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REDUCING ELEVATED HEART RATES IN PATIENTS WITH MULTIPLE ORGAN DYSFUNCTION SYNDROME WITH THE I_F (FUNNY CHANNEL CURRENT) INHIBITOR IVABRADINE

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ABSTRACT—**Introduction:** A heart rate higher than 90 beats/min indicates an unfavorable prognosis for patients with multiple organ dysfunction syndrome (MODS). We sought to investigate the effect of the pacemaker current (I_f) inhibitor ivabradine on heart rate, hemodynamics, and disease severity among patients with MODS. **Patients and Methods:** In this prospective, controlled, randomized, open-label, two-arm phase II trial, 70 patients with MODS, a sinus rhythm of at least 90 beats/min, and contraindications to β-blocker therapy were randomly assigned to receive the standard treatment ± ivabradine (5 mg twice daily) for 96 h via the enteral route. The primary outcome was the percentage of patients with a heart rate reduction of at least 10 beats/min after 96 h. Secondary outcomes included the effect of ivabradine on hemodynamics, disease severity, vasopressor use, mortality, and adverse events. **Results:** There were no significant differences in the primary outcome between the ivabradine and control groups ($P = 0.147$). After 96 h, the daily median heart rate was reduced by 7 beats/min in the control group and by 16 beats/min in the ivabradine group ($P = 0.014$). No differences in secondary outcomes were observed. **Conclusions:** The number of critically ill patients with MODS and a sinus rhythm of at least 90 beats/min that experienced a heart rate reduction of at least 10 beats/min after oral ivabradine treatment did not differ significantly between groups. The moderate but significant reduction of heart rate by 7 beats/min did not affect hemodynamics or disease severity.

KEYWORDS—Autonomous nervous system, heart rate, hemodynamics, ivabradine, multiple organ dysfunction syndrome, tachycardia

INTRODUCTION

Multiple organ dysfunction syndrome (MODS) is defined as a clinical syndrome present in acutely ill patients with consecutive or simultaneous malfunctions of several vital organs. In the medical intensive care unit (ICU), MODS is predominantly either of cardiogenic origin, mostly due to myocardial infarction complicated by cardiogenic shock (coronary MODS), or of septic origin, ''life-threatening organ dysfunction caused by a dysregulated host response to an infection'' (1). The number and extent of impairments in dysfunctioning organs are predictors of mortality in patients with coronary MODS (2) and noncoronary MODS (3). The time between diagnosis and organ-specific intervention is of crucial importance and has prognostic relevance among these patients, and it should be reduced to a minimum (4).

MODS is characterized by an inadequately high heart rate with prognostic relevance (28-day mortality) and has a hazard ratio of 2.3 for patients with a heart rate $\geq$90 beats/min compared with patients with a heart rate $<$90 beats/min (5). Many factors contribute to this inadequately high heart rate in patients with MODS, such as fever, hypovolemia, endogenous and therapeutically applied catecholamines, and systemic and myocardial inflammation as well as more specific factors, such as cardiac autonomic dysfunction (6, 7) with dominant sympathetic tone (8), endotoxin-induced sensitization of the cardiac pacemaker cells to sympathetic neurotransmitters (9), and the partial uncoupling of the cardiac pacemaker from cholinergic neural control (10).

A therapeutic intervention to lower the heart rate of patients with septic shock was attempted using the short-acting β_1-blocker esmolol (8). However, β-receptor blockage not only reduces heart rate but also systemically attenuates sympathetic autonomic dysfunction in a widespread and noncardiac-specific manner. A more direct approach may be reducing the spontaneous depolarization of the sinoatrial pacemaker current I_f by the specific blockage of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, which represent the molecular basis of the pacemaker current I_f. As autonomic control of

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the heart is exerted via the I_f current and inflammatory status as well as endotoxin directly influence this pacemaker current, thus contributing to autonomic isolation of the heart with an ineffectively high heart rate, we strived to specifically block this sinoatrial pacemaker current. Hence, we attempted to reduce the heart rates of patients with MODS and sinus rhythm $\geq$90 beats/min by specifically blocking the sinoatrial pacemaker current I_f with the HCN channel inhibitor ivabradine. A relevant change in disease severity within the first 4 days of treatment has been shown to be a powerful mortality-associated improvement index (11, 12). Therefore, this initial treatment period is considered to be particularly important and a suitable time window to influence prognosis. According to the findings of preliminary works (5), which observed that the median baseline heart rate significantly differed by 9 beats/min between survivors (83 beats/min) and nonsurvivors (92 beats/min), we hypothesized that enteral administration of ivabradine every 12 h in addition to the standard treatment in patients with early MODS (diagnosis $\leq$24 h, Acute Physiology and Chronic Health Evaluation II [APACHE II (13)] score $\geq$20) who have contraindications to β-blocker treatment according to the corresponding Summary of Product Characteristics would significantly lower their heart rate by at least 10 beats/min after 96 h. To demonstrate the efficacy of this treatment, we initiated the MODI_fY trial (''Reducing elevated heart rate in patients with Multiple Organ Dysfunction syndrome with the I_f [funnY channel current] inhibitor ivabradine'' trial).

PATIENTS AND METHODS

The MODI_fY trial was an investigator-driven trial sponsored by Martin Luther University Halle-Wittenberg and has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki and its later amendments. The study protocol was reviewed and approved by the local ethics committee and published in detail elsewhere (14).

PATIENTS

We performed the trial in the 12-bed medical ICU of the Department of Internal Medicine III at the University Hospital Halle (Saale) in Germany after obtaining written informed consent from either the patient, the health care proxy, or a provisional supervisor (14). Enrollment of the 70 patients occurred between May 2010 and October 2011. The last patient finished the trial in May 2012.

The patients had to meet the following inclusion criteria: MODS was diagnosed within the previous 24 h and characterized by an APACHE II score $\geq$20, a coronary or noncoronary etiology, sinus rhythm $\geq$90 beats/min, existing contraindications to β-blockers according to the corresponding summary of product characteristics, written informed consent, and an identified or suspected willingness to undergo the trial treatment. Coronary etiology was defined as primary ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction with cardiogenic shock and subsequent development of MODS, and a noncoronary etiology was defined as cardiac disease or noncardiac disease, such as sepsis/septic shock, accompanying the development of MODS. Exclusion criteria included but were not limited to the following (14): a history of preexisting renal failure with a glomerular filtration rate $<$30 mL/min, a type of shock other than cardiogenic or septic shock, sick sinus syndrome, sinoatrial block, pacemaker dependency, third-degree atrioventricular block, and use of potent cytochrome P450 3A4 inhibitors, such as antifungals of the azole-type (ketoconazole and itraconazole), macrolide antibiotics (clarithromycin, erythromycin per os, josamycin, and telithromycin), HIV protease inhibitors (nelfinavir and ritonavir), and nefazodone (see the Summary of Product Characteristics).

STUDY DESIGN

This study was a prospective, single-center, open-label, randomized, controlled, two-arm phase II trial. Our primary objective was to determine the percentage of patients with at least a 10 beats/min reduction in the mean heart rate 96 h after the start of the trial treatment. A relevant decrease of the APACHE II-score by at least 4 points within the first 4 days of treatment has been shown to be a powerful mortality-associated improvement index (11, 12). Therefore, this initial treatment period was considered to be particularly important and a suitable time window to influence prognosis. Secondary objectives of an explanatory character (14) included the effects of ivabradine treatment on the cardiac index after 96 h, cardiac power index, disease severity (APACHE II score and sepsis-related [sequential] organ failure assessment [SOFA] score) (3), vasopressor use, 28-day and 6-month mortality, and safety. Daily measurements of the plasma ivabradine levels and subgroup analyses (age: $</\geq$70 years; coronary MODS/noncoronary MODS) were performed.

The baseline average heart rate was electronically registered over a period of 6 h (14). Then, before every administration of ivabradine in the ivabradine group, the patients' heart rates were assessed by printing an electrocardiogram with a 1-min duration. Patients were randomly assigned via an Internet-based randomization procedure (day 0). All patients received an established treatment according to the discretion of the responsible physician. Patients in the ivabradine-treated group received an additional enteral preparation (orally via a nasogastric tube or a percutaneous endoscopic gastrostomy probe) of ivabradine for 4 consecutive days (administered twice daily (b.i.d.) at 6 AM and 6 PM from days 1 to 4). The ivabradine dose was 5 mg b.i.d. on days 1 and 2 if the heart rate was $\geq$60 beats/min; 5 mg b.i.d. on days 3 and 4 if the heart rate was $\geq$60 and $<$90 beats/min; and 7.5 mg b.i.d. if the heart rate was $\geq$90 beats/min. Ivabradine was not administered to patients whose heart rates were $<$60 beats/min, patients with newly diagnosed atrial fibrillation, or patients with acute renal failure and a heart rate $<$70 beats/min.

The study ended with a telephone interview on day 180 (survival status).

CLINICAL EXAMINATIONS AND DATA COLLECTION

The enrollment data set, basic data set, autonomous nervous system data set, vascular data set, and laboratory data set are thoroughly described in Nuding et al. (14).

The *catecholamine data set* included the cumulative doses of norepinephrine, epinephrine, and dobutamine in the past 12 h and the vasopressor score (15).

The *scores data set* included the APACHE II (13) and SOFA (3) scores.

The *follow-up data set* included the patients' survival.

The *adverse event (AE) data set (yes/no answers)* included phosphenes, defibrillation, pacemaker placement, amiodarone use, atropine use, orciprenaline use, percutaneous coronary intervention, dialysis, seizure, fever, new antibiotic use, and others.

For the *ivabradine pharmacokinetics measurements*, blood samples were taken daily from day 0 to day 4 to measure the levels of ivabradine (S 16257) and its metabolite, *N*-desmethyl ivabradine (S 18982) (NUVISAN Gmbh, Neu-Ulm, Germany), according to previously described methods.

SAMPLE SIZE CALCULATION

The calculation was based on the analysis of the primary outcome using a two-sided chi-square test. After 96 h of ivabradine treatment, approximately 75% of patients' heart rates were estimated to be reduced by at least 10 beats/min, based on the findings from a small pilot study (14), and approximately 45% of the control group exhibited this reduction, based on data from the Score-Based Immunoglobulin G Therapy of patients with Sepsis (SBITS) study ($n = 303$) (11). Twenty-six patients in each group were required for a significance level of $\alpha = 0.05$ and a power of 60%. Because of an expected dropout rate of 25% (mortality), 35 patients/group were included (14).

STATISTICAL ANALYSIS

Metric and normally distributed data are presented as the mean $\pm$ standard deviation (SD) and were tested for group differences using Student *t* test. Metric, but not normally distributed data, were calculated as medians and interquartile ranges (IQR) and were tested for group differences using the Mann–Whitney *U* test. Ordinal data were evaluated using the Mann–Whitney *U* test, and nominal data were tested using the chi-square test. Missing data were handled using the ''last observation carried forward'' method (16). We calculated the areas under the curves (AUCs) relative to baseline values for

continuous variables with repeated measurements to avoid multiple comparisons (17). We compared the AUCs between two groups using the Mann–Whitney U test. The primary endpoint was confirmed if it achieved a two-sided significance level of $\alpha = 0.05$. All other reported P values are exploratory.

In the intention-to-treat approach, patients were randomly allocated to either the control group or the ivabradine group, as stated above. Death was the only reason for discontinuation, and therefore, the intention-to-treat groups also represent the per-protocol groups.

RESULTS

Patients

From May 2010 to October 2011, 70 out of 831 patients at our medical/cardiological ICU fulfilled the inclusion criteria and were included in the study (Fig. 1). Baseline data for the groups (Table 1) were similar, with the exception of a decrease in the heart rate variability parameter standard deviation of all normal to normal (SDNN) intervals (normal range 141 ± 39 s) (6) in the ivabradine group. Sixty-seven of the 70 patients required respiratory support. One-quarter of the patients had coronary MODS and three-quarters had noncoronary MODS.

Ivabradine pharmacokinetics

Ivabradine was administered via the enteral route b.i.d. (6 AM and 6 PM) from days 1 to 4. The median daily dose (IQR) was 10 mg (10–10 mg) on days 1 and 2, 10 mg (10–12.5 mg) on day 3, and 10 mg (5–12.5 mg) on day 4. eFigure 1 presents the plasma levels of ivabradine (eFigure 1, top, http://links.lww.com/SHK/A639) and its metabolite, *N*-desmethyl-ivabradine (eFigure 1, bottom, http://links.lww.com/SHK/A639).

Heart rate and heart rate variability

Figure 2 shows the time course of the daily average heart rates for each patient. The heart rate-lowering effect of the 96-h ivabradine treatment was visible.

Figure 3 and Table 2 show the median heart rates (IQR) during the 96-h treatment period. Median heart rates of the patients in the control group fell from 103 beats/min (93–123) at 0 h to 96.0 beats/min (89–107) at 96 h ($\Delta = -7$ beats/min), and the median heart rates of patients in the ivabradine group fell from 105 beats/min (93–122) at 0 h to 89 beats/min (77–101) at 96 h ($\Delta = -16$ beats/min), with an intergroup difference of −9 beats/min ($P = 0.014$). The 96-h ivabradine treatment reduced the patients' heart rates (mean ± SD) during the day (84 ± 12 beats/min vs. 93 ± 14 beats/min) and at night (84 ± 14 beats/min vs. 97 ± 15 beats/min); a reduction in the minimal heart rate (70 ± 12 beats/min vs. 82 ± 15 beats/min) but not the maximal heart rate (104 ± 22 beats/min vs. 107 ± 15 beats/min) was observed. More patients in the ivabradine group (55.6%, 20/36) exhibited a heart rate reduction of at least 10 beats/min than patients in the control group (38.2%, 13/34). However, this difference in the primary endpoint was not statistically significant ($P = 0.147$). This result was due to a lower percentage of heart rate reductions in the ivabradine group (55.6%) than was originally predicted (75%), whereas the percentage in the control group (38.2%) was similar to the original prediction (45%) (see "Patients and Methods" section).

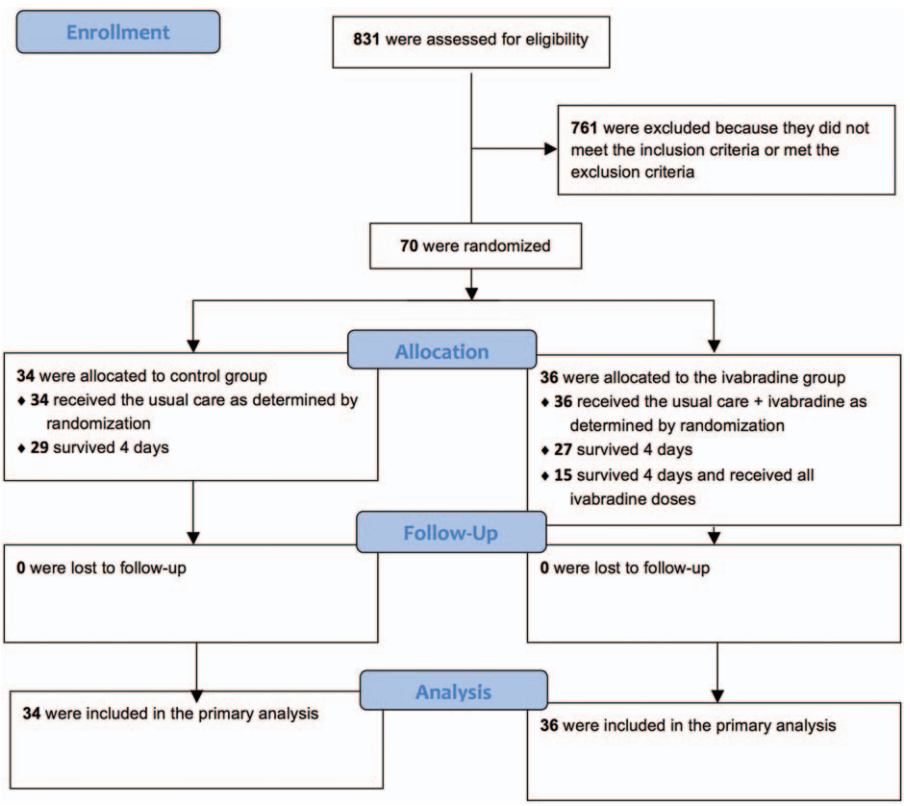

FIG. 1. **MOD*I*Y trial flow diagram.**

TABLE 1. **Baseline characteristics of the study population**

		"Intention-to-treat" group = "per-protocol" group	
		Control group n = 34	Ivabradine group n = 36
Age (yr)	Median (IQR)	62 (50–72)	68 (51–73)
Men	No. (%)	25 (74%)	23 (64%)
BMI (kg/m^2)	Median (IQR)	26 (22–30)	26 (23–28)
APACHE II score	Median (IQR)	35 (29–38)	34 (31–40)
SOFA score	Median (IQR)	16 (13–17)	16 (14–18)
Mean norepinephrine dose (μg/kg $\times$ min)	Median (IQR)	0.26 (0.05–0.55)	0.27 (0.07–0.57)
Vasopressor score (μg/kg $\times$ min)	Median (IQR)	26.6 (5.1–72.3)	27.9 (8.3–61.8)
K^+ (mmol/L)	Median (IQR)	4.6 (4.3–5.0)	4.7 (4.4–5.1)
Lactate (mmol/L)	Median (IQR)	1.7 (1.2–2.8)	2.2 (1.4–4.2)
White blood cells (Gpt/L)	Median (IQR)	12.9 (8.9–18.8)	12.3 (8.7–18.3)
Platelets (Gpt/L)	Median (IQR)	180 (89–283)	152 (101–229)
Hemoglobin (mmol/L)	Median (IQR)	6.5 (5.2–7.4)	6.6 (6.0–7.5)
Creatinine (μmol/L)	Median (IQR)	159 (101–189)	148 (108–242)
MAP (mmHg)	Median (IQR)	77 (68–86)	73 (66–83)
CVP (mmHg)	Median (IQR)	16 (11–18)	14 (10–17)
MPAP (mmHg)	Median (IQR)	35 (25–45)	26 (24–35)
SVR (dyn $\times$ s $\times$ cm^{-5})	Median (IQR)	770 (520–930)	919 (688–1,086)
SVRI (dyn $\times$ s $\times$ cm^{-5}/m^2)	Median (IQR)	423 (258–526)	480 (306–607)
GEDV (mL)	Median (IQR)	881 (759–944)	651 (508–824)
GEDVI (mL/m^2)	Median (IQR)	470 (412–516)	304 (255–379)
ITBV (mL)	Median (IQR)	1100 (949–1180)	802 (635–1018)
ITBVI (mL/m^2)	Median (IQR)	588 (515–645)	375 (318–468)
EVLW (mL/kg)	Median (IQR)	13 (9–21)	10 (8–24)
EVLWI (mL/kg/m^2)	Median (IQR)	6 (5–12)	4 (4–11)
CO (L/min)	Median (IQR)	7.2 (4.9–8.6)	5.6 (3.9–7.1)
CI (L/min/m^2)	Median (IQR)	3.8 (2.6–4.5)	3.1 (2.2–3.5)
Average heart rate (beats/min)	Median (IQR)	103 (93–123)	105 (93–122)
Minimum heart rate (beats/min)	Median (IQR)	94 (85–110)	96 (88–109)
Maximum heart rate (beats/min)	Median (IQR)	112 (101–135)	109 (98–129)
Mean heart rate at day (beats/min)	Median (IQR)	101 (91–111)	100 (94–115)
Mean heart rate at night (beats/min)	Median (IQR)	97 (86–116)	104 (91–116)
24-h SDNN (ms)	Median (IQR)	25 (10–55)	12 (7–33)
Age $<$70 (yr)	No. (%)	24 (71%)	21 (58%)
Age $\geq$70 (yr)	No. (%)	10 (29%)	15 (42%)
APACHE II $\leq$ 35	No. (%)	19 (56%)	22 (61%)
APACHE II $>$ 35	No. (%)	15 (44%)	14 (39%)
Coronary MODS	No. (%)	8 (24%)	9 (25%)
Noncoronary MODS	No. (%)	26 (76%)	27 (75%)
Spontaneous breathing	No. (%)	2 (6%)	1 (3%)
Respiratory support	No. (%)	32 (94%)	35 (97%)
HFOV/PC/BIPAP/ASB	No.	1/11/14/6	0/12/21/2
HFOV/PC/BIPAP/ASB	%	3/32/41/18	0/33/58/6
FiO_2	Median (IQR)	0.55 (0.48–0.76)	0.58 (0.42–0.86)
PEEP (mbar)	Median (IQR)	10 (10–12)	11 (10–13)
PiP (mbar)	Median (IQR)	26 (20–29)	26 (22–29)
Breathing rate (breaths/min)	Median (IQR)	25 (21–27)	22 (20–27)

The vasopressor score (μg/kg/min) was calculated using the following formula reported by Zuppa et al. (15) (dopamine $\times$ 1) + (dobutamine $\times$ 1) + (epinephrine $\times$ 100) + (norepinephrine $\times$ 100) + (phenylephrine $\times$ 100).

APACHE II score, Acute Physiology and Chronic Health Evaluation II score; ASB, augmented spontaneous breathing; BIPAP, biphasic positive airway pressure; BMI, body mass index; CI, cardiac index; CO, cardiac output; CVP, central venous pressure; EVLW (I), extravascular lung water (index); FiO_2, fraction of inspired oxygen; GEDV (I), global end-diastolic volume (index); HFOV, high frequency oscillatory ventilation; ITBV (I), intrathoracic blood volume (index); MAP, mean arterial pressure; MODS, multiple organ dysfunction syndrome; MPAP, mean pulmonary arterial pressure; PAP, pulmonary arterial pressure; PC, pressure-controlled; PEEP, positive end-expiratory pressure; PiP, peak inspiratory pressure; SDNN, standard deviation of all normal to normal (NN) intervals; SVR (I), systemic vascular resistance (index).

Hemodynamics, organ dysfunction, and disease severity

No important intergroup differences in hemodynamics or disease severity were observed during the first 96 h (Table 2), as measured by the APACHE II and SOFA scores.

Adverse events and outcome data

AEs occurred in 65 of the 70 patients, including 31 of the 34 patients in the control group and 34 of the 36 patients in the ivabradine group. Anemia occurred most frequently in the control and ivabradine groups. Other frequent AEs regardless of intensity and preferred terms were infections of any kind, renal failure of any kind, septic shock, fever, tachyarrhythmia, and atrial fibrillation. Regarding the AEs that occurred in patients in the ivabradine group, a causal relationship with the ivabradine treatment was classified as "absent" or "unlikely" in all cases.

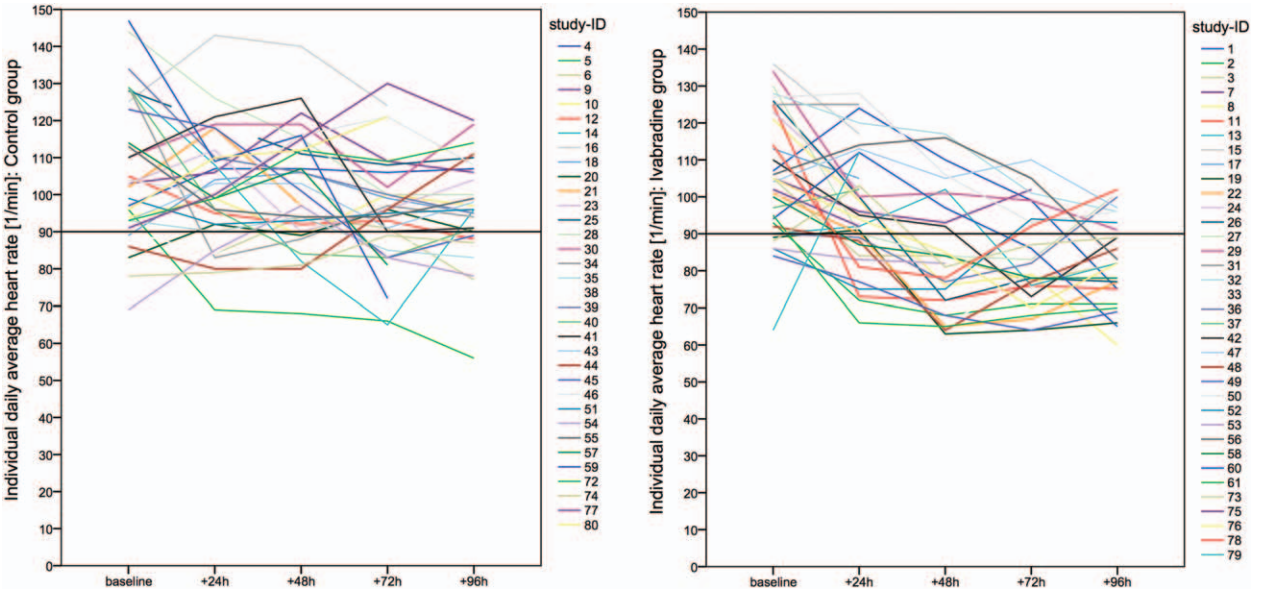

Fig. 2. **Individual time courses of the daily mean heart rate in both groups. Control group (top) and ivabradine group (bottom).** The solid line at 90 beats/min indicates the lower limit of the inclusion criterion for heart rate.

Severe adverse events (SAEs), also recorded as AEs, occurred in 32 of the 70 patients, including 18 SAEs in 14 of the 34 patients of the control group, and 27 SAEs in 18 of the 36 patients of the ivabradine group. Septic shock (6 vs. 5), endocarditis (1 vs. 1), pneumonia (1 vs. 1), pseudomembranous colitis (1 vs. 0), right heart failure (1 vs. 0), tachyarrhythmia (1 vs. 0), ventricular tachycardia (1 vs. 1), cardiogenic shock (1 vs. 3), peripheral ischemia (1 vs. 0), acute respiratory distress syndrome (1 vs. 0), ischemic colitis (1 vs. 0), acute renal failure (1 vs. 4), renal failure (0 vs. 1), fever (1 vs. 0), sepsis (0 vs. 1), anemia (0 vs. 1), disseminated intravascular coagulation (0 vs. 1), MODS (0 vs. 3), bradycardia (0 vs. 1), atrial flutter (0 vs. 1), acute myocardial infarction (0 vs. 1), hemorrhagic shock (0 vs. 1), and liver failure (0 vs. 1) occurred in the control and ivabradine groups, respectively. Regarding the SAEs that occurred in patients in the ivabradine group, a causal relationship with the ivabradine treatment was classified as ''absent'' or ''unlikely'' in all cases.

The 28-day mortality was 47.1% (16/34) in the control group and 63.9% (23/36) in the ivabradine group (Table 3: ''intention-to-treat/per-protocol'') ($P = 0.157$). No deaths were caused by incidental bradycardia or asystole. None of the deaths were considered related to the study treatment by the investigators or by the Safety Monitoring Board. Notably, the 28-day mortalities of the groups (Table 3) were below the approximately 80% mortality risk estimated by the patients' respective APACHE II and SOFA scores.

The 180-day mortality was 61.8% (21/34) in the control group and 75% (27/36) in the ivabradine group (Table 3: ''intention-to-treat/per-protocol'') ($P = 0.233$). The causes of death (control group vs. ivabradine group) within 180 days were MODS (71.4% vs. 85.2%), a defined event other than MODS (19.0% vs. 3.7%), and an unknown event other than MODS (9.5% vs. 11.1%). The five patients with unknown causes of death (two in the control group and three in the ivabradine group) passed away between days 33 and 118. Neither incidental bradycardia nor asystole caused the deaths of these patients.

A similar trend of higher 28-day and 6-month mortality rates was observed in the control patients who survived for at least 4 days (Table 3: ''4-day survivor group''). Nearly identical mortality rates were observed in the ivabradine-treated patients who survived for at least 4 days and had received the full drug regimen of eight doses of ivabradine (Table 3: ''4-day survivors in the control group vs. 4-day survivors that received all 8 ivabradine doses in the ivabradine group'').

Subgroup analysis

The heart rate-reducing effect of ivabradine was prospectively examined in the subgroups of patients with coronary MODS (n = 17) and noncoronary MODS (n = 53), as well as in patients <70 years of age (n = 45) and ≥70 years of age (n = 25). A *post hoc* analysis was also performed for patients with initial APACHE II scores ≤35 (n = 41) and >35 (n = 29).

In all of the tested subgroups (eTable 1, http://links.lww.com/SHK/A640), ivabradine reduced the basal heart rate at 96 h after treatment. Compared with the control group, differences in the heart rate at 96 h after treatment were only observed in the noncoronary MODS group, in patients aged <70 years, and in patients with an APACHE II score ≤35 (eTable 1, http://links.lww.com/SHK/A640).

Regarding the 28-day and 6-month mortality rates, no differences were observed in the tested subgroups (eTable 2, http://links.lww.com/SHK/A641), with the exception of the APACHE II >35 group. The 180-day mortality rate was 9/15 (60%) in the control group and 14/14 (100%) in the ivabradine group, and the difference was statistically significant ($P = 0.02$).

DISCUSSION

The main result of this study is that adding the enteral administration of ivabradine to the standard care in critically

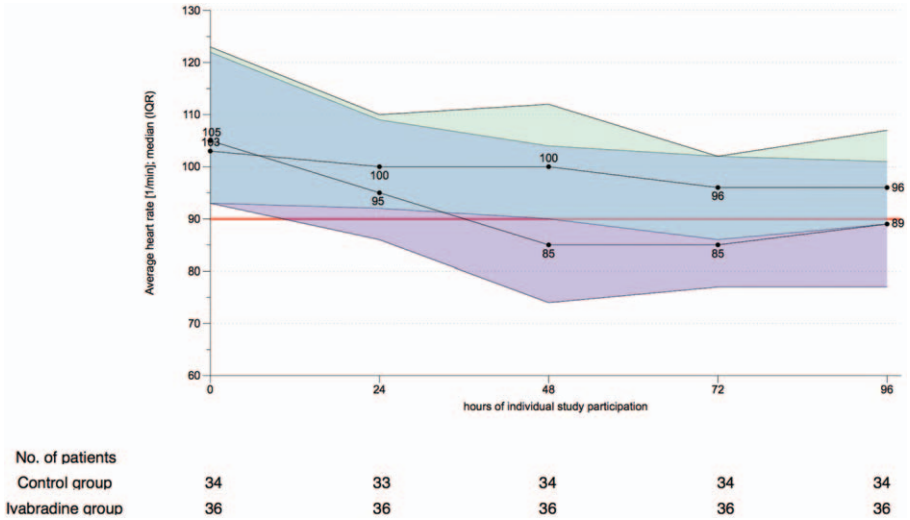

Fig. 3. **Time course of average heart rate in both groups.** The data are presented as the medians (IQR) of the control group (green) and the ivabradine group (blue) during the 96-h study treatment. The continuous red line at 90 beats/min represents the lower limit of the inclusion criterion for heart rate. Missing data for the deceased patients were handled using the "last observation carried forward" method (see "Patients and Methods" section). The numbers of surviving patients in the control group were 34 at 0 h, 34 at 24 h, 33 at 48 h, 30 at 72 h, and 29 at 96 h. The numbers of surviving patients in the ivabradine group were 36 at 0 h, 30 at 24 h, 29 at 48 h, 28 at 72 h, and 27 at 96 h.

ill patients with MODS did not significantly influence the number of patients with a heart rate reduction of at least 10 beats/min. The moderate but significant overall reduction of heart rate by 7 beats/min had no effect on hemodynamics or disease severity.

Pharmacokinetics of ivabradine in patients MODS

With a half-life of 11 h, ivabradine is a heart rate-lowering agent that binds to HCN channels that control the pacemaker current I_f in the sinoatrial node cells of the heart. Ivabradine and six potentially active metabolites are detected in plasma; *N*-desmethyl-ivabradine is the main metabolite (18). In the MOD-I_fY patients who were administered ivabradine via the enteral route, the plasma levels of ivabradine (eFigure 1, top, http://links.lww.com/SHK/A639) and its main metabolite (eFigure 1, bottom, http://links.lww.com/SHK/A639) were in the same range as observed in patients receiving oral treatment with 5 to 7.5 mg b.i.d. (the peak ivabradine concentration was approximately 20 ng/mL, and the steady-state ivabradine concentration was approximately 10 ng/mL), as measured in human volunteers after the oral application of a 5/10/20 mg ivabradine tablet (18, 19).

Pharmacodynamics of ivabradine in patients with MODS

The MODI_fY trial is the first randomized trial to assess the effects of ivabradine on patients with MODS and a sinus rhythm $\geq$90 beats/min. The heart rate reduction observed in patients with MODS (median difference of −9 beats/min after a 4-day treatment) was comparable to the heart rate reduction resulting from orally administered ivabradine in patients with established indications, such as chronic systolic heart failure [$\Delta = -11$ beats/min (20)] and chronic coronary artery disease [$\Delta = -8$ beats/min (21); $\Delta = -9.9$ beats/min (22)]. It is also similar to the reduction reported for experimental ivabradine indications: $\Delta = -13.3$ beats/min in patients with myocardial infarction who were administered an infusion of ivabradine (23); $\Delta = -6.2$ beats/min in patients with myocardial infarction complicated with cardiogenic shock who were orally administered ivabradine (24); and $\Delta = 10.7$ beats/min in patients with acute decompensated systolic heart failure who were orally administered ivabradine (25). Ivabradine infusions were more effective in patients with severe advanced systolic heart failure, who exhibited a heart rate reduction of 20 beats/min (26).

Ivabradine treatments had positive effects on patients with MODS (14, 27, 28) complicated with myocardial infarction (23) with and without cardiogenic shock (24), as well as with advanced (26) and acute decompensated (25) systolic heart failure in small case series and small randomized trials, such as a decrease in left ventricular end-diastolic and end-systolic volumes (23), an increase in stroke volume and left ventricular systolic work (26), an increase in left ventricular ejection fraction, an attenuation of diastolic dysfunction, and a reduction in the amino-terminal pro-brain natriuretic peptide (NT-proBNP) levels (24), without impairing the hemodynamics. In our study, a trend of improvements in cardiac performance parameters, such as the cardiac index and left and right ventricular cardiac power index, was observed in the ivabradine group during the 96-h treatment period, whereas the control group showed a trend of further deterioration (Table 2). In the intergroup comparison of patients treated with and without ivabradine, neither positive nor negative effects on hemodynamics were observed during the 96-h treatment with ivabradine (Table 2). Consequently, no attenuation in disease severity, as measured using the APACHE II (13) and the SOFA scores (3), was observed (Table 2).

AE of ivabradine in critically Ill patients

In 4% of patients with STEMI (23), an 8-h infusion of ivabradine resulted in bradycardia. Two patients in the ivabradine group (n = 82) and none in the control group (n = 42) died. The investigators do not believe that the study treatment caused the death of either patient.

Table 2. **Hemodynamics and disease severity variables for the patients enrolled in this study**

Variable	Group	Baseline	24 h	48 h	72 h	96 h	Cumulative AUC	*P*
Heart rate (beats/min)	Control	103 (93–123)	100 (92–110)	100 (90–112)	96 (86–102)	96 (89–107)	397 (368–438)	0.014
	Ivabradine	105 (93–122)	95 (86–109)	85 (74–104)	85 (77–102)	89 (77–101)	359 (332–421)	
APACHE II score	Control	35 (29–38)	31 (26–37)	32 (25–34)	29 (24–34)	29 (24–36)	126 (103–137)	0.805
	Ivabradine	34 (31–40)	32 (24–27)	31 (23–37)	31 (25–37)	32 (23–37)	124 (199–148)	
SOFA score	Control	16 (13–17)	15 (13–18)	14 (13–17)	14 (11–19)	14 (11–19)	57 (52–71)	0.843
	Ivabradine	16 (14–18)	16 (12–18)	16 (12–19)	16 (14–19)	14 (11–18)	62 (50–70)	
SDNN (ms)	Control	25 (10–55)				46 (36–57)	9 (7–13)	0.655
	Ivabradine	12 (7–33)				59 (36–82)	10 (5–13)	
RAP (mmHg)	Control	16 (11–18)	13 (10–17)	14 (11–17)	12 (9–16)	14 (10–16)	50 (41–64)	0.397
	Ivabradine	14 (10–17)	14 (10–17)	14 (10–17)	13 (10–17)	12 (9–17)	56 (49–65)	
MAP (mmHg)	Control	77 (68–86)	80 (72–89)	84 (69–92)	83 (66–95)	81 (67–93)	330 (292–353)	0.277
	Ivabradine	73 (66–83)	79 (69–90)	76 (65–87)	73 (65–87)	77 (68–94)	313 (289–346)	
MPAP (mmHg)	Control	35 (25–45)	33 (26–44)	33 (29–36)	35 (29–45)	33 (26–41)	136 (121–165)	0.277
	Ivabradine	26 (24–35)	35 (25–38)	32 (25–43)	32 (26–36)	32 (22–36)	132 (102-150	
SVRI ($dyn \times s \times cm^{-5} \times m^{-2}$)	Control	423 (258–526)	380 (256–564)	453 (340–599)	462 (314–635)	467 (314–764)	1568 (1185–2146)	0.701
	Ivabradine	480 (306–607)	462 (305–587)	427 (303–587)	379 (262–529)	418 (285–556)	1878 (1222–2061)	
PVRI ($dyn \times s \times cm^{-5} \times m^{-2}$)	Control	43 (4–66)	73 (56–145)	84 (27–190)	56 (49–119)	71 (19–113)	291 (235–564)	0.867
	Ivabradine	82 (56–124)	83 (45–138)	118 (43–133)	100 (69–118)	81 (66–138)	424 (301–538)	
Cardiac index ($mL/min \times m^2$)	Control	3.8 (2.6–4.5)	3.6 (2.3–4.0)	2.8 (2.3–4.2)	2.9 (2.4–4.4)	3.0 (2.2–3.9)	12 (10–15)	0.984
	Ivabradine	3.1 (2.2–3.5)	3.3 (2.5–3.9)	3.2 (2.2–3.9)	3.3 (2.4–3.8)	3.3 (2.7–4.0)	13 (10–15)	
LV-CPI	Control	0.62 (0.39–0.90)	0.63 (0.39–0.76)	0.52 (0.39–0.88)	0.56 (0.44–0.64)	0.50 (0.37–0.59)	2 (2–3)	0.910
	Ivabradine	0.43 (0.35–0.58)	0.57 (0.42–0.69)	0.55 (0.34–0.74)	0.56 (0.43–0.70)	0.51 (0.38–0.70)	2 (2–3)	
RV-CPI	Control	0.31 (0.15–0.44)	0.30 (0.16–0.38)	0.23 (0.15–0.30)	0.24 (0.17–0.34)	0.25 (0.17–0.32)	1 (1–1)	0.364
	Ivabradine	0.16 (0.10–0.19)	0.21 (0.18–0.26)	0.19 (0.17–0.31)	0.22 (0.17–0.28)	0.19 (0.17–0.26)	1 (1–1)	
GEDVI (mL/m^2)	Control	881 (759–944)	867 (699–911)	717 (592–943)	772 (664–941)	763 (643–940)	3262 (2647–3728)	0.190
	Ivabradine	651 (508–824)	669 (576–808)	720 (612–882)	724 (576–951)	716 (576–837)	2714 (2400–3351)	
EVLWI (mL/m^2)	Control	13 (9–21)	11 (8–12)	12 (9–14)	12 (9–14)	11 (8–14)	47 (38–53)	0.436
	Ivabradine	10 (8–24)	10 (7–13)	11 (7–13)	7 (6–13)	7 (6–13)	38 (28–52)	
Vasopressor score ($\mu g \times kg^{-1} \times min^{-1}$)	Control	26.62 (5.08–72.27)	20.67 (7.00–63.89)	21.96 (2.03–60.42)	7.72 (0–37.05)	3.99 (0–22.37)	85 (22–215)	0.421
	Ivabradine	27.93 (8.28–61.78)	43.29 (8.57–77.63)	15.17 (1.42–54.22)	10.89 (0–97.27)	13.74 (0–92.10)	102 (36–292)	

The data are presented as medians (IQR). The numbers of surviving patients in the control group were 34 at baseline, 34 at 24 h, 33 at 48 h, 30 at 72 h, and 29 at 96 h. The numbers of surviving patients in the ivabradine group were 36 at baseline, 30 at 24 h, 29 at 48 h, 28 at 72 h, and 27 at 96 h. Missing data for the deceased patients were handled using the "last observation carried forward" method (see "Methods" section). Please see the "Methods" section for the AUC calculations.

The vasopressor score (μg/kg/min) was calculated using the following formula reported by Zuppa et al. (15) (dopamine × 1) + (dobutamine × 1) + (epinephrine × 100) + (norepinephrine × 100) + (phenylephrine × 100).

APACHE II score, Acute Physiology and Chronic Health Evaluation II score; EVLWI, extravascular lung water index; GEDVI, global end-diastolic volume index; LV-CPI, left ventricular cardiac power index; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; PVRI, pulmonary vascular resistance index; RAP, right atrial pressure; RV-CPI, right ventricular cardiac power index; SDNN, standard deviation of all normal to normal (NN) intervals; SOFA score, sepsis-related (sequential) organ failure assessment score; SVRI, systemic vascular resistance index.

In patients with STEMI complicated with cardiogenic shock (24), the in-hospital mortality was 6.7% (2/30) for the ivabradine group and 14.3% (4/28) for the control group ($p = 0.416$). No adverse effects attributable to ivabradine were observed.

In our MODI_fY trial, AE and SAE (see "Results" section) were typically observed in patients with coronary and non-coronary MODS, and no symptomatic bradycardia that was attributed to the application of ivabradine occurred. The trend of higher mortality in the ivabradine group (Table 3:

Table 3. **Outcome data for the patients enrolled in this study**

		Control group n = 34	Ivabradine group n = 36	Chi-square	P	Relative risk
Intention-to-treat/per-protocol						
28-d mortality	n (%)	16 (47.1%)	23 (63.9%)	2.007	0.157	1.36
180-d mortality	n (%)	21 (61.8%)	27 (75.0%)	1.421	0.233	1.21
		Control group n = 29	Ivabradine group n = 27	Chi-square	*P*	Relative risk
4-d survivor group						
28-d mortality	n (%)	11 (37.9%)	14 (51.9%)	1.096	0.295	1.37
180-d mortality	n (%)	16 (55.2%)	18 (66.7%)	0.774	0.379	1.21
		Control group n = 29	Ivabradine group n = 15	Chi-square	*P*	Relative risk
4-d survivors in the control group vs. 4-d survivors in the ivabradine who received all 8 ivabradine doses						
28-d mortality	n (%)	11 (37.9%)	6 (40.0%)	0.018	0.894	1.06
180-d mortality	n (%)	16 (55.2%)	8 (53.3%)	0.013	0.908	0.97

''intention-to-treat/per-protocol'') completely vanished in the patients with the most complete ivabradine loading (Table 3: ''4-day survivors who received all 8 ivabradine doses'').

Comparison of heart rate reduction by β-blocker and ivabradine treatments in patients with MODS

Blockade of the excessive sympathetic outflow in critically ill patients in the ICU by β-blockers attenuates sympathetic tone and subsequently reduces heart rate. In a *post hoc* analysis of a prospectively collected database of 702 ICU patients, heart rate-control therapy with β-blockers significantly improved their 4-year survival (hazard ratio 0.57; 95% confidence interval, 0.36–0.94; $P = 0.002$) (27).

Impressive data were reported for the short-acting β_1-blocker esmolol among patients with septic shock and a heart rate ≥95 beats/min who required high-dose norepinephrine (8). A continuous infusion of esmolol, which was titrated to maintain a heart rate between 80 and 94 beats/min for 96 h, was established for all patients, and the primary outcome was achieved in all patients. The esmolol-induced effective median heart rate reduction after 96 h was 22 beats/min (28 vs. 6 beats/min). The esmolol treatment increased the stroke volume index and the left ventricular stroke work index, reduced arterial lactate levels, and maintained the blood pressure and cardiac indexes, despite the reductions in the fluid and norepinephrine requirements. The authors concluded that lowering the heart rate with this β_1-blocker improved ventricular filling during diastole, thereby increasing stroke volume, the efficiency of myocardial work, and oxygen consumption. The 28-day mortality was 80.5% in the control group and 49.4% in the esmolol group (adjusted hazard ratio 0.39; 95% confidence interval, 0.26–0.59; $P < 0.001$).

Further clinical studies (29, 30) confirm and attribute these findings to an improvement in microcirculation (31) and arterial elastance (32). The experimental data (33–36) revealed possible underlying mechanisms, such as the anti-inflammatory cardiovascular effects of β_1-adrenoceptor blockers (36). The β1-blocker esmolol was able to improve *in vivo* myocardial function (mainly via an elevation of left ventricular stoke volume and end-diastolic volume) and *ex vivo* vasoreactivity in experimental septic shock models, even at low doses that do not cause a decrease in heart rate. These benefits were attributable to inflammatory modulation at systemic, cardiac, and vascular tissue levels (37). According to systematic reviews (38), insufficient evidence is available to justify the routine use of β-blockers in patients with sepsis.

On the contrary, the isolated heart rate reduction after the addition of ivabradine per os in experimental septic shock models was not associated with any improvement in cardiac or vascular function and had no impact on the inflammatory response on the systemic or tissue level (39).

As demonstrated by the secondary outcomes of the present MODI_fY trial, the heart rate reduction from enteral administration of ivabradine was not associated with an improvement in hemodynamic values among critically ill patients with MODS. Thus, anti-inflammatory effects may play an important role in exerting the beneficial effects of β1-blocker treatment in addition to the heart rate reduction.

The common findings of the trial by Morelli et al. (8) and of our MODI_fY trial are that the heart rate reductions induced by the esmolol or ivabradine treatments do not induce a deterioration of cardiac function or systemic/pulmonary blood pressure. However, the most striking difference was the significantly lower mortality in the esmolol group, which was a secondary outcome (8), whereas no significant differences were observed between the ivabradine group and the control group in the MODI_fY trial (Table 3). However, when interpreting these data, we must consider three aspects. First, the heart rate reduction achieved with intravenous esmolol ($\Delta = -22$ beats/min) was considerably larger than the reduction achieved with enterally administered ivabradine ($\Delta = -9$ beats/min). If a heart rate reduction of approximately 20 beats/min by ivabradine was intended, then the drug must be administered intravenously (26). Second, we must also consider the different patient groups, i.e., patients with septic shock (esmolol) and MODS (ivabradine). However, mortality in both trials was comparable; MODS plays a prominent role in septic shock, and a large proportion of patients with noncoronary MODS in the MODI_fY trial were complicated with sepsis/septic shock. Third, we must consider the different effects of sympathetic blockade by $\beta_{(1)}$-blockers and of pacemaker current I_f inhibition by ivabradine. However, a direct comparison would necessitate the observation of a similar heart rate reduction using both approaches.

Study limitations

Limitations of this small, monocentric trial include the nonblinded approach and the fact that the control patients did not receive a placebo. Second, an arbitrarily predefined heart rate threshold was selected rather than an individualized approach. We chose a threshold of 90 beats/min because mortality is two-fold higher in patients with MODS who have a heart rate above 90 beats/min (5). Third, although early treatment, within the first 4 days, has the greatest potential to influence prognosis in these critically ill patients and elicit changes in surrogate parameters of mortality (i.e., APACHE II-score), it remains unclear whether treating patients longer than 4 days would influence heart rates and hemodynamics changes. Fourth, we were required to use the enteral route for ivabradine administration because intravenous ivabradine was not available for this trial. This requirement prevented us from achieving a specific heart rate corridor by titration, and thus, we were uncertain whether sufficient plasma levels of ivabradine could be achieved in these critically ill patients with organ dysfunction and hemodynamic instability. However, the measurement of the plasma ivabradine levels confirmed adequate absorption.

Secondary endpoints, such as hemodynamics, disease severity, and mortality, were of an explanatory character only and were shown for the generation of hypotheses.

CONCLUSIONS

The administration of oral ivabradine to critically ill patients with MODS and a sinus rhythm of at least 90 beats/min did not

influence the percentage of patients that experienced a heart rate reduction of at least 10 beats/min. The moderate but significant reduction of heart rate by 7 beats/min had no effect on hemodynamics or disease severity. Although a moderate, isolated heart rate reduction in patients with MODS is well tolerated, additional investigations are warranted to determine whether a more intense heart rate reduction or the expansion of the patient population to include all critically ill patients may reveal distinct hemodynamic effects.

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