Comparison of Early-vs-Delayed Oral Beta-Blockers in Acute Coronary Syndromes and Effect on Outcomes

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Comparison of Early-vs-Delayed Oral Beta-Blockers in Acute Coronary Syndromes and Effect on Outcomes

Brief title: Beta-Blockers in Acute Coronary Syndromes

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ABSTRACT

The aim of this study was to determine if earlier administration of oral beta-blocker therapy in patients with acute coronary syndromes (ACSs) is associated with increased short-term survival and improved left ventricular (LV) function. We studied 11,581 patients enrolled in the International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-TC) registry from January 2010 to June 2014. Of these patients, 6,117 were excluded as they received intravenous beta-blockers or remained free of any beta-blocker treatment during hospital stay, 23 with unknown timing of oral beta-blocker administration was unknown and 182 because they had death before oral beta-blockers could be given. The final study population comprised 5,259 patients. The primary outcome was the incidence of in-hospital mortality. The secondary outcome was the incidence of severe LV dysfunction defined as an ejection fraction <40% at hospital discharge. Oral beta-blockers were administered soon (≤24 hours) after hospital admission in 1,377 patients and later (>24 hours) during hospital stay in the remaining 3,882 patients. Early beta-blocker therapy was significantly associated with reduced in-hospital mortality (odds ratio [OR] 0.41, 95% confidence interval [CI] 0.21 to 0.80) and reduced incidence of severe LV dysfunction (OR 0.57, 95% CI 0.42 to 0.78). Significant mortality benefits with early beta-blocker therapy disappeared when patients with Killip Class III/IV were included as dummy variables. The results were confirmed by propensity score-matched analyses. In conclusion, in patients with ACSs, earlier administration of oral beta-blocker therapy should be a priority with a higher probability of improving LV function and in-hospital survival. Patients presenting with acute pulmonary edema or cardiogenic shock should be excluded from this early treatment regimen.

Key Words: Acute Coronary Syndrome; Beta-Blockers; Timing; In-hospital mortality.

There is a general consensus that pre-discharge oral beta-blocker therapy leads to improved long-term clinical outcome in patients with acute coronary syndromes (ACSs) although, within the framework of an in-hospital treatment strategy, there is a paucity of data on precisely defining when beta-blockers should be started. The most recent practice guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA) recommend that oral beta-blocker therapy should be given in the first 24 hours if patients are at low risk for cardiogenic shock [1,2]. Risk of cardiogenic shock, in turn, is based on findings from the COMMIT/CCS-2 (Chinese Clopidogrel and Metoprolol in Myocardial Infarction Trial) study [3]. American recommendation is not reflected by the practice guidelines of the European Society of Cardiology (ESC) where decisions on whether to give beta-blocker therapy within 24 hours from admission or several days later are left at physicians' discretion [4,5]. When solid evidence exists, guidelines tend to put forward largely overlapping recommendations. Further data are, therefore, needed on the relation between outcome and time to beta-blocker treatment in patients with ACS. The current study was undertaken to examine the effects of early versus late oral beta-blocker therapy in patients who had stabilized after an ACS.

METHODS

The details of the International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-TC) registry protocol (ClinicalTrials.gov: NCT01218776) have been previously published [6,7]. Briefly, the ISACS-TC is both a retrospective -over a one year period- and prospective study which was designed in order to obtain data of patients with ACSs, and herewith control and optimize internationally guideline recommended therapies in countries with economy in transition. Data collection activities began in October 2010 with the aim of collecting data on approximately 3000 patients hospitalized with ACS on an annual basis. A total of 57 cluster sites in 11 countries in Central and Eastern Europe are currently collaborating in

ISACS- TC (Supplemental material). There were 29 tertiary healthcare services providing advanced medical investigation and treatment including percutaneous coronary intervention (PCI) and/ or cardiac surgery, and 28 secondary healthcare services providing intensive care in critical coronary care units.The study was approved by the local research ethics committee from each hospital. Patients provided written consent for evaluation of their medical notes and monitoring of their health status.

To avoid survival bias, as patients who were selected for the study would have to survive enough to received benefits from medications, a landmark time was used. We defined the landmark time as a 24 hours survival interval from beta-blocker administration. The analysis then evaluated patients' outcome from the landmark time through to the end of the follow-up period (death or hospital discharge). Patients were also excluded from the analysis if they received intravenous beta-blockers or if they remained free of any beta-blocker treatment during hospital stay (Figure 1).

The primary outcome was the incidence of in-hospital mortality. The secondary outcome was the incidence of severe left ventricular (LV) dysfunction defined as an ejection fraction by echocardiography <40% at hospital discharge. Moreover, to analyze the risk of shock as a potential confounder, the COMMIT shock index score was calculated for each patient (0 to 2 points=low-risk; 3 to 4 point=high-risk) [3]. The shock index includes the following variables: age >70 years, symptom onset more than 12 hours, systolic blood pressure (BP) <120 mmHg, and heart rate >110 bpm [3].

Patients were stratified by time from hospital presentation to beta-blocker treatment whether early (≤24 hours) or delayed (>24 hours to discharge). Baseline characteristics, in-hospital therapies and clinical outcomes were assessed. Patients were also stratified according to

the index event: ST-segment elevation myocardial infarction (STEMI) versus non-ST-segment elevation ACS (NSTE-ACS) [8] and in-hospital management strategies (overall population versus only routine medical therapy [RMT]). Standard initial routine medical therapies include use of antiplatelet agents with aspirin and P2Y12 inhibitors, and anticoagulation with enoxaparin, bivalirudin, fondaparinux, or unfractionated heparin. In addition to standard initial antiplatelet/anticoagulant therapy, angiotensin-converting enzyme (ACE) inhibitors and beta-blockers could be started and continued indefinitely. Statistical testing was performed using a Chi-square test for baseline categorical variables and a two sample *t*-test for continuous variables. Estimates of the odds ratio (OR) and associated 95% confidence intervals (CI) were obtained using the multivariable logistic regression analysis, adjusting the differences in baseline patient characteristics and medications given in the first 24 hours. Constant covariates included in the analyses were: 1) sex, 2) age, cardiovascular risk factors: 3) hypercholesterolemia, 4) diabetes, 5) hypertension, 6) current smoker, 7) family history of coronary artery disease (CAD), 8) clinical history of cardiovascular heart disease (prior angina, prior myocardial infarction, prior coronary artery bypass graft and PCI, prior heart failure, peripheral artery disease, prior stroke), 9) chronic kidney disease, 10) time from symptom onset to admission < 12 hours and 11) STEMI as index event. Covariates introduced as dummy variables were: use of fibrinolysis, aspirin, clopidogrel, heparins (unfractioned heparin) ACE inhibitors and Killip class III/ IV. For all analysis, statistical significance was defined as a value of $p<0.05$ and STATA 11 (StataCorp. College Station, TX, USA) was used.

Logistic regression analyses were used to obtain the estimated probabilities P and the logits (logit = ln(P/(1-P)), which were considered for the propensity score. The treatment variable (early beta-blocker treatment yes/no) was the outcome and the pre-treatment covariates were the same 11 predictor variables entered in the above mentioned multivariate models. We,

then, assessed early beta-blocker versus delayed treatment effects by NCSS (©) version 9 routines for data matching (NCSS 9. NCSS, LLC. Kaysville, Utah, USA: www.ncss.com). Patients were matched without replacement on a 1:1 basis using a nearest neighbor (Greedy) algorithm based on Mahalanobis distance.

RESULTS

The baseline characteristics, in-hospital treatments, and outcomes of the overall study population (n=5,259) and the RMT sub-group (n=2,601) stratified according to time from hospital presentation to beta-blocker administration are listed in Table 1. Average hospital stay was 7.8 ± 5.4 days among all patients and 8.2 ± 5.7 days among RMT patients. The corresponding values for median stay were respectively 7 and 7 days. Unadjusted in-hospital mortality was higher in the RMT group (4.8% versus 3.4%; OR 2.31, 95% CI 1.68 to 3.19, p<0.001). After adjustment RMT was still associated with higher mortality compared with that of the overall cohort (OR 1.65, 95% CI 1.08 to 2.51, p=0.02). There were no significant differences in the in-hospital rates of death or severe LV dysfunction in patients who underwent beta-blocker therapy ≤6 hours versus those who had such therapy >6 to 24 hours after clinical presentation. In contrast, patients who underwent beta-blocker therapy >24 hours after clinical presentation had higher rates of death and severe LV dysfunction in comparison with those who underwent earlier therapy (Figure 2). The relations between beta-blocker use ≤24 hours and subsequent end-points are shown in Table 2. The use of beta-blockers ≤24 hours was significantly associated with lower in-hospital mortality and lower incidence of severe LV dysfunction in the whole population. A qualitatively similar reduction in risk was seen in the RMT subgroup. After multivariable adjustment for demographic and clinical factors, early beta-blocker treatment remained a strong independent factor associated with better outcomes. STEMI patients treated with early beta-blockers had lower rates of adjusted in-hospital mortality and

incidence of severe LV dysfunction. In the NSTE-ACS subgroup the adjusted OR remained significantly associated with lower incidence of severe LV dysfunction, but not with decreased in-hospital mortality (Figure 3). The adjusted OR associated with early beta-blocker therapy did not change when controlling for fibrinolytic, antiplatelet and anticoagulant agents (Table 2). Additional analysis revealed that the favorable outcomes associated with early beta-blocker treatment disappeared after adjustment for concurrent ACE-inhibitors administration, suggesting an interaction between these two compounds. A regression model was, therefore, used to evaluate whether the treatment effects of these medications may have interacted. Beta-blockers scored significantly for both lower incidence of both in-hospital mortality (OR 0.43, 95% CI 0.20 to 0.92, p=0.03) and occurrence of severe LV dysfunction at discharge (OR 0.42, 95% CI 0.29 to 0.62, p<0.001). On the opposite, ACE-inhibitors did not show significant effects either on death (OR 0.62, 95% CI 0.29 to 1.32, p=0.21) or severe LV dysfunction (OR 1.44, 95% CI 0.98 to 2.14, p=0.06). Significant benefits in mortality with early beta-blocker therapy disappeared when patients with Killip Class > II were included in the analysis (Table 2), indicating that patients with acute pulmonary oedema or cardiogenic shock should be excluded from an early beta-blocker treatment regimen. We also investigated the relation between beta-adrenergic blocker use and clinical correlates of LV function at hospital admission, by using the COMMIT-shock index score. We calculated the COMMIT-shock index estimates only for patients with Killip class I/II, as for definition patients with Killip Class III/IV have shock or high risk for shock (Table 3). In this lower risk population, approximately half (45%) of STEMI patients and almost two thirds (65%) of NSTE-ACS patients had two or more risk factors for shock. Multivariable regression analysis indicated that all of the individual factors entering the shock index were associated with increased in-hospital mortality. However**,** after adjustment for these factors, early beta-blocker use was still significantly associated with better outcomes

(Table 3). Delay to beta-blocker therapy >24 hours after clinical presentation was associated with significant increases in the rates of severe LV dysfunction among high shock risk score (2 or more factors) patients (Figure 2). There were very few deaths (n=23) among patients with Killip class I/II. Therefore the increased risk of death with delayed beta-blocker therapy was not adequately powered to evaluate differences. Finally, the association between acute beta-blocker therapy and in-hospital clinical outcomes also was assessed using propensity score analysis The C-statistic for the propensity score logistic regression-based model was 0.70, thus indicating a good discriminatory power. Based on this propensity score we matched 927 patients using a 1:1 model with 11 covariates for early versus delayed treatment (Table 4). The logit propensity scores of early versus delayed beta-blocker administration were -0.252 ± 0.704 and -0.240 ± 0.692, respectively (p=ns). The incidence of the in-hospital mortality was lower in patients with early beta-blocker treatment as compared with their delayed treatment counterpart: 1.2% (11/927) versus 2.7% (25/927, p=0.018).

DISCUSSION

The main findings of this analysis are: (1) delay to oral beta-blocker administration >24 hours after clinical presentation is a strong, independent predictor of increased in-hospital mortality and incidence of severe LV dysfunction across patients presenting in Killip Class I and II; (2) the relative risk attributable to beta-blocker administration delay is greatest in STEMI patients; (3) benefits of an early administration were independent of an invasive management strategy and COMMIT-shock index scores and (4) the results are confirmed by propensity score matching.

The COMMIT trial's investigators found that while early intravenous beta-blockers reduced the risk of death from ventricular fibrillation, and re-infarction, they also can significantly increase the risk of cardiogenic shock especially during the first day after admission

[3]. In response to the COMMIT results, the ACC/AHA in their updated guidelines on care of patients with STEMI [2] acknowledged that some patients are not appropriate for early, ≤24hours, beta-blocker therapy, namely those patients presenting with high risk for cardiogenic shock. Additionally, the guidelines stated that early intravenous beta-blockers should specifically be avoided in most patient populations. Despite these recommendations, there seems to be no clear consensus among the international cardio-vascular community regarding the appropriate time of treatment with beta-blockers in ACS patients. Accordingly, the ESC treatment guidelines in this setting are vague. Early beta-blocker treatment is feasible, but guidelines recommend waiting for the patient to stabilize before starting therapy. Differences in recommendations stem from a paucity of evidence supporting benefits of one strategy over the other on short-term outcomes. This may cause some degree of confusion among clinicians and low use of beta-blockers ≤24 hours in patients who have not relative contraindications [9-13]. The uncertain treatment recommendations for these patients are reflected in the different therapeutic strategies used in the real life. In the present large-scale, multicenter registry, the vast majority of ACS patients eligible to beta-blocker therapy were classified as being with no or moderate signs of heart failure, but were prescribed delayed beta-blocker therapy. Only one third (26.2%) of these patients received oral beta-blockers within the first 24 hours from hospitalization. Yet, there was a strong, independent association, of beta-blocker therapy delay >24 with subsequent in-hospital mortality and development of severe LV dysfunction. Clear contraindications to early oral beta-blocker use may include only severe LV dysfunction, as significant mortality benefits with early therapy disappeared when patients with frank acute pulmonary oedema or cardiogenic shock were included in the analysis

The ACC/AHA guidelines recommend that caution should be used when administering oral beta-blocker therapy during the first 24 hours of hospital presentation in those patients who

have risk factors for shock. These risk factors derived from the COMMIT trial and include age, systolic blood pressure, heart rate, and prolonged time from symptom onset to presentation. As general beta-blocker contraindications include signs of overt heart failure and evidence of low-output state, the COMMIT-shock risk factors should represent additional criteria for exclusion from early beta-blockers therapy in the remaining patients. We, therefore, examined the effects of early oral beta-blocker therapy according to clinical presentation, i.e. in those patients without documented severe heart failure or shock at admission (Killip Class III/IV). Of note, there was no evidence to suggest different outcomes following early beta-blockade in patients having high COMMIT-shock index scores, which implies that risk factors for shock do not confer additional prognostic information beyond that given by the well established Killip class classification.

Few studies have examined the care and outcomes of patients with ACS who do not receive revascularization therapy [7, 14]. Yet, many of these studies were performed before the use of reperfusion therapy with either fibrinolysis or PCI, and mainly focused on beta-blockers as part of therapy in the secondary prevention [15-19]. There are no contemporary large studies specifically addressing the efficacy of beta-blockers on short-term outcomes in this population. We found that early oral beta-blocker use during an ACS significantly preserves left ventricular function compared with delayed treatment, thereby suggesting significant myocardial salvage. Conversely, the data remains inconclusive regarding the benefit on mortality.

The present investigation is the largest to date examining the impact of orally administered beta-blockers and their treatment-related delays on patient outcomes in ACS patients. There are no randomized controlled trials of oral beta-blockers in the setting of ACS [12, 20-22]. Other observational studies describing the impact of the timing of beta-blocker administration on outcomes of patients with ACS are inconsistent for comparison with our data, since these studies are pooled together patients treated both orally and intravenously [23-25].

Furthermore, we created a propensity score for the likelihood [26-28] of undergoing in-hospital mortality using multiple logistic regressions with early versus delayed beta-blocker treatment as dependent variables and baseline clinical characteristics of the cohort as covariates including the index event. The results of the current study were therefore consistent among the two diagnostic groups: STEMI and NSTE-ACS

Our study has some limitations. This study is a post-hoc analysis, and our findings should therefore be interpreted as hypothesis-generating. Although the propensity score helps to adjust for differences between groups, it does not control for unmeasured differences in clinical care. The lack of beta-blocker dosage restricted our ability to assess the dose-dependent effect of potential drug interaction. The study excluded 6,322 individuals, as they received intravenous beta-blockers or remained free of any beta-blocker treatment during hospital stay. The evidence for beta-blocker benefits in post-ACS patient is strong. Conversely, not all studies have consistently demonstrated benefit of early intravenous beta-blocker therapy. We therefore focused our investigation on the controversial issue on timing of in-hospital oral administration rather than on benefits of beta-blocker use whatever the time or the route of administration is. Despite these caveats, the present findings, taken in concert with those from earlier studies suggest that patients with ACS and low Killip class benefit from urgent oral beta-blocker administration given early (≤24 hours).

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REFERENCES

1. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ; ACC/AHA Task Force Members. 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;130:e344-e426.
2. 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-e425.
3. 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;366:1622-1632.
4. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. 2015 ESC Guidelines for the management of acute

coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2015 doi: 10.1093/eurheartj/ehv320.

5. 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, Blömstrom-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;33:2569-2619.
6. Bugiardini R, Badimon L, Manfrini O, on the behalf of the ISACS-TC Investigators. Rationale and design of the ISACS-TC (International Survey of Acute Coronary Syndromes in Transitional Countries) project. *Eur Heart J Suppl* 2014; 16: A1-A6.
7. Bugiardini R, Dorobantu M, Vasiljevic Z, Kedev S, Knežević B, Miličić D, Calmac L, Trninic D, Daullxhiu I, Cenko E, Ricci B, Puddu PE, Manfrini O, Koller A, Badimon L; ISACS-TC Investigators Unfractionated heparin-clopidogrel interaction in ST-elevation myocardial infarction not receiving reperfusion therapy. *Atherosclerosis* 2015;241:151-156.
8. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *Nat Rev Cardiol* 2012;9:620-633.
9. Goldberger JJ, Bonow RO, Cuffe M, Dyer A, Rosenberg Y, O'Rourke R, Shah PK, Smith SC Jr, PACE-MI Investigators. Beta-Blocker use following myocardial infarction: low prevalence of evidence-based dosing. *Am Heart J* 2010;160:435-442.e1.

10. Green BK, Gordon GD, Horak AR, Millar RN, Commerford PJ. Safety of combined intravenous beta-adrenergic blockade (atenolol or metoprolol) and thrombolytic therapy in acute myocardial infarction. *Am J Cardiol* 1992;69:1389-1392.
11. The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) phase II trial. *N Engl J Med* 1989;320:618-627.
12. Roberts R, Rogers WJ, Mueller HS, Lambrew CT, Diver DJ, Smith UH, Willerson JT, Knatterud GL, Forman S, Passamani E, Zaret BL, Wackers FJT, Braunwald E, for the TIMI Investigators. 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;83:422-437.
13. 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;32:634-640.
14. Tatu-Chitoiu G, Cinteza M, Dorobantu M, Udeanu M, Manfrini O, Pizzi C, Vintila M, Ionescu DD, Craiu E, Burghina D, Bugiardini R. In-hospital case fatality rates for acute myocardial infarction in Romania. *CMAJ* 2009;180:1207-1213.
15. Hjalmarson A, Elmfeldt D, Herlitz J, Holmberg S, Málek I, Nyberg G, Rydén L, Swedberg K, Vedin A, Waagstein F, Waldenström A, Waldenström J, Wedel H, Wilhelmsen L, Wilhelmsson C. Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial. *Lancet* 1981;2:823-827.

16. 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.
17. Van de Werf F, Janssens L, Brzostek T, Mortelmans L, Wackers FJ, Willems GM, Heidbüchel H, Lesaffre E, Scheys I, Collen D. Short-term effects of early intravenous treatment with a beta-adrenergic blocking agent or a specific bradycardiac agent in patients with acute myocardial infarction receiving thrombolytic therapy. *J Am Coll Cardiol* 1993;22:407-416.
18. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* 1981;304:801-807.
19. Hjalmarson A, Herlitz J, Holmberg S, Rydén L, Swedberg K, Vedin A, Waagstein F, Waldenström A, Waldenström J, Wedel H, Wilhelmsen L, Wilhelmsson C. The Göteborg metoprolol trial. Effects on mortality and morbidity in acute myocardial infarction. *Circulation* 1983;67:I26-I32.
20. Risenfors M, Gustavsson G, Ekström L, Hartford M, Herlitz J, Karlson BW, Luepker R, Swedberg K, Wennerblom B, Holmberg S. Prehospital thrombolysis in suspected acute myocardial infarction: results from the TEAHAT Study. *J Intern Med Suppl* 1991;734:3-10.
21. Ibanez B, Macaya C, Sánchez-Brunete V, Pizarro G, Fernández-Friera L, Mateos A, Fernández-Ortiz A, García-Ruiz JM, García-Álvarez A, Iñiguez A, Jiménez-Borreguero J, López-Romero P, Fernández-Jiménez R, Goicolea J, Ruiz-Mateos B, Bastante T, Arias M, Iglesias-Vázquez JA, Rodriguez MD, Escalera N, Acebal C, Cabrera JA, Valenciano J, Pérez de Prado A, Fernández-Campos MJ, Casado I, García-Rubira JC, García-Prieto J, Sanz-Rosa D, Cuellas C, Hernández-Antolín R, Albarrán A, Fernández-Vázquez F, de la Torre-Hernández 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;128:1495-1503.

22. Metoprolol in acute myocardial infarction (MIAMI). A randomised placebo-controlled international trial. The MIAMI Trial Research Group. *Eur Heart J* 1985;6:199-226.
23. Miller CD, Roe MT, Mulgund J, Hoekstra JW, Santos R, Pollack CV Jr, Ohman EM, Gibler WB, Peterson ED. Impact of acute beta-blocker therapy for patients with non-ST-segment elevation myocardial infarction. *Am J Med* 2007;120:685-692.
24. Kontos MC, Diercks DB, Ho PM, Wang TY, Chen AY, Roe MT. Treatment and outcomes in patients with myocardial infarction treated with acute β-blocker therapy: results from the American College of Cardiology's NCDR(®). *Am Heart J* 2011;161:864-870.
25. Park KL, Goldberg RJ, Anderson FA, López-Sendón 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;127:503-511
26. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41-55.
27. D'Agostino RB Jr. Propensity scores in cardiovascular research. *Circulation* 2007;115:2340-2343.
28. Bugiardini R, Eskola M, Huhtala H, Niemelä K, Karhunen P, Miglio R, Manfrini O, Pizzi C, Nikus K. Coronary revascularisation in stable patients after an acute coronary syndrome: a propensity analysis of early invasive versus conservative management in a register-based cohort study. *BMJ Open* 2013;24; 3: pii: e002559.

FIGURE LEGENDS:

Figure 1: Consort flow diagram.

BB indicates oral beta-blockers; RMT indicates routine medical therapy

Figure 2: Timing of beta blocker administration and outcomes

BB indicates oral beta-blockers

Figure 3: Effects of early beta-blocker administration on cardiovascular endpoints according to the index event.

Multivariate model adjusted for sex, age, hypercholesterolemia, diabetes mellitus, hypertension, current smoker, family history of coronary artery disease, clinical history of cardiovascular disease (including prior angina pectoris, prior myocardial infarction, prior coronary artery bypass graft and percutaneous coronary intervention, prior heart failure, peripheral artery disease and prior stroke), chronic kidney disease and time from symptom onset to admission ≤ 12 hours

LV=left ventricular; NSTE-ACS = non-ST-segment elevation acute coronary syndromes; STEMI = ST-segment elevation myocardial infarction;

Table 1. Baseline Clinical Characteristics

	Overall population				Routine medical therapy				
Variable	**All (n=5,259)**	**Early Beta Blockers administration (n=1,377)**	**Delayed Beta Blockers administration (n=3,882)**	**p value***	**All (n=2,601)**	**Early Beta Blockers administration (n=489)**	**Delayed Beta Blocker administration (n=2,112)**	**p value†**	**p value‡**
Women	1,681 (31.9%)	431 (31.3%)	1,250 (32.2%)	0.53	942 (36.2%)	188 (38.5%)	754 (35.7%)	0.25	<0.001
Age (years)	62.1 ± 11.9	61.8 ± 11.7	62.2 ± 12.1	0.33	64.0 ± 12.3	65.7 ± 11.7	63.6 ± 12.4	<0.001	<0.001
Hypercholesterolemia	2,010 (46.8%)	595 (57.0%)	1,415 (43.5%)	<0.001	885 (43.4%)	162 (58.5%)	723 (41.0%)	<0.001	0.01
Diabetes mellitus	1,256 (25.0%)	313 (23.1%)	943 (25.7%)	0.06	680 (27.8%)	141(29.1%)	539 (27.5%)	0.46	0.009
Hypertension	3,570 (69.5%)	993 (75.0%)	2,577 (67.6%)	<0.001	1,768 (69.8%)	352 (77.9%)	1,416 (68.0%)	<0.001	0.78
Current smoker	1,790 (34.6%)	584 (43.4%)	1,206 (31.5%)	<0.001	744 (29.2%)	174 (36.6%)	570 (27.5%)	<0.001	<0.001
Former smoker	408 (7.9%)	157 (11.7%)	251 (6.6%)	<0.001	218 (8.6%)	49 (10.3%)	169 (8.2%)	0.12	0.28

Family history of CAD	2,032 (41.8%)	378 (29.8%)	1,654 (46.0%)	<0.001	878 (36.4%)	103 (23.5%)	775 (39.2%)	<0.001	<0.001
Prior angina pectoris	1,361 (25.9%)	495 (35.9%)	866 (22.3%)	<0.001	721 (27.7%)	225 (46.0%)	496 (23.5%)	<0.001	0.08
Peripheral artery disease	165 (3.1%)	24 (1.7%)	141 (3.6%)	0.001	106 (4.1%)	12 (2.5%)	94 (4.5%)	0.04	0.02
Prior myocardial infarction	921 (17.5%)	185 (13.4%)	736 (18.9%)	<0.001	544 (20.9%)	96 (19.6%)	448 (21.2%)	0.43	<0.001
Prior coronary artery bypass graft	156 (3.0%)	27 (1.9%)	129 (3.2%)	0.01	104 (4.0%)	17 (3.5%)	87 (4.1%)	0.51	0.009
Prior percutaneous coronary intervention	989 (18.8%)	86 (6.3%)	903 (23.3%)	<0.001	330 (12.7%)	34 (6.9%)	296 (14.0%)	<0.001	<0.001
Prior heart failure	263 (5.0%)	160 (11.6%)	103 (2.7%)	<0.001	159 (6.1%)	75 (15.3%)	84 (4.0%)	<0.001	0.04
Prior stroke	268 (5.1%)	53 (3.8%)	215 (5.5%)	0.01	163 (6.3%)	30 (6.1%)	133 (6.3%)	0.89	0.03
Chronic kidney disease	278 (5.3%)	75 (5.5%)	203 (5.3%)	0.80	180 (7.0%)	42 (8.6%)	138 (6.6%)	0.11	<0.001
Killip class I and II	4,840 (92.0%)	1,324 (96.2%)	3,516 (90.6%)	<0.001	2,294 (88.2%)	453 (92.6%)	1,841 (87.2%)	0.001	<0.001
Time from symptom onset to admission ≤12 hours	3,420 (70.3%)	994 (74.1%)	2,426 (68.8%)	<0.001	1,488 (61.9%)	308 (66.2%)	1,180 (60.9%)	0.03	<0.001
Serum Creatinine (μmol/L)	95.5 ± 73.5	92.2 ± 61.7	104.2 ± 97.4	0.002	10.6 ± 86.3	99.1 ± 54.7	112.9 ± 118.6	0.02	0.006
Heart rate (beats/min)	82.3 ± 25.5	82.9 ± 22.8	81.9 ± 27.5	0.28	83.9 ± 24.9	87.4 ± 30.9	82.4 ± 21.8	<0.001	0.05

Systolic blood pressure (mmHg)	140.5 ± 26.9	143.6 ± 25.3	137.9 ± 28.0	<0.001	140.3 ± 27.7	144.1 ± 25.3	138.7 ± 28.4	<0.001	0.71
Index event									
STEMI	3,742 (71.2%)	846 (61.4%)	2,896 (74.6%)	<0.001	1,595 (61.3%)	202(41.3%)	1,393 (65.9%)	<0.001	<0.001
NSTE-ACS	1,517 (28.8%)	531 (38.6%)	986 (25.4%)	<0.001	1,006 (38.7%)	287 (58.7%)	719 (34.0%)	<0.001	<0.001
In-hospital acute medications (within 24 hours)									
Fibrinolytic therapy	767 (14.6%)	122 (8.9) %	645 (16.7%)	<0.001	557 (21.5%)	85 (17.4%)	472 (22.4%)	0.01	<0.001
Aspirin	5,126 (97.8%)	1,363 (99.1%)	3,763 (97.3%)	<0.001	2,498 (96.3%)	479 (98.2%)	2,019 (95.8%)	0.01	<0.001
Clopidogrel	4642 (88.9%)	1,321 (96.2%)	3,321 (86.3%)	<0.001	2,060 (79.7%)	450 (92.6%)	1,610 (76.7%)	<0.001	<0.001
Unfractioned heparins	2379 (46.1%)	729 (53.1%)	1,650 (43.5%)	<0.001	935 (36.8%)	12 0 (24.6%)	815 (39.7%)	<0.001	<0.001
Low molecular weight heparins	1857 (41.9%)	880 (64.2%)	977 (31.9%)	<0.001	1,131 (49.9%)	403 (82.8%)	728 (40.9%)	<0.001	<0.001
Fondaparinux	70 (1.6%)	19 (1.4%)	51 (1.7%)	0.48	46 (2.0%)	3 (0.6%)	43 (2.4%)	0.01	0.23
Glycoprotein IIb/IIIa inhibitors	225 (7.4%)	87 (6.4%)	138 (8.2%)	0.05	20 (1.2%)	1 (0.2%)	19 (1.6%)	0.01	<0.001
Beta-blockers	1377 (26.2%)	1,377 (100%)	-	-	489 (18.8%)	489 (100.0%)	-	-	<0.001
ACE inhibitor	1244 (27.7%)	1,156 (95.2%)	88 (2.7%)	<0.001	432 (19.6%)	404 (96.4%)	28 (1.6%)	<0.001	<0.001

In-hospital procedures									
Coronary angiography	2866 (55.7%)	994 (75.7%)	1,872 (48.9%)	<0.001	266 (10.5%)	115 (26.6%)	151 (7.2%)	<0.001	<0.001
Percutaneous coronary intervention	2585 (49.3%)	878 (64.2%)	1,707 (44.7%)	<0.001	-	-	-	-	-
Coronary artery bypass graft	21 (0.4%)	7 (0.5%)	14 (0.4%)	0.45	-	-	-	-	-
Outcomes									
In-hospital mortality	179 (3.4%)	25 (1.8%)	154 (4.0%)	<0.001	124 (4.8%)	17 (3.5%)	107 (5.1%)	0.13	0.002
Severe LV dysfunction	546 (24.4%)	237 (20.3%)	309 (28.9%)	<0.001	323 (27.8%)	104 (24.2%)	219 (29.8%)	0.04	0.03

Data expressed as mean ± SD or as number (percentage).

* p value derived from comparison between Early versus Delayed beta-blockers administration in the overall population

† p value derived from comparison between Early versus Delayed beta-blockers administration in the Routine medical therapy subgroup

‡ p value derived from comparison between beta-blockers administration in the overall population versus Routine medical therapy subgroup

ACE = angiotensin converting enzyme; CAD = coronary artery disease; LV = left ventricular; NSTE-ACS = non-ST-segment elevation acute coronary syndromes

Table 2. Adjusted In-Hospital Outcomes in Acute Coronary Syndrome Patients Treated with Early Beta-blocker Administration

	Overall population				Routine medical therapy			
	N	**OR**	**95% CI**	**p value**	**N**	**OR**	**95% CI**	**p value**
Multivariate adjusted models:								
Model 1: Demographic and clinical factors*								
In-hospital mortality	3,557	0.41	0.21 - 0.80	0.01	1,681	0.75	0.29 - 1.92	0.56
Severe LV dysfunction	1,421	0.57	0.42 - 0.78	<0.001	659	0.37	0.20 - 0.67	0.001
Model 2: Model 1 including Fibrinolysis								
In-hospital mortality	3,544	0.39	0.20 - 0.77	0.007	1,676	0.74	0.29 - 1.88	0.52
Severe LV dysfunction	1,418	0.55	0.40 - 0.75	<0.001	659	0.37	0.20 - 0.66	0.001
Model 3: Model 1 including Fibrinolysis and Aspirin								
In-hospital mortality	3,535	0.40	0.20 - 0.78	0.008	1,673	0.76	0.30 - 1.94	0.57
Severe LV dysfunction	1,415	0.55	0.40 - 0.75	<0.001	657	0.35	0.19 - 0.64	0.001
Model 4: Model 1 including Fibrinolysis, Aspirin and/or Clopidogrel								

In-hospital mortality	3,544	0.41	0.21 - 0.80	0.01	1,676	0.77	0.30 - 1.94	0.58
Severe LV dysfunction	1,418	0.56	0.41 - 0.76	<0.001	659	0.37	0.21 - 0.67	0.001
Model 5: Model 1 including Fibrinolysis, Aspirin and/or Clopidogrel, and Unfractioned heparin								
In- hospital mortality	3,496	0.37	0.19 - 0.73	0.004	1,638	0.77	0.30-1.98	0.60
Severe LV dysfunction	1,397	0.54	0.39 - 0.75	<0.001	642	0.34	0.18 -0.63	0.001
Model 6: Model 1 including Fibrinolysis, Aspirin and/or Clopidogrel, Unfractioned heparin and ACE-Inhibitors								
In-hospital mortality	1,308	0.57	0.19 - 1.71	0.32	447	1.97	0.47 - 8.22	0.35
Severe LV dysfunction	848	0.59	0.34 - 1.02	0.06	267	0.28	0.11 - 0.74	0.01
Model 7: Model 1 including Killip class III/ IV								
In-hospital mortality	3,557	0.53	0.27 - 1.04	0.06	1,681	0.93	0.36 - 2.38	0.88
Severe LV dysfunction	1,421	0.68	0.50 - 0.92	0.01	659	0.46	0.24 - 0.83	0.01

*__Demographic and clinical factors:__ sex, age, hypercholesterolemia, diabetes mellitus, hypertension, current smoker, family history of CAD, clinical history of cardiovascular disease (including prior angina pectoris, prior myocardial infarction, prior coronary artery bypass graft and percutaneous coronary intervention , prior heart failure, peripheral artery disease and prior stroke), chronic kidney disease, time from symptom onset to admission ≤ 12 hours and STEMI as index event.

ACE = angiotensin-converting-enzyme; CAD = coronary artery disease; LV= left ventricular; STEMI = ST-segment elevation myocardial infarction

Table 3. Associations Among In-Hospital Outcomes, Timing Of Beta-Blockers Administration and COMMIT-Shock Index

	Overall population			Routine medical therapy		
	OR	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
In hospital mortality						
		N=2,991			**N=1,656**	
Beta blockers administration ≤ 24 hours	0.51	0.32 - 0.84	0.008	0.70	0.39 - 1.25	0.23
Age > 70 years	3.08	1.99 - 4.75	<0.001	2.34	1.44 - 3.81	0.001
Time from symptom onset to admission > 12 hours	1.82	1.18 - 2.82	0.007	1.79	1.10 - 2.91	0.01
Systolic blood pressure < 120 mmHg	2.09	1.29 - 3.39	0.003	2.27	1.33 - 3.86	0.003
Heart rate >110 beats/min	2.66	1.45 - 4.89	0.002	2.13	1.10-4.15	0.02
Severe LV dysfunction						
		N=2,183			**N=1,130**	
Beta blockers administration ≤ 24 hours	0.64	0.52 - 0.78	<0.001	0.72	0.54 - 0.96	0.02

Age > 70 years	1.51	1.22 - 1.87	<0.001	1.23	0.94 - 1.62	0.12
Time from symptom onset to admission > 12 hours	1.07	0.86 - 1.34	0.49	1.27	0.96 - 1.67	0.09
Systolic blood pressure < 120 mmHg	1.25	0.96 - 1.64	0.09	1.10	0.77 - 1.58	0.59
Heart rate >110 beats/min	2.30	1.58 - 3.36	<0.001	2.25	1.44 - 3.50	<0.001

COMMIT= Chinese Clopidogrel and Metoprolol in Myocardial Infarction Trial; LV= left ventricular

Table 4. Propensity score matching: Early versus Delayed Beta-Blocker Administration

	Early Beta Blockers administration N=927	**Delayed Beta Blockers administration N=927**	**p value**
Logit propensity score (Ln(PS/(1-PS))), mean ± SD	**-0.252±0.704**	**-0.240±0.692**	**0.99**
Women	292 (31.5%)	305 (32.9%)	0.52
Age (years)	61.1 ± 11.7	61.3 ± 11.9	0.69
Hypercholesterolemia	519 (55.9%)	512 (55.2%)	0.74
Diabetes mellitus	190 (20.5%)	195 (21.0%)	0.77
Hypertension	694 (74.9%)	693 (74.8%)	0.96
Current smoker	400 (43.1%)	404 (43.6%)	0.85
Family history of CAD	304 (32.8%)	310 (33.4%)	0.77
Clinical history of cardiovascular disease*	421(45.4%)	400 (43.1%)	0.33
Chronic kidney disease	48 (5.2%)	43 (4.6%)	0.59
Time from symptom onset to admission ≤ 12 hours	715 (77.1%)	740 (79.8%)	0.16
STEMI	585 (63.1%)	608 (65.6%)	0.26
Primary Outcome			
In-hospital mortality	11 (1.2%)	25 (2.7%)	0.018
Odds ratio (95%Confidence Intervals)	0.43 (0.21 - 0.89)		0.022

Data expressed as mean ± SD or as number (percentage).

CAD = coronary artery disease; PS = propensity score; STEMI = ST-segment elevation myocardial infarction

*Clinical history of cardiovascular disease including prior angina pectoris, prior myocardial infarction, prior coronary artery bypass graft and/or prior percutaneous coronary intervention, prior heart failure, peripheral artery disease and prior stroke.

Figure 1

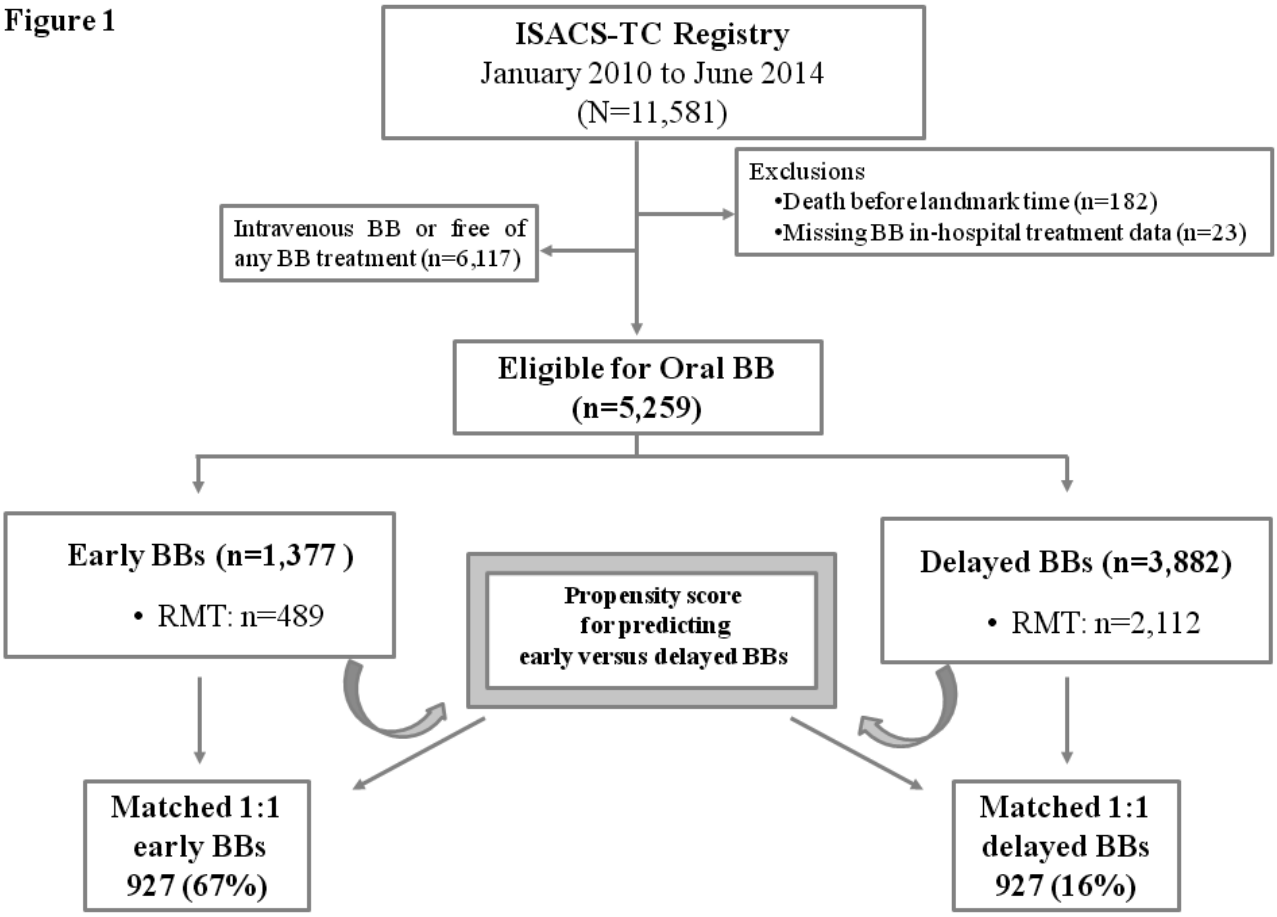

ISACS-TC Registry
January 2010 to June 2014
(N=11,581)
Exclusions
•Death before landmark time (n=182)
•Missing BB in-hospital treatment data (n=23)
Intravenous BB or free of any BB treatment (n=6,117)
Eligible for Oral BB
(n=5,259)
Early BBs (n=1,377)
• RMT: n=489
Propensity score for predicting early versus delayed BBs
Delayed BBs (n=3,882)
• RMT: n=2,112
Matched 1:1 early BBs 927 (67%)
Matched 1:1 delayed BBs 927 (16%)

Figure 2

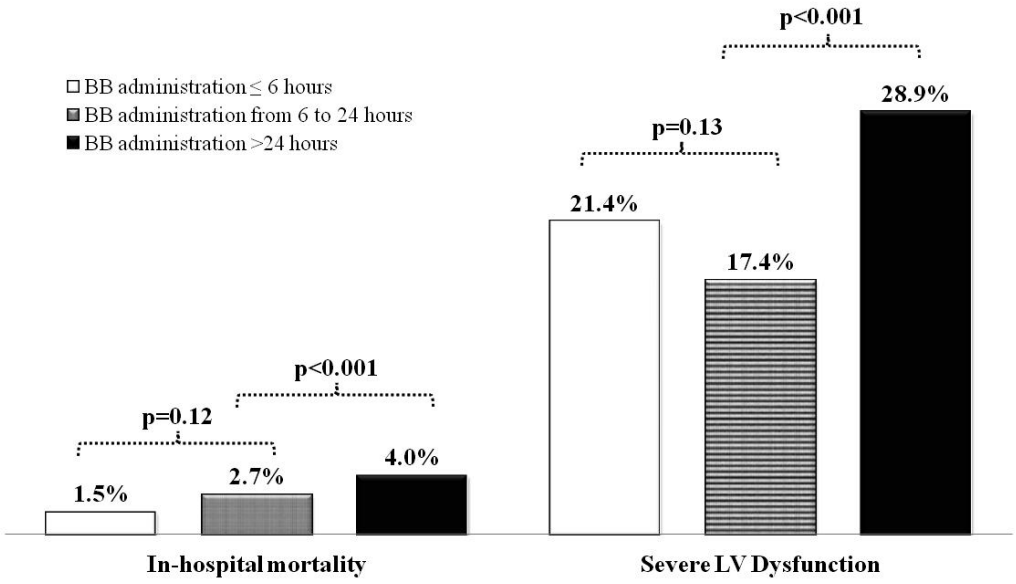
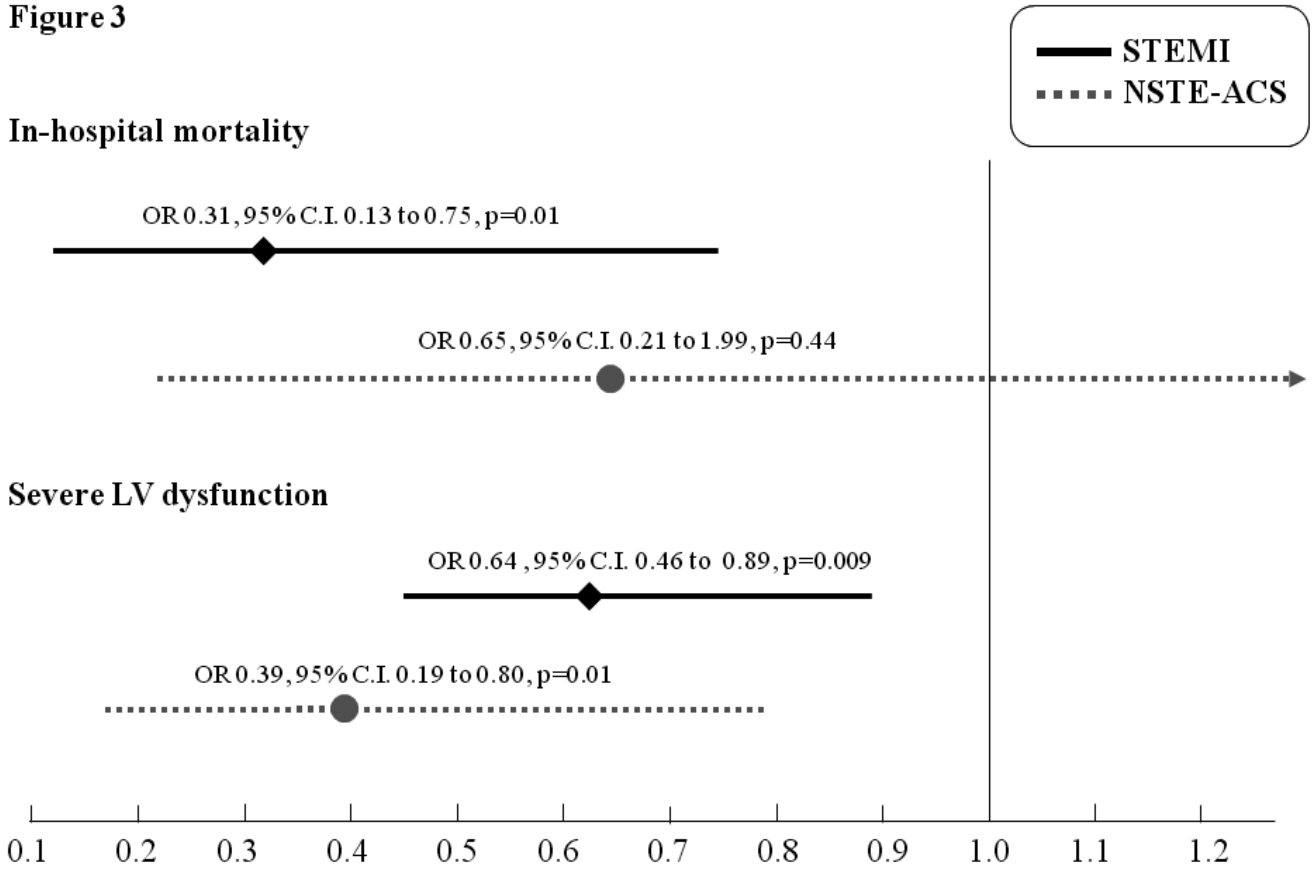

BB administration ≤ 6 hours
BB administration from 6 to 24 hours
BB administration >24 hours
p=0.12
p<0.001
1.5%
2.7%
4.0%
In-hospital mortality
p<0.001
p=0.13
21.4%
17.4%
28.9%
Severe LV Dysfunction

Figure 3


STEMI
NSTE-ACS
In-hospital mortality
OR 0.31, 95% C.I. 0.13 to 0.75, p=0.01
OR 0.65, 95% C.I. 0.21 to 1.99, p=0.44
Severe LV dysfunction
OR 0.64 , 95% C.I. 0.46 to 0.89, p=0.009
OR 0.39, 95% C.I. 0.19 to 0.80, p=0.01
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2