

ORIGINAL ARTICLE

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Diltiazem vs metoprolol for atrial fibrillation with rapid ventricular response in heart failure with reduced ejection fraction in emergency departments

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Abstract: **Objective:** As emergency department (ED) visits for atrial fibrillation (AF) grow, comorbidities lead to challenging treatment scenarios. There are limited data evaluating the safety of diltiazem in the acute management of AF with rapid ventricular rate (RVR) in patients with heart failure with reduced ejection fraction (HFrEF). The objective of this study was to evaluate the safety of diltiazem vs metoprolol in patients presenting to the ED with AF with RVR with HFrEF.

Methods: This multicenter, retrospective, cohort study evaluated patients with AF with RVR with HFrEF who received either intravenous (IV) diltiazem or metoprolol in the ED. The primary endpoint was worsening heart failure, defined as an increase in supplemental oxygen requirement, acute kidney injury (AKI), or inotrope administration. Secondary endpoints included bradycardia, systolic blood pressure (SBP) <90 mmHg, or atropine administration.

Results: Of the 5,465 patients screened, 62 (1.1%) patients were included for analysis. Forty-nine (79%) patients received IV diltiazem and 13 (21%) received IV metoprolol. The primary endpoint of worsening heart failure occurred in 26.5% in the diltiazem cohort and 15.4% in the metoprolol cohort ($P=0.493$). There were no differences in increased need for supplemental oxygen, incidence of AKI, or inotropic support. There were no differences in the secondary safety endpoints.

Conclusion: For ED management of patients with AF with RVR with HFrEF, treatment with IV diltiazem did not lead to an increase in worsening heart failure compared to IV metoprolol. Future prospective trials are needed to evaluate this treatment approach in this population.

Keywords: Atrial Fibrillation; Diltiazem; Heart Failure; Metoprolol

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1. Introduction

Intravenous diltiazem was not associated with increased signs of worsening heart failure compared to metoprolol in emergency department (ED) patients with atrial fibrillation (AF) with rapid ventricular response (RVR) and heart failure with reduced ejection fraction (HFrEF). In this multicenter retrospective cohort study, both agents appeared to be used safely despite guideline recommendations cautioning against the use of non-dihydropyridine calcium channel blockers in this population. These findings contribute to the growing body of evidence supporting the real-world safety of diltiazem in the acute setting.

ED visits for atrial fibrillation have grown 30.7% from 2007 to 2014 in the United States (US) (1). Patients frequently

present with comorbid heart failure (HF), occurring in up to 56% of patients (2-3). Metoprolol and diltiazem are first-line rate control options for AF RVR in hemodynamically stable patients (4-6). However, the 2014 and 2019 American College of Cardiology / American Heart Association / Heart Rhythm Society (ACC/AHA/HRS) clinical practice guidelines recommend avoiding non-dihydropyridine (non-DHP) calcium channel blockers (CCB), such as diltiazem or verapamil, in patients with significant HF due to risk of harm (4,5).

Non-DHP CCBs exert a negative inotropic effect via antagonism of calcium-mediated electromechanical coupling (7). The guideline recommendation to avoid non-DHP CCBs is based on chronic administration and does not include patients with HFrEF (8-13). Although metoprolol, a beta-blocker, is a negative inotrope, there is chronic improve-

ment of cardiac output with beta-blocker use in patients with HFrEF not observed with non-DHP CCBs. Additionally, the negative inotropic effects of diltiazem were demonstrated in vitro at levels 10 times peak plasma concentrations of therapeutic dosing (7). In vivo data suggests diltiazem increases ejection fraction (EF) one hour after administration (7). Overall, there is limited clinical outcomes data on the use of diltiazem in this population.

Despite concerns from guidelines, a scarce amount of safety data, and lack of EF information in the ED, diltiazem is the predominant agent administered for AF with RVR (6). Recent small studies evaluated the efficacy and safety of diltiazem compared to metoprolol in AF with RVR in the ED in patients with varying degrees of HF (14-18). One study evaluated 34 patients with HFrEF in AF with RVR in the ED. No significant difference was detected in rate control, worsening HF, or readmission (14). Another study evaluated 125 patients treated for AF with RVR in ED and HFrEF. No difference was detected in adverse events despite a higher incidence of worsening HF in the diltiazem cohort (15). A 2023 systematic review of AF with RVR management in patients with acute decompensated HF highlighted the lack of evidence to inform safe and effective decision making (19). The purpose of this study is to evaluate safety outcomes of diltiazem compared to metoprolol for the treatment of AF in HFrEF in the ED.

2. Methods

2.1. Study design and population

This was a multi-center, retrospective, cohort study exempt from human subjects research per the institutional review board. Adults ≥ 18 years of age presenting to any of six community hospital EDs and one academic medical center within a health system from July 2016 through June 2021 were evaluated. Included patients had any admission diagnosis containing AF, HF on the encounter problem list, and received either IV diltiazem or IV metoprolol for AF with RVR in the ED. Patients with atrial flutter were included due to their similar pathophysiology, clinical presentation, and management strategies in the ED and similar treatment goals in the acute setting. For the purposes of this study, atrial flutter was defined as a supraventricular tachyarrhythmia characterized by organized atrial activity with a sawtooth pattern on electrocardiogram (5). Patients were excluded if they did not have a prior echocardiogram with an EF of $\leq 40\%$, had a systolic blood pressure < 90 mmHg prior to intervention, or received both IV diltiazem and IV metoprolol in the ED. Patients were included for analysis if they ultimately received IV metoprolol in the IV diltiazem group or IV diltiazem in the IV metoprolol group after admission.

2.2. Data collection and Outcome measures

Baseline characteristics collected included demographics, vital signs, EF, home medication lists, and additional agents ad-

ministered for rate control in the ED. Baseline severity was assessed using the rapid emergency medicine score (REMS), a predictor of in-hospital mortality in critically ill patients (20). The primary composite endpoint was signs of worsening HF within 48 hours of intervention defined as requirement of new IV inotropic support, new or increased requirement of supplemental oxygen (O₂), or development of acute kidney injury (AKI). New inotropic support was defined as initiation of dobutamine, dopamine, epinephrine, milrinone, or norepinephrine. AKI was defined as an increase in serum creatinine (SCr) by ≥ 0.3 mg/dL within 48 hours or any increase in SCr to ≥ 1.5 times baseline (21).

The secondary safety endpoints were the development of hypotension defined by an episode of systolic blood pressure < 90 mmHg and average cumulative dose of loop diuretic in furosemide equivalents administered within 24 hours (22). Although the data collected was based on admission diagnoses for AF with RVR, not all patients presented with a HR ≥ 100 bpm. To evaluate patients with AF with RVR, a subgroup analysis included patients with an initial heart rate ≥ 110 bpm and evaluated time to rate control (HR < 110 bpm) (4-5,23). Endpoints included any episode of bradycardia, defined as heart rate < 50 bpm through 12 and 24 hours, atropine administration, length of stay, and mortality.

2.3. Statistical analysis

All data were electronically extracted from the electronic health record. Univariate descriptive statistics were calculated for all baseline characteristics and endpoints. Continuous variables were reported as mean $\pm$ standard deviation and categorical variables were reported as numbers and percentages. Parametric data were compared using t-tests or Welch's t-tests. Continuous non-parametric data and categorical variables were compared with the Mann-Whitney U test and two-sided Fisher's exact test, respectively. An alpha level of 0.05 was established a priori to determine significance. Statistical analysis was performed via RStudio (version 3.6.3).

3. Results

Initial screening identified 5,465 patients who received either IV diltiazem or IV metoprolol for an admission diagnosis of AF in the ED during the study period (Figure 1). Of these patients, 581 (10.6%) had both an admission diagnosis of AF and HF. 519 (9.5%) patients were excluded due to lack of a historic echocardiogram or a documented EF $> 40\%$ (8.4%) or administration of both IV diltiazem and IV metoprolol (1.1%). In total, 62 (1.1%) patients met eligibility criteria. Of the patients included in analysis, 49 (79%) received IV diltiazem and 13 (21%) received IV metoprolol.

There were no differences in baseline characteristics (Table 1). Mean REMS was 7 for both cohorts ($P=0.800$) conferring a 3% predicted in-hospital mortality. There was no significant difference in documented EF between cohorts. However, the diltiazem cohort had a higher percentage of patients with an

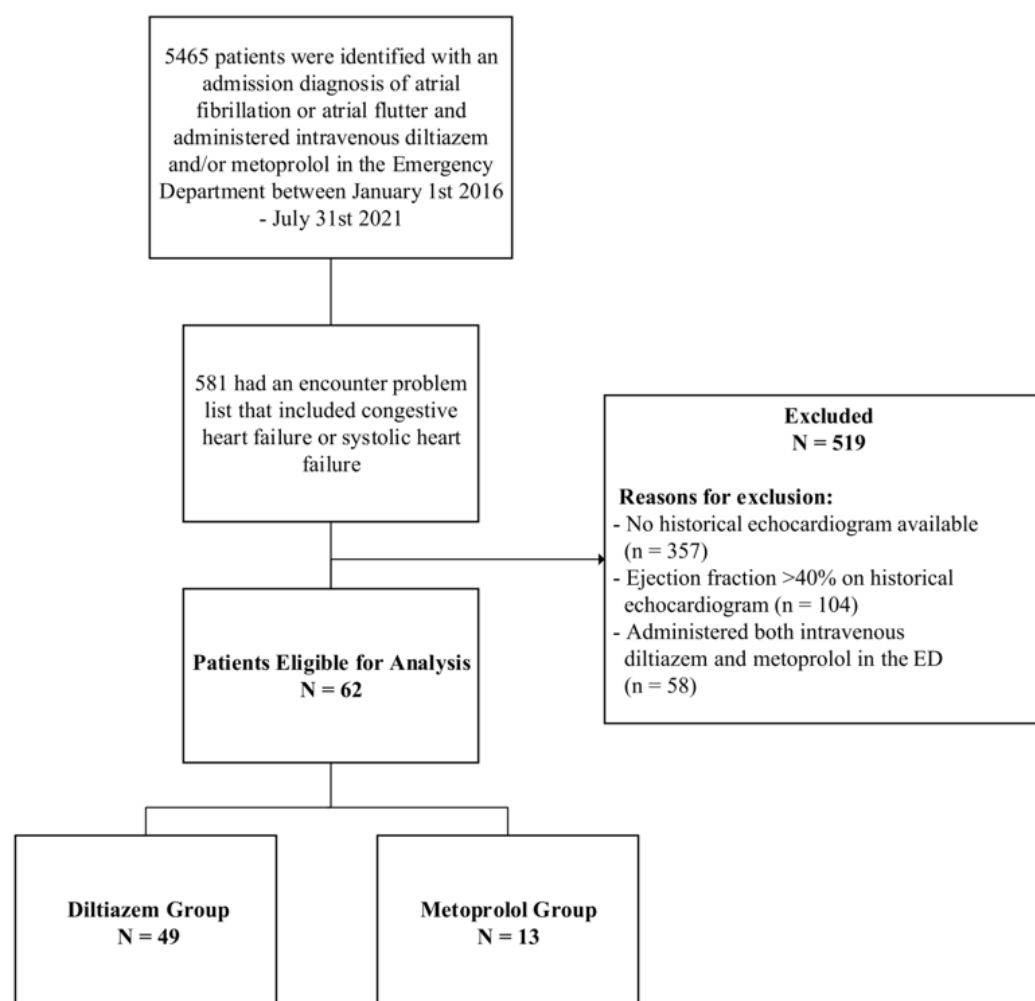


Figure 1 Flow diagram of patient identification, selection, and allotment

EF <25%, 49% vs 23%. Additional comparisons are described in figure 2.

This figure depicts the two rate control medications utilized for AF with RVR in the seven EDs across the health system. The figure provides information regarding medication crossover within 48 hrs, including mean dose and mean number of boluses of diltiazem and metoprolol administered and the incidence of additional agents administered for the management of AF in the ED.

There was no significant difference in the composite endpoint of signs of worsening HF between the diltiazem and metoprolol cohorts (26.5% vs 15.4%, $P=0.493$) (Table 2) or in any of the individual components of the composite. The most frequently met endpoint was an increased need for supplemental O₂ (36.7% vs 23.1%, $P=0.514$) in the diltiazem and metoprolol cohorts, respectively. AKI occurred in 22.4% and 7.7% ($P=0.431$) of patients in the diltiazem and metoprolol cohorts, respectively. New inotropic support was required in 10.2% and 15.4% ($P=0.630$) of patients in the diltiazem and metoprolol cohorts, respectively. There were no significant differences in the secondary safety endpoints (Table 3).

In the efficacy subgroup analysis of patients with a heart rate prior to treatment >110bpm, both cohorts had similar heart rates immediately prior to medication administration, 134 vs 132 bpm ($P=0.440$). There was no significant difference in time to rate control (0.88 vs 0.45 hours, $P=0.493$) between the diltiazem and metoprolol cohorts, respectively (Table 4). There was no difference in rate control at any of the 15, 30, 60, or 90 minute time intervals.

4. Discussion

In this multicenter retrospective cohort, intravenous diltiazem was not associated with increased signs of worsening heart failure compared to intravenous metoprolol in ED patients with HFrEF and AF with RVR. Concerns about the risk of non-DHP CCBs originate from literature in patients with chronic AF and may not reflect the risk in the population studied (9-10). Patients with AF with RVR present with a 15-25% reduction in cardiac output (24). Reductions in cardiac output may be due to beat to beat variability in ventricular filling from rhythm irregularity, neurohormonal changes, and shortened cardiac cycles resulting in inefficient ventric-

Table 1 Baseline characteristics

Characteristic	Diltiazem (n=49)	Metoprolol (n=13)	P-value
Age (years), mean (SD)	67.8 (14)	69.2 (14)	0.744
Race			0.883
Asian, n (%)	2 (67.7)	1 (33.3)	
Black, n (%)	13 (81.3)	3 (18.8)	
Caucasian, n (%)	31 (77.5)	9 (22.5)	
Unavailable, n (%)	3 (100)	0 (0)	
Female sex, n (%)	16 (80)	4 (20)	1.000
Heart rate (bpm), mean (SD)	120 (23.2)	114 (17.8)	0.426
Respiratory rate, mean (SD)	22.1 (4.75)	20.5 (2.79)	0.350
Oxygen saturation (%), mean (SD)	95.9 (3.40)	95.1 (5.09)	0.601
Systolic blood pressure (mmHg), mean (SD)	132 (23.2)	141 (23.3)	0.186
Body mass index (kg/m²), mean (SD)	35.4 (16.7)	33.1 (7.83)	0.838
REMS, mean (SD)	7 (2.56)	7 (1.68)	0.800
Most recent EF, n (%)			0.133
<20%	7 (77.8)	2 (22.9)	
20-25%	17 (94.4)	1 (5.6)	
25-30%	4 (100)	0 (0)	
30-35%	6 (54.5)	5 (45.5)	
35-40%	15 (75)	5 (25)	
End stage renal disease, n (%)	1 (100)	0 (0)	1
Home medication, n (%)			
Diltiazem	4 (100)	0 (0)	0.571
Metoprolol	28 (75.7)	9 (24.3)	0.534
Loop diuretic	39 (78)	11 (22)	1
Admission diagnosis, n (%)			
Atrial fibrillation	48 (81.4)	11 (18.6)	0.109
Atrial flutter	1 (33.3)	2 (66.7)	
Additional medications administered in ED, n (%)			
IV or PO amiodarone	6 (12.2%)	1 (7.7%)	1
IV or PO digoxin	7 (14.3%)	4 (30.8%)	0.221

SD: Standard deviation; bpm: Beats per minute; REMS: Rapid emergency medicine score; EF: Ejection fraction; ED: Emergency department; IV: Intravenous; PO: Oral

Table 2 Composite endpoint of signs of worsening heart failure within 48 hours

Primary endpoint	Diltiazem (n=49)	Metoprolol (n=13)	P-value
Composite endpoint			
Signs of worsening heart failure within 48 hrs, n (%)	13 (86.7)	2 (13.3)	0.493
Composite components			
AKI, n (%)	11 (91.7)	1 (8.3)	0.431
Increase in supplemental O ₂ , n (%)	18 (85.7)	3 (14.3)	0.514
New inotropic support, n (%)	5 (71.4)	2 (28.6)	0.630
Inotrope administered			
Dobutamine, n (%)	1 (33.3)	2 (66.7)	
Milrinone, n (%)	3 (100)	0 (0)	
Norepinephrine, n (%)	1 (100)	0 (0)	

AKI: Acute kidney injury

ular contraction and decreased diastolic filling times (25). Acutely treating AF with RVR with diltiazem in HF has been demonstrated to increase cardiac output and stroke volume while decreasing systemic vascular resistance. Although data suggests diltiazem is safe in this population, there is a paucity of evidence to inform agent selection for acute management. Despite concerns about using diltiazem in patients with HFrEF, this study demonstrated that 79% of patients with

HFrEF received diltiazem for AF. The most recent European Society of Cardiology atrial fibrillation clinical practice guidelines reflect a paradigm shift in suggesting diltiazem as refractory therapy (26). Based on most recent AHA clinical practice guideline recommendations, it would be concerning to administer diltiazem to this population (4-5). However in this study, the diltiazem cohort did not demonstrate worse safety outcomes. These findings are consistent with previ-

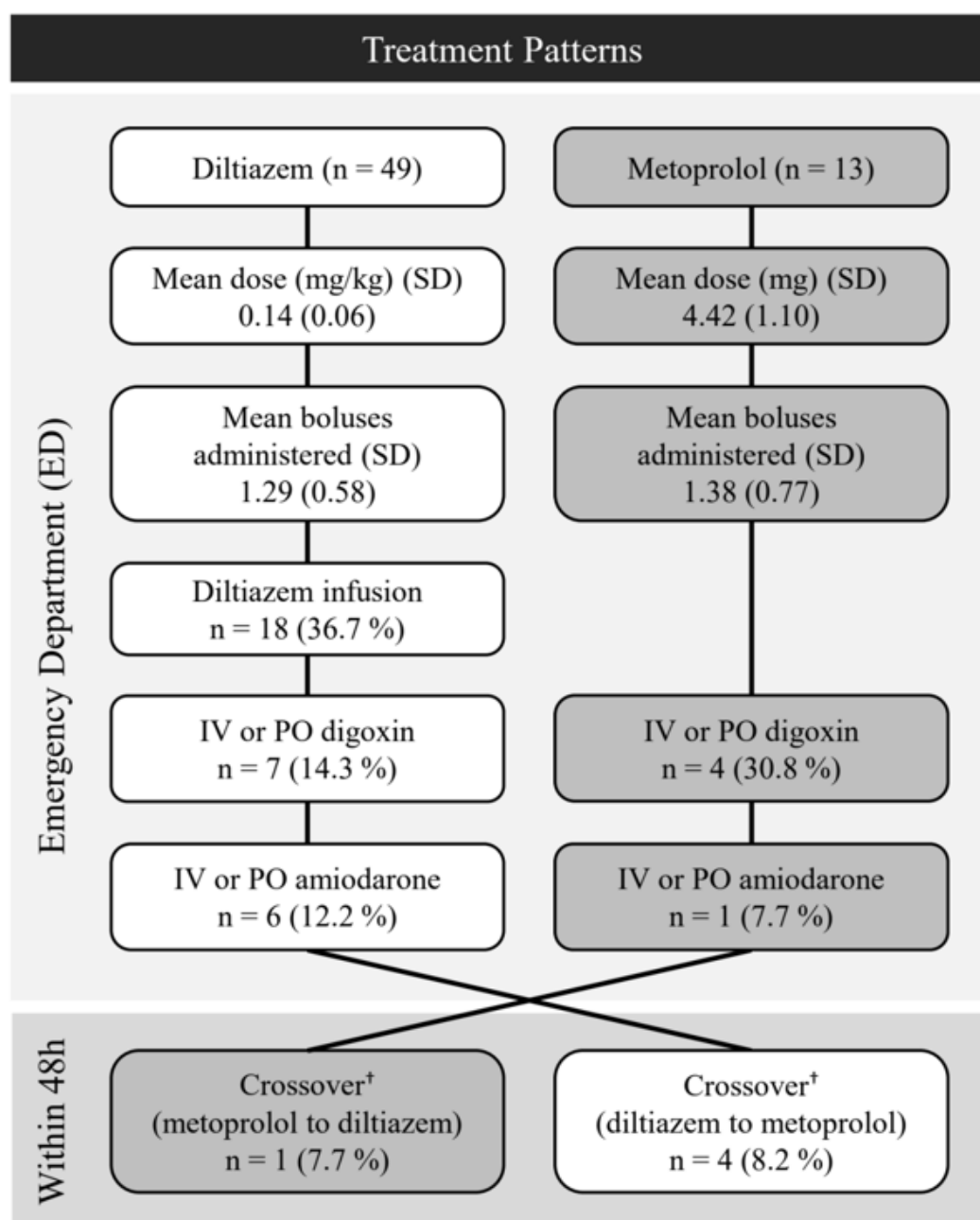


Figure 2 Rate control agent administration patterns in the ED

[†]Crossover indicates intravenous diltiazem or metoprolol only.

Table 3 Secondary endpoints

Secondary endpoint	Diltiazem (n=49)	Metoprolol (n=13)	P-value
SBP <90 mmHg	10 (20.4%)	3 (23.1%)	1.000
Bradycardia, 12 hrs	2 (4.1%)	2 (15.4%)	0.191
Bradycardia, 24 hrs	4 (8.2%)	2 (15.4%)	0.597
Atropine administered	0 (0%)	0 (0%)	-
Cumulative loop diuretic dose in 24hrs (mg), mean (SD)	104.9 (83.6)	93.5 (58.5)	0.656

SBP: Systolic blood pressure; SD: Standard deviation

ous single-center studies (14,16-17). While one study showed an insignificantly longer length of stay, this could be related

Table 4 Efficacy subgroup analysis of patients with HR >110 bpm

Endpoint	Diltiazem (n=34)	Metoprolol (n=10)	P-value
HR prior to medication administration, mean (SD)	134 (15.2)	132 (8)	0.440
Time to HR <110 (hrs), median (IQR)	2.2 (8.2)	1.1 (5.6)	0.493
Rate control within 15 min, n (%)	7 (63.6)	4 (36.4)	0.237
Rate control within 30 min, n (%)	13 (72.2)	5 (27.8)	0.716
Rate control within 60 min, n (%)	20 (74.1)	7 (25.9)	0.716

HR: Heart rate; hrs: Hours; IQR: Interquartile range; SD: Standard deviation; bpm: Beats per minute

to lower EFs at baseline (14). These studies did not demonstrate significant differences in signs or symptoms of worsening outcomes between cohorts or any adverse events (14,16-17).

This was the largest study evaluating the safety of diltiazem in this population conducted across a health system. To increase the generalizability of the sample population, patients were included across 7 different hospitals and no comorbidities were excluded. To capture pragmatic clinical practice, patients were screened for inclusion based on the existence of a historical echocardiogram demonstrating an EF <40%. Furthermore, the cohorts were evenly balanced regarding severity of illness, baseline characteristics, and additional medication administration. The definition of worsening HF in this study was consistent with prior studies that evaluated worsening HF, captured multiple safety parameters, and was evaluated over 48 hours providing adequate time to identify adverse medication effects (27). Lastly, the primary endpoint did not consist of surrogate markers and was a patient-oriented outcome.

5. Limitations

This was a small, observational, retrospective, underpowered study. The use of an admission diagnosis of AF as inclusion criteria excluded patients with other diagnoses who were also treated for AF with RVR. Although admission diagnoses are less accurate than discharge diagnoses, including patients in this manner allowed for greater generalizability to evaluate ED practices. Additionally, 357 patients were excluded due to a lack of echocardiogram data prior to the encounter. Including patients based on historical echocardiogram result may have included patients who ultimately compensated from HFrEF and contributed to selection bias. Treatment cohorts were unbalanced regarding study medication and only 21% of patients received metoprolol. Additionally, the cohorts are unmatched by EF with nearly 80% of patients receiving metoprolol that had an EF >30%. Moreover, approximately 50% of patients receiving diltiazem had an EF <25%. The disparity in these unmatched cohorts may have led to sampling bias resulting in the positive performance of diltiazem. Additionally, the included patients had relatively mild disease severity based on baseline vital signs and REMS, which may limit the generalizability of these findings to patients with more severe presentations.

There were additional limitations regarding selected endpoints. Although requirement of new inotropic support was intended to detect the deleterious effects of diltiazem, this study did not account for other outcomes that may indicate diltiazem intolerance. Furthermore, the continuation or discontinuation of goal-directed medical therapy (GDMT) could have been a surrogate marker of clinical status, but this endpoint required an accurate home medication list to accurately compare inpatient medications. Similarly, outcomes such as the initiation of positive pressure ventilation, administration of isotonic fluids, or cardiopulmonary arrest were not assessed, as these events were infrequent, not consistently documented across sites, and considered outside the original scope of the study. The limitations from this endpoint and lack of endpoints regarding GDMT point towards the lack of complete information regarding incidence of more advanced HF in either cohort. Although decreased EF is one indication of worsening HF, this study does not include other measures to estimate HF prognosis as the primary composite endpoint was intended. Lastly, the primary endpoint focused on events occurring within 48 hours of admission and were not designed to evaluate the treatment of AF outside of the ED and outcomes beyond 48 hours. Despite the efforts made to limit the risk of type II error, these results demonstrate the safety of diltiazem use. A post-hoc power analysis based on the observed difference in the primary outcome between groups yielded an estimated power of 14.3%, highlighting that the study was not powered to detect modest differences in clinical outcomes. Nevertheless, these findings provide important real-world insights and add to the body of literature regarding the acute management of AF with RVR in patients with HFrEF. Larger prospective studies are needed to clarify the role of diltiazem in this population.

6. Conclusion

Overall, concerns for using non-DHPs in patients with HF originate from chronic diltiazem use (9-10). Guideline recommendations to avoid non-DHP CCBs in patients with HF cannot be extrapolated to short courses of non-DHPs used for rapid rate control. Concerns about the use of negative inotropic agents in the acute setting for patients with HFrEF may be unfounded and should be further evaluated with larger studies. In patients with a documented history of HFrEF, the results of this study are consistent with previ-

ous studies suggesting that short-term use of diltiazem for acute management of AF with RVR has similar rates of signs of worsening HF as metoprolol (14,16-17). Despite the limitations, this investigation adds to the body of evidence to further inform treatment decisions regarding patients presenting to the ED with AF with RVR.

7. Declarations

7.1. Acknowledgement

None.

7.2. Authors' contribution

ACJ contributed to study concept and design, acquisition of the data, analysis and interpretation of the data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical expertise. KJM provided analysis and interpretation of the data, critical revision of the manuscript for important intellectual content, and statistical expertise. MAG contributed to study concept and design, acquisition of the data, and analysis and interpretation of the data. MJ and CMW contributed to study concept and design, analysis and interpretation of the data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. SNA contributed to study concept and design, and critical revision of the manuscript for important intellectual content.

7.3. Conflict of interest

None.

7.4. Funding

None.

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