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65th Annual Scientific Session & Expo

Effect of Early Administration of Beta Blockers in patients with STEMI before primary PCI: The EARLY-BAMI trial

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On behalf of the EARLY BAMI investigators.

Disclosers

- The trial was funded by an unrestricted grant of the Dutch Heart Foundation and an unrestricted grant of Medtronic
- There are no other disclosers to report
- There are no potential conflicts of interest

Background

- Early diagnosis and reperfusion therapy has improved outcome of STEMI
- Additional interventions early after onset of ischemia might further improve outcome
- Infarct size is a main determinant of long term morbidity and mortality

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Background

- The effect of early i.v. Beta-blockers on infarct size is unclear:
  - Few randomized trials in the thrombolytic era
  - Only one randomized trial (METOCARD-CNIC* trial) in the primary PCI era (only anterior location, not-placebo controlled)

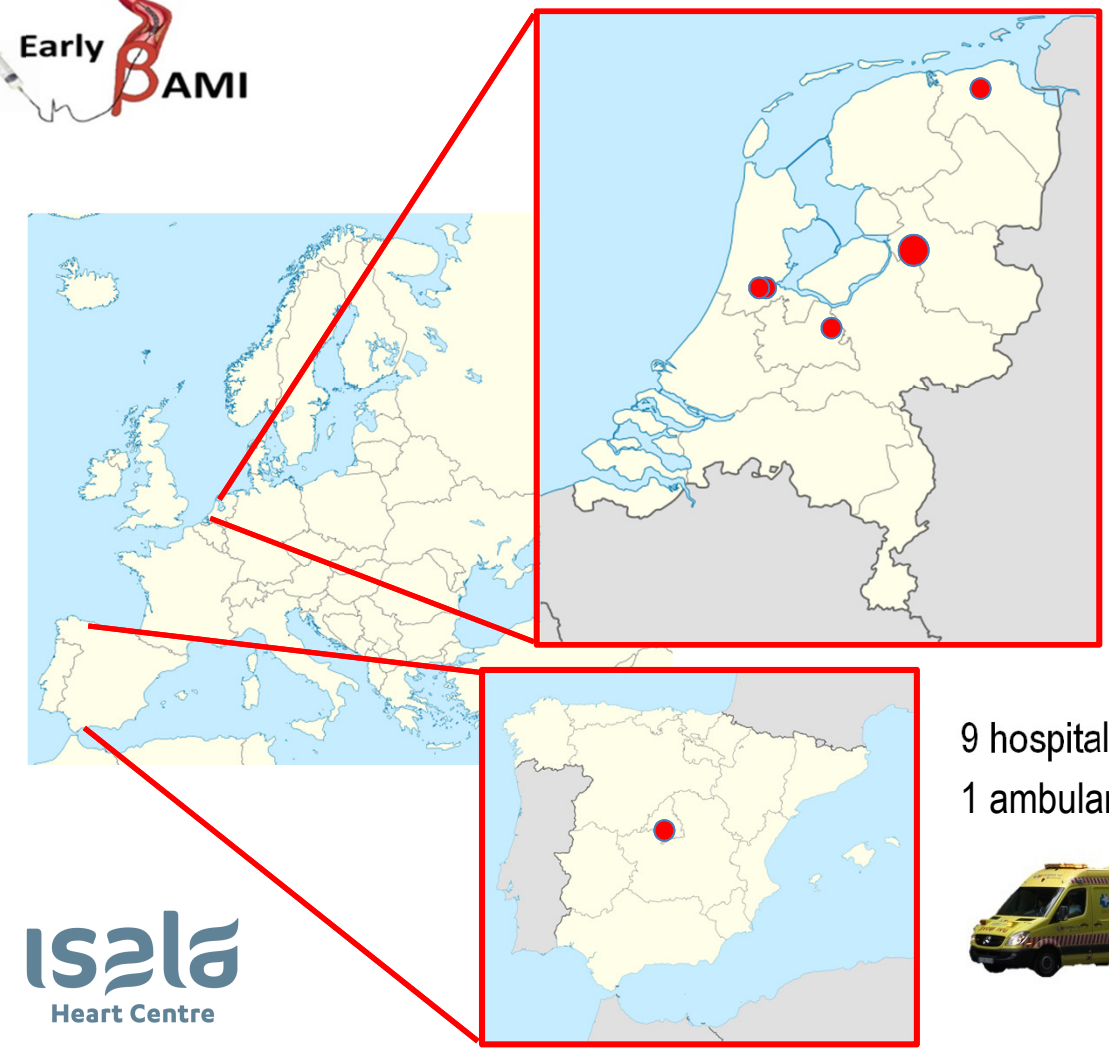
- B. Ibanez et al. Circulation 2013;128:1495-503
- G Pizarro et al. J Am Coll Cardiol. 2014;63:2356-62.

Study aim

- Effects of early Beta-blockers (pre primary PCI) on infarct size in patients with STEMI
- All infarct locations
- Double blind, placebo-controlled

Early BAMI

Methods



rav ijsselland
Regionale Ambulancevoorziening IJsselland

umcg Ambulancezorg

WITTE KRUIS

5 hospitals in the Netherlands

3 ambulance services

9 hospitals in Madrid, Spain

1 ambulance service

SUMMA 112
SaludMadrid
Comunidad de Madrid
Fuente: SUMMA

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Study Design

STEMI (any location)

Inclusion criteria:

- >18 Years old
- <12 h of symptom onset
- ECG: >2 mm ST-elevation or new LBBB

Exclusion criteria:

- BP < 100 mmHg
- HR < 60 bmp
- Type II or III AV block
- Killip klass III or IV
- Prior MI
- ICD or pacemaker (no MRI possible)
- Pregnant or breastfeeding

Metoprolol i.v.
2 x 5 mg
↓
pPCI
↓
MRI (one month)

Placebo i.v.
2 x 5mg
↓
pPCI
↓
MRI (one month)

Study Design

- First bolus in ambulance, 2nd bolus in PCI hospital, before PCI
- Thrombus aspiration, glycoprotein IIb-IIIa inhibitors, at discretion operator, stenting with a 2nd generation DES
- All patients planned to receive oral metoprolol < 12 hours after PCI, according current guidelines
- Initially, enzymatic infarct size primary endpoint. Change in primary outcome was made: 1) reduce sample size
  2) more precise measurement of infarct size by MRI

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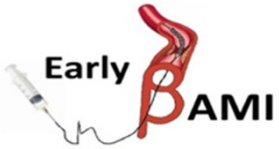
Study Design

- **Primary endpoint:**
  - Myocardial infarct size measured by MRI at one month, blinded for study medication
- **Secondary endpoint:**
  - Enzymatic infarct size (peak CK, area under CK curve, peak troponin)
- **Safety endpoint**
  - Ventricular arrhythmias, bradycardia, cardiogenic shock, MACE
- **Prespecified subgroups:**
  - Anterior infarction
  - Early presentation (<6 h of symptom onset)
  - Occluded vessel at pPCI (TIMI 0/1 flow)



Included
N=684

1 patient randomization unknown

Metoprolol
N=336

Placebo
N=347

No MRI
- 44 Inclusion before amendment
- 1 CABG
- 25 Claustrophobia
- 11 Comorbidity
- 3 Distance
- 1 ICD
- 9 No infarction criteria (enzymes)
- 4 Previous MI
- 14 No written informed consent
- 15 Out of window
- 8 Died
- 17 Refused
- 7 Unable to plan appointment
- 8 Other

No MRI
- 47 Inclusion before amendment
- 3 CABG
- 15 Claustrophobia
- 14 Comorbidity
- 5 Distance
- 2 ICD
- 9 No infarction criteria (enzymes)
- 6 Previous MI
- 15 No written informed consent
- 20 Out of window
- 4 Died
- 18 Refused
- 10 Unable to plan appointment
- 6 Other

Underwent cardiac MRI
N=169

Underwent cardiac MRI
N=173

MRI analyzed
N=162
Excluded (n = 7)
- 3 Acquisition problem
- 4 No infarction criteria (enzymes)

MRI Analyzed
N=169
Excluded (n = 4)
- 1 Previous MI
- 2 Acquisition problem
- 1 No infarction criteria (enzymes)

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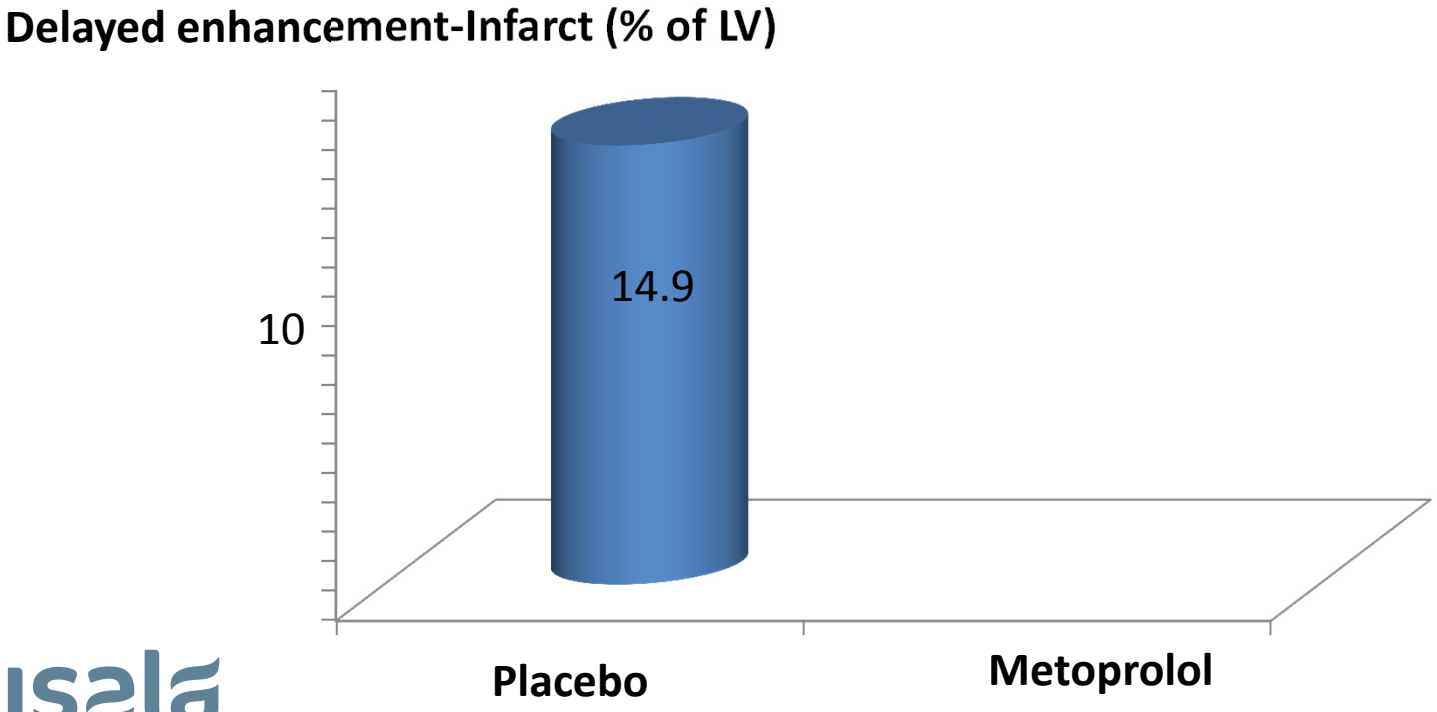
Baseline characteristics

Characteristic	Metoprolol (N=336)	Placebo (N=347)
Mean Age (years) ± SD	62.39 ± 12.42	62.46 ± 12.58
Female gender (%)	25.0	25.4
Mean length (cm) ± SD	174.3 ± 10.2	175.2 ± 9.6
Mean weight (kg) ± SD	82.8 ± 16.4	84.7 ± 16.0
Mean BMI ± SD	27.1 ± 4.5	27.4 ± 4.1
Diabetes (%)	14.3	17.9
Previous hypertension (%)	40.3	38.7
Beta blocker as home medication (%)	18.1	19.5
Anterior location (%)	49.4	52.2
First medical contact (%)		
Referring hospital	5.7	4.6
PCI center	2.4	3.5
Ambulance	91.9	91.9
Time (minutes) from symptom onset till first medical contact		
Mean ± SD	135.5 ± 231.9	147.9 ± 212.5
Early presenters (% within 6 hours)	93.8	89.4
Time (minutes) from symptom onset till reperfusion		
Mean ± SD	195.5 ± 262.5	201.6 ± 262.1
Hemodynamics at randomisation		
Mean Systolic BP (mm Hg) ± SD	147.5 ± 24.7	146.7 ± 25.0
Mean Diastolic BP (mm Hg) ± SD	89.9 ± 15.5	90.5 ± 17.0
Mean Heart Rate (beats/min) ± SD	78.6 ± 15.2	80.5 ± 15.7

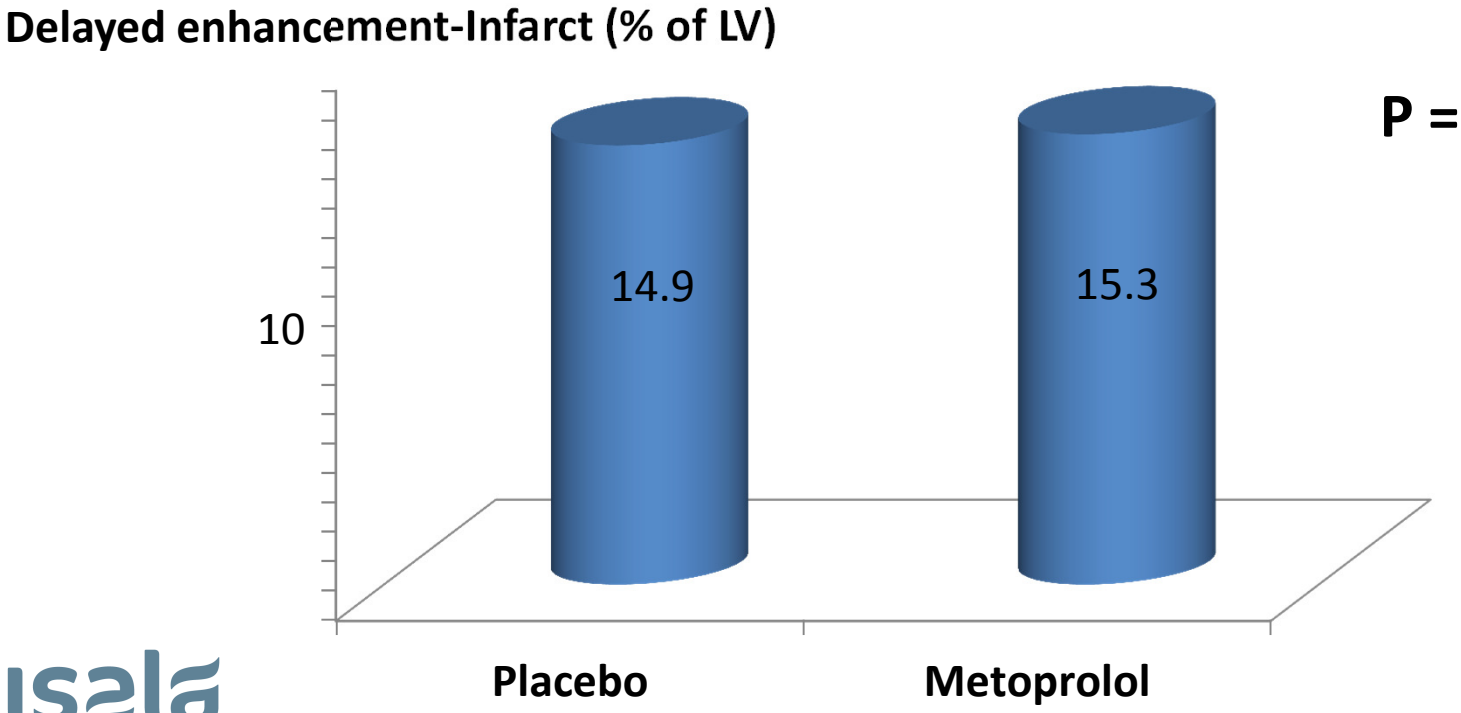
Safety endpoint

Outcome	Metoprolol (N=336)	Placebo (N=347)	P-value
Severe bradycardia (%)	1.5	0.6	0.279
Severe hypotension (%)	2.9	5.5	0.102
Cardiogenic shock (%)	0.6%	0.3	0.618
Malignant ventricular arrhythmias (%)	**3.6**	**6.9**	**0.050**

Primary endpoint



Primary endpoint

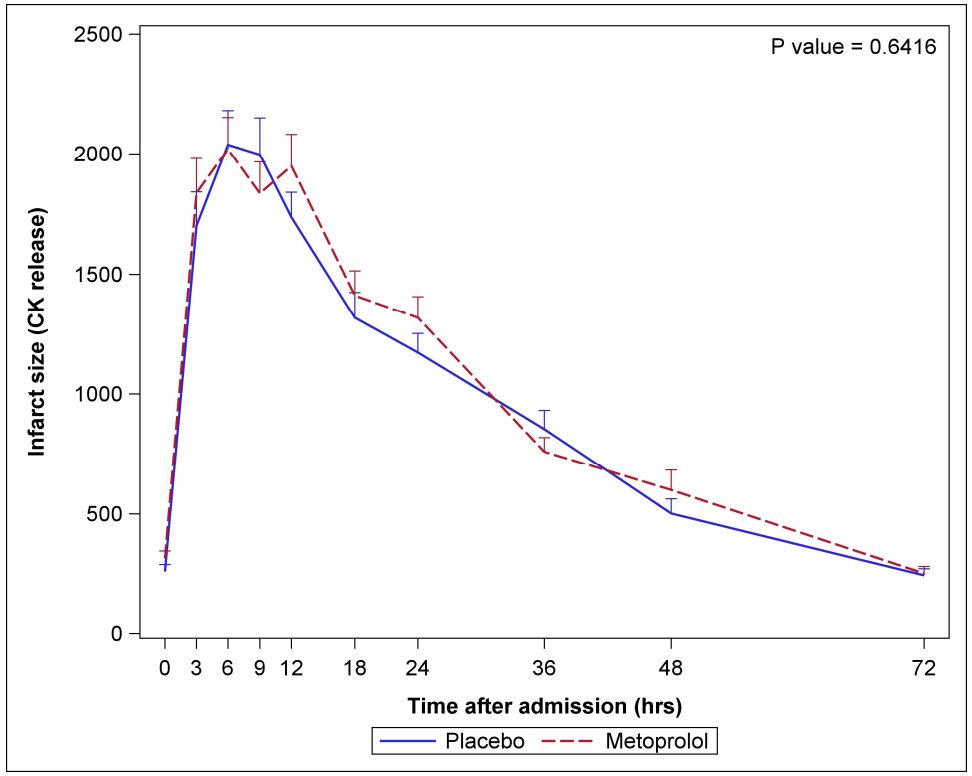


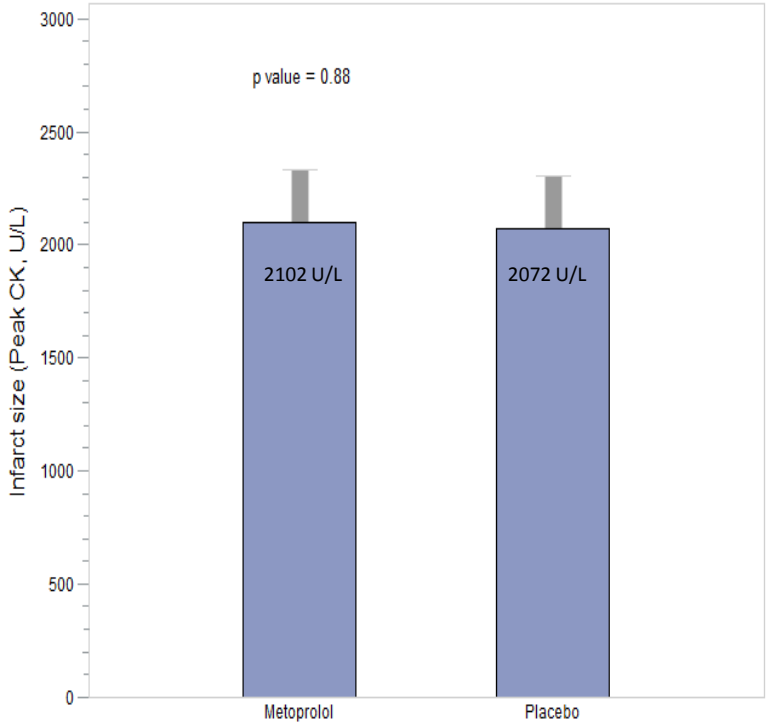
P = 0.62

MRI results

MRI Measurement	Metoprolol (N=162)	Placebo (N=169)	P-value
Delayed enhancement-Infarct (% of LV)			
Mean ± SD	15.3 ± 11.0	14.9 ± 11.5	0.62
Median (IQR)	13.4 (6.4-21.3)	13.3 (5.6-21.3)	
LVEF (%)			
Mean ± SD	51.0 ± 10.9	51.7 ± 10.8	0.68
Median (IQR)	53.0 (44.1-59.3)	53.7 (45.3-58.9)	
LVEDV (ml)			
Mean ± SD	183.9 ± 52.4	184.2 ± 40.1	0.398
Median (IQR)	177.9 (149.1-209.1)	181.8 (157.5-212.0)	
LVESV (ml)			
Mean ± SD	93.3 ± 46.1	90.5 ± 32.9	0.65
Median (IQR)	82.7 (64.0-108.7)	86.3 (65.8-106.1)	
LV mass (g) from function			
Mean ± SD	96.4 ± 25.2	96.5 ± 23.1	0.89
Median (IQR)	96.4 (77.2-110.7)	94.6 (80.6-110.1)	
LV mass (g) from delayed enhancement			
Mean ± SD	104.6 ± 29.4	103.1 ± 25.7	0.78
Median (IQR)	100.6 (85.1-122.5)	101.3 (84.1-119.0)	

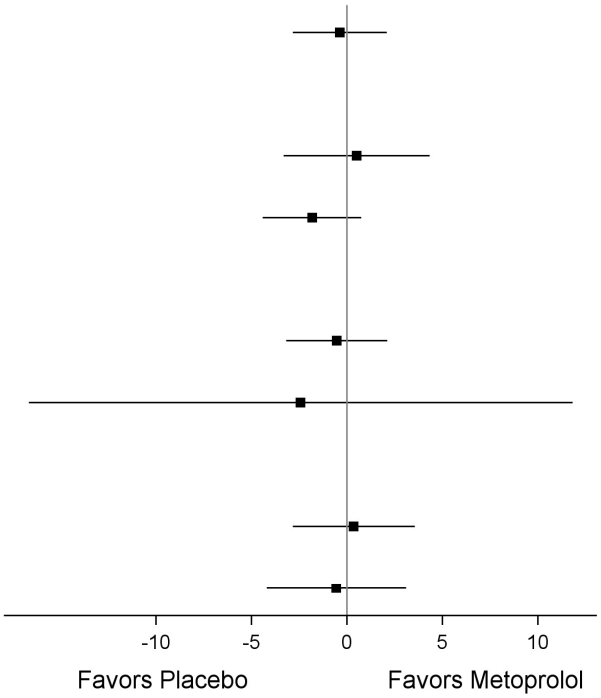
Results: enzymatic infarct size





Results: prespecified subgroups

	Metoprolol	Placebo	Metoprolol	Placebo	Difference in Delayed Enhancement Infarct (95% CI)	P for interaction
All patients	159	167	15.29 ± 10.97	14.91 ± 11.52	-0.38 (-2.84 - 2.07)	
Location of MI						
Anterior infarction	78	88	18.81 ± 12.20	19.30 ± 12.65	0.49 (-3.33 - 4.31)	0.33
Non anterior infarction	75	71	12.24 ± 8.01	10.41 ± 7.78	-1.83 (-4.42 - 0.75)	
Presentation						
Early	135	129	15.11 ± 10.69	14.56 ± 11.09	-0.55 (-3.19 - 2.09)	0.72
Late	9	12	20.87 ± 16.29	18.45 ± 14.76	-2.43 (-16.7 - 11.81)	
Initial timi flow						
Initial 0,1	98	97	17.78 ± 10.81	18.12 ± 11.81	0.35 (-2.85 - 3.54)	0.74
Initial 2,3	43	49	9.59 ± 9.01	9.03 ± 8.55	-0.56 (-4.20 - 3.08)	



% infarct size in prespecified subgroups

Adverse cardiac events at 30 days

Outcome	Metoprolol (N=336)	Placebo (N=347)	P-value
All MACE (%)	6.2	6.9	0.721
Cardiac mortality (%)	2.3	2.2	0.942
Recurrent MI (%)	1.0	0.6	0.681
Target Vessel Revascularization (%)	3.9	4.7	0.625

Discussion

- Our results do not confirm the effect observed in the METOCARD-CNIC trial

Discussion

METOCARD-CNIC:

- Only anterior infarctions, which resulted in larger infarct size (21.2% vs 15.3% in our study)
- Higher dose of metoprolol:15 mg vs 10 mg in our trial
- Excluded long term beta-blocker treatment before admission vs 19% in our study
- Time beta-blocker treatment till primary PCI longer than in our study: recent analyses suggest more effects with increase of time*

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* JM García-Ruiz, V Fuster, B. Ibanez et al. JACC 2016 in press

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Conclusion (1)

- In a non-restricted STEMI population, early intravenous metoprolol before pPCI, was not associated with a reduction in infarct size

- Metoprolol reduced the incidence of malignant arrhythmias in the acute phase and was not associated with an increase in adverse events

Conclusion (2)

- Concerning conflicting results with METOCARD-CNIC, more large randomized trials are needed to clarify whether early beta-blocker treatment has any effect in STEMI treated by pPCI

- Safety profile, low cost, and the reduction of acute malignant arrhythmias, encourage the performance of additional larger trials

Acknowledgment

- Isala hospital, Zwolle, The Netherlands
- Diagram, Diagnostic Research and Management, Zwolle, The Netherlands
- VU University Medical Center, Amsterdam, The Netherlands
- Academic Medical Center, Amsterdam, The Netherlands
- University Medical Center, Groningen, Groningen, The Netherlands
- Meander Medisch Centrum, Amersfoort, The Netherlands
- RAV IJsselland, The Netherlands
- RAV Witte Kruis, The Netherlands
- UMCG ambulancezorg, The Netherlands
- Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain
- Servicio de Urgencia Medica de Madrid (SUMMA 112), Madrid, Spain
- IIS-Fundacion Jiménez Díaz Hospital , Madrid, Spain
- Hospital 12 de Octubre, Madrid, Spain.
- Hospital Clínico San Carlos, Madrid, Spain.
- Hospital Gregorio Marañón, Madrid, Spain.
- Hospital Puerta de Hierro, Madrid, Spain.
- Hospital Fundación Alcorcón, Madrid, Spain.
- Hospital Ramón y Cajal, Madrid, Spain.
- Hospital de La Princesa, Madrid, Spain.
- Hospital Príncipe de Asturias, Alcalá de Henares, Madrid, Spain.
- Hospital de Getafe, Madrid, Spain.
- Hospital Universitario Quirón, Universidad Europea de Madrid, Spain.

… and all patients for participating in this trial!