Early Administration of intravenous Beta blockers in patients with ST-elevation myocardial infarction before primary PCI

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Short title: EARLY Beta-blocker Administration before primary PCI inSTEMI. The EARLY-BAMI trial.

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Abstract

Background: The impact of i.v. β-blockers before primary PCI (pPCI)on infarct size and clinical outcomes is not well established, with only one prior study showing benefit of early i.v. metoprolol before pPCI.The Early- Beta-blocker Administration before primary PCI in patients with ST-elevation Myocardial Infarction (Early-BAMI) trial, is the first double-blinded, placebo-controlled international multicenter study testing the effect of early i.v. β-blockers before pPCI in a general STEMI population.

Methods: STEMI patients presenting <12h from symptom onset, Killip I-II, without AV block,were 1:1 randomized to i.v. metoprolol (2x5 mg bolus) or matched placebo before primary PCI. Primary endpoint was myocardial infarct size as assessed by magnetic resonance imaging (MRI) at 30 days. Secondary endpoints were enzymatic infarct size and incidence of ventricular arrhythmias. Safety endpoints included symptomatic bradycardia, symptomatic hypotension, and cardiogenic shock.

Results: A total of 683patients (mean age was 62±12 years (75% male) were randomized to metoprolol (n=336) or placebo (n=346). MRI was performed in 342 patients (54,8%). No significant differences in baseline characteristics were observed. Infarct size (% of LV) by MRI did not differ between the metoprolol (15.3 ± 11.0%) and placebo group (14.9 ± 11.5% p=0.616). Peak and area under the creatine kinase (CK) curve did not differ between both groups. Left ventricular ejection fraction by MRI was 51.0 ± 10.9% in the metoprolol group and 51.6 ± 10.8% in the placebo group, p=0.68. The incidence of malignant arrhythmias was 3.6% in the metoprolol group vs 6.9% in placebo p=0.050. The incidence of adverse events was not different between groups.

Conclusion: In a non-restricted STEMI population, early intravenous metoprolol before pPCI, was not associated with a reduction in infarct size. Metoprolol reduced the incidence of malignant arrhythmias in the acute phase and was not associated with an increase in adverse events.

Clinical trial: NCT01569178

Keywords: beta-blocker, myocardial infarction, infarct size, primary PCI

Abbreviations:
CK: creatine kinase
MRI: magnetic resonance imaging
PPCI: primary percutnaneous coronary intervention
STEMI: ST-segment Elevation Myocardial Infarction

Background

Despite advances in the care for patients with ST-elevation myocardial infarction (STEMI), mortality in these patients remains relative high, especially in an allcomer population (1). Although early diagnosis and treatment have improved outcome of these patients, additional interventions early after onset of ischemia might further improve outcome. In the clinical guidelines, treatment with β-blockers for STEMI patients is recommended (2), although the evidence of mortality reduction with β-blockers after reperfusion therapy is limited (2-4). Whether administration before reperfusion improves clinical outcome or reduces myocardial infarct size is less clear. Experimental studies have conflicting results whether β-blockers decrease the extent of myocardial necrosis (4-6). In clinical studies in STEMI, the effect of early β-blockade was mostly studied in the prereperfusion era, with inconclusive results (7-10). In the era of thrombolysis, 2 randomized controlled trials testing the effect of β-blockers in STEMI showed no reduction in mortality with β-blocker treatment (11,12). In patients treated by primary percutaneous coronary intervention (pPCI), only 2 randomized controlled trials studied the effect of early β-blocker treatment. Hanada et al observed in a small study (n = 96) that continuous intravenous landiolol immediately *after* primary PCI was associated with an improvement of left ventricular (LV) function (13). The Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial (n=220) showed that intravenous metoprolol administrated before primary PCI reduces infarct size and preserved LV function (14-16). In the latter trial however, only patients with an anterior location of STEMI were included, and the trial was neither blinded nor placebo controlled. We present the results of the Early-BAMI trial, the first double-blinded, placebo-controlled multicenter international study, assessing the effect of early i.v. β-blocker therapy before pPCI in a less restricted STEMI population (17).

Methods

The primary objective of the EARLY-BAMI trial (EudraCT no.: 2010-023394-19.) was to assess the effect of early, prehospital pre-reperfusion administration of intravenous metoprolol on myocardial infarct size in patients with STEMI eligible for primary PCI. The design of the study has previously been published (17). The study was approved by the medical ethical committees of the participating hospitals. It concerns a multicenter, multinational, double-blind, placebo-controlled randomized clinical trial. A total of 5 PCI centers and 3 ambulance services in The Netherlands and 9 PCI centers and 1 ambulance service in Spain enrolled patients. All centers had a long-standing experience in the pre-hospital diagnosis, triage and treatment of STEMI patients in the ambulance and were part of a STEMI network. The trial was conducted with a research grant of the Dutch Heart Foundation (Utrecht, Netherlands, no. 2010B125) and an unrestricted grant of MedtronicInc. (Heerlen, The Netherlands) for additional analyses.

Study protocol

Patients aged > 18 years with symptoms of acute STEMI for >30 minutes but < 12 hours and ST elevation > 1 mV in 2 adjacent ECG leads or new left bundle branch block (LBBB) were eligible for enrollment. The diagnosis of STEMI was made by the ambulance medical personnel. Electrocardiogram transmission to a physician at the PCI center could be performed to allow confirmation of the diagnosis. After the diagnosis of STEMI in the ambulance, medical treatment in all patients occurred as per current guidelines with the administration of 500 mg of aspirin intravenously, 600 mg clopidogrel or 180 mg of ticagrelor orally, and 5,000 International Units of unfractionated heparin intravenously. Exclusion criteria were Killip class III and IV, systolic blood pressure < 100 mmHg, heart rate < 60 bpm, type II and III atrioventricular block, history of previous MI, known asthma bronchiale, pacemaker or implantable cardioverter-defibrillator

(ICD) implantation (no MRI possible), pregnancy or breastfeeding or inability to provide informed consent. If patients fulfilled the inclusion/exclusion criteria, verbal informed consent was obtained. The trained ambulance paramedic completed the administration / enrolment procedure. After informed consent, a blinded study medication box was opened. This box contained 2 vials with metoprolol 5 mg or matched placebo and was labeled with a number that corresponded with the randomization list. Randomization took place without stratification and in blocks of 4. The first bolus of study medication was given in the ambulance, the second bolus in the PCI hospital at the catheterization laboratory before the PCI procedure only if systolic blood pressure was >100 mmHg and heart rate >60 bpm. Given that in the COMMIT CC2 trial (12), 15mg of metoprolol administration in a short interval was associated with a slight increase in cardiogenic shock (although this was restricted to Killip III patients), the reference ethics committee suggested to reduce the dose to 10mg separated into two 5mg boluses: the first 5mg bolus during ambulance transit, and the second 5mg bolus on arrival at the cath lab (i.e. immediately before initiating the PCI). The results of the METOCARD-CNIC trial (using 15 mg metoprolol) were not known at the time of the study design. Patients participating in the trial were treated during hospital admission and thereafter according to current guidelines. During PCI, the use of thrombus aspiration and the use of glycoprotein IIb-IIIa inhibitors was left at the discretion of the operator. In addition, stenting was performed with a second-generation drug-eluting stent. After PCI, patients received detailed written study information in which the protocol and the MRI follow up was explained in more detail, whereafter written informed consent was obtained.All patients were planned to receive oral metoprolol within 12 hours after PCI, according to current guidelines, during hospitalization. At discharge, all patients received

oral metoprolol at a dose recommended by their treating physician. Follow-up included visits at the outpatient clinic at each center and allowed us to obtain data for follow-up.

End points

The primary end point was myocardial infarct size (% infarcted myocardium, % of LV) as measured by MRI at 30 days (±10 days). The secondary efficacy end points were peak creatine kinase (CK), peak CK-MB, troponin at 24 hours, and area under the CK and CK-MB curve during the first 24 hours, residual ST deviation 1 hour after PCI/coronary angiogram, ventricular arrhythmias requiring defibrillation during transportation and hospitalization and major adverse cardiac events (MACE), defined as cardiac death, nonfatal reinfarction, or target vessel revascularization at 30 days. The secondary safety end points include symptomatic bradycardia, symptomatic hypotension, and cardiogenic shock.The following subgroups were prespecified for analysis: anterior versus nonanterior infarctions, patients presenting <6 hours after symptom onset versus patients presenting >6 hours, and occluded (Thrombolysis In Myocardial Infarction (TIMI) 0 and 1 flow) infarct-related vessel at time of PCI versus open (TIMI 2 and 3 flow) infarct-related vessel.

Statistical methods

Sample size calculation

Initially, the study was designed and initiated with enzymatic infarct size as primary end point. However, after inclusion of 164 patients, the primary end point was changed into a MRI based end point (at 3 July 2013), which was approved by the steering committee and the medical ethical committee. The original primary outcome measure was enzymatic infarct size measured by cardiac troponin T, and required 770 patients, based on the assumption that pre-hospital administration of 2x 5mg metoprolol iv would give a relative 20% reduction in infarct size.

(alpha = 0.05, power 80%, mean troponin T 3.34 ng/L, SD:3.30).This original primary outcome, became a secondary outcome after the change in the protocol. The change in the primary outcome was primarily made in order to reduce the necessary sample size and a time limitation of financial funding. Also, infarct size could be studied more precisely with MRI. The change occurred while the investigators were still entirely blinded to trial results, and without any interim analysis performed. The sample size was than determined for the primary end point of the trial by a power analysis with reasonable clinical and statistical assumptions. With an expected infarct size of 28% (18) in a population under standard treatment (no β-blockers pre-PCI), we considered a reduction in infarct size from 28% to 23.5% clinically relevant. Assuming an SD of the myocardial infarction (MI) size measured by MRI equal to 10% (19), the power analysis indicated a total sample size of 326 patients (163 subjects in each group) was needed to achieve 80% power with significance level of 0.05 to detect a difference in infarct size.

Patients who died after completing the MRI study were included in the primary outcome analysis. Patients who died before performance of the MRI were not included in the primary outcome analysis; however, they were included in the secondary outcome analysis because death within 1 year is a secondary end point. Statistical analysis was performed with Statistical Analysis System, SAS, version 9.3 and with the Statistical Package for the Social Sciences (SPSS, IBM) version 22.0. Continuous data was expressed as mean ± SD of mean and categorical data as percentage, unless otherwise denoted. The analysis of variance and the $\chi 2$ test was appropriately used for continuous and categorical variables, respectively. For quantitative variables data were expressed as mean +/- SD and median with first and third quartiles. Non normal data were compared by non-parametric methods (Wilcoxon rank-sum test) and normal data by parametric methods. Categorical data were expressed as percentages and compared by

Chi Square test (or Fischer Exact test when appropriate). For all analyses, statistical significance was assumed when the 2-tailed $P < 0.05$.

Cardiac MRI analysis

All MRI studies were performed blinded to treatment allocation and according to a centralized protocol. Dedicated sequences evaluating cardiac function, myocardial edema, myocardial perfusion, and myocardial necrosis/fibrosis were performed. All MRI studies were stored and further analyzed in a central core laboratory at the Centro Nacional de Intervestigaciones Cardiovasculares Carlos III (CNIC) in Madrid, Spain. Analysis of MRI studies were performed in a random manner by expert observers blinded to treatment allocation. Quantification was performed on a separate workstation using a dedicated software package (QMass MR 7.6; Medis, Leiden, the Netherlands). In all MRI studies, the following information was determined: LV volumes, LV function, and myocardial delayed enhancement. Myocardial necrosis was defined by the extent of abnormal delayed enhancement. All measurements were expressed as percentage of the total LV myocardial volume; the absolute MI size was also quantified in grams. All results were given in absolute numbers and indexed by patients' body surface. Differences between the 2 groups was estimated by multivariable linear regression adjusted for the participating hospital center and the stratification variables.

Results

Between February 2012 and November 2015, 684 patients were enrolled in 14 participating hospitals and 4 ambulance services in the Netherlands and Spain. In one patient the box with the study medication was lost during transportation and this patient was excluded from the analysis. The 683 remaining patients were randomized to metoprolol (n=336) or placebo (n=347) before primary PCI. Mean age was 62±12 years (75% males). A flow diagram is shown

in Figure 1. Baseline characteristics of the study population are presented in Table 1. Although time from onset of complaints till first medical contact was comparable between the two groups, early presenters (< 6 hours after complaints onset) were more often present in the metoprolol group. At inclusion (before randomization), mean blood pressure on admission was comparable between the two groups, while mean heart rate was not-significantly lower in the metoprolol group (78.6 beats/min vs 80.5 beats/min, p=0.09). A total of 20 patients (2.9%) were enrolled at the emergency department of the PCI center, mainly because transportation of the patient to thePCI center was very short. In these patients, the fist study bolus was given as soon as possible at the emergency department, and the second bolus at arrival at the cath lab.

Of the 336 patients allocated to pre-reperfusion metoprolol, 81.1% received also the second bolus, compared to 86% in the placebo group (p=0.08). Blood pressure before the second bolus (administered at the cath lab) was not different between groups, while heart rate was lower in the metoprolol group. Coronary angiography was performed in 99% of patients, similar in the metoprolol and placebo groups. One-vessel disease was observed in 53% of the metoprolol group compared to 59% of the placebo group (p=0.06). Initial TIMI flow 0 or 1 was demonstrated in 62% of the patients in the metoprolol group versus 60% in the placebo group (p= 0.61). Primary PCI was performed in 93% (metoprolol group) and 92% (placebo group, p=0.66), and was successful in 97% in both groups (p=0.70). Oral metoprolol was initiated within 24 hours in 78% in the metoprolol group and 73% of patients in the placebo group (p=0.13).

Primary Endpoint

MRI was performed in 342 of the 520 patients (66%) who were included after the change of the primary end point.(67% in the metoprolol group and 67% in the placebo group, p=0.77).

In the 342 patients who had MRI performed, no major differences in baseline characteristics between the treatment groups were present.In the MRI sample size calculation, we accounted for a drop out of 20%. But the actual drop out rate was higher (34%), so to meet the needed number of MRI, patient recruitment was continued until the needed number of 326 analyzed MRI's was reached. The main reasons why MRI were not performed were claustrophobia, planning out of the time window of one month ± 10 days and refusal by patient due to transfer to a different hospital. All causes are listed in **Figure 1.**

The primary end point, mean infarct size (% delayed enhancement of LV) in the metoprolol group was15.29%±10.97 versus 14.91%± 11.52 in the placebo group (p=0.616). Pre-reperfusion administration of iv metoprolol did not improve LVEF on MRI (50.97%± 10.93% versus 51.65%± 10.83% in the placebo group). These findings are summarized in **Table 2**.

Secondary Endpoints

The peak creatinine kinase (CK), peak CK-MB and troponin levels at 24 hours were available in 591 (86.4%) patients. Peak CK was 2102 ± 2029 U/L in the metoprolol group vs 2072 ± 2018 U/L in the placebo group. p=0.88. Mean single Troponin T measured at 24 hours of hospitalisation period was 3711 ± 3587 ng/L in the metoprolol group versus 3166 ± 3998 ng/L in the placebo group (p=0.1). Results of enzymatic infarct size are summarized in figure 2 and 3 (area under the curve).

Major adverse cardiac events (MACE) at 30 days occurred in 19 patients (6.2%) in the metoprolol group and 22 patients (6.9%) in the placebo group (P=0.72).

Safety Endpoints

Pre-Reperfusion administration of iv metoprolol did not change the incidence of the prespecified secondary safety endpoints. There were 16 (4.8%) safety events in the metoprolol

group and 11(3.2%) events in the placebo group, p=0.271. Safety endpoints and adverse cardiac events are presented in table 3. Bradycardia was observed in 4.2% in the metoprolol group, compared to 2.6% in the placebo group (p=0.25).There was however a borderline significant reduction in the occurrence of malignant arrhythmias in the acute phase in the metoprolol group, 12 patients (3.6%) vs 24 patients (6.9%, P=0.050).

Prespecified subgroup analysis

Infarct size 1 month after STEMI did not differ in patients presenting with an anterior infarction between the metoprolol group (18.8 ± 12.2%) and the placebo group (19.3 ± 12.7%. p=0.33). The infarct size in patients with a non-anterior infarction was 12.2 ± 8.0% in the metoprolol group and 10.4±7.8 in the placebo group. Patients presenting <6 hours after symtom onset also did not benefit from pre-reperfusion metoprolol administration compared to patients presenting > 6 hours after symptom onset. Infarct size in patients with an occluded vessel (TIMI 0 and 1 flow) at the time of coronary angiography did not differ between the metoprolol and placebo group (17.8 ± 10.8 versus 18.1 ± 11.8%. p=0.74). Data from these prespecified subgroups are shown in **Figure 4.**

Discussion

In this double-blind, randomized controlled trial, in patients with STEMI undergoing primary PCI, pre-reperfusion administration of up to 10 mg metoprolol i.v. was safe, but had no effect on infarct size or LVEF.

β-Blockers have multiple actions on the heart. Blockade of β1 receptors results in slowing of heart rate, reduction in myocardial contractility, and lowering of systemic blood pressure. In the context of acute myocardial infarction, which represents a state of reduced oxygen supply to the affected portion of the heart, these effects may be beneficial, as they result in reduced

myocardial workload and oxygen demand. Furthermore, β-blockers decrease the incidence of life-threatening arrhythmias, reinfarction, and recurrent ischemia, preventing LV remodeling (11,13-15,18-21). They have demonstrated to be beneficial, resulting in a mortality reduction in patients with reduced LV function and when administered after MI. However, there is debate whether pre-reperfusion administration of intravenous β-blockers may reduce reperfusion injury as compared with post reperfusion administration (22).

The MIAMI trial tested the effect of pre-reperfusion metoprolol (3 × 5 mg intravenous) versus placebo in STEMI (n = 5778) treated by thrombolysis and demonstrated no effect of metoprolol (11). In the COMMIT CC2 trial (n = 45,825), intravenous metoprolol 3 × 5mg intravenous followed by oral administration up to 4 weeks did not improve survival in STEMI patients (12). However, this was mainly caused by a higher incidence of cardiogenic shock in patients treated by early β-blocker, possibly due to inclusion of patients with heart failure. In the current era of primary PCI, the METOCARD-CNIC trial showed reduced infarct size and increased LV ejection fraction in STEMI patients without signs of heart failure treated with early intravenous metoprolol (14,23). However, this study had a relatively small sample size (N=270), was not blinded, not placebo controlled, and included a selected patient group (anterior STEMI presenting < 6 hours from symptom onset). Our study included all patients with STEMI, with a double-blinded, placebo controlled design. Our results do not confirm the effect observed in the METOCARD-CNIC trial. One possible explanation could be that the METOCARD-CNIC trial included only anterior infarctions, The average infarct size (infarcted myocardium, % LV) in the METOCARD-CNIC trial was 21.2% in patients treated with iv metoprolol, compared to 15.3% in our study. These differences could support this theory. The smaller the infarctions, the less likely an additional treatment effect can be demonstrated. However, also the subgroup with

anterior infarction had no benefit of early beta blocker treatment.In METOCARD-CNIC, the dose of metoprolol was higher, up to 3 times 5 mg (15 mg target dose), whereas in our trial only two times 5 mg (10 mg target dose) was given. Another explanation can be that 18.8% of patients in our trial were on long term beta-blocker treatment before admission, however this was an exclusion criteria in the METOCARD trial. Also the timing of the MRI can be of influence. In the METOCARD trial 2 MRI's were performed: One at 5-7 days, and the second at 6 months. Data from the first MRI at 5-7 days showed an improvement in LVEF in the metoprolol group and a significant reduction in infarct size. The follow-up MRI data at 6 months showed an even more significant difference in LVEF favoring the metoprolol group, but with no significant difference in infarct size any more. Comparing the MRI infarct size as % of LV in the metoprolol group, it was 15.7% ± 9.6 in the METOCARD-CNIC trial at 6 months; vs 15.3% ± 11.0 in our trial at one month. Another potential reason responsible for the different effect observed in this trial compared to the METOCARD-CNIC trial is the timing of metoprolol administration: A recent subanalysis of the METOCARD-CNIC trial (24), showed that the timing of metoprolol administration is a critical factor accouting for its infarct-limiting effect. That subanalysis, showed that only patients receiving i.v. metoprolol long before reperfusion had a reduction in infarct size. METOCARD-CNIC trial patients receiving i.v. metoprolol close to pPCI had significantly larger infarctions than those receiving i.v. metoprolol long before reperfusion, and similar to control patients. In the present Early-BAMI trial, the second 5mg bolus (to complete the 10mg target dose) was administered per protocol immediately before catheterization (median time from bolus and reperfusion 14 min). The first 5mg of iv metoprolol might be insufficient to attain cardio protection, in fact blood pressure after the first bolus of medication (i.e. before second bolus) was not different between metoprolol and placebo arms in

this trial, supporting the low-dosing hypothesis. Based on these data, and the conflicting results with METOCARD-CNIC, additional randomized trials are needed to clarify whether early beta-blocker treatment has any effect in these patients. We advocate that future studies should test the cardioprotective effects of i.v. metoprolol in STEMI patients and should have a target dose of 15mg and administer medication immediately after STEMI diagnosis to allow a maximum "on-board" metoprolol time before reperfusion. Given the reduced observed infarct size, with a trial of our sample size, the reduction in infarct size by metoprolol should be at least 3.5% to demonstrate a significant difference between the borh groups. The safety profile, low cost, and the reduction of acute malignant arrhythmias seen in this trial encourage the performance of additional larger trials in this regard.

In most randomized trials in which infarct size or LVEF was measured with MRI, MRI was performed at one month (25,26). This was the main reason why we choose one month in our trial. All participating PCI centres and ambulance services had a long-standing experience in prehospital triage and treatment of STEMI patients. Regional differences in systems of care in which prehospital drug administration in the ambulance differ (Europe vs US), can lead to different interpretation of these study results to daily practice.

Limitations

During the course of the trial, the primary endpoint was changed from enzymatic infarct size to infarct size measured by MRI. The change in the primary outcome was made in order to reduce the necessary sample size and infarct size could be studied more precisely with MRI. The results from enzymatic infarct size analysis however were completely in line with the results from the primary MRI end point.

The trial was powered with a reduction of infarct size from 28% to 23.5%. The smaller than estimated infarct size in this trial (15.1%) could affect the neutral effect of the trial, (the smaller the infarct size, the less probability thata difference could be found). However, also in the larger anterior infarctions there was no observed effect. Also patients who died before MRI was performed, with probably larger infarctions, may have caused a selection of patients with smaller infarctions who had MRI.

Although we defined several sub analyses, these analyses should be interpreted with caution, since the included patients in several subgroups were small. It was not possible to blind physicians and nurses for heart rate and blood pressure. However, analyses of MRI (primary end point) were blinded for both heart rate and study medication.

Conclusions

Early pre-reperfusion administration ofintravenous metoprolol, at a dose of 10 mg (2 x 5 mg) had no beneficial effects on infarct size in patients with STEMI treated by primary PCI.

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Figure Legends

Central Illustration: Balancing the results of the Early-BAMI and the METOCARD-CNIC trail.

Figure 1: Diagram of patient flow

Figure 2: Enzymatic infarct size estimated by peak creatine kinase (CK)

Figure 3: Enzymatic infarct size estimated by area under the creatine kinase (CK) curve.

Figure 4: Prespecified subgroup analysis. Estimated effect of Metoprolol Compared with Placebo on Delayed enhancement infarct according to prespecified subgroups

Table 1: Baseline characteristics of 684 patients with STEMI, randomized to either metoprolol or placebo before primary PCI

Characteristic	*Metoprolol (N=336)*	*Placebo (N=347)*	*Total (N=684)*	*P-value*
Mean Age (years) ± SD	62.39 ± 12.42	62.46 ± 12.58	62.42 ± 12.49	0.882
Female gender	84/336 (25.0%)	88/347 (25.4%)	172/683 (25.2%)	0.914
Mean length (cm) ± SD	174.3 ± 10.22	175.2 ± 9.59	174.8 ± 9.91	0.327
Mean weight (kg) ± SD	82.82 ± 16.39	84.71 ± 16.04	83.78 ± 16.23	0.102
Mean BMI ± SD	27.14 ± 4.45	27.40 ± 4.11	27.27 ± 4.28	0.246
Diabetes	48/335 (14.3%)	62/347 (17.9%)	110/682 (16.1%)	0.209
Previous hypertension	135/335 (40.3%)	133/344 (38.7%)	268/679 (39.5%)	0.695
Beta blocker use as home medication	54/298 (18.1%)	60/308 (19.5%)	114/606 (18.8%)	0.669
Anterior location	154/312 (49.4%)	166/318 (52.2%)	320/630 (50.8%)	0.677
First medical contact				0.595
Referring hospital	19/335 (5.7%)	16/347 (4.6%)	35/682 (5.1%)	
PCI center	8/335 (2.4%)	12/347 (3.5%)	20/682 (2.9%)	
Ambulance	308/335 (91.9%)	319/347 (91.9%)	627/682 (91.9%)	
Time (minutes) from onset complaints till first medical contact				
Mean ± SD	135.5 ± 231.9	147.9 ± 212.5	141.7 ± 222.3	0.880
Early presenters (within 6 hours)	288/307 (93.8%)	277/310 (89.4%)	565/617 (91.6%)	0.046
Time (minutes) from onset complaints till admission				
Mean ± SD	195.5 ± 262.5	201.6 ± 262.1	198.6 ± 262.1	0.755
	(n =307)	(n =318)	(n =625)	
Hemodynamics at admission				
Mean Systolic BP (mm Hg) ± SD	136.4 ± 22.91	138.7 ± 26.43	137.6 ± 24.75	0.384
Mean Diastolic BP (mm Hg) ± SD	82.25 ± 14.67	82.83 ± 16.16	82.54 ± 15.43	0.702

Mean Heart Rate (beats/min) ± SD	74.35 ± 13.71	78.68 ± 15.69	76.53 ± 14.89	< 0.001
Discharge medication				
ACE-inhibitor	215/333 (64.6%)	209/341 (61.3%)	424/674 (62.9%)	0.379
A II blockers	14/333 (4.2%)	23/341 (6.7%)	37/674 (5.5%)	0.148
Beta Blocker	260/333 (78.1%)	249/341 (73.0%)	249/341 (73.0%)	0.127
Angiographic findings				
One vessel disease	175/330 (53.0%)	201/339 (59.3%)	376/669 (56.2%)	
Two vessel disease	100/330 (30.3%)	71/339 (20.9%)	171/669 (25.6%)	
Three vessel disdease	39/330 (11.8%)	46/339 (13.6%)	85/669 (12.7%)	
Primary PCI	306/315 (97.1%)	306/322 (95.0%)	612/637 (96.1%)	0.164
Additional PCI during admission	16/334 (4.8%)	15/345 (4.3%)	31/679 (4.6%)	0.782
CABG during admission	12/335 (3.6%)	24/345 (7.0%)	36/680 (5.3%)	0.049

SD= standard deviation, BMI:=body mass index, BP= blood pressure, PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting.

Table 2: Magnetic Resonance Imaging (MRI) Data (1 month +/- 10 days after randomization)

Table 2. Magnetic Resonance Imaging Data (1 month ± 10 days after randomization)

Outcome	***Metoprolol (N=336)***	***Placebo (N=347)***	***Total (N=684)***	***P-value***
MRI performed	169/305 (55.4%)	173/319 (54.2%)	342/624 (54.8%)	0.768
MRI analyzed	162/169 (95.9%)	169/174 (97.1%)	331/343 (96.5%)	0.523
Delayed enhancement-Infarct (% of LV)				0.616
Mean ± SD	15.3 ± 11.0	14.1 ± 11.5	15.1 ± 11.2	
Median (IQR)	13.4 (6.4-21.3)	13.3 (5.6-21.3)	13.4 (5.9-21.3)	
Min - Max	0.00 - 44.1	0.00 - 49.9	0.00 - 49.9	
	(n=159)	(n=167)	(n=326)	
LVEF (%)				*0.683*
Mean ± SD	51.0 ± 10.9	51.7 ± 10.8	51.2 ± 10.9	
Median (IQR)	53.0 (44.1-59.3)	53.3 (45.3-58.6)	53.5 (44.9-59.3)	
Min - Max	21.0 – 69.6	15.0 – 75.8	15.0 – 75.8	
	(n=162)	(n=169)	(n=331)	
LVEDV (ml)				0.398
Mean ± SD	183.9 ± 52.4	184.2 ± 40.1	184.0 ± 46.4	
Median (IQR)	177.9 (149.1-209.1)	181.8 (157.5-212.0)	180.0 (153.7-209.9)	
Min - Max	83.6 - 469.7	85.4 - 292.8	83.6 - 469.7	
	(n=162)	(n=169)	(n=331)	
LVESV (ml)				0.651
Mean ± SD	93.3 ± 46.1	90.5 ± 32.91	91.9 ± 39.9	
Median (IQR)	82.7 (64.0-108.7)	86.3 (65.8-106.1)	85.4 (64.8-108.1)	
Min - Max	26.0 - 359.5	27.8 - 187.0	26.0 - 359.5	
	(n=162)	(n=169)	(n=331)	
LV mass (g) from function				0.893
Mean ± SD	96.4 ± 25.2	96.5 ± 23.1	96.5 ± 24.1	
Median (IQR)	96.4 (77.2-110.7)	94.6 (80.6-110.1)	94.8 (79.5-110.6)	
Min - Max	48.4 - 195.4	48.2 - 187.8	48.2 - 195.4	
	(n=162)	(n=169)	(n=331)	
LV mass (g) from delayed enhancement				0.782
Mean ± SD	104.6 ± 29.0	103.1 ± 25.7	103.9 ± 27.5	
Median (IQR)	100.6 (85.1-122.5)	101.3 (84.1-119.0)	100.9 (84.3-121.4)	

Table 2. Magnetic Resonance Imaging Data (1 month ± 10 days after randomization)

Min - Max	50.6 - 244.0	46.7 - 189.6	46.7 - 244.0	
	(n=159)	(n=167)	(n=326)	
Poor quality delayed enhancement images				0.914
No	150/162 (92.6%)	157/169 (92.9%)	307/331 (92.7%)	
Yes	12/162 (7.4%)	12/169 (7.1%)	24/331 (7.3%)	
EDEMA				0.398
Absence	10/86 (11.6%)	11/102 (10.8%)	21/188 (11.2%)	
Small Zone	17/86 (19.8%)	16/102 (15.7%)	33/188 (17.6%)	
Extended Zone	45/86 (52.3%)	48/102 (47.1%)	93/188 (49.5%)	
Black (hemorrhage) core	14/86 (16.3%)	27/102 (26.5%)	41/188 (21.8%)	
Localization				0.742
No evidence of infarction	12/162 (7.4%)	8/170 (4.7%)	20/332 (6.0%)	
Anterior or septal	71/162 (43.8%)	75/170 (44.1%)	146/332 (44.0%)	
Inferior	47/162 (29.0%)	57/170 (33.5%)	104/332 (31.3%)	
Lateral or inferolateral	24/162 (14.8%)	24/170 (14.1%)	48/332 (14.5%)	
Typical of myocarditis	8/162 (4.9%)	6/170 (3.5%)	14/332 (4.2%)	

LVEDV: left ventricular end diastolic volume, LVESV: left ventricular end systolic volume, LVEF: left ventricular ejection fraction, LV: left ventrical

Table 3: Safety endpoints and adverse cardiac events

Table 3. Safety endpoints

Outcome	*Metoprolol (N=336)*	*Placebo (N=347)*	*Total (N=684)*	*P-value*
Severe bradycardia	5/334 (1.5%)	2/345 (0.6%)	7/679 (1.0%)	0.279
Servere hypotension	9/310 (2.9%)	18/326 (5.5%)	27/636 (4.2%)	0.102
Cardiogenic shock	2/334 (0.6%)	1/345 (0.3%)	3/679 (0.4%)	0.618
Ventricular arrhythmias in acute phase	12/335 (3.6%)	24/346 (6.9%)	36/681 (5.3%)	0.050

MACE: Major Adverse Cardiac Events, TVR: Target Vessel Revascularization

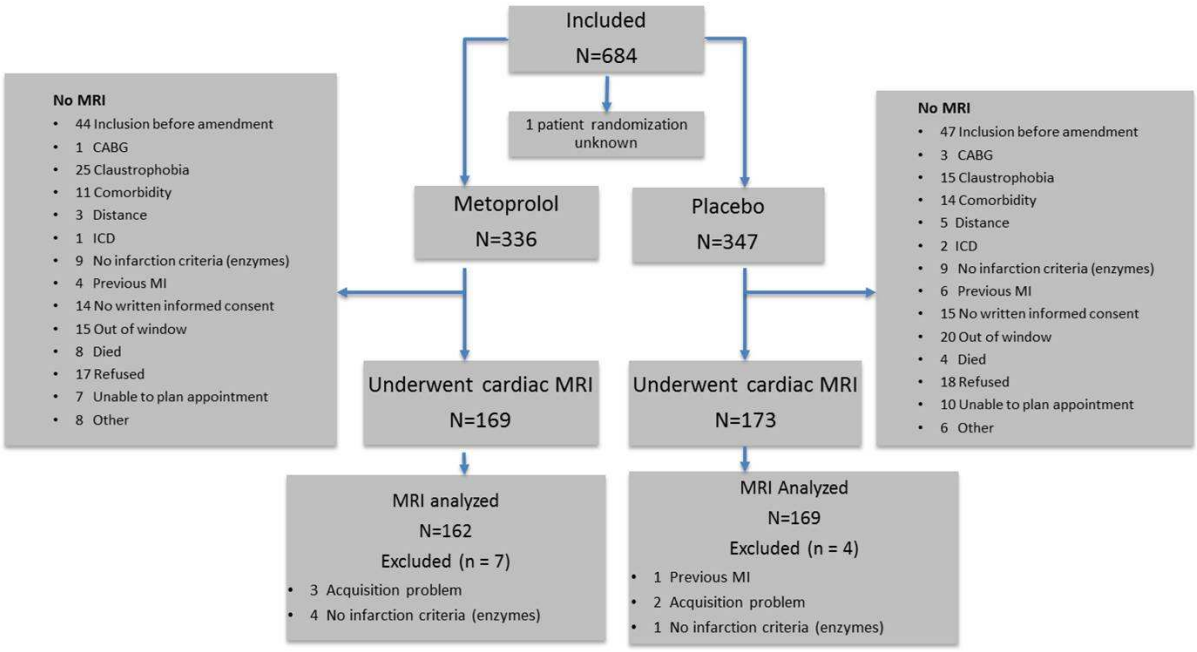
Table 4: Adverse cardiac events at 30 days.

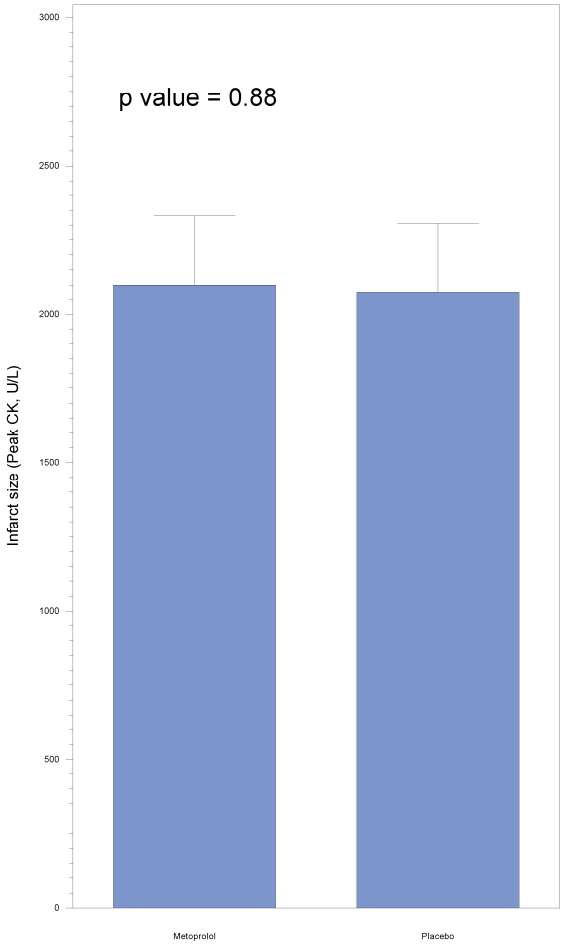
Outcome	*Metoprolol (N=336)*	*Placebo (N=347)*	*Total (N=684)*	*P-value*
MACE	19/307 (6.2%)	22/319 (6.9%)	41/626 (6.5%)	0.721
Cardiac mortality	7/307 (2.3%)	7/319 (2.2%)	14/626 (2.2%)	0.942
MI	3/307 (1.0%)	2/319 (0.6%)	5/626 (0.8%)	0.681
TVR	12/307 (3.9%)	15/319 (4.7%)	27/626 (4.3%)	0.625

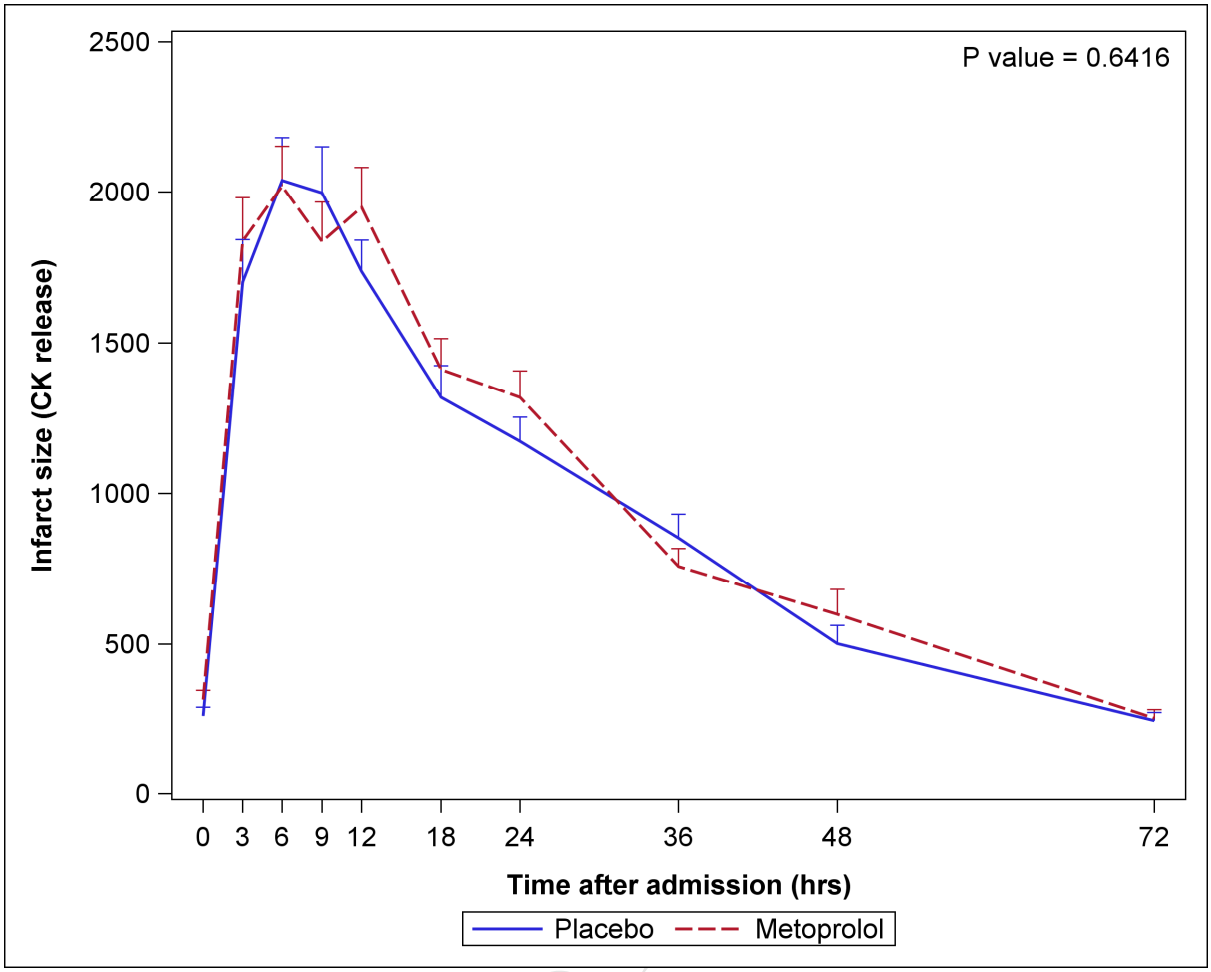
TVR = Target Vessel Revascularization, MACE= major adverse cardiac events, MI=myocardial infarction.

Table 5: Secondary end points

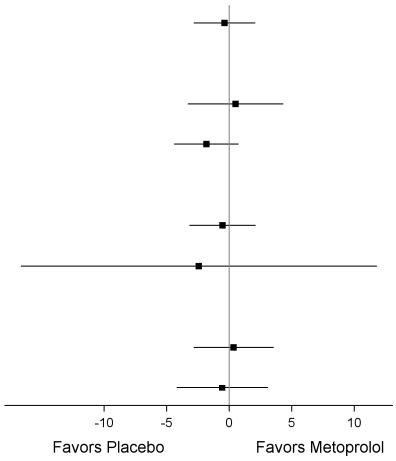
Outcome	*Metoprolol (N=336)*	*Placebo (N=347)*	*Total (N=684)*	*P-value*
Maximal CKMB u/l value				*0.750*
Mean ± SD	224 ± 212	213 ± 195	218 ± 203	
Median (IQR)	148 (65- 327)	167 (57- 300)	155 (62- 317)	
Min - Max	9 - 998	10 - 943	9 – 998	
	(n = 207)	(n = 204)	(n = 411)	
Maximal CKMB ug/l value				*0.181*
Mean ± SD	276 ± 243	232 ± 254	254 ± 248	
Median (IQR)	188 (97- 450)	133 (49- 282)	152 (60- 440)	
Min - Max	3 - 880	0 - 969	0 - 969	
	(n = 52)	(n = 54)	(n = 106)	
Maximal CK-total				*0.880*
Mean ± SD	2102 ± 2029	2072 ± 2018	2087 ± 2022	
Median (IQR)	1370 (538- 3050)	1411 (466- 2980)	1376 (504- 3050)	
Min - Max	47 - 9857	30 - 8769	30 - 9857	
	(n = 298)	(n = 293)	(n = 591)	
hs Trop T (ng/L) 24 hours				0.103
Mean ± SD	3711 ± 3587	3166 ± 3998	3451 ± 3790	
Median (IQR)	2530 (1200- 5450)	1994 (962.5- 3800)	2224 (1059- 4800)	
Min - Max	22.40 - 19480	1.25 - 31700	1.25 – 31700	
	(n = 114)	(n = 104)	(n = 218)	
Trop I (ug/L) 24 hours				0.948
Mean ± SD	42.37 ± 39.85	53.04 ± 56.49	48.26 ± 49.19	
Median (IQR)	32.60 (13.30-58.99)	32.83 (9.28- 74.71)	32.60 (9.70-58.99)	
Min - Max	0.65 - 136.5	0.07 - 177.1	0.07 - 177.1	
	(n = 13)	(n = 16)	(n = 29)	







	Metoprolol	Placebo	Metoprolol	Placebo	Difference in Delayed Enhancement Infarct (95% CI)	P for interaction
All patients	159	167	15.29 ± 10.97	14.91 ± 11.52	-0.38 (-2.84 - 2.07)	
Location of MI						
Anterior infarction	78	88	18.81 ± 12.20	19.30 ± 12.65	0.49 (-3.33 - 4.31)	0.33
Non anterior infarction	75	71	12.24 ± 8.01	10.41 ± 7.78	-1.83 (-4.42 - 0.75)	
Presentation						
Early	135	129	15.11 ± 10.69	14.56 ± 11.09	-0.55 (-3.19 - 2.09)	0.72
Late	9	12	20.87 ± 16.29	18.45 ± 14.76	-2.43 (-16.7 - 11.81)	
Initial timi flow						
Initial 0,1	98	97	17.78 ± 10.81	18.12 ± 11.81	0.35 (-2.85 - 3.54)	0.74
Initial 2,3	43	49	9.59 ± 9.01	9.03 ± 8.55	-0.56 (-4.20 - 3.08)	



Effect of Early Administration of intravenous Beta blockers in patients with ST-elevation myocardial infarction before primary percutaneous coronary intervention.

Short title: EARLY Beta-blocker Administration before primary PCI inSTEMI. The EARLY-BAMI trial.

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Appendix 1:

Characteristics	*MRI (N=342)*	*No MRI (N=341)*	*Total (N=683)*	*P-value*
Age (years)				*0.003*
Mean ± SD	60.93 ± 12.02	63.92 ± 12.80	62.42 ± 12.49	
Median (IQR)	61.17 (52.72-68.52)	62.71 (54.80-73.51)	61.79 (53.72-71.08)	
Min - Max	25.80 - 92.83	29.21 - 93.29	25.80 - 93.29	
	(n =342)	(n =340)	(n =682)	
Gender				*0.013*
Female	72/342 (21.1%)	100/341 (29.3%)	172/683 (25.2%)	
Male	270/342 (78.9%)	241/341 (70.7%)	511/683 (74.8%)	
Length				*0.111*
Mean ± SD	174.2 ± 9.95	175.6 ± 9.81	174.8 ± 9.91	
Median (IQR)	175.0 (168.0-181.0)	176.0 (170.0-184.0)	175.0 (168.0-182.0)	
Min - Max	144.00 - 198.00	150.00 - 196.00	144.00 - 198.00	
	(n =321)	(n =252)	(n =573)	
Weight				*0.434*
Mean ± SD	83.06 ± 15.99	84.64 ± 16.49	83.78 ± 16.23	
Median (IQR)	83.00 (72.00-93.00)	84.50 (73.00-95.00)	83.00 (72.00-94.00)	
Min - Max	43.00 - 135.00	52.00 - 170.00	43.00 - 170.00	
	(n =329)	(n =274)	(n =603)	
BMI				*0.413*
Mean ± SD	27.28 ± 4.06	27.26 ± 4.56	27.27 ± 4.28	
Median (IQR)	26.88 (24.76-29.45)	26.52 (24.41-29.22)	26.73 (24.54-29.32)	
Min - Max	17.67 - 42.61	18.41 - 52.47	17.67 - 52.47	
	(n =320)	(n =250)	(n =570)	
First contact				*<.001*
Referring hospital	25/342 (7.3%)	10/340 (2.9%)	35/682 (5.1%)	
PCI center	16/342 (4.7%)	4/340 (1.2%)	20/682 (2.9%)	
Ambulance	301/342 (88.0%)	326/340 (95.9%)	627/682 (91.9%)	
Time (minutes) between onset date and time and first contact date and time				*0.564*
Mean ± SD	150.5 ± 270.8	133.4 ± 164.1	141.7 ± 222.3	
Median (IQR)	75.00 (41.00-160.0)	77.00 (34.00-150.0)	76.00 (36.00-159.0)	
Min - Max	0.00 - 3090.0	5.00 - 1200.0	0.00 - 3090.0	
	(n =299)	(n =318)	(n =617)	
Early presenters (within 6 hours)				*0.954*
Yes	274/299 (91.6%)	291/318 (91.5%)	565/617 (91.6%)	
Time (minutes) between onset date and time and admission date and time				*0.851*
Mean ± SD	206.2 ± 311.8	186.7 ± 186.2	196.3 ± 255.9	
Median (IQR)	123.5 (81.00-220.5)	120.0 (85.00-200.0)	120.0 (83.00-211.0)	
Min - Max	30.00 - 3187.0	20.00 - 1675.0	20.00 - 3187.0	

	(n =308)	(n =317)	(n =625)	
CKmax				0.009
Mean ± SD	2239± 2059	1936 ± 1976	2087 ± 2022	
Median (IQR)	1590 (704.0 – 3220)	1184 (385.5 – 2924)	1370 (504.0 – 3050)	
Min - Max	47.00 - 9857	30.00 - 9540	30.00 - 9857	
	(n=294)	(n=296)	(n=590)	

Appendix 2.