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Cardiac Abnormalities After Aneurysmal Sub-arachnoid Hemorrhage: Effects of β -Blockers and Angiotensin-Converting Enzyme Inhibitors

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Abstract

Background—Cardiac abnormalities attributed to adrenergic surge are common after aneurysmal subarachnoid hemorrhage. Prescribed medications that block adrenergic stimulation may suppress the onset of cardiopulmonary compromise in patients after aneurysmal subarachnoid hemorrhage.

Objectives—To compare the incidence of early cardiac complications between patients who reported prescribed use of β -blockers and/or angiotensin-converting enzyme inhibitors before aneurysmal subarachnoid hemorrhage and patients who did not.

Methods—A retrospective review of 254 adult patients after acute aneurysmal subarachnoid hemorrhage who were enrolled in an existing R01 study. Demographic data and history were obtained from patients'/proxies' reports and charts. Cardiac enzyme levels, 12-lead electrocardiograms, and chest radiographs were obtained on admission. Holter monitoring and echocardiograms were completed as a part of the R01 study.

Results—Patients reporting prescribed use of angiotensin-converting enzyme inhibitors or β -blockers before aneurysmal subarachnoid hemorrhage had more ventricular and supra-ventricular ectopy on a Holter report than did patients who did not ($P < .05$). When age, race, sex, and injury (Fisher grade) were controlled for, patients reporting use of β -blockers were 8 times more likely than others to have occasional to frequent ventricular ectopy ($P = .02$).

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FINANCIAL DISCLOSURES

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Conclusion—No concrete evidence was found that exposure to adrenergic blockade before aneurysmal subarachnoid hemorrhage provides protection from neurocardiac injury.

Myocardial abnormalities such as cardiac arrhythmias, electrocardiographic (ECG) changes, and neurogenic stunned myocardium have been commonly reported in patients with aneurysmal subarachnoid hemorrhages (aSAHs).^{1–4} Additionally, the average patient in whom such cardiac anomalies develop is relatively young and otherwise healthy.⁵ Stimulation of the sympathetic nervous system, in an attempt to maintain tissue perfusion and oxygenation to the brain, results in the release of catecholamines, which function to stimulate heart rate and cardiac contractility and regulate vascular tone.⁶ Excess catecholamine release from sympathetic and adrenal medullary activation has been posited for the development of central nervous system–mediated myocardial injury.^{7,8}

In patients with aSAH, this adrenergic release results in overstimulation of the sympathetic nervous system, essentially increasing systemic vascular resistance and causing afterload stress of the heart. The inability of the heart to contract effectively against this resistance contributes to heart failure and an even further imbalance between oxygen supply and demand.⁶ In response to the decreased cardiac output by the heart, and subsequent renal perfusion, there is also an increase in renin release by the kidneys, leading to activation of angiotensin II, and excessive vasoconstriction. The culmination of these myocardial events may worsen outcomes after aSAH.^{9,10} Therapeutic interventions that block these pathways intuitively should be beneficial for aSAH patients by counteracting or reducing these adverse responses.

β -adrenergic blockers are indicated for use in the treatment of hypertension, angina pectoris, and cardiac arrhythmias. Therapeutic effects of these medications are achieved by blocking β -adrenergic receptors in the heart to minimize the influence of the sympathetic nervous system, resulting in vasodilatation, and thereby decreasing cardiac workload and oxygen consumption.^{11,12} β -Adrenergic receptors are also responsible for the release of renin from the kidneys. This mechanism is also blocked through β -blocker therapy, leading to a decrease in blood pressure.

Angiotensin-converting enzyme (ACE) inhibitors are indicated in the treatment of hypertension and to reduce the risk of myocardial infarction, stroke, and death in patients with cardiovascular abnormalities. These inhibitors have been associated with improved survival after myocardial infarction. ACE inhibitors function by preventing the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. The inhibition of this conversion leads to decreased peripheral arterial resistance, ultimately resulting in decreased blood pressure. The mechanisms of both the sympathetic nervous system and the renin-angiotensin-aldosterone system can be prevented through the therapeutic effects of β -blockers and ACE inhibitors.¹³

In patients with aSAH, development of cardiac complications has been attributed to increased sympathetic stimulation, most frequently reported within hours to days after aneurysm rupture.^{1–4} Because the therapeutic effect of ACE inhibitors and β -blockers is to minimize the influence of the sympathetic nervous system, the purpose of this analysis of patients with acute aSAH was to (1) evaluate the relationship between preexisting cardiac disease and the development of cardiac complications after injury: elevated cardiac enzyme levels (troponin, creatine phosphokinase-MB [CPKMB] index), ECG changes (12-lead ECG and 24-hour Holter monitor), echocardiographic changes, and pulmonary edema and (2) examine the relationship between the reported use of prehospital β -blockers and ACE inhibitors and the incidence of cardiac complications after aSAH.

Methods

This study was a secondary analysis of data from a larger prospective study of aSAH patients (NIH R01HL074316). Patients were adults (ages, 24–75 years) with the diagnosis of SAH from a ruptured cerebral aneurysm and a Fisher grade greater than 1, admitted to the neurovascular intensive care unit of a regional level I trauma center. Data were excluded from analysis if the patient had renal failure, a recent myocardial infarction, a chronic or debilitating neurological disease, or a hemorrhage resulting from traumatic injury or ruptured mycotic aneurysm. Informed consent was obtained for all patients based on a protocol from the institutional review board. All inpatients received standard nursing and medical care in the neurovascular intensive care unit, including nimodipine and intravenous magnesium therapy, fluid management, temperature control, and blood and intracranial pressure management.

Patient Information and History

Clinical diagnosis, Hunt and Hess criteria, and Fisher score were evaluated and graded by the admitting physician and extracted from the medical record. Past medical history was obtained from the patients and/or their proxies. Specifically, history was obtained regarding the presence or absence of cardiovascular disease, neurological problems, pulmonary disease, hypertension, renal insufficiency, diabetes, cancer, drug and/or alcohol use, and gastrointestinal disturbances. Medications that the patient reported taking before admission were recorded and categorized according to their mechanism of action, including ACE inhibitors and β -blockers as well as antiarrhythmic agents, diuretics, statins, calcium channel blockers, and vasodilators.

Cardiac Complications

Chest radiographs, cardiac enzyme levels, and 12-lead ECGs were obtained routinely as a part of admission orders for patients admitted to this institution with a diagnosis of aSAH. Chest radiography reports were reviewed for the presence of any of 5 documented interpretations, and if 1 of the 5 were present, the patient was considered positive for pulmonary congestion (edema; Table 1). Initial troponin I, creatine phosphokinase, and CPKMB levels were measured on admission and recorded. Troponin I levels were first dichotomized as abnormal for levels exceeding 0.3 ng/mL by local clinical criteria and then further analyzed by placing the report into the following categories for additional analysis (<0.1 ng/mL, 0.1–0.3 ng/mL, and >0.3 ng/mL). An index of CPK to CPKMB (CPKMBRI) exceeding 5% was considered elevated.

Initial ECG reports were reviewed and categorized in 3 specific variables outlined in Table 1. Holter monitors were placed and recorded in 48-hour intervals. Data were uploaded with a Biomedical Systems Century C3000 Holter Analysis System to Advanced Cardiac Monitoring Inc for blinded interpretation using guidelines from the American Heart Association.¹⁵ Holter monitor data used for this analysis are also included in Table 1. Ventricular ectopy and supraventricular ectopy were further divided into 3 groups, rare (0–499 ectopic beats per 24 hours), occasional (500–999 ectopic beats per 24 hours), and frequent (>1000 ectopic beats per 24 hours).

Two-dimensional transthoracic echocardiography (Vivid 7 GE-Vingmed) was performed within 96 hours of aSAH. Left ventricular ejection fraction was assessed with the biplane Simpson's rule by using manual tracing of apical 4- and 2-chamber views in a blinded manner. Normal left ventricular function was defined as an ejection fraction of at least 50%. The wall motion score was calculated by using a standard 16-segment model. Segment scores were as follows: 1 = normal, 2 = hypokinesis, 3 = akinesis, 4 = dyskinesis. The wall

motion score index was calculated as a sum of all segment scores divided by the number of segments visualized.¹⁶ An index of 1 was categorized as normal; an index greater than 1 was categorized as a wall motion abnormality. Cardiac output and stroke volume were also calculated and recorded during echocardiography (Table 1).

Statistics

Exploratory analyses were conducted by using frequencies, percentages, means, and standard deviations as measures of variability. Univariate analyses were conducted by analyzing differences between patients with and without reported use of ACE inhibitors or β -blockers in demographic characteristics, cardiac problems, echocardiographic results, Holter monitor results, and 12-lead ECG changes. A 2-sided Pearson χ^2 exact test for categorical variables and a 1-way analysis of variance or Kruskal-Wallis test for nonnormally distributed continuous variables were used. A multinomial and binomial logistic regression model for each outcome of interest was built by using a backwards elimination procedure that included all significant predictors from the univariate analyses ($P < .10$) and drug use as the primary predictor of interest. All exploratory and multivariate analyses were carried out by using SPSS 16.0 (SPSS Inc).

Survival time was operationalized as all-cause mortality and defined as the number of days from the date of injury to either the date of death or 30 days following the injury date. Recorded death and date of death were confirmed from medical records. Kaplan-Meier curves and the log-rank test of equality across strata for all categorical predictors were used to identify significant associations between drug use and survival. All survival analyses were conducted by using STATA/SE 10.1 (StataCorp LP) for Windows.

Results

Patients

Data were examined on 254 adult patients with aSAH (mean age, 53.3; SD, 10.8 years) who provided informed consent as a part of a larger study funded by the National Institutes of Health. Patients were admitted to the hospital either directly through the emergency department or via transfer from an outlying facility. Most patients in this analysis were white ($n = 218$, 88%) and female ($n = 180$, 73%; Table 2).

Sixty-six patients in this study (27%) reported no notable past medical history. The most common preexisting medical problem was hypertension ($n=94$, 38%), and 22 patients (9%) reported known cardiac disease. More than a third of the patients in this analysis reported taking no prescribed medications before this hospitalization ($n = 101$, 41%). Of interest, 18 patients (7%) reported taking ACE inhibitors, 19 patients (7%) reported taking β -blockers. Six patients (2%) reported taking both types of medications before the aSAH; however, they were excluded from these analyses to avoid misinterpretation of study results (Table 2).

Incidence of Cardiac Complications

Nearly half of the patients in this analysis had a notable cardiac complication develop after aSAH (Table 3). Elevations in the level of cardiac troponin I ($n = 118$, 48%) and pulmonary congestion ($n = 113$, 46%) were the most frequently noted cardiac complications in the patients in this analysis. Abnormalities in admission 12-lead ECG ($n = 88$, 40%) and Holter monitoring ($n = 37$, 16%) were less common, and elevations in CPKMBRI were the least reported ($n = 30$, 12%; Table 3). The development of cardiac abnormalities was infrequently associated with preexisting cardiac disease or hypertension. No relationship was identified between cardiac disease or hypertension and the findings of elevated level of troponin I, ECG abnormalities, wall-motion abnormalities, low ejection fraction, or the presence of

pulmonary congestion. Patients with a history of hypertension were more likely to have Holter monitor changes than were patients without hypertension ($P = .05$). Conversely patients with no prior cardiac disease were more likely to have a positive CPKMBRI after aSAH than were patients with cardiac disease ($P = .01$).

Mean patient age differed significantly between those patients who reported the use of β -blockers or ACE inhibitors and patients who did not. Post-hoc tests showed that the patients who were prescribed β -blockers were older than the patients who were not taking ACE inhibitors or β -blockers, although this result was not statistically significant ($P = .07$; Table 2). No relationship was found between the reported use of prescribed ACE inhibitors and/or β -blockers before acute aSAH and the development of pulmonary congestion, elevation in cardiac enzyme levels (troponin I or CPKMBRI), heart rate, 12-lead ECG changes, or echocardiographic findings (Table 3). A relationship was noted between the use of these medications and the development of ventricular and supraventricular arrhythmias recorded by Holter monitoring. Specifically, patients who reported the use of ACE inhibitors or β -blockers before their aSAH had higher total and average ventricular and supraventricular ectopy than did those patients who did not report use of such medications ($P < .05$; Table 4).

After a relationship of both ventricular and supraventricular ectopy to the use of ACE inhibitors and β -blockers was found, a multinomial logistic regression model was used to analyze the effect of these medications on ectopy after aSAH in the presence of other factors (Table 5). Age had the overall highest impact on predicting ventricular ectopy. When age, race, sex, and injury (Fisher grade) were controlled for, patients taking β -blockers were 8 times more likely to have occasional to frequent ventricular ectopy than were patients who were not taking these medications ($P = .02$). However, when previous cardiac history, specifically hypertension, was added to the model, this effect was reduced to a borderline significant risk of 5.5 ($P = .08$).

A similar binomial logistic regression model was used to analyze the effect of ACE inhibitors and β -blockers on supraventricular ectopy. Although a significant relationship was identified during the univariate analysis ($P = .04$), this relationship was erased after age, sex, Fisher grade, and hypertension were controlled for. Only age remained significant throughout the model, with older patients more likely to have occasional/frequent supraventricular ectopy than were patients in whom supraventricular ectopy was nonexistent or rare (Table 5).

The reported use of ACE inhibitors, β -blockers, or no medications before hospitalization was not a significant predictor of survival ($P = .36$). The effect on mortality based on the prehospital prescription use of ACE inhibitors or β -blockers was explored by using Kaplan-Meier survival estimates. Of interest, no patients who reported the use of β -blockers before aSAH died, and only 1 patient who reported taking ACE inhibitors before aSAH died, as compared with 21 deaths in patients not taking these medications. This difference was not statistically significant ($P = .37$).

Discussion

In patients with aSAH, development of cardiac complications has been attributed to increased sympathetic stimulation following aneurysm rupture.¹⁻⁵ The therapeutic effects of ACE inhibitors and β -blockers are to minimize the influence of sympathetic nervous system effects, so the purpose of this study was to identify if the prehospital use of ACE inhibitors or β -blockers showed any beneficial or blunting effect on the initial cardiac complications in patients after acute aSAH. Unexpectedly, no difference in the incidence of cardiac dysfunction was noted. Rather, the patients who reported the use of prescribed ACE

inhibitors and β -blocking medications had higher incidences of both ventricular and supraventricular ectopy on initial Holter monitor readings. Emphasizing the purpose of this analysis of prescribed prehospital medications before aSAH, one possible explanation for increased incidence of both ventricular and supraventricular ectopy may be a withdrawal effect. Reports of tachycardia (and cardiac ischemia) have been cited in research of cessation of β -blockers used in patients with hypertension.^{17,18} Most recently, in a study of more than 5000 arthroplasty patients, discontinuation of β -blocker prescription was associated with a significant risk of postoperative myocardial infarction (odds ratio, 2.0; 95% CI, 1.1–3.9).¹⁹

Reports of the value of β -blockers during other stress-inducing disease states such as traumatic brain injury, intracranial hemorrhage, and burns have noted positive effects when β -blockers are used during the acute inpatient period in reducing heart rate, arrhythmias, neurogenic pulmonary edema, and other adrenergic driven effects.^{20,21} In a study of 234 aSAH patients, reported prehospital use of β -blockers was associated with a decreased risk of development of neurogenic stunned myocardium ($P = .049$), which may also have been influenced by sex and menopausal status.²¹ This current analysis did not reveal the same effects on presenting cardiopulmonary responses after aSAH in patients taking the key medications before their aSAH event. Patients in this analysis who reported prehospital use of either ACE inhibitors or β -blockers did not differ in baseline heart rate, 12-lead ECG findings, or myocardial function by echocardiogram (left ventricular ejection fraction, wall-motion abnormalities, stroke volume, or cardiac output) from patients who did not report the use of these medications. Likewise, consistent with our previous work, this larger and more comprehensive analysis of 254 patients did not reveal significant relationships between a history of previous cardiac disease and the development of cardiac complications after acute aSAH.⁵ Only elevations in CPKMBRI were noted more frequently in patients with previous cardiac disease; however, the incidence of elevated CPKMBRI was the lowest of all cardiac complications in this analysis. Also as previously reported in analyzing QTc and ventricular arrhythmias, age and severity of injury continue to be identified as major factors in the incidence of ventricular ectopy after aSAH.²²

Researchers examining the effect of prior medical treatments on outcome after acute neurological events and other hospitalization have reported mixed results. In a study of ischemic stroke patients, researchers found that the use of ACE inhibitors alone or in combination with antiplatelets and/or statins was associated with better functional outcomes.²³ Likewise β -blocker exposure was associated with improved survival in patients with severe traumatic brain injury.²⁰ In contrast, β -blocker withdrawal has been associated with increased mortality and poor outcomes in a variety of patient care situations. In a study²⁴ of nearly 39 000 operations during a 12-year span, researchers evaluating the use of perioperative β -blockers as a standardized protocol found that clinical use of β -blockade resulted in reduced perioperative mortality. They also reported, however, that withdrawal of β -blockers during this period was associated with increased short- and long-term mortality.²⁴ Similar to patients in this study, the withdrawal group consisted of patients who reported the use of β -blockers before surgery but did not receive a single dose after surgery. Similar results were also documented in a study of 285 vascular surgical patients where perioperative withdrawal of β -blocker therapy was associated with a higher 1-year mortality compared with nonusers (hazard ratio, 2.7; 95% CI, 1.2–5.9).²⁵ In 2 separate studies^{26,27} of ischemic stroke, prior medical treatment had no effect on stroke severity or outcome. In this analysis, all patients taking β -blockers before aSAH were alive 30 days after their injury, and no significant difference in mortality based on prehospital medication exposure was found.

Limitations

This analysis was reliant on reports of medication use and adherence provided by patients and their representatives. In addition, the relatively small number of patients reporting the use of ACE inhibitors and b-blockers before neurological injury may limit the findings. Drug dosage, hours from last dose, and consistency of use along with continuing medications after admission may also play a role in the effectiveness of these medications during sympathetic stimulation.

Conclusion

Cardiopulmonary compromise is frequently reported in patients after aSAH. Unfortunately, the presence of prescribed prehospital medication or the existence of known cardiac disease could not offer any insight into the subset of patients that exhibit this response. This analysis was unable to provide any concrete evidence that prehospital exposure to adrenergic blockade provides distinct reduction in initial symptoms of catecholamine surge reported after aSAH. This conclusion is not intended to negate the role of these medications in counteracting these symptoms, and further research in this area is necessary to combat the effects of adrenergic stress response that are frequently reported after aSAH. More importantly, current research is providing more support for ensuring the continuation of existing prescribed medications during hospitalization to avoid potential compounding withdrawal effects. Unlike other acute admissions, resuming home medications is very often a secondary consideration in an attempt to strictly manage blood pressure in patients with aSAH. The practitioners who care for patients with aSAH may want to carefully consider the possible cardiovascular side effects of withholding these medications in these patients. Based on this analysis and the potential for withdrawal to cause an additive effect on cardiac abnormalities, future research could target withdrawal in this population.

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Notice to CNE enrollees

A closed-book, multiple-choice examination following this article tests your understanding of the following objectives:

1. Describe the cardiac abnormalities that occur after aneurysmal subarachnoid hemorrhage.
2. Identify the indications for use of angiotensin-converting enzyme (ACE) inhibitors and β -blockers.
3. Discuss the effects ACE inhibitors and β -blockers have on cardiac abnormalities after aneurysmal subarachnoid hemorrhage.

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Table 1

Diagnostic evaluations

Chest radiograph	Hilar edema Hilar fullness	Interstitial edema Pulmonary congestion	Pulmonary edema
Cardiac enzyme levels	CPKMBRI (index of ratio of creatine phosphokinase to creatine phosphokinase MB fraction)		Troponin I
12-lead electrocardiography	Interpretations: within normal limits, arrhythmia present, QT abnormalities, ST-segment abnormalities, injury pattern Ischemia: presence or absence Rhythm: normal sinus rhythm, bradycardia, tachycardia, supraventricular tachycardia, arrhythmia		
Holter monitor	Heart rate Ventricular ectopy	ST-segment depression ST-segment elevation	Supraventricular ectopy Mean QT segment
Echocardiography	Ejection fraction Cardiac output	Wall motion score Stroke volume	

Table 2

Sociodemographic and clinical characteristics by reported medication use

Characteristic ^a	None (n = 211)	ACE inhibitor only (n = 18)	β -Blocker only (n = 19)	Total (N = 248)	P
Sex					.87
Male	57 (27)	6 (33)	5 (26)	68 (27)	
Female	154 (73)	12 (67)	14 (74)	180 (73)	
Race					.10
White	187 (89)	17 (94)	14 (74)	218 (88)	
Nonwhite	24 (11)	1 (6)	5 (26)	30 (12)	
Hunt and Hess score					.27
Low (1–2)	88 (42)	4 (22)	8 (42)	100 (40)	
High (3–5)	123 (58)	14 (78)	11 (58)	148 (60)	
Fisher grade					.94
2	71 (34)	6 (33)	8 (42)	85 (34)	
3	98 (46)	9 (50)	7 (37)	114 (46)	
4	42 (20)	3 (17)	4 (21)	49 (20)	
Past medical history					
None	66 (31)	0 (0)	0 (0)	66 (27)	<.001
Cardiac	16 (8)	2 (11)	4 (21)	22 (9)	.14
Hypertension	60 (28)	18 (100)	16 (84)	94 (38)	<.001
Pulmonary	18 (9)	2 (11)	0 (0)	20 (8)	.50
Neurological problems	13 (6)	0 (0)	2 (11)	15 (6)	.40
Cancer	14 (7)	1 (6)	3 (16)	18 (7)	.31
Diabetes mellitus	10 (5)	0 (0)	2 (11)	12 (5)	.27
Drug abuse	12 (6)	0 (0)	1 (5)	13 (5)	.85
Alcohol abuse	18 (9)	0 (0)	1 (5)	19 (8)	.54
Gastrointestinal problems	13 (6)	1 (6)	3 (16)	17 (7)	.29
Other	66 (31)	4 (22)	3 (16)	73 (29)	.29
Prescribed medications					

Characteristic ^a	None (n = 211)	ACE inhibitor only (n = 18)	β-Blocker only (n = 19)	Total (N = 248)	P
None	101 (48)	0 (0)	0 (0)	101 (41)	<.001
Diuretics	9 (4)	9 (50)	5 (26)	23 (9)	<.001
Vasodilators	2 (1)	1 (6)	2 (11)	5 (2)	.03
Calcium channel blockers	5 (2)	2 (11)	0 (0)	7 (3)	.12
Other	87 (41)	13 (72)	14 (74)	114 (46)	.001
Statins	16 (8)	3 (17)	2 (11)	21 (8)	.42
Age, mean (SD), y	52.4 (10.4)	57.4 (12.1)	58.3 (12.2)	53.3 (10.8)	.02

Abbreviation: ACE, angiotensin-converting enzyme.

^aValues in table are number (percentage) unless otherwise indicated.

Table 3
Development of echocardiographic and cardiac problems by prescribed medications

Characteristic ^a	None	ACE inhibitor only	β-Blocker only	Total	P
Cardiac abnormalities					
Troponin elevation	96 (46)	12 (67)	10 (53)	118 (48)	.29
CPKMBRI elevation	25 (12)	4 (22)	1 (5)	30 (12)	.30
Holter monitor abnormality	26 (13)	6 (33)	5 (26)	37 (16)	.04
12-Lead electrocardiography abnormality	69 (37)	9 (50)	10 (62)	88 (40)	.09
Pulmonary edema	93 (44)	12 (67)	8 (42)	113 (46)	.19
Echocardiography					
Wall motion abnormality (>1)	19 (13)	2 (12)	1 (8)	22 (13)	.91
Abnormal ejection fraction (<50%)	19 (14)	1 (7)	1 (9)	21 (13)	.81
Stroke volume, mean (SD), mL	67.8 (19.7)	67.8 (17.0)	77.0 (20.7)	68.7 (19.5)	.28
Cardiac output, mean (SD), L/min	5.2 (1.6)	5.3 (1.4)	5.7 (1.0)	5.3 (1.6)	.28
Troponin level, mean (SD), ng/mL	1.5 (4.7)	0.6 (1.2)	0.4 (0.9)	1.3 (4.3)	.29

Abbreviations: ACE, angiotensin-converting enzyme; CPKMBRI, index of ratio of creatine phosphokinase to creatine phosphokinase MB fraction.

^aValues are number (percentage) unless otherwise indicated. The percentages are derived from the number of patients with the selected testing with positive findings within each medication group.

Table 4

Holter monitoring and 12-lead electrocardiographic abnormalities by medications

Characteristic ^a	None	ACE inhibitor only	β-Blocker only	P
12-Lead electrocardiography				.57
Within normal limits	64 (45)	3 (20)	3 (27)	
Arrhythmia	1 (1)	0 (0)	0 (0)	
QT interval changes	16 (11)	3 (20)	2 (18)	
ST-segment changes	19 (13)	3 (20)	1 (9)	
Injury pattern	43 (30)	6 (40)	5 (45)	
Ischemia	31 (27)	5 (56)	2 (29)	.19
Rhythm				.10
Normal sinus	107 (67)	15 (100)	11 (92)	
Sinus bradycardia	19 (12)	0 (0)	0 (0)	
Sinus tachycardia	16 (10)	0 (0)	0 (0)	
Arrhythmia	18 (11)	0 (0)	1 (8)	
Holter monitoring				
ST-segment depression	22 (11)	1 (6)	3 (16)	.64
ST-segment elevation	12 (6)	1 (6)	0 (0)	.55
Heart rate, mean (SD), beats per minute				
Mean	81.3 (12.7)	80.4 (10.1)	80.2 (8.7)	.99
Minimum	56.3 (12.1)	57.9 (10.8)	55.4 (9.9)	.92
Maximum	120.4 (18.5)	116.5 (12.7)	121.6 (19.8)	.85
QT interval, mean (SD), s	351.7 (47.8)	339.2 (39.4)	346.6 (44.7)	.54
Ectopy per 24-h period, median (range)				
Ventricular				
Total	5.0 (0–17 092)	28.0 (0–16 811)	13.0 (0–14 452)	.02
Mean	0.1 (0–464.10)	0.8 (0–352)	0.3 (0–303)	.02
Supraventricular				
Total	66.0 (0–12 839)	272.5 (3–7138)	68.0 (6–3831)	.02
Mean	1.8 (0–297)	6.1 (0.10–160.9)	1.5 (0.2–206.6)	.03

Abbreviations: ACE, angiotensin-converting enzyme.

^aValues are number (percentage) unless otherwise indicated. The percentages are derived from the number of patients with the selected testing with positive findings within each medication group.

Table 5

Regression of mean ventricular and supraventricular ectopy

Type of ectopy	<i>P</i>	<i>Odds ratio</i>
Ventricular ectopy, rare (<20 ectopic beats/24 h) ^a		
Age	.001	1.05
White (vs nonwhite)	.09	2.27
Female (vs male)	.23	0.66
Hypertension (vs none)	.44	1.31
Fisher grade (vs Fisher 2)		
3	.66	1.16
4	.65	1.22
Medication use (vs none)		
β-Blocker	.18	2.73
ACE inhibitor	.63	0.73
Ventricular ectopy, occasional/frequent (>20 ectopic beats/24 h) ^a		
Age	.001	1.11
White (vs nonwhite)	.27	3.82
Female (vs male)	.12	0.38
Hypertension (vs none)	.19	2.39
Fisher grade (vs Fisher 2)		
3	.94	0.95
4	.41	1.89
Medication use (vs none)		
β-Blocker	.08	5.53
ACE inhibitor	.92	1.10
Supraventricular ectopy, occasional/frequent (>20 ectopic beats/24 h) ^b		
Age	<.001	1.09
Female (vs male)	.54	0.75
Hypertension (vs none)	.47	1.42
Fisher grade (vs Fisher 2)		
3	.60	1.30
4	.82	0.87
Medication use (vs none)		
β-Blocker	.47	1.64
ACE inhibitor	.48	1.66

Abbreviation: ACE, angiotensin-converting enzyme.

^aReference group: no ectopy.^bReference group: none/rare (0–20 ectopic beats/24 h).