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Long term benefit of early pre-reperfusion metoprolol administration in patients with acute myocardial infarction: results from the METOCARD-CNIC trial.

Brief title: *long term effect of early metoprolol in STEMI*

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ABSTRACT

Objectives: To study the long-term effects of i.v. metoprolol administration before reperfusion on left ventricular (LV) function and clinical events.

Background: Early i.v. metoprolol during ST-segment elevation myocardial infarction (STEMI) has been shown to reduce infarct size when used in conjunction with primary percutaneous coronary intervention (pPCI).

Methods: The METOCARD-CNIC trial recruited 270 patients with Killip-class ≤II anterior STEMI presenting early after symptom onset (<6 hours) and randomized them to pre-reperfusion i.v. metoprolol or control. Long-term magnetic-resonance-imaging (MRI) was performed on 202 patients (101 per group) 6 months after STEMI. Patients had a minimum 12-month clinical follow-up.

Results: Mean (±SD) LV ejection fraction (LVEF) at 6 months MRI was higher after i.v. metoprolol (48.7±9.9% vs. 45.0±11.7% in controls; adjusted treatment effect 3.49%; 95% confidence interval [CI], 0.44 to 6.55%; P=0.025). The occurrence of severely depressed LVEF (≤35%) at 6 months was significantly lower in patients treated with i.v. metoprolol (11% vs. 27%, P=0.006). The proportion of patients fulfilling class-I indications for implantable cardioverter-defibrillator (ICD) was significantly lower in the i.v. metoprolol group (7% vs. 20%, P=0.012).

At a median follow-up of 2 years, occurrence of the pre-specified composite of death, heart failure admission, re-infarction, and malignant arrhythmia was 10.8% in i.v. metoprolol vs. 18.3% in controls, adjusted HR: 0.55; 95% CI, 0.26 to 1.04; P=0.065. Heart failure admission was significantly lower in i.v. metoprolol (HR: 0.32; 95% CI, 0.015 to 0.95; P=0.046).

Conclusion: In patients with anterior Killip-class ≤II STEMI undergoing pPCI, early i.v. metoprolol before reperfusion resulted in higher long term LVEF, reduced incidence of severe LV systolic dysfunction and ICD indications, and fewer admissions due to heart failure.

Key words: Myocardial Infarction, STEMI, receptors-adrenergic-beta (β-blockers), metoprolol, PCI, Heart Failure, ICD, LVEF, Infarct size, magnetic resonance imaging.

ABBREVATIONS

i.v.= intravenous.
ICD= implantable cardioverter-defibrillator.
LVEF= left ventricular ejection fraction.
MRI= magnetic resonance imaging.
NYHA= New York Heart Association.
pPCI= primary percutaneous coronary intervention.
STEMI= ST-segment elevation myocardial infarction.

Introduction

ST-segment elevation myocardial infarction (STEMI) is a major contributor to mortality and morbidity worldwide.(1-3) Beyond the high mortality rate in the acute phase, STEMI survivors are at high risk of recurrent events such as congestive heart failure, arrhythmia or sudden death. Post-infarction patients with severely depressed left ventricular ejection fraction (LVEF) are at the highest risk of long-term adverse outcomes. Pharmacological and non-pharmacological (implantable cardioverter-defibrillator [ICD]) interventions have greatly reduced long term mortality rates in these patients.(4, 5) However, the implementation of such strategies represents a huge economic burden that precludes its universal application. There is therefore a need for additional low cost therapies to prevent severe post-infarction LV dysfunction.

The size of the infarct after a STEMI has been revealed as the main determinant of adverse post-infarction outcomes.(6) Therapies able to reduce infarct size are therefore urgently sought under the hypothesis that smaller infarctions will result in better long term heart performance and that this will translate into fewer adverse clinical events.(7, 8)

Early intervention with intravenous (i.v.) metoprolol before reperfusion (the METOCARD-CNIC trial) was recently shown to significantly reduce infarct size as evaluated by magnetic resonance imaging (MRI) one week post-infarction.(9) Here we present the pre-specified evaluation on long-term LVEF (primary MRI measurement) and the effect on clinical endpoints of the METOCARD-CNIC trial.

Methods:

Study Population.

The design of the study has been previously published.(10) METOCARD-CNIC was a multicenter randomized clinical trial in which STEMI patients undergoing primary percutaneous coronary intervention (pPCI) were randomized to receive i.v. metoprolol or control (no

metoprolol) before reperfusion. Between November 2010 and October 2012, 270 patients were randomized to i.v. metoprolol pre-reperfusion (n=139) or control (n=131). Inclusion criteria were patient age 18-80 years, Killip-class ≤II anterior STEMI, and anticipated symptom onset-to-reperfusion time ≤6 hours. Exclusion criteria were systolic blood pressure persistently <120 mmHg, AV block, heart rate <60 bpm, prior infarction or active treatment with β-blockers. Patients randomized to i.v. metoprolol received up to three 5mg boluses of metoprolol tartrate. Fifty-five percent of the population was recruited and treated during ambulance transfer to the hospital. Apart from i.v. metoprolol pre-reperfusion (or control), all patients received state-of-the-art treatment according to clinical guidelines, including chronic oral treatment with β-blockers (first dose within 24h after admission) in all patients with no contraindication. All patients were treated by local physicians who were blinded to treatment allocation and were responsible for all clinical actions.

The primary readout of the trial (infarct size evaluated by MRI performed one week post-infarction) was available in 220 patients. The results of the one-week MRI have been reported:(9) administration of pre-reperfusion i.v. metoprolol resulted in significantly smaller (20%) infarcts and, with no excess in side effects.

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

Long term MRI data:

The protocol included a follow-up MRI 6 months after infarction in all patients except for those who showed no evidence of infarction on baseline MRI (no detectable gadolinium delayed enhancement). The detailed MRI protocol and methods for analysis have been reported.(10) Analyses were undertaken by the CNIC imaging core laboratory by expert researchers blinded to

treatment arm. Data were quantified using dedicated software (QMass® MR 7.5, Medis, Leiden, The Netherlands). At 6-month MRI follow-up, LV volume, LV mass, LVEF, and the extent of myocardial necrosis (grams of LV tissue on delayed gadolinium enhancement images) were determined.

A post-hoc comparison was performed of the between-group frequencies of long term LV reduced ejection fraction according to established cutoffs for clinical relevance(4) (30%, 35% and 40%).

Evaluation of the indication for ICD implantation:

Given the clinical, social and economic implications of post-infarction ICD implantation, we performed a post-hoc analysis of the rate of ICD indication between study groups. ICD indication was defined according to class I recommendations in current clinical guidelines:(4, 5) chronic LVEF≤30% or chronic LVEF 30-35% in patients in New York Heart Association (NYHA) functional class II or III.

Clinical endpoints:

The pre-specified clinical endpoint was the composite of death, readmission due to heart failure, re-infarction and malignant ventricular arrhythmias.(10) Clinical follow-up was performed by telephone interview and access to hospital reports. Once a potential event was detected, an independent clinical events committee blinded to the treatment arm reviewed the primary source data and adjudicated the event according to the pre-established protocol.

Statistical methods:

The distribution of the continuous variables was analyzed using graphical methods. For quantitative variables, data are expressed as means±SD and compared by parametric methods. For categorical data, percentages were compared using exact methods. MRI data were analyzed

between treatment groups by linear regression models. LVEF was categorized by cutoffs of clinical significance, as described above. To evaluate between group trends, an ordinal regression was performed and the proportional odds assumption was then checked. The survival distributions during follow-up of patients with and without i.v. metoprolol treatment were estimated by the Kaplan-Meier method, followed by the Cox proportional hazards regression model. The proportional hazards assumption was confirmed by inspection of Schoenfeld residuals. Finally, as a pre-specified outcome, the treatment effect on 1-year follow-up MACE incidence was evaluated by logistic regression. Treatment effect estimates of all regression models (and 95% confidence intervals) are presented both without and with adjustment for the four stratification variables used in the randomization: time from symptom onset to enrollment (<1.5 versus ≥1.5 hours), diabetes mellitus status, sex, and age (<60 versus ≥60 years). Differences were considered statistically significant at a p-value <0.05 (two-tailed).

All statistical tests were performed with IBM SPSS Statistics software, v.20.0 (SPSS, Armonk, NY: IBM Corp.) and Stata 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp).

Results:

Long term MRI data:

MRI was scheduled 6 months after STEMI in all 220 patients undergoing one-week MRI except for those with no evidence of infarction in the first MRI study (3 i.v. metoprolol, 6 control). Nine additional patients did not undergo follow-up MRI for the following causes: one death (control), one disabling stroke (control), one technical problem with the MRI (i.v. metoprolol), one emigration (i.v. metoprolol), and five refusals to undergo follow-up MRI (3 i.v. metoprolol, 2 control). Thus a total of 202 patients underwent 6-month MRI (101 i.v. metoprolol and 101

control). Chronic medication with known beneficial effects on LV remodeling was similar in both groups of patients (Supplemental Table 1).

MRI data are presented in Table 1. Pre-reperfusion administration of i.v. metoprolol resulted in a significantly higher long-term mean LVEF on 6-month MRI (48.7±9.9% vs. 45.0±11.7 in controls; adjusted treatment effect 3.49; 95% CI, 0.44 to 6.55%; P=0.025) (Figure 1). LV end-systolic volume was significantly lower in patients treated with pre-reperfusion i.v. metoprolol (98.1±36.0 mL vs. 112.0±45.0; adjusted treatment effect -13.25; 95% CI, -24.47 to -2.03; P=0.021). The LVEF values from the one week study (9) correlated tightly with the 6 month values regardless of treatment group (Supplemental Figure 1). Long term extension of scar tissue was 15.7±10.4 grams in i.v. metoprolol vs. 18.6±11.3 grams in the control group (treatment effect, -2.89; 95% confidence interval [CI], -6.02 to 0.24; P=0.070).

LVEF depression and ICD indications according to clinical guidelines:

The numbers of patients in each treatment group according to clinically relevant LVEF cutoffs are illustrated in Figure 2A. The proportion of patients with depressed LVEF at 6 months was significantly lower in the i.v. metoprolol group (eg 11% vs. 27% with LVEF≤35%, P=0.006), and treatment groups also differed in the distribution of patients by LVEF category. Treatment allocation to i.v. metoprolol was associated with being in a higher LVEF category (common OR 1.84; 95% CI, 1.11 to 3.07; P=0.019).

The 6-month MRI data were analyzed for formal indication for ICD implantation according to current clinical guidelines(4, 5) (Figure 2B). Pre-reperfusion metoprolol administration resulted in a significant reduction of patients with ICD class I recommendation (7% vs. 20% in controls, a risk difference of 12.7% (3.2% to 22.3%); P=0.012; adjusted OR 0.32; 95% CI, 0.13 to 0.81;

P=0.016). The number needed to treat (NNT) to avoid one ICD indication was 8 (95% CI, 4.5 to 31; P=0.015).

Clinical follow-up:

Median follow-up was 2 years after STEMI, with all patients but 6 losses having a minimum of 12 months follow-up. The incidence of the pre-specified MACE endpoint (composite of death, heart failure admission, re-infarction, and malignant arrhythmia) and its individual components by treatment group are summarized in Table 2. There were fewer numerical MACE events after pre-reperfusion i.v. metoprolol administration: 10.8% vs. 18.3% in controls (adjusted HR: 0.55; 95% CI, 0.26 to 1.04; P=0.065). This was mainly driven by a lower rate of re-admission due to heart failure (2.2% in i.v. metoprolol vs. 6.9% in controls; HR: 0.32; 95% CI, 0.015 to 0.95; P=0.046). Kaplan Meier curves are shown in Figure 3.

Discussion:

This pre-specified follow-up of the METOCARD-CNIC trial shows that patients receiving pre-reperfusion i.v. metoprolol have a significantly higher long-term mean LVEF compared with controls and are protected against long-term LVEF depression. These effects were accompanied by a trend towards reduced hard clinical endpoints. To the best of our knowledge, this is the first demonstration of a pharmacologic cardio-protective strategy used in conjunction with pPCI resulting in sustained benefits on overall LVEF and in a significant reduction of cases of chronic severe LV systolic dysfunction.

The design of the METOCARD-CNIC trial included a 6 months MRI study for the evaluation of the effect of the therapy on long term validated prognostic parameters. MRI is the gold standard for the evaluation of heart anatomy and function.(11) In the 6 months MRI we found that besides a higher LVEF, patients in the i.v. metoprolol group had significantly smaller LV end-systolic

volumes, another well-established post-infarction prognostic parameter.(12) We previously reported a significantly higher LVEF in the i.v. metoprolol group in the one-week post-infarction MRI study.(9) As presented, the LVEF values from the one week study correlated tightly with the follow-up values in both groups of treatment, supporting the conclusion that the long term benefits of pre-reperfusion i.v. metoprolol are a consequence of the acute beneficial effects detected at one week post infarction. In order to determine if the attrition of patients between the one-week and 6-month MRI studies could have biased the results reported here, we evaluated the one-week MRI LVEF in those patients who underwent the first scan but not the 6-month follow-up (18 patients): median (first and third quartile) LVEFs were 53.0% (45.5%/59.0%) in the i.v. metoprolol group vs. 52.5% (46.8%/62.0%) in the control group, excluding the possibility of selection bias introduced by patient attrition between one-week and follow-up MRIs.

The long term beneficial effects of pre-reperfusion i.v. metoprolol on LVEF were associated with a non-significant trend toward reduced hard clinical endpoints. The main limitation for the interpretation of this finding is that our trial was not powered to detect differences in clinical events. Other small trials testing the effect of cardioprotective strategies in STEMI have reported a significant reduction in long term events despite being underpowered. In the CONDI trial, Sloth et al. found that remote ischemic conditioning in STEMI seemed to improve long-term clinical outcomes.(13) Their minimum follow-up was three years, while ours was 12 months. In fact the survival curves in the CONDI trial showed a clear diverge after two years of follow-up. In a different study, Stone et al found that intracoronary abciximab in anterior STEMI resulted in a significant events reduction in the non-pre-specified time range (30 days-12 months) post-infarction.(14) Given the strong trend towards events reduction found in our trial, it is plausible that longer follow-up will reveal statistically significant differences. Similarly, not pre-specified

analyses of our study showed statistical significance (heart failure admission HR was 0.32; P=0.046). However we feel that these non-powered or non-pre-specified analyses are of limited value even when statistical significance is shown. We believe that our data form a sufficient basis for a larger STEMI clinical trial of early i.v. metoprolol powered for clinical events reduction.

The implementation of reperfusion strategies over the past decades has significantly reduced the acute mortality associated with STEMI.(15) However, a high proportion of survivors remain at high risk of future cardiovascular events throughout life, including sudden death and repetitive episodes of heart failure. Long-term post-infarction LV systolic function is a major predictor of these clinical events; indeed LVEF remains the principal objective parameter used for the indication for post-infarction heart failure therapies.(4, 5) Extensive clinical research has led to chronic heart failure interventions (pharmacological and device-based) that reduce long term mortality in STEMI survivors with low LVEF.(4, 5) Nonetheless, the implementation of these strategies comes at a high socioeconomic cost.(16, 17) The enormous economic burden for health services is the main factor preventing universal implementation of these new heart failure therapies,(18, 19) and most countries in development cannot afford them,(20) despite having implemented reperfusion strategies for STEMI. Even in advanced economies, economic considerations prevent universal use of the most expensive therapies (ICD and cardiac resynchronization devices).(21, 22) The present trial demonstrates that administration of a low cost therapy (<2€ in Spain. <3$ in the US, <4£ in the UK) results in higher long-term LVEF. Despite the observed 3.7 point absolute difference in mean LVEF could be judged as small, the much lower number of patients with severely depressed LVEF in the treatment group is more clinically relevant, and would translate into a greater socioeconomic impact. Furthermore, the

number of patients with a formal indication for ICD implantation according to clinical guidelines was 1/3 less among the i.v. metoprolol patients. The rate of actual ICD implantation among cases with a formal indication was 33% (9 out of 27, see Table 2). This rate of ICD implantation is in agreement with other dedicated studies (rate between 30-35%),(23, 24) and above what is seen in the general population (around 13%).(25)

In the first report on the METOCARD-CNIC trial we documented an average 20% smaller infarct size in patients randomized to i.v. metoprolol, as evaluated by MRI one week after infarction.(9) At 6 months, total infarct size difference between groups had attenuated (15.6 g in i.v. metoprolol vs. 18.6 g in controls, p=0.07). Thus despite infarct size still being ≈17% smaller in the active treatment group, the natural shrinkage of scar tissue narrowed the absolute difference.(26) It is also important to consider that this trial was powered to detect differences in infarct size in the acute phase (one week after STEMI).

β-blockers have been shown to reduce mortality when used as secondary prevention after infarction,(27) and are an established part of the pharmacological armamentarium, with a class I indication in clinical guidelines.(1, 2) However, very early i.v. administration before reperfusion is not encouraged, mainly due to the results of the COMMIT trial, which showed no short-term net clinical benefit of early metoprolol in STEMI patients undergoing thrombolysis.(28) The COMMIT trial recruited all comers with almost no restriction. In contrast, the METOCARD-CNIC trial recruited Killip-class ≤II patients presenting with systolic blood pressure ≥120 mmHg, heart rate ≥60, and reperfused by pPCI within 6h of infarct onset. Subgroup analyses of the COMMIT trial(28) suggested that patients fitting the inclusion criteria of the METOCARD-CNIC benefited from early i.v. metoprolol in terms of mortality reduction. In addition, the clinical benefits associated with infarct size reduction (and post-infarction LVEF improvement)

are expected to occur late (months to years) after STEMI.(13, 29) In the COMMIT trial, clinical follow-up was less than one month. It is plausible that longer follow-up of the COMMIT trial would show additional benefit of early i.v. metoprolol in survivors. Thus an important lesson from the COMMIT trial is that not all STEMI patients benefit from very early i.v. metoprolol, a deduction supported by the results reported here.

In conclusion, intravenous metoprolol administered before reperfusion results in higher long-term LVEF and lower incidence of post-infarction severe LVEF depression in anterior STEMI patients undergoing primary PCI during the first 6 hours of infarction. This low-cost therapy could have an important socioeconomic impact by reducing the number of patients requiring expensive interventions to treat post-infarction heart failure and prevent sudden death. The results of the METOCARD-CNIC trial warrant a large study powered to detect differences in hard clinical endpoints.

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FIGURE LEGENDS.

Figure 1. Left Ventricular Ejection Fraction on Magnetic Resonance Imaging 6 months after infarction

Left ventricular ejection fraction (LVEF) in patients undergoing magnetic resonance imaging (MRI) 6 months after infarction. Boxplots represent means (±SEM). Circles are individual patient data.

Figure 2. Follow-up Left Ventricular Ejection Fraction Categories and Indications for implantable cardioverter-defibrillator according to treatment allocation.

A. Distribution of patients according to left ventricular ejection fraction (LVEF) categories. Fisher´s exact test P=0.026 and Liner-by-linear association test P=0.006. **B.** Rate of formal indication (class I recommendation in clinical guidelines) for implantable cardioverter-defibrillator (ICD); see text. Fisher´s exact test P=0.012.

Figure 3. Follow-up Clinical endpoints.

Panel A shows the Kaplan-Meier curves illustrating cumulative incidence of the pre-specified composite of death, admission due to heart failure, re-infarction or malignant ventricular arrhythmia. Panel B corresponds to the Kaplan-Meier curves showing the cumulative incidence of re-admission due to heart failure.

Table 1: Magnetic Resonance Imaging Data (6 Months After Infarction)

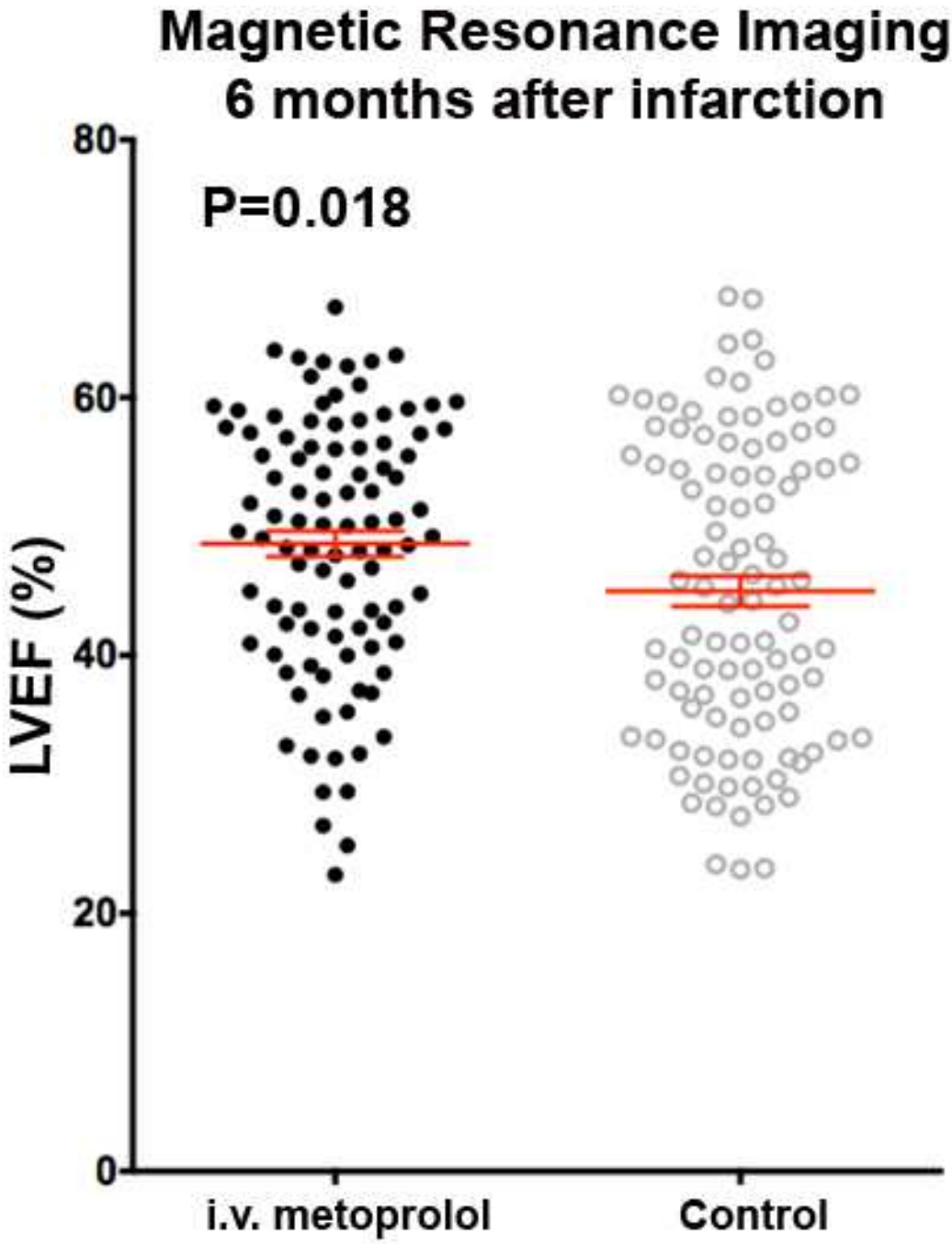
	i.v. Metoprolol (n=101)	Control (n=101)	Unadjusted		Adjusted for Stratification Variables	
	Mean (SD)	Mean (SD)	Difference (95% CI)	*P* Value	Difference (95% CI)	*P* Value
LVEDV, mL	187.0 (38.8)	197.6 (45.7)	-10.62 (-22.45 to 1.22)	0.078	-10.34 (-21.73 to -1.05)	0.075
LVESV, mL	98.2 (36.1)	112.0 (45.0)	-13.87 (-25.22 to -2.51)	0.017	-13.25 (-24.47 to -2.03)	0.021
LV mass, g	84.6 (17.4)	86.8 (18.1)	-2.20 (-7.15 to 2.75)	0.38	-2.09 (-6.81 to 2.63)	0.38
Infarcted myocardium, g	15.7 (10.5)	18.6 (11.3)	-2.89 (-6.02 to 0.24)	0.070	-2.58 (-5.69 to 0.53)	0.10
Infarcted myocardium, % LV	15.7 (9.6)	18.3(9.8)	-2.52 (-5.29 to 0.26)	0.075	-2.30 (-5.09 to 0.49)	0.11
LVEF, %	48.7 (10.0)	45.0(11.7)	3.67 (0.64 to 6.71)	0.018	3.49(0.44 to 6.55)	0.025

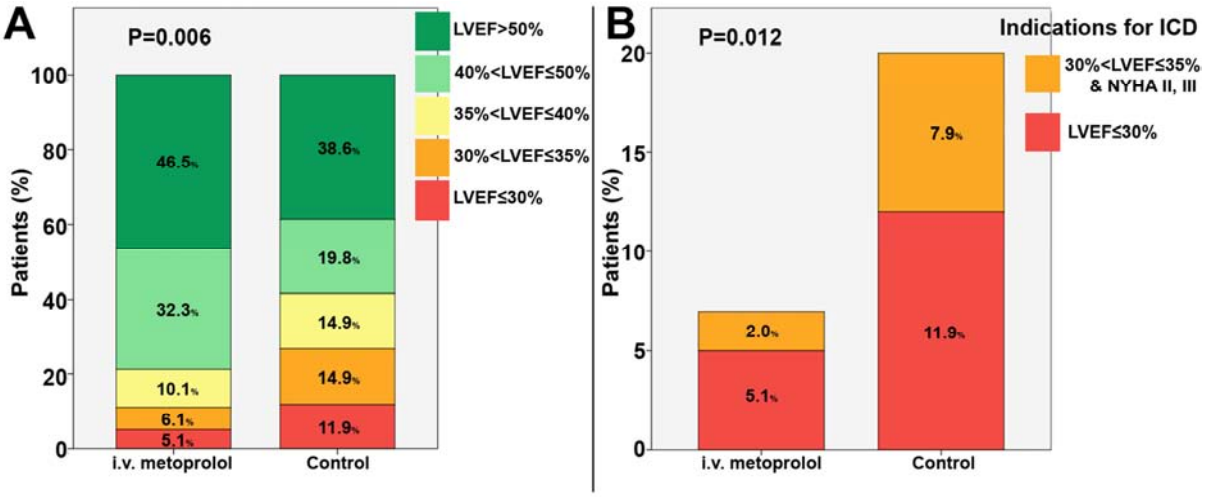
CI, confidence interval; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging

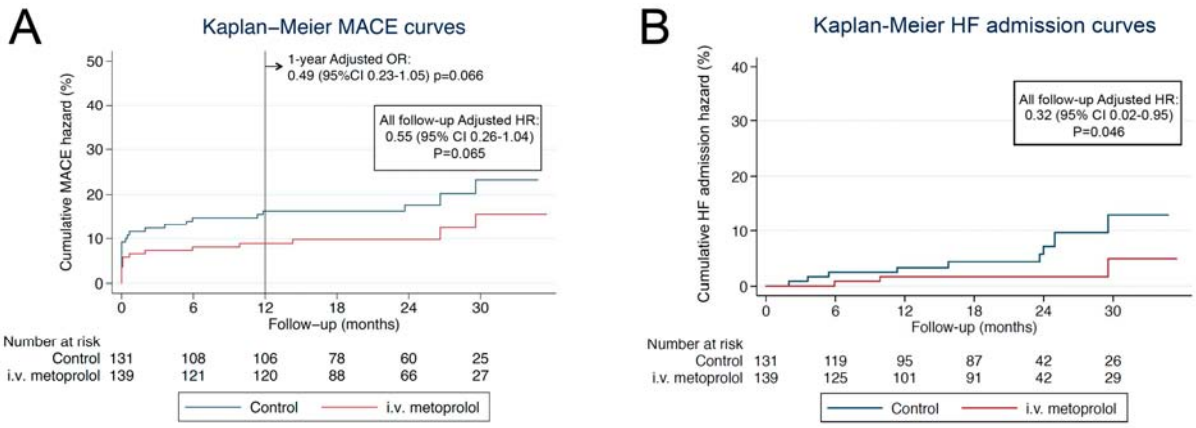
Table 2: Clinical Events

	Intravenous Metoprolol N (%)	Control N (%)	*P* Value
MACE	15 (10.8)	24 (18.3)	0.065
Death	6 (4.3)	6 (4.6)	0.92
Cardiac death	3 (2.2)	5 (3.8)	
non-cardiac death	3 (2.2)	1 (0.8)	
Heart Failure Admission	3 (2.2)	9 (6.9)	0.046
ICD implantation	2 (1.4)	7 (5.3)	
decompensation	1 (0.7)	3 (2.3)	
Re-AMI	1 (0.7)	3 (2.3)	0.15
Malignant ventricular arrhythmia	5 (3.6)	10 (7.7)	0.18

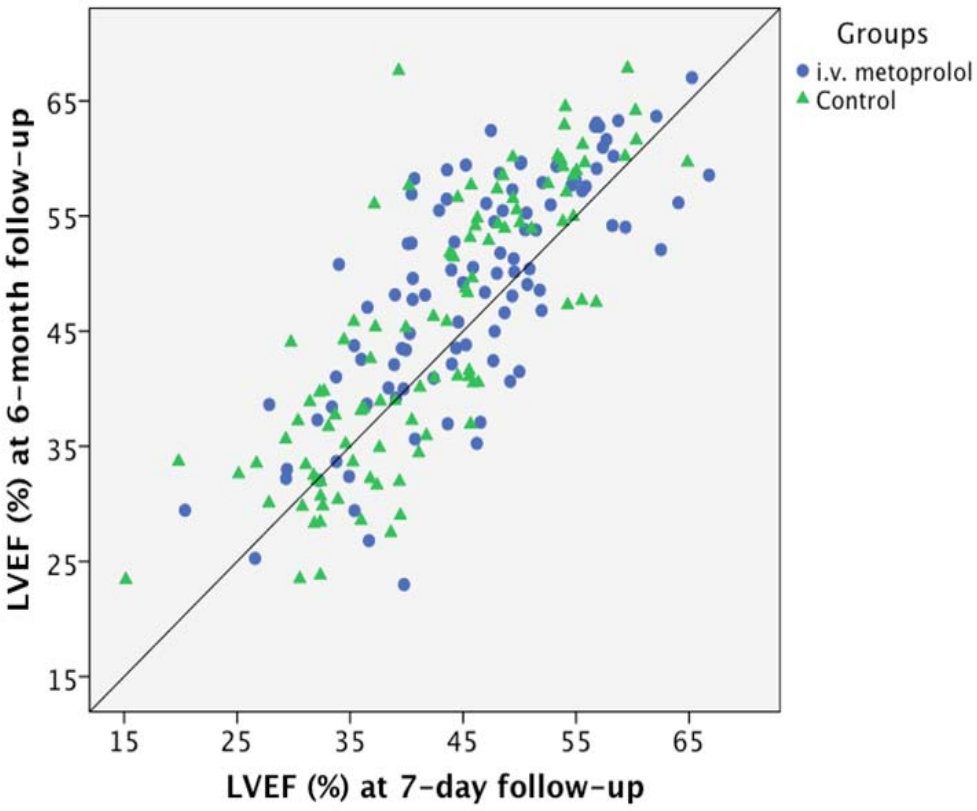
MACE (major adverse cardiac events) was the composite of all cause death, heart failure admission (internal cardioverter defibrillator [ICD] implantation or clinical decompensation), reinfarction and malignant ventricular arrhythmias (ventricular fibrillation/sustained ventricular tachycardia). Values were adjusted for randomization of variables.


Magnetic Resonance Imaging
6 months after infarction
P=0.018
LVEF (%)
80
60
40
20
0
i.v. metoprolol
Control





Supplemental Figure 1.



Plot representing left ventricular ejection fraction (LVEF) of individuals at short-term (one week) and long-term (6 months) magnetic resonance imaging (MRI) examinations. Circles and triangles represent individual patients in the i.v. metoprolol and control groups, respectively.

Supplemental Table 1: Discharge treatment

	Aspirin	Thienopiridine	Beta-blocker	Statin	ACEi	ARB	ARA
Intravenous Metoprolol	99.0%	100.0%	98.0%	99.0%	86.1%	4.0%	18.8%
Control	99.0%	100.0%	97.0%	97.0%	89.1%	3.0%	21.8%

ACEi: angiotensin-converting-enzyme inhibitor; ARB: Angiotensin receptor blockers; ARA: Aldosterone receptor antagonists.

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All authors have read and agreed with this submission, and take full responsibility for the integrity of the findings presented. Simon Bartlett (CNIC) provided English editing.