ORIGINAL ARTICLE

Cardiac Glycosides in Heart Failure With Reduced Ejection Fraction in the Era of Contemporary Guideline-Directed Medical Therapy: A Systematic Review and Meta-Analysis

Glucósidos cardíacos en insuficiencia cardíaca con fracción de eyección reducida en la era del tratamiento médico dirigido por guías clínicas: revisión sistemática y metaanálisis

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ABSTRACT

Background: Heart failure with reduced left ventricular ejection fraction remains a major clinical challenge despite widespread implementation of contemporary guideline-directed medical therapy (GDMT). Cardiac glycosides, historically used for their inotropic and neurohormonal effects, declined in use following the DIG trial (1997), which demonstrated a reduction in HF hospitalizations (HFH) with no mortality benefit. However, that trial predated modern GDMT and device therapy. The recent DIGIT-HF trial (2025) has renewed interest in this drug class by suggesting a potential benefit of digitoxin in optimally treated patients.
Objective: We aimed to evaluate the impact of cardiac glycosides in patients with heart failure with reduced left ventricular ejection fraction, (≤ 40%, HFrEF) and mildly reduced ejection fraction (41%-49%, HFmrEF) receiving contemporary GDMT.
Methods: Four databases were systematically searched for randomized trials (RCTs) or propensity score-matched cohort studies recruiting adults with HFrEF and HFmrEF from the year 2000 onward, comparing cardiac glycosides with standard care or placebo and reporting at least one primary outcome (all-cause mortality or HFH). Data were pooled using an inverse-variance random-effects model.
Results: Six studies met inclusion criteria: one RCT (DIGIT-HF) and five propensity score-matched observational cohorts (2000-2023) studies, comprising around 4500 cardiac glycoside users and 5500 controls. DIGIT-HF evaluated digitoxin whereas the remaining studies assessed digoxin. Pooled analysis demonstrated no significant difference in all-cause mortality (HR 1.01 [95% CI 0.67-1.53]; $I^2 = 77\%$). Cardiac glycosides were associated with a significant reduction in HFH (HR 0.84 [95% CI 0.76-0.93]; $I^2 = 0\%$). No significant effect was observed for all-cause hospitalizations (HR 0.95 [95% CI 0.83-1.10]; $I^2 = 53\%$).
Conclusion: In the post-2000 era, cardiac glycosides may confer clinical benefit by reducing HFH in patients with LVEF < 50% receiving contemporary GDMT. However, interpretation of mortality outcomes is limited by substantial heterogeneity. This study underscores the crucial need for contemporary RCTs to clarify the role of cardiac glycosides as adjunctive therapy in contemporary management of these patients.

Key words: Systematic review - Meta-analysis - Heart failure - Reduced ejection fraction- Cardiac glycosides - Digitoxin - Digoxin

RESUMEN

Introducción: La insuficiencia cardíaca con fracción de eyección reducida continúa siendo un importante reto clínico a pesar del uso generalizado del tratamiento médico dirigido por guías clínicas (TMDG). El uso de glucósidos cardíacos, empleados históricamente por sus efectos inotrópicos y neurohormonales, disminuyó después del ensayo DIG (1997), en el que se demostró una reducción de las hospitalizaciones por IC (HIC), pero ningún beneficio respecto de la mortalidad. Sin embargo, ese ensayo fue anterior al TMDG y al tratamiento con dispositivos. El reciente ensayo DIGIT-HF (2025) ha renovado el interés por esta clase de fármacos al indicar un posible beneficio de la digitoxina en los pacientes tratados de forma óptima.
Objetivo: Nuestro objetivo fue evaluar el efecto de los glucósidos cardíacos en pacientes con insuficiencia cardíaca con fracción de eyección ventricular izquierda (FEVI) reducida (≤40 %, ICFEr) o levemente reducida (41 %-49 %, ICFElr) que reciben TMDG.

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Métodos: Se realizó una búsqueda sistemática en cuatro bases de datos para encontrar ensayos controlados aleatorizados o estudios de cohortes emparejados por índice de propensión en los que se reclutaran adultos con ICFEr o ICFElr a partir del año 2000, se compararan los glucósidos cardíacos con la atención habitual o el placebo, y se informara al menos un criterio de valoración principal (mortalidad por cualquier causa o HIC). Los datos se combinaron mediante el uso de un modelo de efectos aleatorios de varianza inversa.
Resultados: Seis estudios cumplieron los criterios de inclusión: un ensayo controlado aleatorizado (DIGIT-HF) y cinco estudios de cohortes observacionales emparejadas por índice de propensión (2000-2023). Estos estudios incluyeron alrededor de 4500 pacientes que recibían glucósidos cardíacos y 5500 controles. En el ensayo DIGIT-HF se evaluó la digitoxina, y en los demás estudios la digoxina. El análisis combinado no mostró diferencias significativas en cuanto a la mortalidad por cualquier causa (HR 1,01; IC 95% 0,67-1,53; I^2 = 77 %). Los glucósidos cardíacos se asociaron con una reducción significativa de la HIC (HR 0,84; IC 95% 0,76-0,93; I^2 = 0 %). No se observó ningún efecto significativo en cuanto a las hospitalizaciones por cualquier causa (HR 0,95; IC 95% 0,83-1,10; I^2 = 53 %).
Conclusión: En la era posterior al año 2000, los glucósidos cardíacos pueden aportar beneficios clínicos al reducir la HIC en pacientes con IC y FEVI < 50 % que reciben TMDG. Sin embargo, la interpretación de los resultados de mortalidad se ve limitada por la considerable heterogeneidad. En este estudio se destaca la necesidad crucial de realizar ensayos controlados aleatorizados modernos para dilucidar el papel que desempeñan los glucósidos cardíacos como terapia complementaria en estos pacientes..

Palabras clave: Infarto de miocardio - Intervención coronaria percutánea - Mortalidad - Registro

INTRODUCTION

Heart failure with reduced ejection fraction (HFrEF) remains a major global health burden despite remarkable advances in drug therapies and device-based therapies. (1, 2) According to the Heart Failure Association (HFA) Atlas, the median annual number of HF hospitalizations (HFH) in Europe is 2671 per million inhabitants, underscoring the magnitude of this condition. (2, 3) Given its clinical and economic impact, effective strategies to optimize HF management have become increasingly necessary.

The widespread implementation of contemporary guideline-directed medical therapy (GDMT), including angiotensin receptor-neprilysin inhibitors (ARNIs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose linked transporter-2 inhibitors (SGLT2i), has significantly improved survival and reduced hospitalizations over the past two decades. (1) Nevertheless, a substantial proportion of patients continue to experience recurrent decompensations, frequent hospitalizations, and progressive functional decline, highlighting the need for further therapeutic optimization. (1, 2)

Cardiac glycosides have occupied a distinctive role in the management of HF for two centuries. (4) By inhibiting the Na^+/K^+-ATPase pump, these agents increase intracellular calcium availability, thereby enhancing myocardial contractility. Their vagotonic effects also provide rate control in patients with concomitant atrial fibrillation (AF). (5)

The landmark Digitalis Investigation Group (DIG) trial published in 1997 demonstrated that digoxin reduced HFH but did not confer a survival benefit. (6) However, subsequent observational studies and meta-analyses have yielded conflicting results, with some suggesting a potential association between digoxin use and increased mortality, particularly among patients with AF, leading to a progressive decline in its clinical use. (7-12) In contrast, the RATE-AF trial suggested that digoxin may remain a safe and effective option for rate control in selected patients with permanent AF, and demonstrated greater cost-effectiveness than beta-blockers and fewer adverse events and hospitalizations, without compromising quality of life. (13) Importantly, the DIG trial was conducted more than two decades ago, when background HF therapy was limited to ACEI and diuretics. Its findings may therefore not reflect outcomes in the era of contemporary GDMT and device-based therapies, including implantable cardioverter-defibrillators (ICD) and cardiac resynchronization therapy (CRT). (1, 14, 15) Furthermore, the trial had relevant methodological limitations, including substantial crossover to digoxin in the placebo arm, which may have attenuated treatment differences. (6) Post hoc analyses suggested worse outcomes among patients with higher serum digoxin concentrations, raising concerns about dose–response effects and the narrow therapeutic range of the drug. (16, 17)

Growing evidence has renewed interest in this therapeutic class. In particular, the DIGIT-HF trial, which evaluated digitoxin versus placebo in patients with chronic HFrEF receiving optimal GDMT, demonstrated a significant reduction in the composite endpoint of all-cause mortality or HFH (hazard ratio [HR]: 0.82 [95% CI 0.69-0.98]; p=0.03) without an excess of major adverse events. (18) Notably, digitoxin, a glycoside structurally related to digoxin but with a longer half-life and more stable pharmacokinetics, may overcome some of the safety concerns historically associated with digoxin. (19-22)

Additionally, findings from a recent umbrella review of 12 meta-analyses suggest that previously reported mortality risks may have been confounded by indication bias, comorbidities, and outdated treatment contexts rather than reflecting a true causal relationship. (23)

Accordingly, the present meta-analysis aims to assess the effect of cardiac glycosides on clinical outcomes in patients with HFrEF and mildly reduced ejection fraction (HFmrEF) in the context of contemporary management by integrating data from modern

randomized controlled trials and propensity score-matched observational studies.

METHODS

Search Strategy

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (24) (Supplementary Table 1) and was registered in PROSPERO (CRD420251185713).

A systematic search of four electronic databases (Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, EMBASE, and PubMed) was performed between October 10 and November 10, 2025. The search strategy included studies containing the terms "heart failure" and "cardiac glycosides" and was restricted to publications from 2000 onward to ensure inclusion of contemporary cohorts, consistent with the first modern ACC/AHA HF guideline issued in 2001. (25) That guideline incorporated evidence from pivotal trials of the 1990s (MERIT-HF, CIBIS-II, RALES, and Val-HeFT), which established beta-blockers, MRAs, and ARBs as disease-modifying therapies in addition to ACE inhibitors. The full search strategies are provided in Supplementary Table 2. No language restrictions were applied. Reference lists of included studies were manually screened to identify additional eligible records.

Inclusion and Exclusion Criteria

Eligible studies included randomized controlled trials (RCTs) or propensity score-matched cohort studies evaluating the effects of cardiac glycosides in patients with HF with reduced or mildly reduced left ventricular ejection fraction (LVEF <50%). Studies were required to report at least one of the predefined primary outcomes.

The primary outcomes were all-cause mortality and HFH. The secondary outcomes included all-cause hospitalizations and cardiovascular mortality.

Studies were excluded if they lacked a control group, did not provide sufficient data for outcome extraction, evaluated alternative therapeutic interventions, had a recruitment period beginning before 2000, or focused exclusively on a specific subgroup of patients with HF with reduced or mildly reduced LVEF.

Study selection process and data collection

Two reviewers independently screened titles and abstracts after removing duplicate records. Full-text articles of potentially eligible studies were then independently assessed by the same reviewers for inclusion according to the predefined criteria. Disagreements at the full-text stage were resolved based on consensus. No automation tools were used during the screening process. All references were managed using EndNote X9 (Clarivate Analytics).

Three reviewers independently extracted data from each included study using a standardized data extraction form. Extracted information included study design, population characteristics, baseline demographics and clinical features, interventions, and outcomes. For studies with multiple publications, care was taken to avoid duplication of data.

Data were analyzed according to the intention-to-treat principle whenever applicable; otherwise, an as-treated approach was used. For observational studies, only results derived from propensity score-matched analyses were included. All relevant data are presented in the main text and supplementary material.

Quality assessment

Two authors independently assessed the risk of bias of the DIGIT-HF trial using the Cochrane Risk of Bias tool, version 1 (RoB 1). For observational studies, risk of bias was independently evaluated using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool. Publication bias was not formally assessed because fewer than ten studies were included, which limited the reliability of the funnel plot and Egger's regression test. According to established guidance, such tests lack statistical power when applied to a small number of studies and may yield misleading results.

Synthesis methods

A narrative synthesis was used to describe and interpret findings across studies, particularly when analysis was limited by heterogeneity in outcome reporting, study populations, or outcome definitions.

When appropriate, a meta-analysis was conducted using a random-effects model to account for anticipated between-study variability in treatment effects. Summary outcome measures were expressed as HR with the corresponding 95% confidence interval (95% CI), calculated using the inverse-variance method. HRs and incidence rate ratios were considered approximately equivalent estimates of relative risk under the assumption of proportional hazards and were therefore pooled together.

Statistical heterogeneity was assessed by visual inspection of forest plots and quantified using the I^2 statistic (<25% low, 25%-50% moderate, >50% high heterogeneity).

The meta-analysis was conducted using the software package Review Manager (RevMan), version 5.4.1 (The Cochrane Collaboration). All data were evaluated at a 5% significance level ($p<0.05$). Pooled HRs with 95% CI were recalculated for each scenario, and heterogeneity was reassessed using the I^2 statistic. A leave-one-out analysis was also performed for the primary outcomes to evaluate the robustness of the findings.

Ethical considerations

This study is a systematic review and meta-analysis that did not involve direct interaction with human participants or animals, therefore, no ethical approval or informed consent was required. However, the study was conducted in accordance with established standards for ethical scientific reporting outlined by the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org/).

RESULTS

Search results

Figure 1 shows the study selection process. After removing duplicates, 3301 records were screened according to the predefined eligibility criteria. Six studies met the inclusion criteria: the recently published RCT DIGIT-HF, (18) and five propensity score-matched observational studies: one multicenter (26) and four single-center studies. (27-30) The recruitment periods ranged from 2000 to 2023 and included approximately 4500 patients in the cardiac glycoside group and 5500 in the control group. Except for the DIGIT-HF trial, which investigated digitoxin, all other studies evaluated digoxin. Table 1 summarizes the main characteristics of the included studies.

Population characteristics

Table 2 summarizes the characteristics of the study population. Mean age ranged from 52 to 76 years, with a predominance of male participants (47-80%). Hypertension and diabetes mellitus were common comorbidities, reported in approximately 47-67% and 30-70% of patients, respectively, while dyslipidemia affected 36-72%. Atrial fibrillation or flutter was observed in 12-60% of participants, and chronic kidney disease in 5-47%. When reported, ischemic etiology accounted for approximately half of the cases. Baseline LVEF was markedly reduced across studies, generally ranging from 18% to 29%. Most patients were receiving contemporary GDMT. Beta-blocker use ranged from 43% to 97%, ACE inhibitor or ARB use ranged from 70% to 80%, whereas MRA use varied widely from 10 to 76%. SGLT2i use was reported only in DIGIT-HF trial, reaching up to 20%. Device therapy (ICD and/or CRT) ranged from 1% to 29%, reflecting temporal differences in the study design and population characteristics.

Primary outcomes

Across five studies, (18, 26, 28-30) the pooled estimate for all-cause mortality showed no significant difference between the cardiac glycoside therapy group and the control group (HR 1.01, 95% CI 0.67-1.53; I^2 = 77%), indicating substantial heterogeneity (Figure 2A). Cardiac glycoside therapy was associated with a significant reduction in HFH (HR 0.84, 95% CI 0.76-0.93; I^2 = 0%), with no evidence of heterogeneity (Figure 2B).

The leave-one-out sensitivity analysis demonstrated that the statistical significance of the pooled results for all-cause mortality remained robust across all iterations. For HFH, exclusion of the Georgiopoulou study (27) did not change the direction or statistical significance of the pooled effect estimate; however, exclusion of any of the remaining studies led to loss of statistical significance.

Secondary outcomes

For all-cause hospitalizations, there was no significant difference between treatment and control groups (HR

Fig. 1. Literature search flow chart

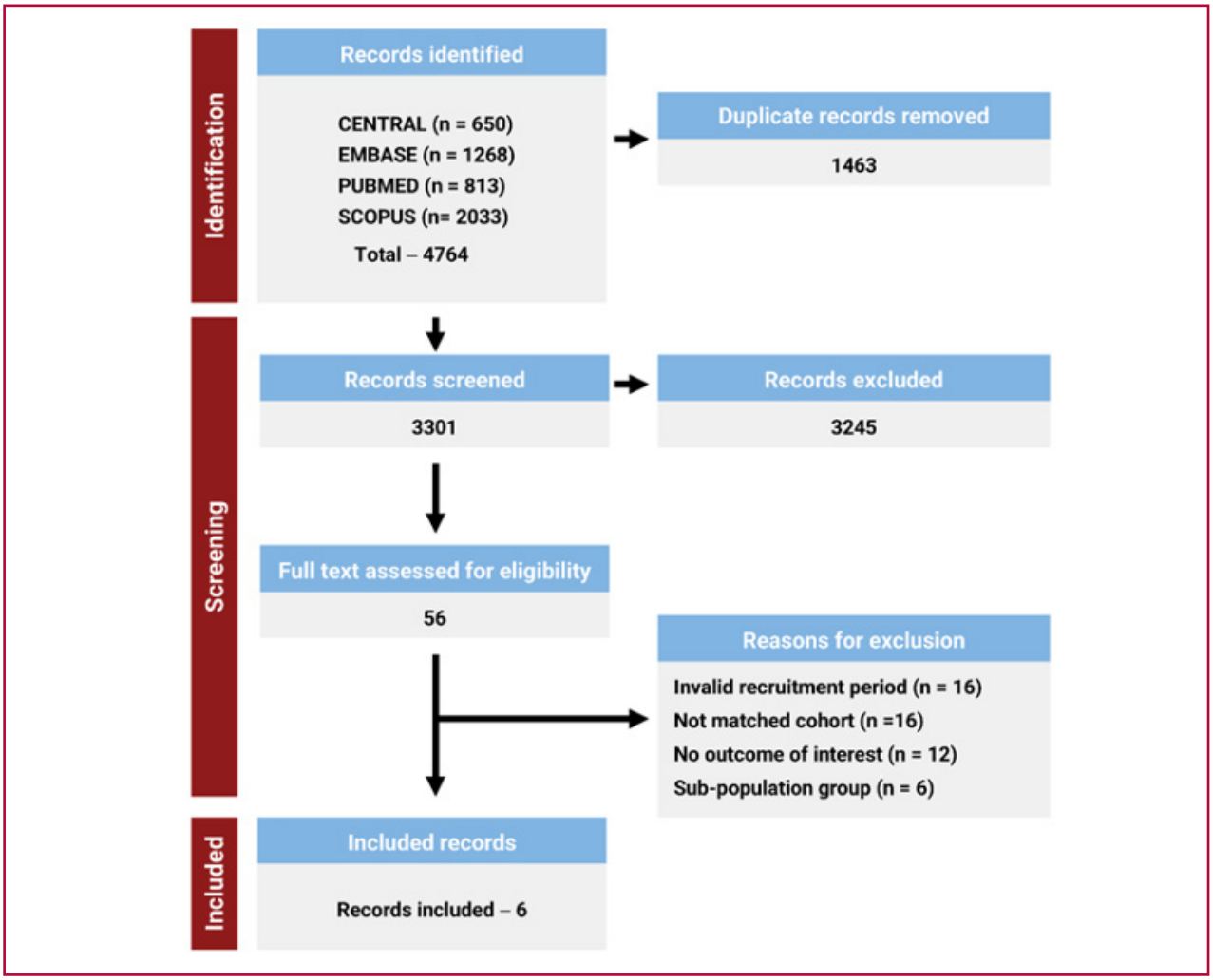


Table 1. Summary of included studies

Study	Inclusion and Exclusion Criteria	Patient Groups and Intervention	Primary outcome
DIGIT-HF (18) **2025** Austria, Germany, Serbia 65 Centers FU: 3 (0-110) years	**Inclusion Criteria:** - NYHA III-IV and a LVEF ≤40%; - NYHA II and a LVEF ≤30%; - GDMT for a duration of at least 6 months. **Exclusion Criteria:** - Recent MI/revascularization/device therapy, planned cardiac surgery, myocarditis or complex CHD; - advanced AV block or ventricular arrhythmia; - severe hepatic/renal disease, major electrolyte imbalance; - amiodarone use.	**Digitoxin** - 613 Control: - 599 **Recruitment period:** 2015-2023	- Composite of death or first HFH
Qamer, S. Z. et al. **2019 (26)** United States 259 Centers FU: 2.4 (0-6) years	**Inclusion Criteria:** - Medicare-linked OPTIMIZE-HF patients with LVEF ≤45%; - discharged alive. **Exclusion Criteria:** - Pre-admission digoxin use; - for sensitivity analysis: bradycardia (<60 bpm) or severe renal dysfunction (eGFR <15 mL/min/1.73m²).	**Digoxin** - 1531 Control: - 1531 **Recruitment period:** 2003-2004	- HF readmission at 30 days, 1 year, and 6 years.
Georgiopoulou et al. **2009 (27)** United States 1 Center FU: 2.3 (1.3-3.5) years	**Inclusion Criteria:** - Adults 18-70 years; - LVEF ≤30%; - NYHA II-IV, on maximally tolerated HF therapy; - referred for heart transplant evaluation. **Exclusion Criteria:** - CHD or planned cardiac surgery within 6 months.	**Digoxin** - 161 Control: - 161 **Recruitment period:** 2000-2006	- Death, urgent heart transplantation, or LVAD implantation.
Andrey, J. L. et al. **2011 (28)** Spain 1 Center FU: 3.8 (3.1-4.7) years	**Inclusion Criteria:** - ≥14 years;- newly diagnosed with HF according to Framingham criteria. **Exclusion Criteria:** - Patients non-permanent resident in the community of reference.	**Digoxin** - 1421 Control: - 1421 **Recruitment period:** 2001-2008	- All cause death
Freeman, J. V. et al. **2013 (29)** United States 1 Center FU: 2.5 (1.4-3.5) years	**Inclusion Criteria:** - Adults ≥21 years old with ≥1 inpatient admission with a primary discharge for HF or ≥3 outpatient encounters for HF; - LVEF ≤40%. **Exclusion Criteria:** - <12 months of continuous drug benefit before index date; - no follow-up after diagnosis; - prior cardiac/renal transplantation.		- All cause mortality
May Al-khateeb et al. **2017 (30)** Saudi Arabia 750+ Centers FU: 3.6 (1.6-6.3) years	**Inclusion Criteria:** - HF and LVEF < 45%. **Exclusion Criteria:** - If their vital status could not be verified.	**Digoxin** - 325 Control: - 750 **Recruitment period:** 2000-2015	- All-cause mortality

AV: atrio-ventricular; CHD: congenital heart disease; FU: follow-up; GDMT: guideline-directed medical therapy; HF: heart failure; HFH: heart failure hospitalization; LVEF: left ventricular ejection fraction; LVAD: left ventricular assist device; MI: myocardial infarction; NYHA: New York Heart Association.

0.95, 95% CI 0.83-1.10; $I^2 = 53\%$) (Figure 2C). Cardiovascular mortality was reported only in the DIGIT-HF trial (18) and showed no statistically significant difference between groups (HR 0.87, 95% CI 0.67-1.11).

Quality assessment

The DIGIT-HF trial was judged to have an unclear risk of bias (Supplementary Table 3). Among the five observational studies, three were judged to have a

Table 2. Summary of baseline characteristics of included patients

	DIGIT-HF (18)		Qamer et al (26)		Georgiopoulou et al. (27)		Andrey et al. (28)		Freeman et al. (29)		Al-khateeb et al. (30)	
	Digitoxin (n=613)	Control (n=599)	Digoxin (n=1531)	Control (n=1531)	Digoxin (n=161)	Control (n=161)	Digoxin (n=1421)	Control (n=1421)	Digoxin (n=529)	Control (n=2362)	Digoxin (n=325)	Control (n=750)
Age, years (mean ± SD)	66.0 ± 11.1	65.8 ± 11.4	75 ± 10	76 ± 10	51,9 ± 12,7	52,2 ± 11,9	70,7 ± 7,4	70,6 ± 7,3	68,2 ± 14,8	69,8 ± 14,4	54,7 ± 13,7	55,5 ± 13,4
Male: No./ total	491/613 (80.1%)	474/599 (79.1%)	856/1531 (55.9%)	855/1531 (55.8%)	112/161 (69.6%)	112/161 (69.6%)	663/1421 (46.7%)	665/1421 (46.8%)	354/529 (66.9%)	1583/2362 (67.0%)	231/325 (71%)	528/750 (70.4%)
HTN	-	-	987/1531 (64.5%)	949/1531 (62.0%)	-	-	668/1421 (47.0%)	665/1421 (46.8%)	316/529 (59.7%)	1577/2362 (66.8%)	194/325 (59.7%)	454/750 (60.5%)
T2DM	-	-	555/1531 (36.3%)	534/1531 (34.9%)	-	-	520/1421 (36.6%)	519/1421 (36.5%)	157/529 (29.7%)	806/2362 (34.1%)	226/325 (69.5%)	543/750 (72.4%)
DLP	377/613 (61.7%)	343/599 (57.6%)	-	-	-	-	511/1421 (36.0%)	513/1421 (36.1%)	329/529 (62.2%	1647/2362 (69.7%)	214/325 (65.8%)	536/750 (71.5%)
AF/AFL	169/613 (27.6%)	161/599 (26.9%)	552/1531 (36.1%)	554/1531 (36.2%)	60/161 (37.3%)	58/161 (36.0%)	849/1421 (59.7%)	850/1421 (59.8%)	209/529 (39.5%)	454/2362 (19.2%)	56/325 (17.2%)	91/750 (12.1%)
Tobacco use	-	-	248/1531 (16.2%)	267/1531 (17.4%)	-	-	435/1421 (30.6%)	435/1421 (30.6%)	-	-	102/325 (31.4%)	228/750 (30.4%)
Prior MI	-	-	-	-	-	-	-	-	42/529 (7.9%)	355/2362 (15.0%)	98/325 (30.2%)	266/750 (35.5%)
IHD	323/608 (53.1%)	310/592 (52.4%)	-	-	59/161 (36.6%)	65/161 (40.4%)	695/1421 (48.9%)	696/1421 (49.0%)	-	-	-	-
CKD	-	-	-	-	-	-	107/1421 (7.5%)	107/1421 (7.5%)	228/529 (43.1%)	1115/2362 (47.2%)	15/325 (4.6%)	41/750 (5.5%)
LVEF (%)	28.4 ± 6.9 (n=613)	28.9 ± 6.7 (n=599)	27 ± 10 (n=1531)	27 ± 10 (n=1531)	18.3 ± 8.7 (n=161)	18.7 ± 7.9 (n=161)	-	-	-	-	28.2 ± 6.4 (n=325)	25.9 ± 6.1 (n=750)
NYHA III/IV	432/613 (70.5%)	421/599 (70.3%)	-	-	-	-	-	-	-	-	23/325 (7.2%)	36/750 (4.8%)
ICD/CRT	-	-	98/1531 (6.4%)	101/1531 (6.6%)	43/161 (26.7%)	47/161 (29.2%)	-	-	4/529 (0.8%)	41/2362 (1.7%)	54/325 (16.6%)	108/750 (14.4%)
Guideline-directed Medical Therapy												
Beta-blocker	593/613 (96.7%)	567/599 (94.7%)	1120/1531 (73.2%)	1145/1531 (74.8%)	149/161 (92.5%)	147/161 (91.3%)	613/1421 (43.1%)	614/1421 (43.2%	209/529 (39.5%)	1205/2362 (51.0%)	313/325 (96.3%)	724/750 (96.5%)
ARNI	248/613 (40.5%)	231/599 (38.6%)	-	-	-	-	-	-	-	-	-	-
ACEi	222/613 (36.2%)	213/599 (35.6%)	-	-	117/161 (72.7%)	119/161 (73.9%)	-	-	196/529 (37.1%)	1112/2362 (47.1%)	262/325 (80.6%)	589/750 (78.5%)
ARB	113/613 (18.4%)	115/599 (19.2%)	-	-	34/161 (21.1%)	33/161 (20.5%)	-	-	40/529 (7.6%)	236/2362 (10.0%)	115/325 (35.4%)	282/750 (37.6%)
ACEi or ARB	-	-	1125/1531 (73.5%)	1095/1531 (71.5%	-	-	1119/1421 (78.7%)	1120/1421 (78.8%)	-	-	-	-
MRA	466/613 (76.0%)	458/599 (76.5%)	319/1531 (20.8%)	317/1531 (20.7%)	73/161 (45.3%)	74/161 (46.0%)	146/1421 (10.3%)	147/1421 (10.3%)	-	-	245/325 (75.5%)	553/750 (73.7%)
SGLT2 inhibitor	121/613 (19.7%)	113/599 (18.9%)	-	-	-	-	-	-	-	-	-	-

ACEi, angiotensin-converting enzyme inhibitor; AF/AFL, atrial fibrillation/flutter; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; DLP, dyslipidemia; HTN, hypertension; ICD, implantable cardioverter-defibrillator; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SD: standard deviation; SGLT2, sodium-glucose linked cotransporter 2; T2DM, type 2 diabetes mellitus.

moderate risk of bias and two a high risk of bias (Supplementary Table 4).

DISCUSSION

Mortality and heart failure hospitalizations

This meta-analysis provides an updated assessment of cardiac glycosides in patients with HF, LVEF < 50% and contemporary GDMT. Consistent with the original DIG trial, our findings suggest that cardiac glycosides may reduce HFH without a consistent impact on all-cause mortality.

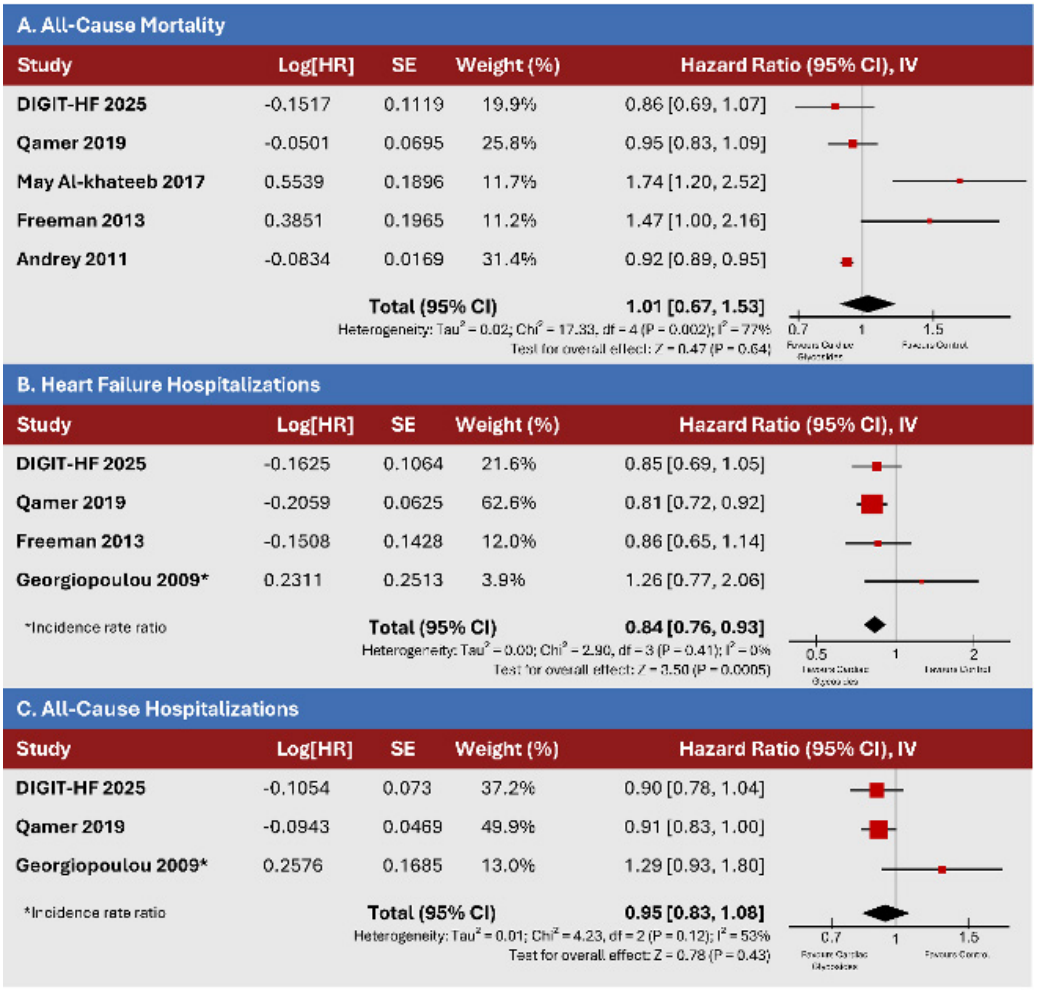
Despite pooled available data, definitive conclusions regarding the effect of cardiac glycosides on all-cause mortality cannot be drawn from the current evidence base. The meta-analytic estimates for mortality are undermined by substantial between-study heterogeneity and the limited number of contemporary high-quality trials. These limitations increase the risk of imprecise and potentially biased estimates, thereby reducing confidence in any pooled mortality effect.

Importantly, the reduction in HFH associated with cardiac glycosides was a consistent finding across heterogeneous study populations. This reproducible finding observed despite variability across studies suggests a robust signal for symptomatic improvement and event reduction that appears less sensitive to between-study differences than mortality outcomes. Nevertheless, the magnitude and clinical implications of HFH reduction should be cautiously interpreted.

Key sources of heterogeneity

Although the included studies generally reflect populations treated with contemporary pharmacotherapy,

Fig. 2. Meta-analysis of cardiac glycoside therapy in heart failure patients with reduced ejection fraction, including randomized controlled trials and propensity-matched cohort studies. Hazard ratios (HR) and incidence rate ratios (IRR) were considered approximately equivalent effect measures and were pooled using a random-effects model with inverse-variance weighting. Forest plots display pooled estimates and 95% confidence intervals (CIs) for (A) all-cause mortality, (B) heart failure hospitalizations, and (C) all-cause hospitalizations



IV: inverse variance; SE: standard error

including beta-blockers, renin–angiotensin–aldosterone system inhibitors, and SGLT2 inhibitors, patients included in this meta-analysis represent a broad and clinically heterogeneous spectrum.

Baseline characteristics , including age, comorbidities, renal function, and rhythm status varied substantially across studies and may influence both the efficacy and safety of cardiac glycosides. Recruitment periods spanned more than two decades, during which HF management evolved considerably, resulting in differences in absolute risk, event rates, and concomitant drug therapy.

Differences in study design, covariate adjustment strategies, and completeness of reporting further contributed to heterogeneity. In addition, the methodological quality of the included studies raises concerns that may undermine the robustness of our findings.
Finally, a key source of variability arises from the specific cardiac glycoside evaluated (digoxin versus digitoxin), which differs in pharmacokinetics, dosing requirements, and safety profiles.

Digoxin and digitoxin

The declining use of digoxin in contemporary HF practice reflects ongoing uncertainty regarding its safety profile. Observational studies and prior meta-analyses have suggested an association between digoxin therapy and increased mortality, particularly in patients with AF, (23, 31-33) an effect that appears more pronounced at higher serum levels.

Values exceeding the therapeutic range have been associated with pro-arrhythmogenic and pro-thrombotic mechanisms, including enhanced endothelial and platelet activation, which may contribute to increased cardiovascular risk. (34-36) These findings are consistent with post hoc analyses of the DIG trial, in which low serum digoxin levels (0.5-0.9 ng/mL) were associated with improved outcomes, whereas higher levels (>1.0 ng/mL) appeared to be harmful. (11, 16, 37) Although the safety and efficacy of cardiac glycosides likely depend on the appropriate serum drug level and dosing, this study was unable to evaluate dose-response relationships due to limited reporting of dosing strategies across studies.

In contrast, recent randomized evidence from the DIGIT-HF trial suggests that low-dose digitoxin may represent a potentially safe and effective therapeutic option. (18) Among patients with chronic HFrEF receiving GDMT, digitoxin significantly reduced the composite endpoint of all-cause mortality or hospitalization for worsening HF, with consistent benefits across prespecified subgroups.

Notably, the DIGIT-HF population exhibited a high symptomatic burden despite optimized GDMT, yet the absolute risk reduction and corresponding number needed to treat were comparable to those observed with other contemporary therapies, including ARNIs and SGLT2i. (18, 38-40) Importantly, these benefits were achieved with few major safety events, particularly in patients with renal dysfunction.

These findings may herald a therapeutic shift from digoxin to digitoxin, a more lipophilic cardiac glycoside with potentially improved safety characteristics.

Other important effect modifiers and interactions

Several clinical variables may meaningfully modify the effects of cardiac glycosides, although available data remain insufficient to elucidate these interactions.

The use of implantable cardiac devices, including ICD and CRT, present in up to 29% of participants in some cohorts, substantially alters the risk of sudden death and HF mortality, and may therefore modify the observed impact of glycoside therapy.

Similarly, the presence of AF and overall rhythm status influence both the clinical indication for glycoside use and dosing strategies, which in turn affect serum concentrations and pharmacodynamic responses. Variability in baseline renal function, together with the absence of standardized drug therapy monitoring further complicates interpretation, as glycoside clearance and toxicity are closely linked to renal function and serum levels.

Finally, concomitant medications that alter glycoside pharmacokinetics or affect renal function may introduce additional residual confounding, thereby influencing outcomes.

Limitations

This meta-analysis has several important limitations. First, the overall quality was suboptimal, as only one contemporary randomized controlled trial was included while the remaining studies were observational and therefore susceptible to selection bias and residual confounding despite the use of propensity score matching.

Second, the substantial between-study heterogeneity, likely attributable to differences in study design, patient characteristics, recruitment periods spanning more than two decades, and evolving background therapies, limits the interpretability of the results.

Third, safety endpoints were not systematically assessed, which is relevant given ongoing concerns regarding glycoside-related toxicity and potential mortality risk signals.

In addition, variability in covariate adjustment strategies across studies may have further contributed to heterogeneity. Finally, the limited number of included studies precluded a formal assessment of publication bias.

Clinical and research implications

Despite these limitations, our findings have relevant clinical and research implications. Cardiac glycosides may continue to provide therapeutic benefit in selected patients with HF and LVEF < 50% receiving contemporary GDMT, primarily through reduction of HFH. This observation suggests that indiscriminate

discontinuation of these agents may overlook a niche population: patients who remain symptomatic, have inadequate rate control in AF, or are intolerant to alternative treatments.

Moreover, digoxin remains an inexpensive and widely available medication that may be particularly valuable in healthcare systems with limited access to the full spectrum of disease-modifying therapies.

Nevertheless, the current evidence base is insufficient to support routine use. Well-designed, adequately powered RCTs are urgently needed to reassess the safety and efficacy of digoxin and/or digitoxin in the context of modern HF management. Future studies should ideally incorporate pharmacokinetic-guided dosing strategies, stratification according to rhythm status, and evaluation of potential interactions with device therapy.

CONCLUSIONS

In conclusion, in this contemporary meta-analysis, cardiac glycosides conferred clinical benefits in patients with HFrEF and HFmrEF, primarily by reducing HFH, an effect consistently observed across diverse populations and time periods. However, no consistent mortality benefit was demonstrated, and the certainty of the evidence is limited by substantial heterogeneity, incomplete dosing data, and the predominance of observational studies. These findings underscore the need for powered randomized controlled trials to more definitively define the role of cardiac glycosides as adjunctive therapy in HF management.

Author contributions

EM and MC contributed equally to this work and shared first authorship.

MC: conceptualization, study design, data curation, formal analysis, methodology, data interpretation, project administration, writing: original draft.

EM: conceptualization, study design, data curation, formal analysis, methodology, data interpretation, project administration, writing: original draft.

LP: data curation, formal analysis, data interpretation, writing: original draft.

BR: data curation, formal analysis, data interpretation, writing: original draft.

AMP: data curation, formal analysis, data interpretation, writing: original draft.

SR: supervision, formal analysis, methodological revision of the manuscript.

JP: supervision, formal analysis, methodological revision of the manuscript.

AL: supervision, writing: review and editing, final approval of the manuscript, guarantor of the study overall content.

All authors reviewed and approved the final manuscript. All authors accept responsibility for the accuracy, reliability and validity of the research data and analysis.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement checklist.

Section and Topic	Item #	Checklist item	Location where the item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria, including how many reviewers screened each record and each report retrieved, whether they worked independently, and, if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and, if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study, and whether they worked independently, and, if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics or data conversions.	
	13c	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13d	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics or data conversions.	
	13e	Describe any methods used to explore possible causes of heterogeneity in study results (e.g., subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess the robustness of the synthesized results.	

(continue)

(continuation)

Section and Topic	Item #	Checklist item	Location where the item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that may appear to meet the inclusion criteria but were excluded and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	
	20b	Present the results of all statistical syntheses conducted. If a meta-analysis was done, present for each one the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present the results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present the results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b		
	24c	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
		Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Supplementary Table 2. Search query

SEARCH TERMS	
Cochrane CENTRAL	("heart failure"):ti,ab,kw AND (digitoxin:ti,ab,kw OR "cardiac glycosides":ti,ab,kw OR digoxin:ti,ab,kw OR digoxine:ti,ab,kw)" with Cochrane Library publication date between Jan 2000 and Sep 2025
EMBASE	'heart failure'/exp AND ('digitoxin'/exp OR 'cardiac glycosides'/exp OR 'digoxin'/exp) AND [embase]/lim AND [01-01-2000]/sd NOT [18-09-2025]/sd AND [humans]/lim AND [abstracts]/lim AND [clinical study]/lim AND ('article'/it OR 'letter'/it OR 'review'/it OR 'short survey'/it OR 'clinical trial'/it) AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)
PUBMED	((("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields]) AND ("digitoxin"[Supplementary Concept] OR "digitoxin"[All Fields] OR "digitoxin"[MeSH Terms] OR ("cardiac glycosides"[Supplementary Concept] OR "cardiac glycosides"[All Fields] OR "cardiac glycosides"[MeSH Terms] OR ("cardiac"[All Fields] AND "glycosides"[All Fields])) OR ("digoxin"[Supplementary Concept] OR "digoxin"[All Fields] OR "digoxin"[MeSH Terms] OR "digoxine"[All Fields] OR "digoxin s"[All Fields]))) AND ("analysis"[MeSH Subheading] OR "analysis"[All Fields] OR "an"[All Fields])) AND (2000:2025[pdat])
SCOPUS	(TITLE-ABS ("heart failure") AND (TITLE-ABS (digitoxin) OR TITLE-ABS ("cardiac glycosides") OR TITLE-ABS (digoxin) OR TITLE-ABS (digoxine))) AND (PUBYEAR > 2000 AND PUBYEAR < 2026)

Supplementary Table 3. Risk of bias assessment using risk of bias in non-randomized studies of interventions I (ROBINS-I).

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall
Qamer, S. Z. *et al.*, 2019	!	✓	✓	!	✓	✓	✓	!
May Al-khateeb *et al.*, 2017	✗	!	!	!	✓	✓	✓	✗
Freeman, J. V. *et al.*, 2013	!	✓	✓	!	✓	✓	✓	!
Andrey, J. L. *et al.*, 2011	!	!	!	!	✓	✓	✓	!
Georgiopoulou *et al.*, 2009	✗	!	✗	!	!	!	✓	✗

✓ **Low risk of bias**
! **Moderated risk of bias**
✗ **High risk of bias**
⊕ **Critical risk of bias**

Supplementary Table 4. Risk of bias assessment of included randomized controlled trials using Risk of Bias Assessment According to the Cochrane Collaboration's Tool

Study	Risk of bias arising from the randomization process	Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias due to missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall risk-of-bias judgement
DIGIT-HF 2025						

 **Low risk of bias**

 **Unclear risk of bias**