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Randomized Control of Sympathetic Drive With Continuous Intravenous Esmolol in Patients With Acute ST-Segment Elevation Myocardial Infarction

The BEtA-Blocker Therapy in Acute Myocardial Infarction (BEAT-AMI) Trial

Fikret Er, MD,[a] Kristina M. Dahlem, MD,[b] Amir M. Nia, MD,[c] Erland Erdmann, MD, PhD,[b] Johannes Waltenberger, MD,[d] Martin Hellmich, PhD,[e] Kathrin Kuhr,[e] Minh Tam Le,[b] Tina Herrfurth,[b] Zulfugar Taghiyev, MD,[f] Esther Biesenbach, MD,[g] Dilek Yüksel, MD,[a] Aslihan Eran-Ergöknil, MD,[a] Maria Vanezi, MD,[b] Evren Caglayan, MD,[b] Natig Gassanov, MD[a]

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CME Objective for This Article: At the end of this activity the reader should be able to: 1) Summarize the indications and contraindications for intravenous beta-blockade in the management of patients presenting with ST-segment elevation myocardial infarction; 2) Identify the current role for intravenous beta-blockers in patients with acute ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention; and 3) Discuss the importance of heart rate as an indicator of sympathetic drive in ST-segment elevation myocardial infarction.

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From the [a]Klinikum Gütersloh, Department of Cardiology and Electrophysiology I, University Hospital Münster, Gütersloh; [b]Department of Internal Medicine III, University of Cologne, Cologne; [c]Division of Cardiology, Pulmonology, and Vascular Medicine, Heinrich Heine University Medical Center Düsseldorf, Düsseldorf; [d]Department of Cardiovascular Medicine, University Hospital Münster, Münster; [e]Institute of Medical Statistics, Informatics and Epidemiology, University of Cologne, Cologne; [f]Department of Cardiac and Thoracic Surgery, BG University Hospital Bergmannsheil, Bochum; and the [g]Department of Cardiology and Electrophysiology, University of Witten/Herdecke, Medical Center Porz am Rhein, Cologne, Germany. The BEAT-AMI trial was initiated, planned and performed, data were collected and analyzed and manuscript was written by the BEAT-AMI investigators. The trial was funded by Baxter Healthcare Corporation, Deerfield, Illinois. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Randomized Control of Sympathetic Drive With Continuous Intravenous Esmolol in Patients With Acute ST-Segment Elevation Myocardial Infarction

The BEtA-Blocker Therapy in Acute Myocardial Infarction (BEAT-AMI) Trial

ABSTRACT

OBJECTIVES This study sought to evaluate the role of esmolol-induced tight sympathetic control in patients with ST-segment elevation myocardial infarction (STEMI).

BACKGROUND Elevated sympathetic drive has a detrimental effect on patients with acute STEMI. The effect of beta-blocker-induced heart rate mediated sympathetic control on myocardial damage is unknown.

METHODS The authors conducted a prospective, randomized, single-blind trial involving patients with STEMI and successful percutaneous intervention (Killip class I and II). Patients were randomly allocated to heart rate control with intravenous esmolol for 24 h or placebo. The primary outcome was the maximum change in troponin T release as a prognostic surrogate marker for myocardial damage. A total of 101 patients were enrolled in the study.

RESULTS There was a significant difference between patients allocated to placebo and those who received sympathetic control with esmolol in terms of maximum change in troponin T release: the median serum troponin T concentration increased from 0.2 ng/ml (interquartile range [IQR] 0.1 to 0.7 ng/ml) to 1.3 ng/ml (IQR: 0.6 to 4.7 ng/ml) in the esmolol group and from 0.3 ng/ml (IQR: 0.1 to 1.2 ng/ml) to 3.2 ng/ml (IQR: 1.5 to 5.3 ng/ml) in the placebo group ($p = 0.010$). The levels of peak creatine kinase (CK), CK subunit MB (CK-MB), and n-terminal brain natriuretic peptide (NT-proBNP) were lower in the esmolol group compared with placebo (CK 619 U/l [IQR: 250–1,701 U/l] vs. 1,308 U/l [IQR: 610 to 2,324 U/l]; $p = 0.013$; CKMB: 73.5 U/l [IQR: 30 to 192 U/l] vs. 158.5 U/l [IQR: 74 to 281 U/l]; $p = 0.005$; NT-proBNP: 1,048 pg/ml (IQR: 623 to 2,062 pg/ml] vs. 1,497 pg/ml [IQR: 739 to 3,318 pg/ml]; $p = 0.059$). Cardiogenic shock occurred in three patients in the placebo group and in none in the esmolol group.

CONCLUSIONS Esmolol treatment statistically significantly decreased troponin T, CK, CK-MB and NT-proBNP release as surrogate markers for myocardial injury in patients with STEMI. (Heart Rate Control After Acute Myocardial Infarction; DRKS00000766) (J Am Coll Cardiol Intv 2016;9:231–40) © 2016 by the American College of Cardiology Foundation.

Admission heart rate in patients with acute myocardial infarction (AMI) is an independent prognostic indicator for cardiovascular morbidity and mortality (1,2). Enhanced sympathetic drive triggers additional myocardial cell damage in the very acute phase of AMI (3–5). Elevated heart rate is the obvious indicator for sympathetic activity.

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Beta-blockade might be helpful to limit unfavorable influences of sympathetic activity on cardiac regeneration during AMI (6,7). The use of beta-blockade during the acute phase of AMI is a matter of discussion. Administration of oral beta-blocker in patients with AMI is recommended and established (8,9). However, routine use of intravenous beta-blockade is not recommended. This reservation is on the basis of historical trials, which demonstrated increasing risk for cardiogenic shock in patients with severe myocardial infarction, reflected by higher Killip classes (10). In daily clinical settings intravenous beta-blocker is usually not given systematically. We hypothesized that beta-blockade in acute ST-segment elevation myocardial infarction (STEMI) might be helpful to suppress the sympathetic drive. We thought that heart rate might be an applicable tool to assess the individual sympathetic activity (11) and determine dosage of intravenous beta-blockade.

The BEAT-AMI (BEtA-Blocker Therapy in Acute Myocardial Infarction) study to our knowledge is the first in which continuous intravenous beta-blocker is

administrated in the very acute phase of STEMI with a predefined goal to effectively control sympathetic activity reflected by a target heart rate of 60 beats/min and mean arterial blood pressure of more than 65 mm Hg (12).

METHODS

STUDY OVERSIGHT. The BEAT-AMI investigators conceived, designed, and conducted the beta-blocker for tight heart rate control in patients with acute STEMI (BEAT-AMI) trial. The study protocol was approved by the ethics committee of the University of Cologne (Uni-Koeln-1392; 11-080) and the Federal Institute for Drugs and Medical Devices (61-3910-4037242). The Center for Clinical Trials Cologne served as the data and study-coordinating institute (CMMC Cologne). All patients provided written informed consent.

STUDY DESIGN. BEAT-AMI was a single center, 1:1 randomized, single-blind, placebo-controlled trial of esmolol in patients with acute STEMI and successful percutaneous coronary intervention (PCI) in a predefined timeline of <6 h between symptom onset and PCI. Patients were required to have a Killip class I or II STEMI, a baseline heart rate >60 beats/min and a mean arterial blood pressure >65 mm Hg (Online Study Protocol).

STUDY DRUG, RANDOMIZATION, AND BLINDING. Study treatment in BEAT-AMI was started immediately after transfer from the catheter laboratory to the intensive care unit within 60 min between PCI and onset of treatment. Active therapy consisted of weight-adapted continuous plus additional bolus esmolol infusion, targeting a heart rate of 60 beats/min. Patients were blinded to the treatment. Placebo-treated subjects received continuous 0.9% sodium-chloride infusion. Follow-up procedures were analyzed by a blinded investigator (E.C.). Randomization with an allocation ratio of 1:1 was on the basis of permuted blocks of varying length and was implemented using sequentially numbered, opaque, and sealed envelopes.

STANDARD CARE PROCEDURES. All patients during PCI received guideline-directed standard medication, including aspirin and clopidogrel, prasugrel, or ticagrelor. There were no limitations on additional indicated drug therapy. All patients received for secondary prevention oral beta-blocker, aspirin, $P2Y_{12}$-receptor antagonist, and statin.

STUDY ENDPOINTS. For the primary endpoint, the maximum change in troponin T from baseline to 48 h (peak troponin T minus baseline troponin T) was chosen as a surrogate marker for cardiac damage and a suitable prognostic indicator (13–16). To compute the maximum troponin values, we used all valid measurements within 48 h after the beginning of the study intervention. The secondary endpoints included concentrations of creatine kinase (CK), CK isoenzyme MB (CK-MB), and n-terminal brain natriuretic peptide (NT-proBNP) at 48 h, the echocardiographic ejection fraction at 48 h, 6 weeks, and 6 months, the 6-min walking test at 6 weeks and 6 months, and assessment of quality of life (EQ5D, data not shown) at 48 h, 6 weeks, and 6 months. The safety endpoints were incidence of cardiogenic shock, symptomatic bradycardia or hypotension, re-angina pectoris, repeated angiography and target vessel revascularization, rehospitalization, cerebral insult, and mortality.

STATISTICAL ANALYSIS AND POWER CALCULATION. The null hypothesis that the maximum troponin T increase over baseline within 48 h is equal in patients with esmolol therapy versus placebo was tested using the Mann-Whitney *U* test. The treatment effect was quantified using an estimator for the difference of the location parameters in the esmolol and placebo groups on the basis of normal approximation, with a corresponding continuity-corrected 95% confidence interval (CI). Note that the estimator for the difference in location parameters does not estimate the difference in medians but rather the median of the difference between a sample from the esmolol group and a sample from the placebo group.

For the secondary endpoints, we used unpaired Student *t* tests, Mann-Whitney *U* tests, and Fisher exact tests to perform pairwise treatment comparisons. To elaborate on the impact of medical treatment on troponin T release, we fitted a multivariable linear regression model using log-transformed peak troponin T level within 48 h as the dependent variable and treatment, and mean heart rate during 24 h of study intervention and log-transformed baseline troponin T level as the independent variables. After transformation, the troponin T values appeared normally distributed. The interaction treatment * mean heart rate was explored. For estimation of myocardial areas at risk during infarction the angiographic Bypass Angioplasty Revascularization Investigation Myocardial Jeopardy Index (BARI) and Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease scores (APPROACH) were calculated as previously described elsewhere (17,18).

ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

APPROACH = Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease score

AUC = area under the curve

BARI = Bypass Angioplasty Revascularization Investigation Myocardial Jeopardy Index

CK = creatine kinase

CK-MB = creatine kinase subunit MB

HR = heart rate

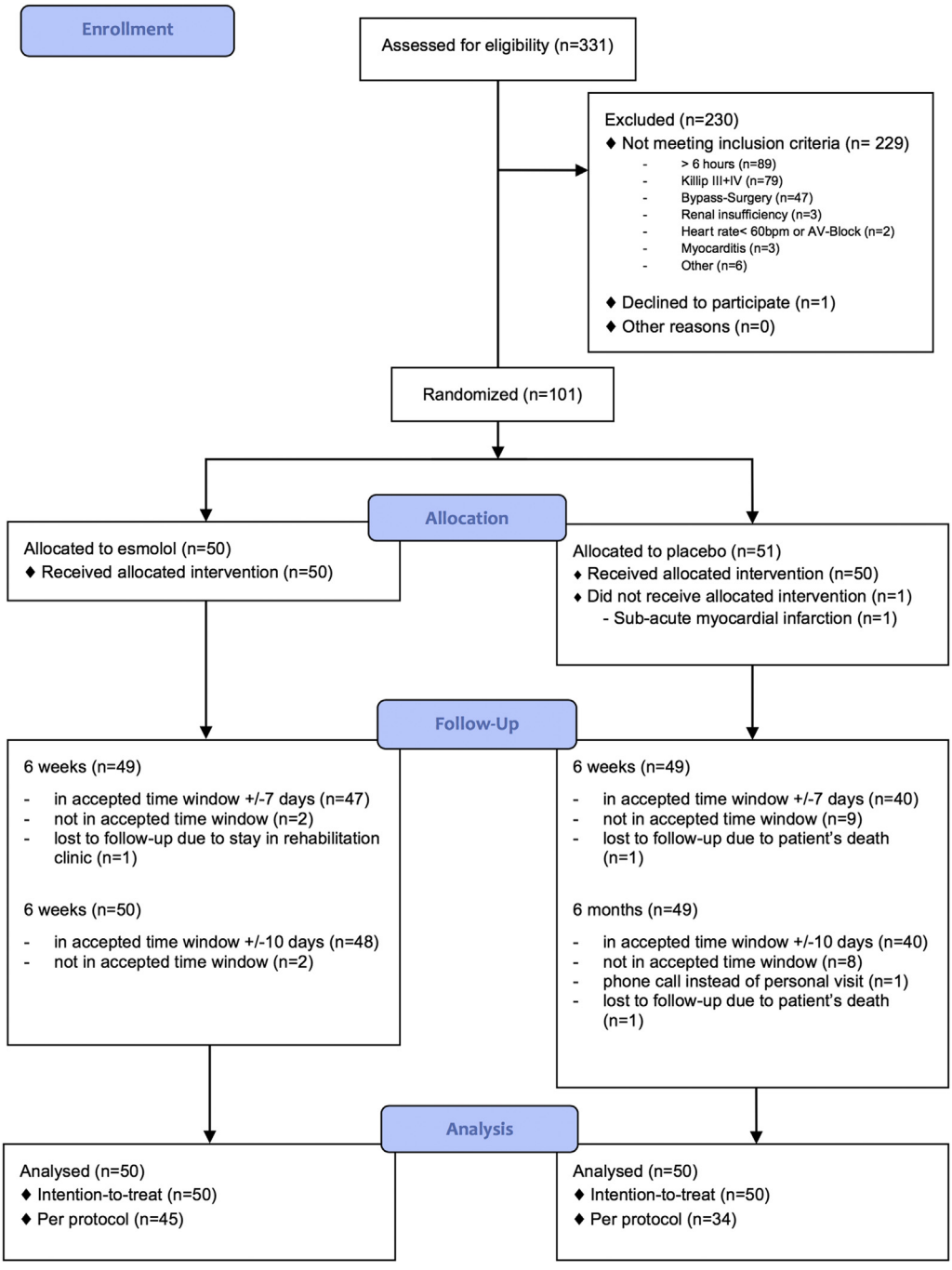
IQR = interquartile range

NT-proBNP = n-terminal brain natriuretic peptide

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

FIGURE 1 Consort Diagram



Consort diagram demonstrating enrollment, allocation, follow-up observation, and analysis.

All reported p values are 2-sided. A difference in the primary endpoint was considered statistically significant if the corresponding test was $p < 0.05$. The further analyses were regarded as explorative, and the p values of the corresponding tests are presented for descriptive reasons only. Analyses were performed for the intention-to-treat analysis set (primary) and the per-protocol analysis set (secondary, yielding similar results [data not shown]). IBM SPSS Statistics version 22 (IBM, SPSS/IBM, Chicago, Illinois)

and R version 3.1.0 (R Foundation, Vienna, Austria) were used for statistical analyses.

On the basis of our own observation (unpublished data), a heart rate reduction of maximum 10 beats/min with esmolol was assumed, and a reduction in mean troponin T max (primary variable) of about 3 ≈ 0.5 * 5.87 μg/l was expected on the basis of the hypothesis that heart rate reduction is responsible for prevention of troponin T release for at least for 50%. Assuming a coefficient of variation of 1, this troponin T reduction may be detected with 92% power, obtained by simulation, using the Welch-modified *t* test with 50 patients per treatment group (at 5% two-sided significance level). In a non-simulation-based approach this roughly corresponds to a delta/sigma of 0.67 (= 3/4.5), assuming equal within-group variances. Thus, a sample size of 50 patients per treatment group (i.e., 100 in total) seems sufficient to assess presumably relevant effects of study treatment. This remains true even when accounting for a maximum 5% dropout rate (we expect virtually none due to the in-hospital setting) and up to 5% power loss due to nonparametric testing.

RESULTS

PATIENTS. A total of 101 patients were enrolled between October 2011 and February 2014 (Figure 1). One patient (placebo group) was excluded per protocol after randomization due to elevated serum-lactate-dehydrogenase indicating subacute myocardial infarction. All patients received the complete allocated therapy. The basic demographic and clinical characteristics of treatment groups were similar as was the estimation of myocardial areas at risk reflected by calculated BARI and APPROACH scores (Table 1). Twenty-one (esmolol group) versus 20 (placebo group) patients were in Killip class II. The mean age of the study population was 59.7 ± 11.8 years, and 77% were men. A frequent comorbidity was hypertension in 54%, and 12% had a history of coronary artery disease. The time between symptom onset and reperfusion (symptom to balloon time) was 157.0 min (IQR: 116 to 236 min) in the esmolol group and 162.5 min (IQR: 85 to 238 min) in the placebo group (p = 0.98). The baseline heart rate was similar in both groups, at 79.5 ± 14.7 beats/min (esmolol group) and 79.4 ± 14.6 beats/min (placebo group, p = 0.97). The 24-h average heart rate was 68.4 ± 9.0 beats/min in the esmolol group and 73.8 ± 12.4 in the placebo group (p = 0.014) (Online Table 1, Online Figure 1). At admission, 11 patients were on oral beta-blocker treatment (Online Table 2). Nineteen patients (esmolol group n = 9 vs. placebo group n = 10) received an oral beta-blocker during the first 24 h, and 86 patients within 48 h (esmolol group n = 45 vs. placebo group n = 41) after PCI.

TABLE 1 Baseline Data

	Total (N = 100)	Esmolol Group (n = 50)	Placebo Group (n = 50)	p Value
Age, yrs	59.7 ± 11.8	57.9 ± 11.2	61.4 ± 12.2	0.14*
Male	77 (77)	41 (82)	36 (72)	0.34†
Body mass index, kg/m^2	26.4 ± 4.0	26.6 ± 3.8	26.1 ± 4.1	0.51*
Known coronary artery disease (%)	12 (12)	5 (10)	7 (14)	0.76†
Previous myocardial infarction (%)	7 (7)	3 (6)	4 (8)	1.00†
Previous coronary intervention (%)	7 (7)	2 (4)	5 (10)	0.44†
Hypertension	54 (54)	27 (54)	27 (54)	1.0†
Smoking	52 (52)	30 (60)	22 (44)	0.16†
Dyslipidemia	29 (29)	13 (26)	16 (32)	0.66†
Diabetes mellitus	12 (12)	6 (12)	6 (12)	1.0†
eGFR (ml/min)	90.7 ± 23.6	91.5 ± 21.0	89.8 ± 26.0	0.71*
Infarct-related artery‡				
LAD	43 (43.4)	17 (34)	26 (53.1)	0.134†
RCX	10 (10.1)	5 (10)	5 (10.2)	
RCA	46 (46.5)	28 (56)	18 (36.7)	
BARI index (%)	38.93 ± 5.38	38.77 ± 5.57	39.09 ± 5.21	0.35*
APPROACH score (%)	41.07 ± 4.41	41.23 ± 4.56	40.91 ± 4.29	0.40*
SBP at baseline, mm Hg	137.8 ± 21.6	137.4 ± 20.7	138.2 ± 22.6	0.87*
Heart rate at baseline, beats/min	79.4 ± 14.6	79.5 ± 14.7	79.4 ± 14.6	0.97*

Values are mean ± SD or n (%). *Student *t* test. †Fisher exact test. ‡One patient with infarct related to LAD and RCX excluded.

APPROACH = Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease; BARI = Bypass Angioplasty Revascularization Investigation Myocardial Jeopardy Index; eGFR = estimated glomerular filtration rate; LAD = left anterior descending; RCA = right coronary artery; RCX = ramus circumflexus; SBP = systolic blood pressure.

PRIMARY ENDPOINT. The maximum change in troponin T within 48 h was statistically significantly

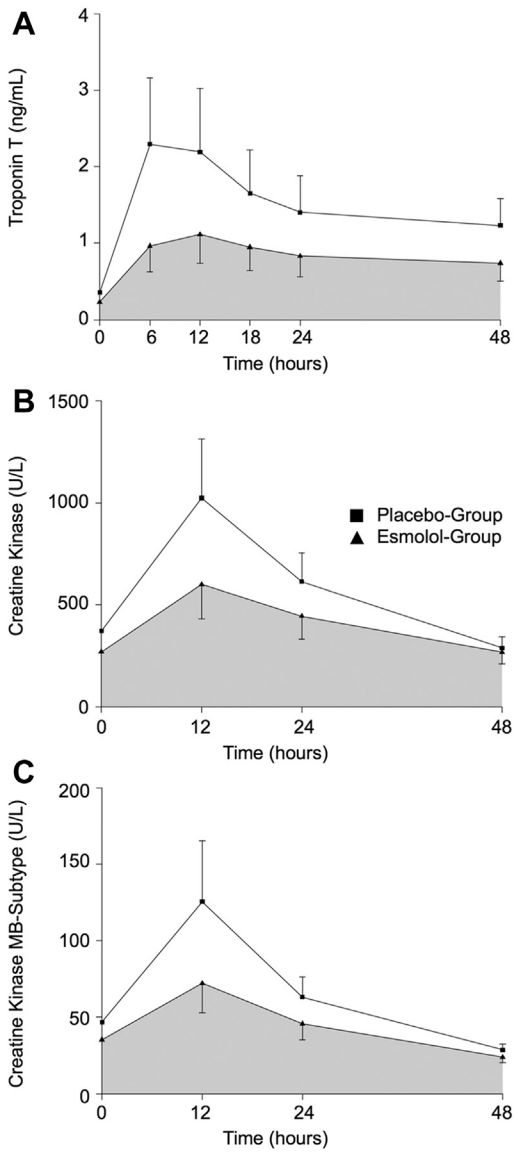
TABLE 2 Primary Endpoint: Troponin T Release in Study Population

	Total (N = 100)	Esmolol Group (n = 50)	Placebo Group (n = 50)	p Value
Baseline troponin T (ng/ml)				0.252
Median (IQR)	0.3 (0.1–1.0)	0.2 (0.1–0.7)	0.3 (0.1–1.2)	
Mean ± SD	0.7 ± 1.0	0.6 ± 0.9	0.8 ± 1.1	
Maximum troponin T (ng/ml)				0.009
Median (IQR)	2.4 (0.9–5.2)	1.3 (0.6–4.7)	3.2 (1.5–5.3)	
Mean ± SD	3.8 ± 4.3	2.9 ± 3.6	4.6 ± 4.8	
Maximum change in troponin T from baseline to 48 h (ng/ml)				0.010
Median (IQR)	1.7 (0.6–3.9)	1.0 (0.3–3.5)	2.5 (1.0–4.0)	
Mean ± SD	3.0 ± 3.9	2.3 ± 3.1	3.8 ± 4.5	
AUC troponin T (ng * h/ml)				0.043
Median (IQR)	70.7 (27.4–143.8)	38.4 (17.5–151.4)	88.3 (40.2–135.6)	
Mean ± SD	104.8 ± 111.7	90.6 ± 108.3	119.1 ± 114.4	
Time to peak troponin T (h)				0.018
Median (IQR)	6 (6–12)	12 (6–18)	6 (6–12)	
Mean ± SD	11.8 ± 10.6	14.0 ± 11.8	9.6 ± 8.7	

The p values are from Mann-Whitney *U* test.

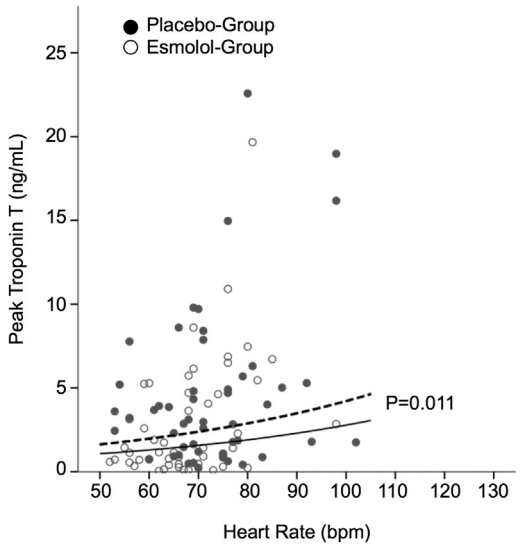
AUC = area under the curve; IQR = interquartile range.

FIGURE 2 Study Endpoints



Time-dependent serum concentration of **(A)** troponin T, **(B)** creatine kinase, and **(C)** creatine kinase subunit MB in patients. Data are presented as back-transformed mean ± 95% confidence bounds for each time point of serum determination after using their natural logarithms for calculations.

FIGURE 3 Association Between Heart Rate and Troponin T Release



Scatter plot displaying correlation between mean heart rate during intervention and peak troponin T level from baseline to 48 h by treatment. Lines show the adjusted effect of esmolol **(solid line)** and placebo **(dotted line)** on troponin T release and result from fitted regression model substituting the mean baseline troponin T level: Peak troponin T level = exp(0.285 − 0.417 * Treatment + 0.619 * log(Baseline troponin T) + 0.019 * mean heart rate during intervention.

higher in the placebo group (2.5 ng/ml, IQR: 1.0 to 4.0 ng/ml) than in the esmolol group (1.0 ng/ml, IQR: 0.3 to 3.5 ng/ml; p = 0.010). The estimated difference in location parameters was −0.89 (95% CI: −1.87 to −0.17). The baseline serum troponin T was similar in both groups, with 0.2 ng/ml (IQR: 0.1 to 0.7 ng/ml) in esmolol group versus 0.3 ng/ml (IQR: 0.1 to 1.2 ng/ml) in placebo group. The peak troponin T was 1.3 ng/ml (IQR: 0.6-4.7) in the esmolol group versus 3.2 ng/ml (IQR: 1.5-5.3) in the placebo group (p = 0.009, **Table 2**; Online Table 3). The peak troponin T was delayed in time in the esmolol group (12 h, IQR: 6-18) compared with the placebo group (6 h; IQR: 6-12; p = 0.018). The time-course of troponin T release revealed an area under the curve (AUC) of 38.4 ng*h/ml (IQR: 17.5-151.4) in the esmolol group and 88.3 ng*h/ml (IQR: 40.2-135.6) in the placebo group (p = 0.043; **Figure 2A**) indicating a significantly higher total troponin T release over time in the placebo group.

The maximum troponin T release was weak, but positively associated with the mean heart rate (Spearman's rank correlation coefficient rho = 0.300; p = 0.002). In the fitted regression model without interaction term, the effect of esmolol-treatment on troponin T release was statistically significant (p = 0.011) after adjustment for baseline troponin T (p < 0.001) and mean heart rate (p = 0.012). Independent of heart rate and baseline troponin T concentration, the troponin T level in the esmolol group was 34% reduced compared with the placebo group (**Figure 3**). The infarct related artery (p = 0.762) and

TABLE 3 CK and CK-MB Release in Study Population

	Total (N = 100)	Esmolol Group (n = 50)	Placebo Group (n = 50)	p Value
Baseline CK (U/l)				0.055
Median (IQR)	291.5 (145–537)	201.5 (126–471.0)	373 (179–550)	
Mean ± SD	509.2 ± 548.0	471.6 ± 554.0	546.8 ± 545.0	
Baseline CKMB (U/l)				0.072
Median (IQR)	34 (22–70.5)	29 (17–61)	41.5 (23–82)	
Mean ± SD	60.6 ± 61.9	55.0 ± 60.9	66.2 ± 62.9	
Peak CK (U/l)				0.013
Median (IQR)	1,033 (391.5–1,842)	619 (250–1,701)	1308 (610–2,324)	
Mean ± SD	1,540.8 ± 1,699.1	1,311.2 ± 1,736.8	1,770.4 ± 1,645.7	
Peak CKMB (U/l)				0.005
Median (IQR)	131 (46.5–244.5)	73.5 (30–192)	158.5 (74–281)	
Mean ± SD	188.5 ± 211.3	145.4 ± 179.7	231.7 ± 232.6	
AUC CK (U*h/l)				0.050
Median (IQR)	27,567 (12,349.5–49,411)	20,385 (8738–49191)	32,182.5 (18,366–52,572.5)	
Mean ± SD	40,364.2 ± 41,167.4	37,152.1 ± 43683.0	43,576.4 ± 38,663.1	
AUC CKMB (U*h/l)				0.015
Median (IQR)	3,258 (1,509–5,032.5)	2167.5 (1,050–4,710)	3725 (2,040–5,478)	
Mean ± SD	4291.9 ± 4013.4	3674.7 ± 3892.3	4909.1 ± 4076.3	

The p values are from the Mann-Whitney *U* test.
AUC = area under the curve; CK = creatine kinase; CKMB = creatine kinase subunit MB; IQR = interquartile range.

time to reperfusion (p = 0.357) did not additionally influence the troponin T release.

SECONDARY ENDPOINTS. Although the creatine kinase (CK) and CK subunit MB (CK-MB) levels were similar at baseline in both groups (Table 3), total CK and CK-MB release was lower in the esmolol group than in the placebo group (CK: esmolol group 619 U/l, IQR: 250 to 1,701 U/l, vs. placebo group 1308 U/l, IQR: 610 to 2,324 U/l; p = 0.013; CK-MB: esmolol group 73.5 U/l, IQR: 30 to 192 U/l, vs. placebo group 158.5 U/l, IQR: 74 to 281 U/l; p = 0.005). The time course calculation of CK release demonstrated an AUC of 20,385 U*h/ml (IQR: 8,738 to 49,191 U*h/ml) in the esmolol group versus 32,183 ng*h/ml (IQR: 18,366 to 52,573 ng*h/ml) in the placebo group (p = 0.050; Figure 2B). Similar relation was seen for CK-MB release (esmolol group AUC 2,168 U*h/l, IQR: 1,050 to 4,710 U*h/l, vs. placebo group AUC: 3,725 U*h/l, IQR: 2,040 to 5,478 U*h/l; p = 0.015) (Figure 2C).

At baseline, the serum concentration of N-terminal pro BNP (NT-proBNP) was 83.5 pg/ml (IQR: 48 to 287 pg/ml) in the esmolol group versus 133.5 pg/ml (IQR: 61 to 341 pg/ml) in the placebo group (p = 0.228), and it increased within 48 h to 1,048 pg/ml (IQR: 623 to 2,062 pg/ml, esmolol group) and 1,497 pg/ml (IQR: 739 to 3,318 pg/ml, placebo group; p = 0.059). The peak NT-proBNP increase from baseline was 766.5 pg/ml (IQR: 325 to 1,443 pg/ml, esmolol group) versus 1134.5 pg/ml (IQR: 591 to 2,610 pg/ml, placebo group; p = 0.040) (Online Figure 2).

CLINICAL AND SAFETY ENDPOINTS. One patient in the placebo group died during index hospitalization due to cardiogenic shock. A total of three patients (esmolol group, n = 0, vs. placebo group, n = 3) developed cardiogenic shock with the necessity of intravenous catecholaminergic therapy (Table 4). During the intravenous treatment period of 24 h, a median number of 63 ventricular extrasystoles

TABLE 4 Safety Endpoints During Index Hospitalization

Event	Total (N = 100)	Esmolol Group (n = 50)	Placebo Group (n = 50)	p Value
Death				
No. of patients with event	1	0	1	1.0
Ventricular tachycardia				
No. of events	21	4	17	–
No. of patients with event	15	4	11	0.091
Atrial fibrillation				
No. of events	5	1	4	–
No. of patients with event	4	1	3	0.617
Bradycardia				
No. of events	2	0	2	–
No. of patients with event	1	0	1	1.0
Cardiogenic shock				
No. of events	3	0	3	–
No. of patients with event	3	0	3	0.242
Reinfarction				
No. of events	2	0	2	–
No. of patients with event	2	0	2	0.495

The p values are from Fisher exact test.

(IQR: 20 to 283, range 0 to 999) were counted in all patients. In the esmolol-treated patients, the ventricular extrasystoles incidence (27/24 h, IQR: 16 to 123 h) was statistically significantly lower than in the placebo group (152/24 h, IQR: 37 to 418 h; p = 0.002). Nonsustained ventricular tachycardia occurred in four patients in the esmolol group and 11 patients in the placebo group (p = 0.091). A higher degree atrioventricular block (II and III) occurred in none of the patients.

The baseline echocardiography after the study intervention revealed a left ventricular ejection fraction of 58.8 ± 10.2% in the esmolol group and 55.0 ± 11.7% in the placebo group (p = 0.087). After 6 weeks, the ejection fraction was 62.5 ± 8.8% in the esmolol group and 58.6 ± 9.3% in the placebo group (p = 0.035), and after 6 months it was 61.7 ± 9.6% in the esmolol group versus 60.1 ± 10.1% in the placebo group (p = 0.407). The median 6-week 6-min walk distance was 550 m (IQR: 490 to 580 m, esmolol group) versus 500 m (IQR: 415 to 550 m, placebo group; p = 0.015). After 6 months, a difference in walking distance was still present with 550 m (IQR: 475 to 580 m, esmolol group) versus 510 m (IQR: 380 to 550 m, placebo group; p = 0.027). The incidence of major cardiovascular events was similar in both groups (Online Table 4).

DISCUSSION

In the present investigator-initiated trial, heart rate and sympathetic control with esmolol limited the troponin T, CK, and CK-MB release by one-third and almost halved the release of NT-proBNP compared with the control patients. Esmolol treatment reduced the incidence of ventricular extrasystoles without increasing the risk for cardiogenic shocks. Use of continuous intravenous esmolol over a period of 24 h was safe and well tolerated.

Although a generally elevated heart rate has been identified as a prognostic indicator in AMI, heart rate has not been evaluated as a potential therapeutic target. The hypothesis of this research was whether heart rate modulation might influence the myocardial damage in the period of early PCI in acute myocardial infarction. The previous VIVIFY VIVIFY (eValuation of the IntraVenous If inhibitor ivabradine after STsegment elevation mYocardial infarction) study demonstrated that isolated slowing of the heart rate with ivabradine was not associated with marked positive effects on cardiac biomarkers. This suggested that heart rate is a surrogate for the sympathetic drive and not detrimental in itself (19).

Early generation cardiologists of the pre-reperfusion era were able to improve the prognosis in AMI with suppression of sympathetic activity simply by sedation of patients (20–22). Several trials in the pre-reperfusion (23,24), thrombolysis (10), and PCI era have evaluated the effects of acute beta-blockade in AMI with controversial results. The BEAT-AMI is the first trial to evaluate the effects of controlling the sympathetic drive with intravenous beta-blockade using the heart rate as an indicator in patients with successful PCI in STEMI.

The exact mechanisms of beneficial effects of early beta-blockers in AMI remain unclear. It has been suggested that early intravenous administration may quickly decrease myocardial oxygen consumption, reduce fatal ventricular tachyarrhythmias, and reduce infarct size by favorable influencing of the coronary blood flow (25,26). In addition, AMI results in substantial and sustained release of catecholamines, which leads to a wide range of hemodynamic, metabolic, and immune changes. Moreover, catecholamines have been shown to up-regulate the function of monocytes and potentiate the stimulating effect of lipopolysaccharides on monocytes and macrophages, which crucially involves the destabilization of atherosclerotic plaques via the interaction of catecholamines with $beta_1$-receptors (27). Thus, early inhibition of the catecholamine-mediated effects on monocytes by beta-blockers may contribute, at least in part, to the beneficial effects of esmolol in AMI. Likewise, the esmolol-induced decreased heart rate improved the stroke volume and thereby the efficiency of myocardial work and oxygen consumption, and reduced the catecholamine-induced toxicity in patients with septic shock (28). There was an associated improvement in 28-day survival.

The recent elegant METOCARD-CNIC (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction) trial evaluated the effects of early administration of metoprolol in STEMI patients (29). Despite some differences in study design compared to the BEAT-AMI trial, the METOCARD-CNIC investigators demonstrated positive effects of pre-PCI intravenous beta-blockade on myocardial salvage in long-term clinical follow-up (30). Controlling the heart rate was not aim of that study, so heart rate comparisons were not performed. In STEMI patients with early PCI, the additional development of potentially beneficial strategies is challenging (31). Our study suggests that heart rate and sympathetic control might be suitable modifiable candidates.

Differentiated calculations in the present trial revealed that a one beat lower heart rate was associated with an average reduction in troponin T by 2%.

Considering the heart rate reduction effect, multivariate regression analysis revealed that esmolol treatment itself was associated with myocardial protection, indicating that the demonstrated results are composed of both heart rate reduction and esmolol effects, independent of the heart rate reduction. Further investigations are needed to identify additional pathways of esmolol effects in myocardial protection.

CONCLUSIONS

Quantification of cardiac damage during STEMI can be performed by cardiac imaging techniques and evaluation of biomarkers. The relation of troponin release and visualization of infarct size via magnetic resonance imaging have been extensively examined, and a strong correlation has been demonstrated (32–36). The BEAT-AMI trial was designed not only to estimate the myocardial infarct size but also to assess differences in prognostic biomarkers as surrogates for cardiac morbidity and mortality. Biomarker evaluation is a limitation of the study due to indirect estimation of myocardial damage. On the other hand, all the evaluated biomarkers—troponin (37–41), CK (42,43), CKMB (38,44), and NT-proBNP (45–48)—have been identified as strong prognostic indicators in patients with AMI. In the BEAT-AMI trial, all four evaluated biomarkers were significantly lowered by esmolol-induced heart rate control, indicating a protective effect of acute intravenous esmolol. Patients in the BEAT-AMI trial were at very low risk (Killip class I and II), and reperfusion was established within 3 h after symptom onset. The BEAT-AMI trial was performed as a pilot trial and was not powered to demonstrate changes in clinical endpoints. Our present study justifies a large, multicenter, prospective evaluation of heart rate control in STEMI patients.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Fikret Er, Klinikum Gütersloh, Department of Cardiology and Electrophysiology, Reckenberger Str. 19, 33332 Gütersloh, Germany. E-mail: fikret.er@klinikum-guetersloh.de.

PERSPECTIVES

WHAT IS KNOWN? Routine intravenous administration of a beta-blocker is not recommended during the acute phase of myocardial infarction.

WHAT IS NEW? In Killip class I and II STEMI patients, intravenous esmolol-induced control of sympathetic activity showed beneficial effects, decreasing troponin T, CK, CK-MB, and NT-proBNP release as surrogate markers for myocardial injury.

WHAT IS NEXT? There is a need for further studies to identify the effects of suggested esmolol-induced infarct size limitation on clinical endpoints.

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KEY WORDS beta-blocker, clinical trial, heart rate, sympathetic nervous system, STEMI

APPENDIX For supplemental tables, figures and study protocol, please see the online version of this article.

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