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ARTICLE

Filling the void: digoxin and the first randomized evidence in rheumatic heart disease

Viana Copeland,[1,2] Andrew J.S. Coats,[3] Javed Butler,[4,5] Stefan Anker[6-8]

[1]Olga and Lev Leviev Heart Center at Sheba Medical Center, Ramat Gan, Israel; [2]Faculty of Medical and Health Sciences, Tel-Aviv University, Israel; [3]Heart Research Institute, University of Sydney, NSW, Australia; [4]Baylor Scott and White Research Institute, Dallas, TX, USA; [5]Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA; [6]Department of Cardiology (CVK) of German Heart Center, Charité, Berlin, Germany; [7]German Centre for Cardiovascular Research (DZHK), Berlin, Germany; [8]Charité Universitätsmedizin, Berlin, Germany

Abstract

The Digoxin in Rheumatic Heart Disease (Dig-RHD) trial marks an important shift in rheumatic heart disease by replacing long-standing therapeutic assumption with direct randomized evidence. In a condition affecting predominantly young patients in low- and middle-income countries, practice has often relied on extrapolation from non-valvular heart failure populations despite clear differences in disease biology, treatment access, and clinical context. By reducing heart failure events in symptomatic patients, Dig-RHD suggests that the value of digoxin in RHD may lie in preventing deterioration and preserving stability, rather than in mortality reduction alone. This distinction matters because worsening heart failure in RHD represents functional decline, recurrent healthcare use, and loss of clinical reserve in settings where advanced interventions may be delayed or unavailable. The findings support reassessment the role of digoxin in symptomatic RHD while underscoring the need to define optimal timing, rhythm-specific effects, disease severity, and background therapy. More broadly, Dig-RHD shows that rigorous outcome trials in RHD are feasible and necessary for a population still under-represented in cardiovascular research.

Key words: Dig-RHD trial; rheumatic heart disease; digoxin; cardiac glycosides.

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**Correspondence to: Viana Copeland, Chaim Sheba Medical Center, Leviev Heart Center University of Tel Aviv, The Grey Faculty of Medicine Ramat Gan, Israel.*
E-mail: vianacopeland@gmail.com

Introduction

Rheumatic heart disease (RHD) remains an important cause of preventable cardiovascular mortality, disproportionately affecting young people in low- and middle-income countries (LMICs).[1-3] Yet for patients with established disease and symptomatic heart failure (HF), the therapeutic evidence base has been remarkably thin.[3-5]

This gap in RHD-specific data has frequently necessitated extrapolation from non-valvular HF populations, despite fundamental differences in underlying pathophysiology.[6-9] This divergence underscores a critical principle where therapeutic effects observed in one cardiovascular context cannot be assumed to translate to another without direct evidence.

Digoxin occupies an uneasy position within this vacuum. Widely used in RHD, particularly in patients with AF or advanced symptoms, yet unsupported by randomized evidence, digoxin's low cost, global availability, and physiological rationale make it especially attractive in resource-limited settings, precisely where RHD burden is greatest.[3] The Digoxin in Rheumatic Heart Disease (Dig-RHD) trial was designed to address this deficit.[10,11]

Materials and Methods

Dig-RHD is the first randomized trial powered for clinical outcomes in symptomatic RHD. Results were presented by senior author Professor Ganesan Karthikeyan at the ACC Scientific Sessions, New Orleans, March 30, 2026.

The trial enrolled 1769 adults with echocardiographically confirmed RHD across 12 academic medical centers in India between February 2022 and August 2024. Patients were randomized 1:1 to digoxin or placebo on a background of standard care. Eligible patients had clinically symptomatic HF, AF, or

both, with additional enrollment of patients already receiving digoxin at their treating physician's discretion. The primary endpoint was a composite of all-cause death and new-onset or worsening HF at two years. Secondary endpoints included HF-related death, hospitalization for HF, sudden death, and quality of life assessed by the EQ-5D-5L.[10,11]

Patient characteristics and key findings

The predominantly female cohort (71%) was young (mean age 46 years) with a mean follow-up of 2.1 years and a low comorbidity burden. Valvular disease was advanced with most patients having moderate-to-severe mitral stenosis, with a mean mitral valve area of 1.2 cm^2. Prior percutaneous mitral valvuloplasty had been performed in 35% of patients. Furthermore, nearly 90% were symptomatic (NYHA class II-IV), predominantly class II (79%), while over 90% were receiving diuretics. AF or flutter was present in 70%, and approximately one-third were already taking digoxin at randomization.

The primary composite endpoint occurred in 31.4% of patients assigned to digoxin *versus* 35.5% in the placebo group, corresponding to an 18% relative risk reduction (HR 0.82, 95% CI 0.70-0.97). This was paralleled by a significant reduction in new or worsening HF events (HR 0.82, 95% CI 0.69-0.98). There was no significant difference in all-cause mortality between groups (HR 0.94, 95% CI 0.70-1.26).

Key takeaways

Clinical interpretation

These findings are clinically consequential, particularly when considered in the context of the population studied. The trial did not enroll patients with advanced or refractory HF, as most were classified as NYHA class II.[11] This reflects the typical ambulatory patient with symptomatic RHD encountered across endemic regions, clinically stable, yet experiencing progressive valvular dysfunction and accumulating symptoms.[3,12,13]

The demonstration of benefit in this relatively stable cohort is of importance. It suggests that the therapeutic window for digoxin in RHD is wider than traditionally assumed and need not be restricted to overt decompensation.[3] More importantly, it shifts attention to timing, suggesting earlier intervention in the disease course, before functional decline, may yield meaningful clinical benefit. Whether similar effects extend to more advanced disease remains uncertain, but the present data support earlier, rather than deferred, use in symptomatic patients with preserved functional reserve (Figure 1).

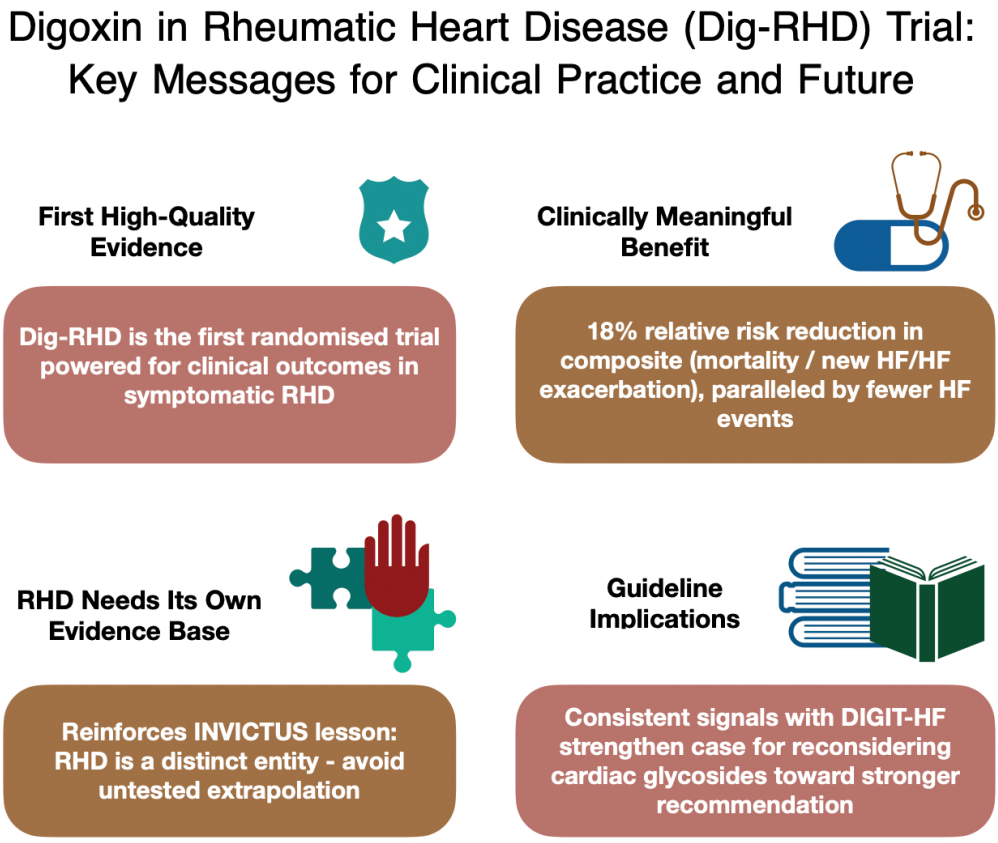

Figure 1. Digoxin in Rheumatic Heart Disease (Dig-RHD) trial. Key messages for clinical practice and future: summary of the Dig-RHD trial highlighting its role as the first high-quality evidence for digoxin in symptomatic RHD.

Treatment gaps and real-world practice

The background medical therapy profile warrants equal attention. Diuretic use was near-universal and beta-blocker uptake substantial, yet ACE inhibitors or ARBs were used infrequently, and SGLT2i virtually absent. This pattern reflects a persistent gap between guideline-directed therapy and real-world practice in RHD-associated HF, shaped by access, cost, and competing clinical priorities in LMIC settings.[12-16]

This gap extends beyond RHD. Registry data consistently document lower rates of renin-angiotensin system blockade and mineralocorticoid receptor antagonist use in valvular versus non-valvular HF cohorts,[17] though whether this reflects appropriate clinical caution or genuine undertreatment is not always clear. The distinction matters: underuse driven by uncertainty demands a different response from underuse driven by inertia or access barriers. Much of contemporary HF management derives from non-valvular trials, and its applicability to RHD remains uncertain.[13]

Guideline implications and future directions

Cardiac glycosides have long occupied an ambiguous position in clinical guidelines. Though acknowledged for reducing symptoms and hospitalizations, they have been persistently downgraded over concerns about safety and the absence of mortality benefit.[18-21] For patients with RHD specifically, this ambiguity was compounded by a more fundamental problem, there was no randomized evidence. Clinicians prescribing digoxin in this population were doing so based on physiological reasoning, clinical habit, drug availability, and data drawn from entirely different disease contexts. Dig-RHD changes that. This trial provides the first direct randomized evidence, and concordant findings from other studies of cardiac glycosides support the biological plausibility of the results.

Whether this warrants formal guideline reclassification is a question that cannot be dismissed. The case against is not trivial as no trial has demonstrated a mortality benefit, concerns about differential risk in females and patients with renal impairment remain incompletely resolved,[18-21] and whether benefit persists above fully optimized quadruple therapy is unknown. The ongoing DECISION trial will provide prospectively collected data in a contemporary HF population and should inform any definitive revision.[22] If concordant, the combined evidence base could constitute a foundation for a unified class recommendation covering both agents across valvular and non-valvular HF would be difficult to resist.

What Dig-RHD does not fully resolve is the question of digoxin in the setting of AF, whether arising in the context of RHD or as a broader clinical problem. AF is the most common sustained cardiac arrhythmia worldwide, affecting tens of millions of patients and carrying substantial risks of stroke, HF, and death.[7,23] In RHD specifically, AF is present in many patients with advanced disease and is itself a driver of hemodynamic deterioration and adverse outcomes.[1-3] Yet the role of cardiac glycosides in AF has remained contested, with prior observational data raising unresolved concerns about mortality risk in this rhythm context.[7-9,18-21] Whether the benefit observed in Dig-RHD is altered by AF status remains both open and consequential. A future analysis of outcomes by AF status within Dig-RHD, interpreted alongside the broader and expanding evidence base for cardiac glycosides across populations and rhythm contexts, will be important for informing definitive guidance in this subgroup. That work is warranted, feasible, and Dig-RHD has made it worth doing (Figure 2).

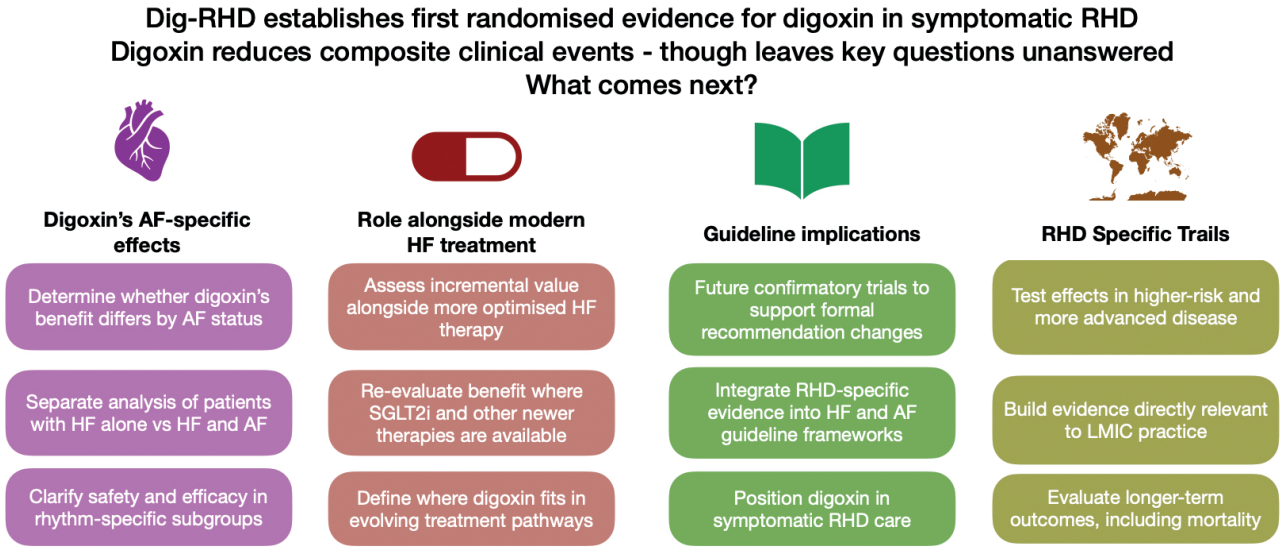

Figure 2. Future directions After Digoxin in Rheumatic Heart Disease (Dig-RHD) trial. Proposed framework summarizing the key next steps arising from Dig-RHD.

Limitations

Several limitations merit acknowledgment. The composite primary endpoint included worsening HF events not requiring hospitalization, a pragmatic choice but one that limits comparability with trials in high-income settings. The absence of mortality benefit leaves open whether longer follow-up or higher-risk populations would yield different results. Finally, the near absence of SGLT2i and neprilysin inhibitors reflects current prescribing realities in LMICs but constrains inference about the incremental value of digoxin atop fully optimized contemporary therapy, an increasingly relevant question as access to these agents expands. Indeed, it is known that the needs of patients with common first world conditions such as heart failure are not well understood in many major guidelines and as RHD based HF is particularly common in South Asia these results are of major relevance to those regions.

Conclusions

The Dig-RHD trial represents a significant advance in the evidence base for the management of rheumatic heart disease, a condition that continues to impose a substantial global health burden yet remains underrepresented in randomized clinical research. By demonstrating a reduction in the composite events, this study provides the first high-quality evidence supporting the clinical benefit of digoxin in symptomatic RHD populations. The broader significance extends beyond a single drug. Taken alongside previous trials, the findings raise serious questions about whether cardiac glycosides deserve formal reclassification in HF guidelines, particularly among AF patients.

Dig-RHD demonstrates that rigorous trials in this population are feasible and that a meaningful evidence base can be built where one has not previously existed. For clinicians caring for patients with RHD in resource-limited settings, it provides what no prior trial has: a direct answer grounded in the patients and practice realities they know. That is a significant achievement, and it should not be the last.

Authors' contributions

All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

VC reports an expected patent in the field of cardiovascular disease detection in women using mammography. JB reports consulting fees from Abbott, Adaptyx, Amgen, Anumana, AskBio, AstraZeneca, Bayer, Berlin Heals, Boehringer Ingelheim, Boston Scientific, BridgeBio, Bristol Myers Squibb, Cardiac Dimension, CSL Vifor, Chugai, CVRx, Cytokinetics, Daiichi Sankyo, Daxor, Diastol, Eccogene, Edgewise, Edwards, Eikonizo, Element Sciences, Faraday, Idorsia, Impulse Dynamics, Imbria, Intellia, Inventiva, Levator, Lexicon, Eli Lilly, Kardigan, Mankind, Medtronic, Merck, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Prolaio, Pulnovo, Recordati, Regeneron, Renibus, Reprieve, Roche, Rycarma, Saillent, Salamandra, Salubris, SC Pharma, Servier, SQ Innovation, Scirent, Secretome, Sequanna, Transmural, TekkunLev, Tenex, Thryv, Tricog, Ultromic, Vera, Zealand Pharma, and Zoll. The other authors declare no conflicts of interest.

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Ethics approval and consent to participate

Not required.

Availability of data and materials

The datasets used and/or analyzed during the current study are available upon reasonable request from the corresponding author.

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