Emergency Department Patients With Atrial Fibrillation or Flutter and an Acute Underlying Medical Illness May Not Benefit From Attempts to Control Rate or Rhythm

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Study objective: Although the management and outcomes of emergency department (ED) patients with atrial fibrillation or flutter have been explored, such studies have typically excluded patients with acute underlying medical illnesses. We seek to describe the ED treatment and outcomes of these complex patients with atrial fibrillation or flutter.

Methods: This retrospective descriptive cohort study used an ECG database from 2 urban EDs to identify consecutive ED patients with an ECG demonstrating atrial fibrillation or flutter from January 1, 2009, to December 31, 2009. We categorized patients with atrial fibrillation or flutter as "complex" according to prespecified criteria and then grouped them as being managed with rate or rhythm control attempts, or not. The primary outcome was safety of rate or rhythm control, measured by whether patients had a predefined adverse event or not. The secondary outcome was the success of rate or rhythm control, defined as rate control decreasing the pulse rate by 20 beats/min and successful rhythm control, both within 4 hours of treatment initiation. Descriptive statistics were used to compare the 2 groups.

Results: Four hundred sixteen complex patients with atrial fibrillation or flutter were identified. Patients managed with rate or rhythm control were similar in all baseline characteristics and illness distribution to patients who were not managed in this manner. The 135 patients with attempted rate control (105) or rhythm control (30) had 55 adverse events (40.7%; 95% confidence interval [CI] 32.5% to 49.5%), whereas the 281 patients not managed with rate or rhythm control had 20 adverse events (7.1%; 95% CI 4.5% to 10.9%), for a risk difference of 33.6% (95% CI 24.3% to 42.5%) and a relative risk of 5.7 (95% CI 3.6 to 9.1). Twenty of 105 patients (19.1%; 95% CI 12.3% to 28.1%) were successfully rate controlled, whereas 4 of 30 (13.3%; 95% CI 4.4% to 31.6%) were successfully rhythm controlled.

Conclusion: In ED patients with complex atrial fibrillation or flutter, attempts at rate and rhythm control are associated with a nearly 6-fold higher adverse event rate than that for patients who are not managed with rate or rhythm control. Success rates of rate or rhythm control attempts appear low. [Ann Emerg Med. 2015;65:511-522.]

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INTRODUCTION

Background

Atrial fibrillation and flutter are 2 commonly encountered dysrhythmias in emergency department (ED) patients, with more than half a million ED visits each year in the United States.[1] Although both rate[2-4] and rhythm control[4-7] strategies appear safe in patients with recent-onset atrial fibrillation or flutter and no acute underlying medical condition, those who have an acute underlying medical condition have been systemically excluded from most ED atrial fibrillation or flutter studies.

The American College of Cardiology/American Heart Association[8] and Canadian Cardiovascular Society[9] guidelines recommend immediate electrocardioversion for all patients with atrial fibrillation or flutter with angina or heart failure if they "do not respond promptly" to pharmacologic treatments, but this is not explicitly defined. Additionally, the entire guidelines and focused updates devote a single paragraph to encouraging "rapid assessment of potential hemodynamic instability, [and] the identification and treatment of the underlying or precipitating cause."[8,9] Although this may seem intuitive,

Editor's Capsule Summary

What is already known on this topic

The optimal management of patients who present to the emergency department with both atrial fibrillation or flutter and an acute medical issue is unknown.

What question this study addressed

This retrospective study of 416 such patients examined the incidence of adverse events in those whose rate and rhythm were actively managed compared with those who received no rhythm-targeted intervention.

What this study adds to our knowledge

Active management produced more major adverse events (13.1%; 95% confidence interval 7.4% to 20.3%). The propensity analysis suggests that this was not due to confounding (eg, the actively managed patients had more complications because they were the sicker patients).

How this is relevant to clinical practice

These data suggest that in patients with atrial fibrillation and flutter, initial management should focus on resuscitation and treatment of the acute illness rather than the control of rate and rhythm.

ED patients with atrial fibrillation or flutter and an acute underlying illness (hereafter also referred to as "complex" patients) may present with vague symptoms, such as weakness or dyspnea, and emergency physicians may face a dilemma: whether to attempt immediate rhythm control to restore hemodynamic stability or undertake additional and prolonged investigations to identify possible underlying issues requiring alternative treatments.

In a rigorous study, patients with atrial fibrillation or flutter with an "alternative" primary diagnosis were found to have a 30-day mortality rate of 11%.[10] However, emergency physician management was not explored; neither were ED-based outcomes such as adverse events, or the success of rate or rhythm control. We hypothesized that management of complex patients with atrial fibrillation or flutter with rate or rhythm control would be associated with increased adverse events compared with that of complex patients with atrial fibrillation or flutter managed without rate or rhythm control. Furthermore, we suspected that compared with that in uncomplicated patients with atrial fibrillation or flutter, attempts to control rate or rhythm would be less successful in complex patients with atrial fibrillation or flutter.

MATERIALS AND METHODS

Study Design and Setting

This was a retrospective cohort study[11-14] at 2 Canadian university-affiliated teaching EDs that are staffed by board-certified emergency physicians and share a common database. St. Paul's Hospital is an inner-city referral center with 70,000 annual ED visits during the study period. It has comprehensive cardiology services, with a coronary care unit, angiography capacity, cardiology ward, and electrophysiology. Mount St. Joseph's Hospital is a community center with 25,000 yearly visits and a general internal medicine ward; a cardiologist is available only for telephone consultations. More than 200 medical students and residents are trained at both sites annually. The ethics review board of Providence Health Care and the University of British Columbia approved this study.

Interventions

During the study period, complex patients were managed at the emergency physicians' discretion. Uncomplicated patients with atrial fibrillation or flutter who had a clear symptom onset time of less than 48 hours were typically treated with first-line electrical or chemical cardioversion, and if successfully converted to sinus rhythm, they were discharged home[12]; patients who were not eligible for rhythm control were typically administered rate control agents if their pulse rate was greater than 100 beats/min and were discharged home if their ventricular rate was less than 100 beats/min within 4 hours.[11]

Selection of Participants

From January 1, 2009, to December 31, 2009, every ECG conducted in the ED at both hospitals was stored in a MUSE database (GE Healthcare Clinical Systems, Waukesha, WI). ECGs are machine-read according to the MUSE algorithm, and results are confirmed by a board-certified cardiologist within 24 hours. The latter confirmation is entered into the MUSE database, which can then be sorted by date, time, heart rhythm, patient, and location; the database was screened to obtain ED patients who had atrial fibrillation or flutter during the study period. If a patient had multiple ECGs during the same ED visit, only the first ECG showing atrial fibrillation or flutter was used for the study. The patient's medical record number and time and date of acquisition were

electronically stamped onto each ECG. This database was entered into an Excel 2008 spreadsheet (Microsoft, Redmond, WA), and all identifiers except medical record number, date, and time were removed. Each patient then had a chart review of his or her ED encounter.

Patients who had cardiac procedures such as coronary artery bypass grafting or percutaneous coronary intervention, pacemaker insertion, or ablation up to 7 days before ED visit were excluded because cardiologists or surgeons provided management. Similarly, patients directly referred to the ED by cardiologists or internists for expedited admission were also excluded. Finally, patients who attended the ED solely for anticoagulation monitoring were excluded.

The sites share an electronic database, which records patient demographics, arrival time, triage complaint,[15] and discharge times. This database also provides a computerized order entry and result system that captures all ED investigations and consultations. The nursing record provided all vital signs; these were typically recorded initially and then at least every hour until discharge, and whenever the rhythm changed. Any medications, including rate or rhythm control agents, as well as all sedative and analgesic medications, were recorded in the nursing notes. Typical rate control agents were metoprolol, diltiazem, and verapamil,[11] procainamide was the common choice for chemical rhythm control,[12] and propofol/fentanyl was the typical choice for procedural sedation and analgesia for electrocardioversion.[11,12] A single physician, assisted by a registered nurse and respiratory therapist, who monitored the patient until physiologic recovery, typically conducted procedural sedations.[11-13]

We adhered to the criteria for medical record review described by Gilbert et al[16] and Worster et al.[17] Four trained reviewers (2 emergency physicians and 2 final-year medical students with previous graduate degrees) who were blinded to all study hypotheses and patient outcomes independently abstracted charts onto standardized electronic spreadsheets to document vital signs, comorbidities, ED treatments, and adverse events. Reviewers were trained on the first 10 charts and submitted data at regular intervals, which were examined for obvious errors such as patients with a previous stroke who had a CHADS2 (congestive heart failure, hypertension, age $>$ 75, diabetes, prior stroke or TIA) score less than 2.[18]

Missing or discrepant data were clarified by reviewing the patient's chart to 1999, which consisted of all clinic visits, ED visits, hospitalizations, discharge summaries, laboratory testing, and imaging, including special testing such as cardiac electrophysiology or catheterization. Conflicting chart information was recorded as an addendum in the spreadsheet and was reconciled at regularly scheduled meetings between the abstractors and the primary investigator. To ensure reliability, 10% of charts were independently assessed by a second reviewer and κ values were determined for 2 key variables: history of atrial fibrillation, and arrhythmia duration before ED arrival—the latter was recorded as either less than or greater than 48 hours.

Two staff emergency physicians who were blinded to study outcomes independently reviewed all charts again and stratified patients[11-14] into 2 a priori categories: complex patients with atrial fibrillation or flutter (those with an acute underlying medical illness), or uncomplicated patients with atrial fibrillation or flutter by a 2-step process. First, the emergency physician reviewers evaluated each chart to determine whether the patient had an acute underlying illness. Second, for patients determined to have one, the reviewer attempted to categorize the illness. The following conditions were also defined a priori as an acute underlying illness, and this algorithm has been previously described[11-14]: sepsis (including pneumonia), acute coronary syndrome, acute decompensated heart failure, pulmonary embolism, chronic obstructive pulmonary disease exacerbation, thyrotoxicosis, hypertensive emergency, drug overdose, acute valvular disease, hypothermia, acute renal failure, or gastrointestinal bleeding. We did not rely on either emergency physician or hospital discharge coding but followed the prespecified criteria outlined in Appendix E1 (available online at http://www.annemergmed.com). A key feature of this algorithm was that all physical examination findings and diagnostic tests had to be available in the ED. For example, a patient with chronic atrial fibrillation who developed acute renal failure 5 days after an admission for gout would not qualify as having an acute underlying illness.

In case the 2 emergency physician reviewers did not agree about whether there was an underlying illness, the chart was referred to 2 physicians—one certified in both internal medicine and cardiology and the other certified in emergency medicine, hematology, and internal medicine—who were not aware of the study hypothesis or any outcomes and who then adjudicated the presence of an underlying illness. If agreement failed at this stage, the principal investigator made the assignation.

Furthermore, both emergency physicians independently reviewed all charts and provided a diagnosis from the above list of conditions. For any patient with a discordant diagnosis (for example, one emergency physician thought that a patient had acute heart failure, whereas the other thought that the same patient had an acute coronary syndrome), the chart was further reviewed by the same 2 adjudicators; if diagnosis

disagreement persisted, the principal investigator assigned a single final diagnosis.

Outcome Measures

All outcomes were determined a priori. The primary outcome was the safety of rate or rhythm control attempts, measured as having a predefined adverse event. Complex patients with atrial fibrillation or flutter were stratified into the following groups: receiving rate or rhythm control attempts, or not receiving them. Rate control was defined as receiving either oral or intravenous rate control agents, whereas rhythm control was defined as having an attempt at either electrocardioversion or administration of oral or intravenous antiarrhythmic medications.

Adverse events are described in Figure 1 and reflect likely complications of atrial fibrillation or flutter treatment. Although previously described,[11-14] they have been recategorized as "major" or "minor." Because the intravenous medications used in rate or rhythm control have a short half-life, adverse events were counted only if they took place in the ED less than 4 hours after the initial attempt at rate or rhythm control; furthermore, in the majority of cases, the internal medicine, cardiology, or intensive care consultants would have assumed patient care by that time. If patients did not have a rate or rhythm control attempt, adverse events were counted if they took place in the ED within 4 hours of presentation. A second emergency physician independently reviewed all potential adverse events, and discrepant cases were referred to both of the adjudicators to ascertain whether an adverse event had truly taken place.

Because patients who had rate or rhythm control attempts may have been systematically different from those who did not, we used propensity scoring adjustments to determine the risk of an adverse event. Potential predictor variables were composed of physician factors (the individual physician), ED factors (whether the patient arrived between midnight and 8 AM, which are the traditional hours of solo physician coverage), and patient-level factors (age, sex, ambulance arrival, initial vital signs, current rhythm [fibrillation or flutter], previous atrial arrhythmia, and previous cardiac risk factors [hypertension, diabetes, previous coronary artery disease, previous stroke or transient ischemic attack]). After adjustment for individual physician, predictor variables most strongly related to adverse events were identified. These variables, plus individual physician, were entered into a logistic regression model to create a propensity score for each patient. A mixed-effects logistic regression model with "use of rate or rhythm control" as the exposure variable and "adverse event" as the outcome variable was fit with the propensity score as an adjustment variable. "Individual physician" was used as the clustering variable and entered as a random effect.

Major AEs

New hypotension requiring vasoactive or inotropic agents

Intubation or noninvasive positive-pressure ventilation

New bradycardia requiring pharmacologic intervention or pacing

Confirmed stroke or thromboembolic event

Chest Compressions

Death

Minor AEs

New hypotension requiring at least 1 crystalloid fluid bolus >500 mL

Supplemental oxygen by bag-valve-mask

AE, Adverse event.

*Patients could have more than 1 AE. For example, a patient might require intubation (major event) and a fluid bolus (minor event). The primary outcome was the number of patients with an AE.

Figure 1. ED adverse events.*

The secondary outcome was the success of rate or rhythm control attempts, measured as reducing the pulse rate by 20 beats/min within 4 hours, and converting to and maintaining normal sinus rhythm throughout the ED stay, respectively.

Additional a priori outcomes included the combined rate of stroke or death at 30 days. To determine mortality, the provincial vital statistics database was queried, using the patient's unique health number. To determine strokes, the regional ED database was interrogated, using the same health number, and regional follow-up ED visits for strokes were ascertained. Patients with ischemic or hemorrhagic stroke were included because anticoagulation can lead to the latter.[19] For all outcomes, descriptive statistics were used to obtain proportions in each group and compare the 2 groups.

Primary Data Analysis

Microsoft Excel 2008 was used for data entry and analysis. Discrete variables were reported as percentages. Continuous variables were presented as means with SDs (if normally distributed) or medians with interquartile ranges (if non-normally distributed). κ Statistics were used to test

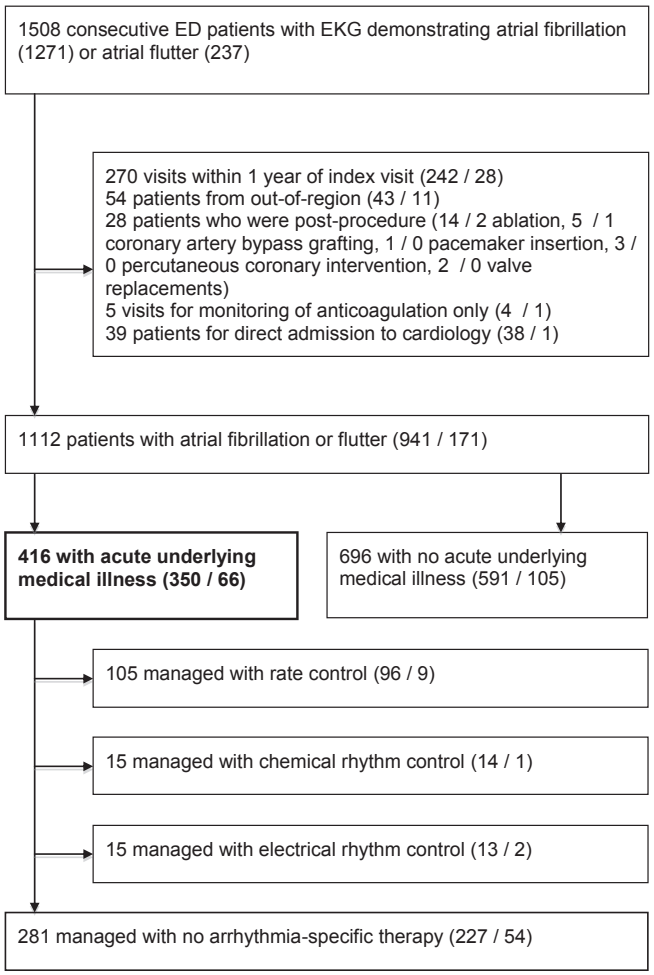

Figure 2. Study flow diagram.

agreement.[20] Propensity score was performed with R MICE, version 2.22.

RESULTS

During the 1-year study period, 1,112 ED patients had an ECG showing atrial fibrillation or flutter, and 416 (37.4%) were characterized as having an acute underlying medical illness, 350 with atrial fibrillation and 66 with atrial flutter. Of the 416 complex patients, 105 received rate control, 15 had chemical rhythm control attempts, 15 had electrical rhythm control attempts, and 281 received no arrhythmia-specific therapy (Figure 2).

Of the 1,112 patients, 23 (2.1%) required adjudication to determine whether there was an acute underlying illness, for a κ value of 0.95 (95% confidence interval [CI] 0.93 to 0.97). For determination of the acute underlying illness itself, 20 of 416 patients (4.8%) required adjudication—17 of these patients had minor elevations in troponin level, or brain natriuretic peptide or creatinine level, and required differentiation between heart failure, acute coronary syndrome, or acute kidney injury—and the primary investigator provided a final diagnosis for 5 patients (1.2%) without agreement by adjudicators. Of 83 potential adverse events, 3 (3.6 %) required adjudication.

For the chart review of the 416 complex patients with atrial fibrillation or flutter with a medically underlying cause, the κ value for interobserver agreement for previous atrial dysrhythmia was 0.70 (95% CI 0.68 to 0.72); for symptom duration, 0.67 (95% CI 0.64 to 0.70).

Characteristics of Study Subjects

Patients had a median age of 81 years and 55.8% were men (Table 1). Most had an unclear onset time, and rather than palpitations or chest pain, the majority of patients arrived with dyspnea or weakness. Comparing the 135 complex patients with atrial fibrillation or flutter who had attempted rate or rhythm control with the 281 patients who did not, there was no difference in age, sex distribution, ambulance arrival, initial vital signs, proportion of deranged vital signs, triage complaints, comorbidities—with the exception of 14 patients with an active malignancy—CHADS2 scores, or medication use. Overall, less than 10% of patients had a pulse rate in excess of 150 beats/min, and less than 5% of patients had a systolic blood pressure below 90 mm Hg.

The illness distribution of complex patients with atrial fibrillation or flutter, stratified into patients who received rate- or rhythm control–specific medications and those who did not, is shown in Table 2. More than 60% of patients had either sepsis or acute heart failure, and there was no statistical difference between the 2 groups for any diagnostic category.

Of patients who received rate or rhythm control, 55 of 135 (40.7%; 95% CI 32.5% to 49.5%) had at least 1 adverse event (Table 3). Of patients who did not receive rate or rhythm control, 20 of 281 (7.1%; 95% CI 4.5% to 10.9%) had an adverse event, for a risk difference of 33.6% (95% CI 24.5% to 42.8%). The relative risk of an adverse event was 5.7 (95% CI 3.6 to 9.1), odds ratio 9.0 (95% CI 5.1 to 15.9). Nineteen patients (14.1%) who received rate or rhythm control had a major adverse event, whereas 3 (1.1%) who did not receive rate or rhythm control had a minor adverse event, for a risk difference of 13.1% (95% CI 7.4% to 20.3%) and a relative risk of 11.7 (95% CI 3.5 to 38.9).

For patients who had rate control, 42 of 105 (40.0%; 95% CI 29.0% to 48.1%) had an adverse event; for patients who had rhythm control, 13 of 30 (43.3%; 95% CI 26.0% to 62.3%) had an adverse event (Appendix E2, available online at http://www.annemergmed.com). The latter can be divided into the following: for electrical conversion, 9 of 15

Table 1. Baseline variables of complex patients with atrial fibrillation or flutter (n=416) managed or not managed with rate or rhythm control.

	Managed With Rate or Rhythm Control (n=135)	Not Managed With Rate or Rhythm Control (n=281)	Difference (95% CI)*
Demographics			
Age (median, IQR), y	81 (71 to 86)	82 (72 to 87)	−1 (−6 to 4)
Age range, y	(26 to 92)	(23 to 100)	Not applicable
Male sex, No. (%)	71 (52.6)	161 (57.3)	−4.7 (−15.2 to 5.8)
EMS arrival, No. (%)	72 (53.3)	158 (56.2)	−2.9 (−13.4 to 7.6)
Initial vital signs, ED arrival (IQR), median			
Pulse rate, beats/min	99 (77 to 126)	94 (74 to 123)	5 (−1 to 11)
Systolic blood pressure, mm Hg	128 (111 to 147)	129 (112 to 148)	−1 (−6 to 4)
Diastolic blood pressure, mm Hg	77 (62 to 83)	74 (72 to 93)	3 (−7 to 2)
Respiratory rate, breaths/min	22 (18 to 24)	22 (18 to 24)	0 (−3 to 3)
Oxygen level, % on room air	95 (92 to 97)	96 (93 to 98)	−1 (−3 to 1)
Temperature, °C	36.7 (36.5 to 37.1)	36.7 (36.5 to 37.1)	0 (−0.2 to 0.2)
Temperature, °F	98.1 (97.7 to 98.8)	98.1 (97.7 to 98.8)	0 (−0.2 to 0.2)
Number (proportion) of patients with deranged initial vital signs, No. (%)			
Pulse rate, beats/min			
>100	66 (48.9)	118 (42.0)	6.9 (−17.4 to 3.6)
101–120	29 (21.5)	55 (19.6)	1.9 (−6.4 to 11.1)
121–140	21 (15.6)	40 (14.2)	1.4 (−5.9 to 9.7)
141–160	9 (6.7)	15 (5.3)	1.4 (−3.5 to 7.7)
161–180	5 (3.7)	7 (2.5)	1.2 (−2.4 to 6.6)
>180	2 (1.5)	1 (0.4)	1.1 (−1.2 to 5.5)
Systolic blood pressure, mm Hg			
<100	21 (15.6)	36 (12.8)	2.8 (−4.4 to 11.0)
90–99	12 (8.9)	25 (8.9)	0 (−7.8 to 5.7)
80–89	6 (4.4)	7 (2.5)	1.9 (−1.9 to 7.3)
<80	3 (2.2)	4 (1.4)	0.8 (−2.1 to 5.5)
Diastolic blood pressure <60 mm Hg	24 (17.8)	56 (19.9)	−2.2 (−10.0 to 6.7)
Respiratory rate >24 breaths/min	44 (32.6)	98 (34.9)	−2.3 (−12.0 to 8.0)
Oxygen level <92% on room air	19 (14.1)	44 (15.6)	1.6 (−6.7 to 8.7)
Temperature >37.5°C	18 (13.3)	32 (11.4)	1.9 (−4.8 to 9.8)
Duration of symptoms before triage, No. (%), time of onset, h			
<48	28 (20.8)	63 (22.4)	−1.7 (−10.0 to 7.6)
>48 or unclear	107 (79.2)	218 (77.6)	1.7 (−7.6 to 10.0)
Chief complaint, No. (%)			
Palpitations	4 (2.9)	4 (1.4)	1.5 (−1.6 to 6.6)
Chest pain	19 (14.0)	29 (10.3)	3.7 (−3.0 to 11.6)
Dyspnea	54 (40.0)	101 (35.9)	4.1 (−6.1 to 14.4)
Weakness	46 (34.1)	113 (40.2)	−6.1 (−4.2 to 16.0)
Acute neurologic symptom	3 (2.2)	12 (4.3)	−2.1 (−5.7 to 3.0)
Other	9 (6.7)	22 (7.8)	−1.1 (−6.4 to 5.4)
Risk factors, No. (%)			
Previous atrial dysrhythmia	89 (66.0)	166 (59.1)	6.9 (−3.6 to 16.7)
Acute coronary syndrome	39 (28.9)	78 (27.8)	1.1 (−8.8 to 11.0)
Hypertension	95 (70.4)	208 (74.0)	−3.6 (−10.1 to 9.3)
Diabetes	29 (21.4)	70 (24.9)	−3.5 (−11.9 to 6.0)
Heart failure	45 (33.3)	103 (36.7)	−3.4 (−13.1 to 7.0)
Previous stroke or TIA	25 (18.5)	55 (19.6)	−1.1 (−9.0 to 7.9)
Active malignancy	0	14 (5.0)	−5.0 (−8.4 to −1.0)
CHADS2 score, No. (%)†			
0	9 (6.7)	25 (8.9)	−2.2 (−7.6 to 4.4)
1	21 (15.5)	31 (11.0)	4.5 (−2.5 to 12.6)
2	39 (28.9)	81 (28.8)	0.1 (−9.2 to 10.1)
3	38 (28.2)	80 (28.5)	−0.3 (−9.6 to 9.4)
4	17 (12.6)	40 (14.2)	−1.6 (−8.5 to 6.4)
5	7 (5.2)	19 (6.8)	−1.6 (−6.3 to 4.6)
6	4 (3.0)	5 (1.8)	1.2 (−2.1 to 6.8)
Median (IQR) score	3.0 (2.0 to 3.0)	3.0 (2.0 to 3.0)	0 (0 to 0)

Table 1. Continued.

	Managed With Rate or Rhythm Control (n=135)	Not Managed With Rate or Rhythm Control (n=281)	Difference (95% CI)*
Medications received as outpatient, No. (%)			
Acetylsalicylic Acid	64 (47.4)	117 (41.6)	5.8 (−2.6 to 17.3)
Clopidogrel	8 (5.9)	10 (3.6)	2.3 (−2.0 to 8.4)
Warfarin	54 (40.0)	106 (37.7)	2.3 (−2.0 to 8.4)
β-Blockers	59 (43.7)	125 (44.5)	−0.8 (−8.5 to 12.9)
Calcium-channel blockers	17 (12.6)	42 (15.0)	−2.4 (−9.2 to 5.7)
Digoxin	19 (14.1)	50 (17.8)	−3.7 (−9.9 to 4.2)
Sotalol	2 (1.5)	5 (1.8)	−0.3 (−4.1 to 3.4)
Propafenone	1 (0.7)	1 (0.3)	0.4 (−1.7 to 4.2)
Amiodarone	1 (0.7)	2 (0.7)	0.03 (−2.2 to 4.0)
Flecainide	0	0	0 (−1.6 to 3.5)
Dronedarone	1 (0.7)	0	0.7 (−1.1 to 4.7)

IQR, Interquartile range; *TIA*, transient ischemic attack.
*(Patients with underlying illness)−(patients with no underlying illness). Wilson's continuity correction was used for the CI of the difference between proportions.
†CHADS2 score=risk stratification for atrial fibrillation, with 1 point each for heart failure, hypertension, age greater than 75 years, and diabetes; and 2 points for a stroke. The range of the scale is 0 to 6 points.

patients (60.0%; 95% CI 32.9% to 82.5%) had an adverse event, and for chemical conversion, 4 of 15 patients (26.7%; 95% CI 8.9% to 55.2%) had an adverse event. Although patients with sepsis or heart failure provided the majority of adverse events, those with acute coronary syndrome, acute renal failure, obstructive lung disease, gastrointestinal bleeding, and stroke also experienced adverse events.

The individual physician was most strongly associated with the decision to use rate or rhythm control ($P<.001$). After adjustment for individual physician, the most likely variables accounting for adverse events were initial pulse rate ($P<.001$), presence of atrial flutter ($P=.003$), and age ($P=.008$). After adjustment for the propensity score, the odds of patients receiving rate or rhythm control having an adverse event were 8.3 times greater (95% CI 4.2 to 16.3) than that of patients who did not have rate or rhythm control.

Overall, 20 of 105 patients (19.0%; 95% CI 12.3% to 28.1%) who received rate control achieved a pulse rate reduction of at least 20 beats/min within 4 hours. When data were stratified for rhythm, 15 of 80 patients (18.8%) with atrial fibrillation had successful rate control, similar to the 5 of 25 patients (20%) with atrial flutter. The majority of rate control attempts involved intravenous metoprolol, whereas some patients received diltiazem,

Table 2. Illness distribution of complex patients with atrial fibrillation or flutter (n=416) managed with and without rate or rhythm control.

Diagnosis, No. (%)	Managed With Rate or Rhythm Control (n=135)	Not Managed With Rate or Rhythm Control (n=281)	Difference (95% CI)*
Acute coronary syndrome	15 (11.1)	30 (10.7)	0.4 (−5.6 to 8.1)
Acute renal failure	9 (6.7)	26 (9.3)	−2.6 (−8.0 to 4.1)
Acute heart failure	43 (31.9)	75 (26.7)	5.2 (−4.3 to 15.1)
Acute valve injury	0	0	0 (−1.4 to 3.7)
Arterial embolus			
Stroke	5 (3.7)	23 (8.2)	−4.4 (−9.1 to 1.4)
Embolus to leg	0	3 (1.1)	−1.1 (−3.3 to 2.4)
Embolus to kidney	1 (0.8)	0	0.8 (−1.1 to 4.7)
Embolus to mesentery	0	1 (0.4)	−0.4 (−3.1 to 2.3)
Chronic obstructive pulmonary disease	6 (4.4)	18 (6.4)	−2.0 (−6.5 to 4.0)
Gastrointestinal bleeding	4 (3.0)	12 (4.3)	−1.3 (−5.1 to 4.0)
Hyperthyroidism	1 (0.8)	4 (1.4)	−0.6 (−3.4 to 3.2)
Hypertensive crisis	0	0	0.8 (−1.1 to 4.7)
Hypothermia	0	1 (0.4)	−0.4 (−3.1 to 2.3)
Pulmonary embolus	3 (2.2)	1 (0.4)	−1.8 (−6.5 to 0.6)
Overdose of medicinal agents	0	2 (0.7)	−0.7 (−2.8 to 2.8)
Sepsis	48 (35.6)	85 (30.3)	5.3 (−4.5 to 15.1)

*(Patients with underlying illness)−(patients with no underlying illness). Wilson's continuity correction was used for the CI of the difference between proportions.

Table 3. ED adverse events for complex patients with atrial fibrillation or flutter, stratified by type and reported by treatment group.

AE, No. (%)	Rate or Rhythm Control (n=135)	No Rate or Rhythm Control (n=281)	Difference (95% CI), No. (%)
Major AEs			
Inotropic agents	8 (5.9)	3 (1.1)	4.8 (1.0 to 10.7)
Intubation	10 (7.4)	0	7.4 (3.4 to 13.5)
Bradycardia	0	0	0 (−1.7 to 3.5)
Stroke/thromboembolism	0	0	0 (−1.7 to 3.5)
Chest compressions	1 (0.7)	0	0.7 (1.1 to 4.7)
Death	0	0	0 (−1.7 to 3.5)
Patients with at least 1 major AE	19 (14.1)	3 (1.1)	13.1 (7.4 to 20.3)
Minor AEs			
Fluid bolus	43 (31.8)	17 (6.0)	25.8 (17.4 to 34.8)
Bag-valve-mask oxygenation	2 (1.5)	3 (1.1)	0.4 (−2.1 to 4.8)
Patients with at least 1 minor AE	45 (33.3)	20 (7.1)	26.2 (17.6 to 35.3)
Patients with at least 1 AE*	55 (40.7)	20 (7.1)	33.6 (24.5 to 42.8)
Total AEs, n	64	23	Not applicable

*Primary outcome. Patients could have more than 1 AE and could have both a major and a minor AE. For example, a patient might require intubation (major event) and a fluid bolus (minor event).

verapamil, and digoxin (Table 4*A*). Overall, the success rates of the calcium channel blockers appeared to be higher than those of metoprolol, whereas the adverse events appeared similar across all groups. Patients receiving digoxin had neither successful rate control nor adverse events.

The median time from ED presentation to the first attempt at rate control was 102 minutes (interquartile range 40 to 181 minutes). Patients who received rate control earlier in their ED visit appeared to have a lower success rates and higher adverse event rates than those who received rate control later in their ED stay; the success rate increased from 16.2% in the first hour to 25.0% in the fourth hour, whereas the adverse event rate decreased from 48.6% to 28.0% during the same time (Table 4*B*).

The median time from ED presentation to first attempt at chemical rhythm control was 77 minutes (interquartile range 45 to 170 minutes), whereas the median time to electrocardioversion was 66 minutes (interquartile range 40 to 123 minutes). For complex patients with atrial fibrillation or flutter who received attempted rhythm control, the overall conversion was 4 of 30 (13.3%; 95% CI 4.4% to 31.6%), stratified into electrical (3/15; 20.0%) and chemical (1/15; 6.7%) success rates. When analyzed by rhythm, 4 of 27 patients (14.8%) with atrial fibrillation converted to normal sinus rhythm, and 0 of 3 patients with atrial flutter. No complex patients with atrial fibrillation or flutter spontaneously converted to normal sinus rhythm.

Patients with no attempts at rate or rhythm control were treated chiefly with intravenous crystalloids; 220 of 281 patients received normal saline solution, with a median of 1 L received in the first 4 hours in the ED. Of the complex patients with atrial fibrillation or flutter who did not have rate control, 125 of 281 (44.5%; 95% CI 38.6% to 50.5%) had a reduction of at least 20 beats/min compared with complex patients who had rate control; the risk difference was 25.4% (95% CI 14.6% to 34.4%).

For complex patients with atrial fibrillation or flutter who received attempted rate or rhythm control and those

Table 4. *A*, Rate control agents, stratified by type, delivery route, and dose.

Rate Control Agent and Dose, mg	Number of Attempts, n	Successes, No. (%)	AEs, No. (%)*
Digoxin 0–0.5, iv	7	0	0
Diltiazem, iv			
0–20	12	4 (33.3)	5 (41.7)
20–40	3	1 (33.3)	2 (66.7)
≥40	2	1 (50.0)	1 (50.0)
Total	17	6 (35.3)	8 (47.0)
Metoprolol			
0–5, iv	36	5 (13.9)	12 (33.3)
6–10, iv	17	3 (17.6)	8 (47.1)
11–15, iv	15	2 (13.3)	7 (46.6)
≥15, iv	2	1 (50.0)	2 (100.0)
0–25, po	2	0	1 (50.0)
Total	72	11 (15.2)	30 (41.6)
Verapamil, iv			
0–10	6	2 (33.3)	2 (33.3)
≥10	3	1 (25.0)	2 (67.0)
Total	9	3 (33.3)	4 (44.4)
Total	105	20 (19.1)	42 (40.0)

Table 4. *B*, Rate control agents, stratified by timing.

Timing of Rate Control Agent, Hours	Number of Attempts, n	Successes, No. (%)	AEs, No. (%)*
0–1	37	6 (16.2)	18 (48.6)
1–2	22	5 (22.7)	10 (45.4)
2–3	21	5 (23.8)	7 (33.3)
3–4	25	5 (25.0)	7 (28.0)
Total	105	20 (19.1)	42 (40.0)

*Patients with at least 1 AE. Four patients had 2 AEs.

who did not, there was 1 stroke in each group. There were 24 of 135 deaths (17.8%) in the group with rhythm-specific treatment and 40 of 281 (14.2%) in the group that was not treated, for a risk difference of 3.5% (95% CI –4.0% to 12.1%).

LIMITATIONS

Several important limitations deserve mention. This review at 2 Canadian teaching sites may not be applicable to other centers; treatment decisions, especially use of rhythm control, may vary; only a minority of patients had recent echocardiography results available. We combined atrial fibrillation and flutter because American College of Cardiology/American Heart Association recommendations make no distinction in managing complex patients with atrial fibrillation or flutter; although the success rates of the 2 arrhythmias were similar, the sample sizes may make generalizations difficult. Our sample of 135 patients, only 30 of whom received rhythm control, is likely too small to draw robust conclusions, and it is possible that there are subgroups that may benefit from rate or rhythm control. Because patients with atrial fibrillation or flutter can have substantial minute-to-minute variations in pulse rate, our use of nursing vital signs to record the rate at a single point may not reflect the true rate. However, overall, our findings related to safety and adverse events are similar to those in the postoperative and intensive care settings.[21,22]

Because this cohort was based on an ECG database, patients with atrial fibrillation or flutter who did not receive an ECG in the ED would not have been included; however, such patients would likely be healthier and unlikely to have had treatment misadventures. Interrater reliability for the chart review may be low.[20] This retrospective, heterogeneous cohort of complex patients had only atrial fibrillation or flutter as a unifying feature, and it is difficult to conclusively prove that the high adverse event and low success rate directly resulted from attempted rate or rhythm control, or from medication type, dosing, or timing. However, after propensity adjustment for the attending physician, ED factors, and patient-level factors, the results were similar.

Objectively defining an "acute underlying medical cause" may be difficult in these patients. It is also often difficult to determine the contribution of atrial fibrillation or flutter to a complex patient's clinical presentation. To illustrate, a 78-year-old diabetic, hypertensive man in rapid atrial flutter, and with a slightly elevated troponin level and radiographic evidence of new heart failure, could be having the arrhythmia as a result of heart failure or mild acute coronary syndrome. Conversely, mild heart failure or acute coronary syndrome could have precipitated an increase in ventricular response of chronic atrial fibrillation. Additionally, defining "hypotension" in this complex atrial fibrillation or flutter population is difficult. Although a blood pressure of 120/80 mm Hg may seem appropriate, for the above 78-year-old patient, this may in fact represent a substantial decrease from baseline values and may be associated with poor volume status and end-organ malperfusion. In elderly trauma patients, for example, those with an initial systolic blood pressure of 130 mm Hg were at increased risk of adverse events compared with those with a higher initial blood pressure.[21] Similarly, caution may be warranted even in seemingly normotensive patients with atrial fibrillation or flutter, especially if they are elderly and normally hypertensive. Similarly, a patient with atrial fibrillation at 85 beats/min who is also receiving β-blockers and unable to mount a robust physiologic response by increasing the pulse rate might be quite ill as well, despite an apparently "normal" pulse rate.

Conditions such as acute myocardial infarction or stroke may require rate control medications for blood pressure control, rather than rate control; however, these accounted for only a minority of patients. Digoxin was used in several patients, but given the slower onset of this medication, rate control success or adverse events may not have occurred within 4 hours. Amiodarone was not used—small studies have concluded that it may be useful for new-onset patients with atrial fibrillation or flutter in the ICU[23]—but the generalizability of these findings to undifferentiated ED patients with atrial fibrillation or flutter is unknown.

The stroke and mortality rates were similar for the 2 groups, and this may imply that ED-based treatments and adverse events did not unduly influence 30-day outcomes. However, unmeasured factors such as ED crowding, left ventricular function, do-not-resuscitate orders, or additional inhospital treatments could have affected physician decisions and outcomes, including stroke or mortality rates. Overall, we believe that our approach, with every chart reviewed by a second abstractor, rigorous reproducible diagnostic definitions, and specialist adjudication, helps to define a population of patients with atrial dysrhythmias and acute underlying medical issues.

DISCUSSION

This series of 416 consecutive ED patients with ECG-proven atrial fibrillation or flutter complicated by an acute underlying illness compared patients in whom rate or rhythm control was used with those in whom it was not. Despite the 2 groups' having similar baseline characteristics and illness distributions, use of rate or rhythm control was associated with a nearly 6-fold increase in adverse events and a nearly 12-fold increase in major adverse events. In

addition, the proportions of patients with successful rate or rhythm control were 19% and 13%, respectively—far lower than historical values for uncomplicated patients with atrial fibrillation or flutter. This study assists clinicians by demonstrating that (1) complex patients with atrial fibrillation or flutter compose nearly two fifths of all patients with atrial fibrillation or flutter; (2) these patients are far older than noncomplex patients with atrial fibrillation or flutter and have substantial baseline comorbidities; (3) rate or rhythm control attempts are associated with a 5.7-fold increase in adverse events and an 11.7-fold increase in major adverse events; (4) delayed administration of rate control may be associated with a lower adverse event rate; and (5) rate or rhythm control is unlikely to be successful as a first-line treatment.

The majority of ED literature about atrial dysrhythmias has been devoted to debating whether rate or rhythm control is appropriate for patients with uncomplicated atrial fibrillation or flutter for less than 48 hours. Uncomplicated patients undergoing rate or rhythm control appear to have an adverse event rate below 10%.[2-7,11-14] Furthermore, success rates for rate control, chemical rhythm control, and electrical rhythm control have been reported at 70%,[11] 90%,[4,5,7,12-14] and 50%,[4,6,13] respectively. Unfortunately, complex patients with atrial fibrillation or flutter, who have been minimally studied outside of the ICU and are little mentioned in the American College of Cardiology/American Heart Association[8] and CCS guidelines[9] or focused updates, appear to fare worse. Although uncomplicated patients described in the guidelines[8,9] typically have a median age of 58 to 65 years and CHADS2 scores of 0 or 1,[2-7,11-14] our complex patients were 15 to 20 years older and had a median CHADS2 score of 3; this may partially explain lower success rates and higher adverse event rates.

Approximately three fifths of our patients had either sepsis or heart failure, and they also accounted for a similar proportion of adverse events. However, the two fifths of patients who did not have sepsis or heart failure also had approximately two fifths of the adverse events, implying that a particular diagnosis may not portend a worse outcome. (For example, patients with atrial fibrillation or flutter with sepsis and those with acute renal failure may fare equally poorly, although the sample sizes are too small to draw definition conclusions.) However, it is possible that, rather than a specific diagnosis, a true unifying feature of the complex atrial fibrillation or flutter cohort is hypovolemia. To illustrate, patients who had delayed administration of rate control (and typically received some intravenous fluids before rate control) had lower adverse event rates and higher success rates than those who received rapid rate control (and likely minimal fluids before rate control). Furthermore, patients with delayed rate control appeared to have fewer adverse events than those with rapid rate control.

The success of rate and rhythm control in decreasing pulse rates or converting rhythms, respectively, must also be noted. Less than one fifth of patients had their pulse rate reduced by 20 beats/min within 4 hours after initiation of rate control; in contrast, more than 44% of patients not treated with rate control agents had a similar reduction. The latter patients appear to have been managed with fluid resuscitation alone and may therefore have had better outcomes. Few patients underwent successful rhythm control. In our study, complex patients with atrial fibrillation or flutter undergoing rate or rhythm control attempts had an adverse event rate substantially exceeding the success rate. Clinicians managing any undifferentiated patients with atrial fibrillation or flutter with a potential serious underlying illness should consider carefully the risks and benefits for any treatments, given that management of the complex atrial fibrillation or flutter group may be dissimilar to the management for noncomplex patients with atrial fibrillation or flutter. Although the cohort of complex patients with atrial fibrillation or flutter is difficult to categorize, our results appear congruent with those for populations undergoing rhythm control in the post–cardiac surgery and intensive care settings.[22-24]

Given our results, it appears as if differentiating complex from uncomplicated patients with atrial fibrillation or flutter may be an important decision facing emergency physicians. In our cohort, almost two fifths of ED patients with atrial fibrillation or flutter appeared to have an underlying illness. Our findings that complex patients with atrial fibrillation or flutter were substantially older and had higher CHADS2 scores, unclear times of symptom onset, presenting complaints of weakness or dyspnea, and a higher proportion of abnormal vital signs may help physicians quickly identify potential complex patients with atrial fibrillation or flutter, some of whom may be harboring "occult" sepsis or other illnesses.

Individual physician behavior seems to have been the strongest predictor of the use of rate or rhythm control; in the absence of clear guidelines[8,9] about the management of complex elderly patients with atrial fibrillation or flutter and a potential underlying illness, it seems plausible that some physicians would be more likely to use a particular management strategy than others. It is also possible that diagnostic uncertainty at ED presentation played a role; 10% to 20% of patients who ultimately receive a diagnosis

of sepsis do not have these criteria at triage,[25,26] implying that physicians who assess such patients may not appreciate how truly ill they are.

We hypothesize that many patients receive rapid rate or rhythm control attempts because their underlying illness is not immediately obvious, and their ECG, a common, rapid, noninvasive test, is often the first investigation returned to the physician; the results of additional diagnostics may take some time. This may predispose clinicians to a "rhythm bias" in which the atrial fibrillation or flutter, which may initially appear to be easily treatable, is managed with rate or rhythm control before other investigations are completed. Supporting this contention is the fact that a large proportion of patients who received rate or rhythm control had this treatment very early in their ED stay, often within 90 minutes of arrival. Furthermore, patients who received early rate control appeared to have worse outcomes. It is therefore conceivable that physicians used rate or rhythm control in these patients to quickly control the dysrhythmia, possibly assuming the atrial fibrillation or flutter was the cause of the symptoms but aggravating the underlying illness. It may therefore be advisable to manage patients who may be at risk of complex atrial fibrillation or flutter—particularly elderly patients with higher CHADS2 scores—with other measures. Judicious administration of intravenous fluids, bedside echocardiography to assess volume status, or frequent reassessments of such patients while waiting for confirmatory diagnostic investigations may therefore be advisable, rather than rapid rate or rhythm control.

In ED patients with complex atrial fibrillation or flutter, attempts at rate and rhythm control are associated with a nearly 6-fold higher adverse event rate than that in patients who are not managed with rate or rhythm control. Success rates of rate or rhythm control attempts appear low.

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APPENDIX E1.

Inclusion criteria for acute underlying medical causes of atrial fibrillation or flutter

The study purpose was to include patients in whom it was (or could have been) apparent to the emergency physician that atrial fibrillation of flutter was confounded by another serious acute medical condition. All physical examination findings must have been apparent in the ED, and the results of all laboratory, ECG, and radiologic investigations must have been available in the ED as well. (The exceptions were blood, urine, or sputum cultures because these take 24 to 48 hours to return. However, if the treating emergency physician was ordering such tests, an infectious process was most likely considered in the ED setting.) All physical examination information was located on the emergency physician's chart or the consulting physician admission note. (At our institutions, the admission note is dictated while the patient is still in the ED.) Results of any tests must have been available during the patient's ED stay. For example, a patient with atrial fibrillation who was admitted with weakness and had no objective criteria of underlying disease while in the ED, but developed a fever and pulmonary infiltrate on postadmission day 4, would not be included as a patient with sepsis.

1. Acute coronary syndrome: ECG findings of new left bundle branch block; ST-segment elevation of 2 mm in precordial or 1 mm in limb leads; elevated cardiac troponin T level (Roche Elecsys; Hoffman LaRoche, Laval, Quebec, Canada; 99th percentile reference limit >0.01 ng/mL, lower limit of detection 0.01 ng/mL, 10% coefficient of variation 0.03 ng/mL, with a change of at least 20% on sequential testing) with no other cause evident; coronary artery revascularization by percutaneous coronary intervention or bypass grafting; admission and treatment for acute coronary syndrome.[1]
2. Acute heart failure: Documented findings on physical examination (S3 gallop, lung crackles, jugular vein distention, or positive abdominojugular test result) or documented new findings on chest radiography (cardiomegaly or pulmonary edema) or brain natriuretic peptic levels (Siemens ADVIA Centaur; Burlington, Ontario, Canada) >400 pg/mL; or diuretic use in the ED with documented improvement of respiratory status; or admission and treatment for heart failure.[2,3]
3. Hypothermia: Documented body temperature <32°C in the ED.
4. Sepsis: Meeting at least 2 of systemic inflammatory response syndrome criteria (temperature <36°C or >38°C; WBC count <4,000 or >12,000/mL; pulse rate >90 beats/min; respiratory rate >20 breaths/min or PCO_2 <32 mm Hg) with evidence of new infection (new infiltrate on chest radiograph; positive blood, urine, or wound culture results; WBCs in the cerebrospinal fluid).[4]
5. Exacerbation of chronic obstructive pulmonary disease: Documented increase in cough, dyspnea, and sputum production, or documented improvement in respiratory function after administration of bronchodilators, or admission and treatment for chronic obstructive pulmonary disease,[5] and no other cause evident.
6. Thyrotoxicosis: Thyroid-stimulating hormone (Siemens ADVIA Centaur Ultra Low [TSH3UL] reagents) <0.02 ng/mL or admission and treatment for thyrotoxicosis.
7. Overdose of medicinal agents: Documented overdose of medicinal agents and treatment for overdose of medicinal agents, with other cause evident.
8. Pulmonary embolism: Proven on computed tomography or pulmonary angiography.
9. Acute valve disease: Echocardiographic evidence of acute valve injury.
10. Hypertensive emergency: Blood pressure >220/100 mm Hg with evidence of new end-organ injury (acutely altered vision with documented grade III/IV papilledema; documented acute aortic dissection; documented new neurologic deficit; acute renal failure; or blood smear demonstrating microangiopathic hemolytic anemia).[6]
11. Acute kidney injury: Increase in baseline creatinine level (Roche enzymatic creatinine [Roche Elecsys; Hoffman LaRoche] run on a Siemens ADVIA 1800 analyzer) of >26 μmol/L, and no other cause evident. Baseline creatinine level was the most recent value within 3 months.[7-9]
12. Stroke or transient ischemic attack: Acute neurologic deficit, whether reversible or not.
13. Gastrointestinal bleeding: Admission and treatment for gastrointestinal bleeding, and no other cause evident.

In cases in which there was overlap, for example, a patient with sepsis and elevated troponin levels, we recorded the more lethal diagnosis (sepsis). If the 2 emergency physician reviewers independently arrived at the same diagnosis, the patient was considered to have received an appropriate diagnosis. However, if the 2 reviewers reached a different conclusion, 2 independent specialists adjudicated the patient and determined a diagnosis; if the diagnoses were discordant, the principal investigator made the final diagnosis.

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APPENDIX E2.

ED adverse events for complex patients with atrial fibrillation or flutter, stratified by (1) type of adverse event, (2) treatment category, (3) illness category.*

AE, No. (%)	Rate Control (n=105)	Chemical Rhythm Control (n=15)	Electrical Rhythm Control (n=15)	No Arrhythmia-Specific Management (n=281)
Major AEs				
Hypotension requiring inotropes	Acute heart failure (1/35) ACS (2/15) Pulmonary embolus (1/3) Sepsis (2/39)	No AE	Gastrointestinal bleeding (1/1) Sepsis (1/5)	Acute heart failure (1/75) Sepsis (2/85)
Respiratory requiring intubation	Acute heart failure (2/35) ACS (1/15) COPD (1/6) Sepsis (2/39)	No AE	Acute heart failure (2/4) Gastrointestinal bleeding (1/1) Sepsis (1/5)	No AE
Bradycardia	No AE	No AE	No AE	No AE
Stroke/thromboembolism	No AE	No AE	No AE	No AE
Chest compressions	Pulmonary embolus (1/3)	No AE	No AE	No AE
Death	No AE	No AE	No AE	No AE
Minor AEs				
Respiratory requiring bag-valve-mask oxygenation	Acute renal failure (1/4)	Acute heart failure (1/4)	No AE	Acute heart failure (1/75) COPD (1/18) Sepsis (1/85)
Hypotension requiring fluid bolus	Acute heart failure (11/35) ACS (4/15) Acute renal failure (2/4) COPD (1/6) Gastrointestinal bleeding (1/3) Stroke (2/5) Sepsis (11/39)	Acute heart failure (1/4) Acute renal failure (1/3) COPD (1/1) Sepsis (1/4)	Acute heart failure (3/4) Acute renal failure (2/2) Sepsis (2/5)	Acute heart failure (3/75) Acute renal failure (4/26) COPD (2/18) Gastrointestinal bleeding (2/12) Overdose (1/2) Sepsis (5/85)
Total AEs	46	5	13	23
Patients with at least 1 AE†	42 (40.0)	4 (26.7)	9 (60.0)	20 (7.1)

ACS, Acute coronary syndrome; *COPD*, chronic obstructive pulmonary disease.

*Proportions in each cell reflect the number of patients who had an adverse event for that particular illness category managed with that particular treatment. Comparisons not provided because of small treatment groups.

†Primary outcome. Patients could have more than 1 AE. For example, a patient could require inotropes and intubation. However, only the most serious AE was recorded for each category. Therefore, a patient who received boluses of intravenous fluids and then required inotropes would be listed only as having hypotension requiring inotropes.