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Beta- blockers after myocardial infarction without heart failure: time for a paradigm shift?

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ABSTRACT

Background. The role of beta- blockers (BBs) after myocardial infarction (MI) without heart failure (HF) and with LVEF ≥40% is uncertain in the contemporary era of PCI, dual antiplatelet therapy and high- intensity statins. Two recent randomized trials - REBOOT- CNIC and BETAMI-DANBLOCK - provide updated evidence but used different endpoints.

Objective. To determine whether BBs confer prognostic benefit after MI in patients without HF and with LVEF ≥40%, to reconcile REBOOT-CNIC and BETAMI-DANBLOCK with REDUCE-AMI and ABYSS and to identify subgroups most likely to benefit.

Methods. Targeted narrative review informed by structured searches of PubMed/MEDLINE, Embase, Cochrane Central, and major congress repositories (January 2018–September 2025). Eligible evidence included RCTs, prespecified/post-hoc subgroup analyses, registries, meta-analyses, and guidelines. Findings available only from pooled analyses or congress communications were treated as preliminary signals.

Results. REBOOT-CNIC reported no overall benefit of routine long-term BB therapy on a hard composite of all-cause death, recurrent MI, or HF hospitalization. BETAMI–DANBLOCK showed a modest reduction in a broader composite (adding stroke, unplanned revascularization, malignant ventricular arrhythmias, and HF hospitalization), driven mainly by fewer recurrent MIs, with no mortality difference. An individual patient-data meta-analysis suggests a benefit signal in patients with LVEF 40–49%, while no clear effect is seen when LVEF ≥50%; REDUCE-AMI aligns with the latter finding, and ABYSS indicates that abrupt discontinuation may be unsafe.

Conclusions. Routine long-term BB therapy is unlikely to improve prognosis in all post-MI patients with LVEF ≥50% and no HF. A selective, time-limited approach appears appropriate, with potential benefit most plausible in LVEF 40–49%; BBs remain valuable for symptom control, and deprescribing should be gradual.

Keywords. beta-blocker; myocardial infarction; preserved ejection fraction; mildly reduced ejection fraction; REBOOT-CNIC; BETAMI–DANBLOCK.

Słowa kluczowe. Beta-adrenolityki; zawał mięśnia sercowego; zachowana frakcja wyrzutowa; łagodnie obniżona frakcja wyrzutowa (LVEF 40–49%); REBOOT-CNIC; BETAMI–DANBLOCK;

INTRODUCTION

For more than fifty years, beta-blockers (BBs) have been part of routine care after myocardial infarction (MI). Early studies from the prereperfusion era - especially BHAT and ISIS-1- showed fewer dangerous ventricular arrhythmias and early deaths when adrenergic drive was blocked, and this set a strong precedent for decades [15,16]. Today the setting is very different: most patients are revascularised with PCI, receive dual antiplatelet therapy and high-intensity statins, and take part in rehabilitation. Because baseline risk is lower, the extra room for any single drug to improve hard outcomes is smaller; at the same time, familiar side effects of BBs - bradycardia, low blood pressure, fatigue, sexual dysfunction, bronchospasm in susceptible patients, and masking of hypoglycaemia - may weigh more heavily in day-to-day care.

Signals from modern registries suggested that long-term BB therapy might not add survival benefit in patients with preserved ejection fraction (EF) and called for contemporary randomized trials [17–20]. Those trials arrived in 2024–2025. REDUCE-AMI (LVEF ≥50%) did not show outcome improvement with starting BBs for prognosis, while ABYSS found that abrupt discontinuation of chronic BB therapy failed to meet non-inferiority, arguing for caution when stopping [4,5]. In 2025, REBOOT (LVEF >40%) reported neutral results on a hard composite of all-cause death, recurrent MI, or heart-failure hospitalization; in contrast, BETAMI–DANBLOCK (LVEF ≥40%) showed a modest reduction in a broader composite, mainly through fewer recurrent MIs [1]. An individual patient-data meta-analysis suggests that routine therapy is unlikely to help when LVEF ≥50%, whereas patients with LVEF 40-49% are most likely to benefit [3]. Current ESC and ACC/AHA guidelines have moved in the same direction - strong for LVEF ≤40% or clinical HF, selective otherwise, and generally against automatic continuation beyond a year without another indication [6–9].

In this review we explain, in practical terms, what REBOOT and BETAMI-DANBLOCK mean for clinicians. We keep the focus on who is likely to benefit, which endpoints matter, how to start, continue, or deprescribe safely and how these choices fit with modern background therapy. Because BBs are not one uniform drug, we close this introduction with a brief overview of the main families: β1-selective agents such as bisoprolol, metoprolol succinate, and nebivolol, which tend to be better tolerated in airway disease, mixed α/β agents such as carvedilol, which add vasodilation and agents with intrinsic sympathomimetic activity (e.g., acebutolol, pindolol), which are generally not recommended after MI or in HF. Lipophilicity also differs across the class (metoprolol/propranolol more, atenolol less) and

may explain central nervous system side effects in some patients; dose, body size, and sex can further shape exposure and tolerability [21].

MATERIALS AND METHODS

This work was conducted as a targeted narrative review informed by a systematic search.

Search Strategy

PubMed/MEDLINE, Embase, and the Cochrane Library were queried for articles published from January 2018 through September 2025. ClinicalTrials.gov and conference repositories (ESC, AHA/ACC) were consulted for ongoing or recently presented trials. Search terms combined controlled vocabulary and free text relating to BBs and post-MI care, for example: ("beta-blocker" OR "beta adrenergic antagonist" OR metoprolol OR bisoprolol OR carvedilol OR nebivolol) AND ("myocardial infarction" OR "acute coronary syndrome") AND ("ejection fraction" OR preserved OR "mildly reduced" OR "40–49%" OR ">=50%") AND (randomized OR registry OR cohort OR "meta-analysis" OR guideline OR ABYSS OR "REDUCE-AMI" OR REBOOT OR BETAMI OR DANBLOCK). Filters were applied for human studies and English language.

Eligibility criteria

Included sources comprised randomized clinical trials, prespecified post-hoc or subgroup analyses, observational registries, individual-patient or study-level meta-analyses, and major society guidelines addressing BB therapy after MI in adults with LVEF ≥40%. Case reports, narrative editorials without original data, non-cardiac populations, and studies focused exclusively on LVEF <40% were excluded unless providing mechanistic insight relevant to threshold effects.

Study selection and data extraction

Titles/abstracts were screened and potentially eligible full texts were assessed against the criteria above. Data were extracted on population (including EF distribution and sex), timing from MI, intervention and comparator (drug, dose, titration), achieved heart-rate separation, endpoints (death, MI, HF hospitalization, composite endpoints), follow-up, and adverse-event profiles. Disagreements were resolved by consensus.

Risk of bias and certainty assessment. Risk of bias was assessed using RoB 2 for randomized trials, ROBINS-I for non-randomized studies, and AMSTAR 2 for meta-analyses. The overall certainty of evidence for key questions (benefit in LVEF ≥50% vs 40–49%; effects of

discontinuation) was summarized using GRADE, expressed as high, moderate, low, or very low.

Synthesis approach

Given heterogeneity in endpoints and populations, findings were synthesized qualitatively. Where available, effect sizes from peer-reviewed RCTs are presented as primary evidence; signals from conference presentations and pooled analyses are explicitly described as exploratory or hypothesis-generating and interpreted with appropriate caution.

WHY BBs HELP (AND WHEN THEY DON'T) (LVEF ≥40%, NO HF)

After an MI, the body stays in a prolonged "fight-or-flight" state. Adrenaline and related signals make the heart beat faster and harder, raise blood pressure and shorten the time the heart has to fill with blood (diastole). Beta-blockers blunt this response. By slowing the heart rate and lowering blood pressure, they lengthen diastole, improve subendocardial blood flow, and reduce the heart's oxygen demand at any given level of activity. At the cell level, blocking β-receptors calms calcium entry and helps stabilise the electrical activity of heart cells, which lowers the chance of dangerous ventricular rhythms - a key reason why early trials saw fewer arrhythmic deaths [15,16,22].

BBs also touch the hormones that drive remodelling. β1-blockade reduces renin release and indirectly damps the renin-angiotensin-aldosterone system. In people with preserved EF, these structural effects are usually small, so a big survival gain is unlikely. In those with mildly reduced EF (40–49%), even modest drops in wall stress and arrhythmic triggers may be enough to translate into fewer non-fatal ischaemic events, which is consistent with the signals seen in modern trials and meta-analyses [1–5]. Heart rate probably acts as a mediator: across contemporary studies, lower achieved resting rates track with better outcomes, although proving cause–and–effect is difficult when background therapy is strong and events are infrequent [17–19,22].

These benefits have trade-offs. Too much slowing or blood-pressure drop can limit other guideline-directed therapies or sap energy for rehabilitation. Lipophilic drugs (e.g., metoprolol, propranolol) are more likely to cause fatigue or sleep disturbance, non-selective agents can worsen bronchospasm in reactive airway disease; and BBs can mask hypoglycemia in people on insulin. Exploratory analyses from REBOOT also suggest greater dose sensitivity in women, so it is safer to start low, titrate to a comfortable resting heart rate (often ~ 60–70 bpm), and review the need regularly rather than chasing a "maximal" dose [2,21].

WHAT THE TRIALS SHOW (REBOOT vs BETAMI)

REBOOT and BETAMI-DANBLOCK were designed for the same clinical question but with different emphases. REBOOT enrolled a broad, contemporary post-MI cohort with LVEF strictly >40%, treated with high rates of PCI, DAPT, and statins and followed them for nearly four years. Its primary endpoint - all-cause death, recurrent MI, or HF hospitalization - was deliberately stringent, privileging hard clinical events. The overall result was neutral, with no reduction in the primary composite or all-cause mortality, post-hoc findings suggested a potential harm signal in women at higher doses and a trend toward benefit when LVEF lay between 40% and 49% [2]. BETAMI–DANBLOCK randomised a similarly revascularised population with LVEF ≥40% within the early convalescent phase and employed a broader composite that included stroke, unplanned revascularisation, HF hospitalisation, and malignant ventricular arrhythmias alongside death and MI. Over a similar follow-up, BB therapy yielded a modest but statistically significant reduction in the composite, driven mainly by fewer recurrent MIs, again without a mortality difference; subgroup findings were compatible with greater relative benefit in LVEF 40–49% [1]. Differences in endpoint composition, event accrual, EF distribution, sex mix, dosing intensity, and achieved heart-rate separation likely account for the apparent discrepancy. When read together - and in light of REDUCE-AMI (neutral in LVEF ≥50%) and ABYSS (failure of non-inferiority after abrupt interruption), taken together, the trials suggest a coherent pattern: benefit is unlikely in preserved EF, but plausible in mildly reduced EF. Findings available only from pooled analyses or congress reports are treated as signals rather than definitive proof.

Table 1. Key differences between REBOOT-CNIC and BETAMI–DANBLOCK

Feature	REBOOT-CNIC	BETAMI–DANBLOCK	Interpretation
Population	Post-MI, LVEF >40%, no HF	Post-MI, LVEF ≥40%, no HF	Very similar populations; treatment era and background therapy are comparable. EF thresholding may modestly change the share with LVEF 40–49%.
Timing	Early post-MI (days–weeks)	Early post-MI (days–weeks)	Comparable clinical window.
Design/endpoint	Multicentre RCT; hard composite (all-cause death/MI/HF hospitalization)	Multicentre RCT (PROBE-style); broader composite (adds stroke, unplanned revascularization, malignant ventricular arrhythmias, HF hospitalization)	Broader composites accrue more nonfatal events and are more sensitive to anti-ischaemic effects.
Follow-up	≈3.5–3.7 years	≈3.5 years	Adequate duration in both trials.
Primary result	Neutral on hard composite	Modest reduction on broader composite, mainly fewer recurrent MIs	Differences align with endpoint breadth rather than true contradiction.
Mortality	No clear difference	No clear difference	Neither trial demonstrates mortality benefit in this population.
Recurrent MI	No clear effect overall	Reduced (component driving the composite)	Consistent with an anti-ischaemic signal

			without mortality change.
Subgroups	Signal: possible dose-related susceptibility in women; signal: benefit more plausible with LVEF 40–49%	Signal: benefit more likely with LVEF 40–49%	Subgroup findings are hypothesis-generating and should be interpreted cautiously.
Certainty (GRADE)	High for the neutral primary result; subgroup signals = low certainty	High for the primary composite; subgroup signals = low certainty	Pooled analyses and congress communications inform signals, not definitive proof.

EF-ejection fraction; HF-heart failure; MI-myocardial infarction; PROBE-prospective randomized open, blinded endpoint; RCT-randomized controlled trial.

ALIGNMENT WITH THE WIDER EVIDENCE BASE AND GUIDELINES

Individual patient-data meta-analysis across the modern RCTs suggests a benefit in LVEF 40–49% for composites encompassing nonfatal ischaemic events, while not showing a clear effect in LVEF ≥50% [3]. Prior randomized and observational work in the PCI era largely points in the same direction: attenuation of prognostic benefit with preserved EF, with symptomatic advantages retained in selected patients [17–20]. Accordingly, contemporary guidelines have converged. The ESC 2023 ACS guideline continues to strongly recommend BBs for LVEF ≤40% or clinical HF, while not endorsing routine long-term use in all post-MI patients; the ESC 2024 CCS guideline stresses individualisation in chronic care [6,7]. The ACC/AHA 2023–2024 guidelines advise against continuation beyond 12 months post-MI in the absence of LVEF ≤50% or another indication such as angina, arrhythmia, or hypertension [8,9].

IMPLICATIONS FOR PRACTICE

In contemporary practice, the default should shift from automatic, indefinite prescribing to selective, time-limited use informed by EF, symptoms, comorbidity, and tolerance. For patients with LVEF ≥50% who are asymptomatic and well revascularized, initiating a beta-

blocker solely for prognostic gain is unlikely to help and may hinder rehabilitation or the uptitration of other therapies [2,3,5]. By contrast, for LVEF 40 49% - especially after anterior MI or when resting tachycardia, residual ischemia, or frequent ventricular ectopy is present - a period of beta-blocker therapy appears reasonable, with conservative, heart-rate–guided titration and periodic reassessment over 12-36 months [1–3]. Independent of EF, beta-blockers retain value for angina relief, rate control in atrial fibrillation, suppression of ventricular ectopy, and blood-pressure management, in line with contemporary guidance [6–9].

When beta-blockers are used, agent selection and dosing matter. Cardioselective β1-blockers (bisoprolol, metoprolol succinate, nebivolol) are generally preferred for tolerability; mixed α/β agents (carvedilol) may be attractive when additional vasodilation is desirable; agents with intrinsic sympathomimetic activity (acebutolol, pindolol) are not recommended post-MI. A low-dose start with slow titration toward a comfortable resting heart rate around 60–70 bpm is pragmatic and guideline-concordant [6-9]. Lipophilic agents (metoprolol, propranolol) more often cause fatigue or sleep disturbance; hydrophilic atenolol has different kinetics. Exploratory REBOOT analyses suggest dose-related susceptibility in women [2]; registry dosing data indicate exposure–response considerations after MI, supporting conservative titration [21].

When discontinuation is appropriate, tapering over weeks is prudent to avoid rebound phenomena; ABYSS reinforces this principle by indicating that abrupt interruption may be unsafe [4]. Shared decision-making aided by home HR/BP logs or ambulatory monitoring can guide timing of taper and the need for re-initiation.

CONCLUSIONS

The totality of contemporary evidence does not support a uniform, indefinite use of beta-blockers after MI in patients without HF. Read together, REBOOT-CNIC (neutral on a hard composite) and BETAMI-DANBLOCK (modest reduction in a broader composite, chiefly fewer recurrent MIs) suggest that prognostic benefit is unlikely when LVEF ≥50%, whereas a plausible benefit signal persists in LVEF 40-49% - particularly for nonfatal ischaemic events—without a demonstrable mortality effect [1–3,5]. This pattern aligns with REDUCE-AMI and with current ESC/ACC/AHA guidance that favours selective rather than routine use [5–9].

For clinical practice, an EF-stratified, time-limited approach appears most appropriate. In patients with LVEF ≥50% who are asymptomatic and well revascularised, routine initiation

solely for prognosis is not supported; beta-blockers retain a role for symptom control (angina, rate control in AF, suppression of ventricular ectopy) [6-9]. In LVEF 40–49%, a period of therapy is reasonable, with careful titration from low doses toward a comfortable resting heart rate (~60–70 bpm), and with periodic reassessment at 12–36 months [1–3]. Attention to exposure is prudent: exploratory analyses from REBOOT suggest dose-related susceptibility in women, and registry data indicate exposure–response considerations that favour conservative titration [2,21]. When discontinuation is appropriate, gradual tapering is advised; ABYSS indicates that abrupt interruption may be unsafe [4].

These conclusions should be interpreted in light of low event rates, potent background therapy, and differences in endpoint definitions across trials, which together limit power for mortality and other hard outcomes. Future studies would be most informative if they focus on LVEF 40–49%, pre-specify sex-aware dosing/PK-PD analyses and heart-rate separation targets and incorporate patient-reported outcomes and functional recovery alongside hard endpoints. Until such data are available, the most defensible position is individualised prescribing that preserves the symptomatic advantages of beta-blockers while avoiding unnecessary exposure where prognostic gain is unlikely.

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