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# **Modeling of amiodarone effect on heart rate control in critically ill patients with atrial tachyarrhythmias**

*Running title:* Amiodarone in critically ill patients with [AT](#)

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## **ABSTRACT**

**Aims:** Amiodarone is the gold standard medication to control heart rate in critically ill patients with atrial tachyarrhythmias (AT). However, effective doses and covariates influencing its efficacy remain unknown. We therefore performed pharmacodynamic modeling of heart rate reduction induced by amiodarone in these patients.

**Methods-Results:** This observational study included 80 consecutive severely ill patients receiving amiodarone to treat atrial tachyarrhythmias. A total of 1348 time-heart rate observations with 361 amiodarone dose administrations were analyzed during up to 6 days after hospital treatment initiation using a nonlinear mixed effect model. Pretreatment with amiodarone before intensive care administration, paroxysmal versus persistent AT, catecholamine infusion, fluid and magnesium loading were among covariates assessed in the model.

In case of paroxysmal AT in a patient not pretreated by amiodarone, a 300 mg intravenous loading dose combined with a 800 mg oral dose on the first day followed by 800 mg/day p.o. for 4 days was effective to achieve a heart rate between 80 and 115 bpm within the first day and to maintain it during the next 4 days. Corresponding doses were twice as high in patients with persistent AT. Use of intravenous magnesium ( $p<0.02$ ) and fluid loading ( $p<0.02$ ) was associated with an earlier and greater heart rate decrease. Dobutamine use had an opposite influence ( $p<0.05$ ).

**Conclusions:** In critically ill patients with AT, dose of amiodarone required to control heart rate is influenced by the type of AT and by other easily measurable conditions which may allow better individualization of amiodarone dosing.

**Key words:** amiodarone, atrial tachyarrhythmia, pharmacology, shock, heart rate.

## **KEY POINTS**

1/ Amiodarone pre-treatment, paroxysmal versus persistent atrial tachyarrhythmias (AT), dobutamine infusion, intravenous magnesium and fluid loading have significant influence on amiodarone effect on heart rate reduction in critically ill patients with AT.

2/ An optimized dosing regimen of amiodarone refining current guidelines indications is proposed to better control heart rate in patients with AT depending on their clinical presentation: paroxysmal AT amiodarone naive, persistent AT amiodarone naive and paroxysmal AT amiodarone pre-treated.

3/ Co-administration of intravenous magnesium with amiodarone is associated with a greater and earlier heart rate control in patients with AT. This suggests that systematic use of IV magnesium as an add-on therapy might be valuable

## **ABBREVIATION**

AT: atrial tachyarrhythmias

bpm: beats per minute

ECG: electrocardiogram

ECV : Electrical cardioversion

HR: heart rate

ICU: intensive care unit

IV : intravenous

mg: milligram

## INTRODUCTION

Atrial tachyarrhythmias (AT), such as atrial fibrillation are highly prevalent and are associated with a poor outcome in critically ill patients admitted in intensive care units (ICU)<sup>[1]</sup>. AT is often characterized by a persistent elevation of ventricular heart rate (HR) above 120–130 beats per minute (bpm) leading to cardiac systolic dysfunction, (i.e ventricular tachycardiomyopathy), responsible for hemodynamic instability, increased morbidity and mortality<sup>[2-5]</sup>. A rate or rhythm control strategy with pharmacological therapy is recommended in patients with AT for the treatment or prevention of ventricular tachycardiomyopathy<sup>[4-5]</sup>. Before initiating antiarrhythmic treatment, factors promoting AT in the critically ill should be sought and corrected (anemia, hypoxia, hypokalemia...). Anticoagulant treatments are also usually administered. Attempts to restore sinus rhythm are frequently unsuccessful in the setting of critically ill patients<sup>[6-8]</sup>, particularly when using electrical cardioversion without antiarrhythmic pretreatment. HR control is thus the main preferred strategy in this situation<sup>[9-11]</sup>. Guidelines in stable patients recommend strict control aiming at a resting HR between 60–80 bpm and 90–115 bpm during stress situations, based on the results of the AFFIRM trial<sup>[4,12]</sup>. There are no specific guidelines for patients in severely ill condition but it is commonly admitted that reaching a HR below 115 bpm is advisable<sup>[2-5]</sup>.

Amiodarone is the recommended agent to control HR in critically ill patients presenting with AT <sup>[4-5]</sup>. However, it can be associated with hypotension and potentially severe liver and pulmonary toxicity, particularly after IV administration <sup>[4,13-15]</sup>. This toxic risk justifies the administration of the lowest possible dose to control heart rate. In addition, patients admitted in ICU present with a diversity of adverse conditions that can affect antiarrhythmic drug pharmacokinetics and dynamics,

including instable hemodynamics, pre-existent or acquired left ventricular dysfunction, hypoxemia, hyperthermia, hypovolemia or acidosis<sup>[16]</sup>.

The choice of amiodarone doses in ICU patients is thus challenging due to inter-patient heterogeneity and limited knowledge of optimal dosing in this setting<sup>[4-5]</sup>. In general, an IV loading dose of 300 mg is administered over 1 hour followed by an additional dose given either intravenously (IV) over the first day (10 - 50mg/h)<sup>[10]</sup> or orally over the next few days (400 mg/day up to 1200 mg /day)<sup>[4,5,17,18]</sup>. In daily practice, amiodarone dosing regimens used in these patients vary widely. Factors that influence amiodarone efficacy in critically ill patients have not been reported. Therefore, a randomized study comparing the efficacy of different amiodarone dosing regimens would be inappropriate without previous knowledge of the sources of variability of drug response in ICU patients. Modelling of amiodarone efficacy in critically ill patients has not been previously reported and is the best initial approach to better characterize the complex interactions of multiple covariates on amiodarone pharmacodynamics.

The objective of this study was to determine optimal doses of amiodarone to achieve a heart rate between 80 and 115 bpm when treating AT after identification and integration of clinical and therapeutic covariates influencing amiodarone efficacy in critically ill patients.

## **MATERIAL AND METHODS**

### **Patients and Study Design**

This observational, cohort study was conducted from January 2007 to April 2012 in the 18-bed medical ICU of a tertiary teaching hospital. Due to the observational design, and in accordance with French bioethics laws, Institutional Review Board authorization was not necessary. The study was approved by the Commission Nationale de l'Informatique et des Libertés to use computerized medical data with protection of patient confidentiality. Data were extracted from the files of 80 consecutive critically ill patients who had received at least one dose of amiodarone to treat or prevent AT during their hospitalization in ICU. Three investigators (JES, MEA, MA) were each responsible of the data extraction during a specified time period resulting in patients inclusion over three distinct time periods. [Figure1]. Patients with paced rhythm or incomplete chart were excluded. HR data were collected at the moment of the first amiodarone administration in ICU and then 4 to 6 times daily after each dosing over 6 days or until death or ICU discharge. Amiodarone could be administered either IV over 20 to 60 minutes or orally. Route, frequency of administration and doses were prescribed at the discretion of the treating physician without any predefined protocol.

### **Variables**

At the time of first amiodarone administration in ICU the following time-independent covariates were collected: gender, age, body weight, height, etiology of the disease leading to ICU admission, Simplified Acute Physiology Score II (SAPS II score), Acute Physiology And Chronic Health Evaluation II (APACHE II score), diabetes, hypertension, past medical history of AT, withdrawal of a chronic antiarrhythmic drug since less than three times its half-life, total bilirubinemia, previous amiodarone treatment before first dose in ICU (yes, no), type of cardiac rhythm (sinus versus

persistent / paroxysmal AT). Paroxysmal and persistent AT were defined as an arrhythmia which started less or more than one week before the first amiodarone administration in ICU, respectively.

Time-dependent covariates potentially interacting with amiodarone pharmacokinetics and/or pharmacodynamics were also collected at the time of each HR collection. These were: temperature, pH,  $paO_2$ , natremia, kalemia, hemoglobin, protidemia, glomerular filtration rate, attempt to electrical cardioversion, magnesium or fluid loading, use of other antiarrhythmic drugs, furosemide or extra-renal dialysis with or without ultrafiltration, catecholamine administration and its type (epinephrine  $< 1\text{mg/h}$ , epinephrine  $> 1\text{mg/h}$ , dobutamine, other  $\beta$ -adrenoceptor agonists), curare and sedative drug use. Fluid loading was defined as administration of more than 0.5 liter of saline solution in 30 minutes. Magnesium loading was defined by any administration of IV magnesium either by bolus or continuous infusion whichever the dose received. Influence of other antiarrhythmic drugs could not be analyzed because such prescription was too rare to be studied.

## **Pharmacodynamic Modeling**

### General model

Amiodarone pharmacokinetics was ascribed to a virtual compartment model including zero or first order input rates. This virtual compartment,  $A(t)$ , represents the biophase in which the amount or concentration is in equilibrium with the observed effect. It is used to extract the kinetic component, KDE or "pharmacodynamic half-life", from the pharmacodynamic data alone describing the equilibrium between the administration rate and the observed effect.  $G(t)$  represents the amiodarone amount in the gut at a given time and  $k_a$ , the first-order absorption rate (fixed to 8) [19-21].

Amiodarone bioavailability (F) was fixed to 0.33 [19-21]. The effect of amiodarone on heart rate, HR(t) was modeled as follows:

$$dA(t)/dt = \text{input} - KDE \times A(t) \quad (1)$$

$$\text{input} = k_a \times G(t) \times F \text{ if administered orally} \quad (2)$$

$$IR = KDE \times A(t) \text{ and } E_{\text{max}} = 1 \quad (3)$$

$$dHR(t)/dt = k_{in} [1 - E_{\text{max}} \times IR / (IR + IR_{50})] - k_{out} HR(t) \quad (4)$$

In the effect model, equation (4), the production rate constant of response HR,  $k_{in}$ , is inhibited by the amiodarone virtual infusion rate, IR (drug amount per time unit) via an hyperbolic function. Finally,  $IR_{50}$  and  $k_{out}$  are the IR that induces 50% of the maximal response and the first-order dissipation rate constant for the HR response. It was shown that the use of the IR function usually performs well and can be used for predictions of drug effects [26], provided the investigated doses extend well beyond the  $IR_{50}$ , which is the case in this study (Table 1).

The initial conditions of these differential equations were  $HR(0) = \text{heart rate at time zero}$ ,  $A(0) = \text{Dose for IV administration}$  and  $G(0) = F \times \text{Dose for oral route}$ .

#### Influence of covariates

Several time-dependent variables were tested, and then included in the response model when they significantly (percent relative standard error (%rse) <50%) modified either  $k_{in}$  (ModKin) or  $k_{out}$  (ModKout) as follows :

$$dHR(t)/dt = M_{od}K_{in} \times k_{in} [1 - IR_{Amio} / (IR_{Amio} + IR_{Amio}50)] - M_{od}K_{out} \times k_{out} HR(t) \quad (5)$$

with

$$M_{od}K_{in} = (1 - t_{MG} MG) \quad (6)$$

$$M_{od}K_{out} = (1 - t_{DOBU} DOBU) (1 + t_{FILL} FILL) (1 + t_{ECV} ECV) (Retro_{HR}) \quad (7)$$

where MG, DOBU, FILL and ECV denote magnesium loading, beta-agonist administration, fluid therapy and electrical cardio-version (only when effectively

restoring sinus rhythm), respectively, with their corresponding  $t_{\text{SUBSCRIPT}}$  influential parameters.

$$\text{where } \text{Retro}_{\text{HR}} = (\text{HR}/\text{HR}_{\text{REF}})^{\text{FRetroHR}} \quad (8)$$

$\text{FRetro}_{\text{HR}}$  denotes the parameter modulating the importance of spontaneous retrocontrol to a reference value,  $\text{HR}_{\text{REF}}$ , depending on the type of cardiac rhythm at the time of first amiodarone administration in ICU.

Several time-independent factors were tested and then included in the response model when they significantly ( $\%rse < 50\%$ ) modified either baseline HR before first amiodarone dose in ICU ( $\text{HR}_{(0)}$ ) or  $k_{\text{out}}$  or  $\text{HR}_{\text{REF}}$  as follows:

$$\text{HR}_{(0)} = 154 \times (\text{Age}/70)^{-0.23} \times [0.85^{(\text{if persistent AT})} \text{ or } 0.67^{(\text{if sinus rhythm})}] \times 0.86^{(\text{if Amio pretreatment})} \quad (9)$$

$$k_{\text{out}} = 0.9 \times 0.37^{(\text{if persistent AT or sinus rhythm})} \quad (10)$$

$$\text{HR}_{\text{REF}} = 78.6 \times 1.73^{(\text{if persistent AT})} \quad (11)$$

Covariates effects on structural parameters were only tested and included if they were physiologically plausible. For example  $\text{HR}_{(0)}$  is known to be faster in patients with AT compared to patients in sinus rhythm, so this covariate effect can be accepted if it is significant.

The inclusion of patients in sinus rhythm was useful for they received the lowest amiodarone doses and thus served to validate the model over a large dose range. These subjects specificities were very well identified during the modeling process, since the ‘‘Sinus rhythm’’ covariate had a significant effect on the three major elements of our model :  $\text{HR}_{(0)}$  (i.e baseline heart rate at the time of amiodarone administration),  $k_{\text{out}}$  and ReferenceHR.

### **Data analysis details**

Data was analyzed using the nonlinear mixed effect modeling software program Monolix version 4.1.3 ([www.lixoft.com](http://www.lixoft.com)). Parameters were estimated by computing the maximum likelihood estimator of the parameters without any approximation of the

model using the stochastic approximation expectation maximization algorithm combined to a Markov Chain Monte Carlo procedure. A combined, proportional plus constant, error model was used to describe residual variability and between-subject variability (BSV) was ascribed to an exponential error model. The Bayesian information criterion (BIC) was used to test different hypotheses regarding the final model, i.e., the covariate effects on parameters, residual variability model (proportional versus proportional plus additive error model), and structure of the variance-covariance matrix for the BSV parameters. Residuals were presented as normalized prediction distribution errors, based on the estimates of unbiased means and variances of the predictions by using 500 Monte Carlo simulations of the final model (the calculation includes a de-correlation step of the prediction errors). The mean of these normalized residues must not be different from 0. Goodness-of-fit plots for the final model of amiodarone pharmacodynamics are represented in Figure 2. Results are expressed as numbers (%), means  $\pm$  standard deviation, or medians (interquartile ranges) as appropriate. A p value  $< 0.05$  was considered significant. Simulation graphics and statistics were derived using the R software program.

## RESULTS

### Patients and Observations

Among the 856 consecutive screened patients admitted to ICU, 97 (11.3%) had received at least one amiodarone dose for AT. Seventeen patients had paced rhythm or incomplete chart and were therefore excluded, leaving 80 patients eligible for analysis [Figure 1]. In these 80 patients, 1348 time-heart rate observations with 361 amiodarone dose administrations were available during a maximum of 6 days after the first dosing in ICU. In our dataset during the observed period, patients with paroxysmal AT (n=47) had heart rate above 115 bpm less frequently than patients with persistent AT (n=25): respectively 37% (261/706) versus 47.7% (224/470) of HR collected (p=0.02). Among patients initially diagnosed with AT in our dataset (n=72), 33 (46%) never returned to sinus rhythm while 39 had at least one ECG in sinus rhythm. Among those latter 39 patients, AT relapsed in 12 patients. Overall, sinus rhythm was restored in only 14 patients (19%) within 24 hours of first amiodarone administration in ICU without recurrence of AT. Electrical cardioversion was delivered to 9 patients and successful in only 4, of whom 2 after several attempts at distinct times of care. Those data confirm the difficulty to achieve and maintain heart rate control or sinus rhythm in clinical practice. More details about heart rate data collection and amiodarone doses are summarized in Table 1. Patients were severely ill, had cardiovascular comorbidities and received amiodarone during their ICU stay mainly for poorly tolerated paroxysmal atrial fibrillation. Dobutamine (10%) or epinephrine (56%) were the only IV catecholamine used. Before first amiodarone administration in ICU, 52 patients were naive of amiodarone pre-treatment (74% patients with paroxysmal AT and 26% with persistent AT) and 28 patients had previously received amiodarone. Thirty patients (37.5%) received magnesium loading

as add-on therapy on top of amiodarone to control heart rate and only two patients received digoxin. The main clinical, demographic and biological patients' characteristics are summarized in Table2. Patients were mainly admitted for cardiogenic shock or sepsis. No stroke was identified during patients stay in ICU. Other treatments received by the patients that could interfere with heart rate control are summarized in Table2.

### **Impact of amiodarone pretreatment and type of atrial tachyarrhythmias on amiodarone doses needed to control heart rate.**

Baseline heart rate before the first administration of amiodarone in ICU (defined as  $HR_{(0)}$ ) was higher (Table3) in amiodarone-naive patients with paroxysmal AT than in amiodarone-pretreated patients with paroxysmal AT or amiodarone-naive patients with persistent AT ( $154 \pm 4$  vs.  $132 \pm 35$  and  $131 \pm 6$  bpm, respectively,  $p < 0.0001$ ).

We modeled the effect of different amiodarone dosing regimen on heart rate reductions in these three different clinical scenarios and took the optimal dosing regimen to achieve a HR of 90 bpm as an example (Figure3). The amiodarone dosages were then extrapolated from these simulations results.

Among patients with paroxysmal AT, slightly higher doses of amiodarone were needed to achieve a heart rate below 115 bpm within the first day and to maintain it around 90 bpm for the 4 subsequent days in amiodarone-naive compared to pretreated patients. This was due to the difference in baseline HR (Figure3A-3B). In silico simulations indicated that the amiodarone dosing regimen to achieve such heart rate control in amiodarone-naive patients with paroxysmal AT should be 300 mg IV loading dose on day 1 plus 800 mg oral dose from day 1 to day 5 (Figure3A). Corresponding doses indicated by the model were slightly lower in patients with paroxysmal AT pretreated by amiodarone: 300 mg IV loading dose on day 1 plus 400 mg oral dose from day 1 to day 5 (Figure3B).

Interestingly, despite lower baseline HR in amiodarone-naive patients with persistent AT, corresponding doses were almost twice those of amiodarone-naive patients with paroxysmal AT (600 mg IV loading dose on day 1 and 1400 mg oral doses from day 1 to day 5, Figure 3C). This relative resistance of persistent AT was associated to a decrease in the amiodarone effect ( $k_{out}$ ) in patients with persistent AT compared to paroxysmal AT (Table3).

### **Impact of dobutamine infusion, electrical cardioversion, magnesium and fluid loading on amiodarone-effect.**

We then assessed the effect of covariates on amiodarone effect. Among the covariates analyzed, electrical cardioversion ( $p<0.05$ ), absence of dobutamine infusion ( $p<0.05$ ), intravenous magnesium ( $p<0.02$ ) and fluid loading ( $p<0.02$ ) had a significant positive impact on amiodarone pharmacodynamics in ICU patients with AT (Appendix1). Use of furosemide, extra-renal dialysis, epinephrine infusion, curare and sedative drugs had no significant impact. Underlying pathologies, hemodynamic conditions, kidney function and baseline clinico-biological values (Table2) had neither significant impact. Figures 3D,E and F show that the use of magnesium and/or fluid loading on the first day were associated with a greater and earlier HR decrease than suggested by amiodarone pharmacodynamic half-life ( $3.33\pm 0.9$  days, Table3). In contrast, efficacy of amiodarone on HR control decreased if dobutamine was used (Figures 3D, E and F).

## DISCUSSION

The present study indicates that amiodarone doses needed to control HR should be almost twice as high in persistent AT compared to paroxysmal AT <sup>[4,19,22]</sup>. Patients who had received amiodarone before first ICU administration required lower doses. Our pharmacodynamic model also showed that the main interventional covariates influencing amiodarone efficacy were dobutamine use, electrical cardioversion, magnesium and fluid loading.

### **A mixed oral and IV loading dose over a few days**

Due to incomplete bioavailability and delayed oral absorption <sup>[19-21]</sup>, a 300 mg IV loading dose is recommended <sup>[4,5]</sup> to rapidly achieve the aimed HR. Thus, the total daily dose that may be given safely is expected to be higher with the oral route, avoiding hypotension, hemodynamic impairment and phlebitis which can specifically occur with IV amiodarone infusion <sup>[4,23-26]</sup>. Oral loading dosing regimen up to 30 to 50 mg/kg over 5 days <sup>[27]</sup> were proved safe and effective. In our model, we therefore chose to test a rapid and safe therapeutic strategy combining IV and oral dosing regimen over 5 days. According to our model, the different proposed dose scheme (300 to 600 mg IV loading dose on day 1 plus 400 to 1400 mg oral dose from day 1 to day 5) in patients with paroxysmal or persistent AT, amiodarone-pretreated or not, agree with the recommended doses <sup>[4,5,18,27]</sup> but provide a more specific approach in each group.

Pharmacologic cardioversion with amiodarone is not effective in the short and medium term. At 24 hours, amiodarone has inconsistently demonstrated increased restoration of sinus rhythm when compared to placebo in some but not all randomized studies <sup>[4,5]</sup>. We therefore, focused on heart rate reduction which is a clinically relevant therapeutic endpoint in critically ill patients <sup>[4,5,10]</sup>.

## **Amiodarone pharmacodynamics in the ICU**

We identified four interventions that influenced amiodarone efficacy in critically ill patients with AT. Dobutamine use was associated with decreased amiodarone efficacy while electrical cardioversion, fluid and magnesium loading were associated with earlier and better HR control.

Fluid therapy, defined as infusion of more than 0.5 liter of saline administered over 30 minutes, was administered to patients with apparent or real hypovolemia and was significantly associated with better HR control. By correcting hypovolemia, reflex tachycardia may have decreased <sup>[28]</sup>. Dobutamine is a beta adrenergic agonist leading to tachycardia and supra-ventricular arrhythmias <sup>[29]</sup> to a greater extent than other catecholamines, such as epinephrine <sup>[30]</sup>. In our model, dobutamine significantly influenced amiodarone pharmacodynamics while this interaction was not found with epinephrine. Interestingly, IV magnesium, which is recommended to prevent post-operative AT <sup>[4,31]</sup> was found to improve HR control of patients with AT treated with amiodarone. Further investigations are required to confirm the present findings before extrapolating our results to other patient populations and procedures for the treatment of AT. Electrical cardioversion (ECV) was rarely used or efficient to restore sinus rhythm in our patients. Ineffective or immediate recurrence of AT after ECV is an important concern in critically ill patients, and even more when AT is persistent <sup>[4]</sup>. ECV success rates as low as 30% are reported in these patients <sup>[32,33]</sup>. Impregnation with antiarrhythmic drugs such as amiodarone increases the probability to restore and maintain sinus rhythm <sup>[4,34,35]</sup>.

There was no significant influence of etiology of shock, sedative and curare drugs on amiodarone efficacy. Neither furosemide administration nor ultrafiltration were identified as significant covariates. We hypothesize that patients treated with these depletive strategies had high pre-therapeutic filling pressures and did not experience

hypovolemia and reactional HR increase<sup>[28]</sup>. Type of atrial tachyarrhythmia was not a significant covariate but caution is needed because patients included in this modelling were mostly patients with atrial fibrillation and few data were available for other types of arrhythmia such as atrial flutter. Amiodarone and its metabolite N-desethylamiodarone are eliminated by hepatic route and marginally by the kidney. In patients on hemodialysis or intermittent peritoneal dialysis, amiodarone and its metabolite were not found in the dialysate<sup>[36]</sup>. In the present study, we did not find any influence of creatinine clearance or extra-renal dialysis on the model parameters. Beta-blockers and verapamil were used exceptionally in this study because of their negative inotropic effects. Digoxin was also very rarely used because of its poor efficacy to rapidly slow HR and of significant interaction with amiodarone that may lead to adverse events<sup>[4,5]</sup>.

### **Limitations**

In this observational study, we may have not taken into consideration other unavailable covariates of interest which may influence drug response. However, this study provides for the first time the basis for designing a future prospective trial of amiodarone dosing in ICU patients with AT. Also, the therapeutic strategy based on our model should now be prospectively tested to compare if a tailored amiodarone dosing strategy according to duration of AT (paroxysmal versus persistent) and other significant covariates (amiodarone pretreatment or not, coadministration of magnesium or not, on/off dobutamine) is more efficient and more convenient (less bradycardia and hypotension issues) to achieve an optimal heart rate control than a lenient strategy relying on physician's decisions without any standardized protocol.

Left atrial volume is inversely correlated to amiodarone dose needed to restore or maintain sinus rhythm after AT<sup>[37]</sup>. To date, influence of left atrial volume on the

ability of amiodarone to control heart rate is still unclear<sup>[18,22,38,39]</sup>. Impact of left atrial size could not be tested in our model due to incomplete data in too many patients.

Plasma levels of amiodarone and its metabolite N-desethylamiodarone, were not tested in our model because amiodarone therapeutic drug monitoring is not recommended<sup>[4,5]</sup> in clinical practice. It is theoretically conceivable that including plasma concentrations of amiodarone and N-desethylamiodarone could have improved our predictions. It is however unlikely since individual plasma concentrations are poorly predictive of pharmacodynamics response<sup>[40,41]</sup>.

Our patients with paroxysmal AT pretreated with amiodarone had very heterogeneous doses before first administration in ICU. Due to our observational design, these pre-admission doses could not be precisely identified. In our model, we found that this covariate significantly influenced baseline HR. Baseline HR in this subgroup of patients were quite scattered ( $132 \pm 35$  bpm) compared to other subgroups and lower than in amiodarone naïve patients with paroxysmal AT ( $154 \pm 3$  bpm). This difference in baseline HR between those latter groups could be explained by the fact that patients pretreated by amiodarone were already under its slowing effect on heart rate. Thus, our recommended doses of amiodarone for this subgroup of amiodarone-pretreated patients with paroxysmal AT was the lowest proposed and will be applicable only if baseline HR are in the 130-135 bpm range. Even lower doses would be needed if this baseline HR is lower than 120 bpm and higher doses would be needed in patients with baseline HR above 140 bpm.

## **Perspectives**

This work, modeling amiodarone efficacy to control HR in critically ill patients with AT, identified several clinically relevant covariates that influenced its pharmacodynamics. Taking into account these covariates might achieve better individualization of amiodarone dosing for poorly tolerated AT in critically ill patients.

Compared to paroxysmal AT, double doses are needed in persistent AT. Amiodarone pretreated patients before ICU admission needed lower doses than amiodarone-naive patients. Correction of hypovolemia, magnesium administration and use of lower dobutamine doses also contributed to a better control of HR.

This study suggests that co-administration of magnesium with amiodarone is associated with a greater and earlier HR control in critically ill patients with AT. Lower amiodarone doses might be needed to slow AT in case of co-administration of magnesium, thereby potentially lowering the incidence of amiodarone adverse events. Administration of high doses of magnesium versus placebo as an adjunct to ibutilide to treat AT, a class III agent, was associated with a higher conversion rate to sinus rhythm and less ventricular arrhythmia <sup>[42]</sup>. To date, prophylactic use of IV magnesium has been shown to reduce the probability of post-operative AT <sup>[31]</sup> but data regarding its efficacy in acute constituted AT remain scarce, particularly when combined with amiodarone. We are planning to further investigate this issue by conducting a prospective study evaluating IV magnesium as add-on therapy to amiodarone to treat AT in critically ill patients.

## **CONCLUSION**

In critically ill patients with AT, our results indicate that doses of amiodarone needed to control heart rate are higher in persistent than in paroxysmal AT. In contrast, patients who had received amiodarone before first ICU administration required lower doses. In critically ill patients, optimization of fluid therapy, decreasing dobutamine infusion as soon as possible and magnesium supplementation may also help control heart rate in AT.

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## **DISCLOSURES**

JES, MEA, MA, JSH, NA, JYLH, CFB, CF, SU declare that they have no conflict of interest.

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## FIGURES AND LEGENDS

### Figure 1. Flow chart of all the screened patients

### Figure 2. Goodness-of-fit plots for the final model of amiodarone pharmacodynamics.

The following data illustrate the robustness of the pharmacodynamic model. You can see the observed versus model-predicted heart rate for individual predictions (A) and normalized prediction distribution errors (NPDE) versus predicted heart rates over time (B). The solid lines represent the identity lines and the dashed blue line represents the regression lines. Correlation between observed and individual predicted heart rate is  $r: 0.84$ . The mean of the NPDE residuals was not significantly different from 0 ( $p: 0.32$ ). Prediction-corrected visual predictive check for heart rate over time in days are presented in figure C. The green lines are the median and quartiles (25<sup>th</sup> and 75<sup>th</sup>) of observed values, with the areas surrounding them representing the 90 % confidence intervals of the corresponding simulated quartiles.

**Figure 3. Model-predicted effect of amiodarone (Amio) on heart rate (HR) in beats per minutes (bpm).**

Shown are the effects in case of paroxysmal atrial tachyarrhythmias (AT) in amiodarone (Amio) naive patients before first administration in ICU (A,D, baseline HR 154 bpm), paroxysmal AT in patients pretreated by Amio (B,E, baseline HR 132 bpm), and persistent AT in patients naive of Amio(C,F, baseline HR 131 bpm). In figure A, B and C, are represented the evolution of HR over five days following several doses of Amio. Shown are the effects for a 300 mg intravenous(IV) loading dose on day 1(D1) combined with a 200/400/600/800/1200 mg (purple, green, light blue, dark blue and dark line respectively) oral dose on the first day followed by an equivalent oral doses for 4 days(D1-5). The orange line represent the effect for a 600 mg IV loading dose on D1 combined with a 1400 mg oral dose on the first day followed by an equivalent oral doses for 4 days(D1-5). Compared to the case of an amio naive patient with paroxysmal AT (A), doses needed to achieve HR between 80 and 115 bpm, are lower in patients with paroxysmal AT pretreated by Amio (B) and higher in amio naive patients with persistent AT Amio(C). In figure A,B and C, the bold line represent the proposed dose scheme to use in clinical practice according to the situation (300/300/600 mg IV loading dose plus 800/400/1400 oral dose respectively in Figure A, B and C). This latter dose scheme (Figure A, B and C) is used in figure D, E and F respectively for further evaluation. In figure D, E and F, are represented the evolution of HR over the first day following a selected Amio dose alone (—) or in case of concomitant dobutamine (DOBU) use (+++), fluid therapy (Fill) over 12 hours (·····) or/and magnesium (Mg) loading over 24 hours: for Mg alone (- - -), for combined Mg and Fill (- · - · -). Use of magnesium or/and fluid loading the first day, as add-on therapy on Amio were associated with a faster and greater HR decrease. Efficacy of Amio on HR control decreased in case of persistent AT or if dobutamine was used.

## TABLES

**Table 1. Heart rhythm characteristics and amiodarone dosing of the 80 patients**

Characteristic	Value
<b>Heart rate</b>	
Total number of HR collected	1348
Median time between consecutive HR collected, <i>hours</i>	5.3(4.1–7.7)
Mean time between consecutive HR collected, <i>hours</i>	6±2.8
Median time between first and last HR collected, <i>days</i>	5.3(3.5–5.9)
Mean time between first and last HR collected, <i>days</i>	4.6±1.8
Minimum/Maximum time between first and last HR collected, <i>days</i>	0.8/6.4
Median number of HR collected by patient	19(12–22)
Mean number of HR collected by patient	16.9±7.3
<b>Amiodarone doses received</b>	
Total number of amiodarone administrations	361
Patients with at least 1 IV dose/First dose delivered IV	15(19%)/11(14%)
Median amiodarone dose (IV route), <i>mg/dose</i>	300 (175–300)
Minimum/Maximum amiodarone dose (IV route), <i>mg/dose</i>	150/300
Minimum/Maximum amiodarone dose (IV route), <i>mg/day</i>	150/600
Patients with at least 1 oral dose / Nasogastric tube (≥ 1 dose)	76(95%)/51(64%)
Median amiodarone dose (oral), <i>mg/dose</i>	400 (200–1200)
Minimum/Maximum amiodarone dose (oral), <i>mg/dose</i>	100/2400
Minimum/Maximum amiodarone dose (oral), <i>mg/day</i>	100/4200
Median time between each dose, <i>days</i>	0.94(0.49–1.01)

*Abbreviations:* HR, Heart rate; IV, intravenous; mg, milligram

*Statistics:* Values are given as the mean ± standard deviation, median (interquartile range 25-75) or number (%).

**Table 2. Main Characteristics of the 80 patients studied**

Characteristic	Value
<b>Demographic status and comorbidities</b>	
Age, year	75±13
Male sex	44(55%)
Body weight, kilogram	72±20
Diabetes/Hypertension	20(25%)/41(51%)
Coronary ischemic disease	36(45%)
Previous history of cardiac insufficiency	31(39%)
Previous history of supra-ventricular tachyarrhythmia	22(28%)
Chronic obstructive pulmonary disease	23(29%)
Chronic renal insufficiency (Clearance <60ml/min/m <sup>2</sup> )	19(24%)
APACHEII/SAPSII at admission in ICU	27±9/59±20
ICU mortality	39(49%)
<b>Bio-clinical values at first administration of amiodarone in ICU</b>	
Mean arterial pressure <65mmHg	29(36%)
Body Temperature, (°Celsius, eardrum)	37.1(36.4–38%)
Non-invasive/invasive mechanical ventilation	9(11%) / 43(54%)
Cardiac systolic dysfunction (Ejection fraction<45%)	31(39%)
Sepsis	35(44%)
Paroxysmal/persistent atrial tachyarrhythmia	47(59%)/25(31%)
Sinus rhythm	8(10%)
pH	7.4(7.26–7.43)
P <sub>a</sub> O <sub>2</sub> (mmHg)	85(72-100)
Na <sup>+</sup> (mmol/l)	137.5(135-141)
K <sup>+</sup> (mmol/l)	3.7(3.2-4.6)
Hemoglobin	10.9(9.1–12)

Creatinine clearance ( <i>ml/min/m<sup>2</sup></i> )	22(44-74.3)
Total bilirubin ( <i>mmol/l</i> )	14(8-26)
TSH (mUi/L)*	1.57 (1.2-4)

**Prior antiarrhythmic treatment before first administration of amiodarone in ICU**

Chronic antiarrhythmic treatment recently withdrawn	30(37.5%)
Chronic amiodarone intake ( <i>&gt;1 month of continuous intake</i> )	14(17.5%)
Sub-acute amiodarone pre-treatment ( <i>&lt;4 grams in the last month</i> )	14(17.5%)
Amiodarone-naive ( <i>&gt;3 months without amiodarone</i> )	52(65%)

**Additional treatments after first amiodarone administration in ICU**

Attempted/Successful electrical cardioversion	9(11%) / 4(5%)
Magnesium loading	30(37.5%)
Catecholamine ( $\beta$ -agonists) : Dobutamine/Salbutamol	8(10%) / 2(2.5%)
Catecholamine ( $\alpha$ and $\beta$ -agonist) : Epinephrine	45(56%)
Catecholamine ( $\alpha$ agonist) : Norepinephrine	0(0%)
Fluid loading / duration longer than 12 hours	54(67.5%) / 11(14%)
Renal replacement therapy/Diuretics	20(25%) / 40(50%)
Sedative drugs/Curare	44(55%) / 20(25%)
Other anti-arrhythmic (digoxin, beta blocker, verapamil)	2(2.5%), 1(1%), 1(1%)

*Abbreviations:* APACHEII, Acute Physiology And Chronic Health Evaluation at intensive care unit admission; ICU, intensive care unit ; SAPSII, simplified acute physiology score at intensive care unit admission

*Statistics:* Values are given as the mean  $\pm$  standard deviation, median (interquartile range 25-75) or number (%).

\* TSH was available in 35 subjects within 10 days before first administration of amiodarone in ICU. Among them, none had a TSH below lower normal limit [ $<0.2$  mUi/L] and three had a TSH above upper normal limit [ $>5.2$ mUi/L].

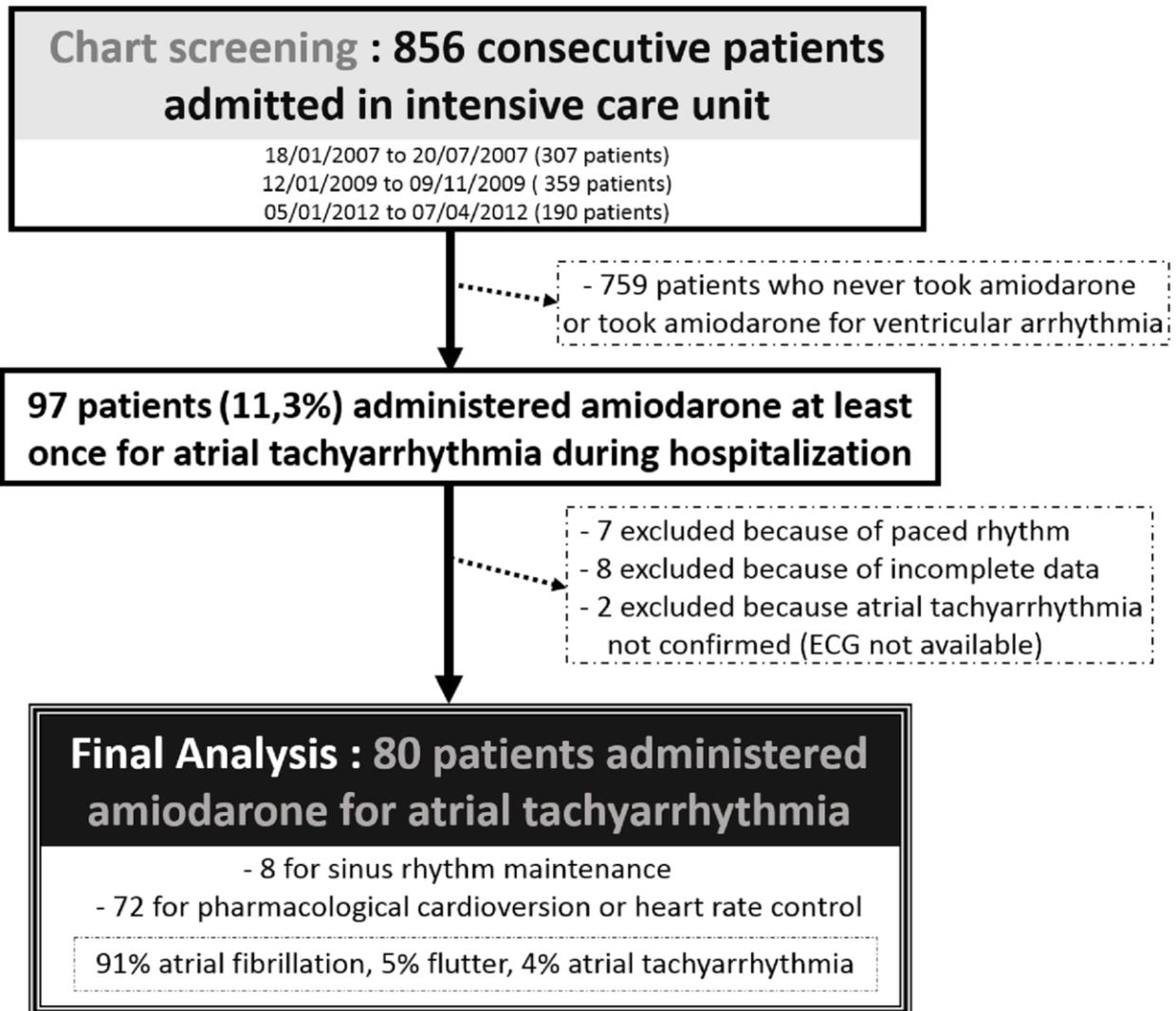
**Table 3. Parameter estimates of the final model of amiodarone effect on heart rate in the 80 critically ill patients studied**

Parameter	Estimate (%rse)	Group Value, units (%rse)	BSV (%rse)
<b>Pharmacodynamic Half-life</b> [Log(2)/KDE], <i>day</i>	3.33 (27)	<b>3.33</b> days (27)	NA
<b>HR<sub>(0)</sub></b> , (if <b>Parox AT</b> , <b>amiodarone naive</b> ), <i>bpm</i>	154 (3)	<b>154</b> bpm (3)	0.14 (11)
× by <b>Age</b> effect, [(Age/70) <sup>-0.23</sup> ]	-0.23 (41)		
× if <b>Persistent AT</b> [vs parox AT]	0.85 (27)	<b>131</b> bpm (4)	
× if <b>Sinus rhythm</b> [vs parox AT]	0.67 (18)	<b>103</b> bpm (20)	
× × if <b>pretreated Amio</b> [vs Amio naive]	0.86 (29)	<b>132</b> bpm (26)	
<b>k<sub>out</sub></b> (if <b>Parox AT</b> ), <i>day<sup>-1</sup></i>	0.9 (28)	<b>0.9</b> day <sup>-1</sup> (28)	1.42 (13)
× if <b>Persistent AT</b> or sinus rhythm [vs parox AT]	0.37 (48)	<b>0.33</b> day <sup>-1</sup> (NA)	
<b>Reference HR</b> , (if <b>Parox AT</b> or <b>sinus rhythm</b> ), <i>bpm</i>	78.6 (20)	<b>78.6</b> bpm (20)	0.8 (11)
× if <b>Persistent AT</b> [vs parox AT]	1.73 (47)	<b>136</b> bpm (29)	
<b>FRetro<sub>HR</sub></b>	0.46 (21)		NA
<b>Amio<sub>50</sub></b> , <i>mg/day</i>	291 (29)		NA
<b>t<sub>MG</sub></b>	0.4 (32)		
<b>t<sub>FILL</sub></b>	0.31 (31)		
<b>t<sub>ECV</sub></b>	0.37 (31)		
<b>t<sub>DOBU</sub></b>	0.26 (46)		
<b>Residual variability</b> , <i>bpm</i>	16 (2)		

*Abbreviations:* **AT** = Atrial fibrillation; **Amio<sub>50</sub>** = Amiodarone dosage that induces 50% of putative maximal effect on HR reduction; **DOBU** = beta-agonist administration; **bpm** = beats per minute; **BSV** = between-subject variability; **ECV** : electrical cardio-version; **FILL** = fluid therapy; **FRetro<sub>HR</sub>** = factor determining the importance of endogenous spontaneous retrocontrol of the HR to a reference HR depending on the type of cardiac rhythm at the time of first administration of amiodarone in ICU; **HR<sub>0</sub>** = heart rate at t<sub>0</sub> before first amiodarone dosing in ICU; **ICU** = intensive care unit; **KDE** = rate constant describing the equilibrium between the administration rate and the observed effect, **k<sub>out</sub>** = first-order constant rate for Amio effect kinetics; **%rse** = percent relative standard error; **NA** = not applicable; **MG** = magnesium loading; **Parox** = Paroxystic atrial tachyarrhythmia which started less than one

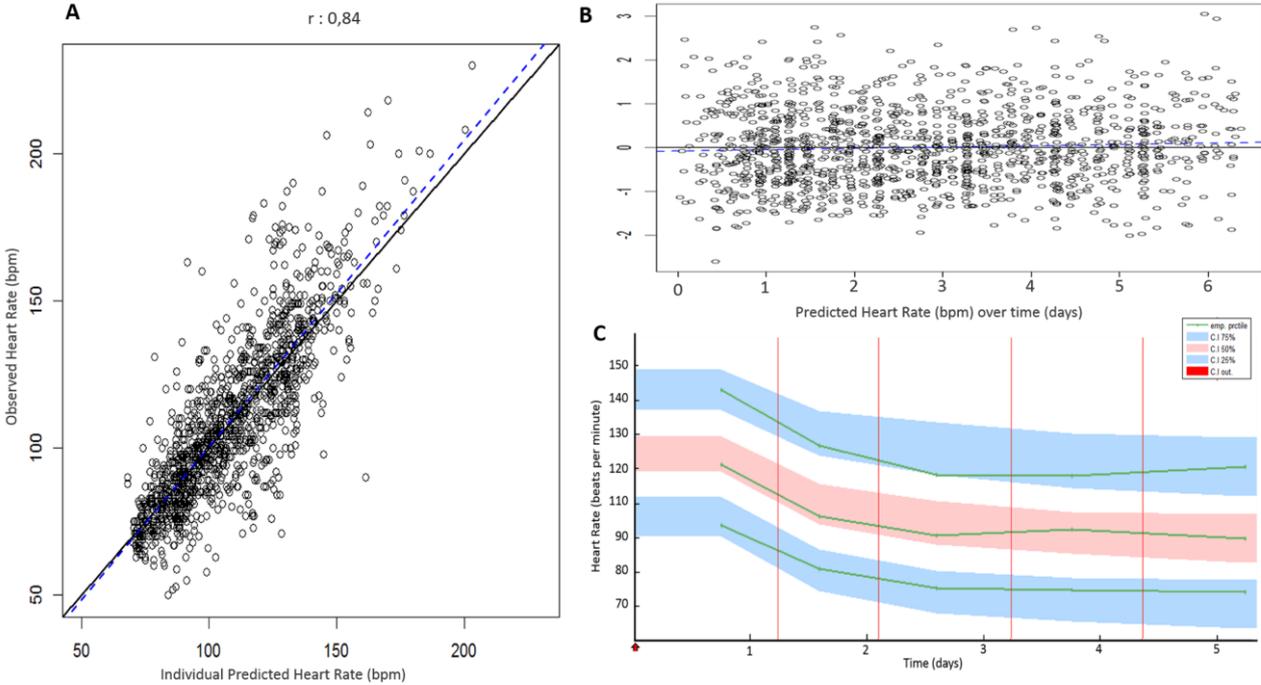
week before the first amiodarone administration in ICU; **Reference HR** = Estimated heart rate that the subject tend to reach spontaneously by endogenous retrocontrol; **vs** = versus.

**FIGURE 1**



Abbreviation : ECG , Electrocardiogram

**FIGURE 2**



**FIGURE 3**

