Ibutilide Effectiveness and Safety in the Cardioversion of Atrial Fibrillation and Flutter in the Community Emergency Department

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Study objective: Little is known about the use of ibutilide for cardioversion in atrial fibrillation and flutter outside of clinical trials. We seek to describe patient characteristics, ibutilide administration patterns, cardioversion rates, and adverse outcomes in the community emergency department (ED) setting. We also evaluate potential predictors of cardioversion success.

Methods: Using a retrospective cohort of adults who received ibutilide in 21 community EDs between January 2009 and June 2015, we gathered demographic and clinical variables from electronic health records and structured manual chart review. We calculated rates of cardioversion and frequency of ventricular tachycardia within 4 hours and estimated adjusted odds ratios (aOR) in a multivariate regression model for potential predictors of cardioversion.

Results: Among 361 patients, the median age was 61 years (interquartile range 53 to 71 years) and most had recent-onset atrial fibrillation and flutter (98.1%). Five percent of the cohort had a history of heart failure. The initial QTc interval was prolonged (>480 ms) in 29.4% of patients, and 3.1% were hypokalemic (<3.5 mEq/L). The mean ibutilide dose was 1.5 mg (SD 0.5 mg) and the rate of ibutilide-related cardioversion within 4 hours was 54.8% (95% confidence interval [CI] 49.6% to 60.1%), 50.5% for atrial fibrillation and 75.0% for atrial flutter. Two patients experienced ventricular tachycardia (0.6%), both during their second ibutilide infusion. Age (in decades) (aOR 1.3; 95% CI 1.1 to 1.5), atrial flutter (versus atrial fibrillation) (aOR 2.7; 95% CI 1.4 to 5.1), and no history of atrial fibrillation and flutter (aOR 2.0; 95% CI 1.2 to 3.1) were associated with cardioversion.

Conclusion: The effectiveness and safety of ibutilide in this community ED setting were consistent with clinical trial results despite less stringent patient selection criteria. [Ann Emerg Med. 2018;71:96-108.]

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INTRODUCTION

Background and Importance

Restoration of sinus rhythm in patients with atrial fibrillation reduces rhythm-related symptoms and functional impairment and improves exercise tolerance and quality of life.[1-3] Sinus restoration also has been shown to improve left ventricular function and may delay the onset of persistent atrial dysrhythmia.[4-8] Moreover, cardioversion of atrial fibrillation and atrial flutter (combined, atrial fibrillation and flutter) in the emergency department (ED) is associated with increased patient satisfaction and reduced hospitalization and costs.[9-11] Pharmacologic cardioversion, although less effective than electrocardioversion (approximately 50% versus 90% successful), avoids the need for procedural sedation and is thereby less resource intensive. Some medical centers begin with a pharmacologic approach and proceed to electrocardioversion only as needed,[12] a practice also used in the community emergency setting.[13]

Ibutilide is among the leading recommended pharmacologic agents for the cardioversion of presumed recent-onset atrial fibrillation and flutter,[14-17] and it is particularly useful in the ED because of its rapid effect and minimal influence on hemodynamics.[18-21] Like other class III antidysrhythmics, however, ibutilide prolongs the QTc interval, increasing risk for ventricular tachycardia. The

Editor's Capsule Summary

What is already known on this topic

Major cardiovascular guidelines recommend ibutilide for cardioversion of atrial fibrillation and atrial flutter, but its use in the real-world emergency department (ED) setting has not been well described.

What question this study addressed

How do emergency physicians use ibutilide with respect to adherence to recommended exclusion criteria, pretreatment with magnesium, dosing, and monitoring?

What this study adds to our knowledge

In this retrospective review of 361 patients, patient selection criteria were usually but not always followed. Despite this, there were very few adverse events, although a number of patients were not given the full dose. Under these circumstances, ibutilide achieved cardioversion in 56.5% of patients by ED discharge.

How this is relevant to clinical practice

Ibutilide appears to be a reasonable option for cardioversion. Because of the need to check K^+ and Mg^{++} levels and observe for four hours post administration, ibutilide may require a longer ED length of stay than alternative modalities.

frequency of ventricular tachycardia in the trial data is concerning: up to 5% for sustained monomorphic ventricular tachycardia and 4% for polymorphic ventricular tachycardia, although most of the latter is unsustained.[22,23] This risk generated a black box warning and is the reason that the standard ibutilide dose of 2 mg is divided into 2 half-doses of 1 mg each (or 0.01 mg/kg for patients <60 kg), separated by 10 minutes. The brief observation period between half-doses allows the assessment of both early cardioversion and ventricular tachycardia, which contraindicate the second half-dose.[19,20] Ventricular tachycardia nearly always occurs during or within 45 minutes of infusion,[23] but given the half-life of ibutilide, US and European cardiology societies recommend continuous ECG monitoring during and for 4 hours after administration.[14,16]

The risk of ibutilide-induced ventricular tachycardia can be reduced by excluding patients with high-risk conditions, particularly congestive heart failure.[20,22,24] Risk-reducing patient selection criteria have been integrated into trial protocols to various degrees. Early trials included patients with significant systolic dysfunction,[20,22,25] but entry criteria have become stricter.[26-28] Excluding patients with hypokalemia, hypomagnesemia, and prolonged QTc interval is nearly universal.[20,21,25,26,28-39] It is unclear, however, how commonly such patient selection criteria are applied in unscripted community emergency medicine practice. The few studies that have evaluated ibutilide in the ED have limited generalizability, being single-center European studies, most of which are hampered by small sample sizes.[30,35,36,40] To our knowledge, this is one of the first multicenter studies to describe ibutilide use and patient outcomes among US community-based EDs.

Goals of This Investigation

We undertook this multicenter retrospective cohort study to improve understanding of ibutilide use in the real-world community ED setting. Our aims were to characterize patient selection, describe cardioversion effectiveness of ibutilide at 90 minutes and 4 hours, analyze the association of candidate predictor variables with cardioversion success, and describe the 4-hour frequency of ventricular tachycardia and other adverse events. The results of this first report of the Pharmacological Cardioversion of Atrial Fibrillation/Flutter Effectiveness (Pharm CAFÉ) study may help inform ED management of atrial fibrillation and flutter patients eligible for cardioversion.

MATERIALS AND METHODS

Study Design and Setting

This retrospective cohort study included adults aged 18 years or older with ECG-confirmed atrial fibrillation or flutter who received ibutilide in the ED between January 2009 and June 2015 in any of 21 community EDs within Kaiser Permanente Northern California, an integrated health care delivery system. Nationally, Kaiser Permanente is the largest nonprofit health care delivery system in the US and operates in 8 states and the District of Columbia.[41] Kaiser Permanente Northern California is composed of 21 nonrural medical centers and more than 240 outpatient facilities and provides care for more than 4 million health plan members. Members represent approximately 33% of the insured population in areas served and are highly representative of the diversity of the general population of Northern California with respect to race and ethnicity, socioeconomic status, and education, except for slightly lower representation at the extremes of age and income.[42] Five of the 21 medical centers host at least 1 residency training program, and another 13 serve as satellite sites for residency rotations of various specialties. Five medical centers participate in emergency medicine residency training. Kaiser Permanente Northern

California is served by a single integrated comprehensive electronic health record, operational since 2008, that links provider records from inpatient and outpatient encounters with laboratory, radiology, and pharmacy data, and also includes records from video visits, telephone-based encounters, and secure messaging.[43,44] The 21 EDs had an aggregate census of 1.06 million visits in 2014 (range 26,000 to 104,000 annual visits) and were staffed by more than 550 residency-trained, board-certified or board-prepared, salaried emergency physicians. Each medical center has an ICU and cardiologists on call around the clock.

No standard policy or protocol for the ED management of atrial fibrillation and flutter was in place throughout the study period. In this setting, ibutilide and procainamide were used at similar rates for the cardioversion of patients with stable atrial fibrillation and flutter,[45] and both were less commonly used for this indication than direct current cardioversion (unpublished data). The quantity of each ibutilide half-dose was standardized by a physician order template in the electronic health record to 1 mg (or 0.01 mg/kg for patients <60 kg), infused during 10 minutes. Administration of a second half-dose required a separate order. Patient management was at the discretion of the emergency physician. Cardiology consultation occurred nearly always by telephone and without transfer of care responsibilities to the cardiologist. The study was approved by the Kaiser Permanente Northern California Health Services Institutional Review Board.

Selection of Participants

We included patients if they received ibutilide in the ED for treatment of ECG-confirmed atrial fibrillation and flutter. Patients were initially identified by searching for completed ibutilide orders made during an ED visit, using the health care system's internal pharmacy database. During manual chart review, we excluded patients transferred into the Kaiser Permanente Northern California ED from a non–health plan hospital (because data may be incomplete), those with an implantable pacemaker or cardioverter defibrillator, patients given ibutilide only after ED discharge, and those with incomplete documentation of ibutilide effectiveness. We included in our analysis only the first visit of patients with multiple eligible ED visits during the study period.

Methods of Measurement

We extracted demographic, comorbidity, vital sign, ECG, laboratory, and treatment variables from the health plan's comprehensive electronic health record.[43,46] Investigators undertook manual review of the patients' electronic health record to confirm eligibility criteria and to abstract the following categories of variables: history of present illness (chief complaint; duration of rhythm-related symptoms; as commonly defined, atrial fibrillation and flutter was *presumed* to be recent onset if rhythm-related symptoms began within 48 hours of ED presentation, as is standard in ED atrial fibrillation and flutter research)[10,47]; medical history of atrial fibrillation and flutter diagnoses; pretreatment with magnesium sulfate, parenteral rate reduction, and rhythm management medications; preibutilide consultation with a cardiologist; ibutilide dosing and timing; ECG results (rate, rhythm, and QTc interval); adverse events (ventricular tachycardia and hypotension); duration of postibutilide ECG monitoring; and disposition. Bazett's formula was used for QTc interval calculation. Comorbidities, except where noted, were defined with criteria from the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) studies.[48] In patients who were nonresponders after the first half-dose of ibutilide and failed to receive the second half-dose, we identified the reasons that physicians documented for withholding the second half-dose.

We entered our findings directly into a standardized electronic data collection instrument, modified to its final form after pilot testing. All abstractors received training on data collection methods. The principal investigator answered and arbitrated coding questions and monitored data collection activities by observing each abstractor performing chart reviews at regular intervals. Abstractors were not blinded to the study objectives. Missing values were reported as such.

We randomly selected 44 cases (12.2%) to undergo an additional abstraction of the electronic health record by a second independent investigator. We measured interrater reliability for medical history of atrial fibrillation and flutter, doses of magnesium sulfate pretreatment and ibutilide, and the rates of 4-hour cardioversion and ventricular tachycardia.

Outcome Measures

The primary effectiveness outcome was restoration of ECG-confirmed sinus rhythm within 4 hours of the initial ibutilide infusion that was sustained to ED discharge. We also reported the frequency of sinus rhythm restoration at 90 minutes, because this is a common endpoint in clinical trials for measuring ibutilide efficacy. In many trials, after 90 minutes of nonresponse to ibutilide (or 60 minutes after the end of the last dose), other interventions were used for cardioversion.[20,26,28-32] The time of cardioversion was captured when nurse or physician providers documented restoration of sinus rhythm. When this was not clearly documented, we identified the time of first detection or confirmation of sinus rhythm.

In addition to patient age and sex, our a priori candidate predictor variables for ibutilide effectiveness included atrial flutter rhythm (versus atrial fibrillation), no history of atrial fibrillation and flutter (versus history), absence of chronic heart failure, and intravenous pretreatment with magnesium sulfate, because these have an established or physiologically plausible association with ibutilide effectiveness. We categorized age by decades.

Our primary safety outcome was ventricular tachycardia. We defined monomorphic and polymorphic ventricular tachycardia as 3 or more ectopic wide-complex beats (>120 ms) occurring at greater than 120 beats/min, classifying these rhythms as sustained (duration of >30 seconds or receiving intervention) or nonsustained.[29] To be designated polymorphic, ventricular tachycardia required beat-to-beat variations in QRS complexes that gradually changed amplitude, twisting around the isoelectric line. Cases of ventricular tachycardia were identified with physician notes, nursing notes, ECG tracings (both 12-lead and rhythm strips), or discharge diagnoses.

We defined ibutilide-induced hypotension as 2 or more measurements of systolic blood pressure less than 100 mm Hg that developed within 1 hour of ibutilide administration. QTc intervals were measured on the initial ED and first postibutilide 12-lead ECG, the difference between them reported as the ibutilide-induced QTc effect. We also calculated the time between QTc measures because the effect of ibutilide on QTc interval decreases over time.

We identified return ED visits and hospitalizations within 24 hours of index ED discharge within the Kaiser Permanente health care system, using our comprehensive electronic health record, as well as outside the Kaiser Permanente health care system according to our insurance claims database. Deaths were identified with a health care system mortality database that includes data from the electronic health record, the Social Security Death Master File, and the California State Department of Vital Statistics file.

Primary Data Analysis

Categorical variables were analyzed with Fisher's exact tests or χ^2 tests. We modeled individual bivariate and multivariable logistic regressions to estimate the odds ratios of cardioversion for the candidate predictor variables, using confidence intervals (CIs) estimated with the Wald method. All statistical analyses were performed with SAS (version 9.3; SAS Institute, Inc., Cary, NC).

RESULTS

We identified 373 individual adult ED patients who received ibutilide during the 6.5-year study period, 12 of whom were excluded (Figure 1). The remaining 361 patients constituted our study cohort. Collectively, these 361 patients received ibutilide on 414 separate occasions, but only their initial encounters were included in the study. We found 100% interrater agreement on key manually abstracted variables.

Ibutilide use varied widely between EDs. Four sites did not use ibutilide during the study period. Of the remaining 17 EDs, the median was 9 uses (range 1 to 91). Two EDs were responsible for nearly half of all ibutilide administration (Figure 2). In approximately two thirds of all cases, cardiology was consulted and recommended ibutilide. The rate of cardiology consultation also varied widely between EDs (range 0% to 100%; median 76.9%) (Figure 2). In 8 cases (2.2%), the cardiologist assisted with patient care at the bedside and placed the order for ibutilide.

Table 1 describes the cohort's demographic and clinical characteristics. The median age was 61 years (interquartile range 53 to 71 years) and 142 were women (39.3%). Nearly all patients had recent-onset atrial fibrillation or flutter (n=354; 98.1%).

Patients selected for ibutilide treatment had a mixed risk profile for ibutilide-induced ventricular tachycardia. The frequency of heart failure and systolic heart failure with ejection fraction less than 40% was low (5.0% and 0.8%, respectively) (Table 1). The frequency of prolonged QTc interval greater than 480 ms was 29.4%; greater than 500 ms, 14.7%. The frequency of hypokalemia (<3.5 mEq/L) and hypomagnesemia (<1.6 mEq/L) was 3.1% and 0.9%, respectively. Table 2 reports presenting vital signs, QTc intervals, and initial electrolyte values in the ED. The distribution of initial serum potassium and magnesium levels, first QTc intervals, and first systolic blood pressure measurements is depicted in Figure E1, available online at http://www.annemergmed.com.

A majority of patients (n=249; 69.0%) received preibutilide rate reduction (Table 3). Half the cohort received pretreatment intravenous magnesium sulfate, almost always a 1- to 2-g dose.

The first ibutilide half-dose was usually 1.0 mg during 10 minutes (n=348; 96.4%). Initially, 144 patients (39.9%) responded to the first half-dose. Of the 217 patients who failed to respond, 173 (79.7%) received a second half-dose, and of these, 60 (34.7%) responded. Figure 1 depicts the treatments, responses, and dispositions of the study cohort.

When the second half-dose of ibutilide was administered to the initial nonresponders (n=173), the interdose interval was greater than the recommended 10 minutes in nearly all

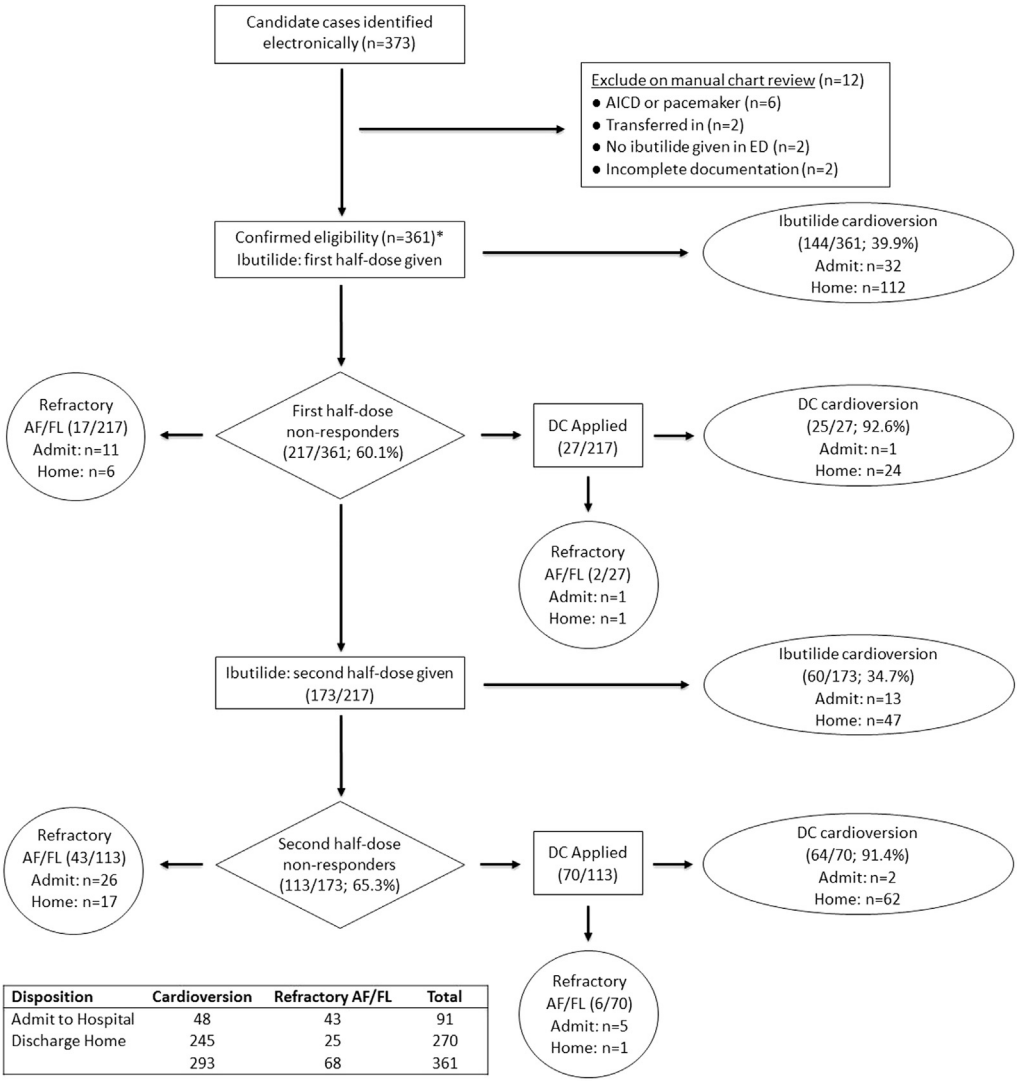

Figure 1. Treatments, responses, and dispositions of a cohort of ED patients receiving ibutilide for the cardioversion of atrial fibrillation and flutter. *AICD*, Automated implantable cardioverter defibrillator; *AF/FL*, atrial fibrillation/flutter; *refractory*, resistant to attempted cardioversion; *DC*, direct current. *Nine patients (2.5%) received ibutilide only after having first failed to respond to attempted DC cardioversion.

cases (n=167; 96.5%). The median interval was 43 minutes (interquartile range 30 to 66 minutes; full range 3 to 510 minutes). Overall, 44 patients (20.3% of 217) with nonresponse to the first half-dose failed to receive the second half-dose: 27 (12.4%) received the application of direct current instead of completing the 2-dose ibutilide regimen and 17 (7.8%) received no further attempts at cardioversion (Figure 1). Reasons for forgoing the second half-dose were documented in only 2 cases: one physician noted ibutilide-induced QTc prolongation and another noted that additional ibutilide was not available from the pharmacy.

Overall, 31 patients (8.6%) failed to complete a 60-minute "effect period" from the end of the last ibutilide infusion, the minimum therapeutic window in the ibutilide literature during which patients were observed for ibutilide effect before receiving other cardioversion interventions.[20,21,26,28-30,35] Patients who were prematurely deemed unresponsive to ibutilide included 25 who underwent attempted electrocardioversion within 60 minutes (8 after the first half-dose and 17 after the second half-dose) and 6 who were discharged home within 60 minutes (3 after the first half-dose and 3 after the second half-dose).

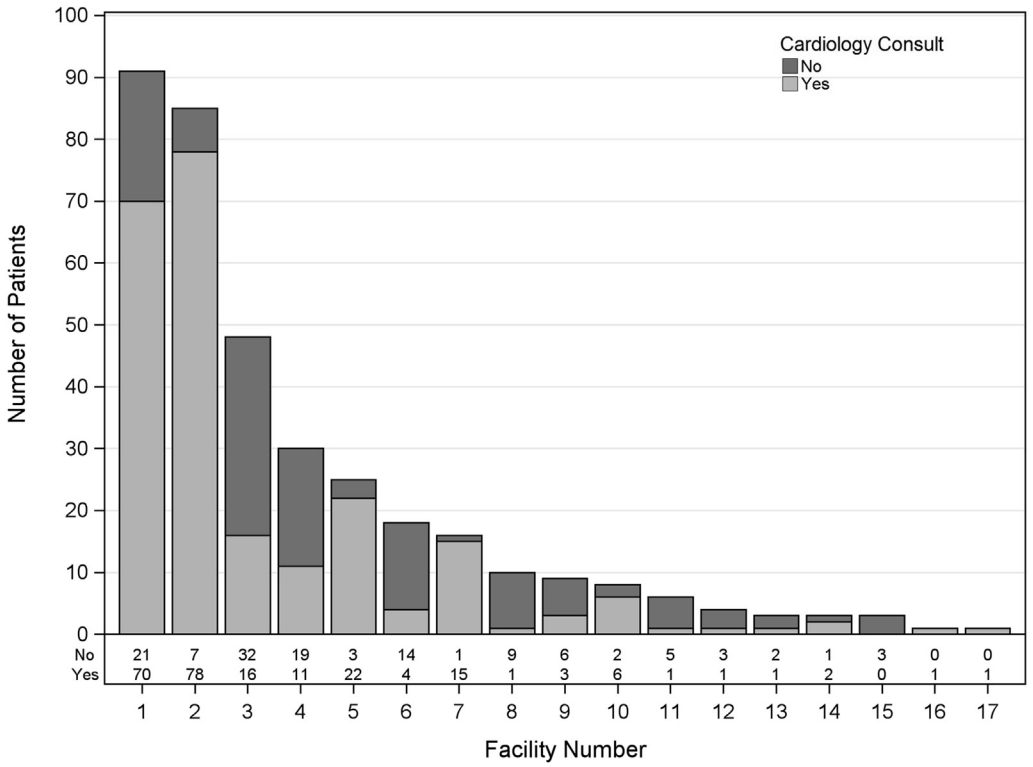

Figure 2. Variation in facility-specific ibutilide use and preibutilide cardiology consultation among 21 community EDs during 6.5 years. No ibutilide was administered during the study period in 4 EDs, which are not depicted here.

Overall, the frequency of ibutilide-induced sinus rhythm restoration at 90 minutes was 44% (95% CI 38.9% to 49.3%), at 4 hours it was 54.8% (95% CI 49.6% to 60.1%), and at ED discharge it was 56.5% (95% CI 51.2% to 61.7%). Table 4 reports rates of cardioversion stratified by atrial rhythm. Patients with both atrial fibrillation and atrial flutter rhythms (ie, any flutter) had a response to ibutilide similar to that of patients with isolated atrial flutter, and so their data were combined for modeling.

Documentation of the precise time of ibutilide-induced cardioversion was noted in only 38 cases (18.6%). In the remainder (n=166; 81.4%), we identified the time of first detection or confirmation of sinus rhythm. Among the 198 patients with a 4-hour cardioversion, the median time to sinus rhythm detection measured from the start of the first infusion of ibutilide was 33 minutes (interquartile range 17 to 74 minutes; full range 2 to 231 minutes).

In adjusted analysis, 3 of our 6 candidate predictor variables were independently associated with cardioversion at 4 hours: older age, atrial flutter, and no history of an atrial fibrillation and flutter diagnosis (Table 5). Magnesium sulfate pretreatment was not associated with ibutilide effectiveness.

Overall, direct-current cardioversion was attempted in 97 patients and effective in 89 (91.8%) (Figure 1).[49] The total rate of sinus restoration by any method at ED discharge was 81.2% (n=293).

ED disposition was as follows: home (n=270; 74.8%), short-term observation in the clinical decision area (n=6; 1.7%), hospitalization with telemetry (n=79; 21.9%), and ICU (n=6; 1.7%). Descriptions of the patients admitted to the ICU are reported in Table E1, available online at http://www.annemergmed.com. Patients who were restored to sustained sinus rhythm during their ED stay had a higher rate of home discharge than those with refractory atrial fibrillation or flutter: 78.4% versus 55.2%.

We identified no cases of hypotension associated with ibutilide, even using a broader definition of hypotension with a systolic cut point of 100 mm Hg rather than 90 mm Hg.[19,20] Three hundred seventeen patients (87.8%) had a postibutilide 12-lead ECG performed before ED discharge, allowing a calculation of the ibutilide-induced change in the QTc interval. As depicted in Figure 3, QTc interval change tended to increase when measured within 3 hours

Table 1. Characteristics of ED patients treated with ibutilide for the cardioversion of atrial fibrillation and flutter.

Patient Characteristics	No. (%), N=361*
Age, y	
Mean (SD)	60.9 (14.8)
Median	61
Interquartile range	53–71
<45	51 (14.1)
45–64	157 (43.5)
65–74	82 (22.7)
≥75	71 (19.7)
Female sex	142 (39.3)
Race/ethnicity	
White/European	295 (81.7)
Black	14 (3.9)
Asian	36 (10.0)
Multiracial	15 (4.2)
Other/unknown	1 (0.3)
Missing	0
Hispanic ethnicity	38 (10.5)
History of AF or AFL	
Paroxysmal	214 (59.3)
Chronic	0
None	147 (40.7)
Outpatient oral antidysrhythmics	
Vaughn Williams class	
Ia	0
Ic	23 (6.3)
II	127 (35.2)
III	9 (2.5)
IV	24 (6.6)
Comorbidities†	
Hypertension	202 (56.0)
Proteinuria	110 (30.5)
Diabetes mellitus	39 (10.8)
Chronic heart failure	18 (5.0)
Systolic ejection fraction <40%	3 (0.8)
End-stage renal disease	18 (5.0)
Cerebrovascular disease	1 (0.3)
Pre-excitation syndrome	1 (0.3)
Charlson index score	
Mean (SD)	1.02 (1.63)
Median	0
No measure (no visits in previous year)	37 (10.2)
0	183 (56.5)
1	66 (20.4)
≥2	75 (23.1)
ATRIA study stroke risk score[48]	
Mean (SD)	4.4 (4.8)
Low (≤5)	239 (66.2)
Medium (6)	29 (8.0)
High (≥7)	93 (25.8)
Chief complaint	
Palpitations	293 (81.2)
Chest pain	25 (6.9)
Shortness of breath	13 (3.6)
Syncope or presyncope	6 (1.7)
Dizziness or lightheadedness	6 (1.7)
Weakness or fatigue	4 (1.1)
Other	14 (3.9)
ED atrial dysrhythmia	
Fibrillation (isolated)	297 (82.3)
Flutter (isolated)	45 (12.5)
Both	19 (5.3)
Recent onset of dysrhythmia-related symptoms (<48 h at presentation)	
Yes	354 (98.1)‡
Median duration (interquartile range)	4 (2, 10)
≤12 h	275 (76.2)

AF, Atrial fibrillation; AFL, atrial flutter.
*Unless otherwise specified.
†Comorbidities are based on ATRIA stroke risk score definitions,[48] except systolic ejection fraction and pre-excitation syndrome (from manual chart review of diagnoses and echocardiographic results).
‡The remaining 7 patients without recent-onset symptoms were hemodynamically stable and were adequately anticoagulated on presentation.

(median increase of 11 ms) but generally dissipated thereafter. Among the 173 patients who received a second half-dose of ibutilide, only 14 (8.1%) had a 12-lead ECG performed before the second half-dose, and 7 of these had a QTc interval greater than or equal to 480 ms before receiving their second half-dose.

Two cases of ventricular tachycardia occurred (0.6%; 95% CI 0.02% to 2.1%), both during the second ibutilide infusion. The first patient had no known ventricular tachycardia risk factors and developed an asymptomatic 3-beat run of monomorphic ventricular tachycardia. He remained stable for 4 hours and was discharged home without sequelae. The second patient had no heart failure or significant left ventricular hypertrophy, a normal pretreatment QTc interval, and an uncorrected serum potassium level of 3.1 mEq/L and magnesium level of 1.8 mEq/L. He developed sustained runs of stable polymorphic ventricular tachycardia, which resolved in 20 minutes with intravenous magnesium sulfate and intravenous amiodarone treatment. His potassium was replaced. He was observed overnight in the ICU without further complications and was discharged home without sequelae.

Only 243 patients (67.3%) in our cohort received 4 or more hours of continuous ECG monitoring after the initial ibutilide infusion. No patients with home discharge before completing the recommended duration of monitoring returned for emergency care or died in the following 24 hours.

LIMITATIONS

The retrospective nature of this study brings its own set of limitations. To ensure complete documentation of our primary effectiveness outcome, we excluded cases with incomplete documentation of sinus rhythm restoration (n=2). Our reported frequency of nonsustained ventricular tachycardia is likely an underestimation; brief runs of

Table 2. Presenting clinical characteristics of ED patients treated with ibutilide for the cardioversion of atrial fibrillation and flutter.

Presenting Clinical Characteristic	No. (%), N=361*
Vital signs	
Systolic blood pressure, mm Hg	
Mean (SD)	132.7 (22.0)
Median	131
≥100	346 (95.8)
≥90–<100	11 (3.0)
<90	4 (1.1)
Pulse rate, beats/min	
Mean (SD)	124.5 (29.2)
Median	128
≥160	35 (9.7)
≥140–<160	82 (22.7)
≥120–<140	106 (29.4)
≥100–<120	63 (17.5)
<100	75 (20.8)
ECG results	
Initial QTc interval, ms	
<460	170 (47.1)
≥460 and <480	84 (23.3)
≥480 and <500	53 (14.7)
≥500	53 (14.7)
Missing (not recorded)	1 (0.3)
Laboratory results	
Serum potassium, mEq/L	
Unmeasured	3 (0.8)
Measured	358 (99.2)
Categorical results	
≥3.5	347 (96.9)†
<3.5	11 (3.1)
Serum magnesium, mEq/L	
Unmeasured	134 (37.1)
Measured	227 (62.9)
Categorical results	
≥1.6	225 (99.1)†
<1.6	2 (0.9)

*Unless otherwise specified.
†Percentages of patients with normal and abnormal electrolyte levels calculated among those with electrolyte measurements.

Table 3. Preibutilide management of ED patients receiving ibutilide for atrial fibrillation and flutter.

Preibutilide Management	No. (%), N=361
Intravenous rate reduction	249 (69.0)
Diltiazem only	164 (45.4)
Metoprolol only	53 (14.7)
Esmolol only	4 (1.1)
Diltiazem plus any β-adrenergic blocker*	25 (6.9)
Any β-adrenergic blocker	83 (23.0)
Intravenous magnesium sulfate, g	185 (51.2)
1	80 (43.2)
2	103 (55.7)
3	0
≥4	2 (1.1)
Consultation before ibutilide administration	
Cardiologist	233 (64.5)
Hospitalist (only)	8 (2.2)
Neither	120 (33.2)

*More commonly diltiazem first (n=16).

asymptomatic ventricular tachycardia may have escaped detection by the health care team or may have failed to be documented. It is unlikely, however, that sustained ventricular tachycardia failed both detection and documentation. Another shortcoming of this retrospective chart review is our inability to explain why patients who were nonresponders to the first half-dose of ibutilide failed to receive the second half-dose. Reasons for forgoing the second half-dose were documented in only 2 of 44 cases. Perhaps some of the 42 patients with an undocumented reason developed abnormalities on the continuous ECG monitor (eg, brief runs of nonsustained ventricular tachycardia) that inclined the physician to forgo administering the second half-dose of ibutilide.

Because of our cohort selection criteria, we were not able to examine patient and physician factors associated with ibutilide use compared with other methods of cardioversion. Another shortcoming is the imprecision in measurements of the time to cardioversion because it more commonly reflects the time of first recognition than the actual time of sinus rhythm restoration. Our results therefore may underestimate the true frequency of cardioversion. Our sample size was relatively small, limiting the detection of uncommon adverse events such as ventricular tachycardia. Last, this study was conducted in community medical centers within an integrated health care delivery system in California and may not be generalizable to other geographic locations and practice settings.

DISCUSSION

In this multicenter retrospective cohort study, we describe the use of ibutilide for the cardioversion of atrial fibrillation and flutter in US community EDs. We found wide interfacility variation in rates of ibutilide use and observed variations in the criteria for patient selection, quantity of dosing, use of magnesium, and duration of observation.

The effectiveness of ibutilide at 4 hours (54.8%) was at the low end of the range reported in clinical trials for patients with recent-onset symptoms (50% to 80%).[28,31,39] It is not uncommon for results from unscripted real-world clinical practice to differ from those of clinical trials, given differences in patient selection, education and experience of practitioners, and treatment protocols. Our lower rates of effectiveness may be attributable in part to incomplete dosing of ibutilide: one fifth of first half-dose nonresponders failed to receive the second half-dose of

Table 4. Frequency of ibutilide-induced cardioversion at different intervals, stratified by atrial dysrhythmia.

	Timing of Ibutilide-Based Cardioversion From Beginning of Initial Ibutilide Infusion					
	90 Minutes,		4 Hours,		On ED Discharge	
Atrial Dysrhythmia	n	% (95% CI)*	n	% (95% CI)	n	% (95% CI)
Atrial fibrillation only (n=297)	119	40.1 (34.5–45.9)	150	50.5 (44.7–56.3)	156	52.5 (46.7–58.3)
Atrial flutter (any) (n=64)	40	62.5 (49.1–74.3)	48	75.0 (62.6–85.0)	48	75.0 (62.6–85.0)
Atrial flutter alone (n=45)	29	64.4 (48.8–78.1)	33	73.3 (58.1–85.4)	33	73.3 (58.1–85.4)
Both (n=19)	11	57.9 (33.5–79.7)	15	78.9 (54.4–94.0)	15	78.9 (58.8–94.0)
Total (n=361)	159	44.0 (38.9–49.3)	198	54.8 (49.6–60.1)	204	56.5 (51.2–61.7)

*All CIs calculated as exact Clopper-Pearson 95% CIs for binomial proportions.

ibutilide for undocumented reasons. Approximately 9% of patients were not given the minimum 60-minute effect period, which also may diminish the measured rate of ibutilide effectiveness. Some of these physicians, however, may have been using ibutilide exclusively to potentiate the effect of direct-current cardioversion, although such intent was not documented in the electronic health record.[49]

In addition to optimizing dosing, another opportunity to improve rates of cardioversion from ibutilide may be routine preadministration of moderate-dose intravenous magnesium sulfate, which we found was rarely used in this clinical setting. The role of magnesium sulfate pretreatment in increasing the rate of ibutilide-induced cardioversion has been well documented, although the optimal dose and duration of infusion (options include 10, 20, and 60 minutes) have not been defined.[31,32,50-53] Studies of magnesium sulfate pretreatment suggest that the higher the dose, the larger the effect on augmenting ibutilide cardioversion rates.[31,32,50-53] In fact, lower doses may not be effective at all.[52,53] The strongest evidence favors a dose of at least 4 g.[51] Only half of our cohort received magnesium sulfate pretreatment, and physicians preferred the 1- to 2-g dose over the 4-g dose 90 to 1 (Table 3). This low dosing may explain why magnesium sulfate was not associated in this study with cardioversion. Intravenous magnesium sulfate has a good safety profile and is well tolerated. Adverse effects are mild and transient even at high doses (10 g during 3 hours).[31]

Table 5. Adjusted association between patient and treatment characteristics and ibutilide-induced 4-hour cardioversion (198 of 361 cardioverted).

Effect	Category	Adjusted Odds Ratio*	95% CI
Age, y†	In decades	1.3	1.1–1.5
Sex	Male	1.0	[Reference]
	Female	1.2	0.7–2.0
Atrial dysrhythmia	Fibrillation	1.0	[Reference]
	Flutter/both	2.7	1.4–5.1
Heart failure	No	1.0	[Reference]
	Yes	1.1	0.4–3.2
History of atrial fibrillation or flutter	Yes	1.0	[Reference]
	No	2.0	1.2–3.1
Magnesium sulfate pretreatment	None	1.0	[Reference]
	≥1 g	1.0	0.7–1.6

*Models adjusted for variables listed in table.
†Modeled as continuous integer representing age in decades. One patient younger than 20 years included in decade 2, and 1 patient older than 90 years included in decade 8.

Our multivariate model identified 3 variables that increased the odds of ibutilide cardioversion: increasing age, atrial flutter (versus atrial fibrillation), and a new diagnosis of atrial fibrillation and flutter. That atrial flutter is more responsive than atrial fibrillation to ibutilide is well established.[18,22] We found that atrial flutter was far more likely than atrial fibrillation to revert to sinus rhythm when treated with ibutilide. In fact, no other intravenous antidysrhythmic medication for the cardioversion of atrial flutter rivals ibutilide.[54]

The association of increased age with ibutilide effectiveness is not a consistent finding in the literature but has been observed in some studies.[33] The reason for this is unclear. We also are not the first to observe that patients without a history of atrial fibrillation or atrial flutter are more responsive to ibutilide.[55] It may be that interventions earlier in the historical time course of recurrent paroxysmal atrial fibrillation and flutter are more successful, before atrial fibrillation has effected changes in the structure and function of the heart that make its interruption more difficult.

Ibutilide-induced ventricular tachycardia was uncommon in this community atrial fibrillation and flutter population. The frequency we observed (0.6%) is significantly lower than that reported in the early trials of ibutilide: 5% for sustained monomorphic and 4% for polymorphic ventricular tachycardia.[22,23] In the trials, most ventricular tachycardia cases occurred in patients with significant heart failure, which is why the 2014 guideline of the American Heart Association states that ibutilide is

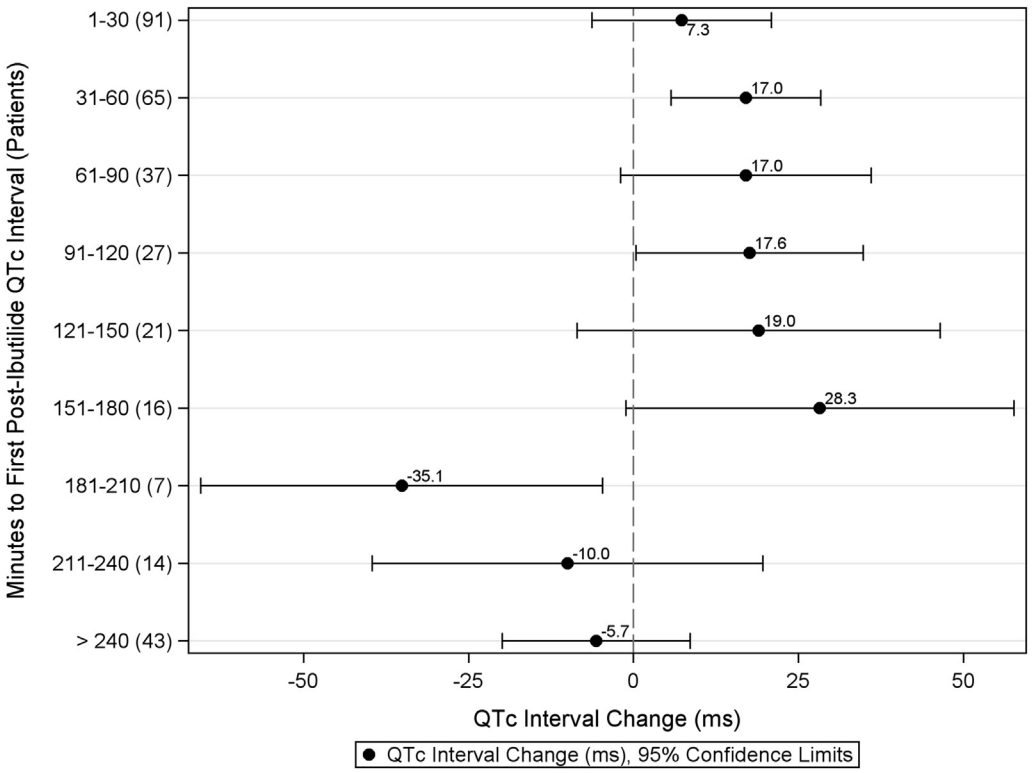

Figure 3. Change in QTc interval after ibutilide administration in 317 ED patients.

contraindicated in patients with an ejection fraction less than 30%.[14] The European Society of Cardiology expands this restriction to include significant left ventricular hypertrophy (≥1.4 cm).[15] With these concerns in mind, one small prospective ED study of ibutilide performed ED echocardiography on candidate patients without known heart failure to identify those with unrecognized left ventricular hypertrophy or dysfunction and exclude them from ibutilide administration.[35] The physicians in our study rarely administered ibutilide to patients with significant systolic heart failure.

In our study, only one case of polymorphic ventricular tachycardia occurred, and that was in a patient with mild hypokalemia, which is not considered an absolute contraindication to ibutilide according to the American Heart Association guideline.[14] The European Society of Cardiology, however, states that ibutilide should be given only when electrolytes are "within the normal range."[16] Some studies have allowed the preibutilide correction of hypokalemia and hypomagnesemia.[31,35] There are few studies on the correlation of hypokalemia with ibutilide-induced ventricular tachycardia, because nearly all trials of ibutilide have excluded patients with potassium levels less than 4.0 mEq/L.[20,38]

Similarly, nearly all prospective studies of ibutilide have excluded patients with prolonged QTc intervals. The definition of *prolonged* has varied between studies but is always greater than 480 ms.[27] Only retrospective studies have reported use of ibutilide in patients with longer QTc intervals.[56] In one such study, 16% of 201 patients had a QTc interval greater than or equal to 500 ms, a frequency similar to that of our cohort.[56] The authors did not report the association of QTc interval with ventricular tachycardia. Neither of our patients with ventricular tachycardia had a prolonged QTc interval.

Careful patient selection may not be the only way to reduce the frequency of ibutilide-induced ventricular tachycardia. One large trial found that high-dose intravenous magnesium sulfate also reduced the risk of ventricular tachycardia. The frequency of polymorphic ventricular tachycardia in the control group (no adjunctive magnesium sulfate) was 3.5% (8/229), and it was 0% (0/247) in patients who received high-dose intravenous magnesium sulfate (5 g before and 5 g after ibutilide).[31] This study has not been replicated but is mentioned in the 2014 American Heart Association guideline with a comment that "some experts administer magnesium sulfate intravenously before administering ibutilide in an attempt to lower this risk."[14] Lower doses of magnesium sulfate (1 to 4 g) have not demonstrated effectiveness in preventing ventricular tachycardia.[31,32,52,53]

It is because of ibutilide's risk of inducing ventricular tachycardia that guidelines recommend a 4-hour period of postibutilide ECG monitoring.[14] We found incomplete adherence (67%) to this recommendation but identified no deaths or return ED visits in the subsequent 24 hours from foreshortened monitoring.

This study identified opportunities for improvement at all stages of ibutilide administration, including attending to electrolyte levels and QTc intervals, increasing adjunctive magnesium sulfate doses, administering both ibutilide half-doses when not contraindicated, allowing at least 60 minutes for the last dose of ibutilide to exert its therapeutic effect, and completing the full 4-hour period of ECG monitoring. Ibutilide was infrequently used in most study EDs. Counting all ED administrations of ibutilide throughout the study period, these 361 patients received ibutilide during 414 separate ED encounters, still a small number when spread over 6.5 years across 17 EDs. This relative unfamiliarity with ibutilide may have contributed to the inconsistent application of evidence-based administration practices. Physician education and an easy-to-use evidence-based treatment pathway might improve ibutilide administration, optimizing its effectiveness and reducing its risks. An example of a clinical decision aid for ibutilide use is depicted in Figure E2, available online at http://www.annemergmed.com.

In conclusion, we found that the effectiveness of ibutilide in this community ED setting was consistent with results in clinical trials. Older age, atrial flutter (versus atrial fibrillation), and a new diagnosis of atrial fibrillation and flutter (versus a history of atrial fibrillation and flutter) were associated with increased effectiveness. The rate of cardioversion at 4 hours for atrial flutter was 75%, supporting ibutilide's status as the preferred medication for the rapid cardioversion of atrial flutter. Intravenous magnesium sulfate pretreatment was given at low doses and failed to facilitate cardioversion. Except for the exclusion of patients with systolic heart failure, community emergency physicians use less stringent patient selection criteria than those used in prospective studies. Nonetheless, the occurrence of sustained ventricular tachycardia was uncommon in this real-world setting. Opportunities exist to optimize ibutilide administration in the community ED.

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Author contributions: DRV conceived the study and its design. DRV, NL, AMR, and MDS performed the manual chart review. EMW undertook the programming. DRV, NL, and EMW analyzed the data, and all authors assisted with data interpretation. DRV drafted the article, and all authors contributed substantively to its critical revision and final approval. DRV takes responsibility for the paper as a whole.

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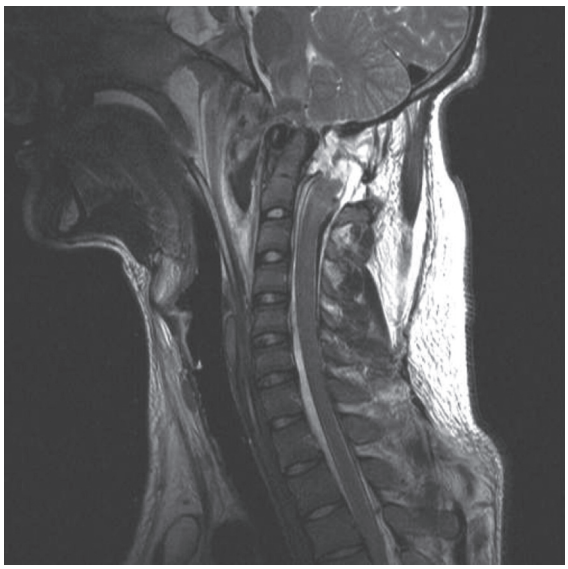

"Long-Term Survival Following Complete Medulla/Cervical Spinal Cord Transection" by Gautschi and Zellweger, April 2007, Volume 49, #1, pp. 540, 545.

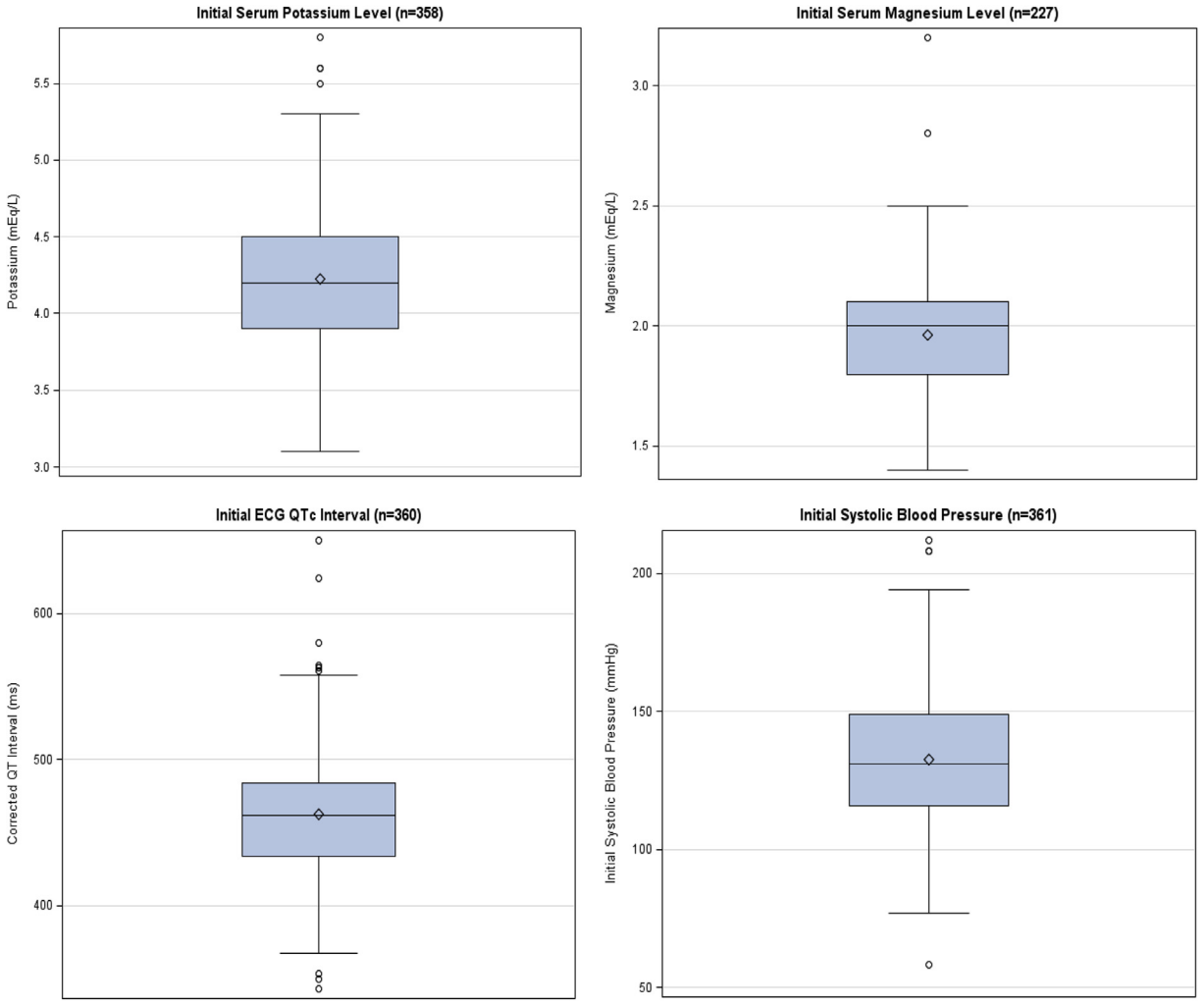

Figure E1. Distribution of initial serum potassium and magnesium levels, first QTc intervals, and first systolic blood pressure measurements. The bottom and top borders of the box indicate the IQR, Q1 and Q3, respectively. The line within the box indicates the median, whereas the diamond in the box indicates the mean in the distribution. The whiskers extend to $-1.5\times$IQR (bottom) and $+1.5\times$IQR (top). Any measured values that are more than 1.5 IQRs away from Q1 or Q3 are plotted as open circles. *IQR,* Interquartile range.

Table E1. Characteristics of 6 patients admitted to the ICU after receiving ibutilide in the ED for the cardioversion of atrial fibrillation or flutter.

Case Number	Age, Years	Sex	Ibutilide Response	Clinical Description
1	76	M	After initial dose of ibutilide, patient converted to sinus rhythm in 10 min.	Presented with hematemesis, chest pain, rapid ventricular response, and hypotension. Blood pressure improved after restoration of sinus rhythm. Observed in the ICU while awaiting endoscopy.
2	61	M	Patient failed to respond to 2 half-doses of ibutilide.	Admitted to the ICU overnight with plans for procedural sedation and electrocardioversion in the morning.
3	84	M	After initial dose of ibutilide, patient converted to sinus rhythm in 46 min.	Hypotension and acute renal failure with hyperkalemia. Blood pressure failed to improve after restoration of sinus rhythm. Elevated lactate level; treated for sepsis.
4	65	M	Patient failed to respond to 2 half-doses of ibutilide.	Rapid ventricular rate had failed to respond to intravenous diltiazem boluses; began receiving diltiazem infusion. Admitted to the ICU overnight with plans for procedural sedation and electrocardioversion in the morning.
5	66	F	After initial dose of ibutilide, patient converted to sinus rhythm in 165 min.	Rapid ventricular rate had failed to respond to intravenous diltiazem boluses; began receiving diltiazem infusion. Persistent low blood pressure was a concern in this patient with moderate to severe aortic stenosis.
6	58	M	Patient failed to respond to 2 half-doses of ibutilide.	Rapid ventricular rate had failed to respond to intravenous diltiazem boluses; began receiving diltiazem infusion, but poor response. Intravenous digoxin administered.

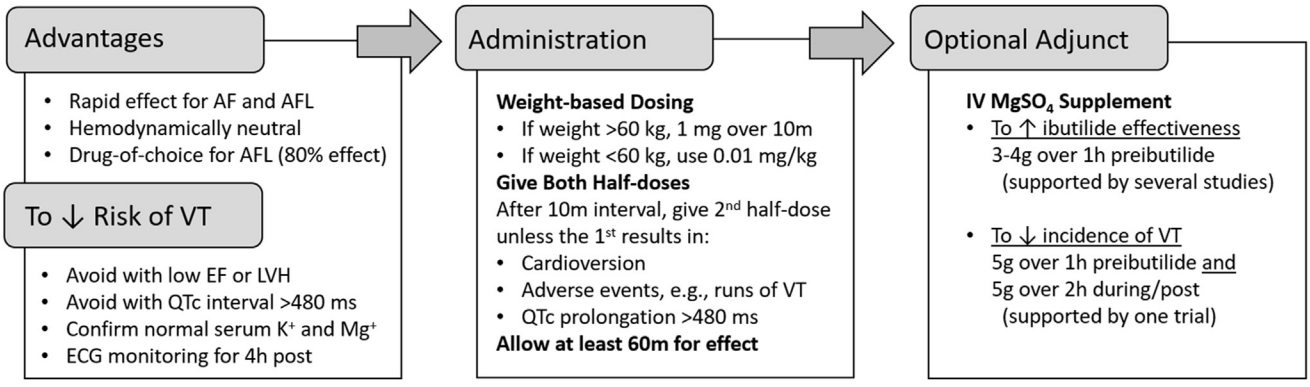

Figure E2. Clinical decision aid for the use of ibutilide for the cardioversion of atrial fibrillation or flutter. *VT*, Ventricular tachycardia; *EF*, ejection fraction; *LVH*, left ventricular hypertrophy.