Original Contribution

Metoprolol vs. diltiazem in the acute management of atrial fibrillation in patients with heart failure with reduced ejection fraction

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A B S T R A C T

Objective: The objective of this study was to examine the effects of metoprolol versus diltiazem in the acute management of atrial fibrillation (AF) with rapid ventricular response (RVR) in patients with heart failure with reduced ejection fraction (HFrEF).

Methods: This retrospective cohort study of patients with HFrEF in AF with RVR receiving either intravenous push (IVP) doses of metoprolol or diltiazem was conducted between January 2012 and September 2016. The primary outcome was successful rate control within 30 min of medication administration, defined as a heart rate (HR) < 100 beats per minute or a HR reduction ≥ 20%. Secondary outcomes included rate control at 60 min, maximum median change in HR, and incidence of hypotension, bradycardia, or conversion to normal sinus rhythm within 30 min. Signs of worsening heart failure were also evaluated.

Results: Of the 48 patients included, 14 received metoprolol and 34 received diltiazem. The primary outcome, successful rate control within 30 min, occurred in 62% of the metoprolol group and 50% of the diltiazem group (p = 0.49). There was no difference in HR control at predefined time points or incidence of hypotension, bradycardia, or conversion. Although baseline HR varied between groups, maximum median change in HR did not differ. Signs of worsening heart failure were similar between groups.

Conclusions: For the acute management of AF with RVR in patients with HFrEF, IVP diltiazem achieved similar rate control with no increase in adverse events when compared to IVP metoprolol.

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1. Introduction

Atrial fibrillation (AF) and heart failure (HF) are frequently encountered in the acute setting. Both AF and HF affect millions of people in the United States and share several common risk factors, including age, hypertension, diabetes mellitus, ischemic heart disease, and valvular heart disease [1]. Of those with AF, 73% of men and 76% of women develop HF, and of patients with HF, 62% of men and 73% of women develop AF [2].

Atrial fibrillation with rapid ventricular response (RVR) is frequently defined as heart rate (HR) ≥ 120 beats per minute (bpm). The 2014 American Heart Association, American College of Cardiology, and Heart Rhythm Society Guideline for the Management of Patients With Atrial Fibrillation recommends intravenous non-dihydropyridine calcium channel blockers or beta-blockers for acute HR control in hemodynamically stable patients presenting with AF without HF [3]. The aforementioned guideline and the 2013 American College of Cardiology Foundation and American Heart Association Guideline for the Management of Heart Failure recommend against the use of non-dihydropyridine calcium channel blockers and beta-blockers for the use of non-dihydropyridine calcium channel blockers and permit the use of beta-blockers in patients with HF with reduced ejection fraction (HFrEF); however, both non-dihydropyridine calcium channel blockers and beta-blockers have negative inotropic effects which can be harmful during an acute HF exacerbation [3,4]. Available literature on non-dihydropyridine calcium channel blockers in patients with HFrEF focus on chronic management in which patients are exposed to the long-term negative inotropic effect without the neurohormonal benefits that beta-blockers provide [3-6]. Furthermore, studies comparing the use of non-dihydropyridine calcium channel blockers and beta-blockers in the acute management of AF with RVR often exclude...
patients with severe, New York Heart Association (NYHA) Class IV, or decompensated HF, and fail to acknowledge use in compensated HFrEF [7-9].

The short-term use of diltiazem for the acute management of AF with RVR in patients with HFrEF has not been fully evaluated. Therefore, the primary objective of this study was to compare the achievement of a goal HR of <100 bpm or a HR reduction of at least 20% in patients with HFrEF receiving intravenous push (IVP) metoprolol versus IVP diltiazem for rate control of AF with RVR in the emergency department (ED).

2. Methods

2.1. Study design

This was a single-center, retrospective cohort study from January 2010 through September 2016 of patients with a diagnosis of AF (International Statistical Classification of Diseases and Related Health Problems-9/10 (ICD-9/10)) treated with IVP metoprolol or IVP diltiazem in the ED. The study site was a tertiary medical center ED with approximately 50,000 to 70,000 patient visits per year during the study period. The study was registered in ClinicalTrials.gov (NCT02938260) and approved by the local Institutional Review Board. The study population was a sample size of convenience.

2.2. Patients

Included patients were ≥18 years of age, treated for AF with RVR, and had a documented EF ≤40%. Rapid ventricular response was defined as HR ≥120 bpm and EF was confirmed via an echocardiogram within the previous five years from the index visit. Patients could receive one additional IVP dose within 30 min after the first dose, but were excluded if crossover occurred between treatment medications. Other exclusion criteria were pregnancy, pre-treatment systolic blood pressure (SBP) ≥90 mm Hg, or decompensated HF. Decompensated HF was defined as presentation with signs and symptoms of worsening HF.

2.3. Methods and measurements

Patients were grouped by medication: metoprolol or diltiazem. Study data were collected and managed using REDCap electronic data capture tools hosted at Rush University Medical Center [10]. Electronic medical records were used to obtain clinical and demographic data, including age, sex, race, SBP (baseline and 30 min), EF, NYHA Class, home medications, past medical history, diastolic BP (baseline), HR (baseline, 30 min, 60 min, and at transfer to an inpatient unit), respiratory rate, Glasgow Coma Scale, oxygen requirement (baseline and increase within 48 h), oxygen saturation, dose and frequency of study medications, other medications administered in the ED, inotropic support, pulmonary edema, and readmission within 7 days. These values contributed to the calculation of a Rapid Emergency Medicine Score (REMS), which is an externally validated tool for in-hospital mortality estimates in nonsurgical patients presenting to the ED [11]. The administration time of the first IVP dose of metoprolol or diltiazem was utilized as time zero and other time points are based off of this.

2.4. Outcomes

The primary outcome was successful rate control (HR < 100 bpm or a HR reduction ≥20%) within 30 min from administration of the first dose of IVP metoprolol or IVP diltiazem [7,12]. Secondary outcomes consisted of HR (30 min, 60 min, and at transfer to an inpatient unit), successful rate control (60 min and at transfer to an inpatient unit) and incidence of hypotension (SBP <90 mm Hg), bradycardia (HR < 60 bpm), and conversion to normal sinus rhythm within 30 min. Maximum median change in heart rate and hospital admission unit were collected. Worsening HF symptoms, defined as new inotropic support, new pulmonary edema, or increased oxygen requirement within 48 h or readmission within 7 days of discharge were also evaluated [13-15].

2.5. Analysis

Analyses were performed on Statistical Package for the Social Sciences (SPSS, Inc., Armonk, NY), version 23.0. Continuous data were reported as median and interquartile range [IQR] and categorical data as frequencies and percentages. The Mann Whitney U test was utilized for continuous data and Pearson chi-square or Fisher’s exact test was used, as appropriate, for categorical data. An a priori significance level was set as p < 0.05.

3. Results

Of 551 screened patients, 48 patients were included, 14 received metoprolol and 34 received diltiazem. The most common reasons for exclusion were an EF > 40% (n = 272) and presentation with a rhythm other than AF with RVR (n = 114, Fig. 1). All baseline characteristics were similar between groups except baseline HR (metoprolol 129 [124–145] bpm versus diltiazem 141 [130–158] bpm; p = 0.02), outpatient beta-blocker use (metoprolol group 100% versus diltiazem group 68%; p = 0.02), and past medical history of coronary artery disease (metoprolol 71% versus diltiazem 38%; p = 0.04). Of note, there was no baseline difference in the median Rapid Emergency Medicine Score (metoprolol 8 [4–9] versus diltiazem 8 [4–9]; p = 0.47; Table 1).

The primary outcome, successful rate control within 30 min, occurred in 8 of 13 patients (62%) in the metoprolol group and 15 of 30 patients (50%) in the diltiazem group (p = 0.49). The primary outcome was not assessed for 5 patients (1 in the metoprolol group and 4 in the diltiazem group) due to documentation omissions within the electronic medical record. No difference was found for incidence of hypotension, bradycardia, or conversion to normal sinus rhythm at 30 min. There was also no difference between groups with respect to successful rate control or heart rate at the pre-specified time points of 60 min and transfer to an inpatient unit. The maximum median change in HR was 30 [10–52] bpm in the metoprolol group versus 32 [18–47] bpm in the diltiazem group (p = 0.60; Table 2). Heart rate at various time points is illustrated in Fig. 2.

No difference was found between groups for any signs of worsening HF. All patients were admitted to the hospital. There was no difference in admission to the intensive care unit versus medical ward. No difference was found between groups in rates of readmission within 7 days (metoprolol 7% versus diltiazem 12%; p = 1.00). For all patients with re-admission within 7 days, discharge diagnoses were evaluated and none contained a diagnosis of worsening HF (Table 2).

While in the ED, patients frequently received 5 mg of metoprolol and 15 mg of diltiazem [15 [10–20]] for the first dose. A second dose was administered in 21% of the patients in each group. The second doses were consistently 5 mg of metoprolol and 10 mg of diltiazem within 30 min with a median time between doses of 23 min [13–23] in the metoprolol group and 16 min [8–30] in the diltiazem group (p = 1.00; Table 3). Concomitant medication administration varied with usage of oral beta-blockers (metoprolol group 43% versus diltiazem group 0%; p < 0.01) and continuous infusions of diltiazem (metoprolol 0% versus diltiazem 44%; p < 0.01). Use of IV diuretics in the ED to control symptoms of HF was also examined and did not vary between groups (Table 3).

4. Discussion

We evaluated the acute management of AF with RVR in patients with HFrEF presenting to the ED. The achievement of successful rate control (HR <100 bpm or a HR reduction ≥20%) in patients receiving IVP metoprolol versus IVP diltiazem did not differ between groups at
A difference existed in baseline HR between groups; however, both groups had similar maximum median changes in HR following treatment. Overall, no difference was noted between groups with regards to HF symptoms. To date, this is the only study to analyze the use of IVP metoprolol versus IVP diltiazem for the acute management of AF with RVR, specifically in patients with non-decompensated HFrEF.

In a recent study, Fromm et al. investigated IV metoprolol versus IV diltiazem for HR control in patients with AF with RVR and reported success (HR of \(<100\) bpm within 30 min) in 46.4% of patients receiving IV metoprolol and 95.8% of patients receiving IV diltiazem \((p < 0.0001)\) [8]. However, this study and others evaluating metoprolol and diltiazem, excluded patients with Class IV HF and acute decompensated HF [7-9]. Scheuermeyer et al. reported the frequency of heart failure in their population (9.0% in the calcium channel blocker group and 8.8% in the beta blocker group); however, the study did not differentiate between patients with HF when looking at response rates [9]. In contrast, HFrEF was necessary for inclusion into our study.

Available literature for the treatment of AF with RVR, specifically in patients with HF, is sparse. A study comparing diltiazem to placebo in patients with AF with RVR and severe HF found that 97% of those treated with IV diltiazem had a reduction in HR of \(\leq 20\%\) and no symptoms of HF exacerbation [12]. A second study of patients with decompensated HF compared the use of IV metoprolol and IV diltiazem for control of AF with RVR. Both agents were equally effective at controlling HR with no difference in reports of worsening HF or adverse events [15].

Current literature focuses on the risks associated with non-dihydropyridine calcium channel blockers and patients with HFrEF, but these effects are with long-term treatment [3-5]. The most referenced study reports an increase in first recurrent cardiac event (cardiac death or nonfatal re-infarction) in patients on diltiazem over placebo. These patients were on therapy for 12 to 52 months, with a mean duration of 25 months [6]. Prior studies, as well as this study; indicate diltiazem is safe in the acute setting [12,16-18]. Both metoprolol and

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Metoprolol (n = 14)</th>
<th>Diltiazem (n = 34)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>69 [51–76]</td>
<td>67 [56–80]</td>
<td>0.65</td>
</tr>
<tr>
<td>Female</td>
<td>5 (36)</td>
<td>12 (35)</td>
<td>1.00</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>6 (43)</td>
<td>9 (26)</td>
<td>0.32</td>
</tr>
<tr>
<td>African American</td>
<td>6 (43)</td>
<td>20 (59)</td>
<td>0.31</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (14)</td>
<td>4 (12)</td>
<td>1.00</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>137 [111–154]</td>
<td>134 [111–155]</td>
<td>0.91</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>129 [124–145]</td>
<td>141 [130–158]</td>
<td>0.02</td>
</tr>
<tr>
<td>New York Heart Association Class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>6 (43)</td>
<td>15 (44)</td>
<td>0.94</td>
</tr>
<tr>
<td>II</td>
<td>3 (21)</td>
<td>7 (21)</td>
<td>1.00</td>
</tr>
<tr>
<td>III</td>
<td>4 (29)</td>
<td>12 (35)</td>
<td>0.75</td>
</tr>
<tr>
<td>IV</td>
<td>1 (7)</td>
<td>0 (0)</td>
<td>0.29</td>
</tr>
<tr>
<td>Home medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-inhibitor(^a)</td>
<td>9 (64)</td>
<td>15 (44)</td>
<td>0.20</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>0 (0)</td>
<td>8 (24)</td>
<td>0.09</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>14 (100)</td>
<td>23 (68)</td>
<td>0.02</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>2 (14)</td>
<td>9 (26)</td>
<td>0.47</td>
</tr>
<tr>
<td>Digoxin</td>
<td>4 (29)</td>
<td>2 (6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Intravenous</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>6 (43)</td>
<td>11 (32)</td>
<td>0.52</td>
</tr>
<tr>
<td>Home loop diuretic dose (mg)(^c)</td>
<td>80 [35–140]</td>
<td>40 [20–80]</td>
<td>0.30</td>
</tr>
<tr>
<td>Past medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>11 (79)</td>
<td>20 (59)</td>
<td>0.32</td>
</tr>
<tr>
<td>Asthma</td>
<td>2 (14)</td>
<td>4 (12)</td>
<td>1.00</td>
</tr>
<tr>
<td>COPD(^d)</td>
<td>2 (14)</td>
<td>4 (12)</td>
<td>1.00</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>10 (71)</td>
<td>13 (38)</td>
<td>0.04</td>
</tr>
<tr>
<td>Rapid Emergency Medicine Score</td>
<td>8 [4–9]</td>
<td>8 [4–9]</td>
<td>0.47</td>
</tr>
</tbody>
</table>

\(^{a}\) All values reported as median [IQR] or n [%].

\(^{b}\) Angiotensin-converting enzyme.

\(^{c}\) Reported dose in furosemide equivalent.

\(^{d}\) Chronic obstructive pulmonary disease.
Diltiazem act as negative inotropes acutely but beta-blockers provide long-term neurohormonal benefits [19]. Our findings contradict the current Heart Failure and Atrial Fibrillation Guidelines on the avoidance of non-dihydropyridine calcium channel blockers in all patients with HF, specifically in the acute management of those in AF with RVR [3,4]. In this study, no patients were re-admitted within 7 days of discharge due to HF exacerbations after the short-term use of diltiazem for the treatment of AF with RVR.

This study has several limitations. The retrospective design relied on medical record documentation, which may have been incomplete or inaccurate. There was no formal treatment protocol; therefore, medication selection, dose, and timing of administration were based on provider preference and nursing monitoring. The study was conducted at a single tertiary medical center, limiting external validity. The sample size was small due to the specificity of this cohort, which may contribute to our inability to detect a difference. Dosing was frequently ordered as a flat dose rather than a weight-based dose, although prior evidence suggests greater success with weight-based dosing [7,8]. Also, despite the lack of a protocol the providers often order set doses of the study medications. Groups also differed in history of atrial

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**Table 2**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Metoprolol (n = 14)</th>
<th>Diltiazem (n = 34)</th>
<th>p-Value</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successful rate control</td>
<td>8/13 (62)</td>
<td>15/30 (50)</td>
<td>0.49</td>
<td>0.63 (0.17–2.36)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>114 [96–124]</td>
<td>110 [100–123]</td>
<td>0.87</td>
<td>–</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td>Conversion</td>
<td>0 (0)</td>
<td>2 (6)</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td>60 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successful rate control</td>
<td>9 (64)</td>
<td>16 (47)</td>
<td>0.28</td>
<td>0.49 (0.14–1.78)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>110 [94–118]</td>
<td>109 [99–120]</td>
<td>0.68</td>
<td>–</td>
</tr>
<tr>
<td>Transfer to an inpatient unit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successful rate control</td>
<td>9 (64)</td>
<td>21 (62)</td>
<td>0.87</td>
<td>0.90 (0.25–3.27)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>111 [97–126]</td>
<td>103 [92–114]</td>
<td>0.79</td>
<td>–</td>
</tr>
<tr>
<td>Maximum change in heart rate (bpm)</td>
<td>30 [10–52]</td>
<td>32 [18–47]</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>10 (71)</td>
<td>30 (88)</td>
<td>0.21</td>
<td>3.00 (0.63–14.27)</td>
</tr>
<tr>
<td>Inotrope within 48 h</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td>Increased pulmonary edema within 48 h</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td>Increased O2 requirement within 48 h</td>
<td>3 (21)</td>
<td>11 (32)</td>
<td>0.51</td>
<td>1.75 (0.41–7.59)</td>
</tr>
<tr>
<td>Readmission within 7 days</td>
<td>1 (7)</td>
<td>4 (12)</td>
<td>1.00</td>
<td>1.73 (0.18–17.05)</td>
</tr>
</tbody>
</table>

* All values reported as median [IQR] or n (%).
* The primary outcome was not assessed for all patients due to a lack of documented vitals within 30 min.
* Intensive care unit.

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**Fig. 2.** Heart rate: baseline, 30 and 60 min post-medication administration, and prior to transfer to an inpatient unit.
fibrillation, home loop diuretic dose, and several home medications but these did not reach significance. Differences in home medications and past medical history could attribute to unequal groups at baseline or be a sign of selection bias. While there was no difference between groups in ICU admission, it is important to note that these rates are high because of the absence of a step-down cardiology floor at the study institution. Therefore, ICU admission should not be used as a surrogate for severity of illness in our study, and we provided the Rapid Emergency Medicine Score for each group.

Future directions given the results of this study would be to conduct a prospective trial in this specific population to validate these results. It is still unclear if metoprolol or diltiazem is more effective in AF with RVR due to conflicting results. Flat doses versus weight-based and maximum doses should be further assessed, as well. Prospective validation of the safety of diltiazem in the acute setting with this patient population is warranted.

5. Conclusion

In conclusion, for the acute management of AF with RVR in patients with HFrEF, IVP diltiazem achieved similar rate control at 30 min, 60 min, and at transfer to an inpatient unit with no difference in adverse events when compared to IVP metoprolol. While this study is limited due to its size, available data is scarce and further studies are warranted in this specific population to validate safety and efficacy in the acute setting.

References


Table 3
Management in the emergency department.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Metoprolol (n = 14)</th>
<th>Diltiazem (n = 34)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual dose (mg)</td>
<td>5 [5–5]</td>
<td>15 [10–20]</td>
<td></td>
</tr>
<tr>
<td>Weight based (mg/kg)</td>
<td>0.06 [0.04–0.08]</td>
<td>0.17 [0.13–0.23]</td>
<td></td>
</tr>
<tr>
<td><strong>Dose 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administration of a second dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual dose (mg)</td>
<td>3 (21)</td>
<td>7 (21)</td>
<td>1.00</td>
</tr>
<tr>
<td>Weight based (mg/kg)</td>
<td>0.03 [0.03–0.03]</td>
<td>0.12 [0.11–0.17]</td>
<td></td>
</tr>
<tr>
<td>Time between doses (min)</td>
<td>23 [13–23]</td>
<td>16 [8–30]</td>
<td>1.00</td>
</tr>
<tr>
<td>Other medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 (7)</td>
<td>7 (21)</td>
<td>0.41</td>
</tr>
<tr>
<td>Oral calcium channel blocker</td>
<td>1 (7)</td>
<td>7 (21)</td>
<td>0.41</td>
</tr>
<tr>
<td>Oral beta-blocker</td>
<td>6 (43)</td>
<td>0 (0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Digoxin</td>
<td>2 (14)</td>
<td>0 (0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Diltiazem infusion</td>
<td>0 (0)</td>
<td>15 (44)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Esmolol infusion</td>
<td>1 (7)</td>
<td>1 (3)</td>
<td>0.50</td>
</tr>
<tr>
<td>Repeat IVP</td>
<td>6 (43)</td>
<td>9 (26)</td>
<td>0.32</td>
</tr>
<tr>
<td>Opposite IVP</td>
<td>1 (7)</td>
<td>1 (3)</td>
<td>0.50</td>
</tr>
<tr>
<td>IV diuretics in ED</td>
<td>1 (7)</td>
<td>4 (12)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>40</td>
<td>30 [20–70]</td>
<td>0.80</td>
</tr>
</tbody>
</table>

*All values reported as median [IQR] or n [%].
† All patients received metoprolol 5 mg IVP and diltiazem 10 mg IVP for dose 2 so no IQR is reported.
‡ Reported dose in furosemide equivalent.