Beta-Blockers after Myocardial Infarction

TO THE EDITOR: The REBOOT (Treatment with Beta-Blockers after Myocardial Infarction without Reduced Ejection Fraction) trial conducted by Ibanez et al. (Nov. 13 issue),[1] which evaluated beta-blockers in patients after myocardial infarction with a left ventricular ejection fraction above 40%, showed no significant difference in death from any cause, reinfarction, or hospitalization for heart failure (the primary composite outcome) between the patients who received beta-blockers and those who did not (hazard ratio, 1.04; 95% confidence interval [CI], 0.89 to 1.22; P=0.63). Although the trial successfully reached its planned sample size, we are concerned that the robustness of the conclusions may be limited.

At the second interim analysis, the incidence of a primary-outcome event was only 6%, which is markedly lower than the 10% incidence anticipated a priori, and in the final analysis, the incidence of a primary-outcome event was only approximately 7.5% in the control group. Under these circumstances, the follow-up duration should ideally have been extended to accrue additional events and preserve the statistical power. Although the investigators prolonged the follow-up duration by 1 year, the data for approximately 25% of the patients in each group were censored without events before 30 months of follow-up. Therefore, the low overall event burden, rather than censoring, may have restricted statistical precision. Although the overall findings of the trial were interpreted as no significant difference between the two groups, the possibility of a modest but clinically relevant treatment effect cannot be definitively ruled out.

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No potential conflict of interest relevant to this letter was reported.

1. Ibanez B, Latini R, Rossello X, et al. Beta-blockers after myocardial infarction without reduced ejection fraction. N Engl J Med 2025;393:1889-900.

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TO THE EDITOR: The significant benefit of beta-blocker therapy in the combined BETAMI (Norwegian Beta-Blocker Treatment after Acute Myocardial Infarction in Revascularized Patients without Reduced Left Ventricular Ejection Fraction)–DANBLOCK (Danish Trial of Beta-Blocker Therapy after Myocardial Infarction without Heart Failure) trial by Munkhaugen et al. (Nov. 13 issue)[1] was driven by a reduction in recurrent myocardial infarction. This finding contrasts with what was observed in the REDUCE–AMI (Randomized Evaluation of Decreased Usage of Beta-Blockers after Acute Myocardial Infarction) trial[2] and REBOOT trial, which showed no substantial difference in reinfarction between patients who received beta-blockers and those who did not. Heterogeneity across trial populations may account for this discrepancy. The BETAMI–DANBLOCK and REBOOT trials allowed for the enrollment of patients with myocardial infarction with nonobstructive coronary arteries (MINOCA), whereas the REDUCE–AMI trial only enrolled patients with obstructive coronary artery disease. Correspondingly, the percentage of patients with coronary artery revascularization was lower in the BETAMI–DANBLOCK and REBOOT trials (approximately 94%) than in the REDUCE–AMI trial (>99%).

In some patients, contemporary revascularization strategies effectively counteract sympathetic hyperactivity after a myocardial infarction, thereby limiting the added benefits of beta-blockers.[3] Yet, beta-blockers may hypothetically confer incremental benefit in patients with unrevascularized or nonobstructive coronary artery disease, in whom their effects on heart rate and blood pressure more directly target underlying pathophysiological mechanisms.[4] Thus, it is possible that the observed benefits of beta-blockers after myocardial infarction in the BETAMI–DANBLOCK trial might stem from patients who had MINOCA or unrevascularized coronary artery disease. Supporting this, the REBOOT trial showed numerically fewer primary end-point events with beta-blockers than without beta-blockers in the subgroup with MINOCA (19.0% vs. 28.8%; hazard ratio, 0.66; 95% CI, 0.24 to 1.81). Further investigation of subgroups

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with MINOCA or unrevascularized coronary artery disease in the BETAMI–DANBLOCK trial would be invaluable to reconcile discrepant trial findings.

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TO THE EDITOR: Recently published trials challenged the prevailing clinical–pharmacologic paradigm: for decades, beta-blockers have been regarded as a cornerstone of therapy after myocardial infarction, but early revascularization reshaped the therapeutic and prognostic landscape. The debate now stirring in the scientific community rightly focuses on whether beta-blockers remain relevant in this context, particularly in view of contradictory emerging evidence on their benefits. What is striking, however, is the limited attention paid to modifiable risk factors. In the REBOOT trial, 45% of the participants were active smokers, as were 28% of those in the BETAMI–DANBLOCK trial. Smoking cessation reduces recurrent cardiovascular events and cardiovascular mortality by approximately 40%,[1] substantially outweighing the relative benefit reported for many pharmacologic strategies, including beta-blockers (up to 15% reduction, according to the BETAMI–DANBLOCK trial).

The ongoing deliberation over optimal pharmacotherapy must not overshadow the urgent need for effective lifestyle interventions. Although beta-blockers and smoking cessation are not mutually exclusive, clinical priorities and quality-improvement efforts should reflect the magnitude of benefit. Firm public health policies that promote smoking cessation should be prioritized as a primary strategy. Ultimately, the best management of myocardial infarction lies in its prevention.

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No potential conflict of interest relevant to this letter was reported.

1. Wu AD, Lindson N, Hartmann-Boyce J, et al. Smoking cessation for secondary prevention of cardiovascular disease. Cochrane Database Syst Rev 2022;8:CD014936.

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TO THE EDITOR: The role of beta-blockers after myocardial infarction with preserved left ventricular ejection fraction remains uncertain. Evidence derives from two trial types. Treatment-initiation (prescribing) trials such as REDUCE-AMI,[1] CAPITAL-RCT (Carvedilol Post-Intervention Long-Term Administration in Large-Scale Randomized Controlled Trial),[2] and REBOOT questioned the prognostic value of beta-blockers in low-risk patients receiving modern therapies. Yet avoiding beta-blockers may open a "Pandora's box," with poorer angina control, more arrhythmias, and inadequate blood-pressure management. Secondary end points and qualitative outcomes remain clinically meaningful, even if not captured by survival curves.

In contrast, the ABYSS (Assessment of Beta-Blocker Interruption 1 Year after an Uncomplicated Myocardial Infarction on Safety and Symptomatic Cardiac Events Requiring Hospitalization) trial, a treatment-withdrawal (deprescribing) trial, tested discontinuation in stable patients after myocardial infarction who were receiving long-term therapy.[3] The trial failed to show noninferiority and showed no quality-of-life benefit, which suggests that late withdrawal may expose patients to ischemia, hypertension, or arrhythmias, which

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would increase hospitalizations. These findings argue against indiscriminate discontinuation. Beta-blockers remain indicated in patients with reduced ejection fraction, heart failure, angina, hypertension, or arrhythmias, and withdrawal should be reserved for carefully selected, revascularized, asymptomatic patients. Ultimately, therapy should balance limited prognostic gains against potential harm regarding clinically significant secondary outcomes, with tailored, pragmatic benefits guiding decisions.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The BETAMI–DANBLOCK trial showed that beta-blocker therapy reduced the risk of death or major adverse cardiovascular events among patients with myocardial infarction and a left ventricular ejection fraction of at least 40%. These findings appear inconsistent with those of the REBOOT trial, which enrolled a similar population and showed no benefit with respect to a composite of death, recurrent myocardial infarction, or hospitalization for heart failure. In the BETAMI–DANBLOCK trial, the primary end point was driven almost entirely by recurrent myocardial infarction, whereas other components showed no significant differences between patients who received beta-blockers and those who did not. In the REBOOT trial, myocardial infarction did not differ between the two groups amid a high prevalence of complete revascularization.

These observations suggest that the protective effect of beta-blockers seen in the BETAMI–DANBLOCK trial may be explained by their role in patients with incomplete revascularization — a context in which beta-blockers may still have a protective effect. In addition, beta-blockers present greater benefit in patients with a mildly reduced left ventricular ejection fraction,[1] whereas their usefulness seems limited in patients with preserved left ventricular ejection fraction.[2] In contemporary practice, the long-term value of beta-blockers after myocardial infarction may reside in patients with incomplete revascularization or a reduced left ventricular ejection fraction, rather than in those with complete revascularization and preserved left ventricular ejection fraction.

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No potential conflict of interest relevant to this letter was reported.

1. Rossello X, Prescott EIB, Kristensen AMD, et al. β blockers after myocardial infarction with mildly reduced ejection fraction: an individual patient data meta-analysis of randomised controlled trials. Lancet 2025;406:1128-37.
2. Yndigegn T, Lindahl B, Mars K, et al. Beta-blockers after myocardial infarction and preserved ejection fraction. N Engl J Med 2024;390:1372-81.

DOI: 10.1056/NEJMc2518019

TO THE EDITOR: In the BETAMI–DANBLOCK trial, Munkhaugen et al. found a lower combined risk of death or major adverse cardiovascular events among patients who received beta-blockers than among those who did not. This finding was driven by a 27% reduction in myocardial infarction. It would be helpful to know the completeness of revascularization achieved during the index event. In the BETAMI cohort, 32% of the patients had left main or multivessel coronary artery disease. This information was unavailable from the DANBLOCK cohort (Table S1 in the Supplementary Appendix to the article, available at NEJM.org). Early separation of the Kaplan–Meier curves for new myocardial infarction (Fig. S5) and the high number of obstructive coronary lesions in patients with new myocardial infarction (Table S8) may be the result of incomplete revascularization. In patients with an acute coronary syndrome, incomplete revascularization is associated with an elevated risk of repeat myocardial infarction.[1,2] Withholding beta-blockers in patients with incompletely

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revascularized disease may predispose them to higher risks of repeat myocardial infarction. In trials with high reported rates of complete revascularization, withholding beta-blockers did not lead to a difference in morbidity and mortality.[3]

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No potential conflict of interest relevant to this letter was reported.

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DR. IBANEZ AND COLLEAGUES REPLY: Rahhal et al. note that the incidence of a primary-outcome event among patients who did not receive beta-blockers (control group) was 7.5%, whereas the sample-size calculation assumed a 10% incidence in the control group.[1] Despite the fact that follow-up was extended to accrue a sufficient number of events, the overall incidence of primary-outcome events remained lower than anticipated, which is consistent with the improved prognosis of patients with myocardial infarction in contemporary practice. Of note, after more than 8500 patients had been enrolled, event rates were numerically higher in the beta-blocker group for the primary outcome as well as for death from any cause and death from cardiac causes. Therefore, it is highly unlikely that a larger sample size or longer follow-up would have revealed any benefit of beta-blocker therapy, and the conclusion of no difference between the treatment strategies is strongly supported by the data.

Regarding concerns about grouping all patients with a left ventricular ejection fraction of more than 40%, the trial was designed to address a patient population without overt left ventricular dysfunction after a myocardial infarction, for whom evidence from modern randomized trials was lacking. A prespecified subgroup analysis according to left ventricular ejection fraction showed numerically fewer events with beta-blockers than without beta-blockers among patients with a mildly reduced left ventricular ejection fraction, whereas no difference was observed among those with a preserved left ventricular ejection fraction. Although underpowered for interaction testing, these findings are consistent with two individual-patient-data meta-analyses pooling REBOOT participants with similar patients from contemporary trials, which showed a benefit of beta-blockers among patients with a mildly reduced left ventricular ejection fraction[2] but no benefit among those with a preserved left ventricular ejection fraction.[3] These meta-analyses close any possible controversy in this field.

Several correspondents suggested that differences between the REBOOT and BETAMI–DANBLOCK trials might be explained by a higher proportion of patients with MINOCA or without complete coronary-artery revascularization. This explanation is unlikely, because the percentages of patients with MINOCA or who did not undergo revascularization were similar in both trials. Moreover, in the REBOOT trial, prespecified subgroup analyses showed no heterogeneity of treatment effect according to the presence of MINOCA or obstructive coronary disease. The most plausible explanation for the modestly positive findings in the BETAMI–DANBLOCK trial as compared with the REBOOT trial is the higher proportion of patients with a mildly reduced left ventricular ejection fraction in the BETAMI–DANBLOCK trial.

We fully agree with Llop et al. that optimization of lifestyle measures and control of cardiovascular risk factors are essential to improve patient prognosis after a myocardial infarction. However, these considerations do not alter the neutral effect of beta-blockers observed in patients in our trial with a preserved left ventricular ejection fraction.

Concerns about potential harm, including increased angina or revascularization, are also not supported by available evidence. Across random-

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ized trials and meta-analyses, the incidence of coronary-artery revascularization appeared to be similar regardless of assignment to beta-blockers or no beta-blockers, and no differences were observed in the incidence of death, reinfarction, or heart failure.

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Since publication of the article, the authors report no further potential conflict of interest.

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DR. MUNKHAUGEN AND COLLEAGUES REPLY: We agree with Chi et al. that between-trial heterogeneity could explain why beta-blockers reduced myocardial reinfarction in the BETAMI–DANBLOCK trial but not in the REDUCE–AMI[1] or REBOOT trials. Our prespecified meta-analyses of individual patient data address this discrepancy by pooling data from relevant contemporary randomized trials.[2,3] In patients with a mildly reduced left ventricular ejection fraction (40 to 49%; 1885 patients), beta-blockers were associated with a lower risk of the composite of death from any cause, new myocardial infarction, or heart failure than no beta-blocker treatment (hazard ratio, 0.75; 95% CI, 0.58 to 0.97; P=0.03).[3] In patients with a preserved left ventricular ejection fraction (≥50%; 17,801 patients), no benefit was observed between the groups for the same composite end point.[2] Heterogeneity was low in both meta-analyses, and effect estimates were consistent across enrolling countries, end points, and subgroups.[2,3] The BETAMI–DANBLOCK trial enrolled more patients with a left ventricular ejection fraction of 40 to 49% than the REBOOT trial (15.3% vs. 11.5%), and patients in the BETAMI–DANBLOCK trial were a median of 2 years older, differences that could increase event rates and explain divergent beta-blocker effects.

Regarding the possibility that the treatment effects observed in the BETAMI–DANBLOCK trial reflect a higher proportion of patients with MINOCA or unrevascularized patients, this is unlikely. Patients with a myocardial infarction without revascularization were included only in the DANBLOCK trial, because all the patients in the BETAMI trial (approximately 50% of the participants) had undergone revascularization. If anything, this would be expected to result in a greater apparent benefit of beta-blockers in the DANBLOCK trial. However, this effect was not observed.[2] The number of patients who did not receive a revascularization procedure was small, and a planned meta-analysis focusing on MINOCA will provide further insight.

We strongly agree with Llop et al. that smoking cessation and other lifestyle modifications should be a priority for patients after a myocardial infarction and deserve greater clinical and research attention. We plan to report tobacco-cessation rates and to explore effect modification according to smoking status in forthcoming analyses.

In response to Cereda et al.: as noted above, the individual-patient-data meta-analyses support a benefit of beta-blockers in patients with a left ventricular ejection fraction of 40 to 49%,[3] similar to patients with heart failure, but not in those with a preserved left ventricular ejection fraction.[2] We agree that beta-blocker therapy should be individualized rather than applied indiscriminately. Of note, all the trials excluded patients with other indications for beta-blocker therapy, including heart failure or uncontrolled hypertension. In fact, approximately half the screened patients in the BETAMI–DANBLOCK trial were excluded for such indications. Consideration of angina and potential side effects is essential when guiding treatment decisions in clinical practice.

In response to Gamardella et al. and Zieminski and Bell: the REBOOT trial showed no substantial difference between groups that did or did not receive beta-blockers stratified according to the completeness of revascularization (hazard

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ratio, 0.90; 95% CI, 0.61 to 1.34). Given the limited number of patients in each of the trials, we plan to investigate whether complete as compared with incomplete revascularization modifies the effect of beta-blockers in a pooled analysis.

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Since publication of the article, the authors report no further potential conflict of interest.

1. Yndigegn T, Lindahl B, Mars K, et al. Beta-blockers after myocardial infarction and preserved ejection fraction. N Engl J Med 2024;390:1372-81.
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Engasertib in Hereditary Hemorrhagic Telangiectasia

TO THE EDITOR: In their article, Al-Samkari et al. (Nov. 27 issue)[1] indicate that hereditary hemorrhagic telangiectasia (HHT) is caused by mutations in the activin receptor–like kinase 1 (ALK1) signaling pathway and that pathogenic variants in ALK1 signaling lead to excessive activation of the serine–threonine kinase AKT downstream, thereby driving the formation of telangiectasia and arteriovenous malformation. Engasertib works by selectively inhibiting AKT1 and AKT2. However, to our knowledge, mutations in the ALK1 signaling pathway result in only one type of HHT. HHT can be caused by DNA variants in *ENG* (encoding endoglin), *ACVRL1* (encoding ALK1), *GDF2* (encoding growth differentiation factor 2, also known as BMP9), or *SMAD4* (encoding a downstream effector), and loss of function of these genes leads to HHT1, HHT2, HHT5, and juvenile polyposis–HHT overlap syndrome, respectively.[2] Because epistaxis may occur with all types of HHT, a limitation of the current analysis is that the authors did not classify patients according to HHT mutation type in order to elucidate whether the results associated with engasertib can be applied to each mutation type of HHT. Moreover, they did not provide information about any corresponding discussions.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Loss-of-function variants in *ENG*, *ACVRL1*, *GDF2*, and *SMAD4* cause HHT, and all these genes code for proteins in the ALK1 signaling pathway.[1] Therefore, ALK1 pathway signaling is impaired in patients with HHT, irrespective of which mutated gene is involved. This impairment results in subphysiologic activation of *PTEN*, a crucial suppressor of AKT, which leads to overactivation of AKT signaling and, ultimately, excessive proangiogenic signaling.[2] Because engasertib targets AKT, which is downstream of the entire ALK1 signaling pathway, its effects on HHT should be similar, regardless of the mutated gene.

To further explore this theory, we performed a subgroup analysis in which patients were categorized into subgroups according to the underlying mutated gene: *ENG*, *ACVRL1*, or other (other gene mutated or mutated gene unknown).

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