# Study Title: Herzfrequenzkontrolle nach akutem Myokardinfarkt

**English Title:** Use of Esmolol for Tight Heart Rate Control for 24 Hours in Patients with Acute ST Elevation Myocardial Infarction: The BEtA-Blocker Therapy in Acute Myocardial Infarction (BEAT-AMI) Trial

**Active Substance:** Esmolol (Brevibloc®)

**Eudra-CT Number:** 2011-000911-26

**Study Short Title:** STEMI, Uni-Koeln-1392

## Final Report (Summary)

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|---|---|
| **Title of study** | Herzfrequenzkontrolle nach akutem Myokardinfarkt |
| **English title of study** | Use of Esmolol for Tight Heart Rate Control for 24 Hours in Patients with Acute ST Elevation Myocardial Infarction: The BEtA-Blocker Therapy in Acute Myocardial Infarction (BEAT-AMI) Trial |
| **Amendments** | None |
| **Study type** | Phase IV clinical trial according to Medicinal Products Act ("Arzneimittelgesetz", AMG) |
| **Sponsor / Representative** | University of Cologne<br>Albertus-Magnus-Platz<br>50923 Cologne<br>Germany<br><br>Represented by<br><br>Fikret Er, MD<br>Department of Internal Medicine I<br>Klinikum Gütersloh<br>Reckenberger Strasse 19<br>33332 Gutersloh<br>Germany<br>Phone: +49-5421-8324402<br>Fax: +49-5421-8324403<br>Fikret.Er@klinikum-guetersloh.de |
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| **Main local investigator** | None |
| **Trial site** | Department III of Internal Medicine<br>Cologne University Hospital<br>Kerpener Strasse 62<br>50937 Cologne<br>Germany<br><br>Single-center trial |
| **Publication (reference)** | In preparation |

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| **Studied period** | Date of first enrollment (FPFV): 13.10.2011<br>Date of last completed (LPLV): 24.02.2014 |
| **Objectives** | To evaluate the efficacy and safety of esmolol-induced heart rate control as compared with placebo when used in addition to standard medical therapy in patients with acute ST elevation myocardial infarction (STEMI) in reducing final infarct size reflected by Troponin T release. The BEAT-AMI trial hypothesize that during the vulnerable period of 24 hours after successful PCI in STEMI tight heart rate control with esmolol is effective in limitation of myocardial damage. |
| **Primary efficacy endpoint** | Maximum change in Troponin T from baseline to 48 hours |
| **Secondary endpoints** | - Peak Troponin T from baseline to 48 hours<br>- Area unter the Curve (AUC) of Troponin T release from baseline to 48 hours<br>- Further laboratory tests (CK, CK-MB, NT-proBNP, endothelial progenitor cells)<br>- Heart rate during study intervention<br>- Functional tests (physical capacity and 6-minutes walk test)<br>- Echocardiography (ejection fraction, wall motion abnormalities)<br>- Neuropsychological and quality of life tests<br>- Rehospitalisation<br>- Reintervention<br>- Repeat PCI<br>- Reinfarction<br>- Death from any cause<br>- Angina pectoris during follow-up<br>- Apoplex during follow-up<br>Safety objectives include symptomatic bradycardia, hypotension up to cardiogenic shock. |
| **Study design** | Design: Single-center, randomized, placebo-controlled, single-blind phase IV clinical trial with two parallel treatment groups<br>Experimental intervention: Esmolol (Brevibloc®)<br>Study population, sample size: 100 patients with successful PCI after acute STEMI<br>Blinding: Single-blinded design with blinded patients. Because study drug esmolol has an obvious effect on heart rate and blood pressure and due to safety reasons drug-administrating physician was not blinded. Follow up data acquisition was strictly performed in a blinded manner of physician and patient. |

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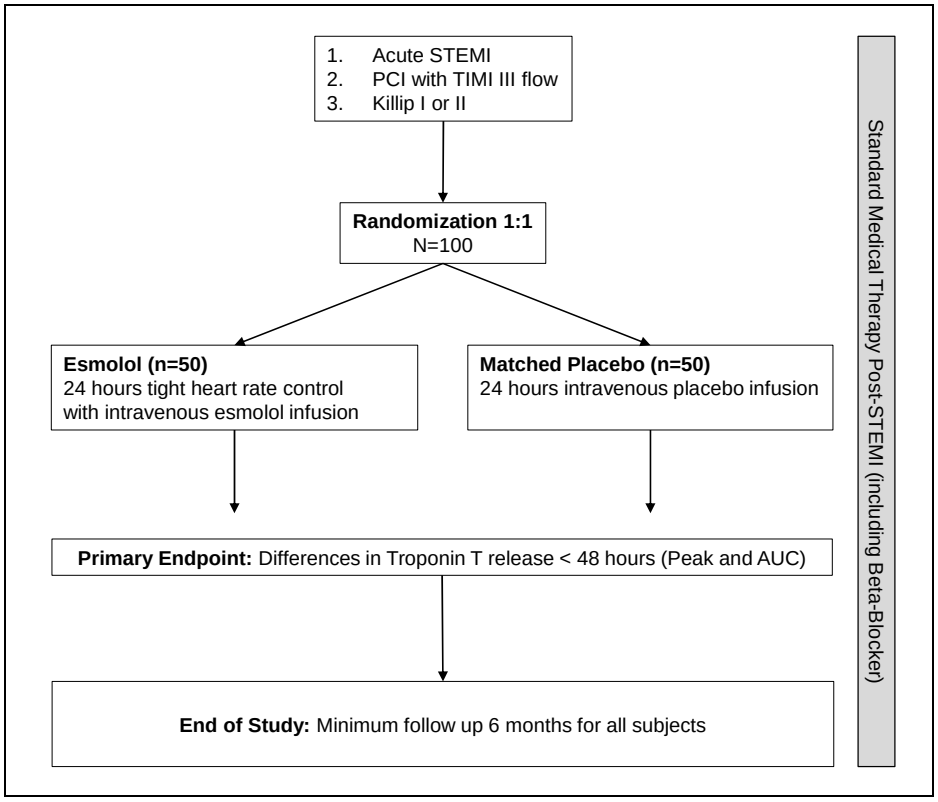
| | Control intervention: Placebo<br><br>Allocation to treatment: Randomisation using randomly generated treatment allocations within sequentially numbered sealed opaque envelopes. Permuted blocks (1:1) with variable block sizes were used.<br><br>Study procedures: Patients admitted with acute ST elevation myocardial infarction were screened. Subjects underwent timely successful percutaneous intervention were identified. Eligible subjects were included and randomly allocated to receive esmolol or placebo for 24 hours. Follow-Up visits were perfomed after end of study intervention and after 6 weeks and 6 months, see Figure 1 for trial schematic.<br><br>  <br>Figure 1: Trial schematic<br><br>Planned interim analysis: None<br><br>Data Monitoring Committee, Clinical Endpoint Committee: None |
| **Test product** | Brevibloc®, esmolol-hcl; 10 mg/ml; intravenous infusion for 24 hours |
| **Duration of treatment** | Continuous intravenous infusion of esmolol or placebo for 24 hours after index PCI for acute STEMI, follow-up visits after end of study intervention and after 6 weeks and 6 months |
| **Reference therapy** | NaCl 0.9%; intravenous infusion for 24 hours (placebo) |

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| **Number of patients** | Planned sample size: 100<br>Assessed for eligibility: 331<br>Patients included: 101<br>Randomized: 101<br>Drop-outs: 1 (before study intervention)<br><br>For more details see Consort Flow Diagram in appendix A |
| **Study population** | Between October 2011 and September 2013 101 patients were randomized, 50 to arm A (esmolol-group) and 51 to arm B (placebo-group) (s. Table 1 and CONSORT Flow Diagram in appendix A).<br><br>Deviations from inclusion-/exclusion criteria, study procedure, patient management:<br><br>- Randomized patients not meeting inclusion criteria: One randomized patient with sub-acute myocardial infarction did not meet the inclusion criteria and did not receive allocated intervention. No further study documentation was done, the patient was excluded from intention-to-treat (ITT) population (s. Table 2). The possibility to exclude sub-acute myocardial infarctions after randomisation is specified in the protocol.<br>- Randomized patients meeting criteria for premature discontinuation, but not excluded: none<br>- Randomized patients not receiving allocated treatment: none<br>- Randomized patients with co-medication not permitted: none, no restriction of co-medication<br><br>Trial populations:<br><br>The full-analysis set for the primary analysis was derived from the intention-to-treat (ITT) principle. This dataset includes all trial subjects enrolled and randomized. Only patients with sub-acute myocardial infarction were excluded after randomization.<br><br>The per-protocol (PP) set includes all trial subjects who were essentially treated according to protocol (e.g. received study medication for 24 hours +/- 1 hour, performed follow-up visits after six weeks +/-7 days and six months +/-10 days in accepted time windows allowing a complete and meaningful documentation of clinical outcome). PP analyses were treated secondary/supportive.<br><br>The valid for safety (VFS) set included all trial subjects who received any trial medication.<br><br>The analysis sets were defined in a blinded manner.<br><br>The ITT analysis set included 100 patients, 50 patients in the esmolol-group and 50 patients in the placebo-group (s. Table 1 and CONSORT Flow Diagram in appendix A). Reasons for exclusion from ITT analysis set are given in Table 2. |

The PP analysis set included 79 patients, 45 patients in the esmolol-group and 34 patients in the placebo-group (s. Table 1 and CONSORT Flow Diagram in appendix A). Reasons for exclusion from PP analysis set are given in Table 3.

All patients in the ITT analysis set received the allocated trial medication, so the VFS set was identical to the ITT analysis set and included 100 patients, 50 patients in the esmolol-group and 50 patients in the placebo-group (s. Table 1 and CONSORT Flow Diagram in appendix A).

**Table 1: Recruitment, sample sizes (all trial populations)**

| | | Allocated Arm | | |
|---|---|---|---|---|
| | | Total | Esmolol | Placebo |
| | | Count | Count | Count |
| Randomisation performed | no | 0 | 0 | 0 |
| | yes | 101 | 50 | 51 |
| | Total | 101 | 50 | 51 |
| ITT population | no | 1 | 0 | 1 |
| | yes | 100 | 50 | 50 |
| | Total | 101 | 50 | 51 |
| PP population | no | 22 | 5 | 17 |
| | yes | 79 | 45 | 34 |
| | Total | 101 | 50 | 51 |
| Safety population | no | 1 | 0 | 1 |
| | yes | 100 | 50 | 50 |
| | Total | 101 | 50 | 51 |

**Table 2: Patients not qualified for ITT**

| Patient ID | Treatment | Date of randomization | ITT | Reason | Investigators comment |
|---|---|---|---|---|---|
| 1-157 | Placebo | 24.11.2012 | No | Screening failure | Due to elevated serum LDH indicating subacute myocardial infarction |

**Table 3: Patients not qualified for PP**

| Patient ID | Treatment | Intervention in time window | Visit performed after 6 weeks | FU6W in time window | Visit performed after 6 months | FU6M in time window |
|---|---|---|---|---|---|---|
| 1-114 | Placebo | Yes | Yes | No | Yes | Yes |
| 1-130 | Placebo | Yes | Yes | Yes | Yes | No |
| 1-140 | Placebo | Yes | Yes | No | Yes | No |
| 1-148 | Brevibloc | Yes | No | | Yes | Yes |
| 1-151 | Brevibloc | Yes | Yes | No | Yes | Yes |
| 1-152 | Placebo | Yes | Yes | No | Yes | Yes |
| 1-153 | Placebo | Yes | Yes | Yes | Yes | No |
| 1-154 | Brevibloc | Yes | Yes | Yes | Yes | No |
| 1-157 | Placebo | | | | | |
| 1-160 | Placebo | Yes | Yes | Yes | Yes | No |
| 1-165 | Brevibloc | Yes | Yes | Yes | Yes | No |

| | | | | | | |
|---|---|---|---|---|---|---|
| 1-168 | Placebo | Yes | Yes | Yes | Yes | No |
| 1-169 | Placebo | Yes | Yes | Yes | Yes | No |
| 1-173 | Placebo | Yes | Yes | Yes | Yes | No |
| 1-174 | Placebo | Yes | Yes | No | Yes | Yes |
| 1-182 | Placebo | Yes | Yes | Yes | Yes | No |
| 1-185 | Brevibloc | Yes | Yes | No | Yes | Yes |
| 1-188 | Placebo | Yes | Yes | No | Yes | Yes |
| 1-193 | Placebo | Yes | Yes | No | Yes | Yes |
| 1-197 | Placebo | Yes | Yes | No | Yes | Yes |
| 1-198 | Placebo | Yes | Yes | No | Yes | Yes |
| 1-201 | Placebo | Yes | Yes | No | Yes | No |

**Inclusion criteria**

- STEMI
- Successful PCI with TIMI III reflow
- Heart rate ≥ 60 bpm
- Onset of symptoms < 6 hours and lactate dehydrogenase < 280 U/I before PCI
- Killip I and II class MI
- Age ≥ 18 years
- Mean arterial blood pressure ≥ 65 mmHg
- Systolic blood pressure > 90 mmHg
- Medication with clopidogrel or prasugrel, aspirin and heparin before PCI
- Peripheral oxygen saturation (SpO2) > 90%
- Written informed consent

**Exclusion criteria**

- TIMI < III reflow
- Onset of symptoms > 6 hours
- Cardiogenic shock
- Killip III and IV class MI
- Symptomatic AV or SA conduction block II°, III°
- Heart rate < 60 bpm
- Mean arterial blood pressure < 65 mmHg or systolic blood pressure ≤ 90 mmHg
- Severe peripheral artery disease (Fontaine > IIb)
- Liver cirrhosis
- Severe acidosis (pH < 7.2)
- Severe renal impairment (serum creatinine > 2 mg/dl)
- Patients on catecholamine
- Women for whom pregnancy cannot be ruled out

- Patients who did not receive standard therapy for AMI in line with the current guidelines, e.g. no clopidogrel or heparin given
- Patients for which a timely and likely follow-up cannot be guaranteed
- Known allergy or intolerance against the studied device
- Patients with advanced AV-block or known allergy against beta blockers
- Subject in dependent relationship to investigator or Baxter Healthcare Corporation
- Persons held in an institution by legal or official order

**Patient demographics and baseline characteristics**

Patient-level analyses were performed for all patients together and stratified by gender. The following results are from ITT analysis, if not stated otherwise. Detailed results for all analyses sets are given in the appendices.

All patients with data (ITT analysis set)

Table 4 shows patient characteristics at baseline. Groups were well balanced without any statistically significant differences between main demographics. Median time between symptom onset to invasive coronary angiogram was 130.5 min. (IQR 80-190; esmolol-group) vs. 128 min. (IQR 85-211; placebo-group; p=0.940). Median ischemia duration, i.e. time between symptom onset to successful PCI was 157 min. (IQR 116-236; esmolol-group) vs. 162.5 min. (117-238; placebo-group; p=0.983). Further details are given in appendix B Table 2, 3, 6 and 7.

**Table 4: Baseline characteristics**

| | Esmolol | Placebo | P-Value |
|---|---|---|---|
| Age, y | 57.9±11.2 | 61.4±12.2 | 0.141[a] |
| Male sex, n (%) | 41 (82) | 36 (72) | 0.342[c] |
| Body mass index, kg/m2 | 26.6±3.8 | 26.1±4.1 | 0.510[a] |
| Hypertension, n (%) | 27 (54) | 27 (54) | 1.0[c] |
| Smoking, n (%) | 30 (60) | 22 (44) | 0.161[c] |
| Dyslipidemia, n (%) | 13 (26) | 16 (32) | 0.660[c] |
| Diabetes mellitus, n (%) | 6 (12) | 6 (12) | 1.0[c] |
| Time between symptom begin and heart catheterization, min | 130.5 [80-190] | 128 [85-211] | 0.940[b] |
| Ischemia duration, min | 157 [116-236] | 162.5 [117-238] | 0.983[b] |
| Infarct artery localisation, n (%) | | | |
| LAD | 17 (34) | 27 (54) | 0.069[c] |
| RCX | 5 (10) | 6 (12) | 1.0[c] |

| | | | |
|---|---|---|---|
| RCA | 28 (56) | 18 (36) | 0.070[c] |
| SBP at baseline, mmHg | 137.4±20.7 | 138.2±22.6 | 0.865[a] |
| Heart rate at baseline, bpm | 79.5±14,7 | 79.4±14.6 | 0.973[a] |

Numeric variables were given as mean±SD or median [IQR], categorical variables as n (%). [a] t test, [b] Mann-Whitney U test, [c] Fisher's exact test

Per protocol analyses

Patient demographics and baseline characteristics for the per protocol analysis set are given in appendix E, Table 2, 3, 6 and 7. There were no relevant differences between ITT and PP analysis regarding main baseline demographics.

Subgroup analyses

Subgroup analyses were performed by gender. Results are given for ITT and PP analysis set, see table 2, 3, 6 and 7 in the appendices C, D, F and G

For women and men, treatment groups were well balanced regarding main baseline demographics.

Comparison of study centres: not applicable

**Efficacy results**

Assessment of compliance: none

Additional analyses/interim analyses: none

Primary endpoint maximum change in Troponin T from baseline to 48 hours:

Baseline Troponin T was similar in both groups. Maximum change in Troponin T within 48 hours was statistically significant higher in placebo group (2.5 ng/ml [IQR: 1.0-4.0]) than in esmolol group (1.0 ng/ml [IQR: 0.3-3.5], p=0.010; see Table 5; Figure 2).

**Table 5: Primary endpoint Troponin T**

| | Esmolol | Placebo | P-Value |
|---|---|---|---|
| Baseline Troponin T (ng/ml) | | | |
| Mean, ± SD | 0.6 ±0.9 | 0.8±1.1 | 0.252 |
| Median, (IQR) | 0.2 (0.1-0.7) | 0.3 (0.1-1.2) | |
| Maximum change in Troponin T from baseline to 48h (ng/ml) | | | |
| Mean, ± SD | 2.3±3.1 | 3.8±4.5 | 0.010 |
| Median, (IQR) | 1.0 (0.3-3.5) | 2.5 (1.0-4.0) | |

P-values are from Mann-Whitney U test.

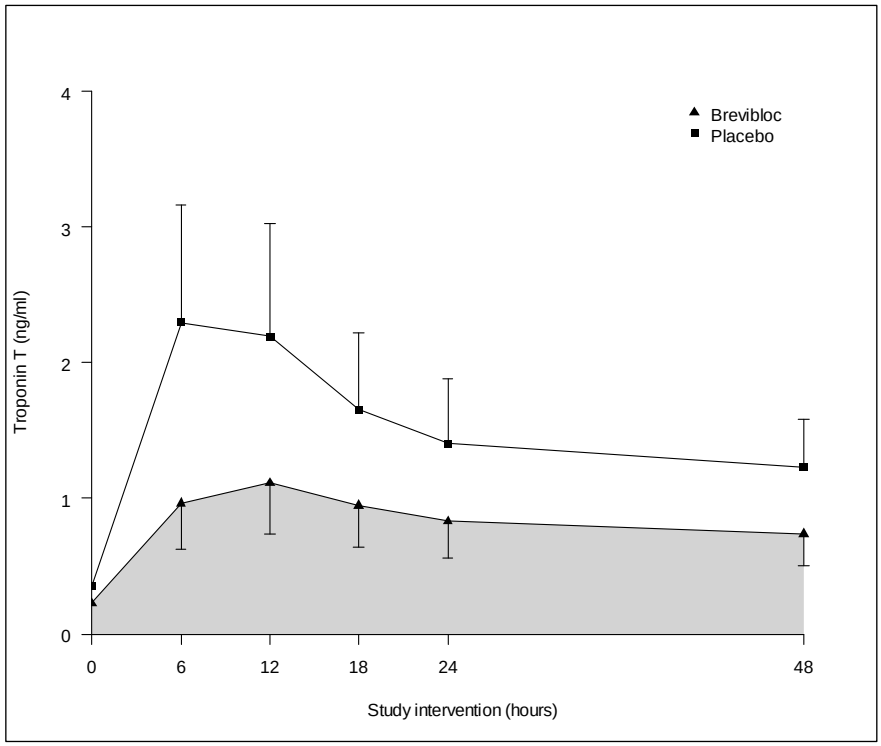


**Figure 2: Troponin T concentrations in esmolol group (Brevibloc) versus placebo group. Data are presented as back-transformed mean±95% confidence bounds for each time point of serum determination after using their natural logarithms for calculations.**

Secondary endpoints

Laboratory values:

Peak Troponin T from baseline to 48 hours was statistically significant higher in placebo group (3.2 ng/ml [IQR: 1.5-5.3]) compared to esmolol group (1.3 ng/ml [IQR: 0.6-4.7], p=0.009). Area under the curve of Troponin T release in 48 hours revealed higher Troponin T release in placebo group (88.3 ng*h/ml [IQR: 40.2-135.6]) than in esmolol group (38.4 ng*h/ml [IQR: 17.5-151.4]; p=0.043). Time to peak Troponin T concentration was longer in esmolol group (12 hours [IQR: 6-18]) versus placebo group (6 hours [IQR: 6-12]; p=0.018; Table 6, Figure 2).

**Table 6: Troponin T release from Baseline to 48 hours**

| | Esmolol | Placebo | P-Value |
|---|---|---|---|
| Maximum Troponin T (ng/ml) | | | |
| Mean, ± SD | 2.9 ± 3.6 | 4.6 ± 4.8 | 0.009 |
| Median, (IQR) | 1.3 (0.6-4.7) | 3.2 (1.5-5.3) | |
| AUC Troponin T (ng*h/ml) | | | |
| Mean, ± SD | 90.6±108.3 | 119.1±114.4 | 0.043 |
| Median, (IQR) | 38.4 (17.5-151.4) | 88.3 (40.2-135.6) | |

| | | | |
|---|---|---|---|
| Time to max. Troponin T (hours) | | | |
| Mean, ± SD | 14.0 ± 11.8 | 9.6 ± 8.7 | 0.018 |
| Median, (IQR) | 12 (6-18) | 6 (6-12) | |

P-values are from Mann-Whitney U test.

Effects of esmolol treatment to CK, CK-MB and NT-proBNP were similar (Figure 3-Figure 5). Numerical details are given in the appendix B, table 4-5.

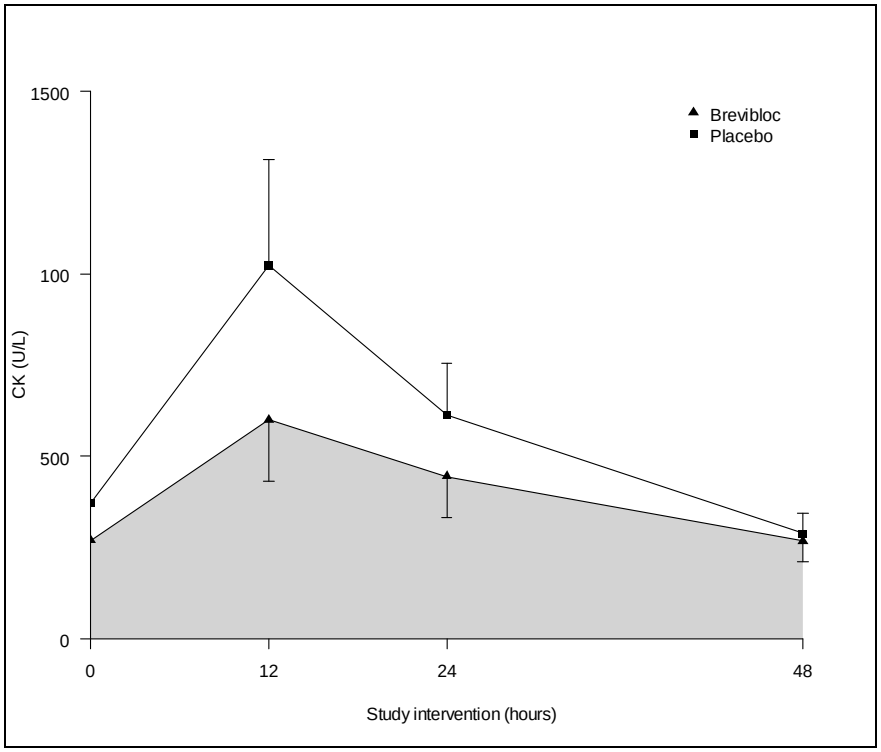


**Figure 3: Creatinin kinase (CK) concentration in esmolol group (Brevibloc) versus placebo group. Data are presented as back-transformed mean±95% confidence bounds for each time point of serum determination after using their natural logarithms for calculations.**

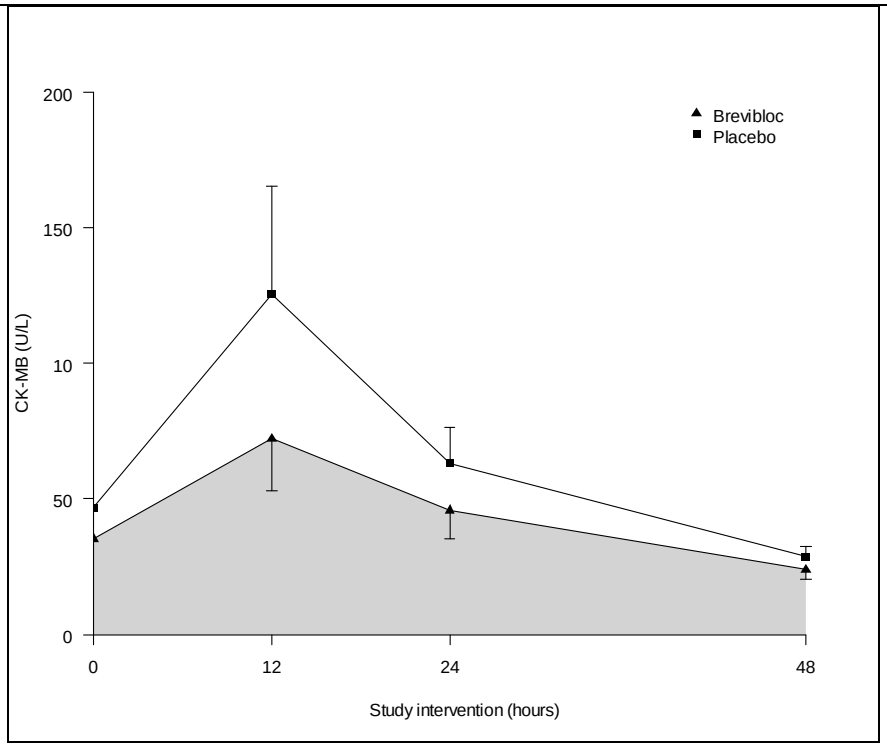


**Figure 4: Creatinin kinase MB (CK-MB) concentration in esmolol group (Brevibloc) versus placebo group. Data are presented as back-transformed mean±95% confidence bounds for each time point of serum determination after using their natural logarithms for calculations.**

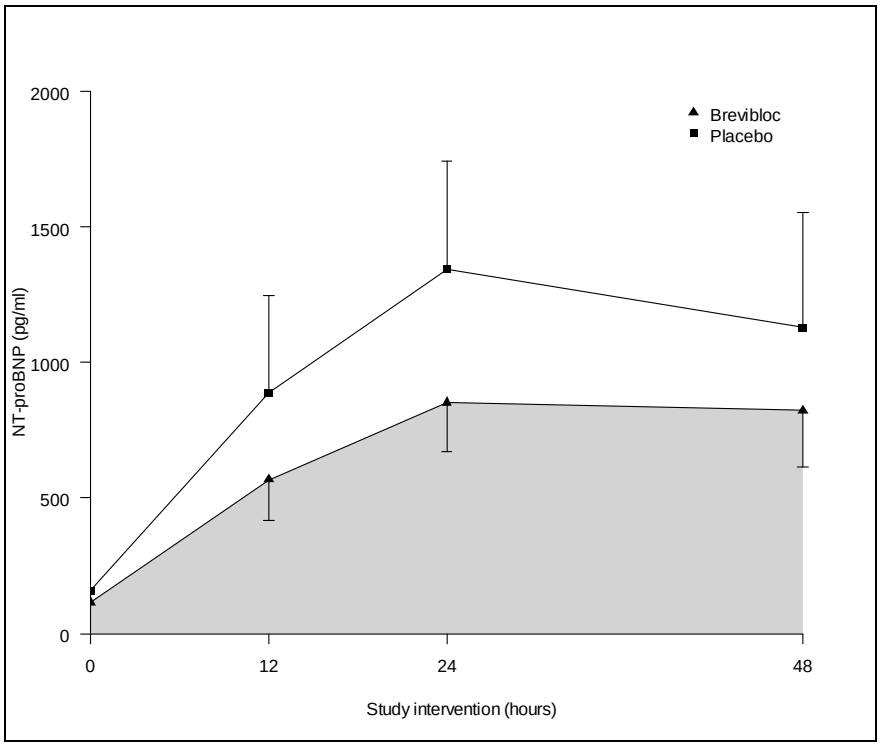


**Figure 5: NT-proBNP concentration in esmolol group (Brevibloc) versus placebo group. Data are presented as back-transformed mean±95% confidence bounds for each time point of serum determination after using their natural logarithms for calculations.**

Heart rate during study intervention:

Before study intervention resting heart rate was similar in both groups (esmolol group: 79.2±14.7 bpm vs. placebo group: 79.4±14.6 bpm; p=0.951). Mean heart rate in 24 hours was 68.4±9.0 bpm (esmolol group) vs. 73.8±12.4 bpm (placebo group; p=0.014; Table 7).

**Table 7: Heart rate during study intervention**

| | Esmolol | Placebo | P-Value |
|---|---|---|---|
| HR 0 hours | | | |
| Mean, ± SD | 79.2±14.7 | 79.4±14.6 | 0.951 |
| Median, (IQR) | 76 (68-86) | 77 (68-89) | |
| Average HR 6 hours | | | |
| Mean, ± SD | 69.5±11.4 | 73.8±10.9 | 0.055 |
| Median, (IQR) | 68 (63-76) | 72 (66-81) | |
| Average HR 12 hours | | | |
| Mean, ± SD | 67.4±10.3 | 71.5±12.0 | 0.071 |
| Median, (IQR) | 66.5 (59-75) | 69 (65-78) | |
| Average HR 18 hours | | | |
| Mean, ± SD | 67.1±9.4 | 71.7±13.0 | 0.045 |
| Median, (IQR) | 67 (60-73) | 71 (64-78) | |
| Average HR 24 hours | | | |
| Mean, ± SD | 68.4±9.0 | 73.8±12.4 | 0.014 |
| Median, (IQR) | 68.5 (63-74) | 73 (66-81) | |

P-values are from two-sample t-test. HR, heart rate.

Association between Treatment, Heart rate and Troponin level

We found a positive association between mean heart rate during 24h of study intervention and average Troponin T level from baseline to 48h, Spearman's rank correlation coefficient was 0.367 in esmolol group and 0.123 in placebo group. We did not find a statistically significant interaction between treatment and mean heart rate during 24h of study intervention (p=0.131) fitting a multivariable linear regression model using log-transformed average Troponin T level from baseline to 48h as dependent variable and treatment, mean heart rate during 24h of study intervention and log-transformed baseline Troponin T level as independent variables. The impact of esmolol on Troponin T release in the finally fitted regression model without interaction term was no longer statistically significant (p=0.072), but still noticeable. The Troponin T level in the esmolol group was 25% reduced compared to the placebo group, adjusted for baseline Troponin T (p<0.001) and mean heart rate

(p=0.010). Figure 6 displays the association between mean heart rate and Troponin T release in both groups. The curves correspond to the fitted regression equations and show the adjusted treatment effect.

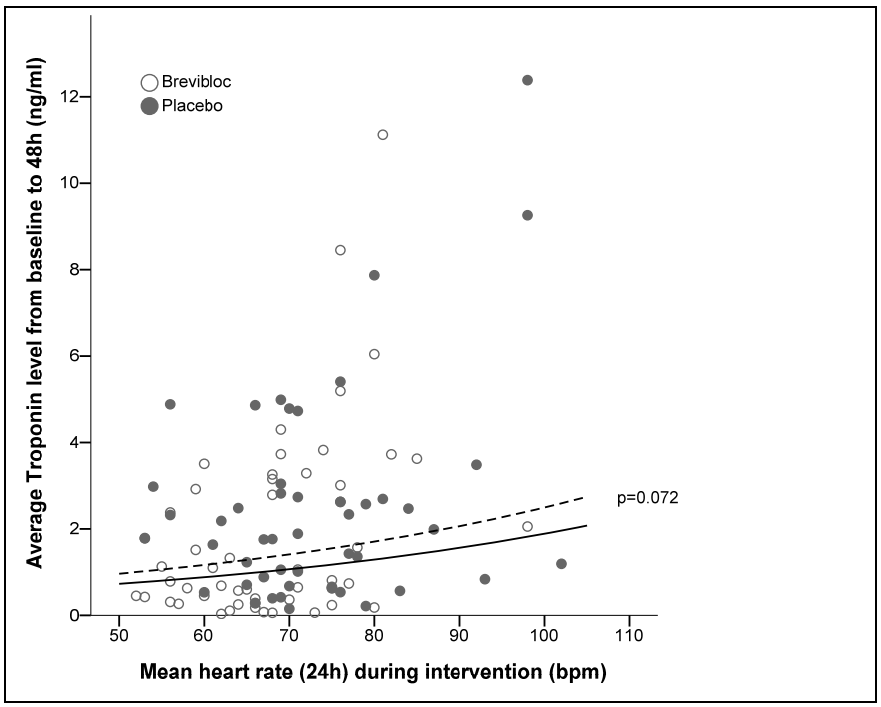


**Figure 6: Scatter plot displaying correlation between mean heart rate during intervention and average troponin T level from baseline to 48h by treatment. Lines show the adjusted effect of esmolol (solid line) and placebo (dotted line) on Troponin T release and result from fitted regression model substituting the mean baseline Troponin T level: Average Troponin T level = exp(-0.262 - 0.279*treatment + 0.599*log(baseline Troponin T) + 0.019*mean heart rate during intervention).**

Analyses of further secondary endpoints are summarized in the appendix B, table 5-7.

Per protocol analyses

The primary efficacy analysis revealed in a very similar result compared to ITT analysis set. Maximum change in Tropoinin T within 48 hours was statistically significant higher in placebo group (2.5 ng/ml [IQR: 1.0-4.0]) than in esmolol group (1.0 ng/ml [IQR: 0.3-2.6], p=0.012).

In the same manner, analysis results of secondary efficacy endpoints were comparable. Peak Troponin T from baseline to 48 hours was statistically significant higher in placebo group (3.3 ng/ml [IQR: 1.8-5.2]) compared to esmolol group (1.2 ng/ml [IQR: 0.6-4.6], p=0.008). Area under the curve of Troponin T release in 48 hours revealed higher Troponin T release in placebo group (88.3 ng*h/ml [IQR: 50.8-131.5]) than in esmolol group (37.8 ng*h/ml [IQR: 17.5-144.5]; p=0.048). Time to peak Troponin T concentration was longer in esmolol group (12 hours [IQR: 6-18]) versus placebo group (6 hours [IQR: 6-9]; p=0.030). Av-

erage heart rate in 24 hours was 68.6±9.3 bpm (esmolol group) vs. 74.1±12.0 bpm (placebo group; p=0.032).

Analyses of further secondary endpoints are summarized in the appendix E, table 5-7.

Subgroup analyses

Subgroup analyses were performed by gender. For women and men, treatment with esmolol was effective. For women, maximum change in Tropoinin T within 48 hours was 0.6 ng/ml [IQR: 0.4-1.7] in esmolol group and 2 ng/ml [IQR: 0.9-4.0] in placebo group, p=0.089. For men, maximum change in Tropoinin T within 48 hours was 1.1 ng/ml [IQR: 0.3-3.7] in esmolol group and 3 ng/ml [IQR: 1.2-4.4] in placebo group, p=0.027

Peak Troponin T from baseline to 48 hours was 1.1 ng/ml [IQR: 0.7-1.9] in esmolol group compared to 3.2 ng/ml [IQR: 1.6-4.7] in placebo group for women (p=0.032) and 1.4 ng/ml [IQR: 0.6-5.2] resp. 3.3 ng/ml [IQR: 1.3-5.8] for men (p=0.048). Area under the curve of Troponin T release in 48 hours was 37.8 ng*h/ml [IQR: 20.5-63.7] in esmolol group and 98.2 ng*h/ml [IQR: 50.8-126.2] in placebo group for women (p=0.032) and 39.0 ng*h/ml [IQR: 17.5-158.0] resp. 88.3 ng*h/ml [IQR: 37.2-144.6] for men (p=0.178). Time to peak Troponin T concentration was 12 hours [IQR: 6-12] in esmolol group versus 6 hours [IQR: 6-12] in placebo group for women (p=0.198) and 12 hours [IQR: 6-18] resp. 6 hours [IQR: 6-10] for men (p=0.041). Average heart rate in 24 hours was 62.4±6.6 bpm (esmolol group) vs. 74.1±9.2 bpm (placebo group; p=0.006) for women and 69.7±9.0 bpm resp. 73.7±13.5 bpm for men (p=0.246).

Further results are given in the appendices C, D, F and G.

**Safety results**

Analysis of adverse events

During study period a total of 420 adverse events (AEs) were reported, 169 in esmolol group and 251 in placebo group. Number of patients with AEs were 45 (90%) in both groups. The number of reported serious adverse events (SAEs) was 51 in total, 17 in esmolol group (12 patients) and 34 in placebo group (16 patients), see Table 8. Further details on number of AEs by system organ class by preferred term, seriousness in primary assessment and assigned treatment are given in appendix H.

**Table 8: Summary of adverse events**

| | | Total | Esmolo | Placebo | P-Value |
|---|---|---|---|---|---|
| Serious or Non-serious Adverse Events | No. of events | 420 | 169 | 251 | - |
| | No.(%) of patients with event | 90 (90) | 45 (90) | 45 (90) | 1.0 |
| Adverse Events | No. of events | 369 | 152 | 217 | - |
| | No.(%) of | 89 (89) | 44 (88) | 45 (90) | 1.0 |

| | | | | | |
|---|---|---|---|---|---|
| | patients with event | | | | |
| Serious Adverse Events | No. of events | 51 | 17 | 34 | - |
| | No.(%) of patients with event | 28 (28) | 12 (24) | 16 (32) | 0.505 |

P-values are from Fisher's exact test.

Listing of deaths, SAEs and significant adverse events

Deaths:

During study period, one patient (placebo group, 73 years, male) died 32 days after beginning of study intervention, see Table 9. Adverse events of this patient are given in Table 10.

**Table 9: Listing of deaths**

| Patient ID | Treatment | Date of randomization | Sex | Age | Date of death |
|---|---|---|---|---|---|
| 1-125 | Placebo | 11.04.2012 | Male | 73 | 13.05.2012 |

**Table 10: Listing of AEs of died patient (placebo group)**

| Patient ID | AE-No derivation | AE Start (date) | intensity | Relatedness drug | Preferred term |
|---|---|---|---|---|---|
| 1-125 | 1 | 11.04.2012 | mild | unlikely | Haematoma |
| 1-125 | 2 | 12.04.2012 | mild | unlikely | Confusional state |
| 1-125 | 3 | 12.04.2012 | mild | unlikely | Panic attack |
| 1-125 | 4 | 14.04.2012 | severe | unlikely | Cardiogenic shock |
| 1-125 | 5 | 15.04.2012 | mild | unlikely | Supraventricular tachycardia |
| 1-125 | 6 | 20.04.2012 | severe | unlikely | Cardiac arrest |
| 1-125 | 7 | 22.04.2012 | mild | unlikely | Cardiac arrest |
| 1-125 | 8 | 22.04.2012 | mild | unlikely | Cardiac arrest |
| 1-125 | 9 | 24.04.2012 | mild | unlikely | Polyuria |
| 1-125 | 10 | 20.04.2012 | mild | unlikely | Constipation |
| 1-125 | 11 | 23.04.2012 | mild | unlikely | Constipation |
| 1-125 | 12 | 25.04.2012 | mild | unlikely | Pancreatitis |
| 1-125 | 13 | 26.04.2012 | mild | unlikely | Pancreatitis |
| 1-125 | 14 | 26.04.2012 | mild | unlikely | Decubitus ulcer |
| 1-125 | 15 | 28.04.2012 | mild | unlikely | Pneumothorax |
| 1-125 | 16 | 28.04.2012 | mild | unlikely | Pleural effusion |

| | | | | | |
|---|---|---|---|---|---|
| 1-125 | 17 | 30.04.2012 | mild | unlikely | Tracheostomy |
| 1-125 | 18 | 01.05.2012 | mild | unlikely | Haemoglobin decreased |
| 1-125 | 19 | 02.05.2012 | mild | unlikely | Tachypnoea |
| 1-125 | 20 | 05.05.2012 | mild | unlikely | Pneumonia |
| 1-125 | 21 | 08.05.2012 | mild | unlikely | Pneumonia |
| 1-125 | 22 | 09.05.2012 | mild | unlikely | Polyuria |
| 1-125 | 23 | 09.05.2012 | mild | unlikely | Ventricular tachycardia |
| 1-125 | 24 | 09.05.2012 | mild | unlikely | Constipation |
| 1-125 | 25 | 10.05.2012 | mild | unlikely | Constipation |
| 1-125 | 26 | 11.05.2012 | mild | unlikely | C-reactive protein increased |
| 1-125 | 27 | 12.05.2012 | moderate | unlikely | Diarrhoea haemorrhagic |
| 1-125 | 28 | 12.04.2012 | moderate | unlikely | Pneumonia |

Serious adverse events:

**SAEs are listed in**

Table 11 for esmolol group and Table 12 for placebo group.

**Table 11: SAEs (esmolol group)**

| Patient ID | SAE-No derivation | Start of medication (date) | AE Start (date) | intensity | Relatedness drug | Preferred term |
|---|---|---|---|---|---|---|
| 1-105 | 1 | 24.10.2011 | 16.11.2011 | moderate | unlikely | Angina pectoris |
| 1-123 | 1 | 30.03.2012 | 14.04.2012 | mild | unlikely | Ventricular tachycardia |
| 1-126 | 1 | 12.04.2012 | 26.04.2012 | moderate | unlikely | Femoral neck fracture |
| 1-128 | 1 | 28.04.2012 | 24.07.2012 | moderate | unlikely | Angina pectoris |
| 1-128 | 2 | 28.04.2012 | 03.09.2012 | mild | unlikely | Angina pectoris |
| 1-129 | 1 | 29.04.2012 | 27.06.2012 | mild | unlikely | Cough |
| 1-148 | 1 | 31.08.2012 | 04.09.2012 | mild | unlikely | Acute coronary syndrome |
| 1-148 | 2 | 31.08.2012 | 08.09.2012 | moderate | unlikely | Altered state of consciousness |
| 1-148 | 3 | 31.08.2012 | 30.10.2012 | moderate | unlikely | Pneumonia |
| 1-148 | 4 | 31.08.2012 | 25.12.2012 | moderate | unlikely | Paraesthesia |
| 1-148 | 5 | 31.08.2012 | 27.01.2013 | mild | unlikely | Paraesthesia |
| 1-149 | 1 | 10.09.2012 | 13.12.2012 | mild | unlikely | Paraesthesia |
| 1-151 | 1 | 26.09.2012 | 01.10.2012 | moderate | unlikely | Infarction |

| | | | | | | |
|---|---|---|---|---|---|---|
| 1-155 | 1 | 02.11.2012 | 13.03.2013 | mild | unlikely | Vessel puncture site erythema |
| 1-159 | 1 | 10.01.2013 | 29.03.2013 | mild | unlikely | Angina unstable |
| 1-163 | 1 | 29.01.2013 | 04.02.2013 | mild | unlikely | Gastrooesophageal reflux disease |
| 1-195 | 1 | 02.08.2013 | 12.08.2013 | moderate | unlikely | Haemorrhage |

**Table 12: SAEs (placebo group)**

| Patient ID | SAE-No derivation | Start of medication (date) | AE Start (date) | intensity | Relatedness drug | Preferred term |
|---|---|---|---|---|---|---|
| 1-114 | 1 | 23.01.2012 | 23.01.2012 | moderate | unlikely | Thrombosis in device |
| 1-114 | 2 | 23.01.2012 | 18.04.2012 | mild | unlikely | Asthma |
| 1-114 | 3 | 23.01.2012 | 05.05.2012 | mild | unlikely | Angina pectoris |
| 1-118 | 1 | 16.02.2012 | 22.02.2012 | moderate | unlikely | Angina pectoris |
| 1-119 | 1 | 15.03.2012 | 16.03.2012 | severe | unlikely | Carotid artery stenosis |
| 1-121 | 1 | 17.03.2012 | 09.06.2012 | severe | unlikely | Thrombophlebitis |
| 1-121 | 2 | 17.03.2012 | 31.07.2012 | moderate | unlikely | Thrombophlebitis |
| 1-124 | 1 | 05.04.2012 | 30.05.2012 | moderate | unlikely | Carotid artery stenosis |
| 1-125 | 1 | 11.04.2012 | 14.04.2012 | severe | unlikely | Cardiogenic shock |
| 1-125 | 2 | 11.04.2012 | 20.04.2012 | severe | unlikely | Cardiac arrest |
| 1-125 | 3 | 11.04.2012 | 12.05.2012 | moderate | unlikely | Diarrhoea haem-orrhagic |
| 1-130 | 1 | 02.05.2012 | 02.05.2012 | severe | unlikely | Back pain |
| 1-130 | 2 | 02.05.2012 | 03.05.2012 | severe | unlikely | Back pain |
| 1-130 | 3 | 02.05.2012 | 03.05.2012 | moderate | unlikely | Nausea |
| 1-130 | 4 | 02.05.2012 | 03.05.2012 | severe | unlikely | Coronary artery stenosis |
| 1-140 | 1 | 04.07.2012 | 05.11.2012 | moderate | unlikely | Acute coronary syndrome |
| 1-140 | 2 | 04.07.2012 | 11.12.2012 | moderate | unlikely | Acute coronary syndrome |
| 1-147 | 1 | 27.08.2012 | 11.10.2012 | moderate | unlikely | Aortic valve replacement |
| 1-156 | 1 | 22.11.2012 | 22.12.2012 | mild | unlikely | Pharyngitis |

| | | | | | | |
|---|---|---|---|---|---|---|
| 1-156 | 2 | 22.11.2012 | 30.03.2013 | moderate | unlikely | Pancreatitis acute |
| 1-168 | 1 | 18.03.2013 | 19.03.2013 | moderate | unlikely | Angina unstable |
| 1-168 | 2 | 18.03.2013 | 25.04.2013 | severe | unlikely | Gastrointestinal haemorrhage |
| 1-168 | 3 | 18.03.2013 | 06.05.2013 | moderate | unlikely | Angina unstable |
| 1-168 | 4 | 18.03.2013 | 13.05.2013 | severe | unlikely | Angina unstable |
| 1-168 | 5 | 18.03.2013 | 19.05.2013 | moderate | unlikely | Pneumonia |
| 1-168 | 6 | 18.03.2013 | 29.08.2013 | moderate | unlikely | Pneumonia |
| 1-169 | 1 | 20.03.2013 | 18.07.2013 | moderate | unlikely | Angina pectoris |
| 1-174 | 1 | 24.04.2013 | 26.04.2013 | severe | unlikely | Ventricular tachycardia |
| 1-174 | 2 | 24.04.2013 | 26.04.2013 | severe | unlikely | Ventricular tachycardia |
| 1-174 | 3 | 24.04.2013 | 05.05.2013 | mild | unlikely | Angina unstable |
| 1-174 | 4 | 24.04.2013 | 13.05.2013 | mild | unlikely | Angina unstable |
| 1-178 | 1 | 26.05.2013 | 20.11.2013 | mild | unlikely | Mitral valve incompetence |
| 1-180 | 1 | 29.05.2013 | 16.07.2013 | moderate | unlikely | Angina unstable |
| 1-201 | 1 | 21.09.2013 | 02.10.2013 | mild | unlikely | Ventricular extrasystoles |

Other important AEs:

During study period no Suspected Unexpected Serious Adverse Reactions (SUSAR) were reported. Three AEs resulting in dose reduction were reported, two in esmolol group and one in placebo group. One of these AEs was possibly related to drug, see Table 13. The relatedness to drug was unlikely for all other reported AEs.

**Table 13: AEs resulting in dose reduction**

| Patient ID | Treatment | Start of medication (date) | AE Start (date) | AE End (date) | intensity | Relatedness drug |
|---|---|---|---|---|---|---|
| 1-145 | Brevibloc | 12.08.2012 | 12.08.2012 | 12.08.2012 | mild | possibly |
| 1-147 | Placebo | 27.08.2012 | 28.08.2012 | 28.08.2012 | severe | unlikely |
| 1-149 | Brevibloc | 10.09.2012 | 10.09.2012 | 10.09.2012 | mild | unlikely |

(continued)

| Patient ID | Preferred term | Outcome | Therapy of event | Action taken with drug | Comment refer to AE no. |
|---|---|---|---|---|---|
| 1-145 | Mitral valve incompetence | resolved without sequelae | reduction of dose of study medication and increase of dose of sterofundin | dose reduced | most likely physical reaction of very stressful reaction |

| | | | | | |
|---|---|---|---|---|---|
| 1-147 | Pulmonary oedema | resolved without sequelae | Diazepam 5mg i.v., MSI 7 mg i.v., Nitro 4 mg i.v., Lasix 720 mg i.v., mask ventilation as support | dose reduced | The dose reduction was performed to avoid a hypervolemia which could impair the situation although the substitution of study medication (=Placebo) was not the reason for the event |
| 1-149 | Paraesthesia | resolved without sequelae | Lasix i. v. 20 mg | dose reduced | dose increased and reduced independantly of hyperkalemia |

A complete line-listing of AEs and medication by patient is given in appendix I and J.

**Statistical methods**

The primary efficacy outcome was the maximum change in Troponin T level from baseline to 48 hours. The null hypothesis that Troponin T release was same in patients with esmolol therapy and placebo was tested using the Mann-Whitney U test. A difference was seen to be statistically significant if the two-sided p-value was $<0.05$. The primary analysis followed the intention-to-treat (ITT) principle. To compute the maximum Troponin values we used all valid measurements within 48 hours after beginning of study intervention. Only patients with valid baseline troponin T values and at least one valid measurement within 48 hours after beginning of intervention were included.

In addition to maximum change in Troponin T level we compared the maximum Troponin T level, the area under the curve (AUC) and the time to peak Troponin T. CK, CK-MB and NT-proBNP levels from baseline to 48 hours were analyzed in the same manner.

At baseline (i.e. before study medication), during study intervention and during follow-up (i.e. at six weeks and at six months) treatment groups were described and compared using mean, standard deviation and percentiles (0, 25, 50, 75, 100) for continuous variables, count and percentage for categorical variables. We used unpaired t-tests, Mann-Whitney U tests and Fisher's 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 average Troponin T level from baseline to 48h as dependent variable and treatment, mean heart rate during 24h of study intervention and log-transformed baseline Troponin T level as independent variables. The interaction treatment * mean heart rate was explored.

All reported p-values are two-sided. For the primary hypotheses of association of esmolol with maximum change in Troponin T the significance level was set at 5%. The further analyses were regarded as explorative, and the p values of the corresponding tests are presented for descriptive reasons only.

| | |
|---|---|
| | Subgroup analyses were performed by gender.<br>All analyses were performed for the ITT analysis set and secondary/supportive the PP analysis set.<br>Interim analyses were not planned and not performed. |

**SUMMARY:**

Long-term medication after STEMI is well established. Acute post-PCI strategies for limitation of myocardial infarct size in patients with STEMI are lacking. While elevated heart rate during STEMI identifies patients at elevated risk, elevated heart rate itself may increase myocardial injury and prevent complete regeneration. Continuous beta-blocker infusion targeting tight heart rate control after successful PCI may protect cardiomyocytes – and in case of heart rate influence on myocardial infarction size – limit the Troponin T release as a surrogate of myocardial necrosis.

The BEAT-AMI trial was carried out to analyse the efficacy of esmolol-induced tight heart rate control versus placebo for reduction of Troponin T release in subjects with acute STEMI in a randomized, single-blind, placebo-controlled trial.

In this single-centre clinical trial performed at the university hospital Cologne a total of 100 patients were treated with esmolol or placebo.

**RESULTS EFFICACY:**

Compared to placebo group, STEMI patients treated with intravenous esmolol infusion after successful PCI had a reduced maximum change in Troponin T within 48 hours after beginning of study intervention (1.0 ng/ml [IQR: 0.3-3.5] vs. 2.5 ng/ml [IQR: 1.0-4.0]; p=0.010). Mean heart rate in 24 hours was reduced in esmolol group compared to placebo group (68.4±9.0 bpm vs. 73.8±12.4 bpm; p=0.014).

**RESULTS SAFETY:**

In patients with Killip class I and II myocardial infarction esmolol increased not the incidence of cardiogenic shock or mortality compared to placebo. No persistent bradycardia was observed. Patients at higher risk for esmolol-treatment were not identified.

**CONCLUSION:**

- In patients with acute myocardial infarction esmolol-treatment reduced the infarction size reflected by the surrogate markers Troponin T, CK and CK-MB.
- Tight heart rate control with esmolol in patients with STEMI (Killip I, II) seems to be safe and effective.

Appendix A: CONSORT Flow Diagram

Appendix B: Analysis of patient data, ITT analysis set, all patients

Appendix C: Analysis of patient data, ITT analysis set, women only

Appendix D: Analysis of patient data, ITT analysis set, men only

Appendix E: Analysis of patient data, PP analysis set, all patients

Appendix F: Analysis of patient data, PP analysis set, women only

Appendix G: Analysis of patient data, PP analysis set, men only

Appendix H: Safety, number of (serious) adverse events by treatment

Appendix I: Safety, line-listing of adverse events by patient

Appendix J: Safety, line-listing of medication by patient