REVIEW ARTICLE

Do β-blockers reduce short-term mortality following acute myocardial infarction? A systematic review and meta-analysis

Abdullah Al-Reesi, MD;[*] Nabil Al-Zadjali, MD;[†] Jeff Perry, MD;[*] Dean Fergusson, PhD;[‡] Mohammed Al-Shamsi, MD;[*] Majid Al-Thagafi, MD;[*] Ian Stiell, MD[*]

ABSTRACT

Objective: Acute myocardial infarction (AMI) remains a major cause of death and β-blockers are known to reduce long-term mortality in post-AMI patients. We sought to determine whether patients receiving β-blockers acutely (within 72 h) following AMI had a lower mortality rate at 6 weeks than patients receiving placebo.

Methods: We conducted a systematic review of randomized controlled clinical trials that assessed 6-week mortality and compared β-blockers with placebo in patients randomized within the first 72 hours following AMI. We searched these databases: MEDLINE (1966–2006), EMBASE (1980–2007), Cochrane Central Register of Controlled Trials, Health Star (1966–2007), Cochrane Database for Systematic Reviews, ACP Journal Club (1991–2007), Database of Abstracts of Reviews of Effect (< 1st quarter 2007) and Conference Papers Index (1984–2007). Two blinded reviewers extracted the data and rated study quality using the Jadad score and the adequacy of allocation concealment score, which was adopted by the Cochrane group. We calculated pooled odds ratios (ORs) using a random effect model and performed sensitivity analyses to explore the stability of the overall treatment effect.

Results: We included 18 studies (13 were rated high-quality) with 74 643 enrolled participants and had 5095 deaths. Compared with placebo, adding β-blockers to other interventions within 72 hours after AMI did not result in a statistically significant reduction in 6-week mortality (OR 0.95, 95% confidence interval [CI] 0.90–1.01). When restricted to high quality studies, the OR for 6-week mortality reduction was 0.96 (95% CI 0.91–1.02). We found similar results including studies that enrolled patients within 24 hours after AMI. However, a subgroup analysis that excluded high-risk patients with Killip class III and above showed that β-blockers resulted in a significant reduction in short-term mortality (OR 0.93, 95% CI 0.88–0.99).

Conclusion: Acute intervention with β-blockers does not result in a statistically significant short-term survival benefit following AMI but may be beneficial for low-risk (Killip class I) patients.

Keywords: acute myocardial infarction, mortality, β-blockers

RÉSUMÉ

Objectif : L'infarctus aigu du myocarde (IAM) demeure une importante cause de décès et il est reconnu que les β-bloquants réduisent la mortalité à long terme chez les patients qui ont subi un

From the Departments of *Emergency Medicine and †Epidemiology and Community Medicine, University of Ottawa, Ottawa, Ont., and the ‡Department of Emergency Medicine, Sultan Qaboos University Hospital, Muscat, Oman

Received: Apr. 27, 2007; revisions received: July 18, 2007; revised: Sept. 23, 2007

This article has been peer reviewed.

CJEM 2008;10(3):215-23

IAM. Nous avons cherché à déterminer si les patients qui ont reçu des b-bloquants en période de soins intensifs (dans les 72 heures) après un IAM ont présenté un taux de mortalité à 6 semaines moins élevé que les patients qui ont pris un placebo.

Méthodes : Nous avons effectué une critique systématique d'études cliniques contrôlées randomisées au cours desquelles on avait évalué la mortalité à six semaines et comparé les β-bloquants au placebo chez des patients choisis au hasard dans les 72 heures suivant un IAM. Nous fait des recherches dans les bases de données suivantes : MEDLINE (1966–2006), EMBASE (1980–2007), Cochrane Central Register of Controlled Trials, Health Star (1966–2007), Cochrane Database for Systematic Reviews, ACP Journal Club (1991–2007), Database of Abstracts of Reviews of Effect (< 1er trimestre 2007) et Conference Papers Index (1984–2007). Deux examinateurs travaillant à l'insu ont extrait les données et évalué la qualité des études au moyen du score de Jadad et du score relatif à la suffisance de la dissimulation de l'affectation des ressources, que le groupe Cochrane a adopté. Nous avons calculé des coefficients de probabilité (CP) regroupés au moyen d'un modèle à effet aléatoire et nous avons procédé à des analyses de sensibilité afin d'explorer la stabilité de l'effet global du traitement.

Résultats : Nous avons retenu 18 études (dont 13 cotées de grande qualité) portant sur 74 643 participants et au cours desquelles on a enregistré 5095 décès. Comparativement au placebo, l'ajout de β-bloquants à d'autres interventions dans les 72 heures après l'IAM n'a pas réduit de façon statistiquement significative la mortalité à six semaines (CP 0,95, intervalle de confiance [IC] à 95 %, 0,90–1,01). Lorsqu'on limite l'analyse aux études de grande qualité, le CP pour la réduction de la mortalité à six semaines atteint 0,96 (IC à 95 %, 0,91–1,02). Nous avons constaté des résultats semblables après avoir inclus des études auxquelles on avait inscrit les patients dans les 24 heures suivant l'IAM. Une analyse de sous-groupes excluant les patients à risque élevé de classe III de Killip et plus a toutefois révélé que les β-bloquants entraînaient une réduction importante de la mortalité à court terme (CP 0,93, IC à 95 %, 0,88–0,99).

Conclusion : L'intervention intensive au moyen de β-bloquants ne produit pas davantage de résultats statistiquement significatifs pour la survie à court terme à la suite d'un IAM, mais elle peut être bénéfique chez les patients à faible risque (classe I de Killip).

Introduction

Despite therapeutic advances, acute myocardial infarction (AMI) remains a major cause of mortality. The in-hospital mortality in the first month after AMI is 12.3%.[1] β-Blockers have been an important component of AMI management for more than 4 decades. Early intravenous administration of metoprolol (within 12 h) has been shown to favourably influence various markers of infarct size.[2,3] However, early administration of β-blockers following AMI may produce an excess risk of cardiogenic shock and mitigate their beneficial effects.

A meta-analysis of short- and long-term studies conducted in 1985 combined studies with early and late β-blocker administration and demonstrated that β-blockers reduced mortality in AMI.[4] However, since then there have been many major treatment advances. Although the long-term benefit of β-blockers for post-AMI patients has been well established,[5] the short-term benefits of adding β-blockers to current AMI therapy is unclear. There is also persisting low use of β-blocker secondary prophylaxis following AMI despite proven long-term efficacy.[6] A recent large randomized controlled trial (RCT)[7] questioned the benefit of β-blockers in the acute phase after AMI.

We conducted a systematic literature review and meta-analysis to identify RCTs comparing β-blockers with placebo in the acute phase (within 72 h) following AMI. The objective of this systematic review was to assess whether β-blockers reduce short-term (6-week) mortality when given within 72 hours after AMI.

Methods

Search strategy

We systematically searched MEDLINE (1966–2007 via OVID), EMBASE (1980–2007 via OVID), Cochrane Central Register Of Controlled Trials, Health Star (1966–2007 via OVID), Cochrane Database for Systematic Reviews (CDSR), ACP Journal Club (1991–2007), Database of Abstracts of Reviews of Effect (DARE < 1st quarter 2006), and Conference Papers Index (1984–2007 via Scholar Portal Search). We used the RCT filter and limited our search to English language articles. The following medical subject heading (MeSH) terms were included for MEDLINE search and adapted for other databases as needed: "myocardial infarction," "coronary artery disease,"

https://doi.org/10.1017/S1481803500010137 Published online by Cambridge University Press

"heart attack," "Adrenergic beta-Antagonists," "beta blockers" and specific trade and generic names for β-blockers (i.e., acebutolol, alprenolol, atenolol, betaxolol, bisoprolol, bupranolol, butoxamine, carteolol, celiprolol, dihydroalprenolol, labetalol, levobunolol, metoprolol, nadolol, oxprenolol, pindolol, practolol, propranolol, sotalol and timolol). The following text words were included with truncation where appropriate: "blockader," "blocker," "antagonist," "myocardial infarct," "arrhythmia" and "Clinical trial." In addition to searching the databases, the reference lists of all included studies and reviews were hand searched. Pharmaceutical companies that manufacture β-blockers were contacted for possible unpublished trials. In addition, 2 experts (cardiologists) were contacted to determine if they were aware of any potentially missed studies.

Inclusion and exclusion criteria

We included RCTs that randomized AMI patients within 72 hours of symptom onset to either a β-blocker (via an intravenous or oral route, or both) or a control group. The control group received either a placebo or no additional treatment over routine care. Studies must have included mortality at 6 weeks following AMI as a primary or secondary outcome. We included studies with patients from emergency departments, coronary care units or other inpatient settings. Studies using a crossover design and studies without a control group were excluded.

Study selection

Studies were selected for inclusion by 2 reviewers (A.R. and M.S.) who independently screened citations and abstracts using the specific inclusion and exclusion criteria mentioned above. Full text articles were then reviewed for inclusion. Disagreements regarding study selection were resolved by consensus.

Data extraction

Data were abstracted from the selected articles into a Microsoft Access database (Microsoft Corporation, Redmond, Washington) using a standardized and piloted form. Abstracted variables included study characteristics such as study population, setting, design, intervention, outcomes, follow-up period, dropouts and methodological quality assessment. The primary outcome was mortality during the 6 weeks after AMI.

Assessment of methodological quality

Two reviewers (A.R. and M.T.) independently assessed each included trial and summarized the quality of each trial using the Jadad score.[8] This score rates the methodological quality of the included trials based on the following items: 1) randomization of participants; 2) blinding of patients, caregivers and those assessing outcome; and 3) full description of withdrawals and dropouts, yielding a score with a range from 0 to 5 points. In addition, allocation concealment was assessed using an approach adapted by the Cochrane group and was scored as A (adequate), B (unclearly concealed trials) or C (inadequate). Studies were considered high-quality if they scored 2 on the Jadad score and had adequate allocation concealment (A), or if they scored 3 or more on the Jadad score with an allocation concealment score of at least B. Discrepancies were resolved by consensus with a third reviewer available if needed.

Statistical analysis

We calculated the odds ratio (OR) for the primary outcome using RevMan Analyses statistical software version 4.2.5

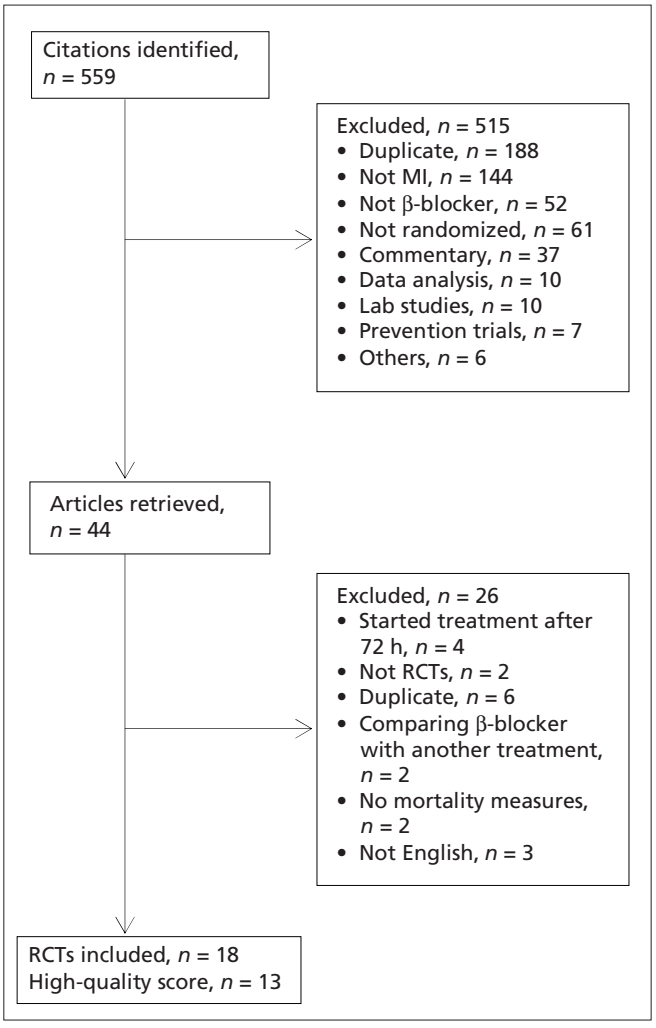

Fig. 1. Flow diagram of selection process to obtain articles chosen for meta-analysis. MI = myocardial infarction; RCT = randomized controlled trial.

https://doi.org/10.1017/S1481803500010137 Published online by Cambridge University Press

(The Cochrane Collaboration, Oxford, England). A p value of < 0.05 was considered statistically significant. To explore the stability of the overall treatment effect, we estimated the OR for mortality both including and excluding the low-quality trials. In addition, we compared trials that reported allocation concealment with trials without allocation concealment. We performed a sensitivity analysis to explore the effects of including only studies that enrolled patients within 24 hours of AMI. We used a random effect model to account for the variability among the trials. Studies were assessed for heterogeneity by examining study characteristics such as population, settings, intervention given, length of follow-up and outcome assessment. We used the χ^2 test to detect statistical heterogeneity between studies. In this setting, a p value of < 0.10 suggests significant heterogeneity. The I^2 statistic was used to quantify statistical heterogeneity across studies. An I^2 value greater than 50% indicates substantial heterogeneity. A funnel plot was constructed to assess for evidence of publication bias.

Results

Study selection

Our search identified 559 original citations. Eighteen studies met our inclusion criteria, of which 13 studies[7,9–20] were classified as high-quality (Fig. 1). Most of the citations were identified in more than 2 of the databases. The reviewers agreed on citation selection 90% of the time. They reached agreement on the other 10% by consensus.

Study description

The characteristics of included studies are displayed in Table 1. The sample sizes ranged from 94 to 45 852, with a median of 450 patients. Three trials enrolled 92.4% of the patients,[7,9,10] with a recent large study[7] enrolling 62.0% of the patients. Four trials were parallel group factorial design[7,11,12,21] with placebo as a control. Sixteen trials reported baseline patient characteristics, the majority of which were well balanced. Men formed the majority of the included patients (77.0%). All the trials except 3[7,9,13] excluded patients with congestive heart failure. All trials excluded patients with hypotension, cardiogenic shock and severe bradycardia. Fourteen trials enrolled patients within 24 hours of the onset of myocardial infarction. Mortality was the primary outcome in 14 trials and a secondary outcome in the 4 remaining trials. Data available for analysis were reported in all 18 trials. All except one[13] reported short-term mortality. One low-quality study[14] had 13% withdrawals, which were not accounted for in the mortality assessment. This study contributed only 0.3% of the included patients.

Table 1. Study characteristics and quality assessment of included studies

Trial and year	Intervention	Entry window, h	Treatment duration, d*	Outcome measured,† wk*	Jadad score‡	Allocation concealment§
Balcon et al, [20] 1966	Propranolol	24	28	In hospital	4	B
Clausen et al,[22] 1966	Propronolol	24	14	2	1	B
Propanolol in MI,[14] 1966	Propranolol	48	28	4	4	B
Norris et al,[15] 1968	Propranolol	72	21	3	4	A
Evemy and Pentecost,[23] 1978	Practorol	24	48 h	4	1	A
Andersen et al,[16] 1979	Alprenolol	24	1 yr	4	4	B
Wilcox et al,[17] 1980	Oxprenolol	24	42	6	4	B
Wilcox et al,[11] 1980	Propranolol	24	1 yr	6	4	A
Hjalmarson et al,[12] 1983	Metoprolol	48	3 mo	6	4	B
Yusuf et al,[18] 1983	Atenolol	12	10	10 d	1	A
Norris et al,[19] 1984	Propranolol	4	27 h	In hospital	3	A
MIAMI group,[9] 1985	Metoprolol	24	15	In hospital	5	A
Salathia et al,[24] 1985	Metoprolol	6	1 yr	In hospital	1	B
ISIS-1,[10] 1986	Atenolol	12	7	1	3	A
ICSG,[25] 1986	Timolol	4	In hospital	In hospital	3	B
Roberts et al, TIMI-IIB,[21] 1991	Metoprolol	24	1 yr	5 d	2	B
Basu et al, SUMIT,[13] 1997	Carvidelol	24	6 mo	6 mo	5	B
Chen et al, COMMIT,[7] 2005	Metoprolol	24	In hospital, 4 wk	In hospital, 4 wk	3	A

MI = myocardial infarction.
*Unless otherwise indicated.
†Mortality was the outcome measured.
‡Jadad score: measures of study design and reporting quality (0 being weakest and 5 being strongest).
§Allocation concealment: A (adequate), B (unclearly concealed trials) or C (inadequate).

https://doi.org/10.1017/S1481803500010137 Published online by Cambridge University Press

Statistical heterogeneity between studies was negligible as indicated by very low I^2 values for the studies included in the main analysis (0%; Fig. 2) and for those included in the sensitivity analyses (0%–11.1%; Fig. 3, Fig. 4 and Fig. 5). The funnel plot showed no clear pattern of publication bias (Fig. 6).

Evidence synthesis

The OR for mortality at 6 weeks for β-blockers, compared with controls, was 0.95 (95% confidence interval [CI] 0.90–1.01; Fig. 2). Although the point estimates indicated benefit from β-blockers, they were not statistically significant.

The subgroup of high-quality studies had an OR for 6-week mortality of 0.96 (95% CI 0.91–1.02; Fig. 3). The OR for the adequately concealed studies was 0.94 (95% CI 0.86–1.02; Fig. 4). Neither of these subgroup results were statistically significant.

The ClOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), the largest trial in this review, was the only one that included Killip class III patients. When we performed a sensitivity analysis that excluded the Killip class III patients from this trial, the estimated OR for 6-week mortality in the β-blocker group, compared with the control group, was 0.93 (95% CI 0.88–0.99; Fig. 5).

Discussion

β-Blockers have been used in the treatment of myocardial infarction for more than 4 decades. Several clinical trials have demonstrated their beneficial effect on long-term survival following AMI. Results from a meta-analysis by Freemantle and colleagues[5] of trials that studied the β-blockade after AMI and showed a 23% reduction in long-term mortality using β-blocker therapy. However, it failed to show a statistically significant reduction in short-term

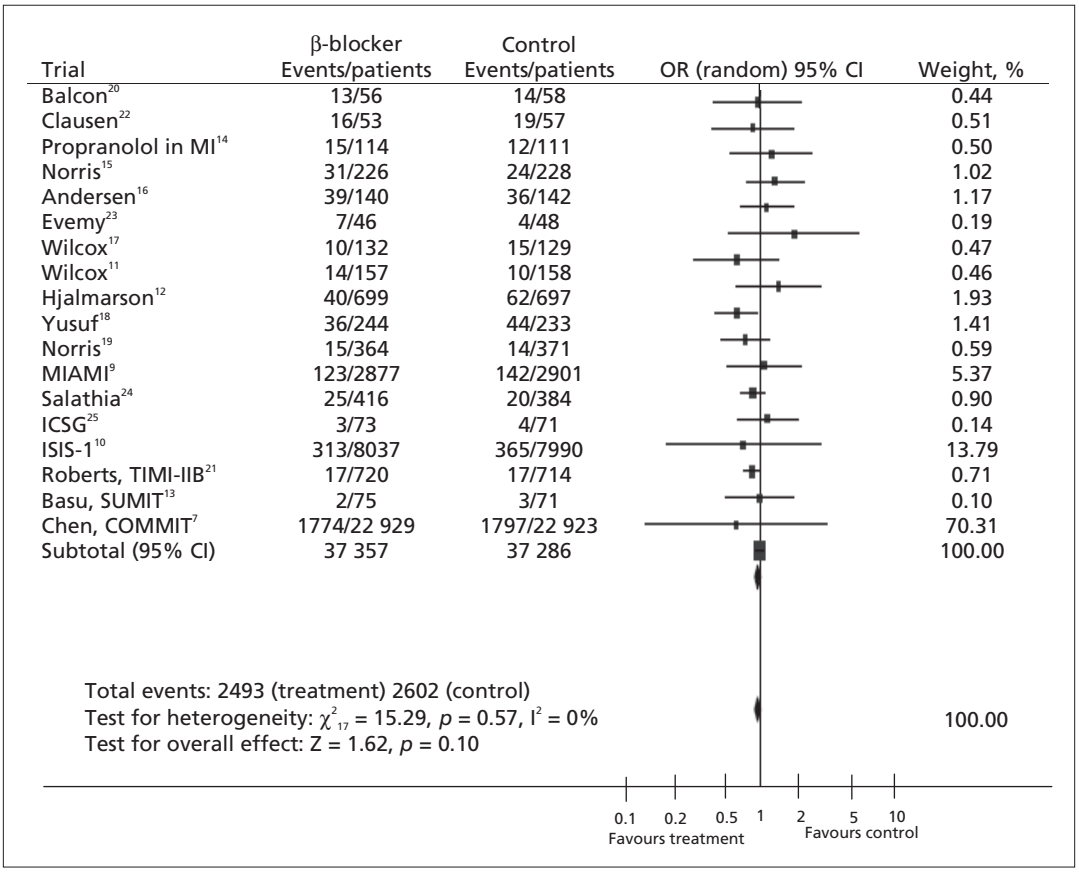

Fig. 2. Meta-analysis of effects of β-blockers on death during the first 6 weeks after myocardial infarction (MI) in 18 randomized trials. Odds ratios (ORs) in each (squares with area proportional to number of events) comparing outcome in patients allocated to a β-blocker group with that in patients allocated to a control group, along with 95% confidence intervals (CIs) (horizontal line). Overall OR and 95% CI are plotted by diamond, with the value and significance given alongside. Squares and diamonds are all to the left of the vertical line, indicating a benefit with β-blockers, but this benefit is significant ($p < 0{\cdot}05$) only if the horizontal line ($p < 0{\cdot}05$) or diamond ($p < 0{\cdot}05$) does not overlap the vertical line. Basu[12] reported the 6-month mortality.

https://doi.org/10.1017/S1481803500010137 Published online by Cambridge University Press

mortality. In contrast to Freemantle and coworkers' review, which enrolled patients at any stage of their AMI, we included only trials that enrolled patients within 72 hours of the onset of AMI symptoms.

Our results provide no evidence that routine use of β-blockers started within 72 hours of symptoms reduces 6-week mortality in patients with AMI. This does not support the current recommendations of the routine use of β-blockers in the acute phase of post–myocardial infarction. A possible explanation for our findings is that the myocardium might be stunned in the period immediately after AMI, resulting in a low-ejection fraction, which usually improves in the long term. Therefore, β-blockers, which are negative inotropes, might worsen myocardial contractility in the acute phase. This effect would mitigate the benefits of decreased oxygen consumption and anti-arrhythmic properties. Our subgroup analysis excluding patients with Killip class III showed a statistically significant 0.4% absolute risk reduction of death in 6 weeks (number needed to treat = 250). This small potential benefit might be owing to the strict exclusion of patients

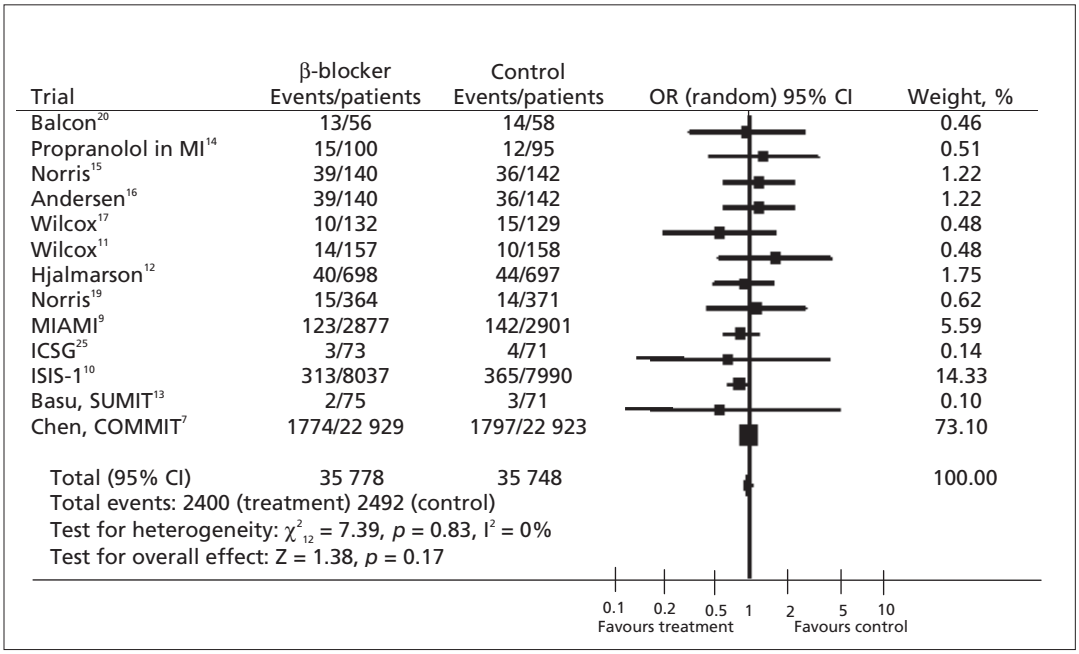

Fig. 3. Meta-analysis of effects of β-blockers on death during the first 6-week period after myocardial infarction (MI) in 13 randomized trials, including high-quality score trials only. CI = confidence interval; OR = odds ratio.

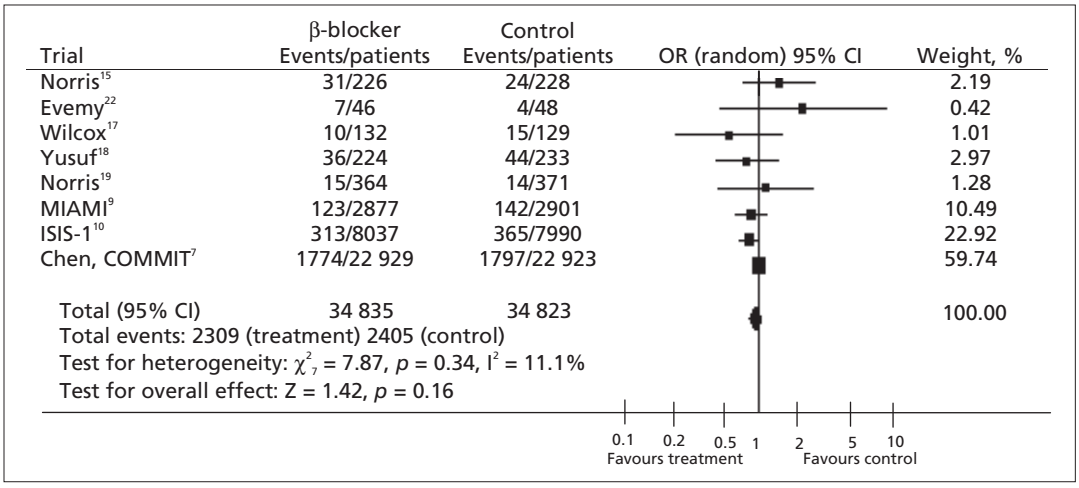

Fig. 4. Meta-analysis of effects of β-blockers on death during the first 6-week period after myocardial infarction in 8 randomized trials, including trials with adequate concealment only. CI = confidence interval; OR = odds ratio.

https://doi.org/10.1017/S1481803500010137 Published online by Cambridge University Press

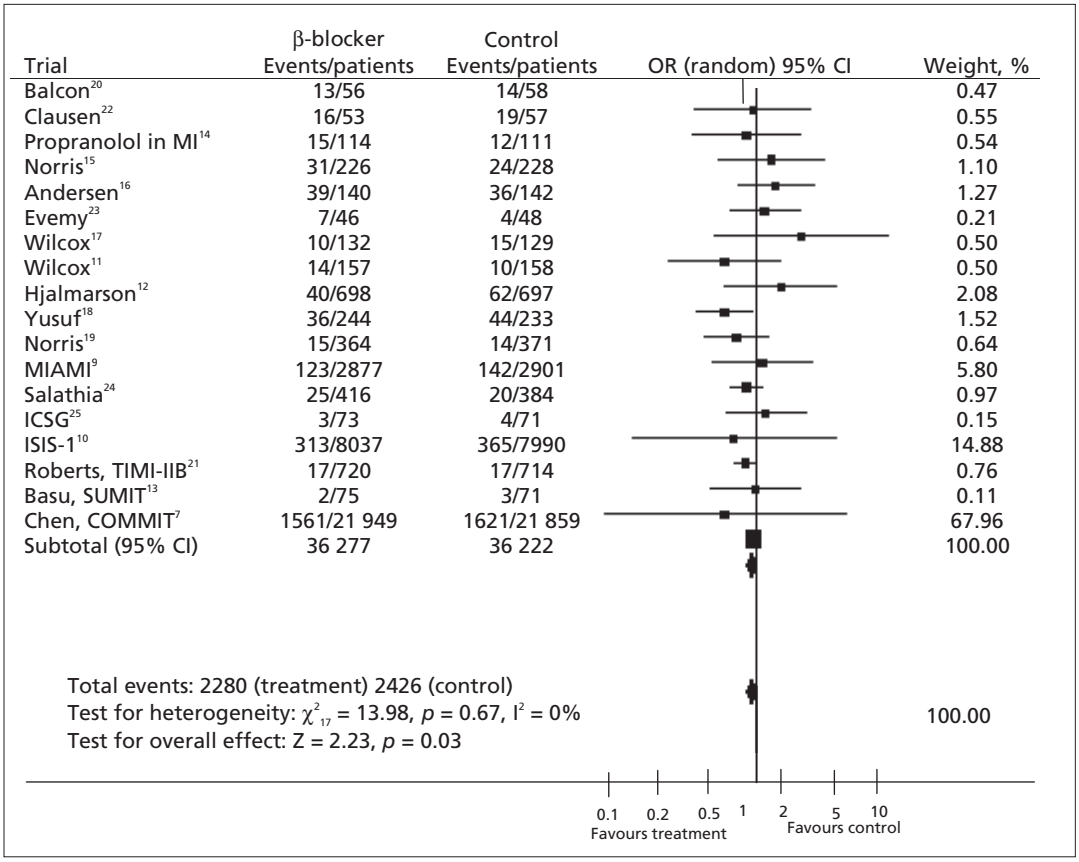

Fig. 5. Meta-analysis of effects of β-blockers on death during the first 6-week period after myocardial infarction (MI) in 18 randomized trials, excluding patients with Killip class III congestive heart failure from the COMMIT trial. CI = confidence interval; OR = odds ratio.

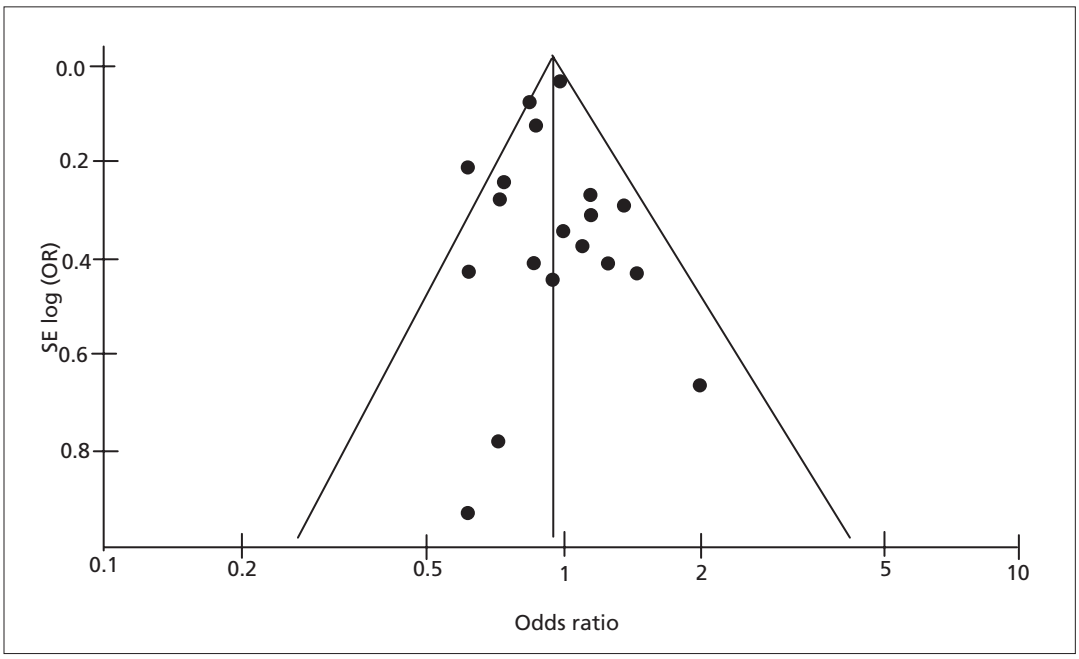

Fig. 6. Funnel plot of β-blocker recipients, compared with control subjects, with pseudo 95% confidence limits. Symmetric distribution of the randomized controlled trials around the vertical line suggests a smaller chance of publication bias. OR = odds ratio; SE = standard error.

https://doi.org/10.1017/S1481803500010137 Published online by Cambridge University Press

with signs of congestive heart failure or lower blood pressure from most trials of β-blockers in the period following AMI and therefore may not apply to the general population of post-AMI patients.

Our review has a number of strengths. The trials we included shared similar patient populations, entry windows, outcomes and intervention characteristics. Most studies were of high-quality and they all reported 6-week mortality, even when the follow-up period was longer than 6 weeks. We minimized the likelihood of bias by developing a detailed protocol before commencing this study, by performing an exhaustive search for both published and unpublished studies and by using explicit methodology for study selection, data extraction and data analysis.

We used systematic and explicit inclusion and exclusion criteria for selecting studies for this review. Potential studies were assessed systematically and rated according to quality. We found negligible statistical heterogeneity between studies included in our review and the funnel plot showed no clear pattern of publication bias (Fig. 6). Our review included a large number of patients (74 643) and, consequently, the present meta-analysis has excellent statistical power to reliably detect clinically worthwhile differences between β-blockers and a control group. A fixed effect model (not presented) did not change either the point estimate or the CIs.

As with any systematic review, there exists the possibility of publication bias. We attempted to minimize this bias with our comprehensive search strategy. However, we limited our search to studies published in English owing to resource and time constraints. We did not look at other adverse outcomes or benefits from using β-blockers, so the result cannot be extrapolated to other outcomes. Including the high-risk patients from the COMMIT trial may have biased our results. However, to remove the effect of this limitation we calculated separate pooled estimates for the lower-risk groups (Killip class I and class II). This resulted in a small change in the pooled ORs from 0.95 to 0.93, supporting the choice of most trials to exclude high-risk patients. In order to increase the external validity of our results, we included Killip class II subjects as was done in the Metoprolol in Acute Myocardial Infarction (MIAMI) and COMMIT trials. We did not explore whether different β-blockers or different routes of administration might influence the outcome. The 1 study in our review that looked at carvedilol had a very low mortality rate (3.2%, compared with 6.8% for all other studies).[13] In addition to being a β-blocker, carvedilol is a vasodilator, making it potentially beneficial for patients with congestive heart failure. Despite this discrepancy, we believe that including this trial did not bias our results as it had a very low-weighted OR (0.1).

Conclusion

This meta-analysis suggests that β-blockers do not provide any short-term survival advantage when given in the first 72 hours after AMI. Future research is needed to explore the optimal time to start β-blockers following AMI. More research is also needed to explore the optimal route of β-blocker administration and which β-blocker gives the most benefit after AMI.

Competing interests: None declared.

References

1. Tu JV, Austin PC, Filate WA, et al. Canadian Cardiovascular Outcomes Research Team (CCORT). Outcomes of acute myocardial infarction in Canada. Can J Cardiol 2003;19:893-901.
2. Herlitz J, Elmfeldt D, Hjalmarson A, et al. Effect of metoprolol on indirect signs of the size and severity of acute myocardial infarction. Am J Cardiol 1983;51:1262-8.
3. Herlitr J, Emanuelsson KJ, Swedberg K, et al. Metoprolol trial: enzyme estimated infarct size. Am J Cardiol 1964;53(suppl): 15D-21D.
4. Yusuf S, Peto R, Lewis J, et al. Beta-blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 1985;27:335-71.
5. Freemantle N, Cleland J, Young P, et al. Beta blockade after myocardial infarction: Systematic review and meta regression analysis. BMJ 1999;318:1730-7.
6. Woods KL, Ketley D, Lowy A, et al. Beta-blockers and antithrombotic treatment for secondary prevention after myocardial infarction. Towards an understanding of factors influencing clinical practice. The European Secondary Prevention Study Group. Eur Heart J 1998;19:74-9.
7. 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 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1622-32.
8. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996;17:1-12.
9. Metoprolol in Acute Myocardial Infarction (MIAMI). A randomized placebo-controlled international trial. the MIAMI trial research group. Eur Heart J 1985;6:199-226.
10. Randomized 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.
11. Wilcox RG, Rowley JM, Hampton JR, et al. Randomized placebo-controlled trial comparing oxprenolol with disopyra-

mide phosphate in immediate treatment of suspected myocardial infarction. Lancet 1980;2:765-9.

12. Hjalmarson A, Herlitz J, Holmberg S, et al. The goteborg metoprolol trial. Effects on mortality and morbidity in acute myocardial infarction. Circulation 1983;67:26-32.
13. Basu S, Senior R, Raval U, et al. Beneficial effects of intravenous and oral carvedilol treatment in acute myocardial infarction. A placebo-controlled, randomized trial. Circulation 1997;96:183-91.
14. Propranolol in acute myocardial infarction. A multicentre trial. Lancet 1966;2:1435-8.
15. Norris RM, Caughey DE, Scott PJ. Trial of propranolol in acute myocardial infarction. BMJ 1968;2:398-400.
16. Andersen MP, Bechsgaard P, Frederiksen J, et al. Effect of alprenolol on mortality among patients with definite or suspected acute myocardial infarction. Preliminary results. Lancet 1979;2:865-8.
17. Wilcox RG, Roland JM, Banks DC, et al. Randomized trial comparing propranolol with atenolol in immediate treatment of suspected myocardial infarction. BMJ 1980;280:885-8.
18. 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;67:32-41.
19. Norris RM, Barnaby PF, Brown MA, et al. Prevention of ventricular fibrillation during acute myocardial infarction by intravenous propranolol. Lancet 1984;2:883-6.
20. Balcon R, Jewitt DE, Davies JPH, et al. A controlled trial of propranalol in acute myocardial infarction. Lancet 1966;2:917-20.
21. Roberts R, Rogers WJ, Mueller HS, 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.
22. Clausen J, Flesby M, Jorgensen FS, et al. Absence of prophylactic effect of propranolol in myocardial infarction. Lancet 1966;2:920-4.
23. Evemy KL, Pentecost BL. Intravenous and oral practolol in the acute stages of myocardial infarction. Eur J Cardiol 1978;7:391-8.
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.
25. Acute myocardial infarct size reduction by timolol administration. The international collaborative study group. Am J Cardiol 1986;57:28F-33F.

Correspondence to: Dr. Abdullah Al-Reesi, Department of Emergency Medicine, Clinical Epidemiology Unit, F6, Ottawa Health Research Institute, 1053 Carling Ave., Ottawa ON K1Y 4E9; alreesi@rogers.com

https://doi.org/10.1017/S1481803500010137 Published online by Cambridge University Press