Initial Pharmacological Treatment of Atrial Fibrillation With Rapid Ventricular Response

Opposing authors provide succinct, authoritative discussions of controversial issues in emergency medicine. Authors are provided the opportunity to review and comment on opposing presentations. Each topic is accompanied by an Editor's Note that summarizes important concepts. Participation as an authoritative discussant is by invitation only, but suggestions for topics and potential authors can be submitted to the section editors.

Editor's Note: *Beta blockers and calcium channel blockers are both effective in managing atrial fibrillation with rapid ventricular response but exhibit differences in onset, effectiveness, complexity of administration and side effects. Authors in this installment of Clinical Controversies present opposing perspectives and guidance on selecting an optimal "first choice" agent.*

CALCIUM CHANNEL BLOCKERS SHOULD BE PREFERENTIALLY USED TO TREAT ATRIAL FIBRILLATION WITH RAPID VENTRICULAR RESPONSE

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Atrial fibrillation is the most common sustained arrhythmia, with an increasing prevalence globally.[1] This increase is multifactorial, compounded by obesity, an aging population, and enhanced atrial fibrillation diagnostic capabilities.[2] Atrial fibrillation is the most common arrhythmia seen in the emergency department (ED), with one study demonstrating a 30% increase over a 7-year period.[3] Rapid ventricular response is a complication of atrial fibrillation that requires prompt treatment to reduce the pulse rate (PR) to prevent complications like stroke and heart failure.[1] If the patient is hemodynamically stable and cardioversion is not indicated, atrial fibrillation with rapid ventricular response treatment includes intravenous rate control with either nondihydropyridine calcium channel blockers or beta blockers.[1] Both work by slowing conduction through the atrioventricular node, which helps to control the ventricular rate. Calcium channel blockers act by inhibiting calcium entry from the slow calcium channels of the myocardium.[1] Calcium channel blockers are contraindicated among patients with heart failure with reduced ejection fraction of 40% or less due to negative inotropic and chronotropic effects, which may worsen heart failure.[1] Among ED patients presenting with atrial fibrillation with rapid ventricular response and an ejection fraction of more than 40%, we recommend calcium channel blockers as they have a faster onset of effect, easily titratable dosing, similar adverse effects profile, and may improve long-term atrial fibrillation-related symptoms compared with beta blockers.

The 2023 American College of Cardiology, American Heart Association, American College of Clinical Pharmacy, and Heart Rhythm Society updated clinical practice guidelines for diagnosis and management of atrial fibrillation recommend either calcium channel blockers (if ejection fraction is more than 40%) or beta blockers for acute rate control in hemodynamically stable patients.[1] Though there are limited comparative data, a recent meta-analysis examined diltiazem versus metoprolol for treatment of atrial fibrillation with rapid ventricular response. It included 17 studies (10 were high quality; n=1,214). Twelve studies were included in the efficacy analysis, and pooled results showed that intravenous administration of diltiazem had higher efficacy (relative risk [RR] 1.11, 95% confidence interval [CI] 1.06 to 1.16) at 30 and 60 minutes (no statistical difference was observed at 5, 10, 90, or 120 minutes).[4] Additionally, in the 411 patients with onset time documented, diltiazem had a faster onset (RR −1.13 and 95% CI −1.97 to −0.28) with a lower ventricular rate relative to metoprolol (RR −9.48 and 95% CI −12.13 to −6.82) at every time point from 5 to 90 minutes.

Diltiazem and metoprolol are the most common calcium channel blocker and beta blocker, respectively, used to treat atrial fibrillation with rapid ventricular response. In addition to a more rapid onset of effect,

diltiazem dosing is an initial intravenous bolus of 0.25 mg/kg followed by a continuous infusion, which can be initiated after the bolus.[1] By contrast, metoprolol is an intravenous bolus of 2.5 to 5 mg for up to 3 doses.[1] Thus, diltiazem may offer a simpler approach in that it requires less frequent repeat bolus doses. Although no literature has directly evaluated the effect of repeated metoprolol doses versus diltiazem bolus plus infusion on ED flow, initiating the bolus and continuous infusion at one time may streamline care and reduce nursing burden. The challenges of rapid reassessments and repeat boluses in the clinical setting may help to explain the difference in time to PR control described above.[4-6]

Though calcium channel blockers are commonly avoided in patients with a history of heart failure with reduced ejection fraction, adverse effects are generally equivocal between calcium channel blockers and beta blockers.[1,4] Furthermore, heart failure with reduced ejection fraction was historically difficult to diagnose in the ED, but the advancements in point-of-care ultrasound can rapidly identify patients with reduced ejection fraction.[7] A recent systematic review and meta-analysis (13 studies; n=1,660) evaluating adverse effects found higher rates of a composite of bradycardia and hypotension with diltiazem relative to metoprolol, though no difference was observed in the rate of bradycardia or hypotension alone.[8] A high rate of publication bias associating diltiazem with adverse effects was reported. Furthermore, the prediction interval (defined as the range of values within which a future observation is likely to fall) suggested that in future studies, metoprolol would be associated with a risk of 0.5 times lower to 1.1 times higher for the composite endpoint. Thus, these results should be interpreted cautiously. Notably, a retrospective cohort of 259 ED patients with no underlying medical illness found a similar rate of hospital admission, ED revisits, and adverse effects between patients who received calcium channel blockers or beta blockers.[9]

After stabilization, a subset of patients may be discharged from the ED. The emergency physician may continue the oral version of the initial medication used to stabilize the patient. A prospective, randomized study including 60 patients with permanent atrial fibrillation (without rapid ventricular response) compared oral diltiazem, verapamil, metoprolol, and carvedilol in an investigator-blinded crossover design.[6] The 24-hour PR was significantly lower in the diltiazem group compared with all other medications. Additionally, diltiazem reduced both the frequency and severity of atrial fibrillation -related symptoms using a symptom checklist questionnaire.[6] In a subsequent, similarly designed study comparing the same interventions in 60 patients with permanent atrial fibrillation , calcium channel blockers preserved exercise capacity and reduced N-terminal pro-B-type natriuretic peptide, a marker of heart failure, compared with baseline, whereas beta blockers decreased exercise capacity and increased N-terminal pro-B-type natriuretic peptide.[10] Thus, in addition to similar adverse effects overall, calcium channel blockers may decrease arrhythmia-related outcomes, including patient symptoms. These studies should not be extrapolated to patients with atrial fibrillation with rapid ventricular response, and further research is needed on the long-term effects of rate control selection in the ED following discharge in terms of health care usage and adverse effects.

In conclusion, we recommend calcium channel blockers in the ED for treatment of atrial fibrillation with rapid ventricular response with normal ejection fraction if ejection fraction is more than 40% as they have a faster onset of action, easier redosing regimen, and similar safety profile relative to beta blockers, with the potential to reduce atrial fibrillation-related symptoms if continued postdischarge.

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BETA BLOCKERS SHOULD BE PREFERENTIALLY USED TO TREAT ATRIAL FIBRILLATION WITH RAPID VENTRICULAR RESPONSE

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Emergency medicine clinicians frequently manage patients with atrial fibrillation with rapid ventricular response. In 2014, approximately 1 in 200 (0.5%) and 1 in 67 (1.5%) of all emergency department (ED) visits and hospitalizations were related to primary atrial fibrillation rapid ventricular response, respectively.[1] In hemodynamically stable patients, rate control is the guideline-recommended treatment for symptom relief and minimizing the risk of progression to left ventricular dysfunction.[2] Guidelines provide a patient-centered approach to rate control, encompassing agents such as β-blockers, nondihydropyridine calcium channel blockers, digoxin, magnesium, and amiodarone. Although β-blockers and calcium channel blockers are often preferred as initial agents for atrial fibrillation rapid ventricular response, this should not preclude consideration of other appropriate therapies, including amiodarone, as outlined in the guidelines.[2] β-blockers and calcium channel blockers achieve rate control by slowing atrioventricular (AV) nodal conduction and prolonging AV nodal refractoriness.[2,3] Intravenous metoprolol is a selective β1 blocker with a half-life of about 6 hours and an onset-of-action of about 20 minutes.[4] Intravenous esmolol and landiolol are also selective β1 blockers with half-lives of about 5 minutes and onsets of action of less than a minute.[5] However, both have limited utility as first-line β-blockers in atrial fibrillation rapid ventricular response due to higher cost, availability, and need for continuous infusions. For patients presenting to the ED with atrial fibrillation rapid ventricular response, we propose that β-blockers (specifically, metoprolol) are the preferred rate control agents due to high efficacy, ability to be used safely in most patients, including those with heart failure, and ease of administration.[2]

In the ED, clinicians may choose calcium channel blockers over β-blockers for rate control in atrial fibrillation with rapid ventricular response due to their perceived faster rate control. However, the evidence suggests otherwise. The largest randomized trial comparing the speed of rate control between metoprolol and diltiazem found that 95.8% of patients in the diltiazem group achieved rate control within 30 minutes versus 46.4% in the metoprolol group.[3] However, the trial was limited by the smaller sample size (52 patients) and potential underdosing of metoprolol.[3] Additionally, a recent retrospective study comparing intravenous metoprolol with diltiazem for rate control within 2 hours of intravenous administration showed no difference in median time to rate control (35 versus 21 minutes, P=.23).[6]

Beyond comparable efficacy, β-blockers offer an important advantage in that they can be used safely in atrial fibrillation with rapid ventricular response complicated by heart failure with reduced ejection fraction (HFrEF). Multiple major professional society guidelines specify that calcium channel blockers are contraindicated in patients with an ejection fraction of less than 40.[2] Calcium channel blockers (verapamil and diltiazem) have negative inotropic effects by inhibiting L-type calcium channels, reducing cardiac contractility.[2,3] This is harmful in HFrEF, where systolic function is already impaired, increasing risk of decompensation and exacerbation of heart failure symptoms. A retrospective study found significantly higher rates of worsening heart failure (necessitating inotropic and oxygen support) in HFrEF patients treated with intravenous diltiazem compared with metoprolol (33% versus 15%).[7] Although some studies suggest comparable incidence of hypotension and bradycardia with both drug classes, the risk of heart failure exacerbation remains an important distinction.[4] Therefore, rapid point-of-care ultrasound evaluation of ejection fraction must be performed in all patients with heart failure before using calcium channel blockers for atrial fibrillation rapid ventricular response to ensure safety.