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ORIGINAL INVESTIGATIONS

Impact of the Timing of Metoprolol Administration During STEMI on Infarct Size and Ventricular Function

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ABSTRACT

BACKGROUND Pre-reperfusion administration of intravenous (IV) metoprolol reduces infarct size in ST-segment elevation myocardial infarction (STEMI).

OBJECTIVES This study sought to determine how this cardioprotective effect is influenced by the timing of metoprolol therapy having either a long or short metoprolol bolus-to-reperfusion interval.

METHODS We performed a post hoc analysis of the METOCARD-CNIC (effect of METOprolol of CARDioproteCtioN during an acute myocardial InfarCtion) trial, which randomized anterior STEMI patients to IV metoprolol or control before mechanical reperfusion. Treated patients were divided into short- and long-interval groups, split by the median time from 15 mg metoprolol bolus to reperfusion. We also performed a controlled validation study in 51 pigs subjected to 45 min ischemia/reperfusion. Pigs were allocated to IV metoprolol with a long (−25 min) or short (−5 min) pre-perfusion interval, IV metoprolol post-reperfusion (+60 min), or IV vehicle. Cardiac magnetic resonance (CMR) was performed in the acute and chronic phases in both clinical and experimental settings.

RESULTS For 218 patients (105 receiving IV metoprolol), the median time from 15 mg metoprolol bolus to reperfusion was 53 min. Compared with patients in the short-interval group, those with longer metoprolol exposure had smaller infarcts (22.9 g vs. 28.1 g; $p = 0.06$) and higher left ventricular ejection fraction (LVEF) (48.3% vs. 43.9%; $p = 0.019$) on day 5 CMR. These differences occurred despite total ischemic time being significantly longer in the long-interval group (214 min vs. 160 min; $p < 0.001$). There was no between-group difference in the time from symptom onset to metoprolol bolus. In the animal study, the long-interval group (IV metoprolol 25 min before reperfusion) had the smallest infarcts (day 7 CMR) and highest long-term LVEF (day 45 CMR).

CONCLUSIONS In anterior STEMI patients undergoing primary angioplasty, the sooner IV metoprolol is administered in the course of infarction, the smaller the infarct and the higher the LVEF. These hypothesis-generating clinical data are supported by a dedicated experimental large animal study. (J Am Coll Cardiol 2016;67:2093–104)

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

HF = heart failure

LV = left ventricular

LVEF = left ventricular ejection fraction

MI = myocardial infarction

MIS = myocardial infarct size

PPCI = primary percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

Timely reperfusion is the mainstay treatment for patients presenting with ST-segment elevation myocardial infarction (STEMI). The preferred reperfusion strategy is primary percutaneous coronary intervention (PPCI), ideally within 120 min of STEMI diagnosis (1,2). Adjunct treatments for patients undergoing PPCI are mainly aimed at preventing thrombotic complications, not reducing myocardial loss per se. Myocardial infarct size (MIS) is a major determinant of post-STEMI mortality and morbidity (3). Patients with a large MIS and associated left ventricular (LV) systolic dysfunction are at high risk of long-term heart failure (HF) readmission and sudden death (4). Indeed, post-STEMI severe LV dysfunction is a Class I indication for insertion of an implantable cardioverter-defibrillator (ICD) (5).

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Administration of 15 mg intravenous (IV) metoprolol before reperfusion in STEMI patients undergoing PPCI was recently shown to reduce cardiac magnetic resonance (CMR)–measured infarct size in the METOCARD-CNIC (effect of METOprolol of CARDioproteCtioN during an acute myocardial InfarCtion) trial (6). Besides reducing acute infarct size, pre-reperfusion 15 mg metoprolol administration was associated with improved long-term LV systolic function, fewer indications for ICD insertion, and fewer HF readmissions (7). In the METOCARD-CNIC trial, patients were recruited and randomized to 15 mg IV metoprolol or control before arterial access, either during ambulance transit or at the PPCI hospital. Patients allocated to IV metoprolol therefore received the drug at varying intervals before reperfusion. No previous evaluation has considered the cardioprotective effect of the timing of pre-reperfusion metoprolol administration (long or short pre-reperfusion interval). Identifying the best timing and setting for metoprolol administration for attaining cardioprotection (the out-of-hospital setting or the more controlled hospital/catheterization laboratory environment) has implications for the chain of care for STEMI patients.

Here we present a post hoc analysis of the METOCARD-CNIC trial and a subsequent large animal ischemia/reperfusion experimental study designed to validate the hypothesis generated with the clinical trial data. In both cases, the effect of the timing of metoprolol administration on cardioprotection (MIS and left ventricular ejection fraction [LVEF]) was evaluated by state-of-the-art CMR.

METHODS

A translational project was designed to evaluate how the timing of pre-reperfusion IV metoprolol administration affects cardioprotection in STEMI patients. First, a hypothesis was generated from an exploratory clinical study (post hoc analysis of METOCARD-CNIC clinical trial). Then, a controlled experimental study in a large animal model of acute myocardial infarction (MI) was designed to confirm the hypothesis generated in the clinical study.

Patients with anterior STEMI undergoing PPCI were recruited within the METOCARD-CNIC trial (6). Patients underwent 2 CMR studies 5 to 7 days and 6 months after STEMI. Inclusion/exclusion criteria and the study protocol have been published previously (8). Briefly, METOCARD-CNIC is a randomized clinical trial that recruited patients with first anterior STEMI who presented early (<6 h from symptom onset) and were undergoing PPCI. Patients were randomized to receive 15 mg IV metoprolol or control before reperfusion. The primary endpoint was MIS assessed by CMR at

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5 to 7 days post-infarction (6); secondary endpoints included LV performance assessed by CMR at 6 months post-infarction (7). A total of 270 patients were recruited to the METOCARD-CNIC trial, 220 of whom underwent CMR for MIS quantification. Patients with complete 5- to 7-day CMR and time period data (n = 218) were included in this analysis. To study the effect of metoprolol timing on cardioprotection, we divided patients allocated to IV metoprolol into 2 groups according to whether the metoprolol-to-reperfusion interval was longer (long-interval group) or shorter (short-interval group) than the median value.

The CMR protocol and methods for imaging analysis are described in detail elsewhere (8).

ANIMAL STUDY DESIGN. Experiments were performed in castrated male Large-White pigs, and MI was induced experimentally by closed-chest, 45-min left anterior descending (LAD) coronary artery occlusion followed by chronic reperfusion. Animals were allocated 1:1:1:1 in a blinded fashion by adaptive randomization to the following treatments: 1) vehicle (control-vehicle group); 2) IV metoprolol (0.75 mg/kg) 25 min before reperfusion (long-interval group); 3) the same metoprolol bolus given 5 min before reperfusion (short-interval group); and 4) IV metoprolol held until 60 min after reperfusion (post-reperfusion group). Metoprolol and vehicle were prepared in numbered syringes before MI induction and administered by blinded operators at each time point according to the animal's allocation. To ensure blinded intervention and analysis, all animals received 3 injections: 1 at each treatment time point, with metoprolol reserved for a single injection on the basis of randomized group. To mimic the clinical scenario, all animals (including those allocated to control-vehicle) received 50 mg of oral metoprolol daily throughout the duration of the study, starting 1 day after reperfusion. The study protocol was approved by the Institutional Animal Research Committee and conducted in accordance with recommendations of the Guide for the Care and Use of Laboratory Animals.

MI PROCEDURE AND INVASIVE HEMODYNAMIC ASSESSMENT. The protocol for MI induction has been detailed elsewhere (9–11). Briefly, the LAD coronary artery immediately distal to the origin of the first diagonal branch was occluded for 45 min with an angioplasty balloon introduced via the percutaneous femoral approach. Balloon location and state of inflation were monitored regularly by angiography. After balloon deflation, a coronary angiogram was recorded to confirm patency of the coronary artery. In cases of ventricular fibrillation (VF), a biphasic defibrillator was used to deliver nonsynchronized shocks as needed. Post-operative animal recovery and care were carried out by CNIC veterinarians and technicians.

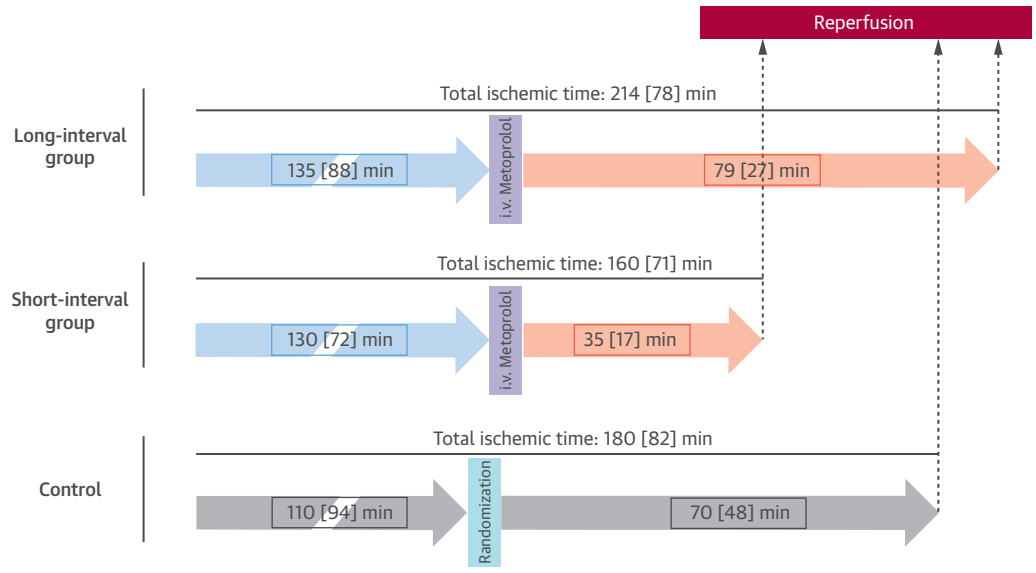
Hemodynamic measures were assessed at 3 time points during the MI procedure: at baseline, after 40 min of ongoing ischemia (5 min before reperfusion), and at 45 min post-reperfusion. Right heart catheterization was performed with a Swan-Ganz catheter introduced percutaneously through the femoral vein under fluoroscopy in the catheterization laboratory. Hemodynamic measurements included systolic, mean, and diastolic systemic artery pressure; systolic, mean, and diastolic pulmonary artery pressure; pulmonary capillary wedge pressure; and right ventricle cardiac output assessed by the thermodilution method.

ANIMAL CMR PROTOCOL. CMR studies were performed 7 and 45 days after acute MI to assess MIS and LV performance. Pigs were anesthetized, and anesthesia was maintained by continuous intravenous infusion of midazolam. CMR studies were performed using a 3-T Achieva Tx whole body scanner (Philips Medical Systems, Best, the Netherlands) equipped with a 32-element cardiac phased-array surface coil. Images were acquired with the use of electrocardiogram gating by operators blinded to the study arm. Segmented cine steady-state free precession was performed to acquire 11 to 13 contiguous short-axis slices covering the heart from the base to the apex to evaluate global and regional LV motion. CMR parameters can be found in the Online Appendix.

All CMR images were analyzed using dedicated software (QMass MR version 7.6, Medis, Leiden, the Netherlands). Images were analyzed by 2 experienced observers (J.M.G.-R. and C.G.-A.) with vast experience in CMR analysis and blinded to study allocation. The analysis protocol has been detailed elsewhere (9). Briefly, LV cardiac borders were traced in each short-axis cine image to obtain LV end-diastolic volume, LV end-systolic volume, and LVEF. LV volumes and mass were normalized to body surface area according to Brody's formula (12). CMR post-processing is described in the Online Appendix.

STATISTICAL ANALYSIS. The distribution of continuous variables was analyzed with graphical methods. For normally distributed variables, results are expressed as mean ± SD; otherwise they are represented as median (interquartile range [IQR]). Categorical variables are expressed as absolute frequency (%). Comparisons among groups were performed by parametric methods (nonpaired Student *t* test and 1-way analysis of variance, applying Welch's

FIGURE 1 Time Interval Periods by Group



Long and short intervals refer to the time from metoprolol administration to reperfusion, split by the median value. Values are median [interquartile range]. i.v. = intravenous.

correction when needed) or nonparametric methods (Kruskal-Wallis, Mann-Whitney *U*, and Fisher exact test) as appropriate. In the clinical study, time from IV metoprolol to reperfusion was converted to a categorical variable by using a median split to generate 2 groups: those with a metoprolol-to-reperfusion interval shorter than the median (short-interval group) and longer than the median (long-interval group); multivariate linear regression methods, adjusting for total ischemic time, were used for comparisons among groups (control, short-interval, and long-interval).

To check consistency of results, 2 sensitivity analyses were performed. First, linear regression was used to assess the association of metoprolol-to-reperfusion time (as a continuous variable) with MIS and other LV performance parameters. Second, because metoprolol-to-reperfusion time was available only for patients who received IV metoprolol, a multivariate linear regression analysis was performed to assess the interaction between treatment group and time from randomization to reperfusion, which was available for the whole cohort, including control subjects (Figure 1 for time-period definitions). Sequential Holm-Bonferroni correction for pre-specified multiple comparisons was applied. Differences were considered statistically significant at p value <0.05 (2-tailed).

Additional information about the methods used is found in the Online Appendix.

RESULTS

CLINICAL STUDY. The clinical study population consisted of the 220 patients in the METOCARD-CNIC clinical trial in whom MIS was assessed by CMR at day 5 to 7 post-STEMI. Time period data were incomplete for 2 patients, who thus were excluded from this analysis. Therefore, the final cohort in the clinical study included 218 patients. In the overall cohort, the median time from symptom onset to reperfusion was 185 min (IQR: 144 to 225 min), whereas median time from randomization to reperfusion was 70 min (IQR: 45 to 94 min). A diagram showing all relevant time intervals is presented in Figure 1. For the analysis, the intervention group was split according to the median time from IV metoprolol to reperfusion (53 min), thus defining long- and short-interval groups. Final group sizes were 52, 53, and 113 patients for the long-interval, short-interval, and control groups, respectively. Total ischemic time was 214 min (IQR: 169 to 248 min) in the long-interval group and 160 min (IQR: 135 to 206 min) in the short-interval group. Baseline characteristics of the clinical study population are presented in Table 1.

TIME-BASED EFFECT OF IV METOPROLOL ON MIS. Infarct size was calculated as percentage of left ventricular mass (%LV). Mean values in the long-interval, short-interval, and control groups were 19.3 ± 10.7%,

22.9 ± 12.2%, and 25.2 ± 13.8%, respectively (p = 0.009); the adjusted treatment effect of long-interval versus control was −5.6% (95% confidence interval [CI]: −10.1% to −1.1%; p = 0.016) and that of long-interval versus short-interval was −4.5% (95% CI: −9.4% to 0.5%; p = 0.076) (Figures 2A and 2B). Consistently, mean LVEF assessed at day 5 CMR in the long-interval, short-interval, and control groups was 48.3 ± 8.5%, 43.9 ± 9.8%, and 43.4 ± 10.3%, respectively; the adjusted treatment effect of long-interval versus control was 5.1% (95% CI: 1.7% to 8.4%; p = 0.003) and that of long-interval versus short-interval was 4.5% (95% CI: 0.8% to 8.3%; p = 0.019) (Figure 2C). At 6-month CMR, the beneficial effect of early IV metoprolol administration on LVEF was maintained, with an adjusted treatment effect of long-interval versus control of 4.6% (95% CI: 0.6% to 8.6%; p = 0.023), and an adjusted treatment effect of long-interval versus short-interval of 3% (95% CI: −1.3% to 7.2%; p = 0.172). Complete CMR data are presented in Table 2.

The consistency of the results was checked with 2 sensitivity analyses. First, analysis of patients allocated to IV metoprolol showed that the sooner the drug was administered, the smaller the MIS and higher the LVEF: every 10 min of "on-board" metoprolol was associated with an MIS reduction of 1.1 g (95% CI: −2.1 to 0.0 g; p = 0.049) and an increase in LVEF of 0.6% (95% CI: −0.1% to 1.2%; p = 0.092) at 5 days post-reperfusion (Table 3, Figure 3A). Second, the analysis was replicated in the complete cohort, using randomization-to-reperfusion time instead of IV metoprolol-to-reperfusion time (see the Methods section); this analysis showed an effect modification (interaction) between IV metoprolol treatment and randomization-to-reperfusion time (Figure 3B).

ANIMAL STUDY. Experimental MI was induced in 51 Large-White pigs (31 ± 2.4 kg) by percutaneous angioplasty (45 min of balloon-mediated, LAD coronary occlusion) followed by reperfusion. Nine animals died before completing the 7-day CMR (3 allocated to the control-vehicle group, 2 to long-interval metoprolol, 1 to short-interval metoprolol, and 3 to post-reperfusion metoprolol). Thus, the final group sizes were 11, 12, 10, and 9 animals for the long-interval, short-interval, post-reperfusion, and vehicle groups, respectively. Six additional animals died suddenly before completing the 45-day CMR. Table 4 contains final numbers of animals per group.

There were no among-group differences in hemodynamic status at baseline, and the timing of IV metoprolol administration was not associated with stable hemodynamic differences among treatment groups. Complete hemodynamic data are presented in Online Table 1.

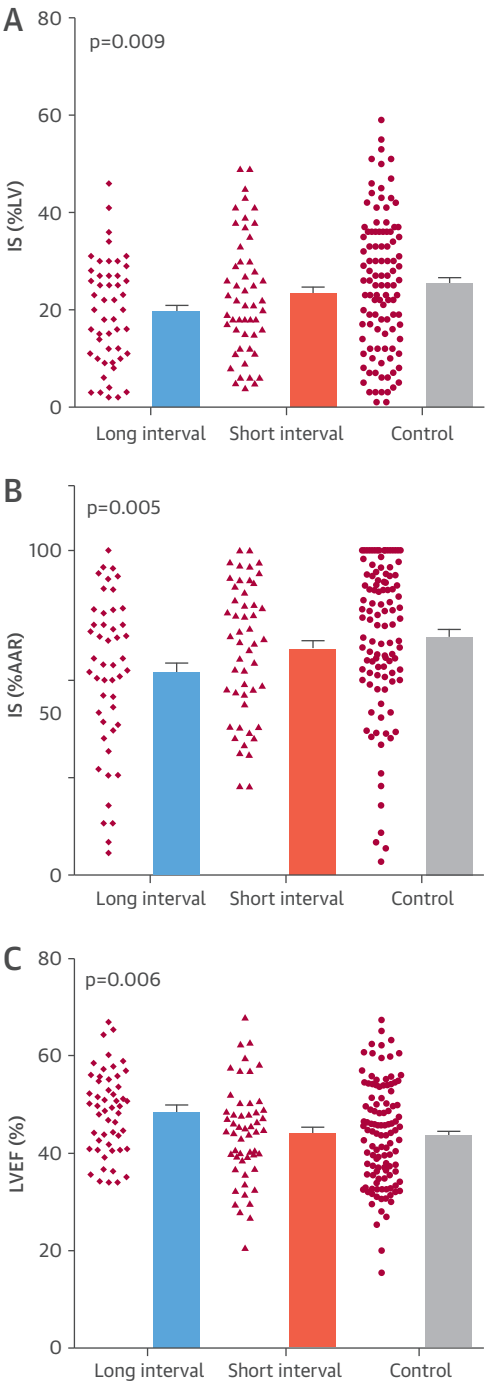
TABLE 1 Baseline Characteristics of the Clinical Study Cohort

	Long Interval (n = 52)	Short Interval (n = 53)	Control (n = 113)	p Value
Age, yrs	58.1 ± 12.8	59.0 ± 12.5	58.6 ± 10.4	0.915
Male	44 (84.6)	47 (88.7)	99 (87.6)	0.832
Body mass index, kg/m^2	27.7 ± 3.2	27.3 ± 3.8	27.8 ± 3.9	0.741
Hypertension	19 (37.3)	20 (37.7)	47 (41.6)	0.869
Smoking				0.964
Current	27 (52.9)	27 (50.9)	60 (53.1)	–
Former (0–10 yrs prior)	6 (11.8)	7 (13.2)	11 (9.7)	–
Dyslipidemia	26 (51.0)	18 (34.0)	46 (40.7)	0.205
Diabetes	11 (21.6)	11 (20.8)	21 (18.6)	0.877
Total ischemic time, min	214 (169–248)	160 (135–206)	180 (143–225)	**0.001**
Time from symptom onset to metoprolol bolus, min	135 (77–165)	130 (105–176)	–	0.430
Time from randomization to PCI, min	95 (84–116)	45 (30–55)	70 (42–90)	**<0.001**
TIMI flow grade 0–1 before PCI	39 (75.0)	45 (84.9)	92 (81.4)	0.425
TIMI flow grade 3 after PCI	33 (63.5)	41 (77.4)	84 (73.4)	0.236
Killip-Kimball I	48 (92.3)	48 (90.6)	100 (88.5)	0.976
Systolic blood pressure at recruitment, mm Hg	144 ± 20	141 ± 16	142 ± 19	0.795
Diastolic blood pressure at recruitment, mm Hg	93 ± 15	86 ± 17	87 ± 15	**0.035**
Heart rate at recruitment, beats/min	80 ± 12	84 ± 15	82 ± 14	0.478
Systolic blood pressure after IV metoprolol, mm Hg	131 ± 19	125 ± 16	–	0.124
Diastolic blood pressure after IV metoprolol, mm Hg	85 ± 17	80 ± 13	–	0.063
Heart rate after IV metoprolol, beats/min	68 ± 8	69 ± 15	–	0.497

Values are mean ± SD, n (%), or median (interquartile range). **Bold** indicates statistical significance.
IV = intravenous; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

CARDIOPROTECTION OF IV METOPROLOL AND TIMING OF ADMINISTRATION. On day 7 CMR, infarcts were significantly smaller in the long-interval group: median 23.3% (IQR: 20.1% to 24.2%) (%LV) versus 26.7% (IQR: 23.1% to 32.1%) in the short-interval group (p = 0.028) and 27.3% (IQR: 23.4% to 31.1%) in the control-vehicle group (p = 0.049) (Figure 4A). Consistent with these data, the long-interval group showed more favorable LV remodeling at day-45 CMR: pigs receiving IV metoprolol early during the ongoing ischemia had smaller LV volumes and higher LVEF than those in the control-vehicle group (LVEF: median 38.9% [IQR: 32.6% to 45.3%] vs. 29.1% [IQR: 25.8% to 35.4%]; p = 0.042) (Figure 4C). Conversely, administration of IV metoprolol just before reperfusion had no significant cardioprotective effect: MIS on day-7 CMR did not differ between the short-interval and control-vehicle groups (26.7% [IQR: 23.1% to 32.1%] vs. 27.3% [IQR: 23.4% to 31.1%]; p = 1.0) (Figure 4A). Full CMR-derived data are presented in Table 4.

FIGURE 2 MIS and LVEF Assessed by CMR



At 5 days post-infarction, cardiac magnetic resonance imaging (CMR) showed myocardial infarct size (IS) expressed as **(A)** a percentage of left ventricle mass (%LV) and **(B)** as a percentage of the area at risk (AAR); **(C)** shows left ventricular ejection fraction (LVEF). **Dots** indicate individual data, **bars** indicate mean (standard error of the mean). MIS = myocardial infarct size.

DISCUSSION

In this study, we evaluated the effect of different pre-reperfusion timings of IV metoprolol on cardioprotection (infarct size and LVEF) in a post hoc analysis of the METOCARD-CNIC trial and in a translational model of ischemia/reperfusion. In the clinical trial, we found that the longer the time between 15-mg IV metoprolol administration and reperfusion, the greater the MIS reduction and the better the LV function at 6-month follow-up (**Central Illustration**). After reviewing these hypothesis-generating data, we conducted a large animal (pig) study specifically designed to confirm the hypothesis. Pigs undergoing experimental myocardial ischemia/reperfusion were randomized to receive vehicle or IV metoprolol with a long or short interval before reperfusion, or after reperfusion. Animals receiving IV metoprolol long before reperfusion had significantly smaller infarcts at short term and a better long-term LV performance than the other groups, consistent with the results of the clinical study. Our results suggested that, in patients with no contraindications, the sooner metoprolol is injected in the course of STEMI, the greater the protection against myocardial death.

We previously demonstrated, using the same animal model, that metoprolol reduces infarct size (13), but only when administered before reperfusion (14). These studies, which set the basis for the METOCARD-CNIC trial, left unanswered the question of whether the infarct-limiting effects of metoprolol are affected by the timing of pre-reperfusion administration, a question tackled in the present combined clinical-experimental study. To answer the main question posed in this study, we converted the time from IV metoprolol to reperfusion into a categorical variable by splitting treated patients into 2 groups according to the median time between metoprolol bolus and reperfusion (53 min). Patients in the long-interval group had smaller infarcts than those receiving metoprolol closer to the time of reperfusion. To exclude the possibility that this artificial division might have biased the results, we also performed a continuous analysis, which documented a negative correlation between metoprolol-to-reperfusion interval and MIS (**Figure 3A**). The animal study results agreed with both clinical analyses: pigs receiving metoprolol long before reperfusion (at midischemia) had significantly smaller infarcts and higher long-term LVEF than animals receiving metoprolol just before or after reperfusion and control subjects. The similar findings from 3 separate analyses provide strong support for the conclusions reached.

TABLE 2 Clinical Study: CMR-Derived Parameters

						Long Interval			
				ANOVA	Linear Trend	vs. Control*		vs. Short Interval*	
	Long Interval	Short Interval	Control	p Value	p Value	Difference (95% CI)	p Value	Difference (95% CI)	p Value
5-day CMR									
n	52	53	113						
LVEDVi, ml/1.73 m^2	149.6 ± 33.7	153.4 ± 23.3	154.8 ± 31.5	0.601	–	−4.6 (−15.6 to 6.5)	–	−4.9 (−6.8 to 7)	–
LVESVi, ml/1.73 m^2	78.7 ± 26.4	86.9 ± 23.5	89.3 ± 29.7	**0.079**	**0.031**	−10.4 (−20.3 to −0.5)	**0.039**	−9.3 (−19.7 to 1)	0.077
LV mass, g	106.8 ± 23	111 ± 26.5	112.9 ± 26.1	0.366	–	−6.6 (−15.2 to 2.0)	–	−3.7 (−14.0 to 6.5)	–
AAR, %LV	29.1 ± 11.5	30.7 ± 11.9	31.3 ± 12.8	0.601	–	−2.0 (−6.2 to 2.3)	–	−1.1 (−602 to 3.8)	–
Infarct size, g	22.9 ± 14	28.1 ± 16.3	32.4 ± 22.2	**0.014**	**0.003**	−9.7 (−16.6 to −2.9)	**0.006**	−6.0 (−12.3 to 0.3)	0.06
Infarct size, %LV	19.3 ± 10.7	22.9 ± 12.2	25.2 ± 13.8	**0.03**	**0.009**	−5.6 (−10.1 to −1.1)	**0.016**	−4.5 (−9.4 to 0.5)	0.076
Infarct size, %AAR	61.8 ± 24.1	69.3 ± 20.5	73.2 ± 22.9	**0.016**	**0.005**	−11.5 (−19.7 to −3.3)	**0.006**	−10.6 (−19.9 to −1.3)	**0.026**
LVEF, %	48.3 ± 8.5	43.9 ± 9.8	43.4 ± 10.3	**0.011**	**0.006**	5.1 (1.7 to 8.4)	**0.003**	4.5 (0.8 to 8.3)	**0.019**
6-month CMR									
n	46	51	100						
LVEDVi, ml/1.73 m^2	165.4 (34.8)	169.8 (32.6)	176 (38)	0.227	–	−9.9 (−23.1 to 3.4)	–	−7.7 (−21.9 to 6.6)	–
LVESVi, ml/1.73 m^2	84.9 ± 30.9	91.7 ± 35.1	99.7 ± 39.1	**0.064**	**0.019**	−13.8 (−26.9 to −0.7)	**0.040**	−10 (−24.1 to 4.1)	0.162
Infarct size, g	14.5 ± 11.4	17.1 ± 9.7	18.6 ± 11.4	0.121	–	−3.9 (−8.1 to 0.3)	–	−3.5 (−8.1 to 1.1)	–
Infarct size, %LV	13.9 ± 9.6	17.5 ± 9.5	18.3 ± 9.9	**0.045**	**0.019**	−4.2 (−7.8 to −0.6)	**0.023**	−4.4 (−8.5 to −0.2)	**0.038**
Infarct size, %AAR†	45.2 ± 25	53.1 ± 19.3	55.5 ± 20.8	**0.032**	**0.012**	−10.6 (−18.8 to −2.4)	**0.011**	−11.6 (−21 to −2.2)	**0.015**
LVEF, %	49.9 ± 11.1	47.4 ± 10.5	45 ± 11.8	**0.038**	**0.011**	4.6 (0.6 to 8.6)	**0.023**	3.0 (−1.3 to 7.2)	0.172

Values are mean ± SD unless otherwise indicated. **Bold** indicates statistical significance. *Adjusted by total ischemic time. †Infarct size normalized by myocardium at risk at 5-day CMR.

AAR = area at risk; ANOVA = analysis of variance; CI = confidence interval; CMR = cardiac magnetic resonance imaging; LV = left ventricle; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume index.

Administration of IV β-blockers is recommended by the American College of Cardiology/American Heart Association guidelines (Class IIa, Level of Evidence: B) as well as the European Society of Cardiology guidelines (Class IIa, Level of Evidence: B) for STEMI patients who are without contraindications and are hypertensive (1,2) or show "signs of ongoing ischemia" (1). Both clinical guidelines specify administration of IV β-blockers at the time of presentation; however, there have been no data to support this recommended timing in patients reperfused by PPCI. The data presented here confirm the value of early IV administration of β-blockers recommended by the clinical guidelines. Obviously, this early administration is only of value if the IV route is used. However, despite IV β-blocker administration being a Class IIa recommendation, penetrance in real-world data is extremely low (15–17), most likely due to the potential side effects of IV β-blockers when administered early in the course of STEMI (18). In the METOCARD-CNIC clinical trial, exclusion criteria included signs of HF, systolic blood pressure <120 mm Hg, or any degree of atrioventricular block (8). Patients in the IV metoprolol and control arms showed no differences in the incidence of side effects, including cardiogenic shock (6).

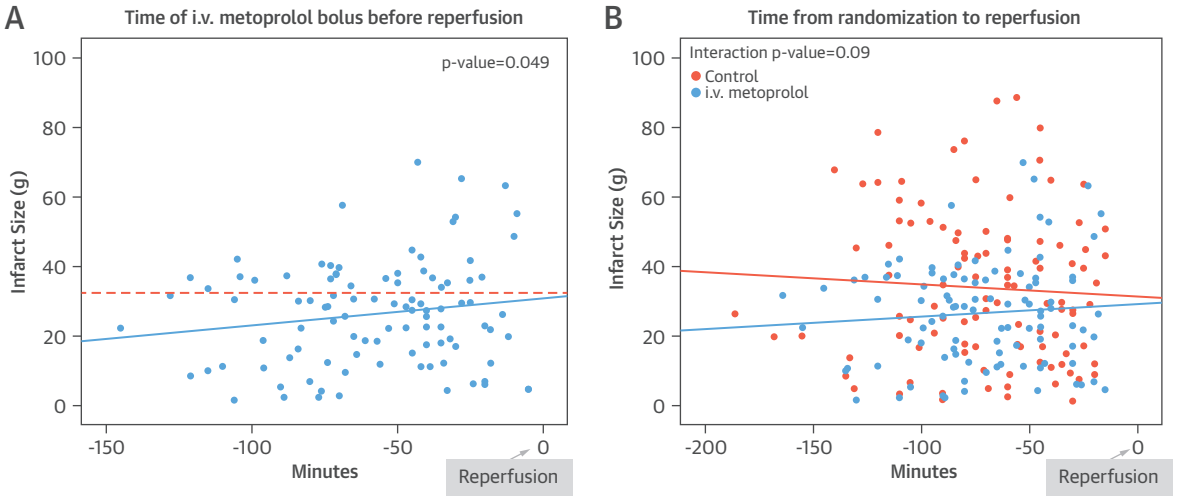
TABLE 3 Sensitivity Analysis of CMR-Derived Parameters in Patients Receiving IV Metoprolol

	Effect on LV Performance Per 10 min "Onboard" Metoprolol Duration*	
	Adjusted Mean Difference (95% CI)	p Value
5-day CMR		
LVEDVi, ml/1.73 m^2	−1.5 (−3.5 to 0.5)	0.144
LVESVi, ml/1.73 m^2	−1.5 (−3.3 to 0.2)	0.088
LV mass, g	−1.1 (−2.8 to 0.7)	0.225
AAR, %LV	−0.2 (−1.1 to 0.6)	0.584
Infarct size, g	−1.1 (−2.1 to 0.0)	**0.049**
Infarct size, %LV	−0.8 (−1.6 to 0.1)	0.071
Infarct size, %AAR	−1.9 (−3.5 to −0.3)	**0.022**
LVEF, %	0.6 (−0.1 to 1.2)	0.092
6-month CMR		
LVEDVi, ml/1.73 m^2	−1.3 (−3.9 to 1.2)	0.297
LVESVi, ml/1.73 m^2	−1.6 (−4.1 to 0.9)	0.214
Infarct size, g	−0.7 (−1.5 to 0.1)	0.071
Infarct size, %LV	−0.8 (−1.5 to −0.1)	**0.032**
Infarct size, %AAR†	−2.2 (−3.8 to −0.5)	**0.012**
LVEF, %	0.5 (−0.2 to 1.3)	0.162

Bold indicates statistical significance. *In the IV metoprolol group (adjusted for total ischemic time). †Infarct size normalized by myocardium at risk at 5-day CMR.

Abbreviations as in Tables 1 and 2.

FIGURE 3 Association Between Metoprolol Bolus-to-Reperfusion Time Interval and Infarct Size



Per sensitivity analyses, **(A)** myocardial infarct size (MIS) decreases in a linear fashion the longer the time from intravenous (IV) metoprolol bolus to percutaneous coronary intervention (PCI) within the subset of patients receiving IV metoprolol. **Blue dots** indicate individual data in the metoprolol-treated group; **blue line** indicates linear relationship between MIS and the time interval from IV metoprolol bolus to PCI; **dashed orange line** indicates mean MIS value for the control group. **(B)** An effect modification was also seen between IV metoprolol treatment and time from randomization to PCI in the complete clinical-study cohort. **Blue dots** indicate individual data in the metoprolol-treated group; **orange dots** indicate individual data in the complete cohort; **lines** indicate linear relation between MIS and time from randomization to PCI. i.v. = intravenous.

Absence of increased metoprolol-related side effects was also apparent in a separate analysis of the subgroup of patients recruited in the out-of-hospital setting (19).

The METOCARD-CNIC clinical trial was the first to compare 2 different strategies of β-blocker administration/initiation in STEMI patients undergoing PPCI: IV metoprolol before reperfusion versus

TABLE 4 Animal Study: CMR-Derived Parameters

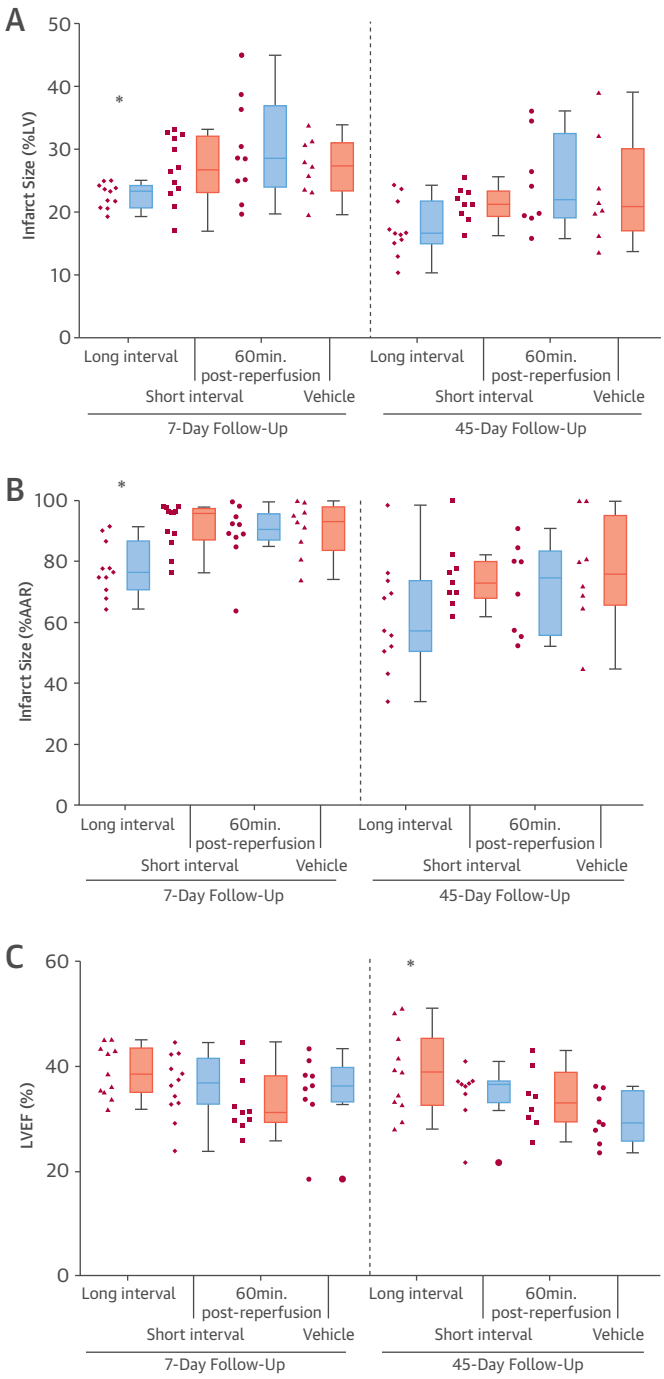
	60 Min					Long Interval	
	Long Interval	Short Interval	Post-Reperfusion	Vehicle	p Value	p Value vs. Vehicle	p Value vs. Short Interval
7-day CMR							
n	11	12	10	9			
LVEDV, ml/m^2	131.4 (120.1–137.9)	132.4 (117.8–139.5)	139.5 (108.9–161.3)	132.1 (121–140.3)	0.909	–	–
LVESV, ml/m^2	79.5 (69.1–91.4)	83.1 (73.5–93.7)	91.3 (74.1–112.4)	81.4 (77.4–94.9)	0.476	–	–
LVEF, %	38.6 (35.1–43.5)	36.9 (32.8–41.6)	31.3 (29.3–38.2)	36.3 (33.3–39.7)	0.102	–	–
AAR, %LV	30.3 (28.8–31.8)	25.7 (23.9–32.8)	31.9 (25–42.8)	29.9 (27.1–33)	0.63	–	–
Infarct size, %LV	23.3 (20.1–24.2)	26.7 (23.1–32.1)	28.6 (24–37)	27.3 (23.4–31.1)	**0.034**	**0.028**	**0.049**
Infarct size, %AAR	76.6 (70.8–86.7)	96.5 (87.1–100)	90.7 (87.3–95.6)	93.1 (83.8–97.9)	**0.005**	**0.007**	**0.004**
45-day CMR							
n	11	9	8	8			
LVEDV, ml/m^2	127 (121.8–132.8)	144.2 (127.8–149.3)	144.1 (127.8–171.4)	148.7 (138–189.1)	**0.030**	**0.012**	0.074
LVESV, ml/m^2	77.6 (67.9–84.7)	91.8 (82.5–98)	90.2 (85.1–118.2)	105.8 (90.8–142.7)	**0.013**	**0.012**	0.063
LVEF, %	38.9 (32.6–45.3)	36.5 (33.2–37.2)	33 (29.6–38.8)	29.1 (25.8–35.4)	**0.058**	**0.042**	0.342
Infarct size, %LV	16.6 (15–21.7)	21.2 (19.3–23.3)	22 (19.1–32.5)	20.9 (17.1–30.1)	0.115	–	–
Infarct size, %AAR*	57.2 (50.5–73.7)	73.0 (58.1–79.9)	74.6 (55.8–83.4)	75.9 (65.8–95.2)	0.148	–	–

Values are median (interquartile range) unless otherwise indicated. **Bold** indicates statistical significance. *Infarct size normalized by myocardium at risk at 7-day CMR. LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; other abbreviations as in Table 2.

oral metoprolol after reperfusion (8). The IV pre-reperfusion metoprolol strategy was associated with smaller infarcts (6), improved long-term LVEF, and fewer cases of chronic severe LV dysfunction and consequent ICD indications (7). The present study added complementary information showing that a longer period of onboard metoprolol before reperfusion resulted in stronger cardioprotection. Infarcts were significantly smaller in the long- versus short-interval patient group, and at 6-month follow-up, only the long-interval group showed a significantly higher LVEF than the control group. Surprisingly, these effects were observed even though total ischemia duration (time from symptom onset to reperfusion) was significantly longer in the long-interval group than in the short-interval group (214 min vs. 160 min; $p < 0.001$). Ischemia duration at the time of bolus administration was similar in the long- and short-interval groups (135 min vs. 130 min), so the difference in total ischemia duration was due to the difference in the bolus-to-reperfusion interval. The likely explanation for this difference is that patients in the short-interval group were diagnosed either at the PPCI hospital or close to it, whereas patients in the long-interval group were likely diagnosed far from the PPCI center.

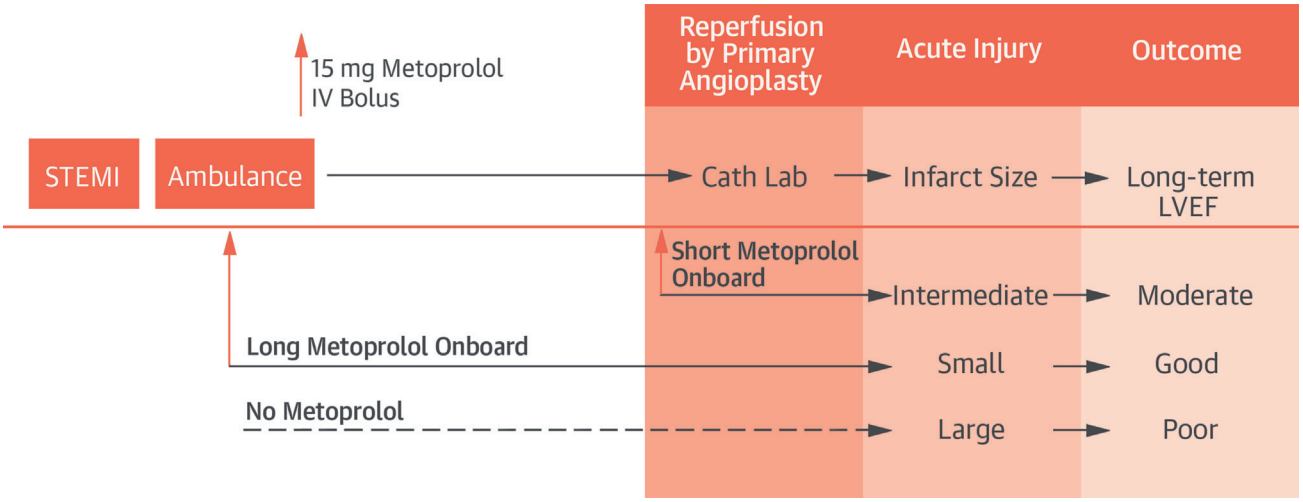
The results thus indicated that early IV metoprolol has a greater cardioprotective effect when followed by a period of continued ischemia before reperfusion, a finding with potentially important implications for managing STEMI patients. For example, in regions with longer transport times to the PCI center, early metoprolol administration might counterbalance the deleterious effect of longer ischemia duration. If so, the cardioprotection afforded by postponing PPCI after early IV metoprolol might strengthen the recommendation for PPCI over thrombolysis in patients who receive this treatment. However, this hypothesis is currently speculative, as no data are available on the effect of metoprolol in patients undergoing thrombolysis. The main report on the METOCARD-CNIC trial showed that patients in the IV metoprolol arm had significantly lower rates of VF (6), and the known effect of metoprolol on primary VF might additionally benefit patients with longer transits between diagnosis site and PPCI center. The sensitivity analysis showed that after normalizing for total ischemia duration, every 10 min of onboard metoprolol reduced infarct size by 1.1 g (**Table 3**). Further analysis of the METOCARD-CNIC cohort has indicated strong benefits of early IV metoprolol in the subpopulation of STEMI patients treated in the out-of-hospital setting (19). This phenomenon is being explored further in the ongoing EARLY BAMI (Early Beta blocker

FIGURE 4 Pig Model of Ischemia/Reperfusion



MIS expressed as %LV **(A)**, AAR **(B)**, and LVEF **(C)** were assessed by CMR at 7 and 45 days post-infarction in the 4 groups of the animal study. **Dots** indicate individual data; **box and whiskers** indicate Tukey boxplots. *$p < 0.05$ compared with other groups. Abbreviations as in **Figure 2**.

CENTRAL ILLUSTRATION **Metoprolol Timing and Cardioprotection in STEMI**



García-Ruiz, J.M. et al. J Am Coll Cardiol. 2016;67(18):2093–104.

The administration of intravenous (IV) metoprolol before reperfusion reduces infarct size in ST-segment elevation myocardial infarction (STEMI) patients undergoing primary angioplasty. However, the cardioprotective effect of metoprolol varies depending on the timing of its administration during ongoing ischemia. The longer the period of onboard metoprolol before reperfusion, the greater the reduction of infarct and the better the long-term left ventricular ejection fraction (LVEF). On the basis of these data, the earlier metoprolol is administered after STEMI diagnosis, the higher the cardioprotection. Cath lab = catheterization laboratory.

Administration before reperfusion in patients with ST-Elevation Myocardial Infarction) trial, a study of patients recruited in the out-of-hospital setting and randomized to IV metoprolol or placebo (20), although the timing and dose of metoprolol in this trial is different from that in METOCARD-CNIC trial.

Using the same animal model, we previously identified pre-reperfusion metoprolol as a strategy able to reduce infarct size (6) and subsequently proposed amelioration of reperfusion injury as the mechanism underlying this effect (14). Preliminary results, led by our group, showed that IV administration of metoprolol exerts cardioprotection against acute MI by inhibiting acute deleterious neutrophil-platelet interactions at reperfusion (21), but a potential effect by decreasing ischemic injury cannot be ruled out. The greater cardioprotective effect with earlier administration of IV metoprolol could correspond to 2 mechanisms: 1) IV metoprolol reduces ischemia-related damage (slows the rate of myocardial death during ischemia) by reducing myocardial oxygen consumption; or 2) to reduce reperfusion-related injury, metoprolol needs to be "onboard" (in the systemic circulation) for some time. We speculate that both mechanisms are implicated in the infarct-limiting effect of metoprolol. This dual effect on ischemia- and reperfusion-related injuries identified metoprolol as a unique agent for reducing ischemia/reperfusion injury; however, the precise mechanism underlying this phenomenon falls beyond the scope of this study.

Infarct size is a major predictor of post-STEMI mortality and morbidity, and there is a need for adjunct therapies that reduce the extent of myocardial damage associated with reperfusion (3). Early administration of 15 mg IV metoprolol is 1 of the few interventions that has been shown to reduce MIS and improve long-term LVEF (6,7): MIS and LVEF are well-validated surrogates of mortality. The ongoing EARLY BAMI trial (20) will determine whether the infarct-limiting effects of early IV metoprolol are consistent in a less restricted STEMI population; unlike METOCARD-CNIC, EARLY BAMI includes patients presenting up to 12 h after symptom onset and evaluates infarctions in the anterior and other locations. Conversely, the dose and the timing of metoprolol administration in EARLY BAMI and METOCARD-CNIC are dissimilar. However, a large clinical trial powered to detect differences in hard endpoints is still needed.

STUDY LIMITATIONS. Post hoc analysis of clinical trials has certain inherent limitations, 1 being the possibility of residual confounders that could affect the results. For this reason, we tested the hypothesis generated in the post hoc analysis in a well-validated

experimental model of STEMI (pig ischemia/reperfusion). We used the same imaging technology (CMR) as the clinical trial and similar short- and long-term follow-up time points. This controlled setting generated similar results to the clinical trial: pigs receiving metoprolol long before reperfusion had significantly smaller infarcts and higher long-term ventricular function. This dual clinical-experimental approach added robustness to the results observed. However, animal models present some limitations. First, myocardial collateral flow may play a role in the final infarct size. Pigs are widely used in this regard because their cardiac size, hemodynamics, and coronary anatomy closely resemble that of humans and also because they have negligible collateral flow, thus reducing this potential bias. Second, experimental protocols (anesthetics, pig strain, adjuvant drugs, and so on) vary across laboratories, and these factors might affect infarct-size progression (22,23). However, although this might influence the differences of our results to that of other laboratories (something obvious for infarct size in control subjects), it should not affect the current results because all experimental groups underwent the same protocol; therefore, the treatment effect of metoprolol is real.

CONCLUSIONS

This study showed that in STEMI patients scheduled for PPCI, the longer the interval between IV metoprolol bolus and reperfusion, the higher the cardioprotection afforded by metoprolol, resulting in smaller infarct size and higher LVEF. These clinical results were validated in a pig study, in which metoprolol administration long before reperfusion was associated with smaller infarcts and better long-term LVEF. Given that reperfusion should not be delayed under any circumstance, the best strategy for attaining cardioprotection with metoprolol is to inject an IV bolus (15 mg according to the METOCARD-CNIC trial) immediately after STEMI diagnosis in patients with no contraindications.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: IV administration of metoprolol before primary angioplasty reduces infarct size in patients with STEMI, and earlier administration is associated with smaller infarct size and higher residual LVEF.

TRANSLATIONAL OUTLOOK 1: Systems should be developed to facilitate earlier IV administration of metoprolol for patients developing STEMI in regions where the time to primary PCI is lengthy.

TRANSLATIONAL OUTLOOK 2: In STEMI patients with no contraindications (i.e., Killip class I to II, no hypotension or atrioventricular block), IV metoprolol (15 mg) should be considered immediately after STEMI diagnosis without delay.

TRANSLATIONAL OUTLOOK 3: Current clinical guidelines recommend IV injection of metoprolol in STEMI patients with ongoing ischemia and no contraindications (Class IIa). Not adhering to this recommendation might result in larger infarctions associated with poor long-term prognosis.

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KEY WORDS cardiac magnetic resonance, cardioprotection, left ventricular ejection fraction, myocardial infarction, reperfusion injury

APPENDIX For a supplemental Methods section as well as a supplemental table, please see the online version of this article.