# Effect of Early Metoprolol on Infarct Size in ST-Segment–Elevation Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Intervention

## The Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) Trial

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***Background***—The effect of β-blockers on infarct size when used in conjunction with primary percutaneous coronary intervention is unknown. We hypothesize that metoprolol reduces infarct size when administered early (intravenously before reperfusion).

***Methods and Results***—Patients with Killip class II or less anterior ST-segment–elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention within 6 hours of symptoms onset were randomized to receive intravenous metoprolol (n=131) or not (control, n=139) before reperfusion. All patients without contraindications received oral metoprolol within 24 hours. The predefined primary end point was infarct size on magnetic resonance imaging performed 5 to 7 days after STEMI. Magnetic resonance imaging was performed in 220 patients (81%). Mean±SD infarct size by magnetic resonance imaging was smaller after intravenous metoprolol compared with control (25.6±15.3 versus 32.0±22.2 g; adjusted difference, −6.52; 95% confidence interval, −11.39 to −1.78; *P*=0.012). In patients with pre–percutaneous coronary intervention Thrombolysis in Myocardial Infarction grade 0 to 1 flow, the adjusted treatment difference in infarct size was −8.13 (95% confidence interval, −13.10 to −3.16; *P*=0.0024). Infarct size estimated by peak and area under the curve creatine kinase release was measured in all study populations and was significantly reduced by intravenous metoprolol. Left ventricular ejection fraction was higher in the intravenous metoprolol group (adjusted difference, 2.67%; 95% confidence interval, 0.09–5.21; *P*=0.045). The composite of death, malignant ventricular arrhythmia, cardiogenic shock, atrioventricular block, and reinfarction at 24 hours in the intravenous metoprolol and control groups was 7.1% and 12.3%, respectively (*P*=0.21).

***Conclusions***—In patients with anterior Killip class II or less ST-segment–elevation myocardial infarction undergoing primary percutaneous coronary intervention, early intravenous metoprolol before reperfusion reduced infarct size and increased left ventricular ejection fraction with no excess of adverse events during the first 24 hours after STEMI.

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**Key Words:** adrenergic beta-antagonist ■ infarction ■ magnetic resonance imaging ■ metoprolol ■ myocardial infarction ■ percutaneous coronary intervention ■ reperfusion injury

Timely reperfusion by primary percutaneous coronary intervention (PCI) is the best therapeutic strategy for ST-segment–elevation myocardial infarction (STEMI),[1,2] and its widespread use has significantly reduced mortality.[3] However, STEMI survivors are at high risk of recurrent cardiovascular events such as congestive heart failure, arrhythmia, and sudden death. A major determinant of postinfarction mortality and morbidity is the extent of myocardial necrosis after STEMI[4]; therefore, strategies to limit infarct size (cardioprotection during STEMI) are important. Several mechanical and pharmacological interventions have been proposed as potential cardioprotective therapies,[5] but their use in clinical practice has been limited.

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The potential of β-blockers to limit myocardial necrosis was proposed long ago,[6] but their cardioprotective capacity during STEMI has been disputed.[7] Most analyses of the infarct-limiting effects of β-blockers were done in the prereperfusion era and yielded conflicting results.[8–11] Data on the cardioprotective effect of β-blockers during thrombolytic reperfusion are scarce, with just 1 randomized[12] and 1 nonrandomized[13] study, with contradictory results. In the era of primary PCI as the treatment of choice for STEMI, no randomized trials aiming to test the infarct-limiting effect of β-blockers have been published.

Data from large-animal models of acute myocardial infarction show that the β1-selective blocker metoprolol is able to markedly reduce infarct size but only when administered intravenously before reperfusion.[14,15] Current clinical guidelines for STEMI recommend the initiation of oral β-blockers within 24 hours after infarction for patients with no contraindications[1,2]; very early intravenous β-blockade, although permitted, is not mandatory.

We aimed to determine whether early pre-reperfusion intravenous β-blocker administration reduces infarct size in STEMI patients treated by primary PCI by performing a multicenter, randomized, controlled, clinical trial.

## Methods

The design of the study has previously been published.[16] The Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial was a multicenter, randomized, parallel-group, single-blinded (to outcome evaluators) clinical trial in STEMI patients comparing pre-reperfusion intravenous metoprolol and no pre-reperfusion metoprolol (control). The primary hypothesis of the trial was that anterior STEMI patients receiving early intravenous metoprolol before reperfusion would have a reduced infarct size compared with control subjects. All patients received oral metoprolol within 24 hours after reperfusion, as recommended by current clinical guidelines.[1,2]

The study was approved by the ethics committees and institutional review boards at each participating center. All eligible patients gave written informed consent.

### Patient Selection and Randomization

Patients eligible for enrollment were 18 to 80 years of age and showed symptoms consistent with STEMI for >30 minutes and ST elevation ≥2 mm in ≥2 contiguous leads in $V_1$ through $V_5$ with an anticipated time of symptom onset to reperfusion of ≤6 hours. To ensure that all patients underwent reperfusion within 6 hours from symptom onset, the inclusion criterion was ≤4.5 hours from symptom onset to randomization.[16] Exclusion criteria were Killip class III to IV acute myocardial infarction, systolic blood pressure persistently <120 mm Hg, PR interval >240 milliseconds (or type II–III atrioventricular block), heart rate persistently <60 bpm, or active treatment with any β-blocker agent.

To avoid a potential selection bias, randomization was done after informed consent was signed by the patient.

Patients randomized to intravenous metoprolol received up to three 5-mg boluses of metoprolol tartrate 2 minutes apart.[17] Patients were identified and randomized either out of hospital by the participating emergency medical services or on arrival at any of the 7 participating hospitals (in 4 regions across Spain). Patients randomized to the intravenous metoprolol group in the out-of-hospital setting received intravenous metoprolol during transfer to the PCI center.

Apart from intravenous metoprolol, patients were treated according to clinical guidelines. Thrombus aspiration and use of glycoprotein IIb/IIIa during PCI were recommended. All patients except those who developed contraindications received oral metoprolol tartrate during hospitalization. The first oral dose was scheduled for 12 to 24 hours after infarction, in line with clinical guidelines.[1,2]

Randomization was stratified by time from symptom onset to enrollment (<1.5 versus ≥1.5 hours), diabetes mellitus status, sex, and age (<60 versus ≥60 years). Patients were randomized 1:1 by telephone with a block size of 4 within strata. The randomization center was located at the SUMMA112 emergency medical services headquarters and was run around the clock by trained nurses.

Magnetic resonance imaging (MRI) was scheduled for 5 to 7 days after infarction. Patients on long-term β-blocker treatment, with a history of previous acute myocardial infarction, or with no final diagnosis of acute myocardial infarction (no enzymatic evidence of infarction) were excluded from the primary analysis according to the protocol and thus did not undergo MRI.[16]

#### *End Points*

The primary end point was infarct size by MRI (extent of myocardial necrosis quantified by delayed gadolinium enhancement). Prespecified efficacy secondary end points were the extent of myocardial salvage on MRI, infarct size quantified by MRI in the subgroup of patients with a pre-PCI Thrombolysis in Myocardial Infarction (TIMI) grade 0 to 1 flow, and infarct size estimated by peak and area under the curve (AUC; 72 hours) release of creatine kinase (CK). The major prespecified safety secondary end point was the incidence of major adverse cardiac events, defined as a composite of death, malignant ventricular arrhythmias, advanced atrioventricular block, cardiogenic shock, and reinfarction during the first 24 hours after STEMI.

MRI and angiography were evaluated at independent core laboratories; end-point events were adjudicated by an independent clinical events committee. All were blinded to treatment group.

#### *MRI Performance and Analysis*

A detailed description of the MRI protocol and methods for analysis is reported elsewhere.[16] Analyses were undertaken by the core laboratory at Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC). Data were quantified with dedicated software (QMass MR 7.5; Medis, Leiden, the Netherlands). Left ventricular (LV)

volume, LV mass, LV ejection fraction (LVEF), and the extent of edema and necrosis were determined. Myocardial necrosis (grams of LV tissue) was defined by the extent of abnormal delayed gadolinium enhancement, whereas myocardium at risk (grams of LV tissue) was defined by the extent of edema (high signal intensity on T2-weighted short T1 inversion-recovery images).[18,19] Myocardial salvage was defined as the difference between myocardium at risk and myocardial necrosis normalized to myocardium at risk.[18,19]

## Statistical Methods

The study was powered for detect a relative reduction in infarct size of 20% in patients receiving intravenous metoprolol. This required 220 evaluable patients to provide 90% power (2-sided $\alpha$=0.05). Sample size calculation was based on a previous MRI-based study reporting mean infarct size and dispersion in anterior STEMI patients.[20] To compensate for ≈20% patients not undergoing MRI,[16] we planned to recruit ≈275 patients. All randomized patients, including those not undergoing MRI, were analyzed for clinical end points.

All efficacy analyses were performed according to the intention-to-treat principle. For quantitative variables, data are expressed as mean±SD and compared by parametric methods. Nonnormal data are reported as medians with first and third quartiles and were compared by nonparametric methods (Wilcoxon rank-sum test). For categorical data, percentages were compared by use of exact methods. Because the variance of peak and AUC CK release data tends to be proportional to the mean, a square-root transformation was used.

MRI data were analyzed by linear regression models, with treatment effect estimates (and 95% confidence intervals [CIs]) presented both without and with adjustment for the 4 stratification variables.

To confirm that the analysis based on MRI-quantified infarct size was not influenced by selection bias, a sensitivity analysis was performed comparing the estimated difference between treatments for peak and AUC CK release between the overall study population and the subset undergoing MRI. All analyses were conducted with the R 2.14.1 statistical language.

# Results

## Study Population

Between November 2010 and October 2012, 270 patients were randomized to receive intravenous metoprolol pre-reperfusion (n=139) or no metoprolol pre-reperfusion (n=131, control subjects). One hundred forty-seven patients (55%) were randomized out of hospital during ambulance transfer to the PCI center. Four patients (2 in each group) withdrew consent. Twenty-four patients (9%) were not scheduled for MRI because of erroneous recruitment criteria (n=14) or no enzymatic evidence of infarction (n=10). Of patients scheduled for MRI, 22 (9%) did not undergo MRI because of poor clinical status (n=7), claustrophobia (n=12), or technical problems with the magnet (n=3). Patients with poor clinical status not undergoing MRI included 4 patients in the intravenous metoprolol group (2 patients with refractory heart failure, 1 patient with cardiac rupture, and 1 patient with massive hemoptysis) compared with 3 patients in the control group (2 patients with refractory heart failure and 1 patient with aortic dissection). Thus, 220 patients (106 receiving intravenous metoprolol and 114 control subjects) had MRI data available for primary analysis. A CONSORT (Consolidated Standards of Reporting Trials) flow diagram is shown in Figure 1. Baseline characteristics of the study population are presented in Table 1.

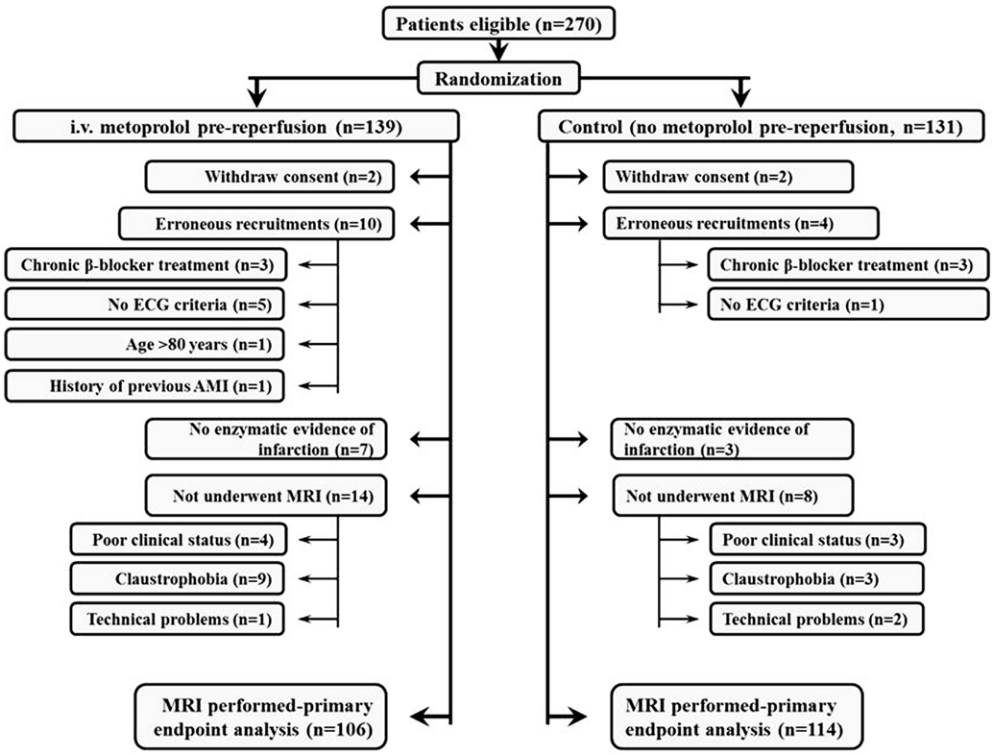


**Figure 1.** Diagram of patients flow in the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial. Patients with no ECG criteria exclusions included the following. Three patients (all 3 allocated to intravenous metoprolol pre-reperfusion) who had no ST-segment elevation ≥2 mm. These patients had no enzymatic evidence of infarction and had a final diagnosis of unspecific chest pain. Two patients (1 in each study group) had ST-segment elevation only in leads II, III, and aVF. One patient (allocated to intravenous metoprolol pre-reperfusion) had junction rhythm. AMI indicates acute myocardial infarction; and MRI, magnetic resonance imaging.

**Table 1. Baseline Characteristics of the Patients***

| | All Patients (n=270) | | Patients Undergoing MRI (n=220) | |
|---|---|---|---|---|
| | Intravenous Metoprolol (n=139) | Control (n=131) | Intravenous Metoprolol (n=106) | Control (n=114) |
| Age, y | 58.7±12.7 | 58.2±10.8 | 58.4±12.4 | 58.7±10.6 |
| Male sex, n (%) | 119 (85.6) | 114 (87) | 92 (86.8) | 99 (86.8) |
| Body mass index, kg/m$^2$ | 27.6±3.7 | 27.9±3.9 | 27.5±3.5 | 27.8±3.9 |
| Hypertension, n (%) | 54 (40.3) | 54 (42.2) | 38 (36.5) | 48 (42.1) |
| Smoking, n (%) | | | | |
| Current smoker | 71 (53) | 69 (53.9) | 56 (53.8) | 59 (51.8) |
| Ex-smoker (0–10 y before) | 14 (10.4) | 14 (10.9) | 12 (11.5) | 12 (10.5) |
| Dyslipidemia, n (%) | 53 (39.8) | 51 (40.2) | 43 (41.3) | 47 (41.2) |
| Diabetes mellitus, n (%) | 31 (23.3) | 24 (18.8) | 21 (20.2) | 22 (19.3) |
| Ischemia duration, min† | 197±61 | 187±66 | 198±62 | 187±67 |
| Killip class at recruitment, n (%) | | | | |
| I | 128 (92.1) | 114 (87.0) | 98 (92.5) | 100 (87.7) |
| II | 11 (7.9) | 17 (13.0) | 8 (7.5) | 13 (11.4) |
| Infarct artery lesion location, n (%) | | | | |
| Proximal LAD | 37 (26.6) | 38 (29.0) | 29 (27.4) | 34 (29.8) |
| Mid LAD | 76 (54.7) | 71 (54.2) | 62 (58.5) | 67 (58.8) |
| Distal LAD | 11 (7.9) | 11 (8.4) | 11 (10.4) | 9 (7.9) |
| Diagonal | 3 (2.2) | 1 (0.8) | 2 (1.9) | 1 (0.9) |
| Left main | 1 (0.7) | 1 (0.8) | 0 (0) | 0 (0) |
| Other | 11 (7.9) | 9 (6.9) | 2 (1.9) | 3 (2.6) |
| TIMI grade 0–1 flow before PCI, n (%) | 104 (76.5) | 101 (77.1) | 86 (81.1) | 92 (80.7) |
| Successful PCI, n (%)‡ | 128 (94.1) | 125 (95.4) | 106 (100) | 111 (97.4) |
| SBP at recruitment, mm Hg | 143±19 | 142±19 | 142±18 | 142±19 |
| HR at recruitment, bpm | 82±14 | 82±14 | 82±13 | 82±14 |
| SBP after intravenous metoprolol, mm Hg | 129±20 | NA | 128±18 | NA |
| HR after intravenous metoprolol, bpm | 69±12 | NA | 68±12 | NA |
| Treatment at the time of PCI, n (%) | | | | |
| Heparin | 123 (95.3) | 119 (96) | 102 (96.2) | 108 (96.4) |
| Aspirin | 127 (98.4) | 121 (97.6) | 105 (99.1) | 109 (97.3) |
| Thienopyridine | 126 (97.7) | 121 (97.6) | 104 (98.1) | 110 (98.2) |
| Thrombus aspiration | 108 (82.4) | 100 (80.6) | 91 (85.8) | 92 (82.1) |
| GP IIb/IIIa during PCI | 92 (70.2) | 99 (79.8) | 76 (71.7) | 90 (80.4) |

There were no significant differences in any of the baseline characteristics. GP indicates glycoprotein; HR, heart rate; LAD, left anterior descending coronary artery; MRI, magnetic resonance imaging; NA, not applicable; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; and TIMI, Thrombolysis in Myocardial Infarction.

*Plus-minus values are mean±SD.

†Ischemia duration means time from symptom onset to reperfusion.

‡Successful PCI was defined as TIMI grade 2 to 3 flow after PCI.

## Metoprolol Administration

Of the 139 patients allocated to pre-reperfusion intravenous metoprolol, 138 (99%) received at least one 5-mg metoprolol intravenous bolus (82% received 2 boluses and 67% received 3 boluses). The same pattern was found for the subset randomized in the out-of-hospital environment. Intravenous metoprolol was administered at a median of 10 minutes (quartiles 1 and 3, 7 and 19 minutes) after STEMI diagnosis. Oral metoprolol was initiated within 24 hours after STEMI in 96% and 92% of patients in the intravenous metoprolol and control groups, with mean±SD initiation times of 15.7±10.6 and 15.9±8.7 hours after reperfusion, respectively.

Two patients allocated to the control group erroneously received pre-reperfusion intravenous metoprolol. These patients were included in the control group for the intention-to-treat analyses and in the intravenous metoprolol group for the safety analysis of major adverse cardiac events. Similarly, 1 patient allocated to intravenous metoprolol did not receive any owing to a vagal reaction and was included in the intravenous metoprolol group for primary analysis and in the control group for the analysis of major adverse cardiac events.

**Table 2. Magnetic Resonance Imaging Data (5 to 7 Days After Infarction)**

| | Patients Undergoing MRI (n=220) | | | | | |
|---|---|---|---|---|---|---|
| | Intravenous Metoprolol (n=106) | Control (n=114) | Unadjusted | | Adjusting for Stratification Variables | |
| | Mean (SD) | Mean (SD) | Difference (95% CI) | *P* Value | Difference (95% CI) | *P* Value |
| LVEDV, mL | 169.0 (33.0) | 172.6 (39.4) | −3.64 (−13.14 to 5.84) | 0.46 | −4.37 (−13.22 to 4.41) | 0.33 |
| LVESV, mL | 91.9 (26.7) | 99.6 (34.8) | −7.70 (−15.92 to 0.41) | 0.063 | −7.85 (−15.70 to −0.09) | 0.047 |
| LV mass, g | 108.8 (24.7) | 112.5 (26.3) | −3.72 (−10.29 to 2.84) | 0.28 | −4.08 (−10.06 to 1.89) | 0.2 |
| Myocardium at risk, g | 37.6 (17.1) | 40.9 (20.0) | −3.30 (−8.19 to 1.44) | 0.19 | −3.44 (−8.29 to 1.26) | 0.16 |
| Infarcted myocardium, g* | 25.6 (15.3) | 32.0 (22.2) | −6.43 (−11.46 to −1.67) | 0.013 | −6.52 (−11.39 to −1.78) | 0.012 |
| Infarcted myocardium, % LV | 21.2 (11.5) | 25.1 (13.9) | −3.85 (−7.28 to −0.51) | 0.029 | −3.77 (−7.17 to −0.46) | 0.032 |
| Salvage index: (MAR–IM)/MAR, %† | 34.9 (22.3) | 27.7 (23.7) | 7.17 (0.80 to 13.30) | 0.028 | 7.20 (0.78 to 13.48) | 0.024 |
| LVEF, % | 46.1 (9.3) | 43.4 (10.4) | 2.74 (0.13 to 5.35) | 0.039 | 2.67 (0.09 to 5.21) | 0.045 |
| Infarcted myocardium in pre-PCI TIMI grade 0–1 flow, g‡ | 26.7 (15.0) | 34.4 (20.0) | −7.72 (−12.82 to −2.85) | 0.004 | −8.13 (−13.10 to −3.16) | 0.002 |
| Infarcted myocardium in pre-PCI TIMI grade 0–1 flow, % LV | 21.9 (11.1) | 26.7 (13.0) | −4.77 (−8.21 to −1.25) | 0.011 | −4.91 (−8.40 to −1.35) | 0.0078 |

CI indicates confidence interval; IM, infarcted myocardium; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MAR, myocardium at risk; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention; and TIMI, Thrombolysis in Myocardial Infarction.

*Primary end point.

†Prespecified secondary end point.

‡Prespecified secondary end point in 178 patients (86 receiving intravenous metoprolol and 92 control subjects).

## Effect on Infarct Size

MRI data are presented in Table 2. Mean±SD infarct size in the intravenous metoprolol group (primary end point) was 25.6±15.3 versus 32.0±22.2 g in the control group (adjusted treatment effect, −6.52; 95% CI, −11.39 to −1.78; *P*=0.012). Myocardial salvage (see Methods) in the intravenous metoprolol group was 34.9±22.3% versus 27.7±23.7% in the control group (adjusted treatment effect, 7.20%; 95% CI, 0.78–13.48; *P*=0.024). Infarct size in the subset of patients with a pre-PCI TIMI grade 0 to 1 flow (prespecified secondary end point) was 26.7±15.0 g in intravenous metoprolol patients versus 34.4±20.0 in the control group (adjusted treatment effect, −8.13; 95% CI, −13.10 to −3.16; *P*=0.0024). In the subset of patients with a pre-PCI TIMI grade 2 to 3 flow (patent artery), infarct size was 20.7±16.4 g in the intravenous metoprolol group versus 22.2±28.3 g in the control group (*P*=0.6). Infarct size distributions in the 2 predefined study groups are illustrated in Figure 2.

Infarct size was also estimated in all study population by peak and AUC CK release as prespecified secondary end points. Pre-reperfusion intravenous metoprolol administration significantly reduced infarct size estimated by peak and AUC CK release. Peak CK in the intravenous metoprolol group was 2397±214 versus 3176±254 IU/L in the control group (adjusted treatment effect, −740; 95% CI, −1361 to −120; *P*=0.019). The AUC CK in the intravenous metoprolol group was 49 427±4013 versus 62 953±4634 IU/L in the control group (adjusted treatment effect, −12 825; 95% CI, −24 346 to −1305; *P*=0.029). Similar results were obtained in the subset of patients undergoing MRI. These findings are shown in Figure 3.

Pre-reperfusion administration of intravenous metoprolol significantly increased LVEF on MRI (46.1±9.3% versus 43.4±10.4%; adjusted treatment effect, 2.67; 95% CI, 0.09–5.21; *P*=0.045). In the subset of patients with a TIMI grade 0 to 1 flow before primary PCI, LVEF was 45.1±8.9% in the intravenous metoprolol group versus 41.0±9.5% in the control group (adjusted treatment effect, 4.13; 95% CI, 1.34–6.85; *P*=0.0031).

## Safety Data

The prespecified safety end point was the incidence of major adverse cardiac events within 24 hours after STEMI in all patients (entire study population). Prereperfusion administration of intravenous metoprolol did not increase the incidence of major adverse cardiac events: There were 10 events (7.1%) in the prereperfusion intravenous metoprolol group and 16

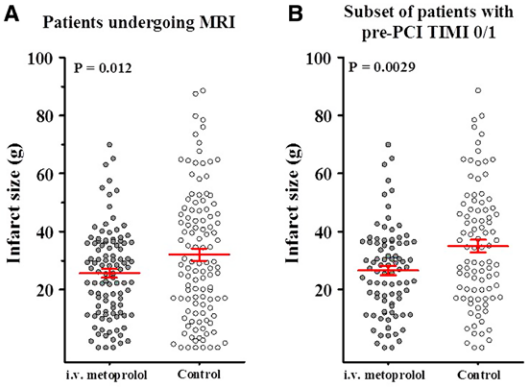


**Figure 2.** Effect of early pre-reperfusion intravenous metoprolol administration on infarct size evaluated by magnetic resonance imaging (MRI) 5 to 7 days after infarction. **A** and **B**, Infarct size assessed by delayed gadolinium enhancement in all patients undergoing MRI (**A**) and in the subset of patients with TIMI grade 0 to 1 flow before primary percutaneous coronary intervention (PCI) (**B**). Red lines represent mean±SEM. Circles are individual patient data. TIMI indicates Thrombolysis in Myocardial Infarction.

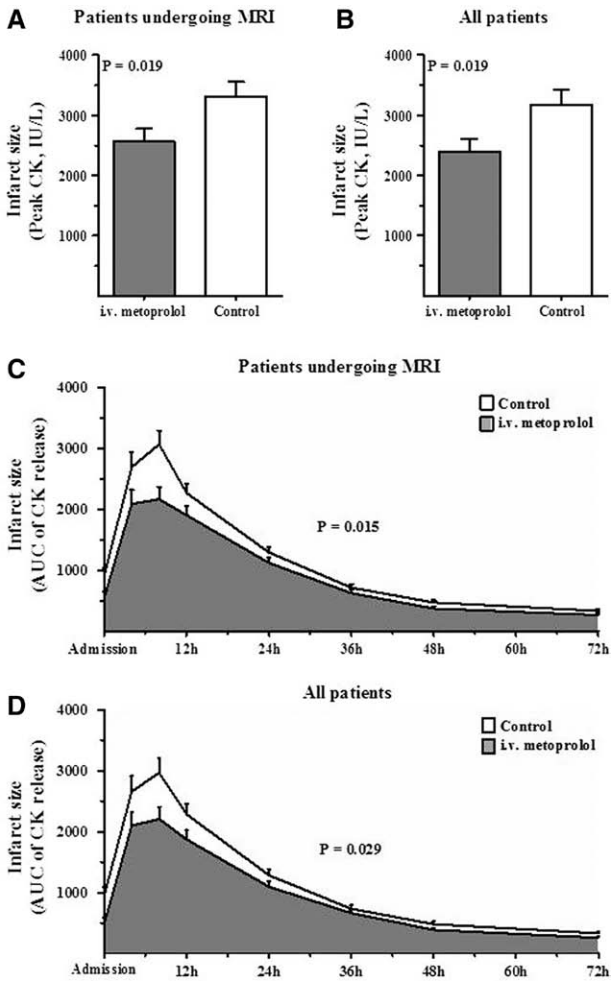


**Figure 3.** Effect of early pre-reperfusion intravenous metoprolol administration on infarct size estimated by peak and area under the curve (AUC) creatine kinase (CK) release. **A** and **B**, Back-transformed mean±SEM of peak CK release in patients undergoing magnetic resonance imaging (MRI; **A**) and in the entire study population (**B**). Nontransformed median of peak CK release in patients undergoing MRI was 2600 IU/L (quartiles 1 and 3, 1306 and 4272 IU/L) in the intravenous metoprolol group vs 3700 IU/L (quartiles 1 and 3, 1311 and 5626 IU/L) in the control group ($P$=0.040). Nontransformed median of peak CK release in the entire study population was 2217 IU/L (quartiles 1 and 3, 877 and 4151 IU/L) in the intravenous metoprolol group vs 3558 IU/L (quartiles 1 and 3, 1118 and 5593 IU/L) in the control group ($P$=0.011). **C** and **D**, AUC CK release in patients undergoing MRI (**C**) and in the entire study population (**D**). Data are presented as back-transformed mean±SEM for each time point of serum CK determination. Nontransformed median AUC CK release in patients undergoing MRI was 49 984 IU/L (quartiles 1 and 3, 28 279 and 76 748 IU/L) in the intravenous metoprolol group vs 65 966 IU/L (quartiles 1 and 3, 28 837 and 10 9329 IU/L) in the control group ($P$=0.042). Nontransformed median AUC CK release in the entire study population was 47 030 IU/L (quartiles 1 and 3, 23 869 and 78 453 IU/L) in the intravenous metoprolol group vs 63 656 IU/L (quartiles 1 and 3, 27 988 and 108 686 IU/L) in the control group ($P$=0.025).

events (12.3%) in the control group ($P$=0.21). Adverse cardiac events are presented in Table 3.

## Discussion

This study shows that early administration of intravenous metoprolol before reperfusion reduces infarct size and increases LVEF in anterior STEMI patients undergoing primary PCI. It also appears safe and does not increase the incidence of cardiac events during admission.

Our objective was to determine whether intravenous metoprolol reduced infarct size in STEMI patients treated according to current clinical guidelines,[1,2] including glycoprotein IIb/IIIa and thrombus aspiration, 2 widely applied interventions with potential infarct-limiting effects.[21,22]

Infarct size was evaluated by 3 different methods: total myocardial necrosis by MRI (the gold standard), relative myocardial necrosis by MRI (normalized to myocardium at risk), and biomarker (CK) release. All 3 methodologies provided evidence of a significant and consistent reduction in infarct size resulting from pre-reperfusion intravenous metoprolol administration. LVEF 1 week after STEMI was significantly increased by intravenous metoprolol, as evaluated by highly accurate MRI technology. Because reduced LVEF is a strong predictor of postinfarction mortality, this finding adds to the clinical value of pre-reperfusion intravenous metoprolol administration.

β-Blockers are a first-line treatment in secondary prevention after acute myocardial infarction with a clear reduction in mortality.[23] Current guidelines recommend oral β-blockade within 24 hours after STEMI[1,2] but with no emphasis on early intravenous initiation before reperfusion. Previous studies of β-blocker effects on infarct size had inconclusive results[7] but were conducted before reperfusion became the standard treatment for STEMI. Recent studies in large animals indicate that metoprolol can reduce infarct size[14] if administered before reperfusion[15] and may reduce reperfusion injury.[24] We therefore hypothesized that the conflicting findings on the cardioprotective capacity of β-blockers in STEMI reflect the facts that very few clinical studies have been performed in the reperfusion era and that no studies testing the ability of β-blockers to reduce infarct size have been done in the era of primary PCI as the treatment of choice for STEMI. Van de Werf et al[12]

**Table 3. Adverse Cardiac Events**

| | Intravenous Metoprolol (n=140), n (%) | Control (n=130), n (%) |
|---|---|---|
| MACE at 24 h | 10 (7.1) | 16 (12.3) |
| Death | 0 (0) | 1 (0.8) |
| Malignant ventricular arrhythmia | 5 (3.6) | 10 (7.7) |
| Advanced AV block | 1 (0.7) | 2 (1.5) |
| Cardiogenic shock | 6 (4.3) | 7 (5.4) |
| Reinfarction | 0 (0) | 0 (0) |
| Death during admission | 3 (2.1) | 3 (2.3) |
| Killip class III or greater during admission | 11 (7.9) | 9 (6.9) |
| Reinfarction during admission | 1 (0.7)* | 0 (0) |

AV indicates atrioventricular; and MACE, major adverse cardiac events (composite of death, malignant ventricular arrhythmias [ventricular fibrillation/sustained ventricular tachycardia], advanced AV block, cardiogenic shock, and reinfarction).

*Periprocedural infarction during percutaneous coronary intervention to a nonculprit coronary artery 4 days after index ST-segment–elevation myocardial infarction.

randomized STEMI patients undergoing thrombolysis to receive prethrombolysis atenolol or placebo. Contrasting with our results, they found no reduction in infarct size by intravenous β-blocker administration. The reason for this disparity is unknown; however, a possible explanation is that ischemia/reperfusion injury differs between patients treated by thrombolysis and primary PCI and that cardioprotective strategies in patients treated by PCI (abrupt coronary opening) do not work in patients treated by thrombolysis (gradual coronary opening). Another potential explanation is that not all β-blockers have the same cardioprotective effect. In this regard, the nonrandomized TEAHAT (Thrombolysis Early in Acute Heart Attack) study found a significant infarct size reduction in STEMI patients undergoing thrombolysis and receiving early intravenous metoprolol.[13] It is also likely to be significant that, in contrast to our trial, only 33% of STEMIs in the Van de Werf et al[12] study were of anterior location and that reperfusion was never achieved in 25% of the study population. Finally, infarct size in our study was evaluated by MRI and was estimated by biomarker release by van de Werf et al.

In the era of primary PCI, a few retrospective studies[25–27] and 1 small randomized trial[28] have evaluated the effect of pre-PCI β-blocker administration on clinical events. Despite none of these studies being designed to detect differences in infarct size, the clinical benefits observed by prereperfusion β-blockade in all of them are in agreement with our results.

It is our hypothesis that metoprolol reduces infarct size by ameliorating reperfusion injury.[24] For that reason, a prespecified secondary end point was infarct size in the subgroup of patients with a pre-PCI occluded artery. Infarct size in the subgroup of patients with pre-PCI TIMI grade 0 of 1 flow was reduced to a larger extent than in the entire study population (Table 2), supporting our hypothesis. In agreement with this idea, infarct size was not reduced in the subgroup of patients with pre-PCI TIMI grade 2 to 3 flow; however, the small number of patients with an open artery precludes a definite statement.

The results of the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) trial[29] are the main reason why clinical practice guidelines do not emphasize early intravenous β-blocker initiation in STEMI.[1] In this trial, STEMI patients undergoing thrombolysis were randomized to early intravenous followed by oral metoprolol or matching placebo. The COMMIT trial did not report data on infarct size but showed significantly reduced rates of reinfarction and ventricular fibrillation in response to early intravenous metoprolol; however, this benefit came at the cost of excess cardiogenic shock, resulting in a net neutral effect on mortality.[29] Although patients in COMMIT presented late (mean time from symptom onset to thrombolysis, 10.3 hours), mortality was lower in Killip class I and II patients receiving intravenous metoprolol. Conversely, total mortality was increased by intravenous metoprolol in Killip class III patients.[29] In addition, metoprolol increased mortality in patients with systolic blood pressure <120 mm Hg. These results reinforce the contraindications for intravenous β-blocker therapy in patients with overt heart failure, and these patients have been systematically excluded from other β-blocker trials. In contrast to the COMMIT trial, we randomized patients presenting early (within 6 hours of STEMI onset), used PCI as the reperfusion strategy, and excluded patients with Killip class III or greater at first medical contact. In METOCARD-CNIC, the number of patients who progressed to Killip class grade III to IV during admission was similar in both treatment groups (7.9% for intravenous metoprolol versus 6.9% for control). Patients with Killip class III to IV STEMI potentially have larger infarctions. Given that we excluded these types of patients (for safety reasons), we might have underestimated infarct size in our population and potentially diluted the benefits of this cardioprotective strategy.

A possible limitation of our trial is that 19% of the recruited patients population did not undergo MRI for primary end-point evaluation. This attrition rate was as we projected[16] and is similar to those in other STEMI trials using MRI.[21,30] Moreover, we analyzed infarct size by peak and AUC CK release in the entire study population to see if the loss of recruited patients introduced a selection bias, and this proved compatible with the MRI findings. A significant reduction in infarct size was observed in patients allocated to intravenous metoprolol before reperfusion in the entire population. Another limitation is that 22 patients scheduled for MRI were withdrawn from the imaging study for various reasons. However, this rate of withdrawal from scheduled MRI is compatible with previous experience[16] and is lower than in other trials performing MRI early after STEMI.[21,30,31]

As shown in Figure 1, there was a significant difference in the proportion of no MRI performance between groups (higher in the intravenous metoprolol group). This was observed despite the fact that the evaluation of the qualifying criteria for MRI performance was done blinded to treatment allocation or other variables that might influence the outcome. In this regard, a sensitivity analysis showed that the estimated difference between treatments for CK release in all study population and in the subset of patients undergoing MRI was similar, ruling out a selection bias.

METOCARD-CNIC was a prospective, randomized, open, blinded end-point (PROBE) trial. Evaluators of all outcomes were nonetheless blinded to treatment allocation. Although evidence suggests that PROBE trials yield results similar to double-blinded trials,[32] we cannot completely rule out an influence of this design on the study results.

Infarct size is a major determinant of postinfarction mortality, so limiting the extent of myocardial necrosis in STEMI is a major therapeutic target.[33] Huge resources have been dedicated to exploring novel therapies that might reduce infarct size but so far with little success.[34] Here, we show that an inexpensive medication already approved for STEMI treatment (intravenous metoprolol) can significantly reduce infarct size simply by being administered before reperfusion. Further evidence is needed to assess potential longer-term clinical benefits in a larger clinical trial.

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## Disclosures

None.

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## CLINICAL PERSPECTIVE

The capacity of β-blockers to reduce infarct size was evaluated extensively in the prereperfusion era with controversial results. In the context of reperfusion as the treatment of choice for ST-segment–elevation myocardial infarction (STEMI), this has been poorly investigated. Experimental data suggest that the β-blocker metoprolol is able to reduce infarct size only when administered intravenously before reperfusion. Here, we present the results of the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial, the first randomized, clinical trial prospectively evaluating the effect of early intravenous β-blockade on infarct size in conjunction with primary angioplasty. A total of 270 patients with anterior STEMI (Killip class II or less) revascularized within 6 hours after symptom onset were randomized to receive intravenous metoprolol or not before reperfusion. All patients received oral metoprolol according to clinical guidelines (first dose, 12–24 hours after infarction). Infarct size, evaluated by magnetic resonance imaging and creatine kinase release, was significantly reduced in the intravenous metoprolol group with no excess side effects. Left ventricular ejection fraction was higher in the intravenous metoprolol group. This cardioprotective effect appeared to be restricted to patients with a preangioplasty Thrombolysis in Myocardial Infarction grade 0 to 1 flow. Here, we show that an inexpensive medication already approved in the context of STEMI can significantly reduce infarct size just by administering it intravenously before reperfusion in patients with no contraindications. Given the important role of final infarct size as a main determinant of long-term mortality in STEMI survivors, the possibility of applying inexpensive strategies available to a wide proportion of STEMI patients is of clinical value.