International Journal of Cardiology 228 (2017) 295–302

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Intravenous beta-blockers in ST-segment elevation myocardial infarction: A systematic review and meta-analysis

Lee H. Sterling [a,b], Kristian B. Filion [a,b,c,1], Renee Atallah [a], Pauline Reynier [a], Mark J. Eisenberg [a,b,c,d,*]

[a] Division of Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital/McGill University, Montreal, QC, Canada
[b] Faculty of Medicine, McGill University, Montreal, QC, Canada
[c] Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada
[d] Division of Cardiology, Jewish General Hospital/McGill University, Montreal, QC, Canada

ARTICLE INFO

Article history:
Received 22 August 2016
Accepted 6 November 2016
Available online 09 November 2016

Keywords:
Beta-blockers
STEMI
Acute coronary syndromes
Systematic review
Meta-analysis

ABSTRACT

Background/objectives: The role of intravenous (IV) beta-blockers in conjunction with percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) remains unclear. We therefore conducted a meta-analysis to assess their role in the acute phase of STEMI.
Methods: We systematically searched the Cochrane Libraries, Medline, and EMBASE for RCTs comparing IV beta-blockers with inactive controls in STEMI patients undergoing PCI. The primary outcome was left ventricular ejection fraction (LVEF). Pooling was performed using DerSimonian and Laird random-effects models.
Results: Four RCTs ($n = 1149$) were included in our meta-analysis. All RCTs only enrolled patients with confirmed STEMI with symptoms lasting <6 or <12 hours, and presenting in Killip Class 1 or 2. Mean age ranged across trials from 58.5–62.5 years. Most patients were male (range: 74.8%–86.3%). Data suggest that IV beta-blockers may improve LVEF at 0–2 weeks (weighted mean difference [WMD]: 1.9%; 95% confidence interval [CI]: −0.7%, 4.5%) and 4–6 weeks (WMD: 1.4%; 95% CI: −3.1%, 5.9%) post-infarct, reaching statistical significance at 24 weeks (WMD: 2.6%; 95% CI: 0.6%, 4.6%). Rates of ventricular arrhythmia (risk ratio [RR]: 0.65; 95% CI: 0.33, 1.29), any arrhythmia (RR: 0.67; 95% CI: 0.36, 1.27), and cardiogenic shock (RR: 0.77; 95% CI: 0.31, 1.95) during index hospitalization were numerically lower with IV beta-blockers, but 95% CIs were wide.
Conclusions: In STEMI patients presenting in Killip Class 1 or 2, IV beta-blockers in conjunction with PCI are associated with improved LVEF at 24 weeks relative to PCI alone.

1. Introduction

Intravenously (IV) administered beta-adrenergic blockade in the acute phase of STEMI is hypothesized to reduce infarct size and improve left ventricular (LV) function, two independent predictors of reduced late adverse events [1,2]. Nevertheless, the role of IV beta-blockers in STEMI remains unclear. The 2013 American College of Cardiology Foundation/American Heart Association guidelines for STEMI treatment provide a class IIa Recommendation (level of evidence B) for IV beta-blocker use at the time of STEMI presentation [3]. These recommendations, however, are based on findings from randomized controlled trials (RCTs) conducted before the contemporary treatment of STEMI with percutaneous coronary intervention (PCI) [4–6]. Since their release, two RCTs examining IV beta-blockers in STEMI have been published [7,8]. Thus, we conducted a systematic review with meta-analysis to re-assess the role of IV beta-blockers during the acute phase of STEMI.

2. Methods

2.1. Search strategy

We followed a pre-specified protocol, reported here in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [9]. We systematically searched the Cochrane Libraries, Medline (via Ovid), and EMBASE (via Ovid) from inception to May 1st, 2016 for RCTs examining IV beta-blocker use in the acute phase of STEMI. Tables S1–S3 show a detailed description of our search strategy. Briefly, we used Medical Subject Heading and EMTREE terms as well as keywords for "beta blocker", "intravenous", and "myocardial infarction". We then combined them with a modified version of the Cochrane Collaboration RCT Hedge to restrict our search to RCTs [10]. Moreover, we hand-searched the references of our included trials to identify other potentially relevant RCTs.

2.2. Study selection

After screening the titles and abstracts of articles identified in the electronic search, the full texts of potentially eligible articles were retrieved and reviewed in detail to

* Corresponding author at: Divisions of Cardiology and Clinical Epidemiology, Jewish General Hospital/McGill University, 3755 Côte Ste-Catherine Road, Suite H-421.1, Montreal, Quebec, Canada H3T 1E2.
E-mail address: mark.eisenberg@mcgill.ca (M.J. Eisenberg).
[1] Dr. Filion holds a Canadian Institutes of Health Research (CIHR) New Investigator Award.

http://dx.doi.org/10.1016/j.ijcard.2016.11.133
0167-5273/

determine if they met our pre-specified inclusion criteria. Articles included in our final qualitative and quantitative reviews: were published in English or French; contained data from an RCT comparing an IV-administered beta-blocker versus an inactive control in STEMI patients who underwent PCI; and reported left ventricular ejection fraction (LVEF) post-treatment. Observational studies, case reports, case series, abstracts, conference proceedings, reviews and letters to the editor were excluded.

2.3. Data abstraction

Two reviewers (LHS, RA) independently abstracted data from the included trials, with discrepancies resolved by consensus or a third reviewer (KBF). Abstracted data included trial name; first author; year of publication; country of enrollment; number of enrolling centers; sample size; patient demographics; number of stenosed vessels; time from symptom onset to balloon; Killip Class; and Thrombolysis In Myocardial Infarction flow grade pre- and post-PCI; our primary outcome: LV function measured by LVEF via any modality (i.e., echocardiography, magnetic resonance imaging [MRI], left ventriculography); and the following secondary outcomes: LV end-diastolic and LV end-systolic volumes; final infarct size as percentage of total LV size; LV size (grams); peak creatine kinase, creatine kinase-myocardial band, Troponins I and T; heart rate, systolic and diastolic blood pressure pre- and post-trial intervention; ventricular arrhythmia (VA), any arrhythmia, and cardiogenic shock during the first 24 h post-infarct or index hospitalization; major adverse cardiovascular events (MACE; as defined by each trial), individual MACE components, and cardiac mortality at all available follow-ups; and re-admission for heart failure after index hospitalization.

2.4. Quality assessment

Quality assessment was performed using the Cochrane Risk of Bias Tool [11], which assesses internal validity by assigning values of "high", "low", or "unclear" risk of bias in the domains of: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other potential sources of bias. Two reviewers (LHS, RA) independently performed quality assessment, with disagreements resolved by consensus or a third reviewer (KBF). We included all RCTs in our study regardless of quality.

2.5. Statistical analysis

DerSimonian and Laird random-effects models with inverse variance weighting were used to pool data across trials. Weighted mean differences (WMDs) with corresponding 95% confidence intervals (CIs) were estimated for LVEF and risk ratios (RRs) with 95% CIs were estimated for clinical outcome data. Heterogeneity was estimated using the I^2 statistic. In all analyses, we used a 0.5 continuity correction to include data from RCTs with 0 events. All analyses were performed using R version 3.2.2. (R Core Team [2015], R Foundation for Statistical Computing).

3. Results

Our database search yielded 1318 publications (Fig. 1). One additional article was identified via hand-search, as it was indexed on Pubmed but not Medline (via Ovid) at the time of the database search. After removing duplicates and screening titles and abstracts, 51 of the 1319 publications underwent full-text review. Four RCTs ($n = 1149$) met our inclusion criteria: EARLY β-blocker Administration before primary PCI in patients with STEMI (EARLY-BAMI) [7], Effect of Metoprolol in Cardioprotection During an Acute MI (METOCARD-CNIC) [12,13], BEtA-Blocker Therapy in Acute MI (BEAT-AMI) [8], and an RCT by Hanada and colleagues on IV landiolol effects in acute MI patients undergoing PCI [14].

3.1. Study characteristics

All included RCTs used a selective beta-1 receptor antagonist and treated STEMI patients with PCI (Table 1). EARLY-BAMI and METOCARD-CNIC administered two and three 5 mg-boluses, respectively, of IV metoprolol prior to primary PCI. BEAT-AMI began a 24-h, continuous, weight-based, with extra bolus esmolol infusion targeting a heart rate of 60 beats per minute immediately after primary PCI. Hanada et al. began a 3-μg/kg per minute, 24-h, continuous landiolol infusion immediately after primary PCI. Finally, the choice of inactive controls differed by study: matched placebo in EARLY-BAMI, continuous 0.9% IV saline solution in BEAT-AMI, and no intervention in METOCARD-CNIC and Hanada et al.

Trials had similar selection criteria and included only patients with confirmed STEMI with symptoms lasting <6 [8,12] or <12 [7,14] hours (Table 1). METOCARD-CNIC excluded patients with non-anterior STEMIs [12]. All trials excluded patients presenting with Killip Class ≥3 MI, signs of atrioventricular block, bradycardia or low systolic blood pressure. Additionally, two trials excluded patients with history of asthma [7] or bronchospasm during treatment [14], respectively.

3.2. Quality assessment

Study quality was generally high (Table S4) [11]. Hanada et al. had an unclear risk of bias in the domain of allocation concealment, as they only mention an "envelope method" without further details. EARLY-BAMI was deemed to have a high risk of bias in the domain of incomplete outcome data due to a 55% attrition rate in patients being assessed for its primary outcome, and due to significant baseline differences between patients who were assessed or not. Finally, EARLY-BAMI and Hanada et al. had high and unclear risks of bias, respectively, in the other risks of bias domain. EARLY-BAMI switched its primary outcome midways through data collection, whereas Hanada et al. did not register their RCT with any clinical trial database.

3.3. Baseline patient and procedural characteristics

Patient baseline and procedural characteristics were similar across included RCTs and between treatment arms (Table 2 and S5). Mean age ranged from 58.5–62.5 years across trials. Most patients were male (range: 74.8%–86.3%). Cardiovascular risk factors did not significantly differ between arms in any RCT. Hemodynamics were assessed pre- and post-trial intervention by all included trials (Table S6). Mean heart rate was consistently lower post-trial intervention with beta-blockers. Among trials reporting systolic and/or diastolic blood pressure, no differences were noted between arms.

Several trials reported medication use pre-MI and at discharge. EARLY-BAMI, BEAT-AMI and Hanada et al. described routine oral beta-blocker use pre-IV beta-blockade (Table 2), ranging from 0% in Hanada et al. to 19% overall in EARLY-BAMI. Oral beta-blocker, angiotensin-converting enzyme inhibitor, and angiotensin receptor blocker use at discharge was reported in EARLY-BAMI, METOCARD-CNIC, and Hanada et al. (Table 2), with no differences between arms. Rates ranged from 73% to 98% for oral beta-blockers, and from 69% to 98% for discharge with either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

3.4. LV function

LVEF data were only available in a subset (724/1149) of patients and at various time points post-infarct (Table 3). This was largely driven by a lack of MRI follow-up in EARLY-BAMI due to the change of its primary endpoint, and to a lesser extent, METOCARD-CNIC. Data suggest IV beta-blockers may improve LVEF at 0–2 weeks (WMD: 1.9%; 95% CI: −0.7%, 4.5%) and 4–6 weeks (WMD: 1.4%; 95% CI: −3.1%, 5.9%) post-infarct, reaching statistical significance at 24 weeks (WMD: 2.6%; 95% CI: 0.6%, 4.6%) (Fig. 2). LV end-diastolic and end-systolic volumes were assessed at 4 weeks post-infarct in EARLY-BAMI, and at 1 and 24 weeks post-infarct in METOCARD-CNIC (Table 3). METOCARD-CNIC findings suggest IV beta-blockers may improve LV end-diastolic volume at 24 weeks. When assessing LV end-systolic volume, METOCARD-CNIC showed potential benefit at 1 week post-infarct, which became statistically significant at 24 weeks. No evidence of differences in LV end-diastolic and end-systolic volumes was found in EARLY-BAMI.

3.5. Infarct characteristics

All trials reported peak rates of various cardiac enzymes post-STEMI (Table S7). Treatment effects were inconsistent across trials: