

# openheart Beta-blocker effect on ST-segment: a prespecified analysis of the EARLY-BAMI randomised trial

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## ABSTRACT

**Objective** The effect of early intravenous (IV) beta-blockers (BBs) administration in patients undergoing primary percutaneous coronary intervention (pPCI) on ST-segment deviation is unknown. We undertook a prespecified secondary analysis of the Early Beta-blocker Administration before primary PCI in patients with ST-elevation Myocardial Infarction (EARLY-BAMI) trial to investigate the effect of early IV BB on ST-segment deviation.

**Methods** The EARLY-BAMI trial randomised patients with ST-elevation myocardial infarction (STEMI) to IV metoprolol (2×5 mg bolus) or matched placebo before pPCI. The prespecified outcome, evaluated by an independent core laboratory blinded to study treatment, was the residual ST-segment deviation 1 hour after pPCI (ie, the percentage of patients with >3 mm cumulative ST deviation at 1 hour after pPCI).

**Results** An ECG for the evaluation of residual ST-segment deviation 1 hour after pPCI was available in 442 out of 683 randomised patients. The BB group had a lower heart rate after pPCI compared with placebo (71.2±13.2 vs 74.3±13.6, p=0.016); however, no differences were noted in the percentages of patients with >3 mm cumulative ST deviation at 1 hour after pPCI (58.6% vs 54.1%, p=0.38, in BB vs placebo, respectively) neither a significant difference was found for the percentages of patients in each of the four prespecified groups (normalised ST-segment; 1–3 mm; 4–6 mm; >6 mm residual ST-deviation).

**Conclusions** In patients with STEMI, who were being transported for primary PCI, early IV BB administration did not significantly affect ST-segment deviation after pPCI compared with placebo. The neutral result of early IV BB administration on an early marker of pharmacological effect is consistent with the absence of subsequent improvement of clinical outcomes.

## INTRODUCTION

Early diagnosis and primary percutaneous coronary intervention (pPCI) have improved

## Key questions

### What is already known about this subject?

► Considering the existing evidence, the beneficial effect of beta-blockers (BBs) before primary percutaneous coronary intervention (pPCI) is not well established; moreover, the effect of beta-blockers on ST-segment deviation is unknown.

### What does this study add?

► We showed that in patients with ST-elevation myocardial infarction, who were being transported for primary PCI, early BB administration did not affect ST-segment deviation after pPCI compared with placebo.

### How might this impact on clinical practice?

► The neutral effect of early BB administration on an early marker of the pharmacological effect is consistent with the absence of subsequent improvement of clinical outcomes. Whether a higher dose of early BB administration may be more effective should be explored in a further large trial.

the outcome of patients presenting with ST-elevation myocardial infarction (STEMI); however, early additional interventions after symptoms onset might further reduce myocardial ischaemia and potentially improve cardiovascular outcomes.

Acute myocardial infarction (MI) represents a state of reduced oxygen supply to the affected portion of the heart. Early intravenous (IV) beta-blockers (BBs), slowing heart rate, reducing myocardial contractility and lowering systemic blood pressure, may be beneficial during MI because the blockade of  $\beta_1$  receptors results in reduced myocardial workload and oxygen demand.<sup>1</sup> Recently, the Early Beta-blocker Administration before

pPCI in patients with ST-elevation Myocardial Infarction (EARLY-BAMI) trial,<sup>2</sup> the first double-blinded, placebo-controlled, multicentre international study assessing the effect of early IV BB before pPCI, showed no beneficial effect on infarct size<sup>2</sup> and clinical events.<sup>3</sup> However, early administration of a BB before reperfusion is still controversial because of conflicting results in the pPCI era<sup>4,5</sup> and the previous positive results of the METOCARD-CNIC trial.<sup>5</sup> Therefore, the potential effect of early BB administration needs to be further explored and better understood. Here we present a prespecified secondary analysis of the EARLY-BAMI trial (EudraCT no.: 2010-023394-19), in order to investigate the potential effect of early IV BB on residual ST-segment deviation after pPCI.

## METHODS

### Study design and treatment

The study design has been published previously.<sup>6</sup> Briefly, the EARLY-BAMI trial was a double-blinded, placebo-controlled randomised clinical trial. Patients aged >18 years with symptoms of acute STEMI for >30 min but <12 hours, plus ST-segment elevation >1 mV in two adjacent ECG leads or new left bundle branch block were eligible for enrolment. After the in-ambulance diagnosis of STEMI, medical treatment proceeded per current guidelines. Exclusion criteria were Killip class III and IV, systolic blood pressure (BP) <100 mm Hg, heart rate <60 beats/min, type II and III atrioventricular (AV) block, history of previous MI, known asthma bronchiale, pacemaker or implanted cardioverter-defibrillator, pregnancy or breastfeeding, or inability to provide informed consent. The emergency physician and trained ambulance paramedic completed the administration/enrolment procedure. After informed consent, a blinded study medication box was opened. This box contained two vials of metoprolol 5 mg or matching placebo and labelled with a number that corresponded with the randomisation list. Randomisation took place without stratification and in blocks of 4. The first bolus of study medication was given in the ambulance, the second bolus was given at the catheterisation laboratory pre-PCI but only if systolic BP was >100 mm Hg and heart rate >60 beats/min. Patients participating in the trial were treated during hospital admission and thereafter according to current guidelines. Outcome analyses were performed in a random manner by expert observers blinded to treatment allocation.

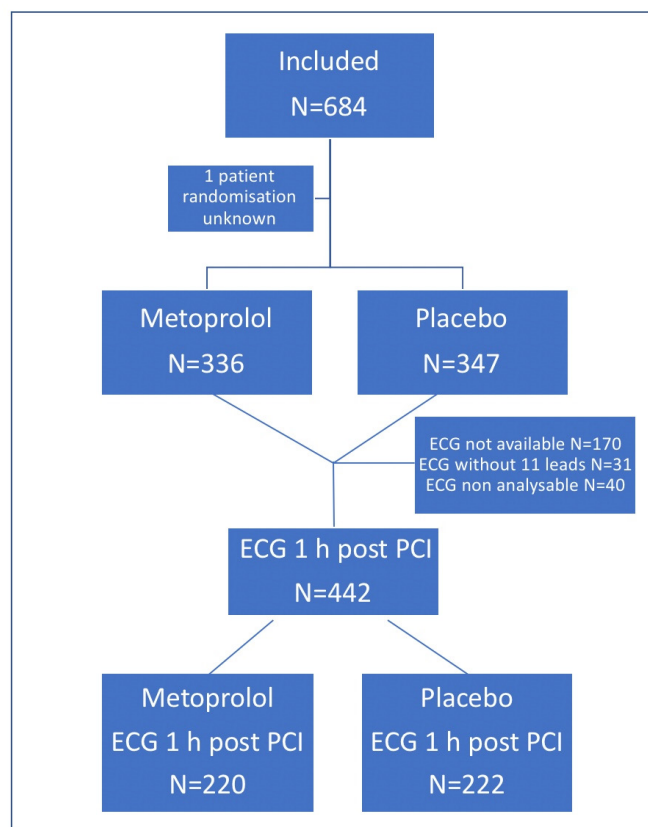
The study was approved by the medical ethical committees of the participating hospitals.

### Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study.

### Study population and ECG outcomes

In the EARLY-BAMI trial, a total of 683 patients were randomised to metoprolol (n=336) or placebo (n=347).



**Figure 1** Patient flow. h, hour; PCI, percutaneous coronary intervention.

The populations included in this prespecified secondary analysis consisted of patients with ECGs 1 hour after pPCI with at least 11 leads analysable. A total of 442 patients were included in the study population because for 170 patients ECG was not available, for 31 patients ECG did not meet the criteria of ECG with 11 leads available and for 40 patients, ECG was not analysable (figure 1).

The absolute level of the ST-segment deviation was measured by digital calliper to the nearest 0.01 mV, 20 ms after the end of the QRS interval using the TP segment as an isoelectric baseline. ECGs were analysed by an independent core laboratory (DIAGRAM, Zwolle, The Netherlands) blinded to study treatment.

The prespecified outcome was the residual ST-segment deviation 1 hour after pPCI, that is, the percentage of patients with >3 mm cumulative ST-segment deviation at 1 hour after pPCI. In addition, the extent of residual ST-segment deviation on the single postprocedure ECG were classified into four groups (no residual ST-segment deviation; residual ST-segment deviation between 1 and 3 mm; residual ST-segment deviation between 4 and 6 mm; residual ST-segment deviation more than 6 mm), as described previously.<sup>7</sup>

As a secondary outcome, ST-segment resolution (STR) from available paired ECGs (baseline and postprocedure ECGs) was calculated. Post-PCI STR was calculated between ECGs recorded at the time of inclusion (prehospital (pre-H)) and ECG recorded 1 hour post-PCI as %

change=100\* (pre-H ST values – post-PCI ST values)/ pre-H ST values. Patients were divided into three groups of STR: complete resolution (>70% resolution), partial resolution (>30% but<70% resolution) and no resolution (<30% resolution), as described previously.<sup>8</sup>

### Statistical analysis

Continuous data were expressed as mean±SD or median with IQR. Categorical data were expressed as percentages. Categorical variables were analysed with the  $\chi^2$  test or Fischer exact test, and continuous variables with the Mann-Whitney U-test (two sided). In addition, the  $\chi^2$  test for trend was used to analyse the percentages of patients

in each of the four prespecified groups of residual ST-segment deviation. Values of  $p<0.05$  were considered statistically significant. All analyses were performed according to the intention-to-treat principle. Statistical analysis was performed with PASW Statistics V.18 (SPSS, Chicago, IL).

## RESULTS

### Baseline clinical and ECG characteristics

A total of 442 patients were included in the study population. Baseline characteristics of this study population and ECG baseline characteristics are reported in [table 1](#).

	Total (N=442)	Placebo (N=222)	Metoprolol (N=220)	P value
<b>Patient demographics</b>				
Age (years)	62.5±11.6	62.9±11.8	62±11.4	0.41
Male sex	331/442 (74.89%)	162/222 (72.97%)	169/220 (76.82%)	0.38
Prior MI	17/440 (3.86%)	8/221 (3.62%)	9/219 (4.11%)	0.81
Prior PCI	29/441 (6.58%)	12/221 (5.43%)	17/220 (7.73%)	0.34
Prior CVA	11/4441 (2.48%)	4/221 (1.81%)	7/220 (3.18%)	0.38
Renal failure	8/436 (1.83%)	5/218 (2.29%)	3/218 (1.38%)	0.72
Peripheral VD	8/441 (1.81%)	5/221 (2.26%)	3/220 (1.36%)	0.72
<b>Risk factors</b>				
Smoking	175/409 (42.79%)	90/202 (44.55%)	85/207 (41.06%)	0.48
Family history	163/391 (41.69%)	82/192 (42.71%)	81/199 (40.07%)	0.75
Hypertension	170/440 (38.64%)	84/220 (38.18%)	86/220 (39.09%)	0.92
Hypercholesterolaemia	108/433 (24.94%)	52/217 (23.96%)	56/216 (25.93%)	0.65
Diabetes mellitus	67/442 (15.16%)	38/222 (17.12%)	29/220 (13.18%)	0.28
<b>Infarct location</b>				
Anterior	173/384 (45.05%)	95/194 (48.97%)	78/190 (41.05%)	
Inferior	174/384 (45.31%)	77/194 (39.69%)	97/190 (51.05%)	
Lateral	27/384 (7.03%)	16/194 (8.25%)	11/190 (5.79%)	
Posterior	6/384 (1.56%)	4/194 (2.06%)	2/190 (1.05%)	
Unknown	4/384 (1.04%)	2/194 (1.03%)	2/190 (1.05%)	
<b>Heart frequency</b>	78.2 (18.1)	77.8 (18.6)	78.6 (17.7)	0.67
<b>Rhythm</b>				
SR	386/409 (94.38%)	193/203 (95.07%)	193/206 (93.69%)	0.25
AF	19/409 (4.65%)	8/203 (3.94%)	11/206 (5.34%)	
Other	2/409 (0.49%)	0/203	2/206 (0.97%)	
<b>ST deviation &gt;3 mm</b>	357/369 (96.75%)	180/184 (97.83%)	177/185 (95.68%)	0.38
<b>Categories of ST deviation</b>				
Normalised ST segment	8/369 (2.17%)	3/184 (1.63%)	5/185 (2.7%)	0.42
1–3 mm deviation	4/369 (1.08%)	1/184 (0.54%)	3/185 (1.62%)	
4–6 mm deviation	30/369 (8.13%)	12/184 (6.52%)	18/185 (9.73%)	
>6 mm deviation	327/369 (88.62%)	168/184 (91.3%)	159/185 (85.95%)	

Data are n/N (%) or mean (±SD).

.AF, atrial fibrillation; CVA, cerebral vascular accident; MI, myocardial infarction; PCI, percutaneous coronary intervention; SR, sinus rhythm; VD, vascular disease.;

**Table 2** Prespecified ECG outcomes

	Total (N=442)	Placebo (N=222)	Metoprolol (N=220)	P value
<b>Heart frequency</b>	72.8 (13.5)	74.3 (13.6)	71.2 (13.2)	0.016
<b>ST deviation &gt;3mm</b>	249/442 (56.33%)	130/222 (58.56%)	119/220 (54.09%)	0.39
<b>Categories of ST deviation</b>				0.44
Normalised ST segment	139/442 (31.45%)	70/222 (31.53%)	69/220 (31.36%)	
1–3 mm deviation	54/442 (12.22%)	22/222 (9.91%)	32/220 (14.55%)	
4–6 mm deviation	81/442 (18.33%)	40/222 (18.02%)	41/220 (18.64%)	
>6 mm deviation	168/442 (38.01%)	90/222 (40.54%)	78/220 (35.45%)	

Data are n/N (%) or mean ( $\pm$ SD).

There was no significant difference between the metoprolol and placebo group at baseline; in particular, there was no significant baseline difference in heart rate or in baseline ST-segment deviation between the two groups.

### Main outcomes

The BB group had a lower heart rate after pPCI compared with placebo (71.2 $\pm$ 13.2 vs 74.3 $\pm$ 13.6,  $p=0.016$ ); however, the prespecified outcome, that is, the percentage of patients with >3mm cumulative ST deviation at 1 hour after pPCI, was not different in BB group compared with

placebo (58.6% vs 54.1%,  $p=0.38$ , respectively) (table 2). In addition, the percentages of patients in each of the four prespecified groups of residual ST-segment deviation (normalised ST-segment, 1–3mm residual ST deviation, 4–6mm residual ST deviation, >6mm residual ST deviation) were similar between groups (table 2).

### Secondary outcomes

There were 361 patients with both pre-H and post-PCI ECG available.

**Table 3** Secondary outcomes: ST-resolution

	Total (N=361)	Placebo (N=181)	Metoprolol (N=180)	P value
<b>% STR for the sum of ST elevation</b>	57.6 (58.0)	59.3 (48.7)	55.8 (66.2)	0.56
				0.45
No STR (<30%)	73/361 (20.2)	33/181 (18.2)	40/180 (22.2)	
Partial STR (30%–70%)	101/361 (28.0)	57/181 (31.5)	44/180 (24.4)	
Complete STR (>70%)	187/361 (51.8)	91/181 (50.3)	96/180 (53.3)	
<b>% STR for the sum of ST elevation or depression</b>	62.9 (44.5)	62.7 (40.7)	63.1 (48.1)	0.94
				0.57
No STR (<30%)	64/361 (17.7)	33/181 (18.2)	31/180 (17.2)	
Partial STR (30%–70%)	102/361 (28.3)	55/181 (30.4)	47/180 (26.1)	
Complete STR (>70%)	195/361 (54.0)	93/181 (51.4)	102/180 (56.7)	
<b>% STR for the maximum ST elevation</b>	56.0 (49.0)	56.2 (47.0)	55.9 (51.1)	0.96
				0.68
No STR (<30%)	79/361 (21.9)	36/181 (19.9)	43/180 (23.9)	
Partial STR (30%–70%)	122/361 (33.8)	68/181 (37.6)	54/180 (30)	
Complete STR (>70%)	160/361 (44.3)	77/181 (42.5)	83/180 (46.1)	
<b>% STR for the maximum absolute ST elevation or depression</b>	57.8 (43.1)	57.5 (43.4)	58.1 (43.0)	0.90
				0.68
No STR (<30%)	72/361 (19.9)	34/181 (18.8)	38/180 (21.1)	
Partial STR (30%–70%)	130/361 (36.0)	69/181 (38.1)	61/180 (33.9)	
Complete STR (>70%)	159/361 (44.0)	78/181 (43.1)	81/180 (45.0)	

Data are n/N (%) or mean (SD).

AF, atrial fibrillation; SR, sinus rhythm; STR, ST-segment resolution.

No significant difference in STR was found between the metoprolol and placebo group for all the ST-segment analysis performed (table 3).

## DISCUSSION

The EARLY-BAMI trial is the first double-blinded, placebo-controlled, multicentre international study assessing the effect of early IV BB therapy before pPCI and for the first time, we evaluated the potential effect of early IV BB on residual ST-segment deviation in the pPCI reperfusion era.

In this prespecified secondary analysis, we found no significant difference between the metoprolol group and the placebo group in terms of the extent of residual ST deviation 1 hour after PCI.

In animal models, previous studies have shown that the extent of ischaemic injury, manifested by ST segment changes, can be decreased by BB<sup>9</sup> and that BB given prior to and continuously during coronary ligation markedly reduces the transmural extent of MI.<sup>10</sup> The cardioprotective effect associated with the  $\beta$ -blockade seems to occur especially when the drug is given before coronary reperfusion,<sup>11</sup> suggesting that BB might have a role in reducing reperfusion injury.

Metoprolol may reduce reperfusion injury by targeting the haematopoietic compartment, indeed metoprolol inhibits neutrophil-platelet interactions in patients with MI by targeting neutrophils.<sup>12</sup> Metoprolol acts during early phases of neutrophil recruitment by impairing structural and functional rearrangements needed for productive engagement of circulating platelets, resulting in erratic intravascular dynamics and blunted inflammation.<sup>12</sup>

Another potential mechanism includes the reduction of oxygen demand, secondary to heart rate reduction during ongoing ischemia.

In the clinical setting of our study early BB administration lowered heart rate ( $p=0.016$  compared with placebo) however this was not translated into a significant improvement of ST-segment deviation after pPCI.

The effect of BB on residual ST-segment deviation found in this study is in line with the absence of beneficial effect of early BB administration on infarct size measured by cardiac magnetic resonance<sup>2</sup> or clinical events<sup>3</sup> compared with placebo.

The neutral effect of early BB administration on an early marker of pharmacological effect is of interest to support and further understand the absence of subsequent improvement of the infarct size. Importantly ST-segment analysis may be considered a useful tool for exploring the impact of new therapies on myocardial reperfusion, and the prognostic importance of electrocardiographic assessments after reperfusion still represents a valid surrogate marker for cardiovascular clinical outcomes in the current era of STEMI treatment.<sup>13</sup>

However, the results of the EARLY-BAMI trial are in contrast with the results of the METOCARD-CNIC trial<sup>5</sup> that showed, in a smaller population, reduced infarct size

and increased left ventricular ejection fraction with early IV metoprolol. The different sample sizes and the inclusion of a selected patient group (anterior STEMI presenting <6 hours from symptom onset) compared with the EARLY-BAMI trial may account for these different results. Moreover, it is interesting to note that the positive results of the METOCARD-CNIC trial were obtained with a higher dose of metoprolol, up to three times 5 mg (15 mg target dose), whereas in the EARLY-BAMI trial, the dose was only two times 5 mg (10 mg target). In addition, patients in EARLY-BAMI could be on long-term BB treatment before admission, which was an exclusion criterion in the METOCARD-CNIC trial. In the EARLY-BAMI trial, the second 5 mg bolus (to complete the 10 mg target dose) was administered in the catheterisation laboratory, thus really close to pre-PCI ECG; therefore, the first 5 mg of IV metoprolol might be insufficient to obtain a significant effect; indeed, in the METOCARD-CNIC trial, patients receiving IV metoprolol close to pPCI had significantly larger infarctions than those receiving IV metoprolol long before reperfusion.<sup>14</sup> Considering these reasons, the limited BB effect on ST-segment could be related to the low dosing hypothesis. Considering also the safety of early BB administration<sup>2</sup> and the confirmed absence of significant high-grade AV block in BB groups, large randomised trials to clarify whether higher IV BB dose before angioplasty is beneficial for patients with STEMI are still needed. Till now, IV BB administration remains recommended (class of recommendation IIa),<sup>15</sup> at the time of presentation in patients undergoing pPCI without signs of acute heart failure and with a systolic blood pressure >120 mm Hg.

## Limitations

In this prespecified analysis, we included a smaller population compared with the total population included in the trial because post-PCI ECGs were not analysable (as described in the Methods section) for all patients and, therefore, a selection bias cannot be excluded. However, baseline characteristics were similar between patients included and excluded in this prespecified analysis (online supplemental table 1).

## CONCLUSIONS

In patients undergoing pPCI, early IV BB administration showed no significant effect on post-PCI ST-segment deviation compared with placebo. The neutral result of early IV BB administration on an early marker of the pharmacological effect is consistent with the absence of subsequent improvement of clinical outcomes. Considering the existing evidence, whether a higher dose of early BB administration may be more effective should be explored in a further large trial.

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