

Digoxin use and outcomes in contemporary heart failure: a propensity score-weighted real-world analysis

Amelia Campos Saenz de Santamaria

ameliacampos97@gmail.com

Lozano Blesa University Clinical Hospital: Hospital Clinico Universitario Lozano Blesa

<https://orcid.org/0000-0002-3998-9325>

Miguel Castán Villanueva

Universidad de Zaragoza Facultad de Medicina

Marc Gómez Godos

Lozano Blesa University Clinical Hospital: Hospital Clinico Universitario Lozano Blesa

Silvia Crespo Aznarez

Lozano Blesa University Clinical Hospital: Hospital Clinico Universitario Lozano Blesa

Laura Esterellas Sánchez

Lozano Blesa University Clinical Hospital: Hospital Clinico Universitario Lozano Blesa

Marta Sánchez Marteles

Lozano Blesa University Clinical Hospital: Hospital Clinico Universitario Lozano Blesa

Vanesa Garcés Horna

Lozano Blesa University Clinical Hospital: Hospital Clinico Universitario Lozano Blesa

Ignacio Giménez López

Instituto de Investigacion Sanitaria Aragon

Jorge Rubio Gracia

Universidad de Zaragoza Facultad de Medicina <https://orcid.org/0000-0002-4769-7154>

Research Article

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Abstract

Background and objectives:

The role of digoxin in heart failure (HF) has been reconsidered following recent evidence suggesting potential benefits when used alongside contemporary guideline-directed medical therapy. The aim was to describe the clinical characteristics of patients receiving digoxin and to evaluate the association between digoxin treatment and one-year clinical outcomes using propensity score-based methods to account for treatment-selection bias.

Methods

A retrospective single-center study including 572 patients admitted for acute decompensated HF to an Internal Medicine Department between 2013 and 2025. Patients were stratified according to digoxin prescription at discharge. The primary endpoint was the composite of all-cause mortality or HF rehospitalization within 365 days. Inverse probability of treatment weighting (IPTW) based on propensity scores was applied to reduce treatment-selection bias, and weighted Cox proportional hazards models were used to assess associations between digoxin use and clinical outcomes.

Results

Digoxin was prescribed in 109 patients (19.1%). Compared with untreated patients, those receiving digoxin were more frequently women and had a higher prevalence of atrial fibrillation, previous HF, preserved left ventricular ejection fraction (HFpEF), higher CA125 levels, and better renal function. After IPTW adjustment, baseline covariates were well balanced. During one-year follow-up, 278 patients experienced the primary composite endpoint, 157 died, and 187 were rehospitalized for HF. Digoxin treatment was not associated with the composite endpoint (hazard ratio [HR] 1.12, 95% confidence interval [CI] 0.73–1.70; $p = 0.61$), all-cause mortality (HR 1.58, 95% CI 0.97–2.59; $p = 0.067$), or HF rehospitalization (HR 0.85, 95% CI 0.50–1.44; $p = 0.55$). No significant interactions were observed according to atrial fibrillation status or HF phenotype, and findings remained consistent in multivariable sensitivity analyses.

Conclusions

In this contemporary real-world cohort, digoxin was primarily prescribed to elderly patients with atrial fibrillation and HFpEF. After rigorous adjustment for baseline differences using propensity score weighting, digoxin treatment was not significantly associated with all-cause mortality or HF rehospitalization within 365 days. These findings highlight the importance of accounting for treatment-

selection bias in observational studies and provide evidence regarding digoxin use in patient populations underrepresented in randomized clinical trials.

Introduction

Heart failure (HF) remains one of the leading causes of hospitalization and mortality worldwide despite major therapeutic advances over the last two decades¹. The implementation of guideline-directed medical therapy, including renin–angiotensin system inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium–glucose cotransporter-2 inhibitors, has substantially improved outcomes across the spectrum of HF². Nevertheless, rates of recurrent hospitalization and death remain high, particularly among elderly patients with multiple comorbidities.

Digoxin has been used in the treatment of HF for more than a century. Following the Digitalis Investigation Group (DIG) trial, which demonstrated a reduction in HF hospitalizations without a significant effect on mortality, the use of digoxin progressively declined as newer therapies with proven survival benefits became available³. More recently, renewed interest in cardiac glycosides has emerged following contemporary randomized studies evaluating digitoxin and low-dose digoxin in patients receiving optimized medical therapy⁴. Although these studies have suggested a potential reduction in HF-related events, uncertainty remains regarding the role of digoxin in current clinical practice.

Importantly, the populations included in historical and contemporary randomized trials differ substantially from the patients who currently receive digoxin in routine care. Digoxin is frequently prescribed to elderly patients with atrial fibrillation, preserved ejection fraction, chronic symptoms, and multiple comorbidities, characteristics that have been underrepresented in most randomized studies. Consequently, the external validity of available trial data for contemporary real-world populations remains uncertain.

In addition, observational studies evaluating digoxin have yielded conflicting results, largely because treatment allocation is strongly influenced by clinical characteristics associated with prognosis. Patients receiving digoxin often differ substantially from untreated patients with respect to age, atrial fibrillation burden, heart failure severity, renal function, and comorbidity profile, making confounding by indication a major methodological challenge⁴.

Therefore, contemporary real-world data are needed to better characterize current digoxin use and its association with clinical outcomes in unselected HF populations. The aim of the present study was to describe the clinical profile of patients receiving digoxin after hospitalization for acute HF and to evaluate the association between digoxin treatment and one-year clinical outcomes using propensity score-based methods to account for treatment-selection bias.

Material and methods

Study design and population

This retrospective observational cohort study included consecutive patients admitted for acute heart failure at a tertiary-care university hospital and enrolled in the institutional Heart Failure Registry of the Heart Failure Research Group of the Aragón Health Research Institute (GIIS-043) between January 2013 and October 2025. Clinical, laboratory, echocardiographic, treatment, and follow-up data were prospectively collected and subsequently analyzed retrospectively. Patients were classified according to digoxin treatment at hospital discharge.

Outcomes

The primary endpoint was a composite of all-cause mortality or heart failure rehospitalization within 365 days after discharge. Secondary endpoints included all-cause mortality and heart failure rehospitalization analyzed separately. Follow-up was censored at 365 days after discharge or at the occurrence of the corresponding event.

Statistical analysis

Baseline demographic characteristics, comorbidities, laboratory parameters, echocardiographic variables, and discharge treatments were summarized according to digoxin exposure. Continuous variables are presented as mean $\pm$ standard deviation or median (interquartile range), as appropriate, whereas categorical variables are presented as counts and percentages. Comparisons between groups were performed using Student's t-test or the Mann–Whitney U test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables.

Because treatment allocation was not randomized, propensity score methods were used to reduce treatment-selection bias. A propensity score representing the probability of receiving digoxin at discharge was estimated using a multivariable logistic regression model. Covariates were selected a priori based on their clinical relevance and potential association with both digoxin prescription and outcomes. These included age, sex, history of atrial fibrillation, chronic heart failure, hypertension, ischaemic heart disease, dyslipidaemia, diabetes mellitus, chronic kidney disease, permanent pacemaker implantation, systolic blood pressure, heart rate, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and serum creatinine at admission. Inverse probability of treatment weighting (IPTW) was applied using stabilized weights derived from the propensity score. Covariate balance before and after weighting was assessed using absolute standardized mean differences (SMDs), with values < 0.10 considered indicative of adequate balance. Propensity score overlap and stabilized weight distributions were visually evaluated. Time-to-event analyses were performed using IPTW-adjusted Kaplan–Meier curves. Associations between digoxin treatment and outcomes were assessed using IPTW-weighted Cox proportional hazards models with robust variance estimation. Results are reported as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Prespecified subgroup analyses were conducted according to atrial fibrillation status and heart failure phenotype (HFpEF versus HFrEF). Interaction terms were evaluated within weighted Cox regression models to assess potential effect

modification. As a sensitivity analysis, a conventional multivariable Cox proportional hazards model including digoxin treatment and established prognostic variables was performed.

All analyses were conducted using R software (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as a two-sided p-value < 0.05. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee. Given the observational and retrospective nature of the study, informed consent was waived according to institutional regulations.

Results

Study population

A total of 572 patients discharged after hospitalization for acute heart failure were included. Digoxin was prescribed at discharge in 109 patients (19.1%), whereas 463 patients (80.9%) did not receive digoxin.

Baseline characteristics

Baseline characteristics according to digoxin treatment are shown in Table 1. Patients receiving digoxin were more frequently female and had a higher prevalence of atrial fibrillation and previous heart failure. Conversely, ischaemic heart disease was less common among digoxin-treated patients. Digoxin-treated patients also exhibited higher left ventricular ejection fraction, higher CA125 concentrations, and lower serum creatinine levels. Significant differences were also observed in discharge medical therapy.

Propensity score weighting

Substantial baseline imbalances were observed before weighting, particularly for sex, atrial fibrillation, left ventricular ejection fraction, renal function, and NT-proBNP levels. After application of IPTW, covariate balance improved substantially, with standardized mean differences below 0.10 for all covariates except for a small residual imbalance in NT-proBNP concentrations (Fig. 1). Propensity score distributions demonstrated substantial overlap between treatment groups and stabilized weights showed no evidence of extreme observations, supporting the robustness of the weighting procedure.

Clinical outcomes

During the 365-day follow-up period, 278 patients experienced the composite endpoint, 157 died, and 187 were rehospitalized for heart failure. In IPTW-adjusted analyses, digoxin treatment was not associated with the primary composite endpoint (HR 1.12, 95% CI 0.73–1.70; p = 0.61), all-cause mortality (HR 1.58, 95% CI 0.97–2.59; p = 0.067), or heart failure rehospitalization (HR 0.85, 95% CI 0.50–1.44; p = 0.55) (Table 2). Weighted Kaplan–Meier curves for the primary endpoint and secondary outcomes are shown in Fig. 2. No significant interaction was observed between digoxin treatment and atrial fibrillation status or heart failure phenotype. Results were consistent across all predefined subgroups (Fig. 3). Results remained unchanged in a conventional multivariable Cox regression model

including established prognostic variables. Digoxin treatment was not associated with the primary endpoint (adjusted HR 1.01, 95% CI 0.70–1.46; $p = 0.96$).

The propensity score distribution according to digoxin treatment status, as well as the IPTW-adjusted Kaplan–Meier survival curves according to atrial fibrillation and heart failure phenotype, are shown in the Supplementary Material (Supplementary Figures S1, S2, and S3, respectively).

Overall, findings were consistent across weighted, subgroup, and sensitivity analyses, providing no evidence of a significant association between digoxin therapy and one-year clinical outcomes.

Discussion

This real-world cohort differs substantially from the populations included in the major randomized trials evaluating cardiac glycosides^{4–10}. Patients were markedly older, with balanced sex representation and a predominance of atrial fibrillation and HFpEF. In this contemporary HF population, digoxin use was not associated with improved one-year clinical outcomes after adjustment for baseline differences using propensity score weighting.

Our findings should be interpreted in the context of the DIG, DIGIT-HF, and DECISION trials^{4–10}. The DIG trial demonstrated that digoxin reduced HF hospitalizations without affecting all-cause mortality in patients with HFrEF in sinus rhythm receiving 1990s-standard therapy^{6,7}. More recently, DIGIT-HF showed that low-dose digitoxin, added to contemporary guideline-directed medical therapy, reduced the composite outcome of all-cause mortality or HF hospitalization, particularly in patients with more advanced HF⁸. Similarly, the DECISION trial, the first modern placebo-controlled trial evaluating low-dose digoxin, did not achieve statistical significance for its primary endpoint but demonstrated a consistent trend toward fewer HF-related events while confirming the safety of low-dose digoxin^{9,10}.

Compared with these trials, our cohort included substantially older patients and a much higher proportion of women. Women represented 50.3% of the study population, whereas they accounted for only 20–28% of participants in previous trials. Digoxin use was concentrated among women, likely reflecting the high prevalence of HFpEF and atrial fibrillation in this subgroup. Indeed, HFpEF is more common in women and is strongly associated with atrial fibrillation, suggesting that digoxin prescription in routine practice is often driven by the need for rate control rather than by heart failure treatment itself^{11,12}.

A particularly relevant aspect of our study is the inclusion of patients across the entire spectrum of left ventricular ejection fraction. While previous randomized trials primarily focused on HFrEF or mildly reduced ejection fraction, nearly 60% of our cohort had HFpEF. Evidence regarding digoxin in HFpEF remains limited, and no contemporary randomized trial has specifically evaluated its role in patients with concomitant HFpEF and atrial fibrillation^{13–15}. Consequently, contemporary real-world data in this

population remain scarce. Given the increasing prevalence of HFpEF and atrial fibrillation in ageing HF populations, this represents a clinically relevant gap in the current evidence base¹⁶.

Although unadjusted analyses suggested differences in outcomes according to heart failure phenotype, these associations disappeared after propensity score weighting. Furthermore, no significant interaction was observed according to either heart failure phenotype or atrial fibrillation status. Taken together, these findings suggest that the neutral association between digoxin use and clinical outcomes was broadly consistent across the main clinical subgroups represented in our cohort.

A key finding of the present study was the substantial difference between crude and adjusted analyses. Patients receiving digoxin exhibited several characteristics associated with a distinct clinical profile, including a higher prevalence of atrial fibrillation, previous heart failure, preserved ejection fraction, and better renal function. These differences reflect current prescribing patterns and highlight the challenges of interpreting observational studies evaluating digoxin. After balancing baseline characteristics through propensity score weighting, the apparent differences in outcomes observed in unadjusted analyses were no longer evident, suggesting that treatment-selection bias may account for part of the heterogeneity reported in previous observational studies.

Renal function appeared to play an important role in digoxin prescribing patterns¹⁷. Patients receiving digoxin had better preserved renal function, likely reflecting clinicians' concerns regarding drug accumulation and toxicity in chronic kidney disease. This observation is consistent with the pharmacokinetic characteristics of digoxin and with the cautious use of cardiac glycosides in patients at increased risk of adverse effects. Although serum digoxin concentrations were not available in the present study, careful monitoring remains essential when prescribing digoxin in elderly patients with multiple comorbidities^{18–19}.

Another notable finding was the lower prevalence of ischaemic heart disease among digoxin-treated patients. This may reflect concerns regarding the potential proarrhythmic effects of cardiac glycosides and their ability to increase myocardial oxygen demand, factors that could influence prescribing decisions in patients with current or previous myocardial ischaemia²⁰.

The absence of a significant association between digoxin use and clinical outcomes in our study should not necessarily be interpreted as evidence of lack of efficacy. Rather, our findings suggest that any potential effect of digoxin in contemporary HF populations is likely to be modest and may be difficult to detect in observational cohorts. Although a numerically higher risk of all-cause mortality was observed among digoxin-treated patients, the confidence intervals were wide and no significant association was identified after adjustment for baseline differences.

Limitations

Our study has several limitations. First, its retrospective observational design precludes causal inference and leaves open the possibility of residual confounding despite the use of propensity score weighting. Second, this was a single-centre study, which may limit the generalizability of the findings. Third, serum digoxin concentrations were not systematically available, preventing assessment of the relationship between drug exposure and outcomes. Finally, treatment changes occurring after hospital discharge were not captured and may have influenced long-term outcomes.

Conclusions

Digoxin is currently used mainly in elderly patients with atrial fibrillation and HFpEF, reflecting contemporary prescribing patterns that differ substantially from those observed in historical clinical trials. After rigorous adjustment for baseline differences using propensity score weighting, digoxin was not significantly associated with one-year clinical outcomes. These findings emphasize the importance of accounting for treatment-selection bias when evaluating digoxin in observational studies and provide contemporary evidence regarding its use in elderly patients with atrial fibrillation and HFpEF, populations that remain underrepresented in randomized clinical trials.

Abbreviations

ACEi
angiotensin-converting enzyme inhibitors
ARB
angiotensin receptor blockers
CA125
cancer antigen 125
HFpEF
heart failure with preserved ejection fraction
HFrEF
heart failure with reduced ejection fraction
iSGLT2
sodium-glucose co-transporter-2 inhibitors
NYHA
New York Heart Association
NT-proBNP
N-terminal pro b-type natriuretic peptide.

Declarations

Conflict of interest: none.

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M et al (2021) 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 42:3599–3726. 10.1093/eurheartj/ehab368
2. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M et al (2023) 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 44:3627–3639. 10.1093/eurheartj/ehad195
3. van Veldhuisen DJ, Bauersachs J (2023) Digitalis in heart failure: declining use and ongoing outcome trials. *Eur Heart J* 44:1976–1978. 10.1093/eurheartj/ehad185
4. Damman K, van Veldhuisen DJ, Bauersachs J, Rienstra M, Mosterd A, Voors AA et al (2026) Efficacy and Safety of Digitalis Glycosides in Heart Failure. *JAMA*. 10.1001/jama.2026.7886
5. He T, Igitalis D, Nvestigation I, Roup G (1997) The Effect of Digoxin on Mortality and Morbidity in Patients with Heart Failure. *N Engl J Med* 336:525–533. 10.1056/NEJM199702203360801
6. Ahmed A, Rich MW, Love TE, Lloyd-Jones DM, Aban IB, Colucci WS et al (2006) Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. *Eur Heart J* 27:178–186. 10.1093/eurheartj/ehi687
7. Bavendiek U, Berliner D, Dávila LA, Schwab J, Maier L, Philipp SA et al (2019) 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* 21:676–684. 10.1002/ejhf.1452
8. Bavendiek U, Großhennig A, Schwab J, Berliner D, Rieth A, Maier LS et al (2025) Digitoxin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 393:1155–1165. 10.1056/NEJMoA2415471
9. van Veldhuisen DJ, Rienstra M, Mosterd A, Alings AM, van Asselt ADJ, Bouvy ML et al (2024) Efficacy and Safety of Low-Dose Digoxin in Patients with Heart Failure. Rationale and Design of the DECISION Trial. *Eur J Heart Fail* 26:2223–2230. 10.1002/ejhf.3428
10. van der Meer P, Voordes GHD, Vijver MAT, Mosterd A, Alings AM, Maas-Soer EL et al (2026) Heart failure patients with reduced or mildly reduced ejection fraction: baseline characteristics of the low-dose digoxin outcome DECISION trial. *Eur J Heart Fail*. 10.1093/ejhf/xuag073
11. Kotecha D, Lam CSP, Van Veldhuisen DJ, Van Gelder IC, Voors AA, Rienstra M (2016) Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation. *J Am Coll Cardiol* 68:2217–2228. 10.1016/j.jacc.2016.08.048
12. Bavendiek U, Aguirre Davila L, Koch A, Bauersachs J (2017) Assumption versus evidence: the case of digoxin in atrial fibrillation and heart failure. *Eur Heart J* 38:ehw577. 10.1093/eurheartj/ehw577
13. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW et al (2006) Effects of Digoxin on Morbidity and Mortality in Diastolic Heart Failure. *Circulation* 114:397–403. 10.1161/CIRCULATIONAHA.106.628347
14. van Veldhuisen DJ, Rienstra M, Mosterd A, Alings M, Voors AA, Damman K et al (2026) Low-dose digoxin in patients with heart failure with reduced or mildly reduced ejection fraction: a randomized

- controlled trial. *Nat Med*. 10.1038/s41591-026-04406-6
15. Abdul-Rahim AH, Shen L, Rush CJ, Jhund PS, Lees KR, McMurray JJV (2018) Effect of digoxin in patients with heart failure and mid-range (borderline) left ventricular ejection fraction. *Eur J Heart Fail* 20:1139–1145. 10.1002/ejhf.1160 PubMed PMID: 29493058
 16. Campbell P, Rutten FH, Lee MM, Hawkins NM, Petrie MC (2024) Heart failure with preserved ejection fraction: everything the clinician needs to know. *Lancet* 403:1083–1092. 10.1016/S0140-6736(23)02756-3
 17. Smith TW (1985) Pharmacokinetics, bioavailability and serum levels of cardiac glycosides. *J Am Coll Cardiol* 5:43A–50A. 10.1016/S0735-1097(85)80462-9
 18. Adams KF, Gheorghiade M, Uretsky BF, Patterson JH, Schwartz TA, Young JB (2002) Clinical benefits of low serum digoxin concentrations in heart failure. *J Am Coll Cardiol* 39:946–953. 10.1016/S0735-1097(02)01708-4
 19. Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM (2003) Association of Serum Digoxin Concentration and Outcomes in Patients With Heart Failure. *JAMA* 289:871. 10.1001/jama.289.7.871
 20. Kim DH, Akera T, Kennedy RH (1983) Ischemia-induced enhancement of digitalis sensitivity in isolated guinea-pig heart. *J Pharmacol Exp Ther* 226(2):335–342 PMID: 6308206

Tables

Table 1 and 2 are available in the Supplementary Files section.

Figures

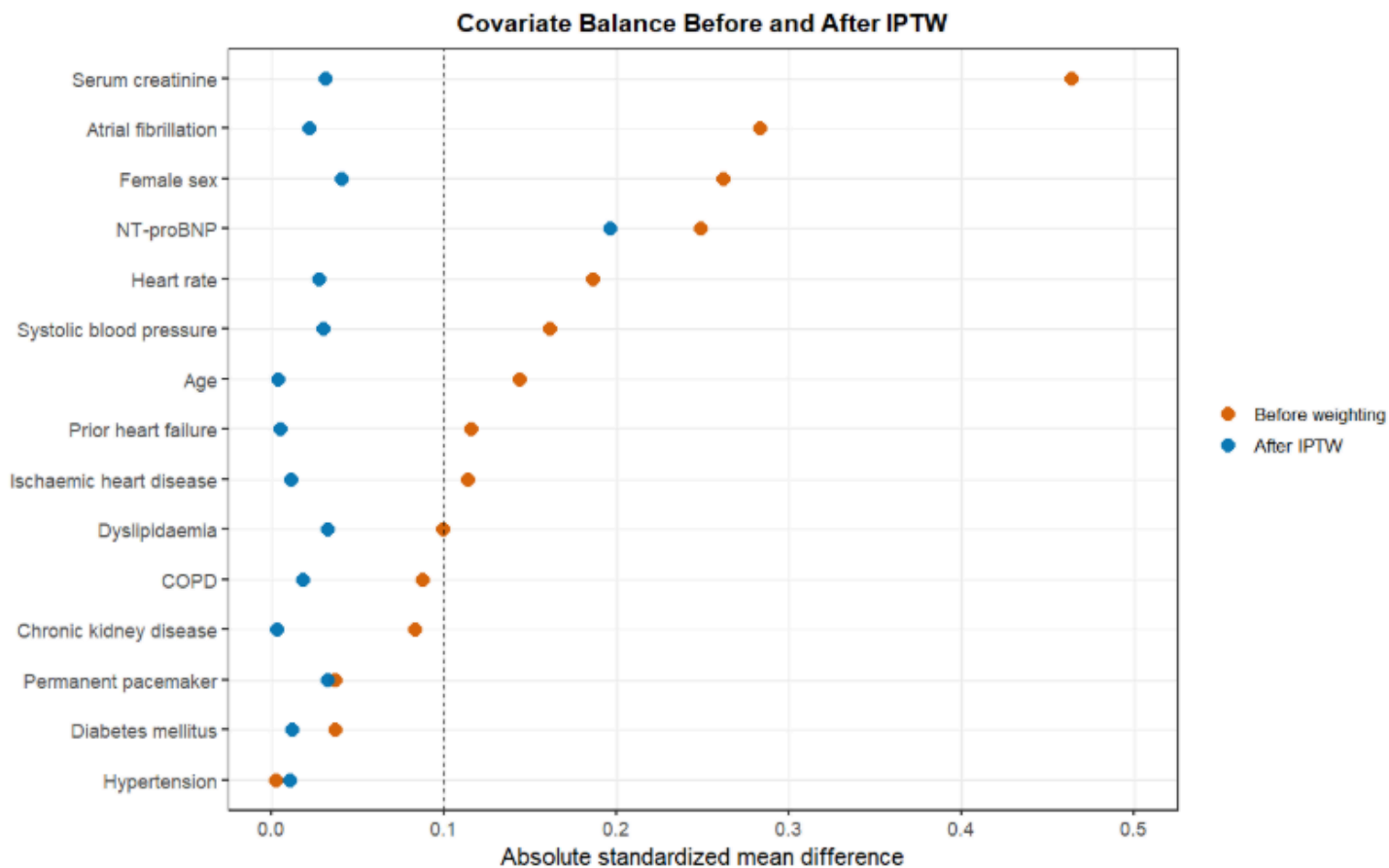


Figure 1

Covariate balance before and after inverse probability of treatment weighting (IPTW).

Absolute standardized mean differences (SMDs) for baseline covariates included in the propensity score model are shown before and after weighting. The dashed vertical line represents the conventional threshold for adequate covariate balance (SMD = 0.10). After IPTW, all baseline covariates achieved satisfactory balance, although a modest residual imbalance persisted for NT-proBNP levels.

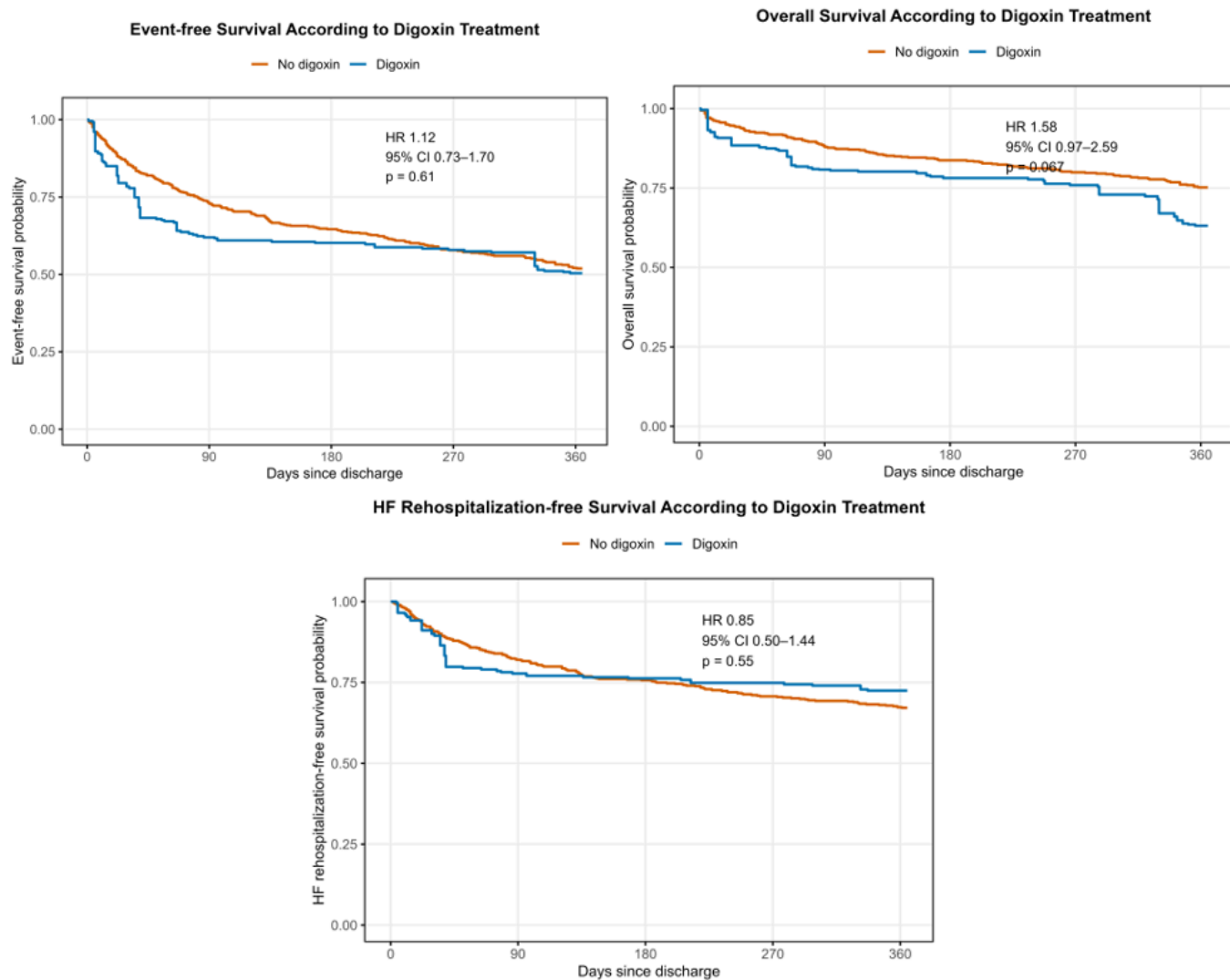


Figure 2

Subgroup analysis of the primary composite endpoint according to digoxin treatment.

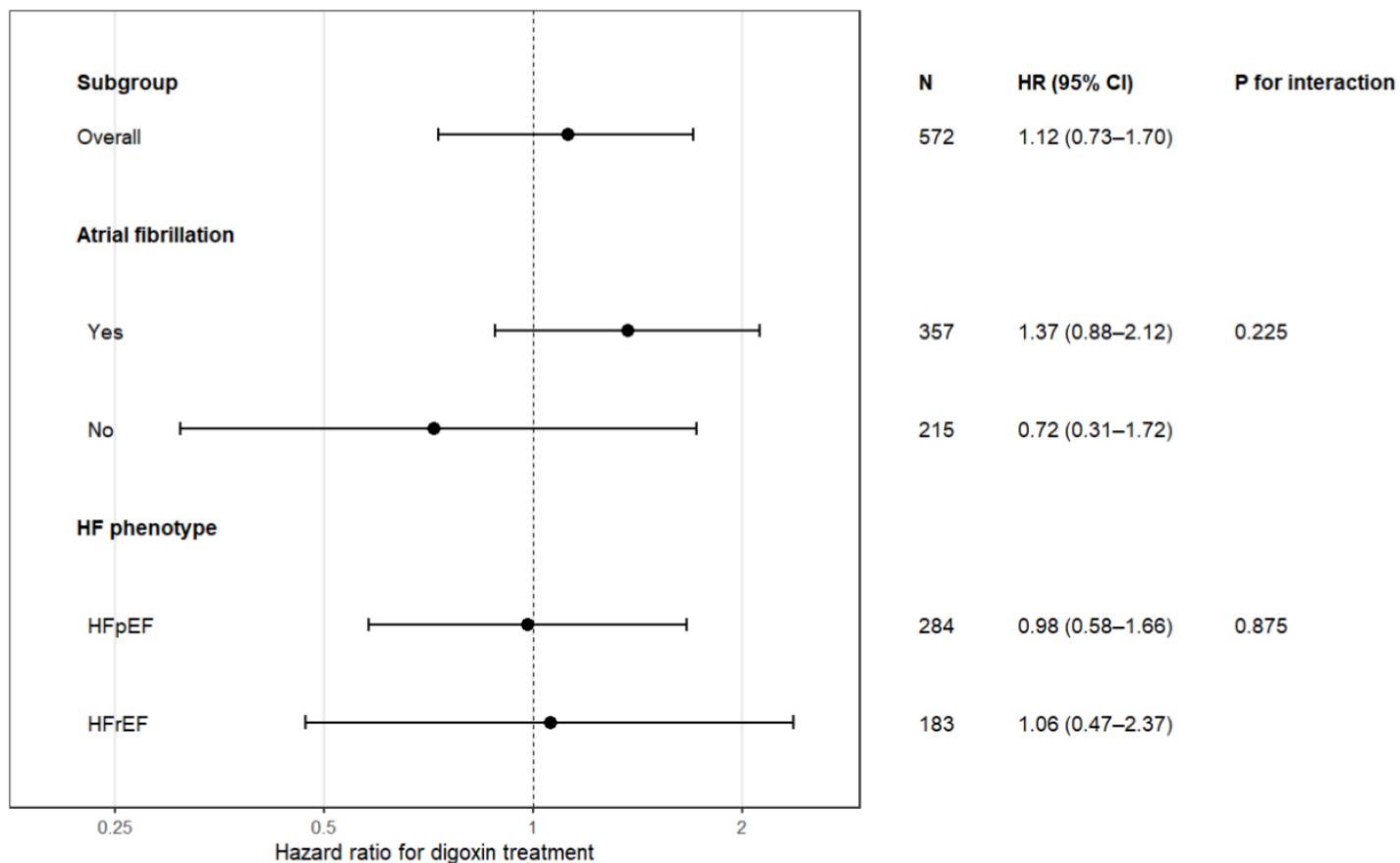


Figure 3

Subgroup analysis of the primary composite endpoint according to atrial fibrillation status and heart failure phenotype

Hazard ratios and 95% confidence intervals for the association between digoxin therapy and the composite endpoint of all-cause mortality or heart failure rehospitalization at 1 year. No significant treatment interaction was observed according to atrial fibrillation status or heart failure phenotype.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryMaterial.docx](#)
- [Table1.Baselinecharacteristics.docx](#)
- [Table2.IPTWadjustedoutcomes.docx](#)