Summary

The effects of β-blocker therapy on clinical outcomes in patients with myocardial infarction and mildly reduced (40–49%) left ventricular ejection fraction (LVEF) are largely unknown. Four recently conducted randomised trials tested the efficacy of β blockers after a recent myocardial infarction in patients without reduced LVEF (LVEF ≥40%). However, none were individually powered to assess these effects in the subgroup of patients with mildly reduced LVEF. We aimed to assess the efficacy of β blockers in patients with myocardial infarction and mildly reduced LVEF during the index hospitalisation.

We conducted an individual patient-level meta-analysis of patients with mildly reduced LVEF and no history or signs of heart failure from four recent clinical trials. These studies were included because they were randomised controlled trials testing long-term effects (median follow-up >1 year) of oral β-blocker therapy in patients who recently had a myocardial infarction (randomisation within 14 days) and had mildly reduced LVEF. No further studies were found in a systematic review (Jan 1, 2020 to June 26, 2025). A one-stage, fixed-effects, Cox proportional hazards regression model was used to assess the treatment effect of β blockers on the predefined primary composite endpoint of all-cause death, new myocardial infarction, or heart failure. All endpoints were independently adjudicated. This meta-analysis was registered with PROSPERO (CRD420251023480).

1885 patients with myocardial infarction and mildly reduced LVEF were included in the meta-analysis: 979 from the REBOOT trial, 422 from the BETAMI trial, 430 from the DANBLOCK trial, and 54 from the CAPITALRCT trial. Overall, 991 patients were assigned to β blockers and 894 to control (no β blockers). The primary composite endpoint occurred in 106 patients (32·6 events per 1000 patient-years) in the β-blocker group and 129 patients (43·0 per 1000 patient-years) in the no β-blocker group (hazard ratio 0·75 [95% CI 0·58–0·97]; p=0·031). No heterogeneity between the trials (trial-by-treatment pinteraction=0·95) or between countries of enrolment was observed (pinteraction=0·98).

In patients with acute myocardial infarction with mildly reduced LVEF without history or clinical signs of heart failure, β-blocker therapy was associated with a reduction in the composite of all-cause death, new myocardial infarction, or heart failure. These results extend the known benefits of these agents in patients with myocardial infarction with reduced LVEF to the subgroup with mildly reduced LVEF.

Introduction

Left ventricular ejection fraction (LVEF) is a key prognostic factor to guide secondary prevention in patients with recent myocardial infarction.1,2 Current guidelines for the management of patients with acute coronary syndrome support the use of β blockers for all patients who have had a myocardial infarction, but the strength of recommendation is higher for patients with reduced LVEF and weaker for those with LVEF above 40%. For patients with no severe reduction in LVEF (ie, with LVEF above 40%), the European Society of Cardiology (ESC) gives a class IIa recommendation (ie, β blockers should be considered for this population), whereas the American College of Cardiology (ACC) and American Heart Association (AHA) give a class I recommendation (ie, β blockers are recommended for this population).1,2 Although the clinical benefits of β blockers for patients with reduced LVEF (≤40%) after a myocardial infarction are undisputed,3,4 the long-term use of these drugs in patients without reduced LVEF has een the subject of intense debate.5–9 Retrospective analyses of patients with heart failure with mildly reduced LVEF (41–49%) suggest that this subgroup might benefit from similar therapies as do those with reduced LVEF.10,11 Although patients with myocardial infarction and mildly reduced LVEF might intuitively be expected to benefit from β blockers as do patients with reduced LVEF (similar to the heart failure scenario), no randomised trials have been conducted to assess the effects of β blockers in this specific population. Only four modern randomised clinical trials have enrolled patients with an acute myocardial infarction, LVEF of 40% or higher, and no history or clinical signs of heart failure to assess the effects of long-term oral β blocker therapy versus no β blocker therapy on major adverse cardiovascular events: the REBOOT study (8505 patients, including 979 [12%] with LVEF 41–49%),6,12 the BETAMI study (2867 patients;

422 [15%] with LVEF 40–49%),8,13 the DANBLOCK study (2707 patients; 430 [16%] with LVEF 41–49%),8,13 and the CAPITAL-RCT study (339 patients; 54 [16%] with LVEF 40–49%).7 Importantly, none of these trials were individually powered to assess the effects of β blockers on clinical outcomes specifically in the subgroup of patients with mildly reduced LVEF. To fill this gap in evidence,1,14 we performed an individual patient data meta-analysis including patients with mildly reduced LVEF from the REBOOT, BETAMI, DANBLOCK, and CAPITAL-RCT trials.

Methods

Search strategy and selection criteria

Our prespecified aim was to assess the efficacy of β blockers in patients with mildly reduced LVEF (LVEF 40–49%) during the index hospitalisation following myocardial infarction. We analysed data from the REBOOT (ClinicalTrials. gov number NCT03596385), BETAMI (NCT03778554), DANBLOCK (NCT03646357), and CAPITAL-RCT (NCT01155635) open-label trials, which were designed to evaluate the superiority of oral β blockers in improving clinical outcomes in patients within 14 days following a myocardial infarction. These trials were included because they were the only recent studies testing the long-term effects of oral β-blocker therapy in patients who had recently had a myocardial infarction without reduced LVEF. The type and dose of β blocker was decided by the treating physician in all trials except in CAPITAL-RCT, in which all patients received carvedilol started orally from low doses and titrated up to the target dose of 20 mg daily, although the initial dose and titration of carvedilol was at the discretion of the attending physician. Key exclusion criteria in all trials were clinical evidence of heart failure or competing indications or contraindications for β blocker therapy. Further information on the included trials, their inclusion and exclusion criteria, and their primary outcomes is provided in appendix 1 (p 2), and additional study design details can be found in previous publications.12,13 To ensure that no relevant trials were overlooked, we (XR and AMDK) conducted a systematic review of MEDLINE via PubMed of randomised controlled trials published since Jan 1, 2000, investigating the mid-term and long-term effects of oral β blocker therapy (median follow-up >1 year) in patients who had recently had a

myocardial infarction (randomisation within 14 days) and had mildly reduced LVEF (LVEF 40–49%). The search was done on June 26, 2025, and identified no additional trials (appendix 1 p 1; see appendix 1 p 3 for search strategy). Data from the REBOOT, BETAMI, and DANBLOCK trials were unpublished at the time of analysis and were included with permission from the respective steering committees and trial sponsors. The protocol and first version of the statistical analysis plan for this metaanalysis were prespecified and registered on PROSPERO (CRD420251023480) before these trial databases were locked. The statistical analysis plan is available in appendix 2. All trial participants provided written consent, and the study protocols were approved by the ethics committees at all participating sites.

Study outcomes

Primary and key secondary endpoints for each individual trial are summarised in appendix 1 (p 4). In each trial, endpoints were adjudicated by a masked clinical endpoints committee. Differences in endpoint definitions are also reported in appendix 1 (p 5). In this individual patient data meta-analysis, the prespecified primary endpoint was the composite of all-cause death, new myocardial infarction, or heart failure. Key secondary endpoints were the individual components of the primary endpoint, cardiac death (for those trials with this endpoint available), and unplanned coronary revascularisation. In addition, the exploratory endpoint of malignant ventricular arrhythmia (a composite of ventricular tachycardia, ventricular fibrillation, or resuscitated cardiac arrest) was prespecified. Safety endpoints were admission to hospital for stroke, and second-degree or third-degree atrioventricular block (for trials with available data).

Data análisis

Data were extracted and harmonised by two authors (AMDK and TLFH), with discrepancies resolved by a third author (XR). Baseline clinical characteristics of patients were either summarised by treatment group or by trial, with means and SDs for continuous variables, and frequencies and percentages for categorical variables. A fixed-effects model was used for this one-stage individual patient data meta-analysis, based on the assumption that the main reason for variation in the estimates between trials was sampling error and that the treatment effect was shared across trials.15 Incidence rates for the β-blocker group and no β-blocker group (control

group), as well as incidence rate ratios, were estimated using Poisson regression models for each trial and for the overall pooled sample. Time-to-first-event curves for the primary endpoint were obtained for the pooled data using the Kaplan–Meier method and compared using the log-rank test. An unadjusted Cox proportional hazards model stratified by country (Spain, Italy, Denmark, Norway, and Japan) was used to estimate the overall hazard ratio (HR) and its 95% CIs for this individual patient data meta-analysis (assuming equal effects across strata but with a baseline hazard unique to each study).16 No covariate adjustment was done. Primary analyses were performed in the full analysis set by intention to treat. The full analysis set included all randomly allocated participants except those who withdrew consent, those with missing consent, and those randomly allocated in error (eg, not meeting the eligibility criteria, or randomly allocated twice). The same approach was used for all time-to-first-event secondary endpoints. Potential departures from the proportional hazards assumption were assessed through visual and statistical methods.17,18 Between-trial heterogeneity of treatment effect was examined with an interaction term between trial and randomly assigned therapy (pinteraction). Additionally, we tested treatment-by-trial heterogeneity of effect using Cochran's Q test and Higgins and Thompson's I^2 from a two-stage meta-analysis for the primary endpoint. Two prespecified sensitivity analyses were done: a multivariable Cox regression adjusted for age (continuous), sex, index myocardial infarction type (ST-segment elevation myocardial infarction [STEMI] vs non-STEMI), and country (Spain, Italy, Denmark, Norway, and Japan), and a two-stage meta-analysis using a fixed-effects model and the treatment estimates derived at the individual patient level. Additionally, a post-hoc sensitivity analysis restricted to those with LVEF 41–49% was done. Subgroup analyses were done using a Cox model stratified by study, with terms for treatment, subgroup, and interaction between treatment and subgroup. The pinteraction value was estimated using a likelihood ratio test. For β-blocker dosage, a Wald test assessing equality of three groups (control vs median or lower dose vs greater than median dose) was done. significant for all analyses. All analyses were done with Stata (version 19.5). Role of the funding source The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.