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Association of digoxin with mortality and rehospitalization in heart failure patients treated with beta-blockers: Results from the Persian Heart Failure Patient Registry

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Original Article

Abstract

BACKGROUND: Numerous clinical trials have reported conflicting results regarding the benefit of digoxin in treating heart failure (HF) patients. This study was conducted with the aim to demonstrate the impact of added digoxin to beta-blocker and beta-blocker alone on all-cause mortality and rehospitalization among these patients.

METHODS: We investigated the data of 1998 patients admitted with a primary diagnosis of decompensated HF in the prospective Persian Heart Failure Patients Registry in Iran. The outcomes of interest were time until death and time until first rehospitalization. Multivariate cox regression was used to compare the impact of beta-blocker plus digoxin and beta-blocker alone on 2.5-year survival and 90-day rehospitalization.

RESULTS: The mean age of the participants was 69.18 ± 13.26 years, and 38.1% of patients were women. The incidence rate of all-cause mortality in the total sample was 0.18 and 0.22 in patients on beta-blocker plus digoxin and beta-blocker alone, respectively [incidence rate ratio (IRR) = 1.25; 95% CI: 0.92-1.7]. The adjusted risk of all-cause mortality was significantly higher in women discharged with beta-blocker plus digoxin than beta-blocker groups [hazard ratio (HR) = 2.31; 95% CI: 1.27-4.19]. Rates of 90-day first rehospitalization were 0.10 and 0.12 in the beta-blocker plus digoxin and beta-blocker alone groups, respectively (IRR = 0.85; 95% CI: 0.53-1.35). After adjustment for covariates, beta-blocker plus digoxin therapy had no significant effect on increasing the risk of 90-day first rehospitalization in the total cohort (HR = 0.77; 95% CI: 0.48-1.23), in men (HR = 0.73; 95% CI: 0.40-1.35), and women (HR = 0.76; 95% CI: 0.36-1.65).

CONCLUSION: In patients hospitalized with decompensated HF, digoxin administration at discharge was associated with increased 30-month mortality risk in women.

Keywords: Adrenergic beta-Antagonists; Digoxin; Heart failure; Hospitalization; Mortality

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Introduction

Heart failure (HF) is the leading cause of hospitalization and hospital readmission. Digoxin is approved for mild-to-moderate HF treatment in order to decrease the risk of HF-related hospitalization. According to the American College of Cardiology (ACC)/American Heart Association (AHA) HF guideline, digoxin can be used to reduce the number of hospitalizations in patients with HF with reduced ejection fraction (HFrEF).[1]

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Numerous studies have been published on the usefulness of digoxin in the treatment of patients with HF. However, the only large randomized trial in this field is the DIG trial published more than 2 decades ago.[2] The mentioned study indicated that digoxin did not increase the rate of mortality and reduced readmission. Subsequent studies have shown contradictory results, and in some studies, the addition of digoxin to standard HF regimens increased the rate of mortality and readmission among patients with HF.[3-7]

However, it should be remarked that older medications have been replaced by newer drugs with better impact on detrimental events. Consequently, the usefulness of digoxin in the presence of newer drugs may be less or limited to specific cases, such as absolute contraindication of beta-blockers or hypotension. Moreover, a narrow digoxin treatment window can also increase the risk of digoxin toxicity. Therefore, it has been hypothesized that adding digoxin to standard regimens such as beta-blockers may not be beneficial and may even increase mortality. The results of some studies support this hypothesis.[3,5,7-9] In the present study, we sought to investigate the effect of adding digoxin to beta-blocker on the rate of readmission and mortality in patients with HF.

Materials and Methods

Data sources: Data were extracted from the Persian Registry of Cardiovascular disease/Heart Failure (PROVE/HF) analysis in Chamran Hospital, Isfahan, Iran. This ongoing registry project was initiated at the end of 2014 and launched in March 2015. Methods used for the survey have been described elsewhere.[10,11] In brief, the registry information was gathered from 18 distinct cardiac centers with personnel trained in diagnosing and managing HF. A data gathering form for the registration of individuals with HF was designed according to the outcomes of the Swedish Heart Failure Registry (SHFR) and Thai Acute Decompensated Heart Failure Registry (Thai ADHERE).[12,13] The list of patients diagnosed with HF based on the International Classification of Diseases 10th Revision (ICD-10) was provided to the data collectors. The recorded information consisted of demographic data, comorbidities, medications, treatments, diagnostic and paraclinical assessments, symptoms, and physical examination results.

Follow-up of the PROVE/HF program was performed via telephone calls and, if necessary, through specialist physician visits about every 6 months after the first admission. During follow-up, the collected data included the patient's current status, medications, death, cause of death, and place of death. In cases of doubt about HF diagnosis or inaccessibility of baseline information, they were invited to a face-to-face meeting with a specialist. If death occurred, the date and etiology of death (cardiac or non-cardiac) as well as place of death (home or hospital) were obtained from the relatives. In addition, for internal quality control of the PROVE/HF, the project was managed by the team's supervisor and externally evaluated by a panel including experienced and trained members who were not one of the PROVE/HF executive members and were unaware of the project. The external panel continuously monitored the entire registration process from start to finish.

All patients provided written informed consent for participation in the study and follow-up.[14] All the procedures conducted in the current study were in line with ethical standards of the 1964 Declaration of Helsinki and its 2013 revised edition. The main project was approved by the National Institute for Medical Research Development (NIMAD) and received the ethical approval code of 971404.

The patients who died at the hospital before discharge were excluded. We also omitted patients whose medical records lacked information on discharge beta-blocker and digoxin status, and those who changed their medications during the follow-up. Survival time was specified as the time interval between the first entry into the PROVE/HF registry database and time of death (based on reports from follow-up telephone calls or hospital data); patients alive until the last follow-up date were denoted by 'censored' and dead patients by 'deceased'.

In this study, all performed procedures were in accordance with ethical standards of the 1964 Declaration of Helsinki and its later amendments in the 2013 edition.

Outcome: The outcomes of interest were time until death within 2.5 years after hospital discharge and time until first 90-day rehospitalization. The subsequent admissions (second, third, etc.) were not accounted as rehospitalization in this analysis.

Statistical analysis: The characteristics of the patients in the 2 treatment groups were presented as frequency (percentages) (categorical variables) and mean and standard deviation (continuous variables). The quantile-normal plot was used to assess the normality of continuous variables. For comparisons by treatment group, chi-square test was used for categorical variables, and Wilcoxon rank-sum test or independent samples t-test for the continuous variables. The observed all-cause mortality and first

rehospitalization were described by the Kaplan-Meier curve. The unadjusted association between treatment and outcome was estimated using the non-parametric log-rank test and univariate Cox proportional hazards model.[15,16] The adjusted relationship between treatments and outcomes was estimated using a multivariate Cox proportional hazards model and was adjusted for age at admission, sex, ischemic heart failure status, systolic blood pressure, smoking within the prior year, serum sodium, serum creatinine, other discharge medications [i.e., angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)], and history of diabetes mellitus, atrial arrhythmia, chronic obstructive pulmonary disease, anemia, chronic obstructive pulmonary disease (COPD), renal insufficiency, and thyroid abnormality. To assess the inconsistency of the effect across subgroups, we accounted for subgroup-by-treatment interactions in separate sex-stratified Cox proportional hazards models. P-values < 0.05 were considered statistically significant. Stata software (version 13; StataCorp LLC, College Station, TX, USA) was used for statistical analysis.

Results

Of the 2462 patients in the PROVE/HF study, 278 patients died at the hospital before discharge. These patients were excluded from the present analysis. We also omitted patients whose medical records lacked information on discharge beta-blocker and digoxin status (94 patients), and those who changed their medications during follow-up (92 patients). Information on digoxin and beta-blocker usage at discharge was available for 1998 patients. Among them, 799 (40.0%) individuals were treated with conventional treatment without beta-blocker or digoxin (DIG−/BB−), 478 (23.9) with a beta-blocker alone (DIG−/BB+), 382 (19.1%) with digoxin alone (DIG+/BB−), and 339 (17.1%) with beta-blocker plus digoxin (DIG+/BB+). Baseline characteristics of patients across the 4 treatment groups (DIG−/BB−, DIG−/BB+, DIG+/BB+, and DIG+/BB−) are provided in table 1. Post-discharge all-cause mortality at 6 months, and 1, 1.5, 2, and 2.5 years were compared between the 4 treatment groups of DIG−/BB−, DIG−/BB+, DIG+/BB+, and DIG+/BB− (Log-rank P-value < 0.001) (Figure 1).

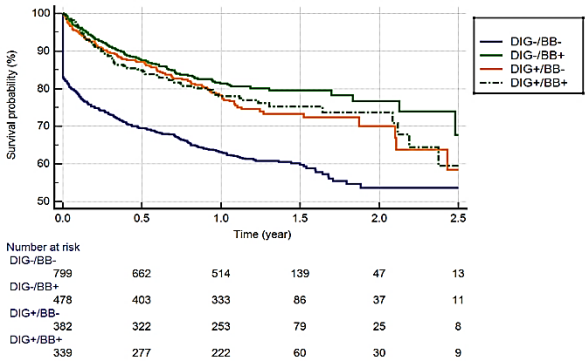

Figure 1. Kaplan–Meier survival curves for beta-blocker (BB) and digoxin (DIG) treatment groups (Log-rank p-value<0.001)

Table 1. Clinical characteristics of patients discharged on a different combination of Beta-blocker and Digoxin

	DIG-/BB-	DIG-/BB+	DIG+/BB-	DIG+/BB+
Number	792	478	382	339
Age (year)	71.73 ± 11.89	69.74±12.91	71.30±12.37	68.40±13.71
SBP(mm/Hg)	134.98 ± 29.67	133.19±27.18	127.75±28.26	128.19±28.77
Heart Rate	86.21 ± 19.36	86.60±19.95	92.18±22.81	94.49±23.78
BMI (kg/m^2)	27.73 ± 17.00	27.15±9.29	26.23±5.02	27.82±31.66
Sex(male)	467 (58.4)	287(60.0)	235(61.5)	219(64.6)
Ischemic Heart Disease	250 (74.1)	399(83.5)	289(75.7)	252(74.3)
Myocardial Infarction	201 (25.2)	150(31.4)	100(26.2)	79(23.3)
Hypertension	522 (65.3)	326(68.2)	231(60.5)	223(65.8)
Diabetes	371 (46.4)	234(49.0)	166(43.5)	156(46.0)
COPD	135 (16.9)	28(5.9)	72(18.8)	18(5.3)
Valvular Dysfunction	259 (32.4)	169(35.4)	156(40.8)	160(47.2)
Thyroid Disease	54 (6.8)	28(5.9)	30(7.9)	20(5.9)
Stroke	42 (5.3)	20(4.2)	16(4.2)	17(5.0)
Anemia	73(9.1)	37(7.7)	40(10.5)	35(10.3)
Renal Dysfunction	205(25.7)	127(26.6)	84(22.0)	80(23.6)
Current Smocking	138(17.3)	69(14.4)	67(17.5)	51(15.0)
ARB/ACE medication	407(50.9)	318(66.5)	243(63.6)	253(74.6)
Sodium (<135 mg/dl)	195(24.4)	126(26.4)	108(28.3)	97(28.6)
Creatinine (>1.5 mg/dl)	278(34.8)	169(35.4)	117(30.6)	104(30.7)

DIG: Digoxin; BB: Beta-blocker; COPD: Chronic obstructive pulmonary disease; ARB: Angiotensin receptor blocker; ACE: Angiotensin-converting enzyme inhibitor; BMI: Body mass index; SBP: Systolic blood pressure

We conducted an analysis based on beta-blocker users with and without digoxin (DIG−/BB+ and DIG+/BB+) at discharge (n = 817). The baseline characteristics of the remaining patients are listed in table 2. In the total sample, the mean age was 69.18 ± 13.26 years, and 311 (38.1%) patients were women. The distribution of sex and mean age were not statistically different between the 2 groups (P > 0.05). Patients treated with DIG+/BB+ had a higher rate of arrhythmia (23.8% vs. 15.1%; P = 0.002) and valvular dysfunction (47.3% vs. 36.1%; P = 0.001), lower rate of previous myocardial infarction (24.1% vs. 31.1%; P = 0.022), and ischemic heart history (74.8% vs. 83.5%; P = 0.012). Moreover, those treated with DIG+/BB+ had a higher mean heart rate (94.42 ± 23.63 vs. 86.85 ± 20.00; P-value < 0.001).

The DIG+/BB+ group were more likely than the DIG−/BB+ group to be prescribed other cardiovascular medications, including ACE inhibitors and ARB (75.1% vs. 66.3%; P = 0.005) (Table 2).

Figure 2 shows the post-discharge survival probabilities of patients in DIG−/BB+ and DIG+/BB+ groups in the total sample (Figure 2a), men (Figure 2b), and women (Figure 2c).

Table 3 shows the risk of all-cause mortality and 90-day rehospitalization in DIG+/BB+ therapy at discharge compared with DIG−/BB+ therapy. We observed the adverse, but non-significant effect of added digoxin therapy on all-cause mortality in the total cohort. After adjustment, the hazard ratio for mortality was 23% higher among patients initiated on DIG+/BB+ therapy, compared with those discharged on DIG−/BB+ therapy (HR = 1.23; 95% CI: 0.91-1.65).

We also compared mortality rates and hazard ratios of the 2 treatment groups by sex. Mortality rate among men was nearly the same as that among those discharged with DIG+/BB+ compared with DIG−/BB+ therapy (0.22 vs. 0.23; IRR = 0.94; 95% CI: 0.65-1.36). After adjustment, DIG+/BB+ had no statistically significant effect on mortality compared with DIG−/BB+ therapy in men (HR = 1.18; 95% CI: 0.86-1.61). However, the mortality rate was higher in women discharged with DIG+/BB+ compared with DIG−/BB+ therapy (0.10 vs. 0.23; IRR = 2.28; 95% CI: 1.26-4.18). After adjusting for covariates, the risk of mortality among women was significantly higher in groups discharged with added digoxin therapy (HR = 2.31; 95% CI: 1.27-4.19).

Rates of 90-day first rehospitalization were 0.10 and 0.12 in groups discharged with DIG+/BB+ and DIG−/BB+ therapy, respectively (IRR = 0.85; 95% CI: 0.53-1.35). After adjustment for covariates, DIG+/BB+ had no significant effect on increasing the risk of 90-day first rehospitalization in the total cohort (HR = 0.77; 95% CI: 0.48-1.23), in men (HR = 0.73; 95% CI: 0.40-1.35), and in women (HR = 0.76; 95% CI: 0.36-1.65), respectively.

Table 2. Clinical characteristics of patients discharged on beta-blocker therapy with and without digoxin

	DIG-/BB+	DIG+/BB+	P-value
Number	478	339	
Age (year)	69.74±12.91	68.40±13.71	0.155 [a]
SBP(mm/Hg)	133.19±27.18	128.19±28.77	0.012 [b]
Heart Rate	86.60±19.95	94.49±23.78	<0.001 [b]
BMI (kg/m^2)	27.15±9.29	27.82±31.66	0.752 [b]
Sex (male)	287(60.0)	219(64.6)	0.186
Ischemic Heart Disease	399(83.5)	252(74.3)	0.011
Myocardial Infarction	150(31.4)	79(23.3)	0.009
Hypertension	326(68.2)	223(65.8)	0.518
Diabetes	234(49.0)	156(46.0)	0.041
COPD	28(5.9)	18(5.3)	0.735
Valvular Dysfunction	169(35.4)	160(47.2)	0.001
Thyroid Disease	28(5.9)	20(5.9)	0.980
Stroke	20(4.2)	17(5.0)	0.574
Anemia	37(7.7)	35(10.3)	0.203
Renal Dysfunction	127(26.6)	80(23.6)	0.297
Current Smocking	69(14.4)	51(15.0)	0.775
ARB/ACE medication	318(66.5)	253(74.6)	0.011
Sodium (<135 mg/dl)	126(26.4)	97(28.6)	0.476
Creatinine (>1.5 mg/dl)	169(35.4)	104(30.7)	0.163

[a] Independent samples t-test, [b] Wilcoxon rank-sum test, Chi-square test for categorical data

DIG: Digoxin; BB: Beta-blocker; COPD: Chronic obstructive pulmonary disease; ARB: Angiotensin receptor blocker; ACE: Angiotensin-converting enzyme inhibitor; BMI: Body mass index; SBP: Systolic blood pressure

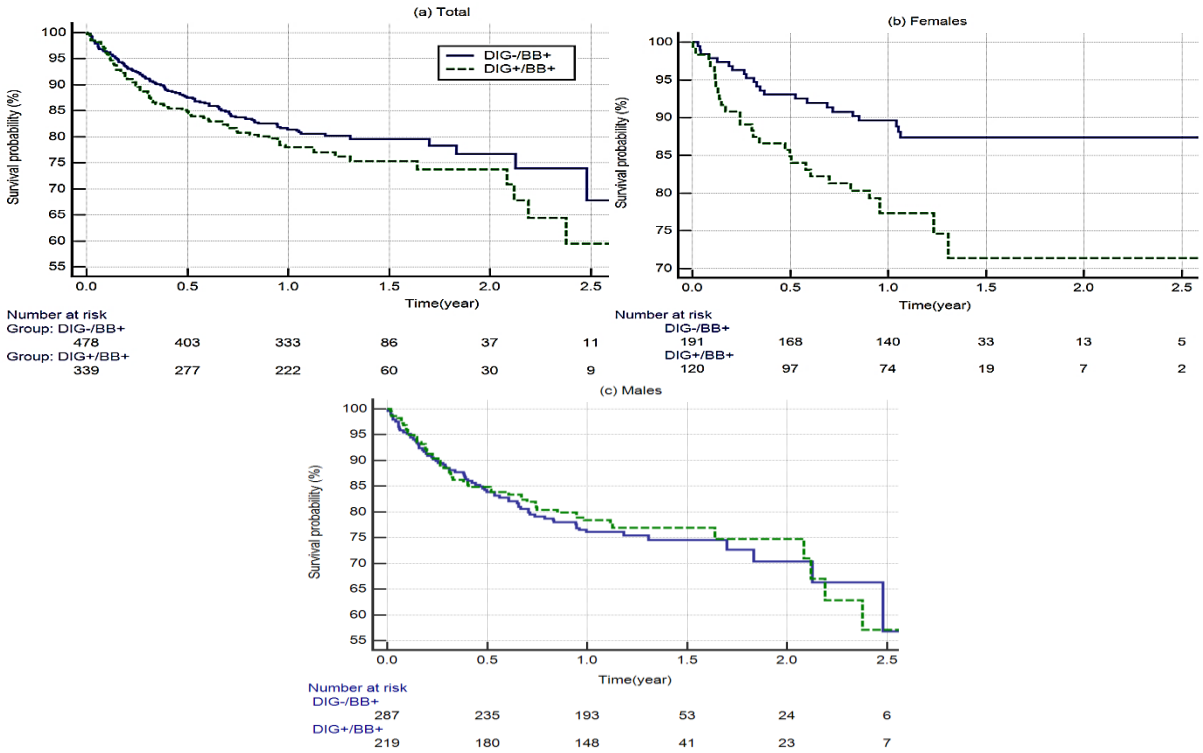

Figure 2. A Kaplan–Meier survival curves for beta-blocker and digoxin treatment groups in the (a) total sample (log-rank p-value=0.168), (b) males (Log-rank p-value=0.714), and (c) females (Log-rank p-value =0.004)

Figure 3 shows the cumulative probability of not being rehospitalized before the 90-day (Figure 3a) and 2.5-year (Figure 3b) follow-ups on DIG−/BB+ versus DIG+/BB+ therapy at discharge. The probability of 90-day first rehospitalization was non-significantly lower in the DIG+/BB+ group, which can be interpreted as short-term remission in patients discharged with added digoxin. However, in the long-term (nearly 1 year after discharge), the probability of rehospitalization has increased in the DIG+/BB+ group compared to the DIG-/BB+ group.

In the sensitivity analyses, we explored outcomes in the subgroups of patients, including patients with and without anemia, diabetes mellitus, and arrhythmia, age groups of < 70 years and ≥ 70 years, creatinine level of < 1.5 and ≥ 1.5 mg/dl, and sodium level of < 135 and ≥ 135 mg/dl through a sex-stratified proportional cox model. Figure 4 shows relatively similar findings for mortality in the subgroups. The assessment of the interaction effect of each subgroup and treatment showed that adjusted hazard ratios for DIG+/BB+ therapy against DIG−/BB+ showed no significant heterogeneity in patients in any subgroups except sex subgroups. Nonetheless, it should be noted that the interaction effect of renal dysfunction (creatinine level) and treatment was marginally significant (P-value = 0.090), suggesting the higher adverse effect of DIG+/BB+ on mortality in patients with renal dysfunction comorbidity.

Discussion

Our study results showed that adding digoxin to beta-blockers in HF patients following a hospital admission for HF exacerbation is associated with an increased long-term (30-months) mortality rate in women. This association remains significant after multivariate adjustment. In contrast, the mortality rate among men was nearly the same as that in those discharged with DIG+/BB+ compared with DIG−/BB+ therapy even after multivariate adjustment. Indeed, our results showed that adding digoxin to beta-blocker was associated with insignificant changes in rehospitalization rate in both men and women. Another important point that our study showed is that about 63.9% of the patients did not receive beta-blockers.

Digoxin is widely used in many HF patients who remain symptomatic or experience frequent hospital readmissions although, the guideline and treatment protocol being optimized.[17,18] The only large randomized clinical trial to study the impact of digoxin in HF patients is the Digitalis Investigation Group (DIG) trial, which reported a weak effect on mortality.[2]

Table 3. Hazard ratios of beta-blocker/digoxin (BB+/DIG+) therapy versus beta-blocker/ no digoxin (BB+/DIG-) therapy

		BB+/DIG-		BB+/DIG+		IRR	HR (unadjusted)	HR (adjusted)*
		n. event/ total	Incidence rate	n. event / total	Incidence rate			
All-cause mortality	Total	95/478	0.18	81/339	0.22	1.25(0.92,1.7)	1.23(0.92,1.66)	1.23(0.91,1.65)
	Male	73/287	0.23	53/219	0.22	0.94(0.65, 1.36)	0.94(0.66,1.33)	1.18(0.86,1.61)
	Female	22/191	0.1	28/120	0.23	2.28(1.26, 4.18)	2.21(1.26,3.86)	2.31(1.27,4.193)
90-day first rehospitalization	Total	54/478	0.12	31/339	0.10	0.85(0.53,1.35)	0.80(0.51,1.24)	0.77(0.48,1.23)
	Male	30/287	0.11	20/219	0.10	0.88(0.48,1.61)	0.85(0.48,1.50)	0.73(0.40,1.35)
	Female	24/191	0.13	11/120	0.11	0.81(0.36,1.73)	0.74(0.36,1.50)	0.76(0.36,1.65)

*Adjusted for sex, age, systolic blood pressure, heart rate, ischemic heart history, anemia, sodium level, creatinine level, diabetes, valvular dysfunction, COPD
DIG: Digoxin; BB: Beta-blocker; HR: Hazard ratio; IRR: Incidence rate ratio

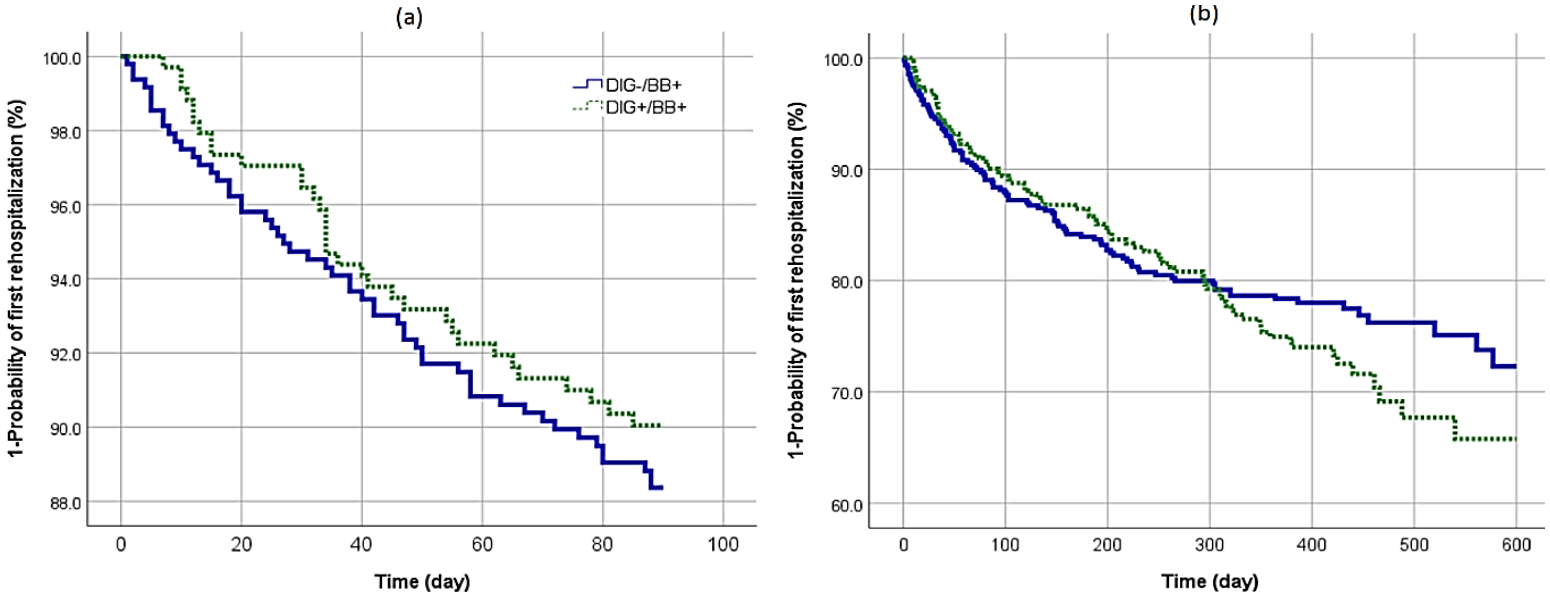

Figure 3. Kaplan-Meier survival curve of the first rehospitalization before 90 days (a) (Log-rank p-value=0.444) and before 2.5 years (b) (Log-rank p-value=0.463) of follow up among patient on DIG−/BB+ therapy versus DIG+/BB+ at discharge

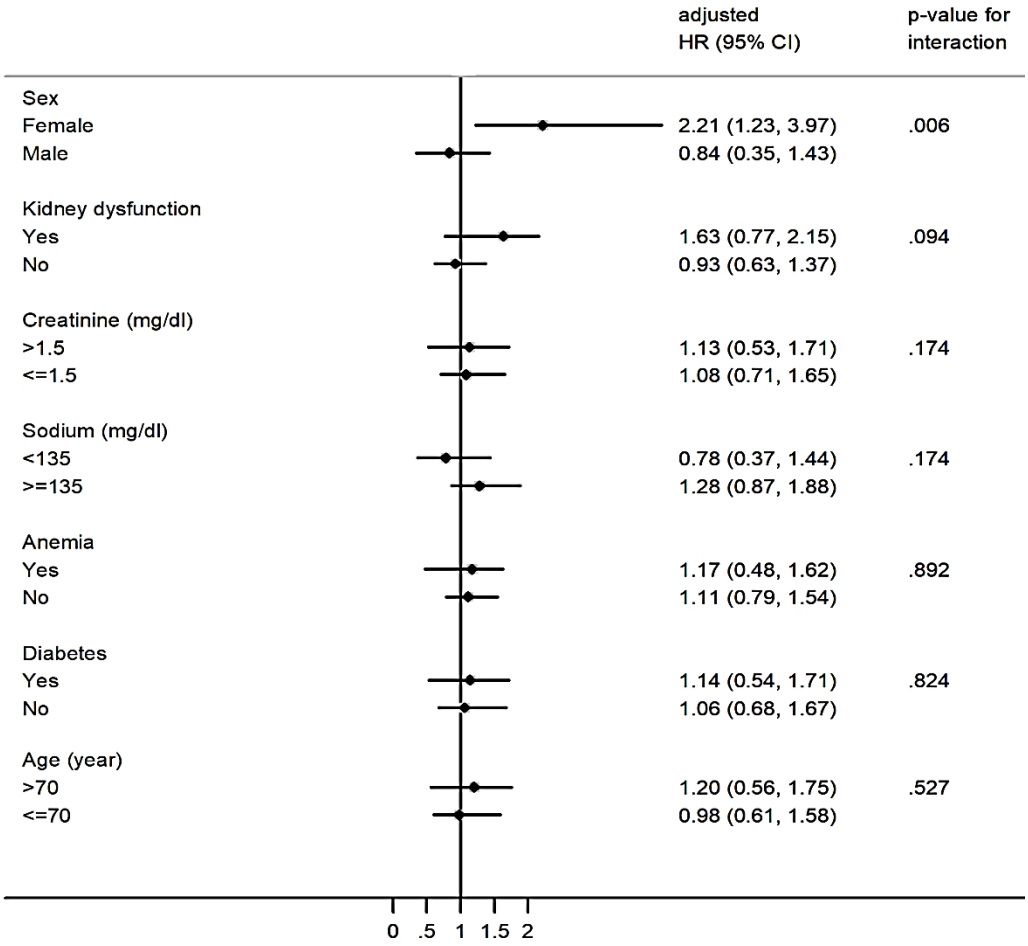

Figure 4. Impact of DIG−/BB+versus DIG+/BB+ therapy on death: subgroup analyses. P values show the significance of effect modification on the multiplicative scale in a sex-stratified proportional cox model adjusted for age, systolic blood pressure, heart rate, ischemic heart disease, anemia, diabetes, valvular dysfunction, COPD, Sodium level, Creatinine level

The DIG trial was conducted more than 2 decades ago, and since then, both diagnosis and treatment of heart failure have changed. However, recommendations regarding digoxin administration in HF patients' treatment are still based on the DIG trial and several other analyses. This point reveals that the DIG trial is still considered the best evidence for digoxin administration in the treatment of HF. The current guideline recommendation is to consider digoxin in HF patients with reduced ejection fraction in sinus rhythm if clinical symptoms persist even after the use of combinations of other treatments.[19]

While most HF patients who had participated in earlier studies that investigated the beneficial effects of beta-blockers were also taking digoxin, it is not clear whether the same results suggesting the beneficial effects of beta-blockers would have been obtained in the absence of digoxin therapy.[20,21] Data on the concomitant use of digoxin and beta-blockers compared with digoxin alone is limited. A prospective study of newly diagnosed HF patients evaluated the impact of digoxin therapy on patients taking modern HF treatment, including beta-blockers in about 40% of patients.[22] This research, unlike our study, demonstrated that adding digoxin to beta-blocker was related to a reduction in morbidity and mortality.[22] Moreover, Dhaliwal et al. studied the effect of digoxin on a group of hospitalized HF patients receiving beta-blockers.[23] They showed that digoxin did not decrease the overall mortality rate.[23]

While numerous trials indicate a correlation between cardiac glycosides and higher mortality rate, a general agreement regarding the validity of this correlation has not been reached.[3,5,7] This notion is more clearly concluded in recent systematic reviews and meta-analyses. In the meta-analysis by Vamos et al., a 14% increase was observed in the risk of mortality in HF patients.[5]

Ziff et al. also reported an increase in the digoxin-associated mortality risk in adjusted analyses (HR = 1.61).[7] However, their data also revealed a non-significant effect (HR = 0.99) in randomized controlled trials, indicating the neutral impact of digoxin on mortality.[7] These studies, which consider the majority of available studies regarding the safety of digoxin, ultimately argue for a large, prospective, randomized, controlled trial evaluating digoxin therapy titrated to target dosing (0.5–0.9 ng/mL) in combination with the current guideline-directed medical treatment.[24]

There are various opinions about the sex-based differences in the effect of adding digoxin in HF patients. A post-hoc analysis of the DIG trial indicated that the effect of digoxin on all-cause mortality was an absolute 5.8% higher in women than in men.[4] However, several observational studies have not affirmed the concern that there is a significantly increased risk of mortality in women.[25] Flory et al. conducted a large nonrandomized clinical trial on 57229 HF patients.[25] They found no evidence of a difference between the 2 sex groups in the relationship of digoxin use with mortality.[25] Several mechanisms have been proposed to justify the sex-based differences in the effect of adding digoxin in HF patients.[4,25] In this regard, serum digoxin levels were measured in less than one-third of patients who participated in the DIG trial 1 month after randomization. The slightly higher serum digoxin levels in women compared to men raise the possibility of sex-associated differences in the pharmacokinetics (what the body does to the drug) of digoxin.[4] Another possible mechanism may involve an interaction between hormone-replacement therapy (HRT) and digoxin. P-glycoprotein, as a digoxin transporter, is inhibited by various steroids, particularly progesterone. Therefore, progesterone can elevate blood digoxin levels by inhibiting P-glycoprotein, and consequently, reduce the excretion of digoxin via the renal tubules.[26] In addition, the Heart and Estrogen/Progestin Replacement study showed an interplay between digoxin and HRT that was related to a higher rate of cardiovascular events.[27] We did not test this hypothesis in our study due to lack of information on the use of HRT. Other endogenous factors associated with sex may also be possible causes.

Unlike the present study, the DIG trial showed that the administration of digoxin slightly reduced the rate of hospitalization.[2] Ahmed et al. reported that digoxin prescription at discharge was associated with decreased 1 year readmission rate.[28] Malik et al. evaluated 11900 HF patients and reported that the cessation of pre-admission digoxin therapy in hospitalized older patients had been associated with lower rate of 4-year rehospitalization.[1] However, Masson et al. showed that digoxin cessation was related to increased readmission in those without beta-blockers, but not among the patients receiving concomitant beta-blocker therapy.[29]

The differential effect of digoxin usage based on concomitant beta-blocker usage is intriguing. The efficacy of beta-blockers in HF patients is significant, and thus, every clinician tries to maintain these patients on some dose of a beta-blocker. The difference in overall clinical severity in patients on and not on beta-blockers is challenging to determine in a retrospective study. It can partially explain differences in results, with the concomitant withdrawal of digoxin being an "innocent bystander". Historically, it is worthwhile to note that the putative mechanism of benefit of cardiac glycoside in HF patients has changed with the prevailing theories of the time from a diuretic to inotrope, and currently, to a neurohormonal modulator. This transition suggests that our knowledge of digoxin's mechanism of benefit is far from complete. Therefore, we need to conduct large, randomized, clinical trials with the consideration of the role of confounding factors to address the potential advantages and disadvantages of adding digoxin to guideline-directed medical therapies.

We are aware of some limitations of the present study that needed to be addressed. First, it was a post hoc analysis of data. Although we have tried to adjust the differences between patients who received beta-blockers and digoxin using multiple regression models, we cannot completely exclude the impact of confounding variables on patients' outcomes. The second limitation was the lack of information regarding serum digoxin levels. Moreover, follow-up through telephone calls may be considered as a limitation. The last limitation of the study was lack of the large sample size.

Conclusion

In patients hospitalized with decompensated HF, beta-blocker plus digoxin administration at discharge was associated with increased 30-month mortality risk in women compared with beta-blocker alone.

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contribution

DS, NS, MGY, and MG contributed to the conception and design of the main study, collection, and data assembly. GhY supervised the current secondary study in the framework of a research project. MY performed the statistical analysis. GhY, MY, MGY, and DS contributed to the interpretation of the results. MY, DS, and GhY drafted the manuscript. All authors read and approved the final version of the manuscript.

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