

Diltiazem versus Amiodarone for New-Onset Atrial Arrhythmias in Non-Cardiac Post Surgical Patients: A Cohort Study

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Abstract

Objective: To evaluate safety and efficacy of diltiazem versus amiodarone for conversion of atrial arrhythmias in non-cardiac post-surgical critically ill patients.

Design: A cohort study of non-cardiac post surgical patients admitted to the surgical intensive care unit with new-onset atrial tachyarrhythmias which were treated by protocol. In the first year patients were treated with diltiazem, and amiodarone was used in the second year.

Setting: Thirty-eight bed surgical intensive care unit in a university medical center.

Patients and participants: Sixty-one patients were treated for new-onset atrial tachyarrhythmias: 31 received diltiazem and 30 received amiodarone.

Interventions: Diltiazem loading dose 0.25 mg/kg

and continuous infusion or amiodarone 150 mg loading dose and continuous infusion.

Measurements and results: Both groups had comparable demographics. Neither 24-hour conversion rates (diltiazem 87.1%, amiodarone 86.7%, $p = 0.96$) nor mean times ($\pm$ Standard Deviation) to conversion were statistically different (diltiazem 6.9 ± 6.3 hours versus amiodarone 5.0 ± 4.2 hours, $p = 0.52$). Three patients developed hypotension (diltiazem 1, amiodarone 2, $p = 0.57$).

Conclusions: Amiodarone and diltiazem led to no differences for treating atrial tachyarrhythmias in non-cardiac surgical patients based on safety and efficacy. Randomized controlled studies are needed to compare diltiazem versus amiodarone for conversion of postoperative atrial fibrillation.

Key words: atrial fibrillation, amiodarone, diltiazem, pharmacotherapy

Introduction

Atrial fibrillation (AF) is the most frequently sustained cardiac rhythm abnormality seen in clinical practice and it is estimated that 2.2 million Americans have AF [1,2]. The incidence of AF increases with age

and 70% of Americans with AF are between 65 and 85 years [2]. Although AF is not lethal, it has been associated with significant morbidity including stroke and deterioration of underlying heart disease. Atrial fibrillation is associated with six-fold increases in the risk of stroke, with approximately 5 % of patients with AF developing ischemic stroke [1,3].

New-onset AF has many risk factors including several acute and chronic conditions. Classic causes of AF include alcohol intake, myocardial infarction, pericarditis, pulmonary embolism, hyperthyroidism and surgery. Treatment of these underlying conditions

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may eliminate AF in some cases. In addition, many chronic cardiovascular conditions may also contribute to AF including congestive heart failure, valvular heart disease, coronary heart disease and hypertension.

New-onset AF occurs fairly frequently following surgical procedures, with an estimated incidence between 4-40% depending on the surgical intervention [1,4-10]. Postoperative AF is more common in patients undergoing cardiothoracic surgery, with reported incidences of 10-40% [4,5,10]. For non-cardiac post-surgical patients the incidence of postoperative AF is estimated to be 4-15% [6-9]. Increasing age has been shown to strongly predict development of post-surgical AF, and the incidence may be increasing as more elderly patients are undergoing surgery today than in the past [1,2,6,7,11].

Perhaps not surprisingly, current data suggest that development of postoperative AF in the non-cardiac post surgical patient contributes to morbidity and possibly mortality. Polanczyk and colleagues demonstrated that lengths of hospitalization were 33% longer for patients who developed supraventricular arrhythmias after undergoing major, non-emergency, non-cardiac surgery [7]. Barthwaite and colleagues have also concluded that development of new-onset AF in non-cardiothoracic post-surgical patients significantly increases intensive care unit (ICU) and hospital lengths of stay [12]. In addition patients that developed new-onset postoperative AF have increased in-hospital mortality (23.4%) compared to patients without AF (4.3%, $p < 0.02$). Seguin and colleagues have also demonstrated that development of AF increases median ICU lengths of stay from 10 days to 22 days in trauma patients ($p < 0.001$), but does not appear to increase mortality [11]. Despite these data, it is possible that development of postoperative AF may be a marker of higher severity of illness, and it is unclear if treatment will decrease length of hospitalization in the non-cardiac post-surgical patient [11,13]. Few data are published regarding treatment of postoperative AF in critically ill non-cardiac post-surgical patients, and it is unknown if treatment of AF will decrease morbidity or length of hospitalization.

In general, conversion from AF to sinus rhythm may be associated with fewer symptoms, better exercise tolerance, improved quality of life and survival, but these findings are in the context of chronic AF [14].

There are currently few data available describing efficacy of treating postoperative AF in non-cardiac surgery patients, and therefore current practice is often inferred from cardiac surgery patients. We originally developed a diltiazem-based protocol to manage postoperative atrial tachyarrhythmias in non-cardiac surgical patients. Subsequently amiodarone became more frequently recommended by our cardiologist and we therefore changed to an amiodarone-based protocol. The purpose of this cohort study was thus to compare the efficacy and safety of these two treatment protocols in non-cardiac post surgical patients in the surgical intensive care unit (SICU).

Materials and methods

All patients with new-onset atrial tachyarrhythmias during two one year periods and admitted to a 38-bed university SICU were eligible for the study. Our SICU is an open unit with patients co-managed by both the primary surgical service and our intensivist led SICU service. The SICU patient population for this study included trauma, burn, plastic, transplant, gastrointestinal, urological, orthopedic, vascular, and neurosurgical surgery. Non-cardiac postoperative patients admitted to the SICU with new-onset atrial tachyarrhythmias were treated by protocol with diltiazem during the first year or amiodarone in the second year. The protocol was developed by the SICU team including surgeons, pharmacist and nurses. Patients eligible for protocol therapy were hemodynamically stable with new-onset atrial tachyarrhythmias. Patients that were receiving beta-blockers or calcium channel antagonists without previous history of arrhythmia were included in the study. Exclusion criteria included patients with a history of arrhythmia or treated with an antiarrhythmic prior to surgery, intra-operative myocardial ischemia or rhythm complication, thoracic or cardiovascular procedures and allergy to diltiazem or amiodarone.

During the first year patients with new-onset atrial tachyarrhythmias were treated by protocol using diltiazem 0.25 mg/kg bolus intravenously, followed by continuous infusion of 5-15 mg/hr titrated to heart rate less than 120 beats per minute (**Figure 1**). In the second year, an amiodarone protocol was used, loading with 150 mg intravenously, over at least 10 minutes, followed by continuous infusion of 1 mg per minute for six hours then decreased to 0.5 mg per minute (**Figure 2**). A 12-lead electrocardiogram was obtained in all patients suspected of developing an arrhythmia. In both protocols, intravenous adenosine 6 mg followed by 12 mg intravenous push could be administered to define the type of tachyarrhythmia. Decisions to continue, discontinue, or change to oral therapy after 48 hours was at the discretion of the managing physicians. Primary outcomes studied included conversion to normal sinus rhythm at 24 hours, time to conversion, and adverse drug reactions (hypotension and bradycardia). Past medical history, drug history, allergies, vital signs, type of surgery, postoperative medications were recorded for all patients. Risk factors for the development of atrial tachyarrhythmias that were recorded included past medical history of coronary artery disease, valvular heart disease, congestive heart failure, hypertension, chronic obstructive pulmonary disease, and concurrent use of inotropes, vasopressors, inhaled beta-agonist, beta-blockers, calcium channel blockers, theophylline or digoxin. Hypoxia was defined as a partial pressure of oxygen less than 60 mmHg and hypotension was defined as a mean arterial pressure less than 60 mmHg attributable to either drug. Secondary endpoints were duration of therapy (intravenous and oral/enteral), antiarrhythmic or rate control medications prescribed at hospital discharge, and duration of ICU stay and hospitalization.

This study received Institutional Review Board approval in accordance with the 1964 Declaration of Helsinki. Data are reported as a mean value $\pm$ standard deviation. Statistical analysis was performed by chi-square analysis for nominal data, and Student's t-test for continuous data. Statistical significance was defined as a p-value less than 0.05.

Results

During the study, 61 patients were treated for atrial tachyarrhythmias, 31 received diltiazem and 30 received amiodarone. Groups were comparable for demographics and types of surgery with gastrointestinal surgery as the most common type of surgery in each group (**Table 1**). Other types of surgical procedures were similar in distribution and included trauma, vascular, neurosurgical, urological, transplant, burn and skin and soft tissue debridement. In the diltiazem cohort, 4 patients underwent neurosurgical procedures while no patients in the amiodarone group underwent neurosurgery. The mean time to onset of tachyarrhythmias from surgery were similar between group (66.1 ± 58.6 hours in the diltiazem group compared to 83.4 ± 50.8 hours in the amiodarone group, $p=0.52$, **Figure 3**). Eleven patients were receiving vasopressors and/or inotropes when atrial tachyarrhythmias developed (diltiazem 8, amiodarone 3, $p=0.18$), and 17 patients were receiving postoperative beta-blockers (diltiazem 6, amiodarone 11, $p=0.16$). The groups were similar in number of patients receiving concurrent inhaled beta-agonist, digoxin or theophylline (**Table 2**). Most patients developed atrial fibrillation (diltiazem 28, amiodarone 27), three patients developed supraventricular tachycardia (diltiazem 2, amiodarone 1) and three developed atrial flutter (diltiazem 1, amiodarone 2).

Similar numbers of patients in each group had at least one risk factor for the development of atrial tachyarrhythmias (diltiazem 15, amiodarone 21, $p=0.12$, **Table 3**). Eleven patients in the diltiazem group and 16 patients receiving amiodarone had only one risk factor while 4 patients receiving diltiazem and 5 patients receiving amiodarone had 2 risk factors. Mean patient ages were similar between groups 68.5 ± 14.6 years in the diltiazem group and 66.1 ± 16 years in the amiodarone group. At the time of onset 8 patients were hypoxic (four in each group, $p>0.99$) and two patients were hypotensive (one in each group $p>0.99$). The mean arterial pressure at onset was 89 ± 17.8 mmHg in the diltiazem group and 91.2 ± 20.3 mmHg in the amiodarone group ($p=0.66$). Nineteen patients in the diltiazem group and 18 in

the amiodarone group were 65 years old or older ($p > 0.99$). All patients survive until discharged except 2 in the diltiazem group ($p = 0.49$).

The only adverse drug reaction noted during the study period was transient hypotension, which occurred in three patients (diltiazem 1, amiodarone 2). In the diltiazem patient, hypotension resolved after decreasing the infusion rate. For the amiodarone recipients, one was treated with fluids, and the other's blood pressure recovered spontaneously. No patients developed bradycardia, ventricular arrhythmias or required emergent cardioversion.

Mean heart rates at the onset of tachyarrhythmia were similar between groups (151 ± 31 beats per minute in the diltiazem group versus 150 ± 21 beats per minute in the amiodarone group, $p = 0.74$). Most patients converted to normal sinus rhythm within 24 hours of therapy. There was no significant difference between percentages of patients who converted to normal sinus rhythm with either diltiazem (87.1%) or amiodarone (86.7%, $p = 0.96$) protocols at 24 hours, and 4 patients in each group required procainamide ($p > 0.99$). At the time of conversion, mean heart rates decreased to 98 ± 19 beats per minute in the diltiazem group ($p < 0.0001$ compared to baseline), 105 ± 23 beats per minute in the amiodarone group ($p < 0.0001$ compared to baseline) and was not statistically different between groups ($p = 0.24$). Mean times to conversion were similar between protocols with 6.9 ± 6.3 hours for treatment with diltiazem and 5.0 ± 4.2 hours for amiodarone ($p = 0.52$, **Figure 3**). The mean maximal infusion of diltiazem was 10.5 ± 3.7 mg/hr. Both groups had similar lengths of ICU stay (13.5 ± 11.9 days in the diltiazem group versus 11.6 ± 10.9 days in the amiodarone group, $p = 0.54$) and hospital length of stay (22.5 ± 18.9 days in the diltiazem group compared to 24.2 ± 24.2 in the amiodarone group, $p = 0.76$).

Although most patients converted to normal sinus rhythm within 24 hours, use of both drugs was continued in many patients beyond 48 hours (**Table 4**). Mean durations of therapy were 11.4 ± 10.5 days for diltiazem, and 7.0 ± 8.1 days for amiodarone ($p = 0.15$).

Intravenous diltiazem was continued for 4.6 ± 4.1 days, and 4 ± 3.0 days for intravenous amiodarone ($p = 0.58$). Similarly, durations of oral/enteral diltiazem were not significantly different than amiodarone (6.8 ± 9.8 days versus 3.0 ± 7.7 days, $p = 0.19$).

Interestingly, 22 patients (36.1%) were discharged on new anti-arrhythmic medications, twelve patients (38.7%) in the diltiazem group and 10 patients (33.3%) in the amiodarone group ($p = 0.86$, **Table 4**). Ten patients in the diltiazem group were discharged on diltiazem, one on amiodarone and one on diltiazem plus sotalol. In the amiodarone group, eight were discharged on amiodarone, one on sotalol and one patient on propafenone plus diltiazem.

Discussion

Our results suggest that protocol driven therapy with diltiazem or amiodarone led to similar outcomes after treatment of atrial tachyarrhythmias in non-cardiac post surgical critically ill patients. These data show that protocol driven therapy was effective with similar conversion rates and rapid times to conversion for both protocols (**Table 2**). Our findings are comparable to a recently published study in patients undergoing lung surgery with the absence of heart rhythm disease, where 80% of patients treated with diltiazem or amiodarone converted to normal sinus rhythm by 48 hours [11]. Both diltiazem and amiodarone protocols were well tolerated, with low overall incidence of adverse effects that were easily corrected with minor interventions.

Potential etiologies for development of postoperative AF are multiple, but few data are available for non-cardiac surgical patients [1]. Risk factors for development of postoperative AF in cardiac surgery patients have been studied often with conflicting results, but age is the most reproducible factor [1,4,15-21]. At what age risks for AF substantially increase is unknown, but the mean patient age and proportion of patients older than 65 years were comparable between groups. Other risk factors include pre-existing atrial enlargement, valvular heart disease, chronic lung

disease or history of preoperative AF. Medications, including vasoactive agents, have also been associated with development of AF. In our study, both groups had comparable risk factors, including preoperative and postoperative medications. Patients with a history of preexisting arrhythmia were excluded due to confounding effects of treatments in these patients for prevention of AF.

Pharmacologic recommendations for the treatment of AF generally include either antiarrhythmic agents for rhythm control or medications that slow ventricular rate, and the best option remains controversial [22]. Many recommend initial treatment of new-onset AF with antiarrhythmics to promote conversion to sinus rhythm [23]. For patients that develop postoperative AF after cardiac surgery, no consensus exists for use of rhythm-control versus rate-control agents, and there are surprisingly few trials addressing maintenance of sinus rhythm after cardiac surgery either (24). Lee and colleagues studied an antiarrhythmic strategy to a rate-control strategy in a study of fifty patients who developed postoperative AF after cardiac surgery [22]. Time to conversion, the primary endpoint, was similar between the antiarrhythmic strategy (11.2 ± 3.2 hours) and the rate-control strategy (11.8 ± 3.9 hours, $p = 0.8$). Although our time to conversion seemed shorter, we saw similar rates of conversion (**Table 2**) and our results are also comparable to those of Bobbio and colleagues [10]. Similarly, numerous studies of patients with recurrent AF have demonstrated no benefit when rhythm control strategies have been compared to rate control strategies [1,25-30]. Thus it seems debatable that rhythm control strategies offer any real advantage in management of new-onset AF.

Although amiodarone is a rhythm control agent currently recommended for rhythm conversion of new-onset postoperative AF after cardiac surgery, there are several disadvantages to its use in this setting [24]. Numerous adverse effects have been associated with amiodarone therapy, and these include hypotension and bradycardia during rapid intravenous administration. Long-term therapy has been associated with development of most adverse effects, including pulmonary fibrosis,

thyroid dysfunction, skin discoloration, reversible liver damage and ocular damage [31]. In one recent trial comparing rate versus rhythm control for persistent AF, amiodarone therapy was discontinued in as many as 25% of patients for adverse effects [28]. It should be noted further that substantial literature is accumulating that suggests acute amiodarone-induced pneumonitis can occur within 1 to 14 days of therapy initiation, and that this adverse effect may go unrecognized [32-35]. Controversy also exists for the optimal dosage required to convert AF to sinus rhythm. Both the American College of Cardiology/American Heart Association Guidelines for management of patients with AF and the American College of Chest Physicians Guidelines for the management of AF in postoperative cardiac surgery patients recommend 5 to 7 mg/kg bolus followed by 1.2 to 1.8 gm over the next 24 hours for intravenous amiodarone [1,24]. We used 150 mg bolus followed by 900 mg over 24 hours and this may not be an optimal dosing. The dosing of amiodarone in our study was similar to the dosing used by Bobbio and colleagues [10]. Our amiodarone protocol was developed before publication of the American College of Cardiology/American Heart Association and American College of Chest Physicians Guidelines, the dosages of amiodarone were chosen based on our previous experience with use in patients with ventricular arrhythmias. In comparison, diltiazem is a non-dihydropyridine calcium channel blocker that is used to control ventricular rate in patients with atrial tachyarrhythmias. Diltiazem also allows does cause conversion to sinus rhythm, presumably by controlling ventricular response allowing spontaneous conversion. Long-term use diltiazem may be advantageous because it is considered less toxic than rhythm control agents with fewer drug interactions [26,27].

Whether appropriate or not, it appears that many patients with new-onset AF are discharged from the hospital receiving whatever antiarrhythmic was used to control their arrhythmia. In this study, decisions to continue AF medication after conversion to normal sinus rhythm were left to individual attending physicians and cardiology consultants. Although most patients converted to normal sinus rhythm by 24 hours,

it is interesting that diltiazem and amiodarone were continued respectively for mean durations of 11.4 days and 7.0 days, and often until patient discharge. Reasons for continuation are unknown and were not controlled for in this study. Approximately one-third of patients were subsequently discharged with rhythm or rate control agents prescribed, despite ongoing normal sinus rhythm. Given that patients discharged on amiodarone may be more likely to develop adverse effects, we have reverted back to our original diltiazem protocol, using amiodarone as second line therapy in treatment of atrial tachyarrhythmias in our non-cardiac surgical population [26-27].

This study has several limitations. First, it is a review of two cohorts, and was not a prospective randomized controlled trial. In addition, the study sample was relatively small in a single center (61 patients), and was thus not powered to detect minor differences between the groups. At the time of designing this study little data was available to determine the efficacy of diltiazem or amiodarone in treating new-onset AF in post surgical patients. In addition, the guidelines for treating AF were not published and the dosage we used maybe too low. Patients with histories of heart rhythm disease, including those receiving antiarrhythmics prior to surgery were excluded to decrease confounding variables, but this substantially decreased numbers of eligible patients.

Development of atrial tachyarrhythmias in non-cardiac postoperative patients might also be self limited, following resolution of atrial distension after fluid resuscitation/mobilization making treatment possibly unnecessary [10]. Currently no data are available to support or refute this hypothesis, and it has been standard recommendations of our cardiologists, and thus our practice, to treat these patients.

Conclusion

In conclusion, diltiazem or amiodarone based protocols led to no difference for treatment of new-onset atrial tachyarrhythmia in non-cardiac surgical patients in this relatively small single institution study. Diltiazem and amiodarone protocols had similar rates of conversion, and short-term adverse drug reactions were few and transient. Interestingly, although approximately 88% of patients converted to normal sinus rhythm, about one third of patients were eventually discharged on antiarrhythmics. More studies including randomized controlled trials are needed to compare the use of diltiazem versus amiodarone for conversion of post-operative AF.

Competing interests: None of the authors have anything to disclose. No outside finances were used to fund this study.

Table 1. DEMOGRAPHICS

	Diltiazem (n =31)	Amiodarone (n =30)
Mean age (years±SD)	68.5±14.6	66.1±16.0
Male:female	18:13	21:9
Surgery type		
• Burn	1	1
• Gastrointestinal	15	11
• Neurosurgical	4	0
• Skin and soft tissue debridement	2	1
• Transplant	0	2
• Trauma	5	9
• Urological	0	1
• Vascular	4	5
Preoperative medications	5	5
• Beta-blockers	3	3
• Calcium channel antagonists	2	2

SD =Standard Deviation

Table 2. CONCURRENT MEDICATION USE, RHYTHM AND ADVERSE EFFECTS

	Diltiazem (n =31)	Amiodarone (n =30)	P-value
Concurrent medication use	17	14	0.62
• Beta-blockers	6	11	0.16
• Digoxin	1	0	>0.99
• Inhaled beta-agonist	6	2	0.26
• Theophylline	0	1	0.49
• Vasopressor/inotrope	8	3	0.18
Rhythm			
• Atrial fibrillation	28	27	0.97
• Atrial tachycardia	2	1	0.57
• Atrial flutter	1	2	0.57
24 hours conversion rate (%)	87.1	86.7	0.96
Mean time to conversion (hours)	6.9	5	0.35
Hypotension with protocol therapy	1	2	0.57

Table 3. RISK FACTORS FOR ATRIAL FIBRILLATION

	Diltiazem (n =31)	Amiodarone (n =30)	P-value
Patients with one risk factor	11	16	0.2
Patients with two risk factors	4	5	0.29
History of chronic obstructive pulmonary disease	6	2	0.26
History of congestive heart failure	0	2	0.11
History of coronary artery disease	4	4	>0.99
History of hypertension	7	14	0.062
History of valvular heart disease	1	0	0.49

Table 4. DRUG THERAPY IN ATRIAL TACHYARRHYTHMIA PATIENTS

	Diltiazem n =31	Amiodarone n =30	P-value
Mean length of therapy (days $\pm$ SD)	11.4 $\pm$ 10.5	7.0 $\pm$ 8.1	0.15
• IV	4.6 $\pm$ 4.1	4.0 $\pm$ 3.0	0.58
• Oral/enteral	6.8 $\pm$ 9.8	3.0 $\pm$ 7.7	0.19
Patients discharged on antiarrhythmics	12	10	0.86

Figure 1. DILTIAZEM BASED PROTOCOL

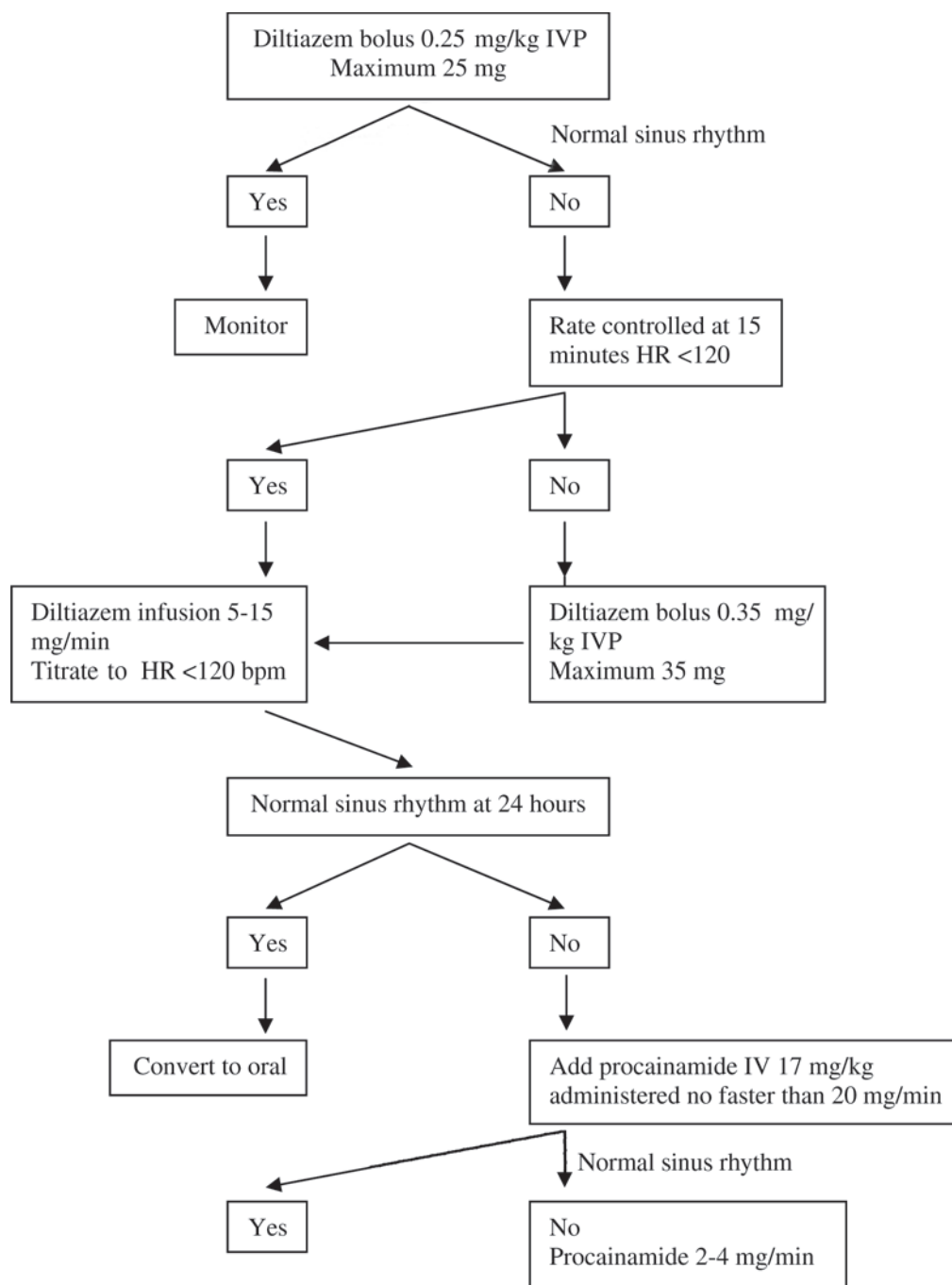


Figure 2. AMIODARONE BASED PROTOCOL

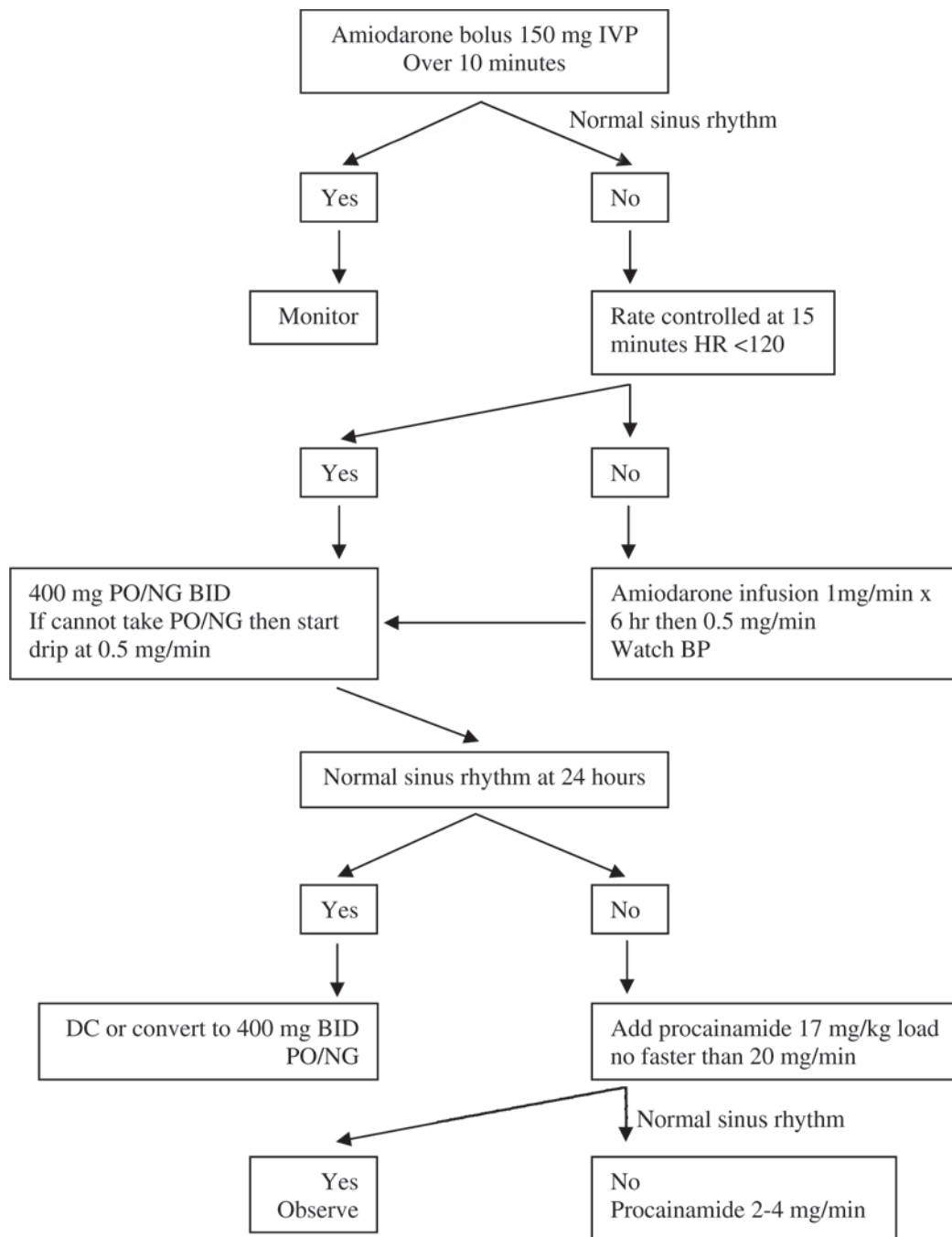
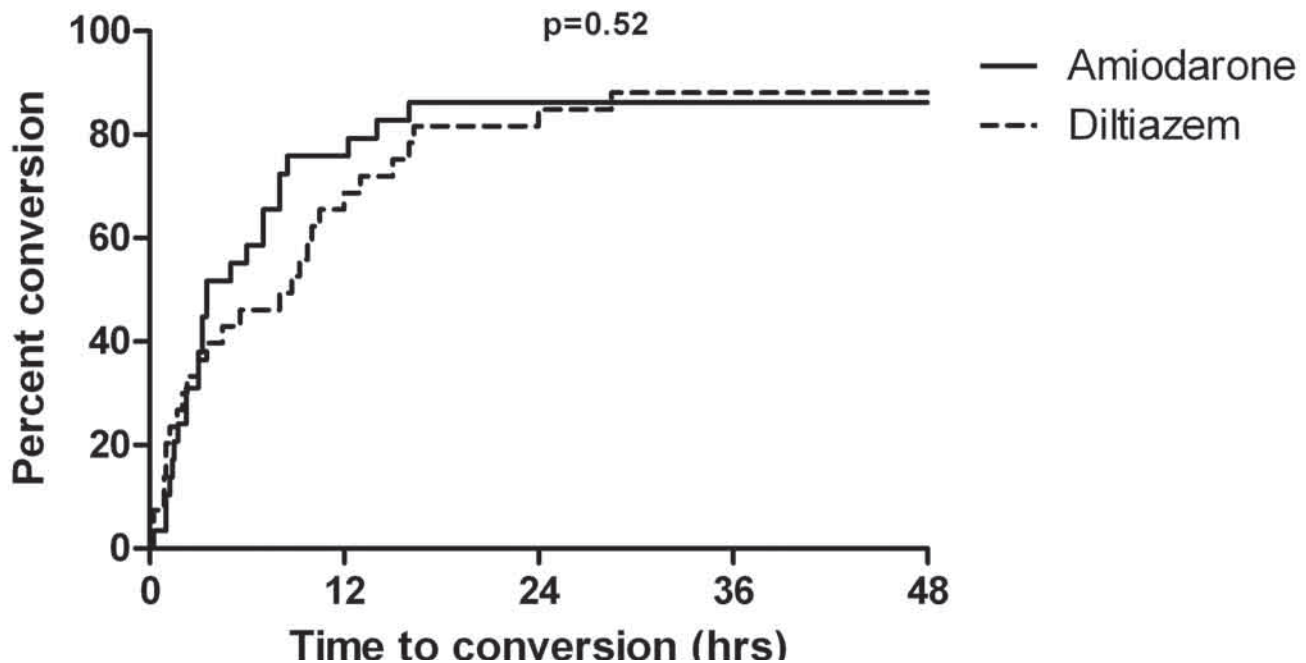


Figure 3. TIME TO CONVERSION



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