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Research paper

Combination diuretic therapies in heart failure: Insights from GUIDE-IT

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ABSTRACT

Introduction: Diuretics are the mainstay of maintaining and restoring euvolemia in the management of heart failure. Loop diuretics are often preferred, however, combination diuretic therapy (CDT) with a thiazide diuretic is often used to overcome diuretic resistance and increase diuretic effect. We performed an analysis of the GUIDE-IT study to assess all-cause mortality and time to first hospitalizations in patients necessitating CDT.

Methods: Patients from the GUIDE-IT dataset were stratified by their requirement for CDT with a thiazide to achieve euvolemia. A total of 894 patients were analyzed, 733 of which were treated with loop diuretics alone vs 161 used either chlorothiazide or metolazone in addition to loop diuretics. Kaplan-Meir curves were derived with log-rank *p*-values to evaluate for differences between the groups.

Results: There was no significant difference in all-cause mortality regardless of CDT utilization status (mean survival of 612.704 days vs 603.326 days, $p = 0.083$). On subgroup analysis, there was no significant difference in all-cause mortality amongst those using loop diuretics compared to CDT in the BNP-guided therapy group, (mean survival time 576.385 days vs 620.585 days, $p = 0.0523$), nor the control group (614.1 days vs 588.9 days; $p = 0.5728$). Time to first hospitalization was reduced in all using CDT compared to loop diuretics alone (280.5 days vs 407.2 days, $p < 0.0001$). On subgroup analysis, both the BNP-guided group as well as the control group had reduced time to first hospitalization in the CDT group compared to those who did not require CDT (BNP group: 287.503 days vs 402.475 days, $p \leq 0.0001$; control group 248.698 days vs 399.035 days, $p = 0.0009$).

Conclusion: Use of CDT is associated with earlier time to hospitalization, though no association was identified with increased all-cause mortality. Further prospective studies are likely needed to determine the true risk and benefits of combination diuretic therapy.

1. Introduction

Acute decompensated heart failure (ADHF) accounts for nearly one million admissions in the United States annually and is a common reason for admission, with 88 % of these patients receiving diuretic therapy [1,2]. Diuretic therapy, most commonly loop diuretics, are widely used due to their ability to restore euvolemia and improve symptoms [3–5]. Despite this, evidence supporting long term mortality benefit, as well as guidance on diuretic dosing, is lacking and therefore although it is a Class I indication in treatment of ADHF, it has a Level of Evidence C. [3–7] Thus far clinical trials have demonstrated symptomatic improvement, however, effects on morbidity and mortality are not known as they have not been studied in randomized control trials, though a Cochrane meta-analysis has indicated that patients with chronic heart failure treated with loop and thiazide diuretics appear to have lower risk of death and worsening heart failure compared with placebo. [7,8] The DOSE (Diuretic Optimization Strategies Evaluation) study demonstrated that high-dose loop diuretics are associated with better symptom improvement than low-dose diuretics and equal efficacy of bolus and continuous dosing of diuretics [9].

Diuretics increase urine production by increasing water and electrolyte excretion by the kidneys [10–12]. The diuretics typically used in heart failure patients increase naturesis, each through a different mechanism of action. Loop diuretics, which affect the ascending limb of

Abbreviations: CDT, combination diuretic therapy; BNP, brain natriuretic peptide; ADHF, acute decompensated heart failure; HfrEF, heart failure with reduced ejection fraction.

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Table 1
Baseline characteristics.

Characteristic	Loop diuretic only (n = 733)	Loop diuretic + thiazide (n = 161)
Age (years) median [25th–75th]	63 [53,72]	63 [53,70]
Sex, no. (% female)	246 (36 %)	40 (25 %)
Race, no. (%)		
White	402 (55 %)	88 (55 %)
Black	261 (36 %)	63 (39 %)
Other	32 (4 %)	5 (3 %)
Ethnicity, no. (% Hispanic)	48 (7 %)	10 (6 %)
Duration of HF (months) median [25th–75th]	9 [1,60]	48 [8,96]
Ejection fraction (%) median [25th–75th]	23 [20,30]	25 [20,30]
NYHA class at enrollment, no (%)		
I	53 (7 %)	6 (4 %)
II	387 (53 %)	60 (37 %)
III	269 (37 %)	89 (55 %)
IV	12 (2 %)	5 (3 %)
History of: no. (%)		
Ischemic heart disease	353 (48 %)	94 (58 %)
Diabetes mellitus	322 (44 %)	88 (55 %)
Chronic kidney disease	234 (32 %)	96 (60 %)
Heart rate (beats/min) median [25th–75th]	76 [66,86]	79 [70,88]
Creatinine (mg/dL) median [25th–75th]	1.34 [1.08,1.94]	1.63 [1.22,2.31]
Beta-blocker, no. (%)	694 (95 %)	151 (94 %)
Angiotensin converting enzyme inhibitor, angiotensin receptor blocker, or angiotensin neprilysin inhibitor, no. (%)	122 (17 %)	27 (17 %)
Mineralocorticoid antagonist (%), no. (%)	375 (51 %)	69 (43 %)
Implantable cardioverter defibrillator (%), no. (%)	282 (38 %)	113 (70 %)

Table 2
Baseline medications.

Medications	Median [25th–75th]	Mean
Total daily dose of diuretics	40 [40,80]	71.886
Total daily dose of beta blocker as percent of target dose	25 [12.5,50]	31.974
Total daily dose of aldosterone antagonist as percent of target dose	0 [0,50]	25.070
Total daily dose of ARB or ACE as percent of target dose	16.67 [6.25,50]	32.061
Total daily dose of torsemide	60 [40,100]	74.379
Total daily dose of bumetanide	1 [1,1]	1
Total daily dose of furosemide	40 [40,80]	63.070

the loop of Henle, specifically the Na^+-K^+-$2Cl^-$ symporter [3,10,12], are the most commonly used diuretics in acute decompensated heart failure (ADHF). They produce a brisk response and have relatively short duration of action, allowing for rapid dose titration that can be tailored to the desired effect [13,14]. Unfortunately, there are multiple well-described mechanisms of loop diuretic resistance which create clinical challenges for optimal decongestion in the setting of ADHF. [3,13,15] One such mechanism is that the failure to augment sodium and water reabsorption despite increasing doses of loop diuretics is because as exposure to loop diuretics build, sodium and water retention is enhanced as there is upregulation and hypertrophy of the electrolyte transporters in the loop of Henle or Distal convoluted table [1]. Adaptive changes are thought to occur secondary to hypertrophy from increased transcellular transport capacity due to increased stimulation by the renin-angiotensin and sympathetic nervous systems [13].

A common practice to overcome diuretic resistance is sequential nephron blockade, where a second diuretic – typically a thiazide, which inhibit the Na^+-Cl^- symporter in the distal convoluted tubule (DCT) – is used in combination with the loop diuretics to potentiate salt and water excretion. [10,12] With sequential nephron blockade, sodium reabsorption is blocked in the DCT, allowing enhanced naturesis. While this strategy typically produces the desired effect of increased urine output in patients with ADHF and refractory congestion over the short term of their hospitallization, concerning trends in regards to diuretics have been identified. [16,17]

These studies are largely retrospective and it remains unclear whether thiazide diuretics cause direct harm in this capacity or whether their use simply identifies patients with more advanced disease and worse cardiorenal pathophysiology, which are themselves independently associated with worse prognosis and increased mortality in ADHF [13]. It is imperative that in diuretic-resistant patients, the daily Na^+ intake should be less than the acute Na^+ loss to ensure a negative sodium balance, and promote diuresis, and a strict low sodium diet must be followed [15]. Notably, patients with chronic kidney disease (CKD) may require higher doses of diuretics due to decreased diuretic delivery to the kidney, though this does not indicate diuretic resistance. This decreased delivery to the kidney is thought to be because of decreased renal blood flow, hypoalbuminemia causing an increased volume of distribution, and a decreased proximal tubule (PT) secretion of the diuretic [15].

Despite diuretics being a cornerstone of heart failure treatment, there is a lack of clinical data to guide diuretic use in the setting of ADHF with diuretic resistance [3]. Despite common use of combination diuretic therapy (CDT), relatively few studies have been published to establish a guide to a standard therapeutic effect [1]. Further, few studies have looked at a class effect of combination diuretic therapy on all-cause mortality and time to first heart failure hospitalization. This study aims to begin answering these questions, and pose questions of future interest.

2. Methods

2.1. Study design and participants

The methods and results of the GUIDE-IT trial have been previously published [14]. The GUIDE-IT study was a randomized multicenter clinical trial conducted between January 16, 2013 and September 20, 2016 at 45 clinical sites in the United States and Canada. The trial was

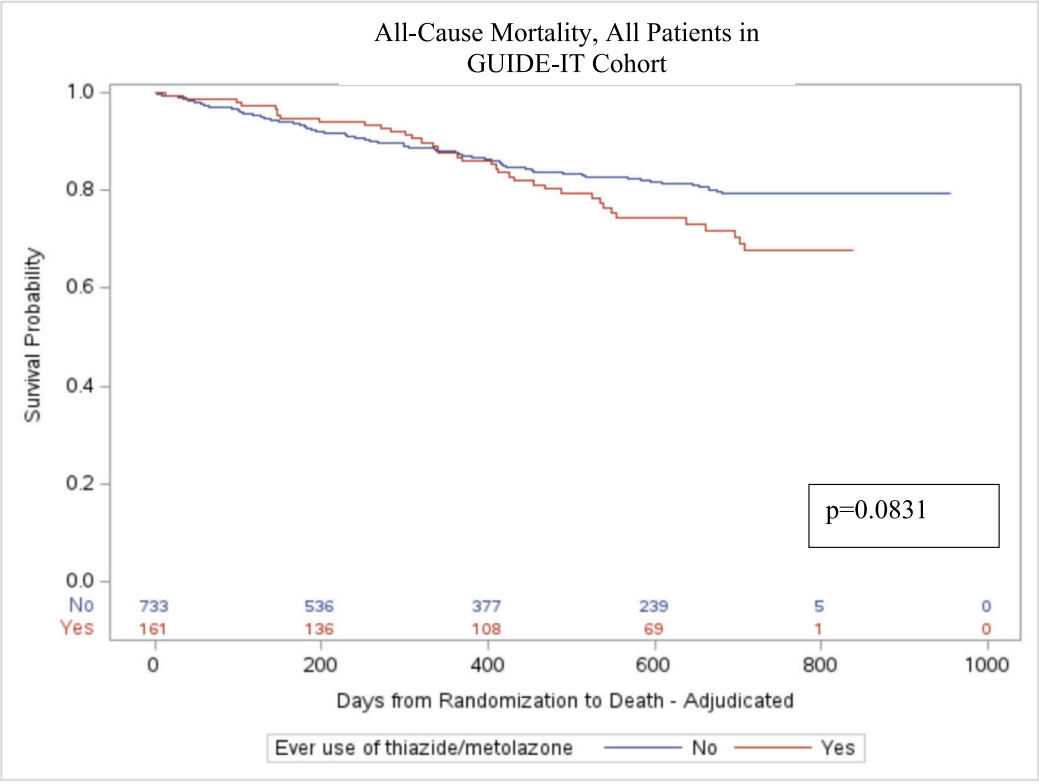

Fig. 1. All-Cause mortality of all patients in GUIDE-IT study.

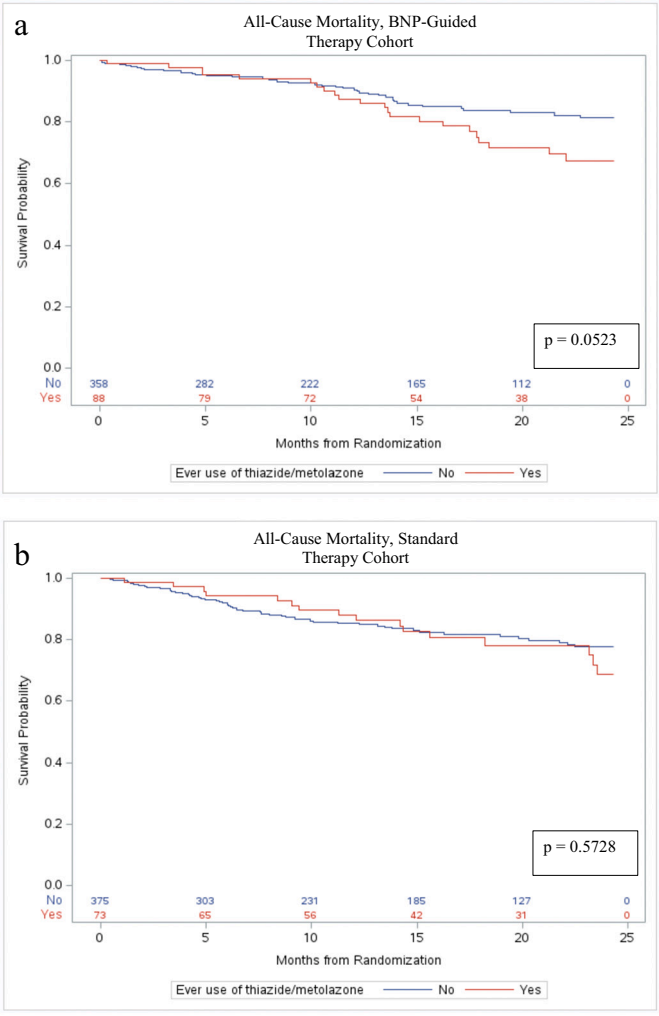

Fig. 2. a. All-Cause Mortality Amongst BNP-guided group.
b. All-Cause Mortality Amongst Standard Therapy group.

designed to determine if a BNP-guided treatment strategy improved clinical outcomes compared to standard care in heart failure with reduced ejection fraction (HfrEF) patients. For our study, we included the patients from the GUIDE-IT study who had complete data, and were treated in the trial with loop diuretics or loop diuretics in combination with a thiazide diuretic.

2.2. Statistical methods

Categorical variables were reported as counts and percentages, while continuous variables were expressed as means with standard deviations if normally distributed, or as medians (inter-quartile range) if not normally distributed. CDT use was defined as ever use of a thiazide diuretic in addition to baseline loop diuretic throughout the trial period (i.e., from time of randomization to death or censoring). Kaplan-Meier curves were plotted to compare the outcomes between use of loop diuretics or not, stratified by types of treatment received (experimental and control). Log rank test was used to test the difference in survival time between groups at 0.05 significance level. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics

Of the 894 patients in the GUIDE-IT trial, 894 had complete data and were included in our study. As in the initial study, the groups were similar (Table 1). The median age was 63 in both groups. In the loop diuretic use group, 30 % were female while in the CDT group 25 % were female. Both groups had similar race and ethnicity distributions. Their NYHA functional class was similar with each study group having approximately 90 % of patients being NYHA II-III and 2–3 % NYHA IV. Other characteristics were similar as outlined in Table 1. Baseline medications, including daily dose of diuretics and parentage of target doses of guideline directed medical therapies are included in Table 2.

3.2. All-cause mortality outcomes

Of the 894 patients with complete data, 733 were treated with loop diuretics without thiazide diuretic, while 161 were treated with combination diuretic therapy. Although there was a trend towards a difference, there was no statistically significant difference in all-cause mortality mean survival time regardless of CDT utilization status ($p = 0.0831$) with no CDT having a mean survival time of 603.326 days and those with use of CDT having a mean survival time of 612.704 days (Fig. 1).

A sub-group analysis was performed by stratifying the BNP-guided therapy group from the control group within the original GUIDE-IT dataset. Within both the BNP-guided subgroup (Fig. 2a), as well as the control group (Fig. 2b), there was no significant decrease in mean survival time between those using CDT compared to loop diuretics alone. Within the BNP-guided therapy group (Fig. 2a), patients using CDT had a mean survival time of 576.385 days, compared to those with only use of a loop diuretic who had a mean survival time of 620.585 days ($p = 0.0523$). Within the control group (Fig. 2b), those using CDT having a mean survival time of 614.105 days compared to no CDT use having a mean survival time of 588.857 days ($p = 0.5728$).

3.3. Time to first heart failure hospitalization outcomes

There was a significant difference in time to first hospitalization for patients who were treated with CDT ($p \leq 0.0001$) with patients who were not treated with CDT having a mean survival time of 407.163 days and those utilizing of CDT having a mean survival time of 280.472 days (Fig. 3).

In both the BNP-guided group as well as the control group (Fig. 4a, b), there was reduction in time to first hospitalization for patients treated with CDT. Within the BNP-guided therapy group, patients using CDT were hospitalized after a mean of 287.503 days, while those never using CDT were hospitalized after a mean of 402.475 days ($p < 0.0001$). In the control group, those using CDT were hospitalized after a mean 248.698 days, and those never using CDT being hospitalized after a mean 399.035 days.

4. Discussion

Our study presents novel data, prospectively collected, evaluating the use of combination diuretic therapy in patients with acute decompensated heart failure. The natriuretic response to diuretics depends on several factors, including salt intake, diuretic dose, renal function, and right atrial pressure [15] and may be affected by excessive sodium intake and frequent NSAID use, amongst others [3,18]. Though loop diuretics remain the foundation of restoring euvolemia in treatment of ADHF, their use is complicated by diuretic resistance which develops overtime, decreasing the amount of natriuresis following a defined dose of loop diuretic decreasing. Strategies to negate diuretic resistance have included use of CDT, most commonly with thiazide and thiazide-like

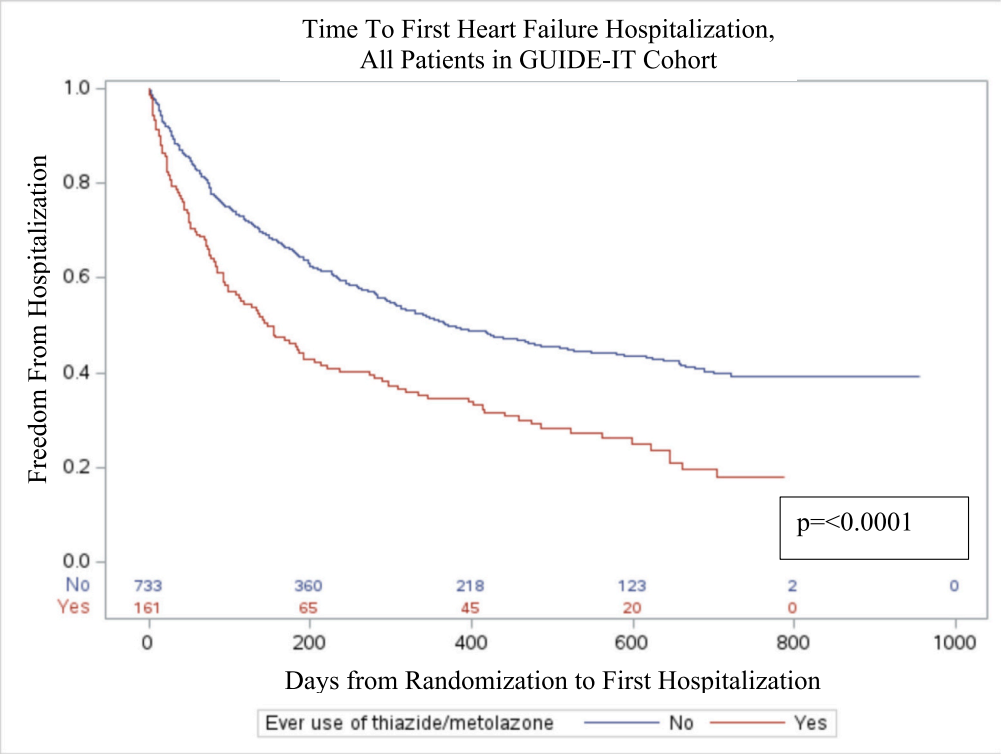

Fig. 3. Time to First hospitalization of all patients in GUIDE-IT study.

diuretics, such as metolazone. There remains little data on the use of CDT, including its effect on mortality, amongst other outcomes.

There was no difference in all-cause mortality between those requiring CDT and those who did not. The outcomes were stratified by treatment arm of the clinical trial, with the rationale of BNP-nonresponse being a signal of more advanced heart failure state destined to poorer outcomes. After stratification, there was a mortality trend that was not statistically different amongst the BNP-guided therapy group. In all groups, the time to first heart failure hospitalization amongst those using CDT was decreased compared to nonusers, supporting patients requiring CDT are at higher risk for more advance heart failure. Further, several studies have implicated a correlation between doses of diuretics and worsening prognosis in patients presenting with acute decompensated heart failure, however, to the authors' knowledge, there are no definite causal relationships established [13], though some studies have implicated increased diuretic resistance predicts death [15]. More recent studies have related mortality to renal function at time of hospital discharge, with renal dysfunction being a prognostic predictor in heart failure patients [19–22], but the pathophysiologic mechanisms remain elusive as there are several pathways [19]. Interestingly, worsening renal function is not necessarily associated with diuretic resistance [15] and is actually associated with improved mortality, whereas improving renal function is associated with increased mortality [22]. This associations remains an area for further exploration of the effect of CDT on renal function as it relates to mortality.

Another possibility is that the BNP-guided group had swifter up-titration of diuretics to lower the BNP. Increased doses of diuretics, particularly use of CDT, have been associated with increased electrolyte derangements [15]. Adjuvant metolazone use has been strongly associated with hyponatremia, hypokalemia, and worsening renal function, notably mostly related to adverse events during ADHF hospitalizations [23]. Typically, as outlined by the DOSE (Diuretic Optimization Strategies Evaluation) trial, up-titration of loop diuretics is preferred in ADHF as there is no increase in mortality, despite noted worsening renal function [9]. This may be supported by our data given the insignificant increased mortality associated with CDT. Thus far, it has been ill-defined at which dose of loop diuretic to initiate CDT given an inability to well-define diuretic resistance. This study demonstrated CDT was not associated with detectable differences in mortality, and that patients who did receive CDT were more likely to be hospitalized for heart failure, however, the rationale for these difference remains an area of future interest and study.

4.1. Limitations

This study has several important limitations. First, the study is a secondary analysis; the data being analyzed was not specifically designed to answer the question of study. Additionally, there may be differences in the patient population of each cohort that drives the use of CDT as these cohorts were not random and the use of CDT may be secondary to patient specific variables.

5. Conclusion

Use of loop diuretic - thiazide CDT is associated with decreased time to first hospitalization, but is not associated with increased all-cause mortality in all patients. This study adds to the current knowledge of the effects of combination diuretic therapy, but would likely require a randomized prospective trial to fully determine the true risk/benefits of combination diuretic therapy.

Statement of ethics

This study protocol was reviewed and approved by University of Florida's Institutional Review board, approval number IRB202001868.

Consent to participate statement

Our study is a reanalysis of the GUIDE-IT dataset, therefore no consent was obtained. Participants in the original study were provided

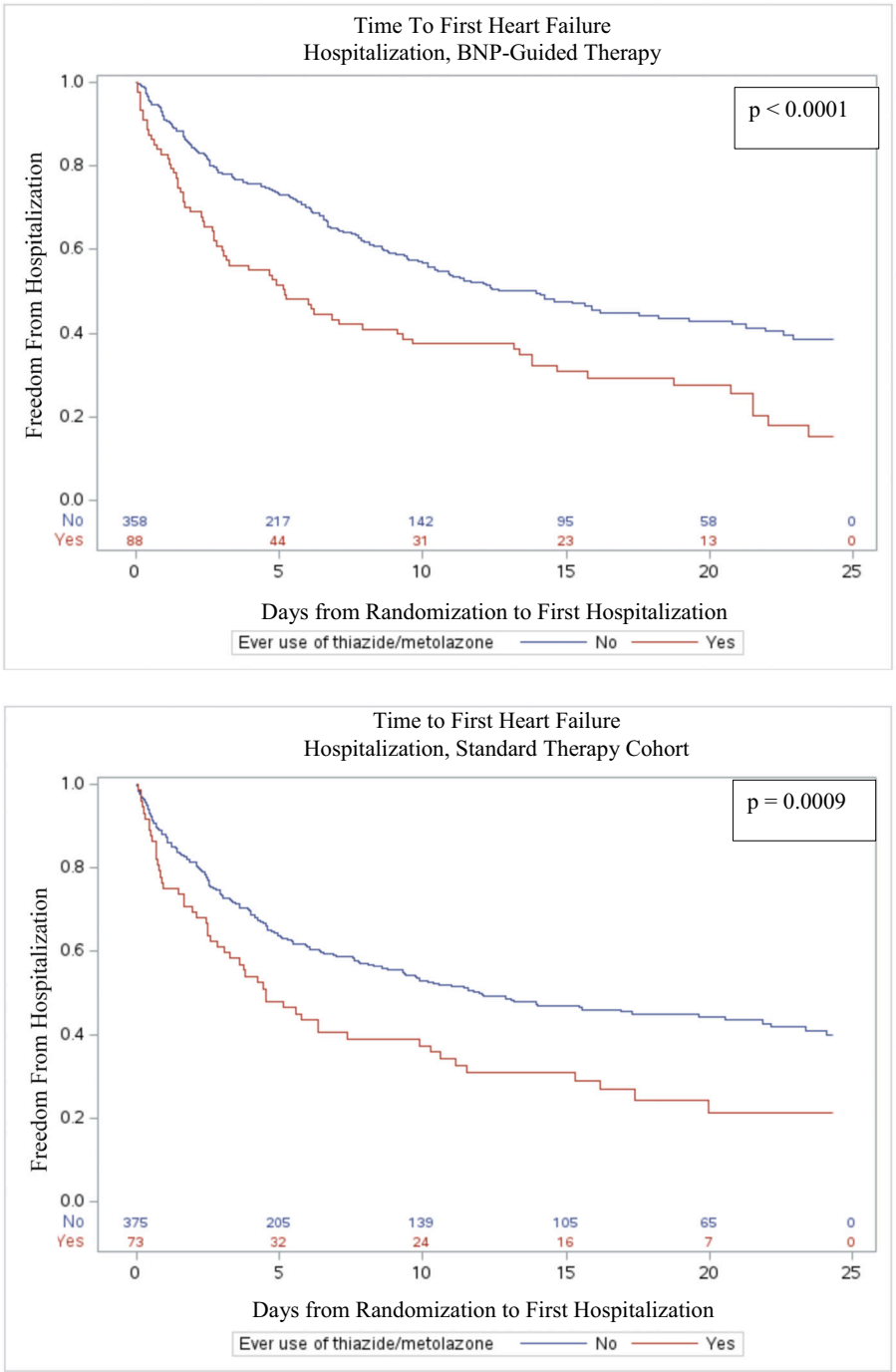

Fig. 4. a. Time to first heart failure hospitalization amongst BNP-guided therapy group.
b. Time to first heart failure hospitalization amongst standard therapy group.

written informed consent. [14].

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CRediT authorship contribution statement

Jeffery Budweg: Investigation, Methodology, Writing – original draft. **Mustafa M. Ahmed:** Conceptualization, Writing – review & editing. **Juan R. Vilaro:** Writing – review & editing. **Mohammad A. Al-Ani:** Conceptualization, Writing – review & editing. **Juan M. Aranda:** Conceptualization, Writing – review & editing. **Yi Guo:** Data curation, Formal analysis, Software. **Ang Li:** Formal analysis. **Sandip Patel:** Conceptualization. **Alex M. Parker:** Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Data availability

The data used in the analysis of this manuscript is publicly available. The data is available by request from the NIH via the BioLINCC website (https://biolincc.nhlbi.nih.gov/studies/guide_it/).

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References

[1] M.P. Moranville, S. Choi, J. Hogg, A.S. Anderson, J.D. Rich, Comparison of metolazone versus chlorothiazide in acute decompensated heart failure with diuretic resistance, Cardiovasc. Ther. 33 (2) (2015) 42–49.
[2] P.E. Marik, M. Flemmer, Narrative review: the management of acute decompensated heart failure, J. Intensive Care Med. 27 (6) (2012) 343–353.
[3] G.M. Felker, D.H. Ellison, W. Mullens, Z.L. Cox, J.M. Testani, Diuretic therapy for patients with heart failure: JACC state-of-the-art review, J. Am. Coll. Cardiol. 75 (10) (Mar 2020) 1178–1195.
[4] K.T. Weber, Furosemide in the long-term management of heart failure: the good, the bad, and the uncertain, J. Am. Coll. Cardiol. United States 44 (2004) 1308–1310.
[5] S.A. Hunt, ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to update the 2001 Guidel), J. Am. Coll. Cardiol. 46 (6) (Sep 2005) e1–82.
[6] R.F. Faris, M. Flather, H. Purcell, P.A. Poole-Wilson, A.J.S. Coats, WITHDRAWN: diuretics for heart failure, Cochrane Database Syst. Rev. 4 (4) (2016 Apr) CD003838.
[7] C.W. Yancy, M. Jessup, B. Bozkurt, J. Butler, D.E.J. Casey, M.H. Drazner, et al., 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, J. Am. Coll. Cardiol. 62 (16) (Oct 2013) e147–e239.
[8] P. Ponikowski, A.A. Voors, S.D. Anker, H. Bueno, J.G.F. Cleland, A.J.S. Coats, et al., 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)developed with the special contribution o, Eur. Heart J. 37 (27) (Jul 2016) 2129–2200.
[9] G.M. Felker, K.L. Lee, D.A. Bull, M.M. Redfield, L.W. Stevenson, S.R. Goldsmith, et al., Diuretic strategies in patients with acute decompensated heart failure, N. Engl. J. Med. 364 (9) (Mar 2011) 797–805.
[10] M.C.A. Kehrenberg, H.S. Bachmann, Diuretics: a contemporary pharmacological classification? Naunyn Schmiedebergs Arch. Pharmacol. 395 (6) (Jun 2022) 619–627.
[11] D.H. Ellison, Clinical pharmacology in diuretic use, Clin. J. Am. Soc. Nephrol. 14 (8) (Aug 2019) 1248–1257.
[12] Wisher D. Martindale, The complete drug reference, 37th ed, J. Med. Libr. Assoc. 100 (2012) 75–76.
[13] G. Casu, P. Merella, Diuretic therapy in heart failure – current approaches, cardiomyopathy and heart failure, Eur. Cardiol. Rev. 10 (1) (2015) 42–47.
[14] G.M. Felker, K.J. Anstrom, K.F. Adams, J.A. Ezekowitz, M. Fiuzat, N. Houston-Miller, J.L. Januzzi Jr., D.B. Mark, I.L. Piña, G. Passmore, D.J. Whellan, H. Yang, L. S. Cooper, E.S. Leifer, P.O.C. Desvigne-Nickens, Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial, JAMA 318 (8) (2017) 713–720.
[15] C.S. Wilcox, J.M. Testani, B. Pitt, Pathophysiology of diuretic resistance and its implications for the management of chronic heart failure, Hypertension 76 (4) (2020) 1045–1054.
[16] A. Ahmed, A. Husain, T.E. Love, G. Gambassi, L.J. Dell'Italia, G.S. Francis, et al., Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods, Eur. Heart J. 27 (12) (Jun 2006) 1431–1439.
[17] H. Schartum-Hansen, K.H. Løland, G.F.T. Svingen, R. Seifert, E.R. Pedersen, J. E. Nordrehaug, et al., Use of loop diuretics is associated with increased mortality in patients with suspected coronary artery disease, but without systolic heart failure or renal impairment: an observational study using propensity score matching, PloS One 10 (6) (2015) e0124611.
[18] E.R. Heerdink, H.G. Leufkens, R.M. Herings, J.P. Ottervanger, B.H. Stricker, A. Bakker, NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics, Arch. Intern. Med. 158 (10) (May 1998) 1108–1112.
[19] M.A. Brisco, S.G. Coca, J. Chen, A.T. Owens, B.D. McCauley, S.E. Kimmel, et al., Blood urea nitrogen/creatinine ratio identifies a high-risk but potentially reversible form of renal dysfunction in patients with decompensated heart failure, Circ. Heart Fail. 6 (2) (Mar 2013) 233–239.
[20] J.S. Bock, S.S. Gottlieb, Cardiorenal syndrome: new perspectives, Circulation 121 (23) (Jun 2010) 2592–2600.
[21] A. Rastogi, G.C. Fonarow, The cardiorenal connection in heart failure, Curr. Cardiol. Rep. 10 (3) (May 2008) 190–197.
[22] J.M. Testani, B.D. McCauley, J. Chen, S.G. Coca, T.P. Cappola, S.E. Kimmel, Clinical characteristics and outcomes of patients with improvement in renal function during the treatment of decompensated heart failure, J. Card. Fail. 17 (12) (Dec 2011) 993–1000.
[23] M.A. Brisco-Bacik, J.M. Ter Maaten, S.R. Houser, N.A. Vedage, V. Rao, T. Ahmad, et al., Outcomes associated with a strategy of adjuvant metolazone or high-dose loop diuretics in acute decompensated heart failure: a propensity analysis, J. Am. Heart Assoc. 7 (18) (Sep 2018) e009149.