

## ANESTHESIOLOGY

# Timing of $\beta$ -Blocker Reintroduction and the Occurrence of Postoperative Atrial Fibrillation after Cardiac Surgery

## A Prospective Cohort Study

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### EDITOR'S PERSPECTIVE

#### What We Already Know about This Topic

- $\beta$ -blockers are usually stopped in cardiac surgical patients
- When best to reintroduce them remains unknown, and is a trade-off between hemodynamic risk and development of atrial fibrillation

#### What This Article Tells Us That Is New

- There was little advantage to reintroducing  $\beta$ -blockers within 48 h
- The odds of atrial fibrillation were significantly reduced by restarting  $\beta$ -blockers between 72 and 96 h after surgery

Many patients who undergo surgical procedures receive chronic cardiovascular medication that must

### ABSTRACT

**Background:** For cardiac surgery patients under chronic  $\beta$ -blocker therapy, guidelines recommend their early postoperative reintroduction to decrease the incidence of postoperative atrial fibrillation. The authors hypothesized that the timing of  $\beta$ -blocker reintroduction affects their effectiveness on the incidence of postoperative atrial fibrillation.

**Methods:** This multicenter prospective French cohort study included patients on  $\beta$ -blockers (more than 30 days before surgery) in sinus rhythm without a pacemaker. The primary outcome, time sequence of  $\beta$ -blocker reintroduction, was analyzed for 192 h after surgery. The secondary outcome, relationship between the occurrence of postoperative atrial fibrillation and timing of  $\beta$ -blocker reintroduction, was analyzed based on pre- and intraoperative predictors (full and selected sets) according to landmark times (patients in whom atrial fibrillation occurred before a given landmark time were not analyzed).

**Results:** Of 663 patients,  $\beta$ -blockers were reintroduced for 532 (80%) but for only 261 (39%) patients in the first 48 h after surgery. Median duration before reintroduction was 49.5 h (95% CI, 48 to 51.5 h). Postoperative atrial fibrillation or death (N = 4) occurred in 290 (44%) patients. After performing a landmark analysis to take into account the timing of  $\beta$ -blocker reintroduction, the adjusted odds ratios (95% CI) for predictor full and selected (increased age, history of paroxysmal atrial fibrillation, and duration of aortic cross clamping) sets for the occurrence of postoperative atrial fibrillation were: adjusted odds ratio (full) = 0.87 (0.58 to 1.32;  $P = 0.517$ ) and adjusted odds ratio (selected) = 0.84 (0.58 to 1.21;  $P = 0.338$ ) at 48 h; adjusted odds ratio (full) = 0.64 (0.39 to 1.05;  $P = 0.076$ ) and adjusted odds ratio (selected) = 0.58 (0.38 to 0.89;  $P = 0.013$ ) at 72 h; adjusted odds ratio (full) = 0.58 (0.31 to 1.07;  $P = 0.079$ ) and adjusted odds ratio (selected) = 0.53 (0.31 to 0.91;  $P = 0.021$ ) at 96 h.

**Conclusions:**  $\beta$ -Blockers were reintroduced early (after less than 48 h) in fewer than half of the cardiac surgery patients. Reintroduction decreased postoperative atrial fibrillation occurrence only at later time points and only in the predictor selected set model. These results are an incentive to optimize (timing, doses, or titration)  $\beta$ -blocker reintroduction after cardiac surgery.

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be managed during the perioperative period. For patients under chronic  $\beta$ -blocker therapy, reintroduction of  $\beta$ -blockers as soon as possible after cardiac<sup>1</sup> and noncardiac<sup>2</sup> surgeries is a grade 1 recommendation and is followed by many institutions and clinicians.<sup>3</sup> Early reintroduction of  $\beta$ -blockers is supposed to attenuate the deleterious effects of excessive sympathetic nervous system activation after surgery.<sup>4</sup>

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In cardiac surgery, postoperative reintroduction of  $\beta$ -blockers is one of the few modifiable risk factors to prevent the occurrence of transient postoperative atrial fibrillation that concerns up to 47% of patients.<sup>5</sup> Prevention of transient postoperative atrial fibrillation is important because its occurrence is independently associated with increased morbidity (namely, stroke), length of stay, and mortality in the immediate postoperative period.<sup>5</sup> Similar statistical associations between transient postoperative atrial fibrillation and morbidity/mortality have been found in noncardiac surgery.<sup>3</sup> Interestingly, transient postoperative atrial fibrillation is also associated with long-term mortality,<sup>6</sup> despite the fact that fewer than 2% of the patients with transient postoperative atrial fibrillation included in a trial were discharged from the hospital with persistent atrial fibrillation.<sup>7</sup>

The relationship between postoperative reintroduction of  $\beta$ -blockers after cardiac surgery and the risk of postoperative atrial fibrillation was investigated in several studies. Mathew *et al.*<sup>8</sup> showed that  $\beta$ -blocker withdrawal after cardiac surgery increased the risk of postoperative atrial fibrillation (odds ratio = 1.91; 95% CI, 1.52 to 2.4). In a more recent article from the same group, similar findings were reported.<sup>9</sup>

Guidelines stipulate that reintroduction of  $\beta$ -blockers should respect contraindications<sup>1</sup> but make no specific statements on the timing of the reintroduction other than “as early as possible.” In the majority of published studies, the time sequence of reintroduction was not explicitly addressed; the reintroduction of  $\beta$ -blockers (oral route) may have a delayed effect related to the much lower postoperative bioavailability of oral as compared with intravenous  $\beta$ -blockers.<sup>10</sup> Furthermore, the nonreintroduction of  $\beta$ -blockers could be explained by the use of catecholamines that have been shown to be independently associated with an increased risk of postoperative atrial fibrillation<sup>11</sup>; other contraindications to  $\beta$ -blocker reintroduction may exist. Finally, side effects of  $\beta$ -blocker reintroduction, such as arterial hypotension with the associated risk of stroke, have to be considered.<sup>12</sup>

Given the widely accepted guidelines-based reintroduction of  $\beta$ -blockers after cardiac surgery but the persistent issues such as those enumerated above, we investigated several aspects of the  $\beta$ -blocker reintroduction after cardiac surgery. We hypothesized that the effectiveness of  $\beta$ -blocker reintroduction in preventing transient postoperative atrial fibrillation may be dependent on the temporal relationship between  $\beta$ -blocker reintroduction and postoperative atrial fibrillation occurrence in the first 192 h after cardiac surgery.

The main goals of this study were to describe the time sequence of  $\beta$ -blocker reintroduction after cardiac surgery with the reason for delayed reintroduction and also to identify potential predictive factors of postoperative atrial fibrillation occurrence with the estimated association between timing of  $\beta$ -blocker reintroduction and postoperative atrial fibrillation occurrence.

## Materials and Methods

### Study Design and Oversight

This is a prospective cohort study performed in three French academic hospitals performing collectively more than 3,000 cardiac surgery procedures per year. It was approved by the Bichat–Claude Bernard Hospital (AP-HP.Nord, Paris, France) institutional review board (CEERB 215-11).

### Inclusion Criteria

Between November 2011 and March 2013, we included patients aged more than 18 yr on chronic  $\beta$ -blocker therapy (at least 30 days before surgery based on their medical record) who were in sinus rhythm, had no pacemaker, and were scheduled for coronary, valve, or combined surgery. Written informed consent was obtained from all the patients. Patients were followed for 192 h (8 days) after cardiac surgery, and the vital status was recorded at 30 days after surgery (telephone interview).

### Management of Anesthesia, Cardiopulmonary Bypass, and Postoperative Care

There was no attempt to homogenize anesthetic, surgical, cardiopulmonary bypass (CPB) procedures in the three centers. Preoperative  $\beta$ -blockers were given on the morning of surgery (7:00 AM). All other chronic medications (including statins) were given the day before surgery. Monitoring techniques used in all patients included five-lead electrocardiography, invasive arterial pressure, and central venous catheter. Additional monitoring concerned pulmonary artery catheters and transesophageal echocardiography as required and per center protocols.

Anesthesia was induced and maintained with etomidate, propofol with sufentanil or remifentanil as opioids given by target controlled infusion. The hypnotic component of anesthesia was titrated using frontal electroencephalography (Bispectral Index [BIS], Medtronic, USA) aiming to maintain BIS values between 40 to 60. Muscle relaxation was obtained with atracurium. Tranexamic acid was routinely used with a bolus after induction of anesthesia and a continuous infusion.

Cardiopulmonary bypass was performed in normothermia. Myocardial protection was performed with intermittent antegrade or retrograde warm blood cardioplegia. Ephedrine or phenylephrine were given as bolus as required to maintain mean arterial blood pressure at values between 60 to 80 mmHg before and during CPB. Perioperative prescription of inotropes, inodilators, vasoconstrictors, and vasodilators followed each institution’s protocol.

All patients were admitted to the postcardiac surgery intensive care unit (ICU) where postoperative care was delivered by anesthesiologists/intensivists trained in cardiac surgery. Sedation with propofol was initiated in the operation room before transfer to the ICU and was stopped when extubation was anticipated according to the institutional

protocols. Postoperative analgesia was initiated with intravenous acetaminophen and intravenous or subcutaneous morphine. Standard care included intravenous magnesium sulfate (1.5 to 3 g/day), glycemic control with intravenous/subcutaneous insulin, and chest physiotherapy.

For reintroduction of chronic medication, including  $\beta$ -blockers, in the postoperative period, there were no specific changes for the study, and physicians (in the ICU and on the ward) followed institutional or international guidelines.  $\beta$ -Blockers were reintroduced orally (no intravenous reintroduction) at the dose decided by the clinicians (in the majority of cases it was the preoperative dose). The treatment of postoperative atrial fibrillation followed international guidelines.<sup>13</sup> Amiodarone was routinely used to prevent recurrence of postoperative atrial fibrillation, and there was no requirement for the physicians to change their clinical practice because of the study.

### Data Collection

Data on patients were collected prospectively in real-time on a specific case report form by research technicians assisted by the principal investigator of each center and centralized by the data management team in Bichat Hospital. Physicians who were in charge of the routine care were informed on the ongoing study but were blinded to the research data.

### Data on $\beta$ -Blockers and Other Drug Reintroduction

The dates/hours of administration of  $\beta$ -blockers and other drugs were determined from the nurses' records or hospital information systems where available. We recorded the last preoperative (date, hour) intake and the first postoperative (date, hour) oral intake of  $\beta$ -blockers.

### Data on Atrial Fibrillation Episodes

Postoperative atrial fibrillation during the first 192 postoperative hours was identified from the continuous electrocardiography tracings while the patients were in the ICU or after discharge from the ICU, from the clinical examination, heart rate measurements, electrocardiogram, and the medical records. The duration of atrial fibrillation was defined by the first documented onset and the first documented return to sinus rhythm.

For each episode (first and recurrent) of atrial fibrillation, the onset and end of the episode and the drugs that were prescribed ( $\beta$ -blockers, amiodarone, digoxin, magnesium sulfate or potassium, unfractionated or low molecular weight heparin, cardioversion) were recorded.

### Data on Potential Covariates for Postoperative Atrial Fibrillation Prediction

We chose the covariates as predictive factors for postoperative atrial fibrillation occurrence according to the Mathew *et al.*<sup>8</sup> study and the chronologic status: preoperative, intraoperative, and postoperative surgery data. The collected

preoperative data were: demographic, anthropometric as well as medical and surgical history, cardiac disease and main reasons for surgery; preoperative hemodynamic variables; preoperative hemodynamic variables; information on chronic preoperative medication with drugs other than  $\beta$ -blockers (angiotensin converting enzyme inhibitors or angiotensin receptor antagonists; calcium channel blockers, statins, diuretics, antiplatelet agents, amiodarone, oral antidiabetics and insulin); routine preoperative hematology and biochemistry data. The collected intraoperative data were the type of surgery, the duration of CPB, and aortic cross-clamping; types (but not the doses) of drugs used for anesthesia; doses of unfractionated heparin, protamine, the lowest mean arterial pressure during CPB as well as the cumulative doses of vasoconstrictors injected during anesthesia and CPB; the number of red blood cells and fresh frozen plasma units given during surgery.

After surgery we collected information on the use (dose, duration) of catecholamines or inodilators, the use of intra-aortic balloon pump or extracorporeal life support, the use of temporary pacemakers and the mode, the first postoperative prescription (date, hour) of calcium channel antagonists, amiodarone, other antiarrhythmia agents, angiotensin converting enzyme inhibitors, or angiotensin receptor II antagonists, diuretics, antiplatelet agents and anticoagulants, and the most abnormal postoperative values of routine hematology and biochemistry values. Postoperative complications requiring interventions (hypoxemia, hyperthermia, stroke or transient ischemic attack, surgical reintervention, initiation of antibiotic therapy, or death) were recorded. The three lowest and the three highest heart rate values on the day before surgery and daily during the first 192 postoperative days were also collected.

### Endpoints and Assessment

The primary endpoints for the study were the delay of the postoperative reintroduction of  $\beta$ -blockers and the reasons for delayed or nonreintroduction of  $\beta$ -blockers. The physicians were asked to choose one or several items from the following list: use of catecholamines, occurrence of arterial hypotension defined as systolic arterial pressure less than 90 mmHg, bradycardia defined as heart rate less than 50 beats per minute or of high degree atrioventricular bloc, anticipated risk of low cardiac output, history or occurrence of bronchial hyperreactivity, stroke in the presence of documented carotid artery stenosis greater than 70%, peripheral vascular disease, or concomitant use of amiodarone or other antiarrhythmic drugs.

The secondary endpoint was the number of episodes of postoperative atrial fibrillation with their chronology. The postoperative reintroduction of  $\beta$ -blockers and the reintroduced concomitant drugs were used as exposure variables for the prediction of the secondary endpoint according to the set of the potential predictive factors

The prescription of catecholamines and the heart rate values during the follow-up were assessed to estimate the clinical effect of chronic  $\beta$ -blockade and of  $\beta$ -blocker reintroduction.

## Statistical Methods

We calculated the sample size on the occurrence of postoperative atrial fibrillation after cardiac surgery (secondary endpoint). Given the 30% estimated incidence of atrial fibrillation and the 21 explanatory selected variables by Mathew *et al.*,<sup>8</sup> with 10 events per covariable this would require 210 events; 210 events divided by the odds of occurrence of postoperative atrial fibrillation results in  $210/0.3 = 700$  patients in total.

All statistical analyses were performed by a dedicated statistician using software SAS 9.4 (SAS Institute Inc., USA). A statistical analysis plan was produced before accessing the data; a predictor full set based on the collected available data was defined. For quantitative variables, descriptive statistics used mean and SD or median and interquartile range according to their distribution. Discrete variables are presented as number and percentages. Odds ratios are presented with the 95% CI. Missing data were not replaced.

For the first objective, delay before  $\beta$ -blocker postoperative reintroduction, the median duration (in hours) between the last preoperative and the first postoperative administration of  $\beta$ -blockers in the first postoperative 192 h was estimated by the Kaplan–Meier method with the CI of 95%. The patients who died during the first 192 postoperative hours were censored at their date of death, and the patients who did not have  $\beta$ -blockers reintroduced before 192 h were censored at 192 h. The reasons of delayed reintroduction were described according to the timing of  $\beta$ -blocker reintroduction.

To identify potential predictive factors of postoperative atrial fibrillation (or death) occurrence (during the first postoperative 192 h), first, a multiple logistic regression model was employed using pre- and intraoperative predictors full set with all included patients. A stepwise selection method with preselective predictors full set in univariate analysis with nominal two-tailed  $P$  less than 0.20 was used to determine the predictor selective set. This selection included interaction terms to evaluate collinearity to limit confounder covariates.

The association between the postoperative reintroduction of  $\beta$ -blockers and the postoperative atrial fibrillation (or death) occurrence was assessed by a logistic regression then adjusted on the predictor full set and on the predictor selective set.

Subsequently, to evaluate the timing of  $\beta$ -blocker reintroduction and postoperative atrial fibrillation (or death) occurrence, landmark analysis<sup>14</sup> was performed at four postoperative times, 24, 48, 72 and 96 h. The consideration of the temporality problem (landmark time) was related to

the fact that if reintroduction of  $\beta$ -blockers is to prevent the occurrence of postoperative atrial fibrillation, the reintroduction of  $\beta$ -blockers must precede the occurrence of postoperative atrial fibrillation (or death). It was therefore necessary to exclude from the logistic regression model the patients who already had an occurrence of postoperative atrial fibrillation before the landmark time.

We performed the same analysis at each landmark time by a logistic regression adjusted on the predictor full set and on the predictor selective set according to the decreased number of patients in whom postoperative atrial fibrillation had already occurred.

No multiple test correction was performed using multiple logistic models. Each model was evaluated using the Hosmer–Lemeshow goodness-of-fit test and the area under the receiver operating characteristic curve. The adjusted on the predictor full set analysis was a *post hoc* sensitivity analysis.

The same process was also performed for the concomitant postoperative prescription of diuretics, angiotensin converting enzyme inhibitors or angiotensin receptor II antagonists, statins, amiodarone, and catecholamines.

The heart rate values were displayed graphically with box and whisker plots on each recorded day (to preoperative day until day 8). A linear mixed effects model was performed to analyze the relationship between reintroduction of  $\beta$ -blockers and the heart rate values.

## Results

Seven hundred two patients were screened for eligibility, and 663 patients were included for analysis (fig. 1). All patients were followed-up in the ICU and on the ward for 192 h after the end of surgery (except those deceased). Patients' characteristics with comorbidities, chronic preoperative medications, cardiac diseases, and types of surgery are shown in table 1.

### Timing of Reintroduction of the $\beta$ -Blockers

During the first 192 postoperative hours, 532 (80.2%) of 663 patients had reintroduction of the  $\beta$ -blockers (see types and doses of reintroduced  $\beta$ -blockers in Supplemental Digital Content 1, <http://links.lww.com/ALN/C134>). For 402 (60.6%) of 663 patients, the  $\beta$ -blockers were not reintroduced at the end of the first 48 h after the end of surgery. The reasons for nonreintroduction of  $\beta$ -blockers are detailed in table 2. Among the 271 (40.9%) of 663 patients for whom  $\beta$ -blockers were reintroduced but after the end of first 48 h, the reasons of delayed reintroduction were only specified for 133 (20.1%) patients (table 2); for 138 (20.8%) patients no reasons were documented. The major reason for delayed or nonreintroduction was the use of catecholamines.

The median duration before reintroduction of  $\beta$ -blockers for all 663 patients was 54 h (95% CI, 52 to 56 h), estimated by using the Kaplan–Meier method. For the 551 (83.1%) of 663 patients who had  $\beta$ -blockers reintroduced

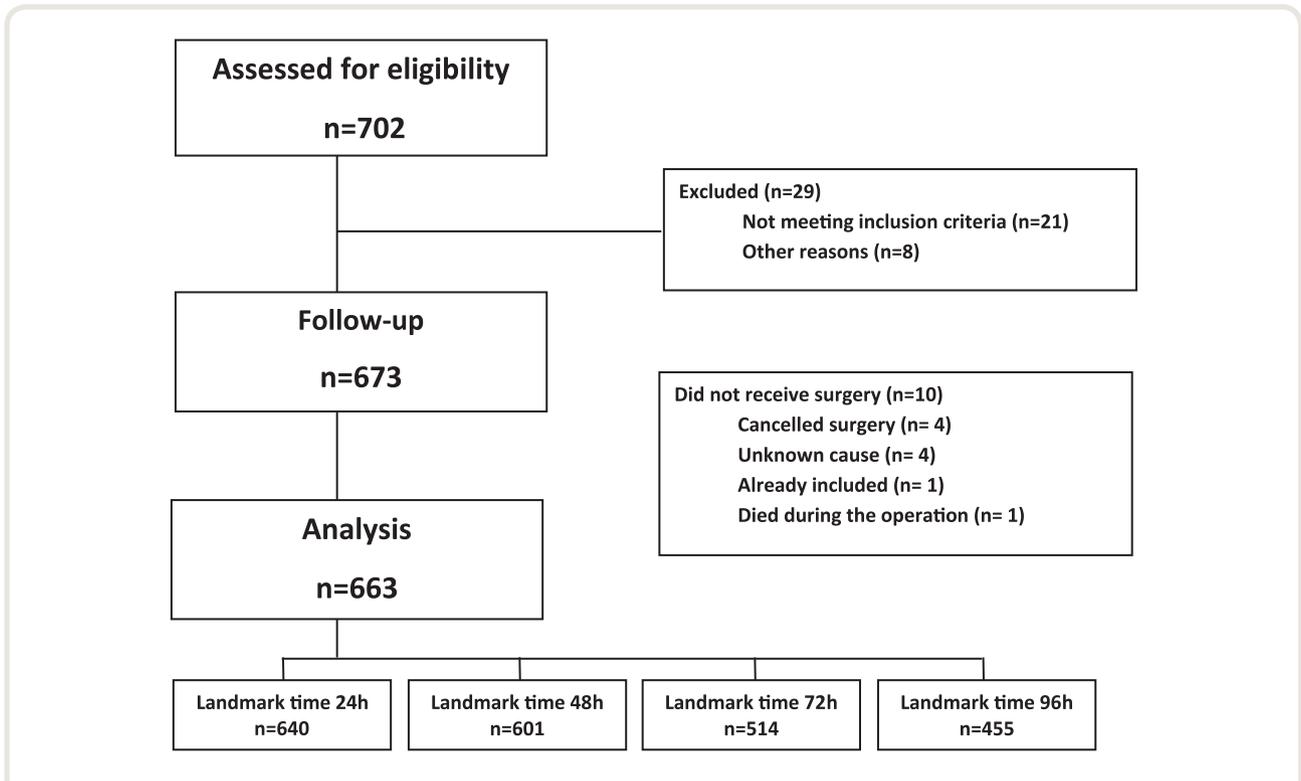


Fig. 1. Patient flowchart of the cohort study.

during follow-up (day 30), the median duration before reintroduction of β-blockers was 49.5 h (95% CI, 48 to 51.5 h), estimated by using the Kaplan–Meier method. The time to reintroduction of β-blockers is shown in figure 2a.

### Chronology of the First Episode of Postoperative Atrial Fibrillation or Death

Transient postoperative atrial fibrillation occurred in 286 (43%) of 663 patients during the study; 190 patients had one episode of postoperative atrial fibrillation, 74 patients had two episodes, and 22 patients had three episodes. There were seven deaths (2%) during the first 192 postoperative hours, of which four were before the first postoperative atrial fibrillation episode and three were after the first postoperative atrial fibrillation. The time to first postoperative atrial fibrillation occurrence or death (N = 4; 290 [44%] of 663 patients) is shown in figure 2b with a median time to occurrence of first postoperative atrial fibrillation of 60 h (interquartile range, 48 to 76 h).

### Prescription of Catecholamines

Among the 356 of 663 patients who received at least one catecholamine (90% the same day of their surgery), postoperative atrial fibrillation (N = 165) or death (N = 4) occurred in 169 (47.5%) patients. The median duration of catecholamine treatment was 21.8 h (interquartile range,

10.0 to 44.6 h). The median delay between the end of postoperative administration of catecholamine and the reintroduction of β-blockers for patients who received at least one catecholamine and for whom β-blockers were reintroduced was 35.6 h (interquartile range, 20 to 59.8 h; data available for 257 of 269 patients). For the 307 patients who did not receive catecholamines, postoperative atrial fibrillation (no death) occurred in 121 patients (39.4%). In univariate analysis, the odds ratio of having at least one episode of postoperative atrial fibrillation or death when given catecholamines was 1.39 (95% CI, 1.02 to 1.89; *P* = 0.037; chi-square; Supplemental Digital Content 1, <http://links.lww.com/ALN/C134>).

### Postoperative Heart Rate Values

To estimate the effectiveness of β-blocker reintroduction, we analyzed the highest heart rate values during the 192 h of the study (fig. 3). The results demonstrate persistently increased postoperative heart rate values with wide interpatient variability and a statistically significant (*P* < 0.0001) change in heart rate values related to β-blocker reintroduction (with a significant [*P* < 0.0001] interaction between time and groups: β-blockers reintroduced vs. β-blockers not reintroduced) only after 96 h.

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**Table 1.** Characteristics of the 663 Included Patients, Comorbidities, Chronic Preoperative Medication, Main Cardiac Diseases, and Surgical Procedures

	Groups	
Demographic and anthropometric data		
Gender	Male	497 (74.9%)
Age, yr (NA = 1)	≤ 65	294 (44.3%)
	65-75	202 (30.5%)
	≥ 75	166 (25.0%)
Weight, kg		78.4 ± 16.2 [32.0–180.0]
BMI, kg/m <sup>2</sup>		26.7 ± 4.8 [13.0–48.0]
Comorbidities		
History of cerebral vascular accident		35 (5.2%)
History of transient ischemic attack		23 (3.4%)
Chronic heart failure		64 (9.6%)
Unstable angina		150 (22.6%)
History of myocardial infarction		161 (24.2%)
History of arterial hypertension		463 (69.8%)
Dyslipidemia		476 (71.7%)
Historic of tobacco 1 yr before surgery		241 (36.3%)
Any use of tobacco	Never	300 (45.2%)
	Active	122 (18.4%)
	Weaned	241 (36.3%)
History of alcohol consumption		49 (7.3%)
History of paroxysmal atrial fibrillation (NA = 3)		50 (7.5%)
Peripheral vascular disease		82 (12.3%)
Type 1 diabetes (NA = 1)		62 (9.3%)
Type 2 diabetes		167 (25.1%)
Previous coronary artery surgery		22 (3.3%)
Previous valve surgery		45 (6.7%)
Previous carotid artery surgery		15 (2.2%)
Previous vascular surgery		70 (10.5%)
History of treated thyroid disease		44 (6.6%)
Chronic preoperative medications		
β-Blockers		663 (100%)
Statins		514 (77.5%)
Diuretics		261 (39.3%)
Amiodarone		31 (4.6%)
Angiotensin-converting enzyme inhibitors		279 (42.1%)
Cardiac diseases		
Ischemic heart disease		441 (66.5%)
Aortic stenosis		181 (27.3%)
Aortic regurgitation		63 (9.5%)
Mitral valve stenosis		22 (3.3%)
Mitral valve regurgitation		83 (12.5%)
Tricuspid valve regurgitation		20 (3.0%)
Pulmonary valve abnormalities		1 (0.1%)
Other types of cardiopathy		105 (15.8%)
Endocarditis		8 (1.2%)
Surgical procedures		
Scheduled surgery		648 (97.7%)
Urgent surgery (< 24 h)		8 (1.2%)
At least one previous surgical intervention		51 (7.7%)
Surgery		
Isolated coronary artery bypass graft		339 (51.2%)
Isolated valve surgery		117 (17.6%)
Coronary artery bypass graft and valve surgery or other surgical procedures		207 (31.2%)
Duration of cardiopulmonary bypass, min (NA = 3)		71.9 ± 36.5 [18.0–370.0]
Duration of aortic cross, min (NA = 5)		56.0 ± 26.4 [0.0–228.0]

Data are presented as N (%) or mean ± SD [minimum–maximum]. NA, not available.

### Relationship between Pre- and Intraoperative Independent Variables and Occurrence of Postoperative Atrial Fibrillation

The results on the univariate and predictor full set association between the first postoperative atrial fibrillation occurrence and the selected pre- and intraoperative predictors are presented in the Supplemental Digital Content 2, <http://links.lww.com/ALN/C141>. In the multiple logistic regression model based on the univariate selection, three predictors were associated with the occurrence of postoperative atrial fibrillation or death during the first 192 postoperative hours (Hosmer–Lemeshow *P* value = 0.89 and area under the curve = 0.70): (1) age of patients (65 to 75 yr): adjusted odds ratio = 2.12 (1.44 to 3.12) and (greater than 75 yr) adjusted odds ratio = 4.30 (2.84 to 6.50); (2) history of preoperative paroxysmal atrial fibrillation: adjusted odds ratio = 2.39 (1.25 to 4.59); and (3) duration of aortic clamping (unit on 10 min) adjusted odds ratio = 1.13 (1.06 to 1.20) defining the predictor selective set. The use of catecholamines was not statistically associated with postoperative atrial fibrillation occurrence in multiple logistic regression analysis based on the predictor selected set.

### Relationship between the Timing of β-Blocker Reintroduction and Postoperative Atrial Fibrillation Occurrence

First, if the timing of β-blocker reintroduction and postoperative atrial fibrillation occurrence is not taken into consideration, as done in most of the previous studies, among the 290 patients with an episode of postoperative atrial fibrillation or death during the first 192 postoperative hours, the β-blockers were reintroduced for 229 (79%) patients. For the 373 patients without postoperative atrial fibrillation occurrence, 313 (84%) had β-blockers reintroduced. The odds ratio of having an episode of postoperative atrial fibrillation when β-blockers were reintroduced was 0.72 (0.48 to 1.07; Wald *P* = 0.10). The odds ratio was 0.79 (0.53 to 1.17; Wald *P* = 0.264) when only the 286 patients with postoperative atrial fibrillation were analyzed. After adjustment on the predictor full set and on the predictor selective set, the adjusted odds ratio of having an episode of postoperative atrial fibrillation when β-blockers were reintroduced was 0.90 (0.54 to 1.49; Wald *P* = 0.673) and 0.90 (0.58 to 1.39; Wald *P* = 0.625), respectively.

In a second analysis we took into consideration the timing of β-blocker reintroduction and postoperative atrial fibrillation occurrence. At four postoperative landmark times (24, 48, 72, and 96 h) the percentages of patients who already had reintroduction of β-blockers are shown in the table 3, with the number of postoperative atrial fibrillation occurrences after each landmark time, and in figure 4. At the 48-h landmark time, among 601 patients, the β-blockers were reintroduced in 233 patients: 81 had a postoperative atrial fibrillation after 48 h with an adjusted odds

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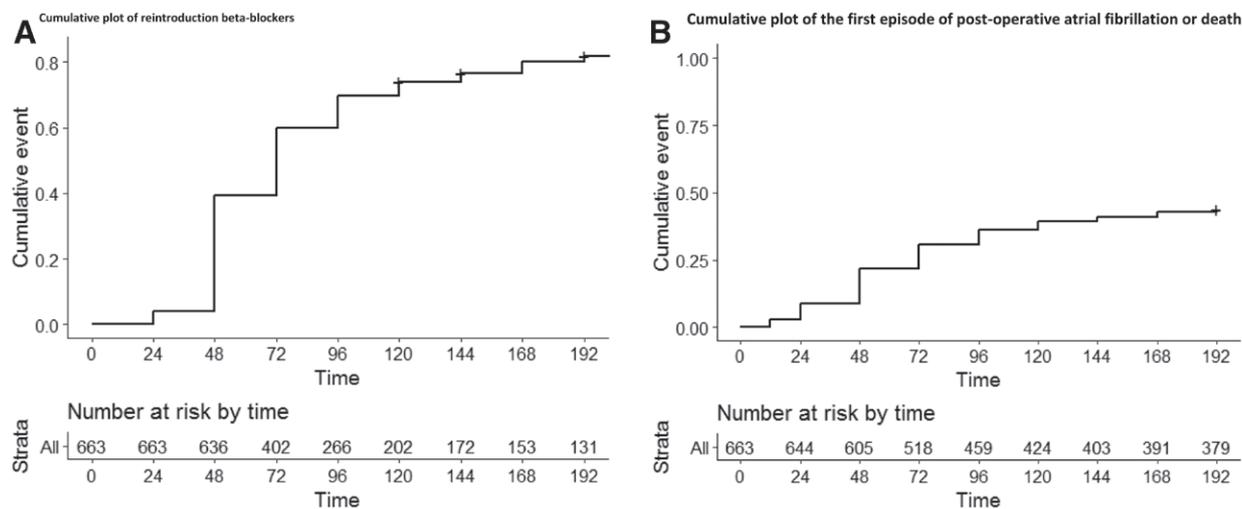
**Table 2.** Reasons for Nonreintroduction of β-Blockers for 402 Patients during the Postoperative 48 h (Reintroduction between 48 h and 192 h) and Patients Who Never Had Reintroduction of β-Blockers during the Postoperative 192 h

Reasons for Nonreintroduction	Patients	
	Delayed Reintroduction* of β-Blockers between Postoperative 48 h and 192 h N = 271/402	Nonreintroduction† of β-Blockers during the Postoperative 192 h N = 131/402
Catecholamines	71	79
Atrioventricular block	10	23
Concomitant use of amiodarone	21	20
Anticipated risk of low cardiac output in the absence of catecholamines	26	16
Arterial hypotension (SAP < 90 mmHg or decrease of SAP of more than 30% from the patient's baseline values)	20	15
Bradycardia (HR < 50 beats per minute)	13	11
Forgotten	8	—
Sepsis	4	—
Reintroduction considered as not necessary	3	7
No oral feeding	2	3
Hypovolemia	—	2
Severe peripheral vascular disease	—	1
Anticipated risk of bronchospasm	2	1
Anticipated risk of CVA in the presence of carotid artery stenosis >70%	1	—
Other causes	13	11
Undocumented reason	138	—

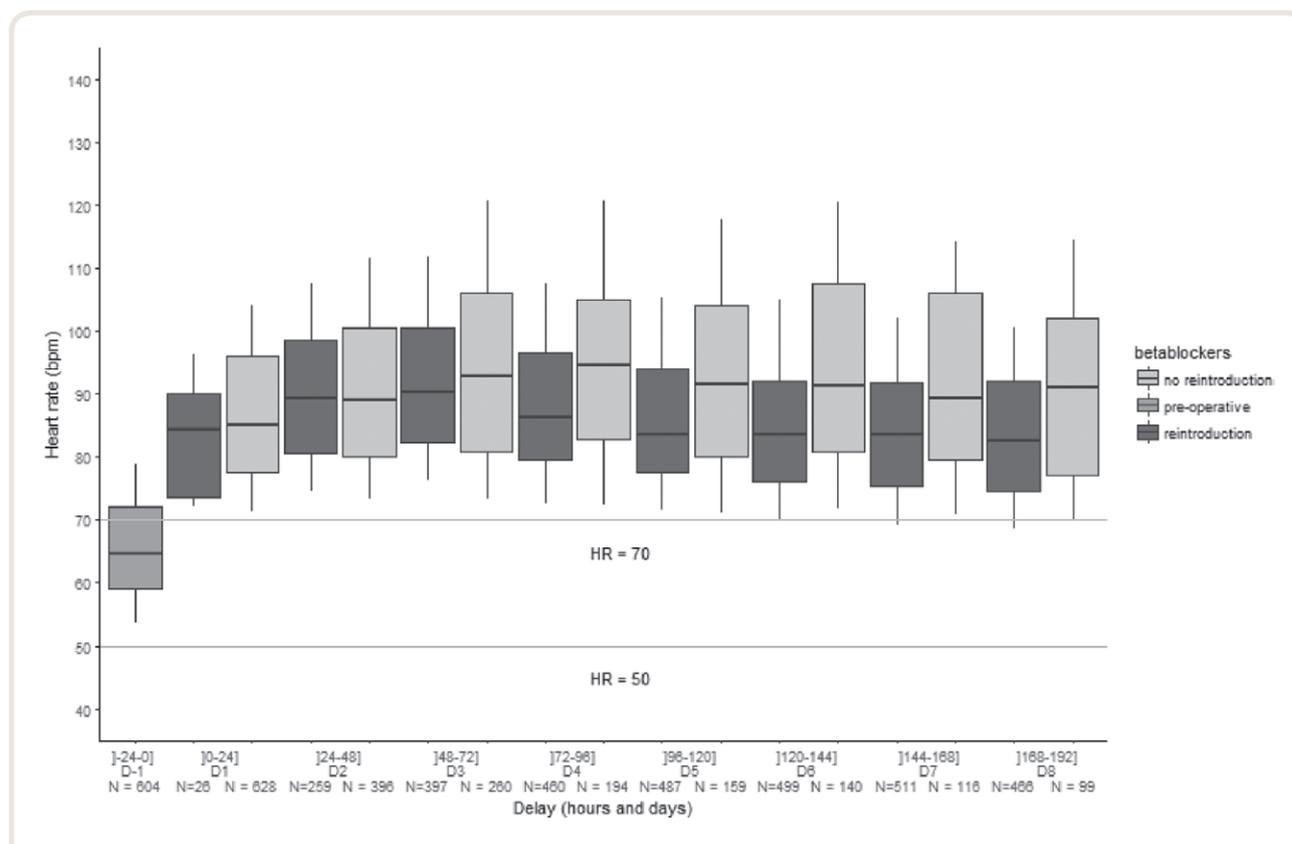
\*One hundred thirty-three patients with at least one specified reason: 90 patients (67.7%) had one reason; 34 patients (25.6%) had two reasons; 9 patients had three or more reasons (6.7%). †Fifty-nine patients (59.5%) had one reason; 40 patients (30.5%) had two reasons; 13 patients had three or more reasons (10.0%). CVA, cerebrovascular accident; HR, heart rate; SAP, systolic arterial pressure.

ratio = 0.84 (0.58 to 1.21; Wald  $P = 0.338$ ). The reintroduction of β-blockers was statistically associated with a decreased risk of occurrence of postoperative atrial fibrillation at the 72-h landmark time (adjusted odds ratio = 0.58; 0.38 to 0.89; Wald  $P = 0.013$ ), and also at 96-h landmark time, not statistically significant ( $P = 0.076$ ) with the

predictor full set. Two sensitivity analyzes were performed, one with the center as adjusted covariate taking into account the three hospitals (*post hoc* analysis) and the second without the four deceased patients (*a priori* analysis). The same results were observed with three associated covariates (results not shown).



**Fig. 2.** Cumulative plot of reintroduction β-blockers (A) and of the first episode of postoperative atrial fibrillation or death (B) for the 663 included patients in the first 192 postoperative hours with a 24-h time intervals; time is expressed in hours.



**Fig. 3.** Highest heart rate values (in beats per minute) before surgery and during the first 192 postoperative hours for the 663 included patients. Box and whisker plots illustrate median (*line through the box*), 75th percentile (*top line of box*), and 25th percentile (*bottom line of box*). There is a significant ( $P < 0.0001$ ) interaction between time and groups ( $\beta$ -blockers reintroduced vs.  $\beta$ -blockers not reintroduced) after 96 h ( $P < 0.0001$ ).

### Relationship between Concomitant Prescribed Drugs and Occurrence of Transient Postoperative Atrial Fibrillation

We also performed landmark time analysis for the relationship between reintroduction timing of the other concomitant therapy and occurrence of postoperative atrial fibrillation or death (table 3). The prescription of amiodarone as therapy for postoperative atrial fibrillation (cannot be considered as reintroduction because only 4.6% of the patients had preoperative amiodarone; table 1) was statistically associated with decreased postoperative atrial fibrillation occurrence whatever the landmark times and the predictor sets. The statins, as the  $\beta$ -blockers, were also significantly associated with decreased postoperative atrial fibrillation occurrence at the 72-h and 96-h landmark times whatever the predictor sets and at 24 h with the predictor full set (table 3).

### Discussion

The patients included in this study are comparable with those described in other recent publications in terms of age, comorbidities, chronic preoperative therapy (except for chronic  $\beta$ -blocker therapy in all patients, the inclusion

criterion of this study) and types of surgery.<sup>6</sup> To the best of our knowledge this is the first attempt to analyze the time sequence of postoperative  $\beta$ -blocker reintroduction in the modern era of cardiac surgery/anesthesia/postoperative care. Our results show that in patients under chronic preoperative  $\beta$ -blocker therapy, oral  $\beta$ -blockers were reintroduced in more than 80% of the patients during the 8 days that followed the end of surgery but in only 40% of them during the first 48 h (median time to the peak of occurrence of postoperative atrial fibrillation being 60 h). For 17% of the patients,  $\beta$ -blockers could be considered as nonreintroduced during the study (192 h) and follow-up (30 days).

The four most frequent reasons for nonreintroduction of  $\beta$ -blockers were the use of catecholamines (more than 50% of the causes), the anticipated risk of low cardiac output, atrioventricular block, and concomitant use of amiodarone. Of interest, arterial hypotension was an infrequent cause of nonreintroduction. This opens the possibility to avoid the nonreintroductions of  $\beta$ -blockers with the use of levosimendan, an inodilator that preserves its positive inotropic effect even in the presence of  $\beta$ -blockers<sup>15</sup>; the use of short-acting intravenous  $\beta$ -blocker whose effects would rapidly disappear

**Table 3.** Association between Introduction of Chronic Medication before Each Landmark Time and the Occurrence of Postoperative Atrial Fibrillation or Death after Each Landmark Time for the 663 Included Patients

Landmark Times	N Patients	Atrial Fibrillation		OR [95% CI] Univariate	P Value	ORa [95% CI] Full	P Value	ORa [95% CI] Selected	P Value
		No N (%)	Yes N (%)						
Time = 24 h	640	373 (58%)	267 (42%)						
β-Blockers		17 (4.6%)	8 (3.0%)	0.65 [0.27–1.52]	0.315	0.58 [0.22–1.53]	0.269	0.72 [0.29–1.73]	0.457
Diuretics		53 (14.2%)	34 (12.7%)	0.88 [0.55–1.40]	0.591	1.09 [0.64–1.86]	0.751	0.84 [0.52–1.37]	0.490
ACEi		9 (2.4%)	5 (1.9%)	0.77 [0.26–2.33]	0.645	0.78 [0.21–2.80]	0.700	0.94 [0.29–2.99]	0.913
Statins		45 (12.1%)	24 (9.0%)	0.72 [0.43–1.21]	0.216	0.50 [0.27–0.91]	0.024	0.59 [0.34–1.04]	0.066
Amiodarone		27 (7.2%)	52 (19.5%)	3.10 [1.89–5.09]	< 0.0001	3.20 [1.79–5.72]	< 0.0001	3.01 [1.78–5.09]	< 0.0001
Time = 48 h	601	373 (62%)	228 (38%)						
β-Blockers		161 (43.2%)	81 (35.5%)	0.72 [0.52–1.02]	0.064	0.87 [0.58–1.32]	0.517	0.84 [0.58–1.21]	0.338
Diuretics		107 (28.7%)	72 (31.6%)	1.15 [0.80–1.64]	0.452	1.17 [0.77–1.77]	0.471	1.07 [0.72–1.56]	0.748
ACEi		18 (4.8%)	6 (2.6%)	0.53 [0.21–1.36]	0.183	0.38 [0.13–1.16]	0.089	0.48 [0.18–1.29]	0.144
Statins		247 (66.2%)	139 (61.0%)	0.80 [0.57–1.12]	0.192	1.06 [0.65–1.72]	0.812	0.92 [0.63–1.34]	0.662
Amiodarone		35 (9.4%)	81 (35.5%)	5.32 [3.42–8.27]	< 0.0001	5.91 [3.51–9.93]	< 0.0001	5.70 [3.56–9.13]	< 0.0001
Time = 72 h	514	373 (73%)	141 (27%)						
β-Blockers		244 (65.4%)	66 (46.8%)	0.47 [0.31–0.69]	0.0001	0.64 [0.39–1.05]	0.076	0.58 [0.38–0.89]	0.013
Diuretics		147 (39.4%)	62 (44.0%)	1.21 [0.82–1.79]	0.348	1.15 [0.72–1.82]	0.561	1.12 [0.73–1.70]	0.609
ACEi		52 (13.9%)	14 (9.9%)	0.68 [0.36–1.27]	0.225	0.77 [0.36–1.67]	0.509	0.85 [0.44–1.64]	0.635
Statins		287 (76.9%)	88 (62.4%)	0.50 [0.33–0.76]	0.0009	0.43 [0.22–0.85]	0.015	0.52 [0.33–0.83]	0.005
Amiodarone		38 (10.2%)	54 (38.3%)	5.47 [3.39–8.82]	< 0.0001	6.80 [3.78–12.2]	< 0.0001	5.85 [3.51–9.75]	< 0.0001
Time = 96 h	455	373 (82%)	82 (18%)						
β-Blockers		276 (74.0%)	44 (53.7%)	0.41 [0.25–0.67]	0.0003	0.58 [0.31–1.07]	0.079	0.53 [0.31–0.91]	0.021
Diuretics		172 (46.1%)	40 (48.8%)	1.11 [0.69–1.80]	0.661	1.05 [0.58–1.88]	0.873	1.13 [0.67–1.90]	0.642
ACEi		80 (21.5%)	13 (15.9%)	0.69 [0.36–1.31]	0.255	0.79 [0.35–1.80]	0.582	0.89 [0.46–1.74]	0.737
Statins		294 (78.8%)	48 (58.5%)	0.38 [0.23–0.63]	0.0001	0.33 [0.15–0.75]	0.008	0.41 [0.24–0.71]	0.001
Amiodarone		38 (10.2%)	27 (32.9%)	4.33 [2.45–7.65]	< 0.0001	4.88 [2.33–10.2]	< 0.0001	4.28 [2.33–7.86]	< 0.0001

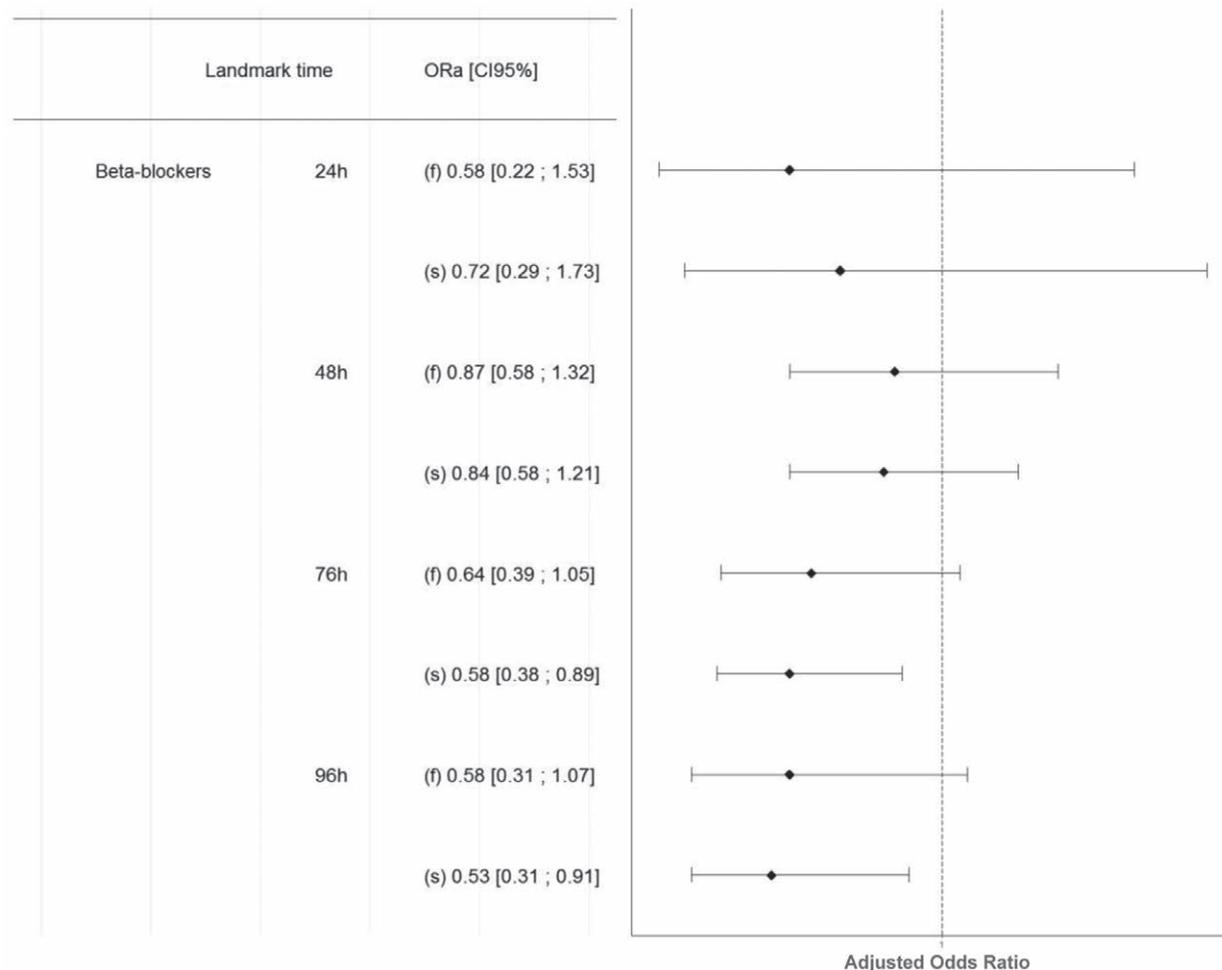
Adjusted odds ratio on the predictors full set and adjusted odds ratio on the predictors selective set of postoperative atrial fibrillation occurrence (age, history of paroxysmal atrial fibrillation and duration of aortic clamping). ACEi, angiotensin-converting-enzyme inhibitor; OR, odds ratio; ORa, adjusted odds ratio.

if low cardiac output or atrioventricular block or bradycardia (upon concurrent use of amiodarone) were to occur.

The use of catecholamines during the postoperative period was not significantly associated (whatever the predictor set) with an increased incidence of postoperative atrial fibrillation in our study. This is relatively unexpected given the accepted pathophysiology of postoperative atrial fibrillation induced both by endogenous sympathetic nervous system activation and the use of exogenous catecholamines.<sup>11</sup> The use of catecholamines is explained by the preoperative systolic dysfunction. When preoperative systolic dysfunction was introduced in the statistical model, the prescription of catecholamines was not statistically associated with an increased risk of postoperative atrial fibrillation.<sup>6</sup> Therefore, the lack of statistical association between catecholamine prescription and postoperative atrial fibrillation in our study is explainable.

The main question raised by our results is why did we only partially confirm previously published results<sup>8,9</sup> that demonstrated in observational studies a statistically significant association between reintroduction of β-blockers and the occurrence of postoperative atrial fibrillation. We suggest that the most plausible explanation for the differences with previous literature is related to the type of statistical analyses

performed and mainly to the issue of temporality. When the timing of β-blocker reintroduction and the occurrence of postoperative atrial fibrillation was not taken into consideration, in univariate analysis, we partly confirmed previous results. Indeed, in our study, the odds ratio of having a postoperative atrial fibrillation episode was 0.72 (0.48 to 1.07; Wald  $P = 0.10$ ) for 290 patients with atrial fibrillation (with four deaths). When temporality was taken into consideration, we found a statistically significant relationship based on the predictor selected model (table 3) between reintroduction of β-blockers and postoperative atrial fibrillation that occurred more than 72 h after the end of surgery (same trends with the predictor full set). A possible cause for the lack of statistical association between β-blocker reintroduction and occurrence of postoperative atrial fibrillation at earlier time points (landmarks 24 and 48 h; table 3) could be the ineffectiveness of β-blocker reintroduction in the present study. Indeed, figure 3 demonstrates that sampled heart rate values were not different between the groups of patients with versus without β-blockers reintroduced, during the first 96 h after the end of surgery; there is nevertheless a significant ( $P < 0.001$ ) time versus group interaction after 96 h, suggesting the effectiveness of β-blocker reintroduction on heart rate values only after 96 h. One of the possible reasons for the lack of effectiveness



**Fig. 4.** Forest-plot of adjusted odds ratio between introduction of  $\beta$ -blockers before each landmark time and the occurrence of postoperative atrial fibrillation or death after each landmark time for the 663 included patients. (f), adjusted on the predictor full set; (s), adjusted on the predictor selective set.

of oral  $\beta$ -blockers to decrease the occurrence of postoperative atrial fibrillation after cardiac surgery in our study could be related to the already reported decreased bioavailability of oral  $\beta$ -blockers after cardiac surgery.<sup>10</sup> In our study, the effectiveness of preoperative chronic  $\beta$ -blocker treatment is clinically acceptable,<sup>4</sup> given the fact that the average preoperative heart rate values were 60 beats per minute (fig. 3). On the contrary, the effectiveness of postoperative  $\beta$ -blocker reintroduction is probably low given the relatively high heart rate values (90 to 100 beats per minute) without differences between the groups of patients with or without reintroduction of  $\beta$ -blockers within the first 48 to 96 h. Interestingly, a recent study published by members of our group could not demonstrate an effect of partly optimized early  $\beta$ -blockade reintroduction on the incidence of postoperative atrial fibrillation after cardiac surgery.<sup>16</sup> The most plausible interpretation is that the current method of reintroduction of oral  $\beta$ -blockers after cardiac surgery does not result in  $\beta$ -blockade.

If this were the main reason, an optimized administration of  $\beta$ -blockers could increase the clinical effectiveness of postoperative  $\beta$ -blockade. Optimization of postoperative reintroduction of  $\beta$ -blockers after cardiac surgery could come from the choice of the intravenous as compared with the oral route. Indeed, this has been reported by Halonen *et al.*<sup>17</sup>; these authors demonstrated a decrease of postoperative atrial fibrillation from 28.1% in patients given oral metoprolol to 16.8% in patients given intravenous metoprolol titrated on the heart rate values. Another possibility of optimization could be related to the choice of the oral  $\beta$ -blockers because it has been suggested that carvedilol is more effective in preventing postoperative atrial fibrillation as compared with metoprolol or atenolol.<sup>18,19</sup>

In the adjusted predictive factors analysis of this study and others,<sup>7,8</sup> we demonstrated a statistically significant association between postoperative use of amiodarone and postoperative atrial fibrillation. This is explained by the fact

that patients with postoperative atrial fibrillation received amiodarone after the occurrence of atrial fibrillation. This is consistent with the results of other reports<sup>6</sup> and is only partly consistent with the guidelines on the management of postoperative atrial fibrillation. Indeed, guidelines recommend that treatment of postoperative atrial fibrillation with rapid ventricular response be treated (preferential order) with β-blockers, a nondihydropyridine calcium channel antagonist, or amiodarone.<sup>13</sup>

Our study also confirmed that reintroduction of statins (but not angiotensin converting enzyme inhibitors or diuretics) is also associated with a decreased risk of postoperative atrial fibrillation occurrence by taking into account the timing of statin reintroduction and postoperative atrial fibrillation occurrence (whatever the predictor sets). Interestingly, reintroduction of statins was associated with a decreased occurrence of postoperative atrial fibrillation only after the 72-h landmark time. This is similar to the time-dependent effect of β-blocker reintroduction and could be related to the reduced bioavailability or too delayed reintroduction.

### Strengths of the Present Study

To the best of our knowledge this is the first study that specifically investigated the temporality of β-blocker reintroduction in a prospective multicenter cohort study in cardiac surgery patients. This approach is different from the recent widespread analyses of administrative/large medical databases where temporality is never analyzed.<sup>20</sup> The results are probably representative of healthcare systems where quality improvement or pay for performance programs do not insist on postoperative reintroduction of β-blockers.

### Limitations of the Present Study

The results are representative of French anesthesia and ICU practice in cardiac surgery patients. The observational design of the study did not result in homogenous practice of anesthesia, surgery, ICU. Furthermore, the diagnosis of postoperative atrial fibrillation was not based on continuous electrocardiography recordings, and this may be associated with an underestimation of the number of atrial fibrillation episodes. The sampling of heart rate values from the nurses' records to estimate the effectiveness of oral β-blocker reintroduction may not reflect the real clinical effect of β-blockers, but if this were the case there would be no reason for a group *versus* time interaction after 72 h. The predictor full set analysis would require a new dataset to confirm the result of predictor selective set analysis.

### Conclusions and Clinical Implications

Our results suggest that oral β-blocker reintroduction, as performed in this cohort study that reflects routine clinical practice, is not effective; this probably explains the lack of statistically significant association between their

reintroduction and a decrease in the incidence of postoperative atrial fibrillation during the first 72 h after cardiac surgery. The directions for improvement of β-blocker reintroduction could be earlier reintroduction, goal-directed (heart rate) titration that could be achieved with intravenous β-blockers (preferably short acting) as a bridge to oral β-blockers, or higher doses of oral β-blockers. Given the statistical association between oral beta blockers prescribed upon discharge after coronary artery bypass graft surgery,<sup>21</sup> it seems plausible that our results should not be interpreted as a proof of lack of clinical effect of immediate postoperative reintroduction of β-blockers but as an incentive to optimize their postoperative reintroduction. Nevertheless, it is also possible that unmeasurable changes in clinical practice have modified the relationship between chronic medication (including β-blockers) and postoperative outcome as confirmed by a recent cohort study.<sup>22</sup>

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### Competing Interests

Dr. Longrois has received speaker's fees from Orion Pharma (Orion Corporation, Espoo, Finland) and Edwards Lifesciences France (Guyacourt, France). Dr. Cholley has received consultancy/conference fees from Orion Pharma, Amomed Pharma France (Meudon La Foret, France), Nordic Pharma France (Paris, France), and Edwards Lifesciences. Dr. Fellahi has received consultancy/conference fees from Baxter (Deerfield, Illinois) and Amomed. The other authors declare no competing interests.

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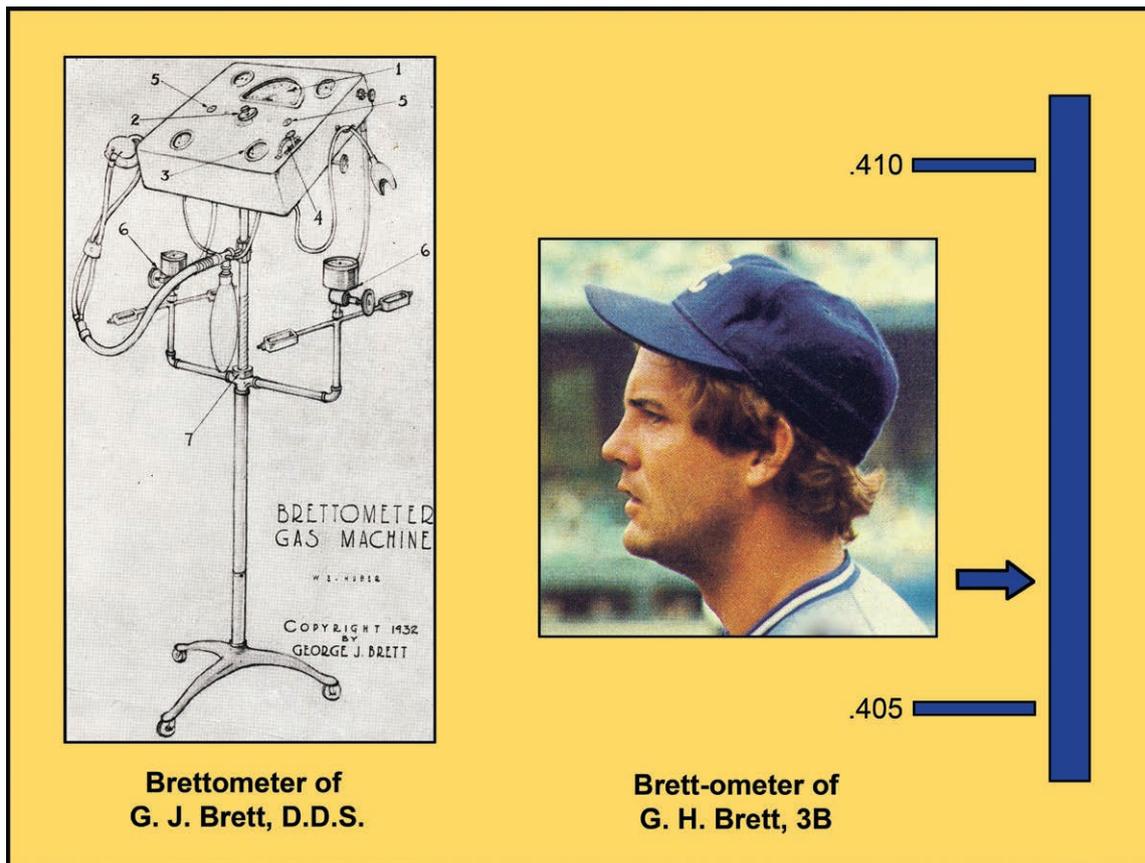
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# George Brett and His Brettometer: The Anesthesia Machine or the Slugging Machine?



In 1932, the U.S. patent office granted Dr. George Jesse Brett (1896 to 1969) patent rights to his Anaesthetizer, which he manufactured as an anesthesia machine branded “Brettometer” (left). Forty-eight years after that patent, a Kansas City Royals third-baseman, George Brett, was intermittently topping a batting average of .400. Soon, many American newspapers began following baseballer Brett with daily “Brett-ometer” or “Brettometer” charts (right) detailing where the slugger’s batting average stood on that given day. So remarkably, the twentieth century ushered in two unrelated gentlemen named George Brett, each of whom was responsible for his own well publicized Brettometer. (Copyright © the American Society of Anesthesiologists’ Wood Library-Museum of Anesthesiology.)

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