decline in renal function and reduced lean mass
Drug interactions	Amiodarone, verapamil, or diltiazem use	Inhibition of P-glycoprotein, increasing bioavailability and reducing renal excretion

GFR: glomerular filtration rate.

Viewpoint

mandatory. The frequency of consultations and digoxin level testing should be every 14 days until stability is achieved (two consecutive measurements within the therapeutic target range of 0.5 to 0.9 ng/mL). From that point on, monitoring can be done monthly, maintaining laboratory and electrocardiographic surveillance at all visits. If these levels remain persistently controlled within the target range, it is possible to further space out digoxin level testing, provided that clinical surveillance is maintained, with a high index of suspicion for any symptoms of intoxication, worsening renal function, or changes in fluid and electrolyte balance. If a dose escalation is required (serum digoxin < 0.5 ng/mL), the dose should be increased carefully by 25% to 50% of the weekly dose, and a new measurement should be performed within 2 weeks. If the serum level is between 0.9 and 1.1 ng/mL, the dose should be reduced by 25% to 50% of the weekly dose. If the serum level is greater than 1.1 ng/mL, digoxin should be discontinued, and a new measurement should be performed in 2 weeks; in this case, if serum levels return to or below target levels, digoxin can be restarted at half the dose that was prescribed. It is essential to measure digoxin levels at least 6 hours after oral administration, ideally after 8 hours. If measured before this interval, the result may be falsely elevated, as the drug will still be concentrated in the blood before distribution to various organs and tissues. It is important to emphasize that a new digoxin level test is indicated in cases where a change of more than 30% in the glomerular filtration rate (up or down) is detected, after episodes of heart failure decompensation, or when new drugs that may influence its bioavailability have been prescribed (for example, amiodarone).

Contraindications

Safety of digoxin use also depends on observing absolute and relative contraindications, which are summarized in Table 2.

Conclusion

Digoxin remains a valuable tool in the therapeutic arsenal for treating HFrEF, capable of reducing hospitalizations and improving quality of life. The “danger” attributed to the medication actually lies in its narrow therapeutic window and inappropriate management. By adopting a precision medicine protocol, stratifying initial risk by clinical characteristics and guiding maintenance by serum levels, we transform an old drug into a safe and modern therapeutic tool.

Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Writing of the manuscript and Critical revision of the manuscript for content: Conceição-Souza GE.

Potential conflict of interest

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Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

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

Table 2 – Contraindicated or high-risk situations for initiating digoxin in patients with heart failure with reduced ejection fraction

Clinical condition	Justification/risk
AVB	Second- or third-degree AVB without pacemaker protection (risk of asystole)
Pre-excitation syndrome	WPW with atrial fibrillation (risk of accelerated anterograde conduction and VF)
Hypertrophic cardiomyopathy	Obstructive form (increased LV outflow tract obstruction)
Acute myocarditis	Inflamed myocardium with increased sensitivity and high arrhythmogenic risk
Electrolyte disturbances	Hypokalemia (< 3.5 mEq/L) or hypomagnesemia (provoking toxicity)
Acute coronary syndrome	Acute phase of AMI (arrhythmogenic risk and increased oxygen consumption)

AMI: acute myocardial infarction; AVB: atrioventricular block; LV: left ventricle; VF: ventricular fibrillation; WPW: Wolff-Parkinson-White syndrome.

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