Enmanuel A. Leiva-Murillo, MD
Department of Internal Medicine, Clinical Institute of Medicine and Dermatology, Hospital Clínic, University of Barcelona, Barcelona, Spain

Oriol Ventosa-Blázquez, MD
Department of Cardiology, Clinical Institute of Cardiovascular Diseases, Hospital Clínic, University of Barcelona, Barcelona, Spain

Eduard Solé-González, MD, PhD
Heart Failure and Heart Transplant Unit, Department of Cardiology, Clinical Institute of Cardiovascular Diseases, Hospital Clínic, University of Barcelona, Barcelona, Spain

Interpreting the DIGIT-HF trial: Time for a new look at digitalis?

ABSTRACT

The DIGIT-HF (Digitoxin to Improve Outcomes in Patients With Advanced Chronic Heart Failure; N Engl J Med 2025; 393(12):1155–1165) trial compared digitoxin with placebo, added to guideline-directed medical therapy in patients with heart failure with reduced ejection fraction (HFrEF). Compared with placebo, digitoxin reduced the incidence of the composite endpoint of death from any cause or first hospitalization for worsening heart failure by 18% over a median follow-up of 36 months (hazard ratio 0.82, 95% confidence interval 0.69–0.98). There were no statistically significant differences in the rates of all-cause mortality, first hospitalization, or serious adverse events.

KEY POINTS

- Digitoxin differs from digoxin in its pharmacokinetic properties.
- The trial used a pragmatic digitoxin dosing protocol, with a single serum level check at 6 weeks.
- The incidence of serious adverse events was numerically greater in the digitoxin group than in the placebo group (4.7% vs 2.8%), but the difference was not statistically significant.
- Digitoxin met the prespecified noninferiority criterion for all-cause mortality vs placebo, with a hazard ratio of 0.86 ($P < .001$); the threshold for noninferiority was 1.303.
- Digitoxin may confer a modest but clinically relevant benefit in patients with advanced, symptomatic HFrEF receiving optimal guideline-directed medical therapy.

doi:10.3949/ccjm.93a.25098

It may be time for a new look at some old drugs: in a large, randomized, placebo-controlled trial published in 2025, the cardiac glycoside digitoxin reduced the incidence of the combined endpoint of death from any cause or first hospitalization for heart failure when added to guideline-directed medical therapy in patients with heart failure with reduced ejection fraction (HFrEF).[1]

Although the study drug was digitoxin, not its more commonly used congener digoxin, and it is no longer available in the United States, it can still be obtained in several countries in Europe and elsewhere.

Heart failure is a major public health problem, affecting more than 56 million people worldwide,[2] and its prevalence continues to rise. About 6.7 million Americans live with heart failure, which is responsible for 45% of cardiovascular deaths. An estimated 1 in 4 Americans will develop heart failure during their lifetime, and its prevalence is projected to reach 11.4 million cases by 2050.[3]

Despite advances in treatment, the mortality rate in patients with heart failure remains about 50% at 5 years.[2] This high residual risk is spurring research into the management of heart failure. In this context, and almost 3 decades after the last trial of a digitalis drug, the recent trial reopens the debate on the usefulness of digitalis therapy in heart failure.

This article reviews the Digitoxin to Improve Outcomes in Patients With Advanced Chronic Heart Failure (DIGIT-HF trial),[1] including its background, design, results, and implications in managing HFrEF.

TABLE 1
Pharmacokinetic differences between digitoxin and digoxin

	Digitoxin	Digoxin
Bioavailability	> 90%	60%–80%
Plasma protein binding	> 90%	25%
Tissue distribution	4–10 hours	6–8 hours
Volume of distribution	0.4–0.7 L/kg	6–7 L/kg
Metabolism	Hepatic cytochrome P-450 (CYP3A)	Hepatic (only 16% of digoxin) Not dependent on cytochrome P-450
Elimination	60% renal (conjugated metabolites) 40% biliary	50%–70% excreted unchanged in urine 25%–28% extrarenal routes
Half life	3–10 days	1.5–2 days

Based on information from references 9–11,13.

BACKGROUND

Digitalis preparations have been used to treat heart failure for more than 2 centuries, first in the form of the leaves of the foxglove plants *Digitalis purpurea* and *Digitalis lanata*, and later as the cardiac glycosides digoxin and digitoxin.[4]

The pivotal Digitalis Investigation Group (DIG) trial,[5] published in 1997, showed that digoxin reduced hospitalizations for heart failure but had no impact on overall survival. Following these results, clinical guidelines recommended digoxin for heart failure, although its efficacy and safety remained debated.[6] Worse, meta-analyses of observational studies have suggested a possible association between its use and increased all-cause and cardiovascular mortality.[7]

As other treatments for HFrEF have been introduced, the role of digitalis compounds has diminished, shifting from the basis of treatment to a complementary role.[8]

Historically, digoxin has been the most commonly used digitalis agent, being widely available, approved by the US Food and Drug Administration,[9] and backed by extensive clinical evidence, while digitoxin lacked clinical trials to support its use. Although digitoxin is not currently marketed in the United States, it remains available in some regions of Europe.[1,10]

How digoxin and digitoxin differ

Digoxin ($C_{41}H_{64}O_{14}$) and digitoxin ($C_{41}H_{64}O_{13}$) are nearly identical in their chemical structures, the difference being that digoxin has a hydroxyl (oxygen-hydrogen) group at a position where digitoxin has only a hydrogen atom.[11,12]

Although the mechanism of action is the same, this subtle difference in structure makes digitoxin more lipophilic, thereby altering its pharmacokinetics (**Table 1**).[9–11,13] It has greater bioavailability, greater plasma protein binding, and a longer half-life, which contribute to more stable plasma levels. In addition, whereas digoxin is mostly excreted unchanged in the kidneys, digitoxin undergoes hepatic metabolism and significant biliary excretion, which may make it safer in patients with renal disease.[13]

Another relevant difference between the drugs is their interaction with P-glycoprotein (P-gp), an active membrane transport protein. Digoxin depends heavily on P-gp for its absorption and elimination; therefore, drugs that modify P-gp such as verapamil, amiodarone, and propafenone, which are commonly used in cardiology, can significantly alter its plasma concentration.[12,13] In contrast, digitoxin, which is more lipophilic, is less dependent on P-gp and relies more on passive diffusion to cross biological membranes.[14]

DIGIT-HF DESIGN

DIGIT-HF was an international, phase 4, multicenter, randomized, double-blind, placebo-controlled trial evaluating digitoxin added to guideline-directed medical therapy in HFrEF. It was conducted at 65 centers in Austria, Germany, and Serbia, and funded by the German Federal Ministry of Research, Technology, and Space.[1]

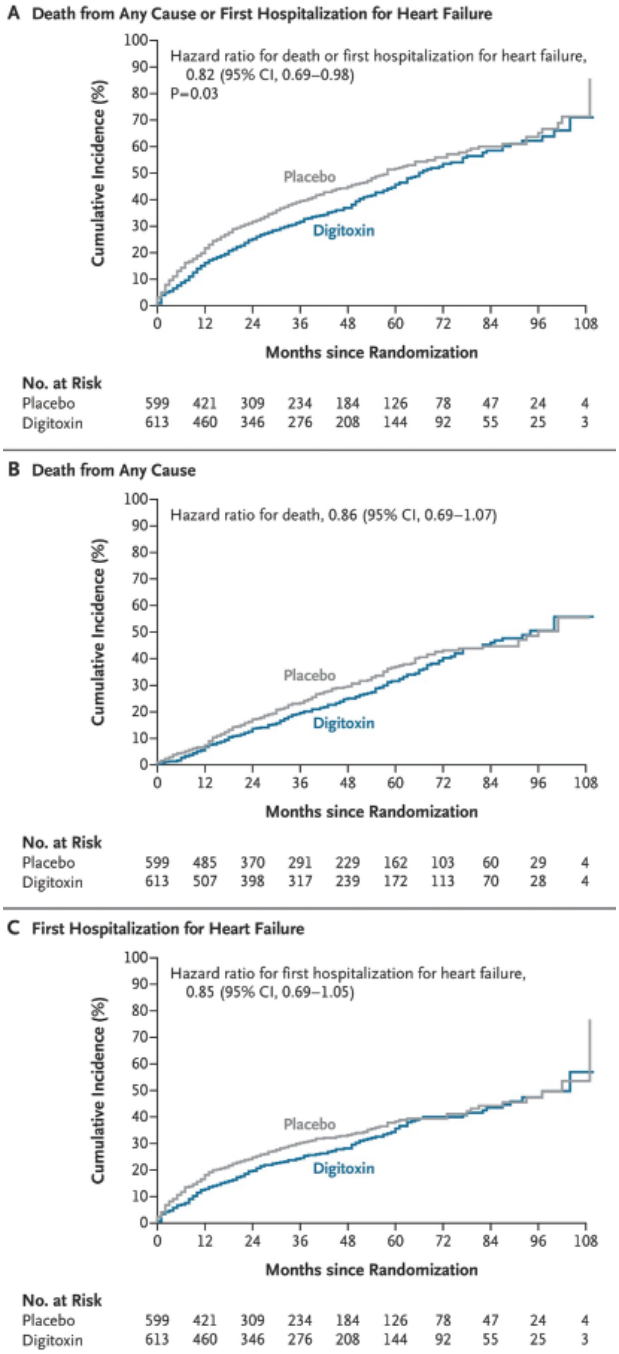


Figure 1. Cardiovascular outcomes in the Digitoxin to Improve Outcomes in Patients With Advanced Chronic Heart Failure (DIGIT-HF) trial.

CI = confidence interval

From Bavendiek U, Großhennig A, Schwab J, et al. Digitoxin in patients with heart failure and reduced ejection fraction. N Engl J Med 2025; 393(12): 1155–1165. doi:10.1056/NEJMoa2415471. Copyright © 2025 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. License No. 6139170247864.

Inclusion and exclusion criteria and digitoxin therapy

Patients could be included if they were age 18 years or older, had heart failure, were receiving guideline-directed medical therapy, were in clinically stable condition for at least 6 months before randomization, and had either of the following:

- Left ventricular ejection fraction 40% or less and were in New York Heart Association functional class III or IV, or
- Left ventricular ejection fraction 30% or less and were in New York Heart Association functional class II.[15]

The exclusion criteria included conditions that could increase the risk of toxicity or interfere with the interpretation of efficacy and safety, including bradyarrhythmias, electrolyte imbalances, acute coronary syndrome, recent coronary revascularization, unstable heart failure, and severe noncardiac comorbidities that limited survival.[15]

Participants were randomized in a 1:1 ratio to receive digitoxin or placebo. Digitoxin was started at 0.07 mg/day, and the serum level was measured once after 6 weeks to adjust the dose and maintain the serum concentration in the range of 8 to 18 ng/mL.[1]

End points and statistical analysis

The primary outcome was a composite of death from any cause or hospitalization for worsening heart failure, whichever occurred first. The key secondary outcome combined death from any cause and any hospitalization for heart failure during follow-up. Additional secondary outcomes included cardiovascular mortality, death from heart failure, sudden cardiac death, noncardiovascular death, and all hospitalizations, both cardiovascular and noncardiovascular.[15]

The trial was designed to detect an absolute difference of 5% between groups in the primary outcome, with an expected incidence of 26% in the digitoxin group and 31% in the control group. The planned sample size was 2,190 patients with 734 events over a 36-month recruitment period and up to 48 months of follow-up.[1]

The primary analysis was by intention-to-treat. Two main hypotheses were tested:

- Digitoxin would be superior to placebo in terms of the primary outcome, and
- Digitoxin would not be inferior in terms of mortality (to rule out a possible harmful effect of digitoxin).[1]

TABLE 2
Key findings from Digitoxin to Improve Outcomes in Patients With Advanced Chronic Heart Failure (DIGIT-HF) trial

	Digitoxin group (n = 613)	Placebo group (n = 599)	Hazard or rate ratio (95% confidence interval)
Primary composite outcome (death from any cause or first hospitalization for heart failure)	39.5%	44.1%	0.82 (0.69–0.98)
Death from any cause	27.2%	29.5%	0.86 (0.69–1.07)
First hospitalization for heart failure	28.1%	30.4%	0.85 (0.69–1.05)
Key secondary outcome (death from any cause and hospitalization for heart failure)	537 events	531 events	0.85 (0.67–1.09)
Select subgroup analyses (statistically significant results)			
Ejection fraction < 30%	40.3%	46.8%	0.77 (0.59–0.99)
Nonischemic heart failure	34.0%	42.2%	0.70 (0.53–0.93)
Heart rate ≥ 75 bpm	42.0%	48.2%	0.63 (0.48–0.83)
Systolic blood pressure ≤ 120 mm Hg	39.6%	49.3%	0.61 (0.48–0.79)
Body mass index < 30 kg/m^2	38.0%	46.1%	0.74 (0.58–0.93)
No hypertension	26.4%	40.3%	0.57 (0.34–0.93)
No diabetes	34.9%	42.8%	0.76 (0.60–0.96)
Estimated glomerular filtration rate ≤ 60 mL/min/1.73 m^2	50.2%	55.3%	0.73 (0.56–0.94)
No implantable cardioverter–defibrillator therapy	31.8%	43.2%	0.57 (0.41–0.80)
No cardiac-resynchronization therapy	35.0%	43.7%	0.72 (0.58–0.90)

Based on information from reference 1.

DIGIT-HF RESULTS

Population

Between May 2015 and September 2023, 1,240 patients were randomized, of whom 1,212 were included in the analysis, with 613 in the digitoxin group and 599 in the placebo group.[1]

The mean age of the participants was 66 years, and 20.4% were women. Most had advanced heart failure: 70.4% were in New York Heart Association functional class III or IV, and their mean left ventricular ejection fraction was 29%. In addition, 27.2% had atrial fibrillation.

Regarding guideline-directed medical therapy, 95.7% of the patients were receiving a beta-blocker, 36.0% were receiving an angiotensin-converting enzyme inhibitor, 18.8% were receiving an angiotensin II receptor blocker, 39.5% were receiving an angiotensin receptor-neprilysin inhibitor, 76.2% were receiving a mineralocorticoid receptor antagonist, and 19.3% were receiving a sodium-glucose cotransporter 2 inhibitor. Regarding device therapies, 64.3% had an implantable cardioverter-defibrillator and 25.2% had received cardiac resynchronization therapy.[16]

Impact on end points

Over a median follow-up of 36 months, the primary outcome occurred in 39.5% of patients in the digitoxin group, compared with 44.1% in the placebo group (hazard ratio [HR] 0.82, 95% confidence interval 0.69–0.98, $P = .03$). Thus, 22 patients needed to be treated with digitoxin to prevent 1 primary outcome event. However, neither the all-cause mortality rate nor the rate of first hospitalizations (the components of the composite outcome) was statistically different between groups (**Figure 1** and **Table 2**).[1]

TABLE 3
Comparison of main findings from DIGIT-HF and other contemporary clinical trials in heart failure with reduced ejection fraction

Trial	Study drug[a]	Primary outcome	Hazard ratio (95% confidence interval)	Number needed to treat	Effect on mortality?
DIGIT-HF[1]	Digitoxin	Death or first hospitalization for heart failure	0.82 (0.69–0.98)	22	No
PARADIGM-HF[17]	Sacubitril-valsartan	Cardiovascular death or first hospitalization for heart failure	0.80 (0.73–0.87)	21	Yes
DAPA-HF[18]	Dapagliflozin	Cardiovascular death or worsening heart failure	0.74 (0.65–0.85)	20	Yes
EMPEROR-Reduced[19]	Empagliflozin	Cardiovascular death or hospitalization for worsening heart failure	0.75 (0.65–0.86)	19	No
VICTOR[20]	Vericiguat	Cardiovascular death or first hospitalization for heart failure	0.93 (0.83–1.04)	91[b]	Yes[b]

[a]Digitoxin is a cardiac glycoside, sacubitril-valsartan is a combination neprilysin inhibitor and angiotensin II receptor blocker, dapagliflozin and empagliflozin are sodium-glucose cotransporter 2 inhibitors, and vericiguat is a soluble guanylate cyclase stimulator.
[b]The primary outcome was not statistically significant, and all-cause mortality was an exploratory outcome.

DAPA-HF = Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DIGIT-HF = Digitoxin to Improve Outcomes in Patients With Advanced Chronic Heart Failure; EMPEROR-Reduced = Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction; PARADIGM-HF = Prospective Comparison of ARNI to Determine Impact on Global Mortality and Morbidity in Heart Failure; VICTOR = Vericiguat in Adults With Chronic Heart Failure and Reduced Ejection Fraction

The all-cause mortality rate was 27.2% in the digitoxin group and 29.5% in the placebo group (HR 0.86, 95% confidence interval 0.69–1.07), satisfying the prespecified noninferiority condition (HR < 1.303). No significant differences were observed in the other secondary outcomes.[1]

Subgroup analysis of the primary outcome showed positive trends in nearly all subgroups, but the results were statistically significantly better with digitoxin only in the following subgroups:

- Ejection fraction less than 30%
- Nonischemic heart failure
- Heart rate 75 beats per minute or higher
- Systolic blood pressure 120 mm Hg or lower (Those with higher systolic pressure actually had a slightly higher rate with digitoxin, but it was not statistically significant.)
- Body mass index 30 kg/m^2 or lower
- No hypertension
- No diabetes
- Estimated glomerular filtration rate 60 mL/min/1.73 m^2 or lower
- Without advanced devices.

Safety

At least 1 serious adverse event was recorded in 29 patients (4.7%) in the digitoxin group and in 17 (2.8%) in the placebo group, including cardiac disorders in 3.4% and 1.8%, respectively.

Digitoxin or placebo was discontinued due to an adverse event in 56 patients (9.1%) in the digitoxin group and 61 (10.2%) in the control group.[1]

STRENGTHS OF THE TRIAL

Novelty and design

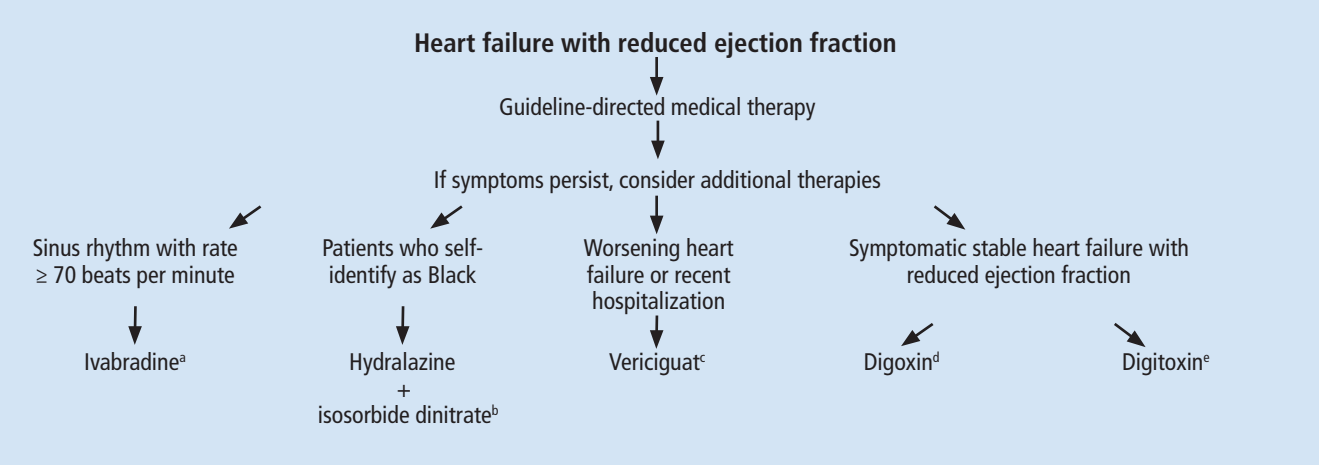
DIGIT-HF is the first trial to evaluate a digitalis drug since the DIG trial.[1,8] The use of digitoxin, whose benefit was uncertain, stands out as its main novelty. It was not sponsored by a pharmaceutical corporation, and it evaluated a drug that costs much less than most recent therapies for heart failure.[15]

Meaningful population

DIGIT-HF enrolled a cohort of patients with advanced HFrEF and a high symptom burden. This group was underrepresented in other contemporary clinical trials in heart failure.[17–20] However, in a population with advanced heart failure, we would have expected more events and more deaths.

Simple protocol

The authors used a simple digitoxin dosing protocol, with a single level measurement at 6 weeks to adjust



[a]Class 2a recommendation; decreased heart failure hospitalization and cardiovascular death.[26,27]

[b]Class 2a recommendation; decreased heart failure hospitalization and death.[26]

[c]Class 2b recommendation; decreased heart failure hospitalizations or cardiovascular death.[20,26,27]

[d]Class 2b recommendation; decreased heart failure hospitalizations.[26,27]

[e]May be considered as an adjunctive therapy for patients with symptomatic and stable heart failure with reduced ejection fraction despite optimized guideline-directed medical therapy; decreased death or first heart failure hospitalizations in the Digitoxin to Improve Outcomes in Patients With Advanced Chronic Heart Failure (DIGIT-HF) trial.[1]

Figure 2. Integration of digitoxin in treatment of heart failure with reduced ejection fraction.

Based on information from references 1, 26, and 27.

the dose.[15] This contrasts with the complex management of digoxin, which requires frequent monitoring of blood levels.[13]

After measurement, 58% of patients continued on the same dose, and 34% required a dose reduction.[1] Dose reduction was mainly associated with female sex, age 75 years and older, estimated glomerular filtration rate less than 50 mL/min/1.73 m², and body mass index less than 27 kg/m²; in such patients, an initial dose of 0.05 mg/day may be reasonable.[21]

Clinical applicability and impact

Patient selection was based exclusively on clinical characteristics, without the need for biomarkers or complex tests, making it applicable in real-world practice.[15] Even in patients with advanced disease on guideline-directed medical therapy and with a high rate of device therapy, in whom the incremental benefit of a new therapy may be marginal, digitoxin offers a relevant additive effect, with a number needed to treat of 22, comparable to that in trials of newer drugs (**Table 3**).[1,16,21]

Efficacy in relevant subgroups

Subgroup analysis suggests the benefit of digitoxin is maintained in patients with elevated heart rates, low systolic blood pressure, and renal disease, which are highly prevalent in patients with advanced heart failure who often cannot tolerate guideline-directed medical therapy.[1]

Safety

The rate of serious adverse events was low, and discontinuation of treatment due to these events was similar across all groups. No signs of unexpected toxicity were detected, nor was there any increase in mortality attributable to digitoxin.[1] These findings contrast with historical concerns about the safety of digitalis compounds.[7,8,22] Consistent with the post hoc analyses of DIG, DIGIT-HF suggests that digitalis compounds are beneficial at low concentrations.[22–24]

LIMITATIONS OF THE TRIAL

Population and underrepresented subgroups

The trial was conducted in an exclusively European population, with fewer women (20%) and fewer patients with atrial fibrillation than in comparable trials.[16] These characteristics partially restrict the generalizability of the results.

Unblinding and performance bias

Unblinding occurred in a limited number of cases (54 in the digitoxin group, 28 in the placebo group).[1] However, the relatively low number limits its overall impact and bias risk.

Lower recruitment and rate of events than expected

DIGIT-HF, with 1,212 patients and 506 events, did not meet the planned sample size or event rate.[1] This reduced the study's statistical power and limited its ability to detect differences with treatment. The inclusion rate was 2.4 patients per center per year, which was well below usual practice. Recruitment had to be extended from 36 to 84 months, the planned interim analysis could not be performed, and the protocol had to be amended, all of which may have introduced additional biases and warrant cautious interpretation.[25]

These limitations should be viewed in the context of contemporary guideline-directed medical therapy, particularly following the approval of sodium-glucose cotransporter 2 inhibitors, which significantly reduce heart failure hospitalizations.[18,19] Compared with previous trials, DIGIT-HF included one of the largest populations receiving guideline-directed medical therapy.

Significant composite outcome, nonsignificant individual components

The reduction in statistical power was probably part of the reason that although the primary composite outcome reached statistical significance, none of its components did when analyzed separately. However, effects for the components were directionally consistent with the overall result. Secondary outcomes were also not statistically significant.[1]

Discontinuation rate and losses

Treatment was discontinued for reasons other than death in 58.9% of the digitoxin group and 55.1% with placebo.[1] This high discontinuation rate can dilute treatment effects. Although the intention-to-treat analysis partially mitigates this problem, the actual benefit may be underestimated in patients who stay on the drug. The authors do not specify clear reasons for these high discontinuation rates.

Absence of functional parameters and quality of life

Mortality and readmissions are not the only essential factors in heart failure. Other parameters, such as quality-of-life tests, the 6-minute walk test, or the N-terminal probrain natriuretic peptide (NT-proBNP) level, could strengthen the potential benefits of digitoxin and would have allowed us to compare DIGIT-HF with the most recent heart failure trials.

TRANSLATING DIGIT-HF TO EVERYDAY PRACTICE

Digoxin carries a class 2b (weak) recommendation, level of evidence B (moderate) for patients with HFrEF whose symptoms persist despite guideline-directed medical therapy in guidelines from the American College of Cardiology and the European Society of Cardiology.[26,27] In this same setting, digitoxin offers an additional benefit by reducing the risk of death or first hospitalization for heart failure in patients with symptomatic HFrEF despite guideline-directed medical therapy.[1]

Other therapies complementary to guideline-directed medical therapy, such as ivabradine (which has a 2a recommendation) or vericiguat (2b recommendation), can help selected patients, but each has practical limitations. Ivabradine is ineffective in patients with atrial fibrillation and is only indicated if the heart rate is higher than 70 beats per minute despite optimal use of beta-blockers.[26,27] Vericiguat, for patients with recent worsening, may be limited by hypotension, and its benefit appears to diminish with very high levels of NT-proBNP.[26,27]

Given these limitations, digitoxin might be considered an additional option. **Figure 2** summarizes a potential new therapeutic approach if the benefits of digitoxin are confirmed in the near future.[1,20,26,27]

Finally, given its inotropic properties, neurohormonal effects, and pharmacokinetic profile, digitoxin may benefit patients who cannot tolerate guideline-directed medical therapy because of hypotension or worsening renal function, common problems in real-world clinical practice.[1,10,21]

UNANSWERED QUESTIONS

DIGIT-HF brings digitoxin back into the field of heart failure care. But questions remain:

Is digitoxin better than digoxin? The 2 drugs have never been directly compared, and lacking such a trial, the DIGIT-HF results cannot be extrapolated to other digitalis compounds.[1]

Does digitoxin truly benefit all subgroups? Although the benefit of digitoxin was consistent across subgroups, the study lacked sufficient statistical power to confirm these findings in all subgroups, leaving uncertainty in specific populations.[1]

Is digitoxin truly safe? Although low in absolute terms, the incidence of serious adverse events was higher in the digitoxin group.[1] Further research is needed to define its safety profile, especially in patients with comorbidities.

Does digitoxin offer an advantage in patients with atrial fibrillation? Given evidence suggesting

that beta-blockers are more beneficial in patients with HFrEF who are in sinus rhythm than in those with atrial fibrillation,[28,29] digitoxin may offer an opportunity in the latter group, especially if they have serious symptoms. This hypothesis will need to be shown in future studies.

FUTURE IMPLICATIONS

The good results from DIGIT-HF are exciting. Following DIGIT-HF, digitoxin might be considered in future guidelines, alongside digoxin. Furthermore, its use is expected to increase in countries where it is available. Its low cost also makes market entry in other countries plausible. However, we need more evidence from clinical trials and real-world experience regarding the use of digitoxin in routine clinical practice.

The DECISION trial (Digoxin Evaluation in Chronic Heart Failure: Investigational Study in Outpatients in the Netherlands),[30] testing low-dose digoxin in heart failure, is ongoing. This evidence will contribute to defining more precisely the role of digitalis in the current treatment of heart failure.

DISCLOSURES

Dr. Solé-González disclosed teaching and speaking for Bayer and Novartis and other activities from which remuneration is received or expected for Rovi. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Bavendiek U, Großhennig A, Schwab J, et al.** Digitoxin in patients with heart failure and reduced ejection fraction. N Engl J Med 2025; 393(12):1155–1165. doi:10.1056/NEJMoa2415471
2. **Khan MS, Shahid I, Bennis A, Rakisheva A, Metra M, Butler J.** Global epidemiology of heart failure. Nat Rev Cardiol 2024; 21(10):717–734. doi:10.1038/s41569-024-01046-6
3. **Writing Committee Members.** HF STATS 2025: heart failure epidemiology and outcomes statistics an updated 2025 report from the Heart Failure Society of America. J Card Fail 2026; 32(2):439–498. doi:10.1016/j.cardfail.2025.07.007
4. **Hauptman PJ, Kelly RA.** Digitalis. Circulation 1999; 99(9):1265–1270. doi:10.1161/01.cir.99.9.1265
5. **Digitalis Investigation Group.** The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997; 336(8):525–533. doi:10.1056/NEJM199702203360801
6. **Crane AD, Militello M, Faulx MD.** Digoxin is still useful, but is still causing toxicity. Cleve Clin J Med 2024; 91(8):489–499. doi:10.3949/ccjm.91a.23105
7. **Gazzaniga G, Menichelli D, Scaglione F, Farcomeni A, Pani A, Pastori D.** Effect of digoxin on all-cause and cardiovascular mortality in patients with atrial fibrillation with and without heart failure: an umbrella review of systematic reviews and 12 meta-analyses. Eur J Clin Pharmacol 2023; 79(4):473–483. doi:10.1007/s00228-023-03470-y
8. **van Veldhuisen DJ, Bauersachs J.** Digitalis in heart failure: declining use and ongoing outcome trials. Eur Heart J 2023; 44(22): 1976–1978. doi:10.1093/eurheartj/ehad185
9. **DailyMed.** DIGOX, digoxin tablet. Updated June 29, 2018. dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7b64ac77-71a5-47e3-976e-9b5d7f7eb530. Accessed March 13, 2026.
10. **Iisalo E.** Clinical pharmacokinetics of digoxin. Clin Pharmacokinet 1977; 2(1):1–16. doi:10.2165/00003088-197702010-00001
11. **National Center for Biotechnology Information.** PubChem Compound Summary for CID 2724385, Digoxin. pubchem.ncbi.nlm.nih.gov/compound/Digoxin. Accessed March 13, 2026.
12. **National Center for Biotechnology Information.** PubChem Compound Summary for CID 441207, Digitoxin. pubchem.ncbi.nlm.nih.gov/compound/Digitoxin. Accessed March 13, 2026.
13. **Belz GG, Breithaupt-Grögler K, Osowski U.** Treatment of congestive heart failure—current status of use of digitoxin. Eur J Clin Invest 2001; 31(suppl 2):10–17. doi:10.1046/j.1365-2362.2001.0310s2010.x)
14. **Pauli-Magnus C, Mürdter T, Godel A, et al.** P-glycoprotein-mediated transport of digitoxin, alpha-methyldigoxin and beta-acetyldigoxin. Naunyn Schmiedebergs Arch Pharmacol 2001; 363(3):337–343. doi:10.1007/s002100000354
15. **Bavendiek U, Berliner D, Dávila LA, et al.** Rationale and design of the DIGIT-HF trial (DIGitoxin to Improve ouTcomes in patients with advanced chronic Heart Failure): a randomized, double-blind, placebo-controlled study. Eur J Heart Fail 2019; 21(5):676–684. doi:10.1002/ejhf.1452
16. **Bavendiek U, Thomas NH, Berliner D, et al.** DIGitoxin to Improve ouTcomes in patients with advanced chronic Heart Failure (DIGIT-HF): baseline characteristics compared to recent randomized controlled heart failure trials. Eur J Heart Fail 2025; 27(7): 1224–1233. doi:10.1002/ejhf.3679
17. **McMurray JJ, Packer M, Desai AS, et al.** Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014; 371(11):993–1004. doi:10.1056/NEJMoa1409077
18. **McMurray JJV, Solomon SD, Inzucchi SE, et al.** Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019; 381(21):1995–2008. doi:10.1056/NEJMoa1911303
19. **Packer M, Anker SD, Butler J, et al.** Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020; 383(15):1413–1424. doi:10.1056/NEJMoa2022190
20. **Butler J, McMullan CJ, Anstrom KJ, et al.** Vericiguat in patients with chronic heart failure and reduced ejection fraction (VICTOR): a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet 2025; 406(10510):1341–1350. doi:10.1016/S0140-6736(25)01665-4
21. **Bavendiek U, Großhennig A, Schwab J, et al.** Simple and safe digitoxin dosing in heart failure based on data from the DIGIT-HF trial. Clin Res Cardiol 2023; 112(8):1096–1107. doi:10.1007/s00392-023-02199-z
22. **Aguirre Dávila L, Weber K, Bavendiek U, et al.** Digoxin-mortality: randomized vs. observational comparison in the DIG trial. Eur Heart J 2019; 40(40):3336–3341. doi:10.1093/eurheartj/ehz395
23. **Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM.** Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA 2003; 289(7):871–878. doi:10.1001/jama.289.7.871
24. **Ahmed A, Rich MW, Love TE, et al.** Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. Eur Heart J 2006; 27(2):178–186. doi:10.1093/eurheartj/ehi687
25. **Bavendiek U, Berliner D, Thomas NH, et al.** The DIGIT-HF trial: key amendments of study design. Eur J Heart Fail 2025; 27(3):606–608. doi:10.1002/ejhf.3575
26. **McDonagh TA, Metra M, Adamo M, et al.** 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021; 42(36):3599–3726. doi:10.1093/eurheartj/ehab368
27. **Heidenreich PA, Bozkurt B, Aguilar D, et al.** 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2022; 79(17):e263–e421. doi:10.1016/j.jacc.2021.12.012

28. **Kotecha D, Holmes J, Krum H, et al.** Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet 2014; 384(9961):2235–2243. doi:10.1016/S0140-6736(14)61373-8
29. **Kotecha D, Flather MD, Altman DG, et al.** Heart rate and rhythm and the benefit of beta-blockers in patients with heart failure. J Am Coll Cardiol 2017; 69(24):2885–2896. doi:10.1016/j.jacc.2017.04.001
30. **van Veldhuisen DJ, Rienstra M, Mosterd A, et al.** Efficacy and safety of low-dose digoxin in patients with heart failure. Rationale and design of the DECISION trial. Eur J Heart Fail 2024; 26(10): 2223–2230. doi:10.1002/ejhf.3428

Address: *Enmanuel A. Leiva-Murillo, MD, Department of Internal Medicine, Hospital Clínic, Carrer de Villarroel, 170, L'Eixample, 08036 Barcelona, Spain; ealeiva@clinic.cat*