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Early intravenous beta-blockers in patients with acute coronary syndrome—A meta-analysis of randomized trials

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Abstract

Background—Intravenous (IV) beta-blockade is currently a Class IIa recommendation in early management of patients with acute coronary syndromes (ACS) without obvious contraindications.

Methods—We searched the PubMed, EMBASE and the Cochrane Register for Controlled Clinical Trials for randomized clinical trials from 1965 through December, 2011, comparing intravenous beta-blockers administered within 12 hours of presentation of ACS with standard medical therapy and/or placebo. The primary outcome assessed was the risk of short-term (in-hospital mortality-with maximum follow up duration of 90 days) all-cause mortality in the intervention group versus the comparator group. The secondary outcomes assessed were ventricular tachyarrhythmias, myocardial reinfarction, cardiogenic shock, and stroke. Pooled treatment effects were estimated using relative risk with Mantel–Haenszel risk ratio, using a random-effects model.

Results—Sixteen studies enrolling 73,396 participants met the inclusion / exclusion criteria. In-hospital mortality was reduced 8% with intravenous beta-blockers, RR=0.92 (95% CI, 0.86–1.00; $p=0.04$) when compared with controls. Moreover, intravenous beta-blockade reduced the risk of ventricular tachyarrhythmias (RR=0.61; 95 % CI 0.47–0.79; $p=0.0003$) and myocardial reinfarction (RR=0.73, 95 % CI 0.59–0.91; $p=0.004$) without increase in the risk of cardiogenic shock, (RR=1.02; 95% CI 0.77–1.35; $p=0.91$) or stroke (RR=0.58; 95 % CI 0.17–1.98; $p=0.38$).

Conclusions—Intravenous beta-blockers early in the course of appropriate patients with ACS appears to be associated with significant reduction in the risk of short-term cardiovascular outcomes, including a reduction in the risk of all-cause mortality.

Keywords

Meta-analysis; Myocardial Infarction; Cardiovascular Pharmacology; Beta-Blocker; IV; Mortality

1. Introduction

Beta-blockers have long been a mainstay for the treatment of acute coronary syndromes (ACS) [1]. Beta-blockers decrease heart rate and hence the myocardial oxygen demand thereby improving myocardial oxygenation following an ACS [2,3].

However the optimal mode of administration and time course of administration has long been under scrutiny. Recent studies [4] as well as a meta-analysis [5] including all studies using both intravenous and PO beta-blockers have shown mixed results. The benefits of early administration of beta-blockers might be offset by greater incidence of cardiogenic shock [6]. As such, ACC/AHA guidelines have been revised to make intravenous beta-blockers a class IIa indication for appropriate subjects with ACS (both STEMI as well as NSTEMI). However, the data to support the early use of IV beta-blockers early in ACS are sparse. There is no consensus opinion on the optimal mode of administration of a beta-blocker on presentation with ACS.

Previous meta-analyses on the role of early beta blockade in ACS did not find significant mortality benefit of early beta-blocker administration in ACS-especially for short-term outcomes [5,6,26]. In addition, there is a reported increased risk of cardiogenic shock when beta blockade is initiated shortly after admission of ACS patients. However, results from modern studies (in the era of reperfusion-mechanical or pharmacological) [7,11,20,33] using very early intravenous beta-blocker initiation during ACS have been systematically neglected in such previous analyses, precluding an integral overview of the benefits of an early intravenous beta blockade strategy.

Our objective was to assess the effect of early intravenous beta blockade on short term clinical outcomes for patients with ACS.

2. Methods

2.1. Data sources and searches

We systematically searched PubMed, EMBASE and Cochrane Central Register of Controlled Trials, for trials that randomized study participants to an intravenous beta-blocker versus placebo/standard therapy without a beta-blocker, from 1966 through December, 2011. The following medical subject heading (MeSH) terms were included for MEDLINE search and adapted for other databases as needed-‘beta-blocker’, ‘acute coronary syndrome’, ‘coronary artery disease’, ‘myocardial infarction’, and ‘heart attack’. Specific trade and generic names for β -blockers were also searched (i.e., acebutolol, alprenolol, atenolol, betaxolol, bisoprolol, bupranolol, butoxalol, carvedilol, celiprolol,

dihydroalprenolol, labetalol, levobunolol, metoprolol, nadolol, oxprenolol, pindolol, practolol, propranolol, sotalol and timolol). In addition to searching the databases, the reference lists of all included studies, meta analyses and reviews were manually searched. There was no language restriction for the search.

2.2. Study selection

We included trials that studied adult (18+ years) patients who had a recent (<48 hours) onset of their anginal symptoms consistent with an acute event or suspected of having ACS. Eligible trials had to be randomised clinical trials comparing intravenous beta-blockers versus comparators; and be able to report the outcomes of interest. We included trials where the subjects were given the intervention or comparator within 12 hours of presentation. This early intervention requirement mirrors the emergency physician's real-life experience of using only limited clinical information to decide to either give or withhold beta-blockers to ACS subjects. The use of other agents or therapies such as thrombolysis or angioplasty was not an exclusion criteria for the analysis. We excluded trials of patients with chronic stable angina, those in which a beta-blocker was also used in the control group, and those that did not report outcomes of interest. Also most of the trials excluded subjects with acute decompensated heart failure, acute pulmonary edema (except the COMMIT-CCS2) and advanced degrees of heart block-and we acknowledged that the benefits would vary with patient selection.

2.3. Data extraction and quality assessment

Two authors (SC, DC) reviewed the trials to ensure that they met inclusion criteria, abstracted the data and this was checked for accuracy by the other authors. Disagreements were resolved by consensus (10% of the time). We performed objective assessment of the trials using the method specified in the Cochrane Handbook of Systematic Reviews- assessing for randomization, concealment, blinding, intention to treat, baseline comparisons, concomitant interventions, and completeness of follow-up.

Our primary outcome was short-term mortality ie, all cause mortality at the end of the index hospitalization for ACS. Secondary outcomes of interest (all selected a-priori) were in-hospital ventricular tachyarrhythmias (all hemodynamically significant ventricular tachyarrhythmias reported as per primary trial publication definitions), myocardial reinfarction, cardiogenic shock and stroke. We also performed exploratory subanalyses to identify and delineate the benefits of early IV beta-blockers in different subgroups.

2.4. Data synthesis and analysis

Meta analysis was performed as per the recommendation of Cochrane collaboration and in line with the PRISMA statement [25]. Pooled treatment effects were estimated using RR with Mantel-Haenszel risk ratio, using a random-effects model. Heterogeneity was assessed by chi-square tests and the I^2 statistic-we defined $I^2 < 25\%$ to be low heterogeneity, as per the Cochrane Handbook of Systematic Reviews. Publication bias was estimated using funnel plots, and the regression test of Egger.

2.5. Trial quality

We used the published standard criteria for reporting of randomized clinical trials studies (PRISMA) [25] to identify the studies for selection for this review (Fig. 1), and Cochrane metrics for assessment of individual studies (Table 3).

We performed a sensitivity analysis to explore the effects of excluding the study with the largest sample size. We assessed quality for each included trial — all randomized controlled trials included for the primary analysis were of high quality. In addition an exploratory subset analyses was performed for intravenous beta-blockers in common usage for treatment of ACS at present such as atenolol and metoprolol. Most of the studies did not report outcomes with STEMI/NSTEMI status on presentation separately-and hence determination of benefits in these groups separately could not be ascertained. For statistical analysis we used Review Manager Version 5.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008).

The author(s) of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

3. Results

Our MEDLINE search returned 2217 studies. After elimination of duplicate results, the EMBASE and Cochrane registries did not return any additional studies. Through a review of titles and abstracts, 2,097 studies were rejected for relevance. The remaining 120 articles were reviewed and assessed for satisfaction of the inclusion or exclusion criteria. The 16 articles that met all criteria were included in this analysis (Fig. 1).

3.1. Study characteristics

Trials were fairly homogenous with respect to inclusion and exclusion criteria, with a few key differences (Tables 1 & 2). Timing from the initial symptoms to hospital presentation varied from 4 to 48 hours. The majority of the studies only included subjects with definite myocardial infarction (MI), while a few defined entry criteria based only on signs and symptoms suggestive of MI. Most studies excluded subjects with high degree atrioventricular blocks, hypotension, pulmonary edema, cardiogenic shock, or bronchial asthma. All relevant studies except COMMIT (CLOpidogrel and Metoprolol in Myocardial Infarction Trial) excluded subjects in acute decompensated heart failure. Five studies excluded subjects with advanced age (>75 years) [9,15,22–24]. Many studies [9,13,21–24] excluded subjects with prior MIs and those subjects already taking beta-blocking agents. It is important to note that some of the studies were done in an era that preceded thrombolytic therapy and percutaneous coronary interventions. The COMMIT trial excluded subjects who were going directly for percutaneous coronary interventions [4]. Trials were quite variable with respect to sample size. The smallest of the studies included only 43 subjects. The largest trial, COMMIT enrolled 45,852 subjects. Seven studies enrolled more than 500 subjects. Males made up the majority of all subjects studied, ranging from 70% to 94%. There was heterogeneity with respect to study medication and dosages of individual medications. Metoprolol was the most commonly used beta-blocker (5 studies), followed by propranolol (4 studies), atenolol (3 studies), practolol (1 study), pindolol (1 study), timolol

(1 study), and labetalol (1 study). All studies reported short-term outcomes ranging between 72 hours to 90 days. (We could not include a few important studies for not being RCTs [7,11,20]).

3.2. Primary outcome

We identified 16 articles, accounting for 73,396 subjects that met our inclusion and exclusion criteria. Short-term mortality was reduced 8% with early intravenous beta-blockers, $RR=0.92$ (95% CI, 0.86–1.00; $p=0.04$) (Fig. 2). There was low heterogeneity in the analysis ($I^2=6\%$). Also publication bias was assessed by constructing a funnel plot and an Egger's test with 2-tailed p -value ($p=0.18$).

In an exploratory sub-analysis, intravenous beta-blockers in common usage at present, i.e., atenolol and metoprolol, also showed short term mortality benefit, $RR\ 0.89$ (95% CI, 0.80–1.00; $p=0.05$). A sensitivity analysis to look at the effect of excluding patients with acute decompensated heart failure, pulmonary edema and Killip class III heart failure by excluding the COMMIT CCS2 Study which was the only study to have enrolled such patients, as well as being the largest study, produced an even greater benefit in the pooled RR of in-hospital/short-term mortality ($RR=0.85$, 95% CI=0.76 to 0.94; $p=0.003$) to favor beta-blocker administration. In addition, excluding just the subjects in Killip class III from both groups of the COMMIT study yielded significant mortality benefit for patients receiving beta-blocker ($RR=0.89$, 95% CI 0.79–0.99; $p=0.04$). And including studies with a large sample size only (>50 patients in each subgroup) did not change the outcome ($RR=0.91$, 95% CI 0.82–1.00; $p=0.05$), although pooled evaluation of the smaller studies (<50 patients in each arm) was inconclusive of the benefits of early IV beta-blockers [Supplemental Figs. 1 and 2].

It is well-known that propranolol irreversibly depresses cardiac function when administered with a relatively overdose. This is why the benefits of early administration of beta-blockers might be offset by greater incidence of cardiogenic shock-hence we also performed a subgroup analysis excluding the 4 studies of propranolol [16–18,21]-and we found similar mortality benefits with early use of IV beta-blockers when restricting our analysis to studies that evaluated beta-blockers other than propranolol (Supplemental Fig. 3).

3.3. Secondary outcomes

Intravenous beta-blocker therapy significantly reduced the risk of ventricular tachyarrhythmias ($RR=0.61$; 95 % CI 0.47–0.79; $p=0.003$) (Fig. 3); and myocardial reinfarction rates ($RR=0.73$, 95 % CI 0.59–0.91; $p=0.004$) (Fig. 6) when compared with controls *without any increase in the risk of cardiogenic shock* ($RR=1.02$; 95% CI 0.77–1.35; $p=0.91$), although the meta-analytic data do not conclusively rule out a risk increase; (Fig. 5) or stroke ($RR=0.58$; 95 % CI 0.17–1.98; $p=0.38$) (Fig. 4). Also publication bias was assessed by constructing individual funnel plots.

4. Discussion

Our analysis with data from >73,000 patients suggests a short term benefit (in-hospital mortality, ventricular arrhythmias, reinfarction) with intravenous beta-blockade early in the

course of appropriate patients with ACS (ie, *without obvious contraindications like decompensated heart failure and pulmonary edema*) when compared with controls, without increase in the risk of cardiogenic shock. Specifically, we observed a pooled mortality reduction of 8%. When considered in addition to the evidence available for usage of beta-blockers in ACS, our meta-analysis indicates that an approach combining intravenous beta-blockers on presentation in the ER for ACS followed with PO beta blockers in continuation for appropriately selected patients may be an optimal management strategy.

The mechanism of benefit of early intravenous beta-blockers in ACS remains unclear [27]. It has been suggested that early intravenous administration leads to quicker onset of action, achieves better rate-pressure product thereby decreasing myocardial oxygen consumption, favorably influences coronary blood flow, reduces infarct size, improves ejection fraction, and reduces fatal ventricular tachyarrhythmias [28].

Our hypothesis is based on the fact that immediately following an ACS event, the homeostasis is deranged to a large extent and may compromise and make the bioavailability of orally administered medications variable-and hence intravenous administration with avoidance of the first pass metabolism may be more prudent and predictable.

Another potential beneficial effect of early intravenous beta blockade could be an infarct size reducing effect [29]. In fact, preclinical studies have shown that the cardioprotective effect of early intravenous beta blockade is abrogated when beta-blockers are initiated orally [30]. Infarct size has been recently shown to be a strong independent predictor of mortality [31].

Previous authors have reported results from meta-analysis on this topic. These analyses have shown no net mortality benefit from early beta-blocker administration in ACS [5,6,26,33]. Some authors have proposed that beta-blockers reduce ischemia/reperfusion injury and this might result in clinical benefits. In fact, the results from these studies change the whole picture of the effect of early intravenous beta blockade in ACS, being the main reason of the different results found in the present work in comparison with previous ones. The RCTs in our present study were limited to those that investigated only intravenous beta-blockers administered early in ACS, which differs from previous meta-analyses that have included trials of both oral and intravenous beta-blockers. Thus, we believe that the mortality benefit observed in our analysis may reflect the superior effect of intravenous (vs. oral) beta-blocker administration.

While any selected time period is arbitrary, from an evidence-based perspective, the longer the survival period, the greater the utility. However, as the time from drug to measured outcomes increases, the number and the effect of confounders also increases. Because we were interested in the balance between risks and benefits of the early administration of intravenous beta-blockers we chose the earliest clinically identifiable point in time when the study reported mortality data. However the selection of appropriate subjects remains a challenge as the potential to harm by inducing cardiogenic shock and fatal bradyarrhythmias is indeed quite real as evidenced by the COMMIT CCS2 study. Beta-blockade of ACS patients has also been linked to long-term mortality benefits related to reduced reinfarction

rates, left ventricular remodeling, ventricular tachyarrhythmias, postinfarction angina, and potentially infarct size reduction-and hence our recommendation would be to load the appropriate subjects with intravenous beta-blockers on presentation in the ER and continue them on oral therapy, in the absence of obvious contraindications.

In this study we have not compared intravenous vs oral beta-blockade strategies, and therefore we cannot fully rule out that an early oral beta-blockade initiation would result in similar benefits. However, as we stated above, we hypothesize that intravenous route of initiation is important in order to attain certain threshold of circulating levels of beta-blocker agent.

It is important to remark that there is not a single prospective trial comparing early (within 12–24 hours) intravenous vs oral route of betablocker initiation. The METOCARD- CNIC trial (“Effect of METO-prolol in CARDioproteCtioN during an Acute Myocardial InfarCtion”) trial (NCT01311700) is an ongoing randomized single-blind clinical trial comparing the effect of intravenous vs oral metoprolol initiation in patients with anterior wall acute myocardial infarction on infarct size. This study will be the first to compare these 2 strategies of metoprolol initiation [32].

4.1. Limitations

Like in other meta-analyses, given limited data, we did not adjust our analysis for the type of beta-blocker used nor with the dosage administered. We evaluated short-term outcomes only. In addition, we did not adjust our analysis for multiple testing and hence the results can be best described as hypothesis generating. We only included randomized trials for analysis, without significant heterogeneity ($I^2=6\%$).

4.2. Conclusion

Our meta-analysis appears to favor administration of early intravenous beta-blockers early in the treatment course of patients with an acute or suspected myocardial infarction to improve short-term mortality, without an increase in potentially lethal complications (i.e., cardiogenic shock). In addition, early intravenous beta-blockers were associated with significant reduction in the risk of ventricular arrhythmias and reinfarction rates without increase in the risk of cardiogenic shock or stroke. Further prospective randomized studies are needed to confirm this result (see supplementary appendix), and to test the mechanistic hypotheses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Viskin S, Barron HV. Beta blockers prevent cardiac death following a myocardial infarction: so why are so many infarct survivors discharged without beta blockers? *Am J Cardiol.* 1996; 78:821–2. [PubMed: 8857489]
2. Maroko PR, Kjekshus JK, Sobel BE, et al. Factors influencing infarct size following experimental coronary artery occlusions. *Circulation.* 1971; 43:67–82. [PubMed: 5540853]

3. Reimer KA, Rasmussen MM, Jennings RB. Reduction by propranolol of myocardial necrosis following temporary coronary artery occlusion in dogs. *Circ Res.* 1973; 33:353–63. [PubMed: 4746723]
4. Chen ZM, Pan HC, Chen YP, et al. COMMIT (CLOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Early Intravenous then oral metoprolol in 45,852 subjects with acute myocardial infarction: randomized placebo-controlled trial. *Lancet.* 2005; 366:1622–32. [PubMed: 16271643]
5. Al-Reesi A, Al-Zadjali N, Perry J, et al. Do beta-blockers reduce short-term mortality following acute myocardial infarction? A systematic review and meta-analysis. *CJEM.* 2008; 10(3):215–23. [PubMed: 19019272]
6. Brandler E, Paladino L, Sinert R. Does the early administration of beta-blockers improve the in-hospital mortality rate of subjects admitted with acute coronary syndrome? *Acad Emerg Med.* 2010; 17:1–10. [PubMed: 20078433]
7. Halkin A, Grines CL, Cox DA, et al. Impact of Intravenous beta-blockade before primary angioplasty on survival in subjects undergoing mechanical reperfusion therapy for acute myocardial infarction. *J Am Coll Cardiol.* 2004; 43:1780–7. [PubMed: 15145099]
8. Yusuf S, Sleight P, Rossi P, et al. Reduction in infarct size, arrhythmias and chest pain by early intravenous beta blockade in suspected acute myocardial infarction. *Circulation.* 1983; 67(6 Pt 2):I32–41. [PubMed: 6851037]
9. Evemy KL, Pentecost BL. Intravenous and oral practolol in the acute stages of myocardial infarction. *Eur J Cardiol.* 1978; 7:391–8. [PubMed: 699938]
10. Hjalmarson A, Herlitz J, Holmberg S, et al. The Goteborg metoprolol trial. Effects on mortality and morbidity in acute myocardial infarction. *Circulation.* 1983; 67(6 Pt 2):I26–32. [PubMed: 6342837]
11. Pfisterer M, Cox JL, Granger CB, et al. 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. [PubMed: 9741504]
12. Heber ME, Rosenthal E, Thomas N, et al. Effect of labetalol on indices of myocardial necrosis in subjects with suspected acute infarction. *Eur Heart J.* 1987; 8:11–8. [PubMed: 3816835]
13. Reduction of infarct size with the early use of timolol in acute myocardial infarction. *N Engl J Med.* 1984; 310:9–15. [PubMed: 6358896]
14. First International Study of Infarct Survival Collaborative Group. Randomised trial of Intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. *Lancet.* 1986; 2:57–66. [PubMed: 2873379]
15. The MIAMI Trial Research Group. Metoprolol in acute myocardial infarction (MIAMI). A randomised placebo-controlled international trial. *Eur Heart J.* 1985; 6:199–226. [PubMed: 2863148]
16. Norris RM, Clarke ED, Sammel NL, et al. Protective effect of propranolol in threatened myocardial infarction. *Lancet.* 1978; 2:907–9. [PubMed: 81925]
17. Norris RM, Sammel NL, Clarke ED, et al. Treatment of acute myocardial infarction with propranolol. Further studies on enzyme appearance and subsequent left ventricular function in treated and control subjects with developing infarcts. *Br Heart J.* 1980; 43:617–22. [PubMed: 7426142]
18. Norris RM, Barnaby PF, Brown MA, et al. Prevention of ventricular fibrillation during acute myocardial infarction by Intravenous propranolol. *Lancet.* 1984; 2:883–6. [PubMed: 6148617]
19. Owensby DA, O'Rourke MF. Failure of Intravenous pindolol to reduce the hemodynamic determinants of myocardial oxygen demand or enzymatically determined infarct size in acute myocardial infarction. *Aust N Z J Med.* 1985; 15:704–11. [PubMed: 3914879]
20. Harjai KJ, Stone GW, Boura J, et al. Effects of prior beta-blocker therapy on clinical outcomes after primary coronary angioplasty for acute myocardial infarction. *Am J Cardiol.* 2003; 91:655–60. [PubMed: 12633793]
21. Peter T, Norris RM, Clarke ED, et al. Reduction of enzyme levels by propranolol after acute myocardial infarction. *Circulation.* 1978; 57:1091–5. [PubMed: 639229]

22. Roberts R, Rogers WJ, Mueller HS, et al. Immediate versus deferred beta-blockade following thrombolytic therapy in subjects with acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) II-B Study. *Circulation*. 1991; 83:422–37. [PubMed: 1671346]
23. Van de Werf F, Janssens L, Brzostek T, et al. Short term effects of early Intravenous treatment with a beta-adrenergic blocking agent or a specific bradycardiac agent in subjects with acute myocardial infarction receiving thrombolytic therapy. *J Am Coll Cardiol*. 1993; 22:407–16. [PubMed: 8335810]
24. Salathia KS, Barber JM, McIlmoyle EL, et al. Very early intervention with metoprolol in suspected acute myocardial infarction. *Eur Heart J*. 1985; 6:190–8. [PubMed: 3896811]
25. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009; 6:e1000100. [PubMed: 19621070]
26. Freemantle N, Cleland J, Young P, et al. beta Blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ*. 1999; 318:1730–7. [PubMed: 10381708]
27. Faxon DP. Beta-blocker therapy and primary angioplasty: what is the controversy? *J Am Coll Cardiol*. 2004; 43:1788–90. [PubMed: 15145100]
28. Mehta RH, Harjai KJ, Grines L. Sustained ventricular tachycardia or fibrillation in cardiac catheterization laboratory among patients receiving primary percutaneous coronary intervention: incidence, predictors and outcomes. *J Am Coll Cardiol*. 2004; 43:1765–72. [PubMed: 15145097]
29. Ibanez B, Prat-González S, Speidl WS, et al. Early metoprolol administration before coronary reperfusion results in increased myocardial salvage: analysis of ischemic myocardium at risk using cardiac magnetic resonance. *Circulation*. 2007; 115:2909–16. [PubMed: 17515460]
30. Ibanez B, Cimmino G, Prat-González S, et al. The cardioprotection granted by metoprolol is restricted to its administration prior to coronary reperfusion. *Int J Cardiol*. 2011; 147:428–32. [PubMed: 19913314]
31. Wu E, Ortiz JT, Tejedor P, et al. Infarct size by contrast enhanced cardiac magnetic resonance is a stronger predictor of outcomes than left ventricular ejection fraction or end-systolic volume index: prospective cohort study. *Heart*. 2008; 94:730–6. [PubMed: 18070953]
32. Ibáñez B, Fuster V, Macaya C, et al. Modulation of the beta-adrenergic system during acute myocardial infarction: rationale for a new clinical trial. *Rev Esp Cardiol* Jul. 2011; 64(Suppl. 2): 28–33.
33. Yusuf S, Peto R, Lewis J, et al. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis* Mar. Apr; 1985 2(5):335–71.

Fig. 1.
Selection of studies for inclusion in review/meta-analysis.

Fig. 2.
Forest plot of Mortality data.

Fig. 3.

Forest plot of benefit of IV Beta-Blockers in development of Ventricular Tachyarrhythmias.

Fig. 4.

Forest plot of effect of IV Beta-Blockers in development of Stroke.

Fig. 5.

Forest plot of effect of IV Beta-Blockers in development of Cardiogenic shock and /or acute decompensated heart failure.

Fig. 6.

Forest plot of benefit of IV beta-blockers in development of reinfarction after Myocardial Infarction.

Table 1

Baseline characteristics of studies.

Trial name	Treatment group	Control group	Inclusion criteria	Exclusion criteria
COMMIT [4]	IV then PO Metoprolol-5 mg IV every 2–3 min for 15 mg then 50 mg PO every 6 hours for 48 hours, then 200 mg controlled release PO once a day for 28 days	Placebo	chest pain<24 h	contraindications to study drugs, hypotension, patients going for primary PCI
Early IV Atenolol-Yusuf [8]	IV then PO Atenolol-5 mg IV then 50 mg PO then 50 mg PO 12 hours later then 100 mg PO QD for 10 days	Placebo	chest pain<12 hours	asthma, HR<40 beats / min, BP <90 mm Hg, heart failure requiring digoxin or more than 80 mg of furosemide, on beta-blocker
Eveny [9]	IV then PO Practolol-15 mg IV over 2 minutes, then 200 mg PO every 12 h	Standard medical therapy	chest pain<24 hr	prior MI, HR<60, BP<95 mm Hg, second- or third-degree AV block, bundle branch block
Göteborg metoprolol [10]	IV then PO Metoprolol-15 mg IV loading, then 200 mg PO QD X 90 days	Placebo	chest pain <48 hr	Hypotension, bradycardia, AV block, bronchial asthma
Heber [12]	IV then PO Labetalol-dosed by blood pressure	Standard Medical Therapy	chest pain<6 hr	asthma, sBP<100 mm Hg, sBP>200 mm Hg CHF, conduction delay, valvular heart disease, on verapamil
ICSG [13]	IV Timolol-1 mg IV then 0.6 mg / hr then 10 mg PO BID	Placebo	chest pain<4 hr	asthma, HR<50 beats / min, BP<100 mm Hg, severe left ventricular failure, prior MI, contraindication to beta-blockade, heart failure requiring digoxin or more than 80 mg of furosemide, taking beta- blocker at time of study entry
ISIS-1 [14]	IV Atenolol-5 mg IV repeated once then 50 mg PO every 12 hr for one day, then 100 mg PO every 24 hr	Standard Medical Therapy	chest pain<12 hr	asthma, sBP <100 mm Hg, HR<50 beats / min, second or third degree AV block, on beta- blocker or verapamil
MIAMI [15]	IV then POMetoprolol-15 mg IV over 5 min then 50 mg PO every 6 hr for 2 days then 100 mg PO every 12 hr	Standard Medical Therapy	chest pain<24 hr	age >75 yr
Norris 1 [16]	IV then PO Propranolol-0.1 mg/ kg IV then 320 mg PO (divided doses) over the next 27 hr	Standard Medical Therapy	chest pain<4 hr	history of unstable angina, CHF, bronchial asthma, HR<60 beats / min, on beta-blocker
Norris 2 [17]	IV then PO Propranolol-0.1 mg/ kg IV then 320 mg PO (divided doses) over the next 27 hr	Standard Medical Therapy	chest pain<4 hr	asthma, HR<60 beats / min, BP<100 mm Hg interstitial edema or pulmonary edema by chest x-ray, age>65 yr
Norris 3 [18]	IV then PO Propranolol-0.1 mg/ kg IV then 320 mg PO (divided doses) over the next 27 hr	Standard Medical Therapy	chest pain<4 hr	asthma, cardiac failure, BP<110 mm Hg, HR<60 beats / min, presence of dyspnea, widespread rales
Owensby [19]	IV then PO Pindolol-3 mg IV every 8 hr for 24 hr, then 5 mg PO every 8 hr	Standard Medical Therapy	chest pain<12 hr	asthma, bradycardia, AV block, CHF, on beta-blocker”

Trial name	Treatment group	Control group	Inclusion criteria	Exclusion criteria
Peter [21]	IV then PO Propranolol-0.1 mg/kg IV then 320 mg PO (divided doses) over the next 27 hr	Standard Medical Therapy	chest pain<12 hr	asthma, HR<60 beats / min, AV block, contraindications to propranolol, pulmonary edema, on beta-blocker, direct current cardioversion
TIMI IIB [22]	IV then PO Metoprolol-5 mg IV every 2 min for a total of 15 mg then 50 mg PO every 12 hr for 24 hr then 100 mg every 12 hr	Beta-blockers begun in the control group orally only on Day 6	<75 years of age and were treated <=4 hours after the onset of chest pain	history of a cerebrovascular event, blood pressure of .180 mm Hg systolic or >110 mm Hg diastolic, bleeding disorder, surgery within the previous 2 weeks, recent prolonged cardiopulmonary resuscitation, PTCA or severe trauma within 6 months, previous coronary artery bypass surgery, prosthetic heart valve replacement, left bundle branch block, dilated cardiomyopathy, or other serious illness.
Van de Werf [23]	IV then PO Atenolol-5 mg IV repeated once, then 25–50 mg every 12 hr for 14 days	Placebo	chest pain<5 hr	contraindications to beta-blocker therapy, prior PTCA or CABG, contraindications to thrombolytic therapy, on beta- blockers, or calcium channel blockers
Very Early Metoprolol-Boyle/Salathia [24]	IV then PO Metoprolol-15 mg IV over 5 min then 50 mg PO every 6 hr for 2 days then 100 mg PO every 12 hr	Placebo	chest pain<12 hr	sBP <90 mm Hg with HR>100 beats / min. initial rhythm ventricular fibrillation, initial rhythm agonal, bradycardia, AV block, CHF, on beta-blocker or a type I antiarrhythmic

COMMIT=CiOpidogrel and Metoprolol in Myocardial Infarction Trial.

ICSG=International Collaborative Study Group trial with early use of timolol in acute myocardial.

ISIS-1=First International Study of Infarct Survival MIAMI=Metoprolol in acute myocardial infarction TIMI=Thrombolysis in Myocardial Infarction.

Standard Medical Therapy-Implies current (at the time of the individual studies) guidelines based Rx for ACS excluding IV beta-blocker.

[CABG=Coronary Artery Bypass Grafting, PCI=Percutaneous Coronary Intervention, CHF=Congestive Heart Failure, PTCA=Percutaneous Transluminal Coronary Angioplasty, MI=Myocardial Infarction, sBP=Systolic Blood Pressure, HR=Heart Rate, AV Block=Atrio-ventricular block].

Table 2

Baseline characteristics of subjects.

Trial	Mean age (years) beta blockers	Mean age (years) – comparator group	Males (%) Beta Blocker	Males (%) comparator	Duration of follow-up
COMMIT [4]	61.4	61.3	72	72.4	28 days
Early IV Atenolol-Yusuf [8]	56	56	87.7	81.6	10 days
Eveny [9]	<70	<70	80.4	87.5	7 mt
Göteborg metoprolol trial [10]	<64:65%;65–74:35%	<64:66.5%;65–74:33.5%	76.2	75.6	90 days
Heber [12]	61	58	78.3	86.7	5 days
ICSG [13]	57	57	85	85	D/C
ISIS-1 [14]	58.8	58.9	77	77	7 days
MIAMI [15]	59.1	58.8	78	77.2	15 days
Norris 1978 [16]	52	52	74	74	D/C
Norris 1980 [17]	51	51	94	94	D/C
Norris 1984 [18]	70	70	80	80	23 days
Owensby [19]	54	54.9	77.2	81.8	D/C
Peter [21]	54	53.6	87	75	D/C
TIMI IIB [22]	54.8	55.2	86.1	84.4	1 year
Van de Werf [23]	59	57	80	85	14 days
Very early metoprolol-boyle/salathia24	<=65:69%,>65:31%	<=65:68%,>65:32%	69.7	73.4	1 year

D/C=Discharge (from hospital, for index hospitalization); mt=month; yr=year.

Table 3

Assessment of studies.

Trial name	Sequence generation: yes, no, unclear	Allocation concealment: yes, no, unclear	Blinding of participants, personnel and outcome assessors	Use of ITT: yes, no, unclear	Free of incomplete outcome data: yes, no, unclear	Free of selective outcome reporting: yes, no, unclear
COMMIT [4]	Y	Y	Y	Y	Y	Y
Early IV Atenolol-Yusuf [8]	Y	N	Y	Y	Y	Y
Eveny [9]	Y	UC	UC	Y	Y	Y
Göteborg metoprolol [10]	Y	UC	UC	Y	Y	Y
Heber [12]	Y	UC	UC	Y	Y	Y
ICSG [13]	Y	Y	Y	Y	Y	Y
ISIS-1 [14]	Y	UC	N	Y	Y	Y
MIAMI [15]	Y	Y	Y	Y	Y	Y
Norris 1978 [16]	Y	Y	N	Y	Y	Y
Norris 1980 [17]	Y	Y	N	UC	Y	Y
Norris 1984 [18]	Y	Y	N	Y	Y	Y
Owensby [19]	Y	Y	UC	Y	Y	Y
Peter [21]	Y	Y	UC	Y	Y	Y
TIMI IIB [22]	Y	Y	Y	Y	Y	Y
Van de Werf [23]	Y	Y	Y	Y	Y	Y
Very Early Metoprolol-Boyle/Salathia [24]	Y	Y	Y	Y	Y	Y