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Impact of intravenous calcium with diltiazem for atrial fibrillation/flutter in the emergency department

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abstract

Objective: The purpose of this study was to evaluate the effect of early intravenous (IV) calcium on systolic blood pressure (SBP) when administered with IV diltiazem in subjects with atrial fibrillation (AF) or flutter (AFL) with rapid ventricular response (RVR) in the Emergency Department (ED).

Methods: This was a multicenter, retrospective cohort study that evaluated adults admitted to the ED with documented AF or AFL, heart rate (HR) > 120 bpm, SBP 90 to 140 mmHg, and received treatment with IV diltiazem for rate control. The primary outcome was the change in SBP 60 min (+/− 30 min) after initial IV diltiazem administration. Secondary outcomes included time to initial rate control (HR < 100 bpm), time to sustained rate control (HR < 100 bpm for 3 h), change in HR, rates of hypotension, bradycardia, hypercalcemia, and line extravasation within 24 h of initial diltiazem administration.

Results: There were 198 subjects in the diltiazem monotherapy group and 56 subjects in the diltiazem with calcium group meeting the inclusion criteria. The primary outcome, median change in SBP 60 min after initial IV diltiazem administration, was similar between groups (−2 mmHg vs −1.5 mmHg; $p = 0.642$), but this difference was not statistically significant. All secondary outcomes were found to be similar between groups. Although not statistically significant, hypotension occurred more often in the diltiazem with calcium group (20.2% vs 32.1%; $p = 0.060$) while bradycardia occurred more often in the diltiazem monotherapy group (4.5% vs 0%; $p = 0.213$). In terms of achieving rate control, the administration of calcium with diltiazem did not significantly change the time to initial rate control (1.4 h vs 1.8 h; $p = 0.141$) or time to sustained rate control (7.9 h vs 7.7 h; $p = 0.570$) compared to diltiazem alone.

Conclusions: In the setting of AF/AFL with RVR, administration of IV calcium with IV diltiazem did not show a significant impact on clinical or safety outcomes compared to IV diltiazem monotherapy.

1. Introduction

Supraventricular tachycardia (SVT) is an encompassing term used to describe arrhythmias involving the atrioventricular (AV) node of the heart [1]. A 2003 study evaluated the frequency of SVT related emergency department (ED) visits in the United States and concluded that SVT is responsible for over 50,000 ED visits per year. Additionally, in comparison to non-SVT related ED visits, SVT visits were significantly more likely to have patients over 65 years of age [2]. Atrial fibrillation (AF) or flutter (AFL), the most common subtype of SVT, affects approximately 2 million people in the United States and greater than one third of AF/AFL patients are over 80 years of age [3]. Due to the increased prevalence of AF/AFL in the aging population, it can reasonably be expected to continue to be a prominent disease state requiring optimized medication management and medical surveillance.

Current practices for the management of AF/AFL include rhythm and rate control, with rate control typically being the preferred initial strategy in the acute setting, due to fewer adverse effects, considerations for the duration of symptoms, and requirements for anticoagulation duration compared to rhythm control. Rhythm control can be attempted via electrical cardioversion or pharmacological cardioversion with various antiarrhythmics. Rate control strategies include synchronized electrical cardioversion in hemodynamically unstable patients and intravenous (IV) non-dihydropyridine calcium channel blockers

Abbreviations: SVT, supraventricular tachycardia; AV, atrioventricular; ED, emergency department; AF, atrial fibrillation; AFL, atrial flutter; IV, intravenous; non-DHP CCB, non-dihydropyridine calcium channel blocker; RVR, rapid ventricular response; EMR, electronic medical record; SBP, systolic blood pressure; HR, heart rate; BMI, body mass index.

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(non-DHP CCB), beta-blockers, amiodarone, or digoxin in stable patients without pre-excitation [3]. Non-DHP CCBs, verapamil and diltiazem, block the influx of calcium into cardiac and vascular smooth muscle during membrane depolarization. This makes them effective rate control agents for SVT due to their direct effects on the AV node which results in slowed AV nodal conduction time and prolonged AV nodal refractoriness. Additionally, in the setting of AF/AFL with rapid ventricular response (RVR), these agents decrease the ventricular rate. The effect on vascular smooth muscles is the origin of decreased systolic and diastolic blood pressure due to the reduction in total peripheral resistance. In an analysis of over 400 clinical trials, it was found that hypotension occurred in 4.3% of patients [4].

One postulated method to reduce the occurrence of hypotension is the administration of IV calcium prior to the infusion of the non-DHP CCB. Calcium's mechanism of action in reducing hypotension is not well established, but it is theorized that an increase in extracellular calcium will flood the calcium receptors and competitively antagonize the CCB, therefore decreasing the negative inotropic effects [5-8]. Calcium's impact on the negative chronotropic effects produced by non-DHP CCBs is also not well understood due to a paucity of high-quality evidence evaluating this, especially in human subjects. Additionally, the optimal dose of calcium has not been fully elucidated for reducing hypotension induced by non-DHP CCBs. In most acute settings, calcium is often available as either calcium gluconate or calcium chloride. A 1 g dose of 10% (100 mg/mL) calcium gluconate provides 93 mg of elemental calcium, while a 1 g dose of 10% (100 mg/mL) calcium chloride providers 270 mg of elemental calcium [9,10]. The majority of studies evaluating the use of elemental calcium prior to a non-DHP CCB are with verapamil. These studies mostly used 90 mg of elemental calcium as calcium gluconate or calcium chloride and showed success in reducing hypotension induced by verapamil [5,6,8].

The efficacy of IV calcium prior to diltiazem in the management of AF has been evaluated in one study to date. This was a prospective, randomized, double-blind, placebo-controlled study involving 78 patients. The test group received 90 mg of IV elemental calcium chloride IV immediately prior to each dose of IV weight-based diltiazem. The study found no statistically significant difference in systolic blood pressure (SBP) and similar incidence of hypotension between the groups [9]. The authors' discussed limitations for this study include the small sample size and low doses of calcium used, therefore warranting the need for further research [11].

With data available for calcium pretreatment for verapamil, there is a need for additional research on diltiazem to clarify the existing limited and conflicting evidence. Hypotension could further complicate the treatment process and lead to unfavorable outcomes, such as decreased organ perfusion and subsequent shock. Having a safe and effective option for decreasing the incidence of diltiazem induced hypotension during AF/AFL treatment can significantly impact patient care. The purpose of this study was to evaluate the effect of early IV calcium administration in subjects receiving IV diltiazem for the treatment of AF/AFL with RVR in the ED.

2. Methods

2.1. Study design

This was a multicenter, retrospective cohort study of adults admitted to the ED at three community hospitals and two freestanding EDs, with over 100 ED beds. The study was approved by the local Institutional Review Board. A report was generated from the electronic medical record (EMR) identifying subjects that had IV calcium and IV diltiazem orders placed while in the ED between January 1, 2013 and February 1, 2022. The subject list was filtered for duplicate subject encounters, randomized, and evaluated for inclusion and exclusion criteria.

2.2. Subjects

Subjects were included if they were ≥ 18 years of age, had documented AF/AFL (confirmed by electrocardiogram), a heart rate (HR)≥ 120 bpm, a SBP 90–140 mmHg, and received at least one dose of IV diltiazem for rate control. A HR ≥ 120 bpm was used to define RVR to match previous studies [12,13]. Exclusion criteria included: hemodynamic instability requiring electrocardioversion, prior treatment with another rate control agent (beta-blockers, amiodarone, and digoxin) on the same admission, incomplete SBP readings documented during the specified primary outcome time frame, pregnant, or incarcerated.

2.3. Methods and measurements

Baseline data collected from the EMR included ED admission dates, subject demographics, new onset versus chronic AF/AFL, relevant past medical history, applicable home medications, vital signs, and laboratory values. Additional data points included: type of IV access (central or peripheral); calcium salt (gluconate or chloride), dose, and administration times; and diltiazem bolus doses, bolus administration times, drip initial rate, drip maximum rate, and drip initiation times. Subjects were divided into two groups "diltiazem monotherapy" and "diltiazem with calcium". Diltiazem monotherapy was defined as not having IV calcium administered 120 min prior to or 24 h following the first IV diltiazem administration. Diltiazem with calcium was defined as having IV calcium administered within 60 min prior to or 30 min after the first IV diltiazem administration. A single investigator collected data using a standardized data collection spreadsheet.

2.4. Outcomes

The primary outcome was change in SBP 60 min (+/− 30 min) after initial IV diltiazem administration. Secondary outcomes included time to initial rate control; time to sustained rate control; change in HR 60 min (+/− 30 min) after initial IV diltiazem administration; and hypotension (SBP < 90 mmHg), bradycardia (HR < 50 bpm), hypercalcemia (serum calcium >10.5 mg/dL), line extravasations within 24 h of initial IV diltiazem administration. To account for documentation limitations regarding repeat SBP and HR measurements, a time interval of 30–90 min was used, but the closest measurement to 60 min after initial IV diltiazem administration was collected. Serum calcium levels were adjusted for serum albumin levels for subjects with a documented serum albumin <4 g/dL using corrected calcium for hypoalbuminemia formula, while subjects with a serum albumin >4 g/dL or an omitted serum albumin were evaluated based on the serum calcium level alone. The definitions for rate control, HR < 100 bpm, and sustained rate control, HR < 100 bpm for 3 consecutive hours, were used to align with previous studies assessing rate control in AF/AFL with RVR [12,13].

A subgroup analysis was performed to assess the primary outcome in subjects within the diltiazem with calcium group that received IV calcium prior to or at the exact same time as the initial IV diltiazem administration. The purpose of this analysis was to evaluate the potential impact of calcium administration time in relation to diltiazem administration.

2.5. Statistical analysis

A priori power calculation estimated that a total of 264 subjects at a 3:1 ratio (198 diltiazem monotherapy group and 66 diltiazem with calcium group) would be required to detect a mean difference in SBP of ≥5 mmHg between groups with a standard deviation of 12.5 mmHg, one-sided alpha of 0.025, and a power of 80%. Student's *t*-test or Mann-Whitney U were used to assess continuous outcomes, including the primary outcome, while Chi-Square test or Fisher's exact test were used for nominal data. Cox proportional hazards was used to analyze time to event data. All analyses were completed in SAS® OnDemand for Academics.

3. Results

A total of 660 randomized subjects were screened for inclusion in this study with 198 subjects in the diltiazem monotherapy group and 56 subjects in the diltiazem with calcium group meeting the inclusion criteria. Of the 406 excluded subjects, the most common reason for exclusion was inappropriate baseline vital signs (n = 160) (Fig. 1).

Baseline characteristics slightly differed between groups, with a few notable differences including body mass index (BMI), past medical history, laboratory values, SBP, and initial diltiazem bolus dose (Table 1). The diltiazem monotherapy group had a higher median BMI, albumin, and serum calcium. The diltiazem with calcium group had a greater percentage of subjects with chronic kidney disease and active malignancy. Median baseline SBP in the diltiazem with calcium group was significantly lower than the diltiazem monotherapy group (109 mmHg vs 123 mmHg, $p \leq 0.0001$, respectively). Initial diltiazem bolus doses were significantly higher in the diltiazem monotherapy group compared to the diltiazem with calcium group (15 mg vs 10 mg, p = 0.004). Diltiazem drip initiation doses and maximum drip doses were similar between groups. For the diltiazem with calcium group, the average time between calcium administration and diltiazem initiation was 6.5 min. Additionally, calcium gluconate was used more frequently than calcium chloride (89.3% vs 10.7%, respectively) and the median elemental calcium dose used was 93 mg. All subjects received the evaluated medications via peripheral IV lines. Of the 6 subjects that received calcium chloride, 4 subjects had this administered as an IV piggyback and 2 subjects as an IV push.

The primary outcome, median change in SBP 60 min (+/− 30 min) after initial diltiazem administration, was similar between groups with diltiazem monotherapy having a slightly greater change (−2 mmHg vs −1.5 mmHg, p = 0.642), but this difference was not statistically significant. The subgroup analysis of the primary outcome included 45 subjects from the diltiazem with calcium group that received calcium before or at the exact same time as the initial diltiazem dose. When these subjects were compared to the diltiazem monotherapy group, there was no difference in the median change in SBP at 60 min of initial diltiazem dose (−2 mmHg vs −2 mmHg, p = 0.877).

All secondary outcomes were found to be similar between groups (Table 2). Although not statistically significant, hypotension occurred more often in the diltiazem with calcium group (20.2% vs 32.1%, p = 0.060) while bradycardia occurred more often in the diltiazem monotherapy group (4.5% vs 0%, p = 0.213). In terms of achieving rate control, the administration of calcium with diltiazem did not significantly change the time to initial rate control (1.4 h vs 1.8 h, p = 0.141) or time to sustained rate control (7.9 h vs 7.7 h, p = 0.570) compared to diltiazem alone. Additionally, there was a similar median reduction in HR 60 min after diltiazem administration between groups (−33 bpm vs −34 bpm, p = 0.428).

Table 1
Baseline characteristics.

Variable	Diltiazem monotherapy (n = 198)	Diltiazem with calcium (n = 56)	p-value
Age - years, median (IQR)	72 (63–80)	74 (63–81)	0.545
Female, n (%)	97 (49)	26 (46.4)	0.735
Race, n (%)			0.211
White	178 (89.9)	47 (83.9)	-
Black	18 (9.1)	7 (12.5)	-
Other	2 (1)	2 (3.6)	-
Weight - kg, median (IQR)	86 (68.1–106)	75.5 (60.5–104)	0.053
Body mass index - kg/m^2, median (IQR)	28.4 (24.2–35.1)	27.3 (22.5–32.1)	0.043
Baseline rhythm, n (%)			0.679
Atrial Fibrillation	154 (77.8)	45 (80.4)	-
Atrial Flutter	44 (22.2)	11 (19.6)	-
New onset AF/AFL, n (%)	80 (40.4)	24 (42.9)	0.742
Vitals, median (IQR)			
Heart Rate - bpm	140 (130–152)	143 (133–159)	0.182
Systolic Blood Pressure - mmHg	123 (114–132)	109 (101−121)	<0.0001
Laboratory values, median (IQR)			
Serum Albumin - g/dL	3.9 (3.4–4.2)	3.4 (3.1–3.9)	0.0004
Serum Calcium - mg/dL	9.2 (8.9–9.6)	9.0 (8.5–9.4)	0.0036
Past medical history, n (%)			
Heart failure	32 (16.2)	11 (19.6)	0.540
Hypertension	152 (76.8)	46 (82.1)	0.392
Diabetes mellitus	53 (26.8)	17 (29.4)	0.231
Thyroid disorder	35 (16.8)	10 (17.9)	0.904
Chronic kidney disease	17 (8.6)	12 (21.4)	0.008
Active malignancy	12 (6.1)	9 (16.1)	0.026
Home medications, n (%)			
Non-DHP calcium channel blocker	44 (22.2)	7 (12.5)	0.094
Beta blocker	88 (44.4)	27 (48.2)	0.839
Calcium	12 (6.1)	5 (8.9)	0.543
Diltiazem bolus dose - mg, median (IQR)	15 (10−20)	10 (10–20)	0.004
Diltiazem drip rate, median (IQR)			
Initial rate - mg/h	5 (5–5)	5 (5–5)	0.164
Maximum rate - mg/h	10 (7.5–15)	10 (5–12.5)	0.125
Calcium salt, n (%)			
Chloride	-	6 (10.7)	-
Gluconate	-	50 (89.3)	-
Elemental calcium dose - mg, median (IQR)	-	93 (93–186)	-
Time between calcium and diltiazem - min, median (IQR)	-	6.5 (0−21)	-

Legend: IQR = interquartile range, AF = atrial fibrillation, AFL = atrial flutter, non-DHP = nondihydropyridine, IV = intravenous.

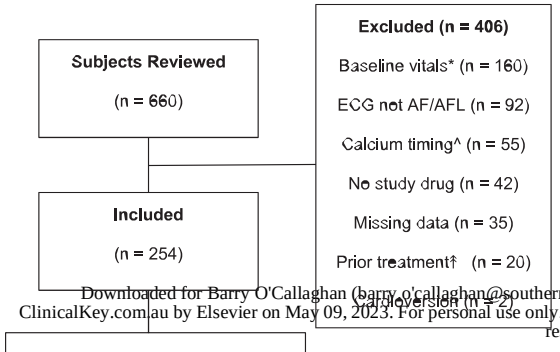

Fig. 1. Subject Enrollment Flowchart. *Heart rate < 120 bpm, systolic blood pressure < 90 mmHg, systolic blood pressure > 140 mmHg. ^Intravenous calcium administration not within defined time frames. †Prior treatment with intravenous amiodarone, beta-blocker, or digoxin ECG = electrocardiogram, AF = atrial fibrillation, AFL = atrial flutter.

4. Discussion

For the management of AF/AFL with RVR in the ED, our study findings suggest that the use of IV calcium did not impact the change in SBP that occurred following IV diltiazem administration when compared to IV diltiazem monotherapy. This observation remained consistent in the subgroup analysis assessing only those that received IV calcium before or at the exact same time as IV diltiazem. These findings may also suggest that the administration time of IV calcium in relation to diltiazem administration, pre-treatment compared to post-treatment, may not play a significant role in outcomes. Time to initial rate control, sustained rate control, and change in HR were not significantly different between groups, highlighting that IV calcium

Table 2
Primary and secondary outcomes.

Outcome	Diltiazem monotherapy (n = 198)	Diltiazem with calcium (n = 56)	p-value
Change in SBP at 60 min - mmHg, median (IQR)	−2 (12 to 8)	−1.5 (−13 to 4.5)	0.642
Time to initial rate control - h, median (IQR)	1.4 (0.5 to 4.0)	1.8 (0.6 to 4.8)	0.141
Time to sustained rate control - h, median (IQR)	7.9 (5.6 to 10.9)	7.7 (5.5 to 11.8)	0.570
Change in HR at 60 min - bpm, median (IQR)	−33 (−49 to −20)	−34 (−62 to −18)	0.428
Adverse Events, n (%)			
Hypotension	40 (20.2)	18 (32.1)	0.060
Bradycardia	9 (4.5)	0 (0)	0.213
Hypercalcemia	2 (1.2)	1 (1.9)	0.568
Line Extravasation	0 (0)	0 (0)	-

Legend: IQR = interquartile range, SBP = systolic blood pressure, min = minutes, h = hours, HR = heart rate, bpm = beats per minute.

administration did not compromise the rate controlling effects of diltiazem. In this study, adverse events did not differ significantly between groups, but the diltiazem with calcium group experienced more hypotension than the diltiazem monotherapy group. Notably, at baseline, the diltiazem with calcium group had a lower SBP prior to receiving any treatment, which may have contributed to providers' decisions to use calcium and lower initial diltiazem bolus doses in these subjects. Additionally, it might also explain the increased incidence of hypotension in this group. Our decision to set the subject inclusion baseline SBP range to 90–140 mmHg was in hopes to mitigate this potential treatment bias and difference in incidences of hypotension that could be expected in those with baseline hypotension compared to those with baseline hypertension. In contrast, bradycardia occurred more often in the diltiazem monotherapy group; it is unclear if calcium administration may have played a role in there being a difference between groups for this finding, since this could also be attributed to the higher initial diltiazem doses in the diltiazem monotherapy group.

The available evidence for the use of IV calcium with a non-DHP CCB is mostly in the setting of verapamil for the management of SVT with small sample sizes [5-7]. A 1983 prospective study conducted by Weiss and colleagues, examined the effect of IV calcium gluconate pre-treatment and post-treatment on reversing or preventing verapamil induced hypotension in 31 subjects with supraventricular tachyarrhythmias and RVR. Twenty-one subjects received 5 mg of IV verapamil followed immediately by 1 g of IV calcium gluconate, while 13 subjects received the same agents and corresponding doses in reverse order. The study found that calcium pre-treatment prevented a reduction in blood pressure and calcium post-treatment increased blood pressure to baseline, all while not impacting the HR [5]. In 1992, Kuhn and colleagues conducted a retrospective study, assessing 135 subjects with supraventricular tachyarrhythmias that received IV verapamil alone (n = 117) or pre-treatment with low-dose, 90 mg IV calcium gluconate (n = 18). The authors stated that the low-dose of calcium used was due to their false interpretation of the amount of elemental calcium used by Weiss. Although this study was limited by its small sample size, it found that low-dose calcium pre-treatment increased SBP while verapamil monotherapy decreased SBP (4 mmHg vs −5 mmHg, p = 0.024) [7].

The efficacy of IV calcium prior to diltiazem in the management of atrial fibrillation has been evaluated in one study to date, conducted by Kolkebeck and colleagues in 2004. This was a prospective, randomized, double-blind, placebo-controlled study involving 78 patients. The test group was administered 90 mg of elemental calcium IV (3.33 mL of 10% calcium chloride) immediately prior to each dose of IV diltiazem dosed initially at 0.25 mg/kg (max 20 mg) over 2 min; if the first dose was not successful at 15 min of observation then an additional 0.35 mg/kg (max 25 mg) dose was administered. The authors found that there was no statistically significant difference in SBP (p > 0.05), rate control, or incidences of hypotension between groups. Some limitations to this study include a small sample size, low doses of calcium, and doses of diltiazem used to initiate therapy [11]. The dose of diltiazem used in Kolkebeck's study are the guideline recommended doses for the management of AF/AFL, which differ from the median doses of 10 mg and 15 mg used in our study [3,4]. At our institution, it is common provider practice to use empirically lower doses of diltiazem and if an adequate response is not seen, to then provide additional doses as needed. This decision to use lower doses of diltiazem is often due to provider preference and experience with hypotension occurring after diltiazem administration when used at the recommended weight-based doses, especially in the elderly and underweight patients. The overall use of these lower doses in our study could have had an effect on our incidence of hypotension overall. Additionally, Kolkebeck used 90 mg of elemental calcium and considered this to be a low dose of calcium, although the majority of the studies with verapamil used this amount or elemental calcium as well and saw a positive blood pressure response [5,6,8,11]. Similarly our study had a median dose of 93 mg of elemental calcium and our findings did not show a significant difference in SBP between groups, as these previous studies did. Therefore, it remains unclear whether 90 mg of elemental calcium should be considered too low of a dose when used with diltiazem.

The results of our study are more closely aligned to those found by Kolkebek, even in the setting of varying calcium salts, calcium doses, calcium administration times, and diltiazem regimens used in the included subjects. This brings into question if there might be a difference between the use of verapamil versus diltiazem and why the results may be different from the studies that used verapamil as the rate control agent. Pharmacokinetically, verapamil and diltiazem share a rapid onset of action, but differ slightly in elimination half-life and estimated volumes of distribution [4,14]. There are limited studies comparing verapamil and diltiazem in the management of acute rate control in AF/AFL. Based on small sample size retrospective studies, verapamil and diltiazem have been found to have similar efficacy in terms of achieving rate control and safety outcomes, including hypotension and bradycardia [15-17]. The difference between the effects of calcium administration on these agents remains unclear and could be a focus for future research.

To note, current practice guidelines do not provide a HR definition for RVR nor do they define the parameters for rate control in the acute setting. In the present study, we defined RVR as a HR ≥ 120 bpm, rate control as a HR < 100 bpm, and sustained rate control as a HR < 100 bpm for 3 consecutive hours. These definitions coincide with previous studies conducted that compared IV diltiazem and metoprolol for the management of RVR in AF/AFL in emergency departments [12,13]. It is important to highlight that these are not unanimous definitions in the literature and may vary depending on practice location and provider preference.

There were several limitations to this study. First, there was an increased risk of documentation bias, inherently due to the retrospective study design. This was especially a concern for the EMR documentation of the study drugs administration times, outcome vitals, and adverse events which were not always available. Intravenous diltiazem has a rapid onset of action and an estimated half-life of around 3 h, therefore its effects on SBP and HR would be expected to occur shortly after administration [4]. Due to documentation limitations for repeat vital

measurements after initial diltiazem administrations found during this study, a target reassessment time of 60 min (+/− 30 min) was used for the primary outcome and change in HR, as repeat measurements were likely to be documented during this time frame. Time to initial rate control and time to sustained rate control were also affected by not having frequent vital documentation and the results may have been impacted, possibly resulting in prolonged times compared to what would be expected based on diltiazem's pharmacokinetic profile. Second, this study failed to meet power, therefore limiting the ability to definitively conclude statistical significance of the desired outcomes. Third, the lower doses of diltiazem used in our study compared to the commonly recommended weight-based regimens may decrease the applicability of our results to other institutions. Fourth, this study was limited to subjects in the emergency department, which could have contributed to a smaller sample size and may not be generalized to patients outside of this practice setting. Further limitations included not collecting data on potential medication administration by emergency medical services, implementation of non-pharmacological techniques to reduce HR (i.e. vagal maneuvers, etc.), administration of IV fluids to support blood pressure, and the use of other antihypertensive agents that could have impacted the outcomes.

Despite these limitations, to our knowledge, this study is the largest study to date evaluating the use of IV calcium with diltiazem in the management of AF/AFL with RVR. This study contributes to the limited literature on the use of calcium with non-DHP CCB in this clinical scenario. Additionally, the multicenter design and varying diltiazem and calcium regimens used provide a real world assessment of a clinical theory that is not fully elucidated at this time.

5. Conclusion

In the management of AF/AFL with RVR in the ED, the results of this study suggest that the administration of IV calcium concurrently with IV diltiazem may not significantly impact the change in SBP compared to IV diltiazem monotherapy. However, diltiazem's ability to achieve and maintain rate control was not affected by the administration of calcium. Lastly, rates of adverse events were similar between groups, suggesting the use of calcium appears to be safe in this patient population. Further studies should be conducted to evaluate for a potential benefit of cal- cium in this patient population.

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Declaration of Competing Interest

The authors of this manuscript declare there are no known financial and personal relationships with other people or organizations that could be viewed as inappropriately influencing this work.

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