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CLINICAL RESEARCH — Acute Coronary Syndrome

Long-Term Benefit of Early Pre-Reperfusion Metoprolol Administration in Patients With Acute Myocardial Infarction

Results From the METOCARD-CNIC Trial (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction)

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Objectives The goal of this trial was to study the long-term effects of intravenous (IV) metoprolol administration before reperfusion on left ventricular (LV) function and clinical events.

Background Early IV 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 (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction) trial recruited 270 patients with Killip class ≤II anterior STEMI presenting early after symptom onset (<6 h) and randomized them to pre-reperfusion IV metoprolol or control group. Long-term magnetic resonance imaging (MRI) was performed on 202 patients (101 per group) 6 months after STEMI. Patients had a minimal 12-month clinical follow-up.

Results Left ventricular ejection fraction (LVEF) at the 6 months MRI was higher after IV metoprolol (48.7 ± 9.9% vs. 45.0 ± 11.7% in control subjects; 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 IV metoprolol (11% vs. 27%, p = 0.006). The proportion of patients fulfilling Class I indications for an implantable cardioverter-defibrillator (ICD) was significantly lower in the IV 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, reinfarction, and malignant arrhythmias was 10.8% in the IV metoprolol group versus 18.3% in the control group, adjusted hazard ratio (HR): 0.55; 95% CI: 0.26 to 1.04; p = 0.065. Heart failure admission was significantly lower in the IV metoprolol group (HR: 0.32; 95% CI: 0.015 to 0.95; p = 0.046).

Conclusions In patients with anterior Killip class ≤II STEMI undergoing pPCI, early IV metoprolol before reperfusion resulted in higher long-term LVEF, reduced incidence of severe LV systolic dysfunction and ICD indications, and fewer heart failure admissions. (Effect of METOprolol in CARDioproteCtioN During an Acute Myocardial InfarCtion. The METOCARD-CNIC Trial; NCT01311700) (J Am Coll Cardiol 2014;63:2356–62) © 2014 by the American College of Cardiology Foundation

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 nonpharmacological (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 left ventricular (LV) dysfunction.

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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 (IV) metoprolol before reperfusion (METOCARD-CNIC [Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction] trial) was recently shown to significantly reduce infarct size as evaluated by magnetic resonance imaging (MRI) 1 week post-infarction (9). Here, we present the prespecified 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 IV metoprolol or control group (no metoprolol) before reperfusion. Between November 2010 and October 2012, 270 patients were randomized to IV metoprolol pre-reperfusion (n = 139) or control group (n = 131). Inclusion criteria were patient age 18 to 80 years, Killip class ≤II anterior STEMI, and anticipated symptom onset-to-reperfusion time ≤6 h. Exclusion criteria were systolic blood pressure persistently <120 mm Hg, atrioventricular block, heart rate <60 beats/min, prior infarction, or active treatment with β-blockers. Patients randomized to IV metoprolol received up to 3 5-mg boluses of metoprolol tartrate. Fifty-five percent of the study group was recruited and treated during ambulance transfer to the hospital. Apart from IV metoprolol pre-reperfusion (or control group), all patients received state-of-the-art treatment according to clinical guidelines, including long-term oral treatment with β-blockers (first dose within 24 h 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.

Abbreviations and Acronyms

CI = confidence interval

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

IV = intravenous

LV = left ventricular

LVEF = left ventricular ejection fraction

MACE = major adverse cardiac event(s)

MRI = magnetic resonance imaging

pPCI = primary percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

The primary readout of the trial (infarct size evaluated by MRI performed 1 week post-infarction) was available in 220 patients. The results of the 1-week MRI have been reported (9): administration of pre-reperfusion IV metoprolol resulted in significantly smaller (by 20%) infarcts and with no excessive 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 Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) imaging core laboratory by expert researchers blinded to treatment arm. Data were quantified using

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The main sponsor of the METOCARD-CNIC trial was the Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), through the competitive grant "CNIC translational 01-2009." Other sponsors were the Spanish Ministry of Health and Social Policy (EC10-042), the Mutua Madrileña Foundation (AP8695-2011), and a Master Research Agreement (MRA) between Philips Healthcare and the CNIC. Dr. Ibanez is a recipient of the ISCIII grants "Fondo de Investigación Sanitaria" PI10/02268 and PI13/01979 that relate to the topic of this work. The magnetic resonance images were analyzed with dedicated software (QMass MR version 7.5), partially supported by a scientific collaboration with Medis Medical Imaging Systems BV. Dr. Pizarro, Dr. Fernández-Friera, Ms. Escalera, Mr. García-Prieto, Dr. Mirelis, Dr. Goicolea, and Dr. Ibanez are members of the Spanish "Red de Investigación Cardiovascular" (RIC; Program 4: HISPANICVS). Dr. Sánchez-González is an employee of Philips Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Pizarro and Fernández-Friera contributed equally to this work.

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dedicated software (QMass MR version 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 (30%, 35%, and 40%) (4).

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% to 35% in patients in New York Heart Association functional class II or III.

Clinical endpoints. The pre-specified clinical endpoint was the composite of death, readmission because of heart failure, reinfarction, 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 mean ± SD and compared by parametric methods. For categorical data, percents 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 in the preceding text. 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 IV 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 the incidence of 1-year follow-up major adverse cardiac events (MACE) was evaluated by logistic regression. Treatment effect estimates of all regression models (and 95% confidence intervals [CIs]) are presented both without and with adjustment for the 4 stratification variables used in the randomization: time from symptom onset to enrollment (<1.5 h vs. ≥1.5 h), diabetes mellitus status, sex, and age (<60 years vs. ≥60 years).

Differences were considered statistically significant at a p value <0.05 (2-tailed).

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

Results

Long-term MRI data. MRI was scheduled 6 months after STEMI in all 220 patients undergoing 1-week MRI except for those with no evidence of infarction in the first MRI study (3 IV metoprolol, 6 control subjects). Nine additional patients did not undergo follow-up MRI for the following causes: 1 death (control group), 1 disabling stroke (control group), 1 technical problem with the MRI (IV metoprolol group), 1 emigration (IV metoprolol group), and 5 refusals to undergo follow-up MRI (3 IV metoprolol, 2 control subjects). Thus, a total of 202 patients underwent 6-month MRI (101 IV metoprolol and 101 control subjects). Long-term medication with known beneficial effects on LV remodeling was similar in both groups of patients (Online Table 1).

MRI data are presented in Table 1. Pre-reperfusion administration of IV metoprolol resulted in a significantly higher long-term mean LVEF on 6-month MRI (48.7 ± 9.9% vs. 45.0 ± 11.7% in control patients; adjusted treatment effect 3.49; 95% CI: 0.44% to 6.55%; p = 0.025) (Fig. 1). LV end-systolic volume was significantly lower in patients treated with pre-reperfusion IV metoprolol (98.1 ± 36.0 ml vs. 112.0 ± 45.0 ml; adjusted treatment effect −13.25; 95% CI: −24.47 to −2.03; p = 0.021). The LVEF values from the 1-week study (9) correlated tightly with the 6-month values regardless of treatment group (Online Fig. 1). Long-term extension of scar tissue was 15.7 ± 10.4 g in the IV metoprolol group versus 18.6 ± 11.3

Table 1 MRI Data (6 Months After Infarction)

	IV Metoprolol Group (n = 101)	Control Group (n = 101)	Unadjusted		Adjusted for Stratification Variables	
			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

Values are mean ± SD unless otherwise indicated.

CI = confidence interval; IV = intravenous; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MRI = magnetic resonance imaging.

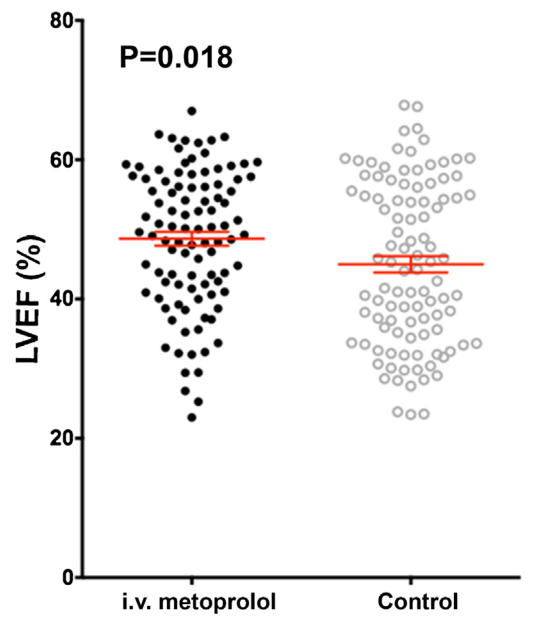

Figure 1 LVEF on MRI 6 Months After Infarction

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

g in the control group (treatment effect −2.89; 95% 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 cut-offs are illustrated in Figure 2A. The proportion of patients with depressed LVEF at 6 months was significantly lower in the IV metoprolol group (e.g., 11% vs. 27% with LVEF ≤35%, p = 0.006), and the treatment groups also differed in the distribution of patients by LVEF category. Treatment allocation to IV metoprolol was associated with being in a higher LVEF category (common odds ratio 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) (Fig. 2B). Pre-reperfusion metoprolol administration resulted in a significant reduction of patients with ICD Class I recommendation (7% vs. 20% in the control patients, a risk difference of 12.7% [95% CI: 3.2% to 22.3%]; p = 0.012; adjusted odds ratio 0.32; 95% CI: 0.13 to 0.81; p = 0.016). The number needed to treat to avoid 1 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 lost to follow-up having a minimum of 12 months follow-up. The incidence of the pre-specified MACE endpoint (composite of death, heart failure admission, reinfarction, and malignant arrhythmia) and its individual components by treatment group are summarized in Table 2. There were fewer numerical MACE events after pre-reperfusion IV metoprolol administration: 10.8% versus 18.3% in control group (adjusted hazard ratio [HR]: 0.55; 95% CI: 0.26 to 1.04; p = 0.065). This was mainly driven by a lower rate of readmission because of heart failure (2.2% in the IV metoprolol group vs. 6.9% in the control group; 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 IV metoprolol have a significantly higher long-term mean LVEF compared with control groups and are protected

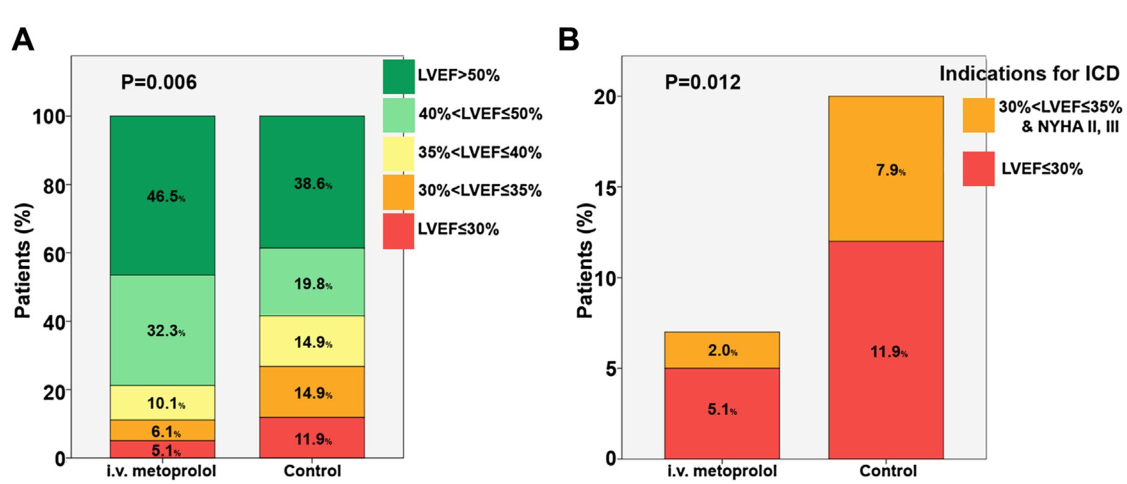

Figure 2 Follow-Up LVEF Categories and Indications for ICD According to Treatment Allocation

(A) Distribution of patients according to LVEF categories. Fisher exact test p = 0.026 and linear-by-linear association test p = 0.006. **(B)** Rate of formal indication (Class I recommendation in clinical guidelines) for ICD; see text. Fisher exact test p = 0.012. NYHA = New York Heart Association; other abbreviations as in Figure 1.

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Table 2 Clinical Events

	IV Metoprolol	Control	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)	
Noncardiac 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

Values are n (%). MACE 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.

AMI = acute myocardial infarction; IV = intravenous; MACE = major adverse cardiac event(s).

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 pharmacological cardioprotective 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 IV 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 IV metoprolol group in the 1-week post-infarction MRI study (9). As presented, the LVEF values from the 1-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 IV metoprolol are a consequence of the short-term beneficial effects detected at 1 week post-infarction. In order to determine whether the attrition of patients between the 1-week and 6-month MRI studies could have biased the results reported here, we evaluated the 1-week MRI LVEF in those patients who underwent the first scan, but not the 6-month follow-up (n = 18): median (first and third quartile) LVEF values were 53.0% (45.5% to 59.0%) in the IV metoprolol group versus 52.5% (46.8% to 62.0%) in the control group, excluding the possibility of selection bias introduced by patient attrition between 1-week and follow-up MRIs.

The long-term beneficial effects of pre-reperfusion IV metoprolol on LVEF were associated with a nonsignificant 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 (Remote Ischemic Conditioning in Primary PCI) trial, Sloth et al. (13) found that remote ischemic conditioning in STEMI seemed to improve long-term clinical outcomes. Their minimum follow-up was 3 years, whereas ours was 12 months. In fact, the survival curves in the CONDI trial showed a clear divergence after 2 years of follow-up. In a different study, Stone et al. (14) found that intracoronary abciximab in anterior STEMI resulted in a significant events reduction in the non–pre-specified time range (30 days to 12 months) post-infarction. Given the strong trend towards events reduction found in our trial, it is plausible that longer follow-up will reveal statistically significant differences. Similarly, non–pre-specified analyses of our study showed

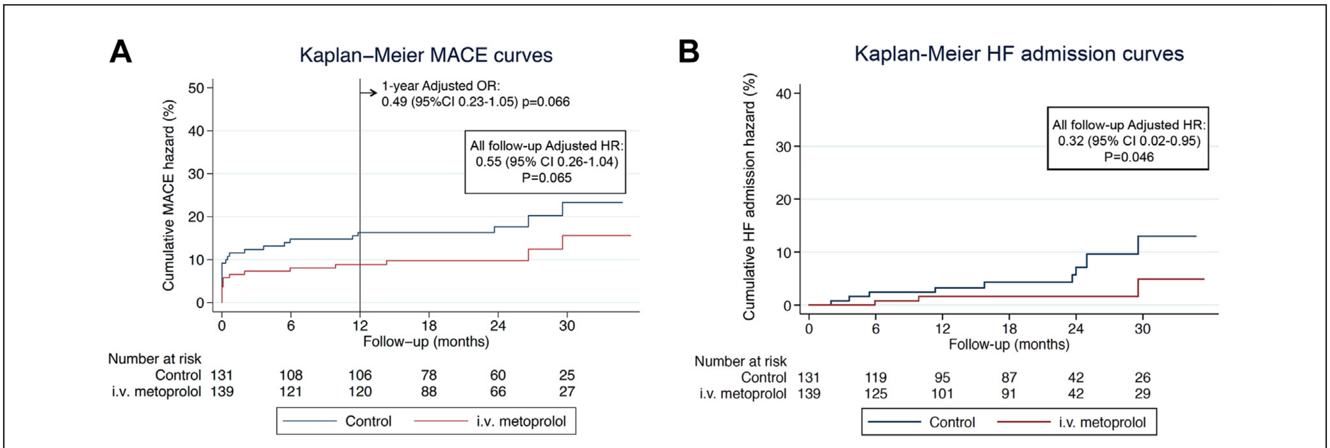

Figure 3 Follow-Up Clinical Endpoints

(A) Kaplan-Meier curves illustrating cumulative incidence of the pre-specified composite of death, admission as a result of heart failure (HF), reinfarction, or malignant ventricular arrhythmias. **(B)** Kaplan-Meier curves showing the cumulative incidence of readmission as a result of heart failure. CI = confidence interval; HR = hazard ratio; i.v. = intravenous; MACE = major adverse cardiac events.

statistical significance (heart failure admission HR: 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 IV 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 United States) results in higher long-term LVEF. Although 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 two-thirds less among the IV metoprolol patients. Overall, the rate of actual ICD implantation among cases with a formal indication was 33% (9 of 27, Table 2). This rate of ICD implantation is in agreement with other dedicated studies (rate between 30% and 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 IV metoprolol, as evaluated by MRI 1 week after infarction (9). At 6 months, total infarct size difference between groups had been attenuated (15.6 g in the IV metoprolol group vs. 18.6 g in the control group, $p = 0.07$). Thus, despite the 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 (1 week after STEMI).

Beta-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 IV administration before reperfusion is not encouraged, mainly because of the results of the COMMIT (Efficacy and Safety of Adding Clopidogrel to Aspirin or Use of Metoprolol in Myocardial Infarction) 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. By contrast, the METOCARD-CNIC trial recruited Killip class ≤II patients presenting with systolic blood pressure ≥120 mm Hg, heart rate ≥60 beats/min, and reperfused by pPCI within 6 h of infarct onset. Subgroup analyses of the COMMIT trial (28) suggested that patients fitting the inclusion criteria of the METOCARD-CNIC trial benefited from early IV 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 <1 month. It is plausible that longer follow-up of the COMMIT trial would show additional benefit of early IV metoprolol in survivors. Thus, an important lesson from the COMMIT trial is that not all STEMI patients benefit from very early IV metoprolol, a deduction supported by the results reported here.

Study limitations. This trial was not powered to detect differences in hard clinical endpoints, and thus, the results on this outcome should be taken with caution.

Conclusions

Intravenous metoprolol administered before reperfusion results in higher long-term LVEF and a lower incidence of post-infarction severe LVEF depression in anterior STEMI patients undergoing primary PCI during the first 6 h 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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Key Words: beta-adrenergic receptors ▪ heart failure ▪ ICD ▪ infarct size ▪ LVEF ▪ magnetic resonance imaging ▪ metoprolol ▪ myocardial infarction ▪ PCI ▪ STEMI.

APPENDIX

For a supplemental table and figure, please see the online version of this article.