Comparative effectiveness of heart rate control medications for the treatment of sepsis-associated atrial fibrillation

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Abbreviations: AF: atrial fibrillation; BPM: beats per minute; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; HR: heart rate; ICU: intensive care unit; MAP: mean arterial pressure; RVR: rapid ventricular response; SOFA: sequential organ failure assessment; SPO2: hemoglobin oxygen saturation

Abstract

Background

Atrial fibrillation with rapid ventricular response frequently complicates the management of critically ill patients with sepsis and may necessitate the initiation medication to avoid hemodynamic compromise. However, the optimal medication to achieve rate control for atrial fibrillation with rapid ventricular response in sepsis is unclear.

Research question

What is the comparative effectiveness of frequently-used AF medications (beta-blockers, calcium channel blockers, amiodarone, and digoxin) on heart rate reduction among critically ill patients with sepsis and atrial fibrillation with rapid ventricular response?

Study Design and Methods

We conducted a multicenter retrospective cohort study among patients with sepsis and atrial fibrillation with rapid ventricular response (heart rate >110 BPM). We compared the rate control effectiveness of beta-blockers to calcium channel blockers, amiodarone, and digoxin using multivariable-adjusted, time-varying exposures in competing risk models (for death and addition of another atrial fibrillation medication), adjusting for fixed and time-varying confounders.

Results

Among 666 included patients, 50.6% initially received amiodarone, 10.1% a beta-blocker, 33.8% a calcium channel blocker and 5.6% digoxin. The adjusted hazard ratio for HR<110 BPM by 1 hour was 0.50 (95% CI 0.34-0.74) for amiodarone vs beta blocker, 0.37 (95% CI 0.18-0.77) for digoxin vs beta blocker, and was 0.75 (95% CI 0.51-1.11) for calcium channel blocker vs beta blocker. By 6 hours, the adjusted hazard ratio for HR<110 BPM was 0.67 (95% CI 0.47-0.97) for

amiodarone vs beta blocker, 0.60 (95% CI 0.36-1.004) for digoxin vs beta blocker, and 1.03 (95% CI 0.71-1.49) for calcium channel blocker vs beta blocker.

Interpretation

In a large cohort of patients with sepsis and atrial fibrillation with rapid ventricular response, a beta-blocker treatment strategy was associated with improved heart rate control at 1 hour, but generally similar heart rate control at 6 hours compared to amiodarone, calcium channel blocker, or digoxin.

Key Words: Atrial fibrillation, rate control, sepsis, comparative effectiveness

Atrial fibrillation (AF) occurs in nearly a quarter of critically ill patients with sepsis and is associated with short- and long-term morbidity and mortality[1,2]. During sepsis, high circulating catecholamines may increase the risk of rapid AV-nodal conduction in AF, leading to reduced diastolic filling time and an increased risk for hemodynamic compromise[3,4]. Thus, practice guidelines[5] recommend medications to reduce heart rate in AF with rapid ventricular response (RVR) in patients that do not require emergent electric cardioversion. However, the optimal medication to achieve rate control for AF with RVR in sepsis is unclear. In this multicenter retrospective cohort study, we sought to compare the effectiveness of commonly used medications for AF rate and rhythm control during sepsis[6] (beta-blockers, calcium channel blockers, amiodarone, and digoxin) on heart rate (HR) reduction among critically ill patients with sepsis and AF with RVR admitted to the intensive care unit (ICU).

Methods

Cohort

We used the eICU Collaborative Research Database[7,8], a multi-center 20% subset of patients admitted from 2014-2015 to 208 US hospitals participating in Philips telehealth system (eCareManager), to identify adult patients (≥18 years) with sepsis and AF with RVR who were treated with an intravenous AF medication (metoprolol, esmolol diltiazem, verapamil amiodarone, or digoxin). We identified patients with sepsis using previously validated[9] International Classification of Diseases, Ninth Edition codes (as the eICU database does not contain reliable culture information to use Sepsis-3 definitions[10]). We identified the presence and timing of AF using physician documentation in the active diagnosis/treatment sections of eCareManager. AF with RVR was defined as a HR >110 beats per minute (BPM), a heart rate

evaluated as the upper limit definition of heart rate control in prior trials[11,12] . We limited our cohort to those patients who had a HR ≥110 BPM at the time that the AF medication was initiated. For patients with multiple admissions, we evaluated the initial admission for inclusion in the study.

Outcomes

The primary outcome of interest was the risk-adjusted rate of HR <110 BPM by 1 hour hours after administration. Secondary effectiveness outcomes included (1) the risk-adjusted rate of HR <110 BPM by 6 hours after administration, (2) the percent change in heart rate at 1 and 6 hours after initial AF medication administration, and (3) the per-person average heart rate during the first 1 hour and during the first 6 hours following initial AF medication administration. Secondary safety outcomes included (1) incidence of at least one mean arterial pressure (MAP) reading <65 mmHg by 6 hours (hypotension that may reflect hemodynamic instability and worse outcomes in sepsis[3]), (2) incidence of HR <60 BPM by 6 hours (bradycardia), (3) incidence of a vasopressor medication started or increased in dose by 6 hours, (4) incidence of initiation of at least one additional AF medication by 6 hours, (5) incidence of undergoing direct current cardioversion by 6 hours, and (6) the proportion of patients undergoing pacemaker placement by 6 hours; (7) hospital length of stay and (8) incidence of death during hospitalization.

Exposures and covariates

Among patients with AF with RVR, we identified the type and timing of the first intravenous AF medication. The AF medication types of interest were beta-blockers (metoprolol and esmolol), calcium channel blockers (diltiazem and verapamil), amiodarone, and digoxin. We used an “intention to treat treatment strategy” where the initial AF medication used was assigned

as the treatment strategy selected for that patient. AF medication was included as a time-varying exposure variable.

Because different clinical characteristics may influence both the type of AF medication given and the heart rate response, we measured multiple potentially confounding fixed and time-varying covariates. At the time of admission, we identified each patient's age, race, sex, use of home AF medications (amiodarone, beta-blockers, calcium channel blockers, and digoxin), history of pre-existing AF, congestive heart failure (CHF) and asthma or chronic obstructive pulmonary disease (COPD). Within 24 hours of first AF medication, we identified per-os (PO) orders for amiodarone, beta-blockers, calcium channel blockers, and digoxin. We also identified the time in hours from AF with RVR diagnosis to first AF medication administration. Time-varying covariates identified from the time of first AF medication administration included heart rate, MAP, hemoglobin oxygen saturation (SPO2), sequential organ failure assessment (SOFA) score[13], vasopressor and inotrope use, blood magnesium, potassium, troponin I, white blood cell count level, and use of mechanical ventilation and hemodialysis. Last value carried forward imputation was used for time-varying covariates with missing entries for a given time.

Statistical Analysis

We used means to summarize continuous baseline characteristics, and counts and percentages to summarize categorical baseline characteristics, in subjects taking AF medication with HR $\geq$ 110 at time of medication. These characteristics are stratified by AF medication type. Baseline is defined as the time of AF medication initiation. Because receipt of additional medications after a failed initial AF treatment may produce spurious conclusions regarding the effectiveness of the initial treatment strategy, we used competing risk models to determine sub-

distribution hazard ratios for each AF medication estimating the effect of each AF medication on heart rate response in the setting of competing risk of death and addition of a new AF medication class. Given the clinical importance of understanding short and medium-term rate control effectiveness, as well as non-proportional hazards after 6 hours, we evaluated heart rate control at 1- and 6-hour time points. We included death and use of additional AF medications as competing risks. The sub-distribution hazard ratios can be interpreted as the increase in the rate of AF with RVR resolution (heart rate <110 BPM) associated with the AF medication of interest among patients who had heart rate ≥110 BPM at the time of AF medication or who have experienced a competing event. We calculated E-values for each hazard ratio to determine the strength of association between a theoretical unmeasured confounder, initial AF medication type, and the primary outcome that the unmeasured confounder must have to bring the observed effect estimate to the null[14].

For other secondary effectiveness and safety outcomes, we limited our cohort to those patients with a HR ≥110 BPM at the time of initial AF medication administration and to those subjects who had available HR data at both 1 hour and 6-hour time points. For each secondary effectiveness and safety outcome, we used linear models for continuous outcomes (e.g. percent change in heart rate) and logistic regression models for dichotomous outcomes (e.g. hypotension). For secondary outcome models (except bradycardia, vasopressor use, direct cardioversion, and pacemaker placement that had low outcome rates that precluded the use of adjusted models), we adjusted for covariates (age, sex, race/ethnicity, CHF and asthma or COPD history, HR, MAP, SOFA score, vasopressor dose, magnesium, potassium, troponin, and white blood cell count levels, SPO2, mechanical ventilation and hemodialysis) at the time of initial AF

medication. In all primary and secondary outcome models, beta blockers were used as the reference AF medication group to which all other AF mediation effect estimates were compared.

All tests were 2-sided (alpha 0.05). SAS version 9.4 (SAS Institute Inc) was used for statistical analyses. This study was designated by the Boston University IRB as not Human Subjects Research.

Results

Among 2328 ICU patients with sepsis and AF with RVR, 666 were started on an AF medication where HR ≥110 BPM at the time of AF medication (Figure 1). 337 (50.6%) patients were started on amiodarone, 67 (10.1%) on a beta-blocker, 225 (33.8%) on a calcium channel blocker and 37 (5.6%) on digoxin. The average age was 72 years (SD 12 years) and 208 (31.2%) patients died during the index hospitalization (Table 1). At the time of AF medication administration, the average HR was 128 BPM (SD 15 BPM) and 246 (36.9%) patients were mechanically ventilated.

Competing risk models

After adjusting for covariates and accounting for competing risks of death and use of additional AF rate or rhythm control medications, the adjusted hazard ratio for HR<110 BPM by 1 hour was 0.50 (95% CI 0.34-0.74, p<0.001, E-value 2.61) for amiodarone vs. beta-blocker, 0.37 (95% CI 0.18-0.77, p=0.007, E-value 3.37) for digoxin vs beta-blocker, and 0.75 (95% CI 0.51-1.11, p=0.15, E-value 1.74) for calcium channel blocker vs beta-blocker. By 6 hours, the adjusted hazard ratio for HR<110 BPM was 0.67 (95% CI 0.47-0.97, p=0.03, E-value 1.97) for amiodarone vs beta-blocker, 0.60 (95% CI 0.36-1.004, p=0.052, E-value 2.20) for digoxin vs beta-blocker, and 1.03 (95% CI 0.71-1.49, p=0.88, E-value 1.17) for calcium channel blocker vs beta-blocker.

Effectiveness outcomes

636 patients were evaluated in our secondary effectiveness outcomes analyses having HR measurements at both 1 and 6 hours. The results of the secondary effectiveness outcomes show that patients who received a beta-blocker had a larger reduction in HR at 1 hour, but not at 6 hours, following administration compared to those patients who received other AF medications (Table 2). For example, the average adjusted HR during the first 1 hour after treatment among patients who received a beta-blocker (115 BPM [95% CI 112-118 BPM]) was lower compared to patients who received other AF medications (amiodarone 122 BPM [95% CI 122-123 BPM, p<0.001], calcium channel blocker 122 BPM [95% CI 120-124 BPM, p<0.001]), and digoxin 124 BPM [95% CI 119-129 BPM, p=0.002]). However during the first 6 hours, the average adjusted HR of patients who received a beta-blocker (110 BPM [95% CI 106-114 BPM]) was only significantly lower compared to patients who received digoxin (118 BPM [95% CI 112-123 BPM, p=0.03]) but not amiodarone (114 BPM [95% CI 112-115 BPM, p=0.11]) or a calcium channel blocker (110 BPM [95% CI 108-112 BPM, p=1.00]). Compared to patients initiated on a beta-blocker, patients initiated on amiodarone (aOR 0.40, 95% CI 0.17-0.93, p=0.03) and a calcium channel blocker (aOR 0.32, 95% CI 0.13-0.78, p=0.01), but not digoxin (aOR 2.30, 95% CI 0.73-7.25, p=0.15), had a lower odds of being administered at least one additional AF medication type by 6 hours.

Safety outcomes

Safety outcomes stratified by initial AF medication type are shown in Table 3. Safety outcomes were rare – occurring in less than 10% of patients - across all AF medication treatment strategies except for hypotension (MAP<65 mmHg – beta-blocker 58.5%, amiodarone 69.4%, calcium channel blocker 56.0% and digoxin 51.4%) and hospital mortality (beta-blocker 27.4%,

amiodarone 37.6%, calcium channel blocker 19.8% and digoxin 18.4%). Compared to patients who received beta-blockers, the adjusted odds of hypotension (MAP <65 mmHg) was lower in patients who received digoxin (aOR 0.20, 95% CI 0.07-0.63, p=0.006) but not in patients who received amiodarone (aOR 0.72, 95% CI 0.34-1.54, p=0.40) or calcium channel blockers (aOR 0.72, 95% CI 0.34-1.56, p=0.41).

The average adjusted length of stay (beta-blocker [8.1 days], amiodarone [9.0 days, p=0.61], calcium channel blocker [10.4 days, p=0.18], and digoxin [9.4 days, p=0.63]) and odds of death during hospitalization (amiodarone [aOR 1.23, 95% CI 0.61, 2.51, p=0.56], calcium channel blocker [aOR 0.63, 95% CI 0.30-1.34, p=0.23], and digoxin [aOR 0.33, 95% CI 0.09-1.22, p=0.10]) were not different between patients initiated on a beta-blocker and patients initiated on other AF medications.

The numbers of patients with bradycardia (21, 3.2%), who had a vasopressor medication started or increased in dose (21, 3.2%), who underwent direct cardioversion (9, 1.4%) and who underwent pacemaker placement (6, 0.9%) by 6 hours were low (Table 3). Thus, we were unable to construct models to determine adjusted odds ratios for these safety outcomes.

Discussion

AF with RVR during sepsis is a common clinical problem, however the comparative effectiveness of medications to achieve heart rate control is unclear. We performed an observational comparative effectiveness study comparing the ability of beta-blockers, calcium channel blockers, digoxin, and amiodarone to achieve heart rate control during AF with RVR among critically ill patients with sepsis. Although beta-blockers were associated with improved heart rate control at 1 hour after administration, by 6 hours difference in rate control between AF

medications was minimal (all AF medications were associated with a 10-20% reduction in HR). We also found that amiodarone, despite being the most frequently administered medication in our study, was associated with the longest times to rate control. Our results have implications for clinicians managing critically ill patients with sepsis and AF with RVR.

Our results should be viewed in the context of previous studies. In a single-center observational study, Moskowitz et al.[15] found that among patients admitted to the ICU (irrespective of diagnosis) with AF with RVR, administration of beta-blockers within 2-hours of AF with RVR onset was associated with lower odds of failure (defined by the use of a second agent prior to the end of a RVR episode) compared to amiodarone. Although our study also identified beta-blockers as the AF medication associated with the fastest time to RVR resolution, our secondary analysis also suggested that all medications achieved similar heart rate responses by 6 hours. When comparing a beta-blocker treatment strategy to other treatment strategies, patients treated with beta-blockers were also more than twice as likely (19% vs 7%) to receive an additional AF medication by 6 hours compared to the most frequently administered AF medications: amiodarone and calcium channel blockers. Thus, although beta-blockers may achieve faster time to initial rate control that may be valuable in the short-term, it is unclear if other medications or more frequent dosing may be needed to achieve longer term rate control. Differences in AF mechanism between the undifferentiated general ICU population in Moskowitz et al. and the sepsis-specific patients included in our study may impact the effectiveness and duration of effectiveness of specific AF medications. Unlike our previous observations[6] among patients with AF during sepsis, we did not find that beta-blockers are associated with lower hospital mortality compared to other AF medications. In sum, these results suggest that, in absence of contraindications (decompensated heart failure, uncontrolled

bronchospasm) and RCT evidence, clinicians aiming to reduce heart rate rapidly among patients with sepsis and AF with RVR who do not require cardioversion should consider beta-blockers as first line therapy. Rapid reduction in HR may be particularly beneficial in patients with new-onset AF during critical illness, given that up to 37% may develop hemodynamic compromise in association with their AF[16]. However, if a rapid reduction is not necessary, there appears to be less difference in the ability to achieve rate control between beta-blockers, amiodarone, calcium channel blockers, and digoxin. Clinicians should also continue to monitor patients and prepare to potentially initiate additional AF medications, or consider more frequent dosing or continuous infusion, in the event that HR response is of short duration. Future RCTs are needed to make specific treatment recommendations for optimal strategies for heart rate control in AF during sepsis.

Our study has several strengths. Our results were robust to potential time-varying confounders and to strong unmeasured confounding. In addition, we were able to quantify the estimates of the association between AF medication and heart rate control, the estimate of the association between initial AF medication and the use of subsequent AF medications, and the average reduction in heart rate that can be expected at 1 and 6 hour time points from each medication. Knowing the risk of the need for additional AF medications is particularly valuable to clinicians, especially when the risk of hemodynamic compromise with treatment failure is high (e.g., significant diastolic dysfunction) or when patients have limited venous access. Lastly, the combined results from our multiple secondary effectiveness and adverse event outcomes provide clinicians with novel data that quantifies the average reductions in heart rate expected at different time points for commonly used medications, and evaluates risks and benefits of different strategies for heart rate control of AF during sepsis.

Our study also has several limitations. While characteristics of patients receiving beta blockers, calcium channel blockers, and digoxin were generally similar, patients receiving amiodarone had higher rates of mechanical ventilation and vasopressor needs at baseline, which may also suggest a greater risk of unmeasured confounding for comparisons with amiodarone. However, the E-value of 2.65 suggests that unmeasured variables associated with a 2 to 3-fold higher odds of both receiving amiodarone and not achieving heart rate control would be needed to substantively change the results. For example, we did not include attending of record in our models, a variable previously associated with receiving amiodarone for AF during sepsis (OR 1.36)[6]. Thus, if attending of record was also associated with HR control, then attending of record could be an unmeasured confounder in our study. However, the E-value of 2.61 suggests that the strength of the associations between attending of record, amiodarone use, and HR control would have to be at least 2.61 to substantively change our conclusions. The optimal HR at which to start AF medications during sepsis is unclear and our choice of 110 BPM, though consistent with cutpoints chosen in prior clinical trials looking at outpatient HR control, may not represent the ideal target during critical illness. Further studies of optimal HR targets for AF during critical illness are needed. However, results using continuous analysis of HR supported the HR >110 analyses. We were not able to identify the time of resolution of AF in our cohort, and thus we were unable to compare rhythm control between medications or time to conversion to sinus rhythm, a finding of particular interest when evaluating effects of amiodarone. In addition, the use of PO medication order, rather than PO medication administration in our models might affect our results as we cannot be sure if PO medications that were ordered were actually given. Lastly, future randomized controlled studies are needed to confirm the hypothesis-generating comparative effectiveness findings in our study.

Interpretation

We found that in a large US multicenter cohort of patients with sepsis and AF with RVR, a beta-blocker treatment strategy was associated with improved HR control compared to amiodarone, calcium channel blocker, or digoxin treatment strategies at 1 hour. However, the relative improvement in HR using a beta-blocker strategy was diminished after 6 hours, and we did not find evidence that a beta-blocker treatment strategy improved non-hemodynamic related outcomes (i.e. hospital death).

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Figure legend

Fig. 1. Flow Diagram for inclusion and exclusion into the study cohort.

Table 1: Characteristics of intensive care unit patients with sepsis and treated atrial fibrillation with rapid ventricular response

Characteristic	Overall (n = 666)	Amiodarone (n = 337)	Beta-blocker (n = 67)	Calcium channel Blocker (n = 225)	Digoxin (n = 37)
Age years, mean (SD)	72 (12)	72 (12)	72 (12)	73 (12)	75 (11)
Female Gender, No. (%)	362 (54.4)	192 (57.0)	36 (53.7)	115 (51.1)	19 (51.4)
Race/Ethnicity, No. (%)					
Asian	7 (1.1)	4 (1.2)	1 (1.5)	2 (0.9)	0 (0.0)
Black	37 (5.6)	19 (5.6)	5 (7.5)	12 (5.3)	1 (2.7)
White	559 (83.9)	272 (80.7)	61 (91.0)	191 (84.9)	35 (94.6)
Hispanic	31 (4.7)	20 (5.9)	0 (0.0)	11 (4.9)	0 (0.0)
Other	2 (0.3)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	30 (4.5)	20 (5.9)	0 (0.0)	9 (4.0)	1 (2.7)
History of CHF, No. (%)	181 (27.2)	97 (28.8)	16 (23.9)	56 (24.9)	12 (32.4)
History of asthma or COPD, No. (%)	121 (18.2)	58 (17.2)	9 (13.4)	47 (20.9)	7 (18.9)
History of atrial fibrillation, No. (%)	243 (36.5)	114 (33.8)	25 (37.3)	92 (40.9)	12 (32.4)
Home medications, No. (%)					
Amiodarone	15 (2.3)	11 (3.3)	1 (1.5)	3 (1.3)	0 (0.0)
Beta Blocker	101 (15.2)	49 (14.5)	4 (6.0)	44 (19.6)	4 (10.8)
Calcium Channel Blocker	30 (4.5)	10 (3.0)	2 (3.0)	17 (7.6)	1 (2.7)
Digoxin	18 (2.7)	6 (1.8)	1 (1.5)	10 (4.4)	1 (2.7)
Per-os medication order within 24 hours of first medication, no. (%)					
Amiodarone	12 (1.8)	7 (2.1)	0 (0.0)	5 (2.2)	0 (0.0)
Beta Blocker	76 (11.4)	29 (8.6)	13 (19.4)	31 (13.8)	3 (8.1)
Calcium Channel Blocker	5 (0.7)	1 (0.3)	0 (0.0)	3 (1.3)	1 (2.7)
Digoxin	9 (1.4)	2 (0.6)	2 (3.0)	5 (2.2)	0 (0.0)
Heart rate at the time of AF with RVR - BPM, Mean (SD)	128 (15)	128 (15)	132 (15)	127 (14)	132 (14)
Time from AF with RVR to first medication – hours, median (IQR)	1.9 (0.5-11.9)	1.3 (0.5-7.9)	10.2 (1.6-22.7)	1.8 (0.4-10.8)	4.9 (1.3-24.9)
Mean arterial pressure at the time of AF with RVR - mmHg, Mean (SD)	78 (18)	74 (14)	85 (32)	82 (16)	78 (18)
Serum magnesium level at the time of AF with RVR – mg/dL, Mean (SD)	2.0 (0.4)	2.0 (0.4)	2.0 (0.3)	2.0 (0.4)	2.0 (0.3)
Serum potassium level at the time of AF with RVR – mEq/L, Mean (SD)	4.1 (0.6)	4.1 (0.7)	4.0 (0.6)	4.0 (0.6)	4.1 (0.6)
Maximum SOFA score at the time of AF with RVR, Mean (SD)	8 (3)	9 (4)	7 (3)	7(3)	8 (4)
Mechanically ventilated at the time of AF with RVR, Mean (SD)	246 (36.9)	146 (43.3)	18 (26.9)	72 (32.0)	10 (27.0)
Vasopressor or inotrope at the time of AF with RVR, Mean (SD)	254 (38.1)	188 (55.8)	16 (23.9)	43 (19.1)	7 (18.9)
Hospital mortality, No. (%)	208 (31.2)	132 (39.2)	21 (31.3)	50 (22.2)	5 (13.5)
Pneumonia sepsis source, No. (%)	336 (50.5)	159 (47.2)	33 (49.3)	124 (55.1)	20 (54.1)

AF: atrial fibrillation; COPD: chronic obstructive pulmonary disease; CHF: congestive heart failure; RVR: rapid

ventricular response; SOFA: sequential organ failure assessment

Table 2: Secondary effectiveness outcomes associated for atrial fibrillation with rapid ventricular response during sepsis stratified by initial AF medication

Outcome	Beta-blocker (n=61)	Amiodarone (n=322)	Calcium channel blocker (n=217)	Digoxin (n=36)
Average percent change in HR at 1 hour, % (95% CI)				
Unadjusted	-15.2 (-18.3, -12.2)	-6.2 (-7.6, -4.9)	-7.8 (-9.5, -6.2)	-6.0 (-9.9, -2.0)
Adjusted[a]	-15.3 (-18.5, -12.1)	-6.8 (-8.3, -5.3)	-8.0 (-9.9, -6.1)	-4.9 (-9.8, -0.1)
Average percent change in HR at 6 hours, % (95% CI)				
Unadjusted	-15.9 (-20.0, -11.8)	-15.0 (-16.8, -13.3)	-19.1 (-21.3, -17.0)	-15.9 (-21.2, -10.6)
Adjusted[a]	-15.2 (-19.2, -11.2)	-16.3 (-18.1, -14.4)	-20.5 (-22.8, -18.1)	-11.3 (-17.2, -5.3)
Average HR during the first 1 hour, BPM (95% CI)				
Unadjusted	118 (114-121)	122 (121-124)	120 (118-122)	126 (121-131)
Adjusted[a]	115 (112-118)	122 (120-123)	122 (120-124)	124 (119-129)
Average HR during the first 6 hours, BPM (95% CI)				
Unadjusted	112 (108-116)	114 (113-116)	110 (108-112)	117 (112-122)
Adjusted[a]	110 (106-114)	114 (112-115)	110. (108-112)	118 (112-123)

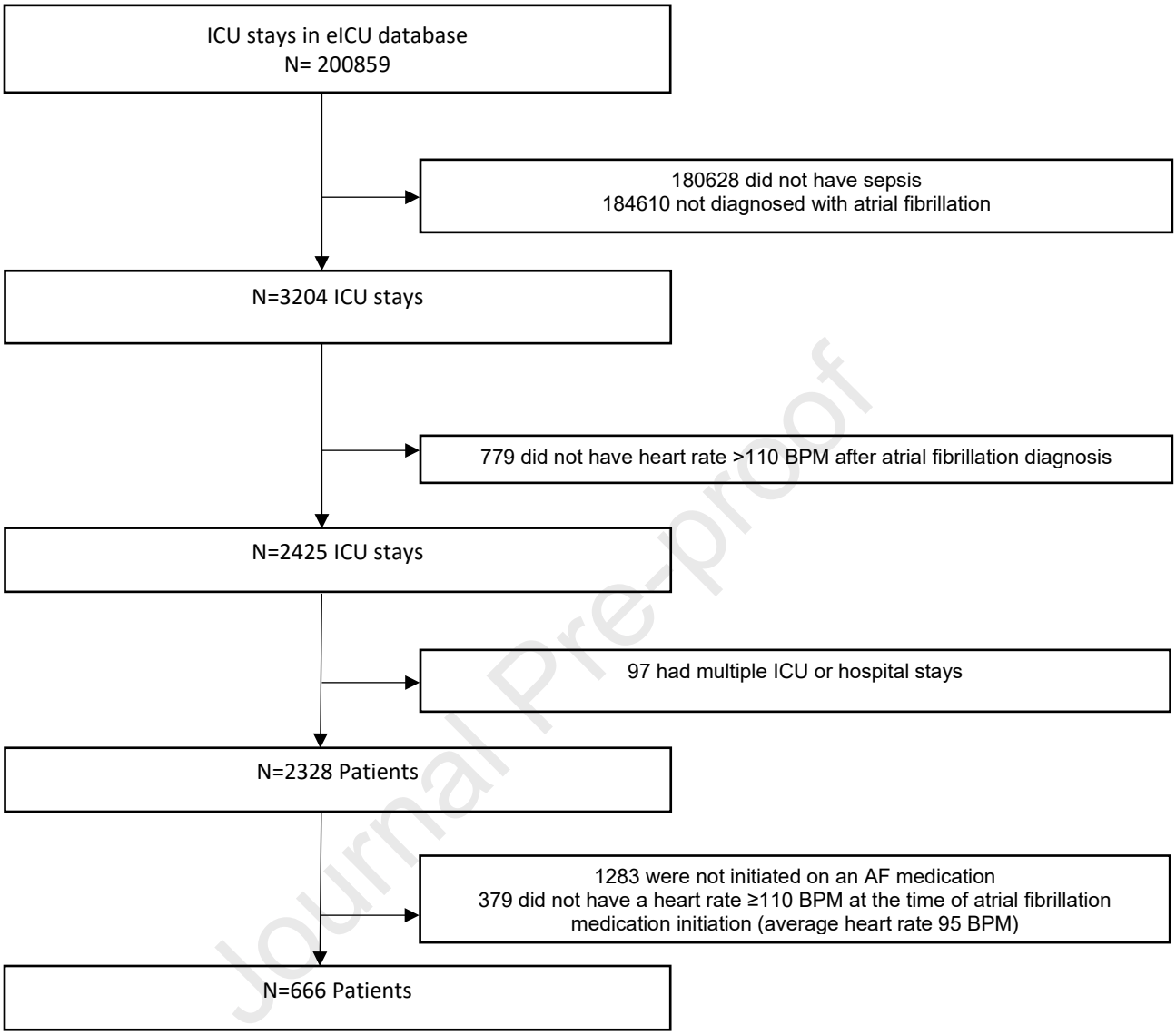
HR: heart rate

[a]Adjusted for heart rate at the time of initial AF medication administration, age, sex, race/ethnicity, congestive heart failure and asthma or chronic obstructive pulmonary disease history, mean arterial pressure, sequential organ failure assessment score, vasopressor or inotrope use, magnesium, potassium, white blood cell count, and troponin I levels, SPO2, and presence of mechanical ventilation and hemodialysis.

Table 3: Safety outcomes stratified by AF medication type

Medication	Beta-blocker (n=113)	Amiodarone (n=529)	Calcium channel blocker (n=354)	Digoxin (n=49)
MAP< 65 mmHg by 6 hours, % (95% CI)	58.2 (46.4-70.0)	69.4 (64.5-74.4)	56.0 (49.5-62.5)	51.4 (35.2-67.5)
HR <60 BPM by 6 hours, % (95% CI)	3.0 (1.1-7.1)	4.5 (2.2-6.7)	0.9 (0.3-2.1)	5.4 (1.9-12.7)
Vasopressor medication started or increased in dose by 6 hours, % (95% CI)	0.0 (0.0-0.0)	5.3 (2.9-7.7)	0.9 (0.3-2.1)	2.7 (2.5-7.9)
Direct cardioversion by 6 hours, % (95% CI)	0.0 (0.0-0.0)	2.1 (0.6-3.6)	0.4 (0.4-1.3)	2.7 (2.5-7.9)
Pacemaker by 6 hours, % (95% CI)	1.5 (1.4-4.4)	1.2 (0.0-2.3)	0.4 (0.4-1.3)	0.0 (0.0-0.0)
Additional AF medications by 6 hours, % (95% CI)				
None	79.1 (69.4-88.8)	92.3 (89.4-95.1)	91.1 (87.4-94.8)	75.7 (61.9-89.5)
One	19.4 (9.9-28.9)	7.1 (4.4-9.9)	7.6 (4.1-11.0)	24.3 (10.5-38.1)
Two	1.5 (0.0-4.4)	0.6 (0.0-1.4)	0.9 (0.0-2.1)	0.0 (0.0-0.0)
Three	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.4 (0.0-1.3)	0.0 (0.0-0.0)
Hospital length of stay (days), median (95% CI)	6.3 (4.6-7.4)	5.6 (4.4-6.6)	6.4 (5.3-7.5)	5.1 (3.5-8.4)
Hospital Mortality, % (95% CI)	31.3 (27.7-34.8)	39.2 (34.0-44.4)	22.2 (16.8-27.7)	13.5 (2.5-24.5)

AF: atrial fibrillation; HR: heart rate; MAP: mean arterial pressure



Abbreviations list

AF: atrial fibrillation; BPM: beats per minute; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; HR: heart rate; ICU: intensive care unit; MAP: mean arterial pressure; RVR: rapid ventricular response; SOFA: sequential organ failure assessment; SPO2: hemoglobin oxygen saturation