Intravenous beta-blocker therapy in ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention is not associated with benefit regarding short-term mortality: a Swedish nationwide observational study

Moman A. Mohammad[1], MD; Pontus Andell[1], MD, PhD; Sasha Koul[1], MD, PhD; Liyew Desta[2], MD, PhD; Tomas Jernberg[3], MD, PhD; Elmir Omerovic[4], MD, PhD; Jonas Spaak[2], MD, PhD; Ole Fröbert[5], MD, PhD; Jens Jensen[6], MD, PhD; Thomas Engstrøm[7], MD, PhD; Claes Hofman-Bang[2], MD, PhD; Hans Persson[2], MD, PhD; David Erlinge[1]*, MD, PhD

1. Department of Cardiology, Clinical Sciences, Lund University, Skane University Hospital, Lund, Sweden; 2. Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden; 3. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; 4. Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden, and Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden; 5. Örebro University, Faculty of Health, Department of Cardiology, Örebro, Sweden; 6. Department of Medicine, Capio S:t Görans Sjukhus, Karolinska Institutet, Stockholm, Sweden; 7. The Heart Center, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Abstract

Aims: Our aim was to investigate the impact of intravenous (IV) beta-blocker therapy on short-term mortality and other in-hospital events in patients with ST-segment elevation myocardial infarction (STEMI) treated with dual antiplatelet therapy (DAPT) and primary percutaneous coronary intervention (PCI).

Methods and results: Using the nationwide Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry, we identified all patients with STEMI undergoing PCI between 2006 and 2013. Patients with cardiogenic shock and cardiac arrest at presentation were excluded. The primary endpoint was mortality within 30 days. Secondary endpoints were in-hospital events (mortality, cardiogenic shock and left ventricular ejection fraction [LVEF] <40% at discharge). We adjusted for confounders with a multivariable model and propensity score matching. Out of 16,909 patients, 2,876 (17.0%) were treated with an IV beta-blocker. After adjusting for confounders, the IV beta-blocker group had higher 30-day all-cause mortality (HR: 1.44, 95% CI: 1.14-1.83), more in-hospital cardiogenic shock (OR: 1.53, 95% CI: 1.09-2.16) and were more often discharged with an LVEF <40% (OR: 1.70, 95% CI: 1.51-1.92).

Conclusions: In this large nationwide observational study, the use of IV beta-blockers in patients with STEMI treated with primary PCI was associated with higher short-term mortality, lower LVEF at discharge, as well as a higher risk of in-hospital cardiogenic shock.

Corresponding author: Department of Cardiology, Clinical Sciences, Lund University, Skane University Hospital, 221 85 Lund, Sweden. E-mail: david.erlinge@med.lu.se

Abbreviations

BB	beta-blocker
BP	blood pressure
CABG	coronary artery bypass graft
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
DAPT	dual antiplatelet therapy
HS troponin I	high-sensitivity troponin I
IV	intravenous
LAD	left anterior descending artery
LVEF	left ventricular ejection fraction
MI	myocardial infarction
PCI	percutaneous coronary intervention
PS	propensity score
RCA	right coronary artery
STEMI	ST-segment elevation myocardial infarction
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies

Introduction

Beta-blocker therapy in the early phase of myocardial infarction (MI) has been shown to reduce infarct size and improve LVEF and survival over time[1,2]. Unless contraindicated, guidelines recommend starting beta-blocker therapy in all patients with STEMI within 24 hours and thereafter up-titrating treatment during and after hospitalisation as tolerated[2,3]. The role of IV beta-blocker therapy is more controversial and less clear. IV beta-blockade was studied nearly 40 years ago in animal models[4]. Shortly thereafter, Hjalmarson et al randomised patients to IV metoprolol or placebo and demonstrated a 36% reduction in mortality in the group randomised to IV metoprolol followed by oral metoprolol as a monotherapy[5]. A number of trials followed in both the pre-thrombolytic and thrombolytic era with varying results. Most of these studies investigated a combination of initial IV beta-blocker followed by long-term per oral treatment compared to placebo[6-10]. The suggested mechanisms for the observed benefit of beta-blockers included a reduction in myocardial oxygen demand and less malignant arrhythmia.

Editorial, see page 149

Studies on IV beta-blockade in the modern percutaneous coronary intervention (PCI) era have shown mixed results[11-14]. The METOCARD CNIC trial (effect of METOprolol in CARDioproteCtioN during an acute myocardial InfarCtion) showed a promising reduction in infarct size with IV beta-blocker therapy. However, these findings could not be replicated in the EARLY-BAMI trial (beta-blocker administration before primary PCI in patients with ST-elevation myocardial infarction trial)[12-14].

In Sweden, the use of IV beta-blockers is highly variable in patients with acute myocardial infarction, ranging from 2% to 40% between centres. Most hospitals, however, use it in less than 20% of patients with acute myocardial infarction[15].

The objective of this Swedish nationwide registry-based study was to assess the impact of IV beta-blocker therapy on short-term mortality as well as other in-hospital clinical events in patients with STEMI undergoing primary PCI.

Methods

STUDY POPULATION

A total of 39,209 patients with STEMI were enrolled in the SWEDEHEART registry between 2006 and 2013 **(Figure 1)**. Detailed information about the registry and variable definitions is available upon request[16]. In the present study, patients were excluded if they were not treated with PCI (n=4,390), if they did not receive upstream DAPT before the start of PCI with aspirin and a $P2Y_{12}$ inhibitor (n=9,948), if they were on regular beta-blocker therapy at the time of hospitalisation (n=7,077) or presented with cardiac arrest or cardiogenic shock (n=801). If patients had more than one admission during the study period, later admissions were excluded (n=49). Patients with incomplete data regarding the use of IV beta-blockers during hospitalisation were also excluded (n=35). The remaining 16,909 patients constituted the final study population and were divided into two groups, those who received IV beta-blockers during hospitalisation (n=2,876) and those who did not (n=14,033). The Regional Ethical Review Board in Lund, Sweden, approved this study.
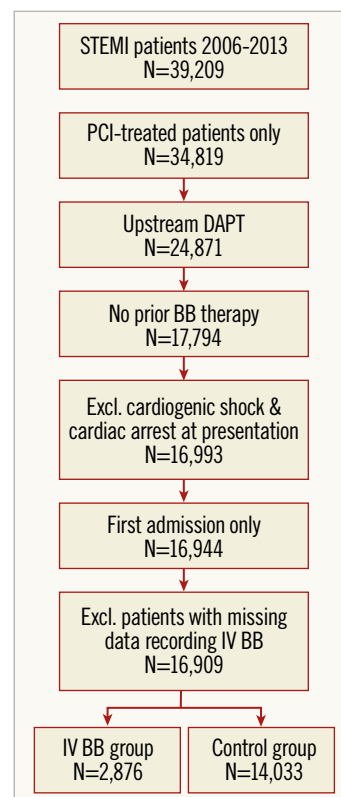

Figure 1. *Study flow chart. Patients with STEMI who received upstream DAPT and PCI were included in this study. The numbers of patients remaining after each step of the inclusion and exclusion criteria are shown. BB: beta-blocker*

ENDPOINTS

The primary endpoint of this study was all-cause mortality within 30 days from admission. The secondary endpoints were in-hospital events (mortality, cardiogenic shock) and LVEF <40% at a discharge echocardiogram. All subgroup analyses were predefined.

STATISTICAL ANALYSES

A detailed statistical analysis plan is available upon request. There were 7.2% individuals with missing values and they were therefore excluded from the primary analyses. All statistical analyses were performed using Stata version 14.1 for Mac (StataCorp, College Station, TX, USA). A two-sided p-value <0.05 was considered statistically significant.

Results

PATIENT CHARACTERISTICS

Patients treated with IV beta-blockers were younger (64.0 years, IQR 57-74 vs. 66.0 years, IQR 57-75) **(Table 1)**. Comorbidities at presentation were similar in the groups. There was a longer system delay in the IV beta-blocker group; 73.4% of subjects in the IV beta-blocker group presented with a system delay of less than two hours compared to 78.3% in the control group. The IV beta-blocker group had a higher heart rate at presentation (80 bpm, IQR 68-95 vs. 73 bpm, IQR 62-85) as well as higher blood pressures (SBP 150 mmHg, IQR 130-170 vs. 140 mmHg, IQR 121-160). Atrial fibrillation in the presenting ECG was more common in the IV beta-blocker group (5.3% vs. 3.4%). The use of IV beta-blockers was significantly higher at the start of the study period **(Figure 2)**, and 63.9% of IV beta-blocker administrations occurred between 2006 and 2009. The IV beta-blocker group more often presented with LAD lesions than the control group (55.8% vs. 41.6%), less often with right coronary artery (RCA) lesions (25.9% vs. 40.4%) and had higher peak cardiac enzyme values. A total of 1,517 cases and 1,517 controls remained after matching.
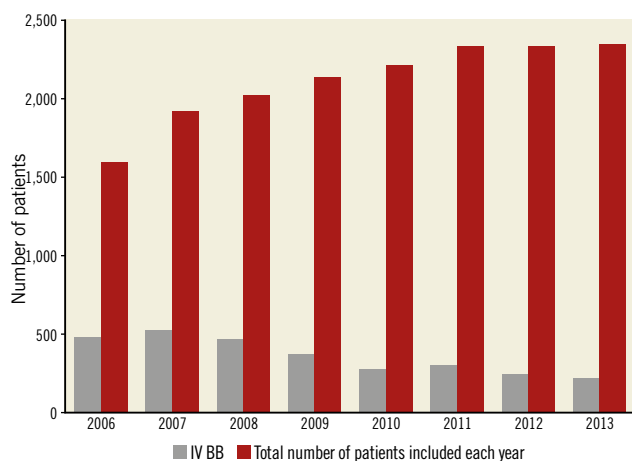

Figure 2. *Trend of intravenous beta-blocker (IV BB) administration during the study period.*

Analysis on the matched population was performed with complete cases. Differences in patient characteristics after propensity score matching are shown in **Table 1.** Predictors of IV beta-blocker usage are available upon request.

ENDPOINTS

The Kaplan-Meier event rate for all cause-mortality within 30 days was statistically significantly higher in patients treated with an IV beta-blocker (3.6% compared to 2.6% [unadjusted HR: 1.37, 95% CI: 1.10-1.70]) **(Figure 3)**. Results were consistent and statistically significant after multivariable adjustments and propensity score (PS) matching **(Table 2)**. In-hospital mortality was numerically higher in the IV beta-blocker group (Kaplan-Meier event rates: 2.7% vs. 2.0%, [unadjusted HR: 1.13, 95% CI: 0.88-1.46]). In-hospital cardiogenic shock was more frequent in the IV beta-blocker group (1.9% vs. 1.3%, [unadjusted OR: 1.45, 95% CI: 1.07-1.95]). The proportion of patients discharged with an LVEF <40% was statistically significantly higher in the IV beta-blocker group (31.4% compared to 18.1%, [unadjusted OR: 2.07, 95% CI: 1.88-2.29]). Results of the secondary endpoints were consistent after multivariable adjustment and propensity score matching adjustment except for cardiogenic shock **(Table 2)**.

SUBGROUP ANALYSES

Results of the primary endpoint, all-cause mortality within 30 days, were consistent across a wide range of subgroups **(Figure 4)**. A statistically significant p-value for interaction was observed for patients with heart rate ≥100 beats per minute at presentation, with a greater hazard in patients with higher heart rate.

SENSITIVITY ANALYSIS

A landmark analysis was performed for patients alive 30 days after the initial event, showing no additional association with mortality between days 31-60 in patients receiving IV beta-blocker therapy (unadjusted HR: 1.02, 95% CI: 0.66-1.56, p=0.94) **(Figure 3C)**. Including patients with previous regular beta-blocker treatment in a sensitivity analysis resulted in an associated higher all-cause mortality within 30 days with the use of an IV beta-blocker (unadjusted HR: 1.22, 95% CI: 1.05-1.45, p=0.01). A sensitivity analysis addressing the DAPT inclusion criteria was carried out evaluating the primary endpoint of 30-day mortality in patients who were not pre-treated with DAPT and compared to the current study population. The 30-day mortality was higher in the group of patients that was not pre-treated with DAPT (3.7% vs. 2.8%, p=0.001), indicating a sicker group at baseline. The association of higher mortality with IV beta-blockers remained when including this subpopulation, (3.6% vs. 2.9%, p=0.022 [unadjusted HR 1.241, 95% CI: 1.03-1.49]).

Discussion

In this Swedish nationwide observational study, we found no evidence of benefit with the use of IV beta-blocker therapy in patients with STEMI treated with primary PCI in terms of short-term

Table 1. Baseline characteristics.

		Entire population n=16,909	Before matching		After matching		p-value
			IV beta-blocker group n=2,876	Control group n=14,033	IV beta-blocker group n=1,517	Control group n=1,517	
Age		65 (57-74)	64 (56-73)	66 (57-75)	64 (56-73)	64 (55-72)	0.61
Males		12,437 (73.6%)	2,189 (76.1%)	10,248 (73.0%)	1,176 (75.5%)	1,193 (78.6%)	0.45
Body mass index		26.2 (24.1-28.8)	26.4 (24.3-29.3)	26.1 (24.0-28.7)	26.3 (24.3-29.0)	26.3 (24.2-28.7)	0.48
Current smokers		5,613 (33.2%)	1,003 (34.9%)	4,610 (32.9%)	533 (35.1%)	513 (33.8%)	0.47
Past medical history	Hypertension	5,374 (31.8%)	886 (30.8%)	4,488 (32.0%)	378 (24.9%)	377 (24.9%)	1.0
	Diabetes	2,611 (15.4%)	459 (16.0%)	2,152 (15.3%)	185 (12.2%)	188 (12.4%)	0.87
	Heart failure	384 (2.3%)	68 (2.4%)	316 (2.3%)	15 (1.0%)	10 (0.7%)	0.28
	Chronic kidney disease	136 (0.8%)	20 (0.7%)	116 (0.8%)	8 (0.5%)	7 (0.5%)	1.0
	COPD	710 (4.2%)	104 (3.6%)	606 (4.3%)	42 (2.8%)	37 (2.4%)	0.65
	Cancer	249 (1.5%)	28 (1.0%)	221 (1.6%)	11 (0.7%)	14 (0.9%)	0.06
	Stroke	865 (5.1%)	130 (4.5%)	735 (5.2%)	50 (3.3%)	57 (3.8%)	0.56
	Coronary artery disease	1,279 (7.6%)	193 (6.7%)	1,086 (7.7%)	80 (5.3%)	73 (4.8%)	0.62
	Myocardial infarction	1,128 (6.7%)	165 (5.7%)	963 (6.9%)	69 (4.5%)	67 (4.4%)	0.93
	PCI	668 (4.0%)	94 (3.3%)	574 (4.1%)	40 (2.6%)	45 (3.0%)	0.66
	CABG	223 (1.3%)	31 (1.1%)	192 (1.4%)	11 (0.7%)	12 (0.8%)	0.84
	Peripheral artery disease	335 (2.0%)	51 (1.8%)	284 (2.0%)	27 (1.8%)	23 (1.5%)	0.67
Inclusion years	2006-2009	7,686 (45.5%)	1,837 (63.9%)	5,849 (41.7%)	749 (49.4%)	753 (49.6%)	0.91
	2010-2013	9,223 (54.5%)	1,039 (36.1%)	8,184 (58.3%)	768 (50.6%)	764 (50.4%)	
Clinical findings	Heart rate	74 (63-87)	80 (68-95)	73 (62-85)	75 (65-90)	76 (65-89)	0.77
	Systolic BP	140 (124-160)	150 (130-170)	140 (121-160)	144 (125-160)	144 (125-160)	0.91
	Diastolic BP	85 (73-97)	90 (80-100)	82 (71-95)	88 (75-100)	85 (74-100)	0.04
	eGFR >60 ml/min/1.73 m²	13,642 (85.0%)	2,420 (85.6%)	11,222 (84.9%)	1,290 (86.5%)	1,295 (89.1%)	0.03
System delay	Less than 2 hrs	12,819 (77.5%)	2,051 (73.4%)	10,768 (78.3%)	1,222 (80.6%)	1,217 (80.2%)	0.86
	Time from system delay (hours/min)	1:15 (0:50-1:54)	1:20 (0:54-2:05)	1:13 (0:48-1:51)	1:15 (0:51-1:47)	1:12 (0:47-1:46)	0.13
	Symptoms to PCI (hours/min)	3:19 (2:10-5:50)	3:33 (2:19-6:20)	3:15 (2:08-5:50)	3:20 (2:10-5:43)	3:15 (2:05-5:41)	0.81
ECG rhythm at arrival	Sinus	15,899 (94.1%)	2,666 (92.7%)	13,233 (94.3%)	1,444 (95.2%)	1,453 (95.8%)	0.19
	Atrial fibrillation/flutter	625 (3.7%)	151 (5.3%)	474 (3.4%)	42 (2.8%)	41 (2.7%)	
	Other	284 (1.7%)	44 (1.5%)	240 (1.7%)	26 (1.7%)	14 (0.9%)	
Cardiac enzymes	Troponin-I	24.0 (4.53-50.0)	30.0 (5.80-50.0)	23.0 (4.30-50)	27.9 (5.6-50.0)	22.7 (5.43-50.0)	0.19
	Troponin-T	3.04 (0.91-7.90)	3.8 (1.30-9.50)	2.88 (0.85-7.60)	4.17 (1.43-9.90)	2.92 (0.72-7.71)	0.01
	HS troponin-T	2,235 (642-5,260)	2,986 (946-7,102)	2,120 (617-5,083)	3,285 (961-7,250)	2,700 (697-5,639)	0.30
	CKMB	146 (53-284)	207 (75-409)	131 (48-248)	153 (89-358)	123 (41-224)	0.24
Treatment prior to PCI	Clopidogrel	13,419 (79.4%)	2,510 (87.3%)	10,909 (77.7%)	1,238 (81.6%)	1,271 (83.8%)	0.13
	Ticagrelor	2,819 (48.7%)	241 (39.5%)	2,578 (49.8%)	187 (41.1%)	199 (43.6%)	0.46
	Prasugrel	834 (8.7%)	141 (12.9%)	693 (8.2%)	103 (12.9%)	62 (7.9%)	0.001
Infarct lesion location	Left main	114 (0.7%)	28 (1.0%)	86 (0.6%)	10 (0.7%)	8 (0.5%)	0.91
	LAD	7,438 (44.0%)	1,605 (55.8%)	5,833 (41.6%)	826 (54.4%)	812 (53.5%)	
	Circumflex	2,351 (13.9%)	425 (14.8%)	1,926 (13.7%)	190 (12.5%)	188 (12.4%)	
	RCA	6,407 (37.9%)	745 (25.9%)	5,662 (40.4%)	458 (30.2%)	470 (31.0%)	
	Other	594 (3.5%)	72 (2.5%)	522 (3.7%)	33 (2.2%)	39 (2.6%)	
Vascular approach	Femoral artery	7,813 (46.2%)	1,634 (56.8%)	6,179 (44.0%)	770 (50.8%)	774 (51.0%)	0.99
	Radial artery	8,991 (53.2%)	1,223 (42.5%)	7,768 (55.4%)	727 (47.9%)	723 (47.7%)	
	Combined/other	105 (0.6%)	19 (0.7%)	86 (0.6%)	20 (1.3%)	20 (1.3%)	
Other in-hospital treatments	CPAP	432 (2.6%)	123 (4.3%)	309 (2.2%)	61 (4.1%)	45 (3.0%)	0.24
	Inotropes	477 (4.0%)	116 (4.0%)	361 (2.6%)	67 (4.4%)	38 (2.5%)	0.006
Discharge medications	Beta-blocker	14,997 (88.7%)	2,665 (92.8%)	12,332 (88.6%)	1,413 (93.2%)	1,364 (90.9%)	0.52
	ACE inhibitor	12,341 (73.0%)	2,125 (74.0%)	10,216 (73.4%)	1,135 (74.9%)	1,122 (74.8%)	0.27
	Angiotensin receptor blockers	1,432 (8.6%)	220 (7.7%)	1,212 (8.7%)	106 (7.0%)	108 (7.2%)	0.60
	Aspirin	16,261 (96.9%)	2,775 (96.6%)	13,486 (96.9%)	1,468 (96.8%)	1,456 (97.1%)	0.88
	Statins	15,926 (94.9%)	2,707 (94.3%)	13,219 (95.0%)	1,433 (94.5%)	1,421 (94.7%)	0.61
	P2Y$_{12}$ inhibitor	12,954 (76.6%)	2,439 (84.8%)	10,515 (74.9%)	1,224 (80.7%)	1,218 (80.3%)	0.78

p-values are shown for differences after propensity score matching. BP: blood pressure; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; HS: high-sensitivity; LAD: left anterior descending artery; PCI: percutaneous coronary intervention; RCA: right coronary artery
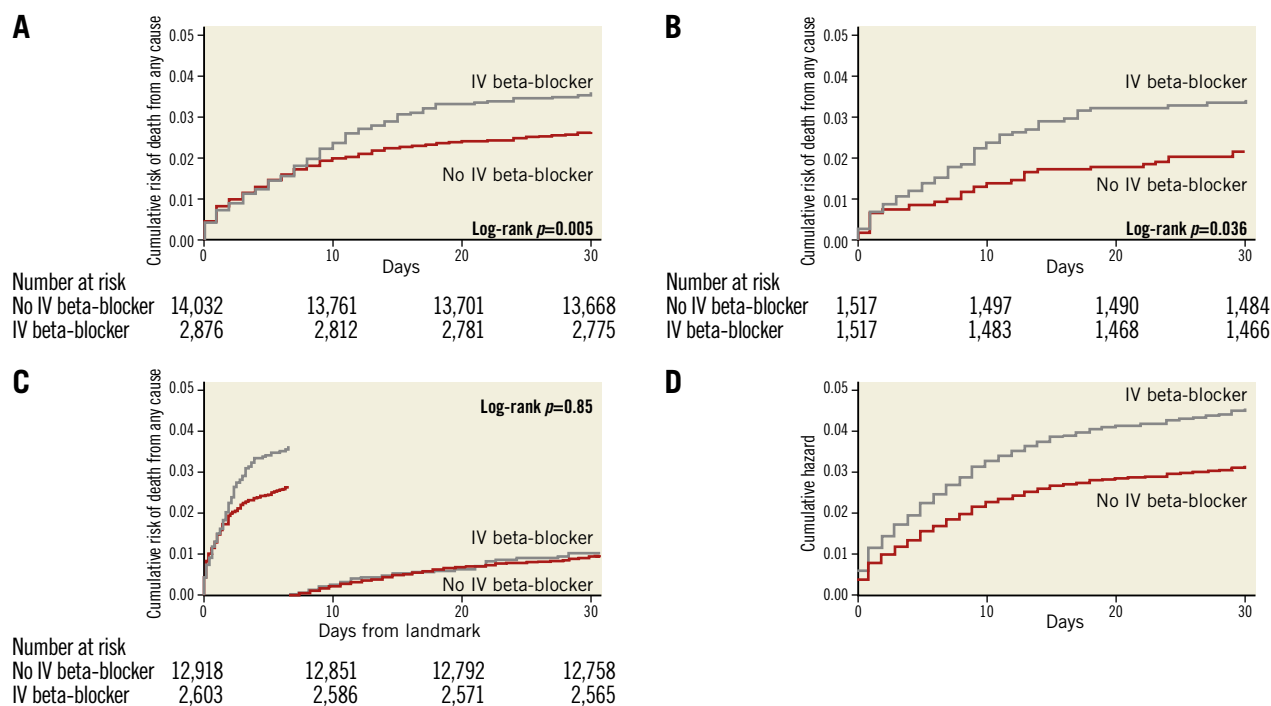
Figure 3. *Survival graph for all-cause mortality within 30 days, landmark analysis and Cox proportional regression model. A) Failure estimates for the entire population. B) Failure estimates for the PS-matched population. C) Landmark analysis. D) The cumulative hazard for a Cox proportional regression model. IV: intravenous*

patient survival or other in-hospital clinical outcomes. After adjustment for confounders with a multivariable model and propensity score matching, the all-cause mortality at 30 days after admission was higher in patients treated with IV beta-blockers compared to the control group. The risk of in-hospital death, cardiogenic shock and LVEF <40% at discharge was statistically significantly higher in the IV beta-blocker group. Results were consistent throughout a number of subgroups.

Current guidelines issued by the European Society of Cardiology as well as the American College of Cardiology Foundation/ American Heart Association recommend the consideration of IV beta-blocker treatment as a class II recommendation (level of evidence B) at the time of presentation in patients without contraindications, with high blood pressure, tachycardia and no signs of heart failure[2,17]. Furthermore, the European Society of Cardiology STEMI guidelines emphasise that it is prudent to wait for the patient to stabilise before starting beta-blocker therapy and preferably to use oral administration, rather than IV. Oral treatment with beta-blockers should be considered during hospitalisation and continued thereafter in all STEMI patients without a contraindication[2,17].

Our aim was to investigate the impact of IV beta-blockers in patients with STEMI, treated according to current guidelines.

Table 2. Results of primary and secondary endpoints.

	IV beta-blocker group	Control group	Unadjusted HR (95% CI)	Multivariable adjusted[1] HR (95% CI)	PS matching adjusted HR (95% CI)
Primary endpoint					
30-day mortality	103 (3.6%)	368 (2.6%)	1.37 (1.10-1.70)**	1.44 (1.14-1.83)**	1.59 (1.02-2.45)*
Secondary endpoints					
In-hospital mortality	77 (2.7%)	272 (2.0%)	1.13 (0.88-1.46)	1.23 (0.93-1.61)	1.43 (0.82-2.47)
			Unadjusted OR (95% CI)	Multivariable adjusted OR (95% CI)	PS matching adjusted OR (95% CI)
LVEF at discharge ≤39%	743 (31.4%)	2,138 (18.1%)	2.07 (1.88-2.29)***	1.70 (1.51-1.92)***	1.72 (1.43-2.08)***
Cardiogenic shock	56 (1.9%)	189 (1.3%)	1.45 (1.07-1.95)*	1.53 (1.09 -2.16)*	1.62 (0.90-2.94)

*p<0.05; **p<0.01; ***p<0.001. [1] Adjusted for age, heart rate and systolic blood pressure (all divided into quartiles), sex, comorbidities (diabetes, hypertension), congestive heart failure, peripheral artery disease, chronic obstructive pulmonary disease, previous MI, previous stroke, previous PCI, previous coronary artery bypass grafting, culprit vessel, vascular approach (radial vs. femoral puncture site), atrial fibrillation on ECG, choice of $P2Y_{12}$ inhibitor (ticagrelor vs. clopidogrel), system delay ≤2 hours vs. >2 hours and inclusion year. PCI centres was adjusted for as a random effect. LVEF: left ventricular ejection fraction
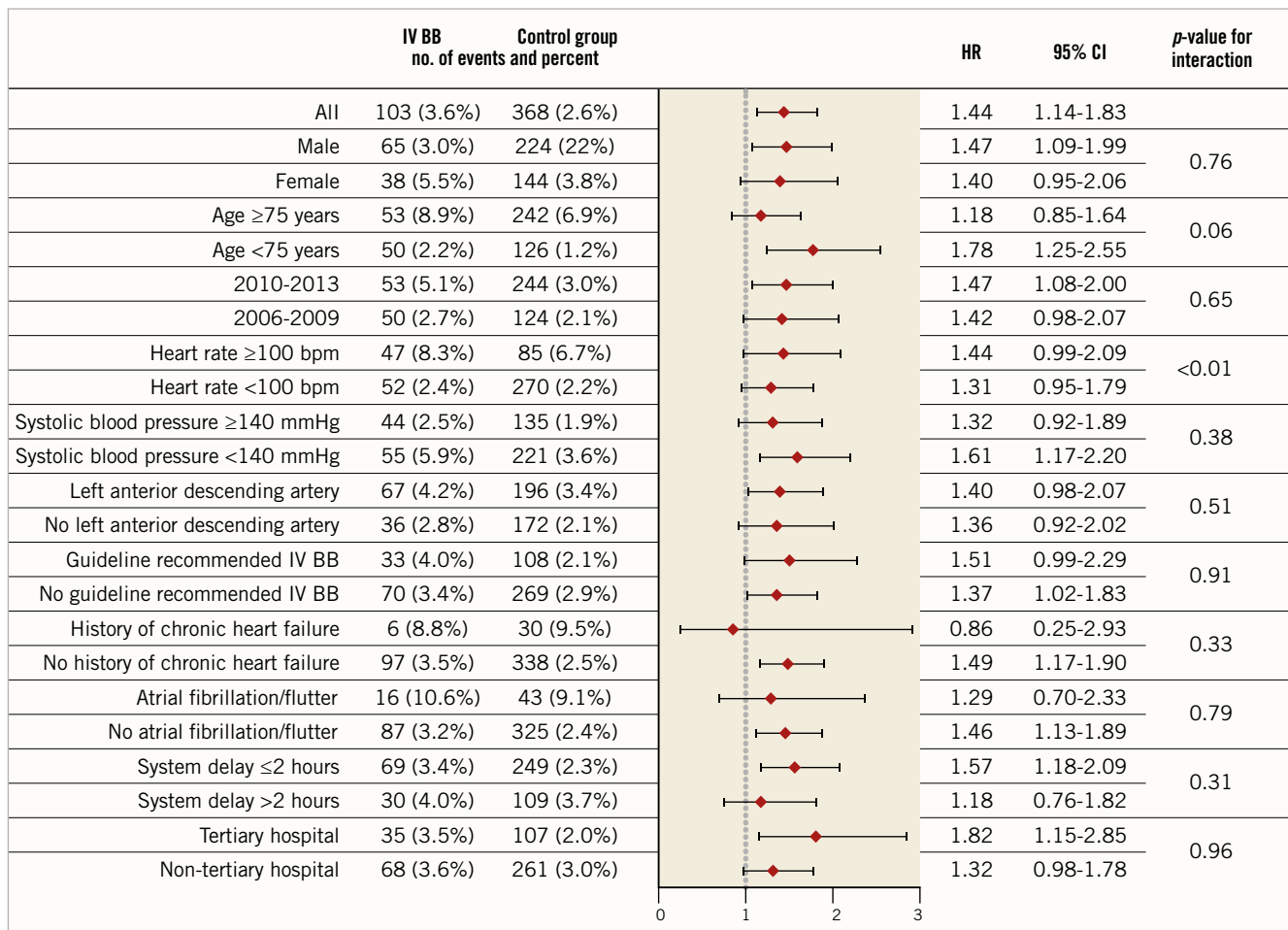
	IV BB	Control group		HR	95% CI	*p*-value for interaction
	no. of events and percent					
All	103 (3.6%)	368 (2.6%)		1.44	1.14-1.83	
Male	65 (3.0%)	224 (22%)		1.47	1.09-1.99	0.76
Female	38 (5.5%)	144 (3.8%)		1.40	0.95-2.06	
Age ≥75 years	53 (8.9%)	242 (6.9%)		1.18	0.85-1.64	0.06
Age <75 years	50 (2.2%)	126 (1.2%)		1.78	1.25-2.55	
2010-2013	53 (5.1%)	244 (3.0%)		1.47	1.08-2.00	0.65
2006-2009	50 (2.7%)	124 (2.1%)		1.42	0.98-2.07	
Heart rate ≥100 bpm	47 (8.3%)	85 (6.7%)		1.44	0.99-2.09	<0.01
Heart rate <100 bpm	52 (2.4%)	270 (2.2%)		1.31	0.95-1.79	
Systolic blood pressure ≥140 mmHg	44 (2.5%)	135 (1.9%)		1.32	0.92-1.89	0.38
Systolic blood pressure <140 mmHg	55 (5.9%)	221 (3.6%)		1.61	1.17-2.20	
Left anterior descending artery	67 (4.2%)	196 (3.4%)		1.40	0.98-2.07	0.51
No left anterior descending artery	36 (2.8%)	172 (2.1%)		1.36	0.92-2.02	
Guideline recommended IV BB	33 (4.0%)	108 (2.1%)		1.51	0.99-2.29	0.91
No guideline recommended IV BB	70 (3.4%)	269 (2.9%)		1.37	1.02-1.83	
History of chronic heart failure	6 (8.8%)	30 (9.5%)		0.86	0.25-2.93	0.33
No history of chronic heart failure	97 (3.5%)	338 (2.5%)		1.49	1.17-1.90	
Atrial fibrillation/flutter	16 (10.6%)	43 (9.1%)		1.29	0.70-2.33	0.79
No atrial fibrillation/flutter	87 (3.2%)	325 (2.4%)		1.46	1.13-1.89	
System delay ≤2 hours	69 (3.4%)	249 (2.3%)		1.57	1.18-2.09	0.31
System delay >2 hours	30 (4.0%)	109 (3.7%)		1.18	0.76-1.82	
Tertiary hospital	35 (3.5%)	107 (2.0%)		1.82	1.15-2.85	0.96
Non-tertiary hospital	68 (3.6%)	261 (3.0%)		1.32	0.98-1.78	

Figure 4. *Forest plot. Adjusted hazard ratios are shown for the primary endpoint. All the subgroups were pre-specified.*

To omit high-risk patients, a core set of exclusion criteria was adopted. Patients already treated with beta-blockers, patients presenting with cardiac arrest or cardiogenic shock and patients who did not receive upstream DAPT were excluded. The rationale behind excluding patients with no upstream DAPT was to exclude patients initially considered unsuitable for invasive intervention. Results were consistent in a sensitivity analysis including patients not pre-treated with DAPT. Our study did not cover the topic of long-term treatment with oral beta-blockers post MI. However, in Sweden oral beta-blockers are usually started within 24-48 hours and up-titrated in-hospital before being prescribed at discharge. In our population, nearly 90% of patients were discharged with a prescription of an oral beta-blocker with a slightly higher rate in the IV beta-blocker group.

STUDY ENDPOINTS

We could not demonstrate any benefit of IV beta-blockers and our results even suggest potential harm. In contrast to the ClOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), our IV beta-blocker group had higher mortality. In accordance with the COMMIT trial, patients treated with IV beta-blockers in our study had a higher incidence of cardiogenic shock than did patients not treated with IV beta-blockers[9]. We also observed a higher incidence of LVEF <40% on discharge echocardiograms in patients treated with IV beta-blockers, perhaps contributing to the higher 30-day mortality in this group. We believe that the observed higher mortality in our study is most likely due to beta-blocker-induced cardiogenic shock, as suggested by the higher rates of cardiogenic shock and the higher usage of IV inotropic drugs during hospitalisation in the IV beta-blocker group. This could possibly explain the delayed curve diversion in our study, as patients who received IV beta-blocker therapy developed cardiogenic shock with subsequent intensive care treatment to a higher extent, resulting in higher mortality at a later stage of hospitalisation. A similar mortality curve was observed in the MIAMI trial in the subgroup of patients considered a low-risk group[6]. It is possible that the over-representation of LAD infarctions in the IV beta-blocker group manifested in reduced LVEF at discharge and contributed to the observed higher mortality. However, our results remained consistent after adjusting for culprit vessel and, although hidden confounding cannot be ruled out, results were consistent in the PS-matched population, in which rates of LAD infarction were

equal between both groups. Furthermore, no difference in outcome was observed in the subgroup analysis of LAD infarctions vs. non-LAD infarctions. In the sensitivity analysis of LVEF <40% at discharge in LAD vs. non-LAD infarctions, IV beta-blocker use was associated with lower LVEF at discharge in both subgroups with no interaction indicating that the association of reduced EF was independent of culprit vessel **(Figure 5)**. Interestingly, the association of decreased ejection fraction at discharge with IV beta-blocker therapy was observed in the COMMIT trial as well as in the GUSTO-1 experience as an increase in patients developing heart failure in the IV beta-blocker group, whereas the opposite was noted in the METOCARD-CNIC trial; patients allocated IV metoprolol had a higher EF at discharge and fewer heart failure hospitalisations[9,12,13].

In our study, patients treated with IV beta-blockers were younger, had a comparable comorbidity pattern compared to controls and were equally well treated at discharge. Our results are therefore not likely to be biased by the IV beta-blocker group being frailer, although this cannot be excluded. The higher mortality was not observed in the landmark analyses after 30 days from admission, further suggesting a low rate of residual confounding, although it cannot definitely be ruled out.

In an observational study with data from the Global Registry of Acute Coronary Events (GRACE), Park et al presented data on patients treated between 2000-2007. In this study, only 40% were treated with PCI, and results were in accordance with our study with cardiogenic shock being more prevalent in patients treated with an IV beta-blocker therapy[18]. In a substudy from the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial, the 30-day mortality was significantly reduced with IV beta-blockers. In this study, the IV beta-blocker group was four years younger at baseline, had lower rates of previous myocardial infarction and renal failure and higher rates of LAD infarction. Furthermore, there were significant differences in discharge medications, i.e., oral beta-blocker, ACE-inhibitor and statin prescription rates were significantly higher in the IV beta-blocker group[11].
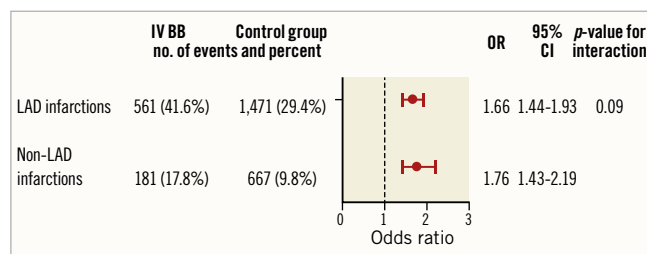
TRENDS IN THE USE OF IV BETA-BLOCKERS
During the study period we observed a steady decline in the use of IV beta-blockers in STEMI patients and an increase in patients treated with PCI and DAPT. This could indicate that clinicians have become more restrictive with IV beta-blocker therapy in favour of watchful waiting for patients to stabilise and slowly up-titrating oral beta-blockers to minimise the risk of cardiogenic shock. This trend was also seen in the GRACE study[18].

CURRENT PERSPECTIVES
METOCARD-CNIC and EARLY-BAMI are the most recent trials assessing the effect of early IV beta-blocker administration on myocardial infarct size[19]. Although the METOCARD-CNIC trial did show reduced infarct size in patients who received an IV beta-blocker, only patients with anterior infarctions were included and a trend towards larger myocardium at risk was also observed in the control group. The EARLY-BAMI trial on the other hand failed to show any superiority with preprocedural IV beta-blocker therapy and with no association of any adverse events[14].

The limited available data from contemporary trials thus show conflicting results. Our study shows no clinical improvement with IV beta-blocker therapy in STEMI patients undergoing primary PCI, results in accordance with the EARLY-BAMI trial. In addition, we observed potential harm from IV beta-blocker use, most likely due to beta-blocker-induced cardiogenic shock. IV beta-blocker therapy in STEMI patients undergoing primary PCI should perhaps be reserved for selected patients only, although this would require a larger randomised trial to confirm.

Limitations
Because of this study's observational design, residual confounding and indication bias cannot be ruled out. Despite neutralising most of the baseline differences with PS matching, remaining baseline differences were still observed. As with all observational studies, hidden confounding may have affected the results. Since IV beta-blocker treatment decreased over time, time bias may have affected our results in favour of the control group. This is illustrated with the radial puncture approach and switching to ticagrelor, which were both less common in the IV beta-blocker group. Although we adjusted for both inclusion year and vascular approach, there could remain unmeasured time-dependent period effects biasing the results. Therefore, no definite conclusion of causality can be drawn and the results should be seen as hypothesis-generating. The exclusion of patients on previous regular beta-blocker treatment has been used in other beta-blocker studies, i.e., the METOCARD-CNIC trial; however, it cannot be excluded that this might have resulted in increased rates of patients with relative or absolute contraindication to beta-blockers in our population, as supported by the slightly lower HR in the sensitivity analysis. A more specific limitation is the lack of information regarding the exact time and dose of IV beta-blocker administered.

Our study has a number of strengths. It is a nationwide study, including nearly 17,000 patients treated according to up-to-date

	IV BB	Control group	OR	95% CI	*p*-value for interaction
	no. of events and percent				
LAD infarctions	561 (41.6%)	1,471 (29.4%)	1.66	1.44-1.93	0.09
Non-LAD infarctions	181 (17.8%)	667 (9.8%)	1.76	1.43-2.19	

Figure 5. *Sensitivity analysis. Adjusted odds ratios are shown for the endpoint LVEF <40% in LAD vs. non-LAD infarctions, showing an associated higher OR for LVEF <40% at discharge with IV beta-blockers in both subgroups with no interaction, indicating that the association of reduced EF was independent of the culprit vessel.*

guidelines with PCI and upstream DAPT, and was retrieved from a validated large population-based registry.

Conclusions

In this large nationwide Swedish observational study, the use of IV beta-blockers in patients with STEMI treated with primary PCI was associated with higher short-term mortality, lower LVEF at discharge as well as a higher risk of in-hospital cardiogenic shock. A clinical trial investigating these questions, as relevant today as they were almost 40 years ago, is therefore needed. Until then, routine IV beta-blocker administration is questionable and should perhaps be reserved to carefully selected patients.

Impact on daily practice

Intravenous beta-blockers are still commonly used for STEMI patients treated with PCI despite the lack of solid evidence of benefit. Our registry results indicate a lack of benefit and even a potential risk of harm. Randomised studies regarding the use of IV beta-blockers in patients with STEMI revascularised with PCI are warranted. Until then, routine IV beta-blocker administration should perhaps be reserved to carefully selected patients.

Conflict of interest statement

P. Andell has received speaker honoraria from AstraZeneca. D. Erlinge has received speaker honoraria from AstraZeneca. T. Jernberg has received lecture and consultant fees from AstraZeneca and Aspen. S. Koul has received speaker honoraria from Pfizer, BMS and AstraZeneca. H. Persson has received lecture fees from Novartis. J. Spaak has received speaker honoraria from MSD, Hospira Nordic, ResMed, Baxter, Astellas Pharma and Medtronic. The other authors have no conflicts of interest to declare.

References

1. Freemantle N, Cleland J, Young P, Mason J, Harrison J. beta Blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ.* 1999;318:1730-7.

2. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* 2012;33:2569-619.

3. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;127:e362-425.

4. Rasmussen MM, Reimer KA, Kloner RA, Jennings RB. Infarct size reduction by propranolol before and after coronary ligation in dogs. *Circulation.* 1977;56:794-8.

5. Hjalmarson A, Elmfeldt D, Herlitz J, Holmberg S, Malek I, Nyberg G, Ryden L, Swedberg K, Vedin A, Waagstein F, Waldenstrom A, Waldenstrom J, Wedel H, Wilhelmsen L, Wilhelmsson C. Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial. *Lancet.* 1981;2:823-7.

6. Metoprolol in acute myocardial infarction (MIAMI). A randomised placebo-controlled international trial. The MIAMI Trial Research Group. *Eur Heart J.* 1985;6:199-226.

7. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative Group. *Lancet.* 1986;2:57-66.

8. Pfisterer M, Cox JL, Granger CB, Brener SJ, Naylor CD, Califf RM, van de Werf F, Stebbins AL, Lee KL, Topol EJ, Armstrong PW. Atenolol use and clinical outcomes after thrombolysis for acute myocardial infarction: the GUSTO-I experience. Global Utilization of Streptokinase and TPA (alteplase) for Occluded Coronary Arteries. *J Am Coll Cardiol.* 1998;32:634-40.

9. Chen ZM, Pan HC, Chen YP, Peto R, Collins R, Jiang LX, Xie JX, Liu LS; COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet.* 2005;366:1622-32.

10. Roberts R, Rogers WJ, Mueller HS, Lambrew CT, Diver DJ, Smith HC, Willerson JT, Knatterud GL, Forman S, Passamani E, et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) II-B Study. *Circulation.* 1991;83:422-37.

11. Halkin A, Grines CL, Cox DA, Garcia E, Mehran R, Tcheng JE, Griffin JJ, Guagliumi G, Brodie B, Turco M, Rutherford BD, Aymong E, Lansky AJ, Stone GW. Impact of intravenous beta-blockade before primary angioplasty on survival in patients undergoing mechanical reperfusion therapy for acute myocardial infarction. *J Am Coll Cardiol.* 2004;43:1780-7.

12. Ibanez B, Macaya C, Sanchez-Brunete V, Pizarro G, Fernandez-Friera L, Mateos A, Fernandez-Ortiz A, Garcia-Ruiz JM, Garcia-Alvarez A, Iniguez A, Jimenez-Borreguero J, Lopez-Romero P, Fernandez-Jimenez R, Goicolea J, Ruiz-Mateos B, Bastante T, Arias M, Iglesias-Vazquez JA, Rodriguez MD, Escalera N, Acebal C, Cabrera JA, Valenciano J, Perez de Prado A, Fernandez-Campos MJ, Casado I, Garcia-Rubira JC, Garcia-Prieto J, Sanz-Rosa D, Cuellas C, Hernandez-Antolin R, Albarran A, Fernandez-Vazquez F, de la Torre-Hernandez JM, Pocock S, Sanz G, Fuster V. Effect of early metoprolol on infarct size in ST-segment-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial. *Circulation.* 2013;128:1495-503.

13. Pizarro G, Fernandez-Friera L, Fuster V, Fernandez-Jiménez R, Garcia-Ruiz JM, Garcia-Alvarez A, Mateos A, Barreiro MV, Escalera N, Rodriguez MD, de Miguel A, Garcia-Lunar I, Parra-Fuertes JJ, Sanchez-Gonzalez J, Pardillos L, Nieto B, Jiménez A, Abejon R, Bastante T, Martinez de Vega V, Cabrera JA, Lopez-Melgar B, Guzman G, Garcia-Prieto J, Mirelis JG, Zamorano JL, Albarran A, Goicolea J, Escaned J, Pocock S, Iniguez A, Fernandez-Ortiz A, Sanchez-Brunete V, Macaya C, Ibanez B. 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). *J Am Coll Cardiol.* 2014;63:2356-62.

14. Roolvink V, Ibanez B, Ottervanger JP, Pizarro G, van Royen N, Mateos A, Dambrink JE, Escalera N, Lipsic E, Albarran A, Fernandez-Ortiz A, Fernandez-Aviles F, Goicolea J, Botas J, Remkes W, Hernandez-Jaras V, Kedhi E, Zamorano JL, Navarro F, Alfonso F, Garcia-Lledo A, Alonso J, van Leeuwen M, Nijveldt R, Postma S, Kolkman E, Gosselink M, de Smet B, Rasoul S, Piek JJ, Fuster V, van 't Hof AW, EARLY-BAMI Investigators. Early Intravenous Beta-Blockers in Patients With ST-Segment Elevation Myocardial Infarction Before Primary Percutaneous Coronary Intervention. *J Am Coll Cardiol.* 2016;67:2705-15.

15. Jernberg T. SWEDEHEART Annual report 2014. 2015. http://www.ucr.uu.se/swedeheart/arsrapport-2015/aeldre-arsrapporter-older-reports/arsrapport-2014.

16. Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A, Lagerqvist B, Lindahl B, Stenestrand U, Wallentin L. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *Heart.* 2010;96:1617-21.

17. American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions, O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;61:e78-140.

18. Park KL, Goldberg RJ, Anderson FA, Lopez-Sendon J, Montalescot G, Brieger D, Eagle KA, Wyman A, Gore JM; Global Registry of Acute Coronary Events Investigators. Beta-blocker use in ST-segment elevation myocardial infarction in the reperfusion era (GRACE). *Am J Med.* 2014;127:503-11.

19. Roolvink V, Rasoul S, Ottervanger JP, Dambrink JH, Lipsic E, van der Horst IC, de Smet B, Kedhi E, Marcel Gosselink AT, Piek JJ, Sanchez-Brunete V, Ibanez B, Fuster V, Van't Hof AW, EARLY-BAMI investigators. Rationale and design of a double-blind, multicenter, randomized, placebo-controlled clinical trial of early administration of intravenous β-blockers in patients with ST-elevation myocardial infarction before primary percutaneous coronary intervention: EARLY β-blocker administration before primary PCI in patients with ST-elevation myocardial infarction trial. *Am Heart J.* 2014;168:661-6.