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Propranolol Versus Metoprolol for Treatment of Electrical Storm in Patients With Implantable Cardioverter-Defibrillator

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ABSTRACT

BACKGROUND Electrical storm (ES), characterized by unrelenting recurrences of ventricular arrhythmias, is observed in approximately 30% of patients with implantable cardioverter-defibrillators (ICDs) and is associated with high mortality rates.

OBJECTIVES Sympathetic blockade with β-blockers, usually in combination with intravenous (IV) amiodarone, have proved highly effective in the suppression of ES. In this study, we compared the efficacy of a nonselective β-blocker (propranolol) versus a β_1-selective blocker (metoprolol) in the management of ES.

METHODS Between 2011 and 2016, 60 ICD patients (45 men, mean age 65.0 ± 8.5 years) with ES developed within 24 h from admission were randomly assigned to therapy with either propranolol (160 mg/24 h, Group A) or metoprolol (200 mg/24 h, Group B), combined with IV amiodarone for 48 h.

RESULTS Patients under propranolol therapy in comparison with metoprolol-treated individuals presented a 2.67 times decreased incidence rate (incidence rate ratio: 0.375; 95% confidence interval: 0.207 to 0.678; $p = 0.001$) of ventricular arrhythmic events (tachycardia or fibrillation) and a 2.34 times decreased rate of ICD discharges (incidence rate ratio: 0.428; 95% CI: 0.227 to 0.892; $p = 0.004$) during the intensive care unit (ICU) stay, after adjusting for age, sex, ejection fraction, New York Heart Association functional class, heart failure type, arrhythmia type, and arrhythmic events before ICU admission. At the end of the first 24-h treatment period, 27 of 30 (90.0%) patients in group A, while only 16 of 30 (53.3%) patients in group B were free of arrhythmic events ($p = 0.03$). The termination of arrhythmic events was 77.5% less likely in Group B compared with Group A (hazard ratio: 0.225; 95% CI: 0.112 to 0.453; $p < 0.001$). Time to arrhythmia termination and length of hospital stay were significantly shorter in the propranolol group ($p < 0.05$ for both).

CONCLUSIONS The combination of IV amiodarone and oral propranolol is safe, effective, and superior to the combination of IV amiodarone and oral metoprolol in the management of ES in ICD patients. (J Am Coll Cardiol 2018;71:1897–906)

Patients with an implantable cardioverter-defibrillator (ICD) carry a significant baseline risk for the development of recurrent ventricular arrhythmias (1). Furthermore, approximately 30% of ICD recipients ultimately develop an electrical storm (ES), which is a life-threatening syndrome presenting with recurrent episodes of ventricular arrhythmias in a short period of time that subsequently results in appropriate device interventions (2,3). The incidence of ES varies depending on

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ATP = antitachycardia pacing

CI = confidence interval

ES = electrical storm

HF = heart failure

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

ICU = intensive care unit

IRR = incidence rate ratio

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

VF = ventricular fibrillation

VT = ventricular tachycardia

the under-investigation populations; interestingly, 10% to 58% of ICD recipients for secondary prevention while 4% to 7% for primary prevention experience an ES during their lives (2).

Given its poor short- and long-term prognosis, developing effective strategies for the ES episodes is of paramount importance (4,5). Sympathetic blockade with β-blockers, usually in combination with intravenous (IV) amiodarone, has proved highly effective in the suppression of ES in patients with recent myocardial infarction (6). Our initial experience indicates that a nonselective β-blocker is more effective in the suppression of ES compared with a selective one (7). However, large cohort studies comparing the efficacy of selective and nonselective β-adrenergic blockade on ES in ICD patients are missing. The aim of the present study was to investigate the short-term effects of oral metoprolol (β_1-selective blocker), in comparison with propranolol (nonselective β-blocker), on the termination of ES in ICD patients.

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METHODS

STUDY SETTING AND POPULATION. In this prospectively designed study, we analyzed data from patients with an ES initiated within 24 h before their admission. Patients were recruited between January 2011 and December 2016 from the "Alexandra" Hospital, Athens, Greece. The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board and all participants provided written consent forms. The diagnosis of ES was defined as 3 or more episodes of ventricular tachycardia (VT) or ventricular fibrillation (VF) separated by a period of at least 5 min that developed within a 24-h period and resulted in device intervention. Exclusion criteria were defined as coexistence of at least 1 of the following comorbidities: 1) drug-induced arrhythmias, or arrhythmias secondary to acute myocardial ischemia or acute congestive heart failure (HF); 2) patients with prolonged QT interval defined as >0.50 s; 3) patients with hypokalemia, impaired renal or hepatic function; and 4) baseline systolic blood pressure <90 mm Hg. Acute coronary syndrome was ruled out by detailed patient history, physical examination, electrocardiographic criteria for myocardial ischemia, and serum kinetics of creatine kinase-myocardial band and troponin I and T, which—although slightly increased due to ICD discharges—were not indicative of ischemia. High suspicion for myocardial ischemia in 2 patients necessitated the performance of coronary angiography that eventually revealed no significant coronary artery lesions in both cases.

STUDY PROTOCOL AND RANDOMIZATION. Patients were randomly assigned to an antiarrhythmic drug therapy with either a nonselective β-blocker (short-acting propranolol, peak plasma time 1 to 4 h) or a β_1-selective blocker (short-acting metoprolol tartrate, peak plasma time 1.5 to 2 h) in a 1:1 ratio. The study was blinded to all except for a designed third party who did not participate in the evaluation or the care of patients. Each β-blocker was administered per os for 48 h in every patient. Group A patients initiated on 40-mg propranolol followed by 40 mg every 6 h (cumulative dose 160 mg/24 h). Group B patients initiated on 50-mg metoprolol followed by 50 mg every 6 h (cumulative dose 200 mg/24 h). At the same time, amiodarone was administered intravenously in both groups with an initial rapid infusion rate of 30 mg/min over 10 min, followed by continuous infusion with a maintenance dose of 1,000 mg/24 h for 48 h.

All patients were admitted to the intensive care unit and were closely monitored by continuous electrocardiography telemetry and blood pressure monitoring. VT or VF events as well as changes in blood pressure or heart rate, or adverse reactions, were recorded every 60 min for a total period of 48 h. Following 48 h, patients continued the treatment with propranolol (Group A) or metoprolol (Group B) at the same dose, in combination with per os amiodarone 200 mg once daily until hospital discharge. In case of serious adverse events, namely severe hypotension, congestive HF, bronchospasm, or arrhythmia exacerbation, the study had to be discontinued and patients were treated accordingly.

In all patients, previous antiarrhythmic medications, including β-blockers (carvedilol, metoprolol, or bisoprolol), calcium-channel antagonists, and amiodarone were discontinued upon entering into our study. Other necessary therapies including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, aldosterone antagonists, and diuretics were continued in accordance to the respective clinical guidelines (8). After hospital discharge, all patients were advised to continue on the maximum tolerated dose of the β-blocker they were receiving before the study enrollment, in combination with 200-mg oral amiodarone per day for the following 2 months.

DATA COLLECTION AND ENDPOINTS. ICDs were interrogated to rule out inappropriate shock delivery and define the causative arrhythmia (VT or VF). No alterations were made in ICD programming throughout the study, since device interventions, including antitachycardia pacing (ATP) and discharges, were found to be effective at the pre-defined zones of VT and VF. Detailed clinical and laboratory characteristics including sex, age, type of heart disease, degree of dyspnea (New York Heart Association [NYHA] functional class), left ventricular ejection fraction (LVEF), and the number of events 24 h before the treatment initiation were recorded. A subsequent follow-up visit occurred 2 months after hospital discharge and ICD interrogation, electrocardiogram, clinical examination, and complete laboratory test were performed. The primary endpoint was the time to the last occurrence of an arrhythmic event (VT or VF) requiring ICD intervention (ATP or shock delivery) for termination. Secondary outcomes were the event rate (events per unit time), the proportion of patients that remained free of VT or VF at pre-specified time points, the total number of ICD discharges, and the length of hospital stay.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD or as median and interquartile range (25th and 75th percentile) when normally distributed or skewed, respectively. Shapiro-Wilk test and visual inspection of histograms and Q-Q plots were used to evaluate the normality of continuous variables. Categorical variables are presented as absolute (n) and relative frequencies (%). Categorical variables were tested using the Pearson chi-square or Fisher exact test as appropriate. Continuous variables were evaluated using the Student's *t*-test and Mann-Whitney *U* test when normally distributed or skewed, respectively.

To evaluate the effect of treatment (propranolol vs. metoprolol) on the number of VT or VF events and ICD discharges per patient across 6-h time windows (intensive care unit [ICU] admission to 48 h), we implemented multilevel generalized mixed-effects linear models. The negative binomial family was selected for the distribution of events (i.e., counts) that included zero values with a log link to fixed effects. Two random effects (random intercept and random coefficient of time) with unstructured variance-covariance matrix were incorporated to account for more flexibly for the within-subjects correlation across multiple measurements. Fixed effects included treatment type and time (i.e., distinct measurements) and their interaction as well as age, sex, EF, NYHA functional class, type of HF, arrhythmia (VT, VF, mixed), and arrhythmic events before admission. At the last point of the study (42 to 48 h), Group A (propranolol) had zero counts for both arrhythmic events and ICD discharges and no specific comparison for this time window has been performed. The effect size in mixed generalized models is provided as incidence rate ratio (IRR) with 95% confidence interval (CI). Respectively, multilevel mixed-effects logistic regression with random intercept and time coefficient was used to analyze the probability per patient for event-free time periods. Mixed model analyses were performed with the meglm and melogit packages of Stata version 11.1 (StataCorp, College Station, Texas).

Time to last arrhythmic event was estimated following generation of Kaplan-Meier curves and the log-rank test was employed to perform comparisons between the 2 groups. The association between probability of arrhythmia termination and type of therapy was evaluated by Cox proportional hazards modeling. Data were censored at the time of the last arrhythmic event or at 48 h. Patients that discontinued treatment with β-blockers before terminating the events, were censored at the time of exit (right censoring). Associations are presented as hazard ratio (HR) with 95% CI. The proportional hazards assumption of Cox models was assessed using the appropriate graph and statistical test (Schoenfeld residuals). Multivariable Cox proportional hazards modeling was conducted to examine the effect of therapy after controlling for patients' baseline characteristics. Statistical analysis was performed with Stata. All p values reported are 2-sided with the significance level set to 0.05.

RESULTS

SCREENING AND ELIGIBILITY. Between January 2011 and December 2016, a total of 68 ICD patients presented to the "Alexandra" Hospital with ES developed within 24 h before admission and were screened for trial eligibility. Of these, 60 patients met the aforementioned inclusion criteria and were included in the study. The remaining 8 patients were excluded due to inappropriate discharges (n = 2), contraindications to β-blockers (n = 2), worsening HF (n = 3), and electrolyte disturbances (n = 1).

BASELINE CHARACTERISTICS OF PATIENTS. Table 1 demonstrates the clinical and laboratory characteristics of the ES patients treated either with propranolol (Group A) or metoprolol (Group B). No significant differences were found between the 2 groups in terms of sex, previous heart disease, type of arrhythmia, NYHA functional class, age, LVEF, number of events, and medications before entering the study. In

TABLE 1 Baseline Characteristics of Patients by Group (n = 60)

	Group A (n = 30)	Group B (n = 30)	p Value
Sex			0.766
Female	8 (26.7)	7 (23.3)	
Male	22 (73.3)	23 (76.7)	
Heart disease			0.92
CAD	21 (70.0)	22 (73.3)	
DCM	5 (16.7)	5 (16.7)	
Other	4 (13.3)	3 (10.0)	
Type of arrhythmia			0.21
VT	19 (63.3)	19 (63.3)	
VF	7 (23.3)	8 (26.7)	
VT and VF	4 (13.4)	3 (10.0)	
NYHA functional class			0.678
I	17 (56.7)	20 (66.7)	
II	11 (36.7)	9 (30.0)	
III	2 (6.6)	1 (3.3)	
Age, yrs	65.0 ± 8.0	64.0 ± 8.5	0.646
LVEF, %	25.0 ± 5.0	26.0 ± 5.5	0.354
Total number of events before treatment	6.5 (4.0–12.0)	5.0 (4.0–9.0)	0.484
Medication used before entering into study			
Amiodarone	25 (83.3)	27 (90.0)	
Sotalol	3 (10.0)	3 (10.0)	
Beta-blocker	22 (73.3)	24 (80.0)	
Carvedilol	20 (66.7)	21 (70.0)	
Metoprolol	2 (6.7)	2 (6.7)	NS
Bisoprolol	0 (0)	1 (3.3)	
ACE inhibitor	16 (53.3)	17 (56.6)	
Angiotensin receptor blocker	12 (40.0)	10 (33.3)	
Aldosterone antagonists	17 (56.6)	15 (50.0)	
Furosemide	28 (93.3)	27 (90.0)	

Values are n (%), mean ± SD, or median (interquartile range).

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; DCM = dilated cardiomyopathy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; VF = ventricular fibrillation; VT = ventricular tachycardia.

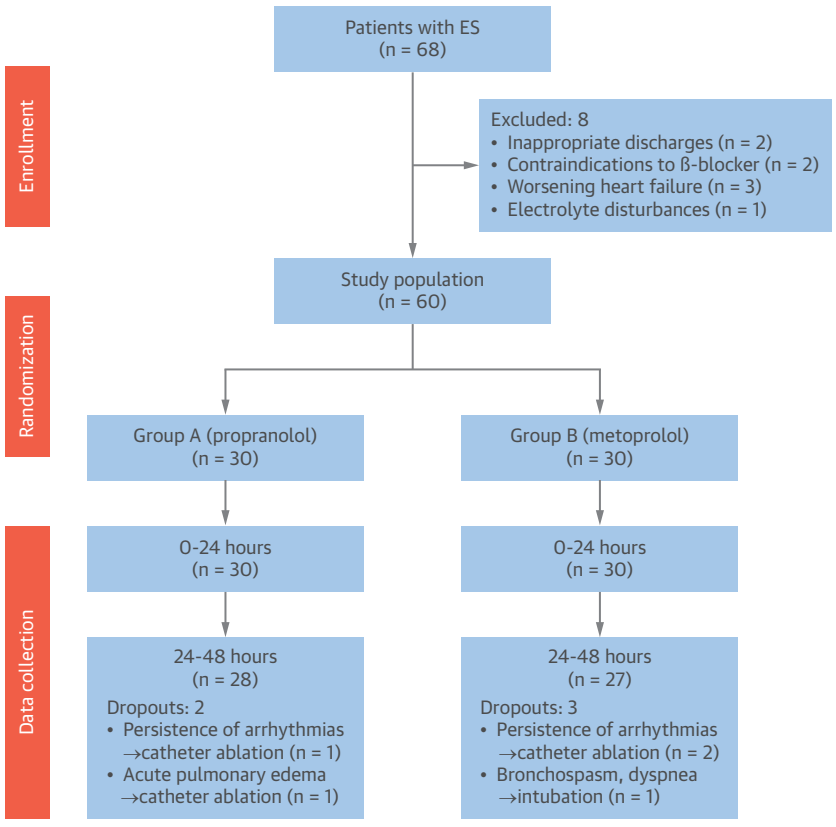
particular, the majority of the patients in Groups A and B had coronary artery disease (70.0% and 73.3%, respectively), followed by dilated cardiomyopathy (16.7% in both groups). All patients were characterized by NYHA functional class I or II, except for 3 patients (2 in Group A, 1 in Group B) with class III symptoms. Mean LVEF was 25.0 ± 5.0% in Group A, and 26.0 ± 5.5% in Group B (p = 0.354). The total number of events recorded before the initiation of treatment was comparable between the 2 groups (median 6.5 vs. 5.0; p = 0.484). Importantly, there was no difference in the antiarrhythmic treatment with regard to β-blockers before the randomization between Group A (carvedilol 66.7%, metoprolol 6.7%) and Group B (carvedilol 70.0%, metoprolol 6.7%, bisoprolol 3.3%; p >0.05).

Target doses of the under-investigation β-blockers were achieved in all 60 patients within the first 24 h of the study period. Nevertheless, 5 patients with severe ES (2 from Group A and 3 from Group B) did not accomplish the 48-h study period. In particular, Group A patients had persistence of arrhythmia with ensuing hemodynamic instability (n = 1) and acute pulmonary edema (n = 1), while Group B patients had persistence of arrhythmia (n = 2) as well as bronchospasm and dyspnea (n = 1). Treatment with β-blockers was discontinued and inotropic support with dobutamine was applied to retain hemodynamic stability. Importantly, these patients were retained in all relevant analyses up to exit time (right-censoring). In these patients, other approaches were followed for the treatment of ES, as previously suggested, including catheter ablation (9) in 4 patients (2 from Group A and 2 from Group B), and cardiac life support measures and intubation (1 from Group B) (**Figure 1**). Changes in concomitant drugs were kept to a minimum. The dose of diuretics was increased in 4 patients of the propranolol-assigned group and 3 patients of the metoprolol-assigned group.

VT OR VF EVENTS AND ICD DISCHARGES. The number of VT or VF events and ICD discharges per 6-h interval in the metoprolol and propranolol groups are shown in **Table 2**. Group A (propranolol) patients experienced fewer VTs or VFs compared with Group B (metoprolol) in all 6-h intervals of the study period (p < 0.05) except for the first (0 to 6 h; p = 0.632) and last (43 to 48 h) (**Table 2**). Propranolol therapy in comparison to metoprolol was associated with a 2.67 times decrease in the rate (IRR: 0.375; 95% CI: 0.207 to 0.678; p = 0.001) of VT or VF events per patient across the 48-h period in ICU, after adjusting for age, sex, EF, NYHA functional class, HF type, arrhythmia type (VT vs. VF), and arrhythmic events before admission (**Table 2**). Respectively, treatment with propranolol decreased the expected rate of ICD discharges per patient by 2.34 times (IRR: 0.428; 95% CI: 0.241 to 0.759; p = 0.004) as compared with metoprolol (**Table 2**).

FREEDOM FROM EVENTS. Patients in Group A presented significantly increased odds for being free of arrhythmic events compared with Group B in most examined time points (12 h: 23 vs. 11; p = 0.006; 18 h: 24 vs. 15; p = 0.011; 24 h: 27 vs. 16; p = 0.003; 30 h: 28 vs. 17; p = 0.007; 36 h: 28 vs. 21; p = 0.013; 42 h: 28 vs. 23; p = 0.033) except for the first (6 h; p = 0.128) and the last study points (comparison not performed due to zero count events in Group A), after taking into account differences in age, sex, EF, NYHA functional

FIGURE 1 Flowchart of the Study Protocol and Data Collection



Patients were randomly assigned to either a nonselective β-blocker (short-acting propranolol) or a β_1-selective blocker (short-acting metoprolol tartrate) along with intravenous amiodarone in a 1:1 ratio. Only 5 patients with severe electrical storm (ES) (2 from Group A and 3 from Group B) did not accomplish the 48-h study period.

class, HF and arrhythmia type, and arrhythmic episodes before ICU admission (**Central Illustration**).

TIME TO VT OR VF TERMINATION. The median time from initiation of therapy to termination of VT or VF event according to the intention to treat was 3 h (95% CI: 1 to 8 h) versus 18 h (95% CI: 8 to 37 h) in the propranolol and metoprolol groups, respectively (log-rank test, $p = 0.001$). A Kaplan-Meier curve for the cumulative percentage of event-free patients in Groups A and B is shown in the **Central Illustration**. In fact, 3 patients from Group B terminated the arrhythmic events beyond the 48-h study period (58 h, 72 h, and 80 h, respectively). At the end of the first 24-h post-treatment period, 27 of 30 patients (90%) in Group A (propranolol) were free of arrhythmic events, whereas 16 of 30 patients (53.3%) in Group B (metoprolol) remained free of events.

LIKELIHOOD OF ARRHYTHMIA TERMINATION. The termination of arrhythmic events within the 48-h follow-up period was 61.5% less likely in Group B compared with Group A (HR: 0.385; 95% CI: 0.216 to 0.688; $p = 0.001$). Similar results were detected even after controlling for potential confounders, including patients' age, sex, heart disease, NYHA functional class, EF, type of arrhythmia before the initiation of treatment, and total number of events before the treatment (**Table 3**). In particular, it was found that type of therapy (propranolol vs. metoprolol) was a significant determinant of the termination of arrhythmic events; termination was 77.5% less likely in Group B compared with Group A (HR: 0.225; 95% CI: 0.112 to 0.453; $p < 0.001$).

LENGTH OF HOSPITAL STAY AND OUTCOMES PAST THE FIRST 48 H. After termination of VT or VF events, patients remained hospitalized in the ICU for a period depending on their response to antiarrhythmic treatment, hemodynamic condition, and heart rate control. The median length of stay in Group

TABLE 2 The Effect of Treatment on Number of Events and ICD Discharges, Detected in Each Time Period After ICU Admission, in 2 Groups of Interest (Group A [Propranolol] Versus Group B [Metoprolol])

	Events			ICD Discharges		
	Group A (n = 30) Propranolol	Group B (n = 30) Metoprolol	p Value*	Group A (n = 30) Propranolol	Group B (n = 30) Metoprolol	p Value*
Time period after the initiation of treatment						
0–6 h	62	59	0.632	40	41	0.585
7–12 h	21	50	0.001	13	34	0.004
13–18 h	9	36	0.001	6	23	0.003
19–24 h	9	33	0.002	5	19	0.01
25–30 h	9	31	0.002	5	16	0.01
31–36 h	7	25	0.002	5	12	0.036
37–42 h	4	18	0.01	2	7	0.107
43–48 h	0	9	†	0	4	†
Total	121	261		76	156	
Overall IRR (95% CI)‡	0.375 (0.186–0.764)		0.001	0.428 (0.227–0.892)		0.004

*Comparisons between groups are performed by multilevel generalized (negative binomial) mixed model analysis for repeated measurements of counts (i.e., number of events or discharges per patients) across 6-h time windows after the initiation of treatment. The generalized mixed model was adjusted for age, sex, ejection fraction, NYHA functional class, type of arrhythmia (VT, VF, mixed) and heart failure (HF) (ischemic vs. dilated), and arrhythmic episodes before intensive care unit (ICU) admission. †Comparisons not performed due to overall zero counts in Group A. ‡Incidence rate ratio (IRR) corresponds to the expected average decrease in rate of counts (events or discharges) across the ICU stay per Group A patient in comparison with Group B, after taking into account the effect of age, sex, ejection fraction, NYHA functional class, type of arrhythmia (VT, VF, mixed) and HF (ischemic vs. dilated), and arrhythmic episodes before ICU admission.

CI = confidence interval; ICD = implantable cardioverter-defibrillator; other abbreviations as in Table 1.

A was significantly shorter compared with Group B (3 days [IQR: 3 to 4 days] vs. 4 days [IQR: 4 to 6 days]; p = 0.038). All patients survived to hospital discharge.

During the follow-up period of 2 months, no recurrences of ES were recorded in patients from both groups. ICD interrogation revealed 4 events of VT or VF (1 discharge, 3 ATP) in 3 patients of Group A and 5 events of VT or VF (2 discharges, 3 ATP) in 3 patients of Group B. All individuals were alive at last follow-up.

DISCUSSION

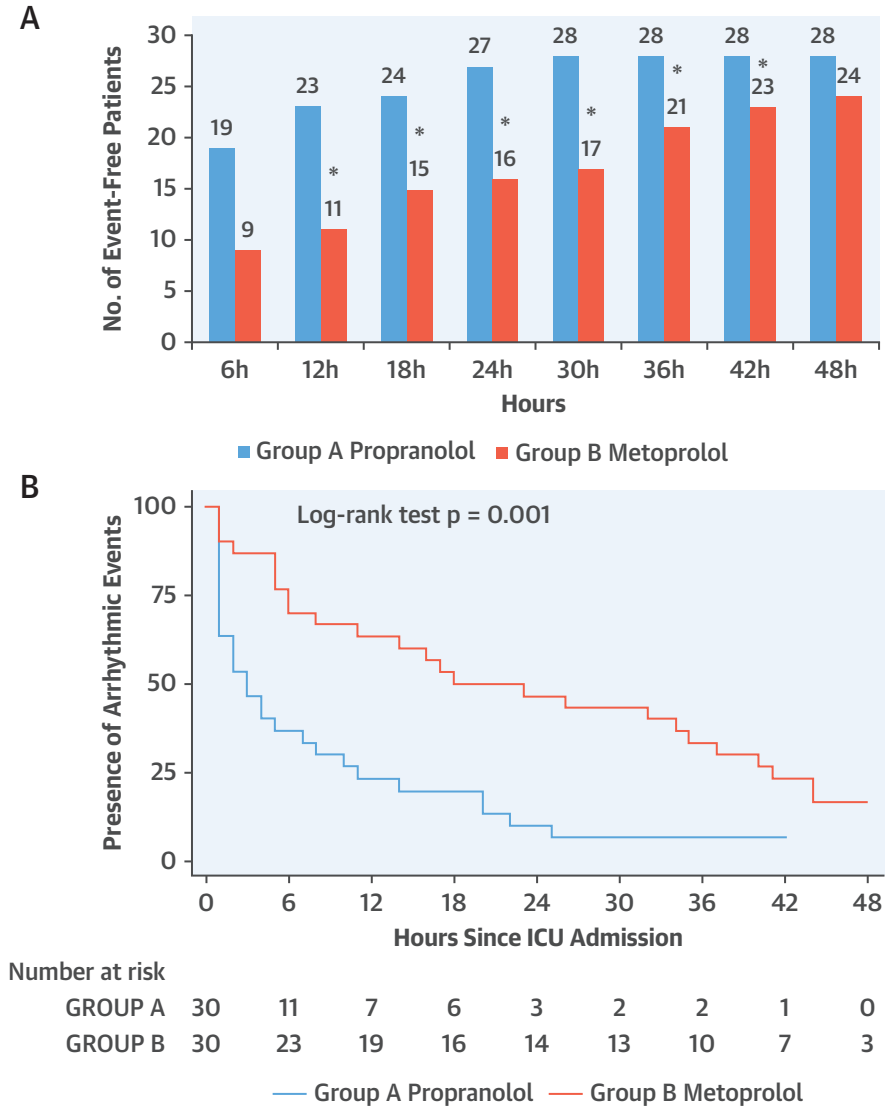
Our results indicate that propranolol is more efficient and acts earlier than metoprolol in the treatment of ICD patients who develop an ES. In particular, propranolol-treated patients showed a marked decrease in VT or VF events in almost all 6-h intervals under investigation, resulting in a higher number of event-free patients at the end of the first 24-h period in the propranolol group compared with the metoprolol group (90.0% vs. 53.3%; p= 0.002). Of note, the median time to arrhythmia termination was significantly shorter in the former group, providing these patients with a relief in a shorter time period while also decreasing the total number of ICD discharges. To the best of our knowledge, this is the first study comparing the efficacy of a nonselective versus a selective β-blocker in the management of ES.

Electrical storm, defined as 3 or more sustained episodes of VT, VF, or appropriate ICD shocks during a 24-h period, is associated with poor prognosis (4). Additionally, incessant recurrences of VT or VF events, in combination with the successive painful ICD shocks provoke a feeling of impending death and hopelessness to patients, making suppression of ES imperative. In general, acute administration of β-blockers, amiodarone, and mild sedation suppresses sympathetic tone and increases VT or VF threshold. Depending on the underlying cause of ES, alternative measures may include correction of electrolyte abnormalities, coronary reperfusion, therapeutic moderate hypothermia, and management of acute HF (4,10).

During the last decades, numerous interventions have been developed for the treatment of refractory ES, including catheter ablation (11,12), renal denervation (13), stellate ganglionic blockade, and bilateral cardiac sympathetic denervation (14). Of note, cardiac sympathetic denervation has recently been shown to successfully decrease sustained ventricular tachyarrhythmias and related ICD discharges in patients with refractory ES (15). Nevertheless, regardless of the therapeutic option, either conventional or interventional, the principal aim of the ES management is the sympathetic blockade and the modulation of the autonomic nervous system (15,16).

Several studies have demonstrated the significant role of autonomic nervous system in arrhythmiogenesis (17). More specifically, it has been claimed that high levels of catecholamines exhibit proarrhythmic properties and thus may exacerbate ventricular arrhythmias, resulting in cardiac arrest. In fact, epinephrine predisposes patients to VF development, contributes to myocardial dysfunction and increases myocardial oxygen demand by stimulating β-adrenergic receptors (18). Moreover, the baroreflex sensitivity, a marker that provides information on the capability to augment the vagal activity, is remarkably depressed in patients with life-threatening arrhythmias (19). Therefore, a persistent reduction of vagal reflexes may contribute to the genesis of malignant ventricular events. Previous studies have recorded the efficacy of sympathetic blockade in the management of ES (14,20), as well as the combination of IV amiodarone and β-blockade over sotalol alone (21). Importantly, our data suggest that in ICD patients with ES, treatment with a nonselective β-blocker, namely propranolol, is a safe and more effective approach compared with a selective β-blocker both orally administered.

CENTRAL ILLUSTRATION **Propranolol Versus Metoprolol for the Acute Treatment of Electrical Storm in Patients With Implantable Cardioverter-Defibrillator**



Chatzidou, S. et al. J Am Coll Cardiol. 2018;71(17):1897-906.

(A) Freedom from events. Patients in Group A (propranolol) presented significantly increased odds for event-free 6-h time periods compared with Group B (metoprolol) in all examined time points ($p < 0.05$) except for the 0 to 6 h and 42 to 48 h periods. The **asterisk** denotes observed level of statistical significance <0.05 as derived from multilevel mixed logistic regression for the per-patient probability of event-free 6-h time period. **(B)** Kaplan-Meier curve for time to arrhythmia termination in Groups A (propranolol) and B (metoprolol). The median time from initiation of therapy to termination of VT or VF events was 3 h (95% confidence interval: 1 to 8 h) versus 18 h (95% confidence interval: 8 to 37 h) in Group A (propranolol) and Group B (metoprolol), respectively (log-rank test, $p = 0.001$). ICU= intensive care unit.

The rationale of the selectivity of β-blockade is based on the properties of the failing heart and the fact that the vast majority of ICD patients who develop ES suffer from HF. The failing human heart has increased sympathetic tone, which aids in maintaining cardiac performance by increasing contractility and heart rate (22,23). As a result, patients with HF have increased sympathetic activity, which is associated with exercise intolerance, hemodynamic abnormalities, and increased risk of sudden

TABLE 3 Multivariable Cox Proportional Hazards Model Examining the Effect of Therapy After Controlling for Patient Baseline Characteristics

	HR	95% CI	p Value
Type of therapy			
Group B	Reference	—	—
Group A	0.225	0.112–0.453	<0.001
Sex			
Female	Reference	—	—
Male	1.49	0.757–2.930	0.248
Heart disease			
CAD	Reference	—	—
DCM	0.607	0.203–1.820	0.373
Other	0.565	0.330–2.440	0.230
Type of arrhythmia			
VT	Reference	—	—
VF	0.491	0.211–1.140	0.098
VT and VF	0.431	0.138–1.340	0.147
NYHA functional class			
I	Reference	—	—
II	0.819	0.383–1.750	0.607
III	0.227	0.023–2.290	0.209
Age	1.00	0.958–1.040	0.987
LVEF	0.983	0.915–1.060	0.629
Total events before treatment	0.926	0.877–0.978	0.006

HR = hazard ratio; other abbreviations as in Table 1.

death (24,25). In contrast, adrenergic drive in a normally functioning human heart is generally lower than that of a failing heart and regulated to a level so as cardiac contractile function adapts to physiologic metabolic demands. Particularly, there are 3 main adrenergic receptors (β1, β2, and α1) in cardiac myocytes coupled to a positive inotropic response and cell growth. In healthy human left and right ventricles, the β_1-to-β_2 ratio is approximately 70:30 and 80:20, compared with 60:40 in failing ventricles, due to selective down-regulation in the β_1 subtype (26). Therefore, on the one hand, the selective blockade of β_1 receptors may facilitate continuous sympathetic signal transductions through unblocked cardiac β_2 receptors, which is not cardiostimulatory, but may also increase the likelihood of ventricular arrhythmias (27). On the other hand, blockade of β_2 receptors may be particularly salutary in patients with HF, considering that β_2 receptors are not down-regulated in the failing heart (26).

Concerning nonselective blockade, experience in post-infarction trials have suggested that agents blocking both β_1 and β_2 receptors may provide more complete protection against catecholamine toxicity compared with agents acting exclusively on β_1 receptors (28). Furthermore, previous studies have demonstrated that in patients with HF, administration of a β_1-selective antagonist (metoprolol) was associated with increased cardiac norepinephrine spillover, while administration of nonselective β-blocker (propranolol) with adjustment to hemodynamic endpoints caused a reduction in cardiac norepinephrine spillover (an indirect index of norepinephrine release) (29,30). Importantly, propranolol is lipid soluble; therefore, apart from its action on peripheral β receptors, propranolol also has the potential to act on the central nervous system by blocking central and prejunctional receptors (31). In our study, all patients had been diagnosed with congestive HF, mostly due to coronary artery disease, resulting in increased sympathetic activity, which as mentioned previously, plays an important role in arrhythmiogenesis.

Interestingly, Nademanee et al. (20) investigated the efficacy of sympathetic blockade in the management of ES by comparing propranolol, esmolol, and left stellate ganglionic blockade with combined therapy with Class I antiarrhythmic drugs (lidocaine, procainamide, and bretylium). Patients included in their study had experienced a recent myocardial infarction and >20 episodes of VT within 24 h or >4 episodes/h. Despite the fact that the trial was nonrandomized, sympathetic blockade seemed to be superior to class I antiarrhythmic drugs (78% vs. 18% at 1 week and 67% vs. 5% at 1 year). The aforementioned authors have suggested that the combination of amiodarone and propranolol improves survival rates and should be the mainstay of therapy in the management of ES in patients with prior myocardial infarction. Similarly, in our protocol β-blockers were administered orally, and provided favorable results in terms of safety, tolerance, and efficacy.

In a recent meta-analysis, ES was found to be associated with a 3-fold increase in mortality (32). It has been speculated that ICD shocks themselves could contribute to the increased mortality rates. Interestingly, Sweeney et al. (33) suggested an 20% increased risk of mortality per shocked episode related to the presence of VT or VF events in ICD patients compared with patients with no antiarrhythmic therapies or patients treated only with ATP. In addition, multiple shocks can contribute to systolic dysfunction and lead to heart decompensation, especially in the case of patients with HF (34). In our study, although no difference was observed between propranolol and metoprolol groups in terms of mortality (zero mortality in both) after a follow-up of 2 months, ICD discharges were significantly lower in the propranolol group. Therefore, we can speculate that propranolol, apart from earlier and more efficient termination of VT or VF events, could significantly

aid in preserving the systolic function of the heart, which is of paramount importance in patients with pre-existing HF.

STUDY LIMITATIONS. Although nonselective and selective β-blockers are thought to exhibit similar pharmacokinetic properties, including onset of action, bioavailability, half time elimination, and excretion (35), our data suggest that propranolol is more effective than metoprolol in the management of ES. However, apart from β-blockers, patients were also treated with IV amiodarone, which is widely used in the treatment of ES (4). Given that rapid IV administration of amiodarone has sympatholytic action, by inhibiting norepinephrine release (36,37), the high efficacy of propranolol may be a multiplier effect of amiodarone.

CONCLUSIONS

ES is a severe and potentially life-threatening syndrome with no consensus on the optimal management. The combination of IV amiodarone and oral propranolol is safe and effective in the management of ES in ICD patients and provides significant benefits over the combination of IV amiodarone and metoprolol. Larger cohort studies are needed to verify our results and determine the preferable pharmaceutical agents that may effectively reduce morbidity and mortality rates associated with ES episodes.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The combination of IV amiodarone and oral propranolol is safe and effective for management of ES patients with implanted defibrillators and associated with shorter time to arrhythmia termination, lower frequency of ICD discharge, and reduced length of hospital stay compared with the combination of amiodarone and metoprolol.

TRANSLATIONAL OUTLOOK: Additional randomized trials are needed to identify the optimum pharmacological regimen for management of ES in patients with ICDs.

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