
Secondary prevention with beta-blockers after myocardial infarction

PERSPECTIVES

JOHN MUNKHAUGEN

johmun@vestreviken.no

John Munkhaugen PhD, specialist in internal medicine and cardiology, head of section and professor II at the Department of Medicine, Drammen Hospital and the Department of Behavioural Medicine, Oslo University. Head of the Working Group for Preventive Cardiology in the Norwegian Society of Cardiology.

The author has completed the ICMJE form and declares no conflicts of interest.

ARNHILD BAKKEN

Arnhild Bakken PhD, physiotherapist and postdoctoral fellow at the Department of Cardiology, Oslo University Hospital, Ullevål.

The author has completed the ICMJE form and declares the following conflicts of interest: she receives consultancy fees as the National Coordinator Trainer in the SOS-AMI study (Idorsia, Switzerland).

ANNA META DYRVIG KRISTIANSEN

Anna Meta Dyrvig Kristiansen, doctor and PhD candidate at Copenhagen University Hospital

The author has completed the ICMJE form and declares no conflicts of interest.

THOR EDVARDSEN

Thor Edvardsen MD, PhD, specialist in cardiology, senior consultant at the Department of Cardiology, Oslo University Hospital, Rikshospitalet, and professor II at the University of Oslo

The author has completed the ICMJE form and declares the following conflicts of interest: he has received speaker fees from Pfizer and Bristol Myers Squibb.

RUNE WISETH

Rune Wiseth MD, PhD, specialist in cardiology, senior consultant at the Department of Cardiology, St Olav's Hospital, Trondheim University, and professor emeritus at the Norwegian University of Science and Technology (NTNU).

The author has completed the ICMJE form and declares no conflicts of interest.

TERJE KRISTIAN STEIGEN

Terje Kristian Steigen MD, PhD, specialist in cardiology, senior consultant at the Department of Cardiology, University Hospital of North Norway, and professor at UiT The Arctic University of Norway

The author has completed the ICMJE form and declares no conflicts of interest.

HENRIK SCHIRMER

Henrik Schirmer PhD, specialist in cardiology, senior consultant at the Department of Cardiology, Akershus University Hospital, and professor II at the University of Oslo

The author has completed the ICMJE form and declares the following conflicts of interest: he has received consultancy fees from Pharmacosmos, Bayer and Novartis, speaker fees from AstraZeneca, Biogen, Boehringer Ingelheim, Sanofi and Novo Nordisk, and he has a pending patent application for an algorithm to improve the detection of valve defects by auscultation.

ALF-INGE LARSEN

Alf-Inge Larsen MD, PhD, specialist in cardiology, senior consultant at the Department of Cardiology, Stavanger University Hospital, and professor II at the University of Bergen

The author has completed the ICMJE form and declares the following conflicts of interest: he has received fees from Pfizer for chairing a doctoral symposium.

JARLE JORTVEIT

Jarle Jortveit PhD, specialist in internal medicine and cardiology, researcher and senior consultant at the Department of Cardiology, Sørlandet Hospital, Arendal. He is chair of the advisory board in the Norwegian Myocardial Infarction Registry.

The author has completed the ICMJE form and declares the following conflicts of interest: he has received speaker fees from Amgen, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Novartis, Novo Nordisk, Pfizer and Sanofi.

KJELL VIKENES

Kjell Vikenes MD, PhD, specialist in cardiology, director of the Cardiology Clinic, Haukeland University Hospital and professor II at the University of Bergen

The author has completed the ICMJE form and declares no conflicts of interest.

SIGRUN HALVORSEN

Sigrun Halvorsen MD, PhD, specialist in internal medicine and cardiology, head of the Department of Cardiology, Oslo University Hospital, Ullevål, and professor of cardiology at the University of Oslo

The author has completed the ICMJE form and declares the following conflicts of interest: she has received speaker fees from AstraZeneca.

DAN ATAR

Dan Atar MD, PhD, specialist in internal medicine and cardiology, head of research at Oslo University Hospital, Ullevål, and professor of cardiology at the University of Oslo

The author has completed the ICMJE form and declares the following conflicts of interest: he has received speaker fees from Abbott, Actelion, Amarin, Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, GSK, Idorsia, MSD, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Philips, Roche Diagnostics, Sanofi, Takeda, Viartis and Vifor, and research funding from BMS/Pfizer, Medtronic, Bayer and Roche Diagnostics.

Recent studies and meta-analyses show that treatment with beta-blockers improves prognosis after myocardial infarction in patients with mildly reduced left ventricular function, but not in patients with normal function who have no other indications for beta-blockers. The results of these new studies will be incorporated into future guidelines and are likely to inform clinical practice worldwide.

Treatment with beta-blockers after myocardial infarction has been a cornerstone of secondary prevention since the early 1980s. Changes in the prevalence of risk factors, more precise diagnostics and effective treatment of myocardial infarction have led to a substantial improvement in prognosis. Should beta-blockers continue to play a key role in treatment?

Beta-blockers inhibit the agonistic effects of catecholamines on the heart, reducing heart rate, cardiac workload, contractility and blood pressure [\(1\)](#). They have been standard therapy for more than 40 years, since randomised, placebo-controlled trials demonstrated significant reductions in all-cause and cardiovascular mortality, as well as a lower incidence of recurrent myocardial infarction [\(2, 3\)](#). Treatment with beta-blockers is also associated with relief of angina and a reduced incidence of ventricular arrhythmias and heart failure [\(2, 4, 5\)](#). The introduction of modern reperfusion therapy, particularly percutaneous coronary intervention (PCI), and effective secondary preventive treatment, including statins, antiplatelet agents and angiotensin blockade,

has further lowered the incidence of new cardiovascular events and post-infarction mortality (6, 7). In addition, high-sensitivity cardiac troponin assays have improved diagnostic accuracy, allowing identification of more infarcts than previously (6, 7).

«Beta-blockers have been standard therapy for more than 40 years, since randomised, placebo-controlled trials demonstrated significant reductions in all-cause and cardiovascular mortality, as well as a lower incidence of recurrent myocardial infarction»

Beta-blockers are strongly recommended (Class 1 recommendation) for patients with heart failure, uncontrolled tachyarrhythmias and myocardial infarction with reduced left ventricular ejection fraction (LVEF < 40 %), based on data from studies conducted in the 2000s (8–10). The benefit of beta-blocker therapy for patients with normal (LVEF ≥ 50 %) or mildly reduced (LVEF 40–49 %) left ventricular function has been less certain (9, 10). Meta-analyses of observational studies have produced conflicting results, and in 2016 Norwegian researchers questioned whether beta-blockers should continue to be routinely prescribed after myocardial infarction (11).

Findings from recent randomised controlled trials

Since 2018, five randomised controlled trials, comprising a total of 23,531 patients, have evaluated the effect of beta-blocker therapy compared with no beta-blocker treatment after myocardial infarction (12–16). All studies were open-label, with no placebo tablets. Patients with clear indications for beta-blockers (e.g. heart failure or arrhythmias) and/or contraindications (e.g. bradycardia, hypotension) were excluded. The mean age of participants was approximately 63 years, around 20 % were women, and over 90 % received PCI and were discharged with statins and aspirin as recommended (Table 1). The incidence of recurrent myocardial infarction, heart failure and all-cause mortality over roughly 3.5 years of follow-up varied somewhat between studies but was substantially lower than in observational cohorts: 2–5 % versus 10–26 % (17).

The Swedish REDUCE-AMI study, published in 2024, included 5020 patients admitted with acute myocardial infarction and with normal LVEF (> 50 %) at discharge (13). After a median follow-up of 3.5 years, the study found no effect of beta-blocker therapy on the composite primary endpoint, which consisted of recurrent myocardial infarction and death (hazard ratio [HR] 0.96; 95 % confidence interval [CI] 0.79–1.16, $p = 0.64$). However, the study had limited statistical power, and the confidence interval included the possibility of a 21 % effect of beta-blocker therapy.

The French ABYSS study, also published in 2024, randomised 3698 patients with normal or mildly reduced LVEF (> 40 %) to either continue or discontinue beta-blocker therapy a median of 2.9 years after myocardial infarction (14). Contrary to the initial hypothesis, which was that discontinuation would not result in worse outcomes than continued therapy, patients who stopped beta-blocker treatment had a 16 % higher risk of a composite cardiovascular endpoint (HR 1.16; 95 % CI 1.01–1.33). These

differences were driven by more frequent hospitalisations for cardiovascular causes, but no differences were observed in the incidence of mortality or myocardial infarction between groups.

«Contrary to the initial hypothesis, which was that discontinuation would not result in worse outcomes than continued therapy, patients who stopped beta-blocker treatment had a 16 % higher risk of a composite cardiovascular endpoint»

In autumn 2025, the results of the Spanish–Italian REBOOT-CNIC study (15) and the Norwegian–Danish BETAMI-DANBLOCK study (16) were published. Both studies included patients with myocardial infarction and LVEF > 40 %, assessed within the first few days after discharge. REBOOT-CNIC (15) randomised 8438 patients to beta-blocker therapy (86 % received bisoprolol) or no beta-blocker. After a median follow-up of 3.7 years, no significant effect of beta-blocker treatment was observed on the primary endpoint, which consisted of a composite of all-cause mortality, recurrent myocardial infarction or hospitalisation for heart failure (HR 1.04; 95 % CI 0.89–1.22; $p = 0.63$). Subgroup analyses indicated that beta-blockers reduced the incidence of the primary endpoint among patients with LVEF 40–49 %.

The BETAMI-DANBLOCK study randomised 5574 patients to beta-blocker therapy (> 95 % sustained-release metoprolol) or no beta-blocker (16). Over a median follow-up of 3.5 years, the primary composite endpoint of all-cause mortality and new cardiovascular events occurred in 394 patients (14.2 %) in the beta-blocker group and 454 patients (16.3 %) in the no-beta-blocker group (HR 0.85; 95 % CI 0.75–0.98; $p = 0.03$). The largest effect was observed for endpoint recurrent myocardial infarction (5.0 % vs. 6.7%; HR 0.73; 95 % CI 0.59–0.92), but numerical trends in favour of beta-blocker therapy were also seen for all-cause mortality (4.2 % vs. 4.4 %) and heart failure (1.4 % vs. 1.9 %). There were no differences between groups in the incidence of serious ventricular arrhythmias, admissions for unplanned coronary revascularisation or high-grade atrioventricular block or pacemaker implantation.

Meta-analyses of contemporary randomised controlled trials

Two prespecified meta-analyses based on individual patient data from all the contemporary beta-blocker trials have recently been published (18, 19). The first meta-analysis included 1853 patients with LVEF 40–49 % from REBOOT, BETAMI-DANBLOCK and a small Japanese study (CAPITAL-RCT) (18). The primary endpoint, comprising all-cause mortality, recurrent myocardial infarction or heart failure, occurred in 106 patients (10.7 %) in the beta-blocker group and 129 patients (14.4 %) in the no-beta-blocker group. This corresponds to a 25 % relative risk reduction (HR 0.75; 95 % CI 0.58–0.97; $p = 0.031$). Consistent effects were observed for all individual components of the primary endpoint, as well as for cardiovascular mortality. The findings were also consistent across the four studies and the countries involved (Spain, Italy, Norway, Denmark and Japan).

The second meta-analysis included 17,801 patients with LVEF ≥ 50 % from the aforementioned studies, as well as the Swedish REDUCE-AMI trial (19). The primary endpoint, comprising all-cause mortality, recurrent myocardial infarction or heart failure, occurred in 717 patients (8.1 %) in the beta-blocker group and 748 patients (8.3 %) in the no-beta-blocker group (HR 0.97; 95 % CI 0.87–1.07; $p = 0.54$). Results were consistent for each component of the primary endpoint, for the secondary endpoints and across all prespecified subgroups, including sex, age, type of beta-blocker and dose.

Implications for clinical practice

All contemporary beta-blocker trials tested current clinical practice for beta-blocker therapy. Median doses were moderate (equivalent to 50 mg/day of sustained-release metoprolol) and lower than those used in earlier beta-blocker studies. Moderate doses, together with a 10–15 % crossover rate from beta-blocker to no beta-blocker (and vice versa), likely diluted the observed effect of beta-blocker therapy. It is conceivable that higher doses and greater adherence could have produced different results. However, none of the meta-analyses showed any indication that higher beta-blocker doses were associated with greater efficacy (18, 19). It is important to note that none of the studies can draw conclusions regarding the optimal duration of therapy.

«Moderate doses, together with a 10–15 % crossover rate from beta-blocker to no beta-blocker (and vice versa), likely diluted the observed effect of beta-blocker therapy»

The trials included patients at lower risk than those seen in everyday clinical practice. Approximately 70 % of all screened myocardial infarction patients were excluded from participation in the BETAMI-DANBLOCK study (16). The main reason for exclusion was indication for beta-blockers, such as symptoms of heart failure, persistent ventricular arrhythmias, rapid atrial fibrillation and extensive infarcted left ventricular tissue (regardless of LVEF). Only 20 % of participants were women, and the proportion with known coronary artery disease prior to admission, as well as the incidence of new cardiovascular events, was lower than that reported in observational studies and registries (6, 7).

Quality of life and other patient-reported outcomes

Beta-blockers are inexpensive, safe and well-tested therapies. However, adverse effects such as hypotension, bradycardia and cold hands and feet can occur (2–5). Earlier studies have also reported a possible increased incidence of impotence, fatigue and depression (2–4); conditions that could potentially have a negative impact on patients' quality of life. These adverse effects have been assumed to be dose-dependent and mainly associated with the use of non-selective beta-blockers (timolol and propranolol), which are no longer used in the treatment of myocardial infarction. It is reassuring that the ABYSS study (14) and substudies from REDUCE-AMI (20, 21)

indicate that beta-blockers do not appear to affect health-related quality of life or increase symptoms of anxiety or depression. A large number of substudies in the coming years will provide further insight into the effects of beta-blocker therapy on angina, physical activity, sleep/nightmares and sexual function.

«The authors are affiliated with the BETAMI-DANBLOCK study. Munkhaugen and Atar serve as principal investigators, Bakken is the research coordinator, and the remaining co-authors are members of the steering committee»

REFERENCES

1. Task Force On Beta-Blockers of the European Society of Cardiology. Expert consensus document on beta-adrenergic receptor blockers. Eur Heart J 2004; 25: 1341–62. [PubMed][CrossRef]
2. Pedersen TR. The Norwegian Multicenter Study of Timolol after Myocardial Infarction. Circulation 1983; 67: 149–53. [PubMed]
3. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. JAMA 1982; 247: 1707–14. [PubMed][CrossRef]
4. Safi S, Sethi NJ, Korang SK et al. Beta-blockers in patients without heart failure after myocardial infarction. Cochrane Database Syst Rev 2021; 11: CD012565. [PubMed]
5. Rydén L, Ariniego R, Arnman K et al. A double-blind trial of metoprolol in acute myocardial infarction. Effects on ventricular tachyarrhythmias. N Engl J Med 1983; 308: 614–8. [PubMed][CrossRef]
6. FAST MI Investigators. Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. JAMA 2012; 308: 998–1006. [PubMed][CrossRef]
7. Hall M, Dondo TB, Yan AT et al. Association of clinical factors and therapeutic strategies with improvements in survival following non-ST-elevation myocardial infarction, 2003–2013. JAMA 2016; 316: 1073–82. [PubMed][CrossRef]
8. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021; 42: 3599–726. [PubMed][CrossRef]
9. ESC Scientific Document Group. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J 2023; 44: 3720–826. [PubMed][CrossRef]
10. Peer Review Committee Members. 2025 ACC/AHA/ACEP/NAEMSP/SCAI guideline for the management of patients with acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2025; 85: 2135–237. [PubMed][CrossRef]

11. Otterstad JE, Munkhaugen J, Ruddox VDB et al. Utdatert kunnskapsgrunnlag for betablokkere etter hjerteinfarkt? Tidsskr Nor Legeforen 2016; 136: 624–7. [PubMed] [CrossRef]
12. CAPITAL-RCT investigators. Long-term use of carvedilol in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. PLoS One 2018; 13. doi: 10.1371/journal.pone.0199347. [PubMed] [CrossRef]
13. REDUCE-AMI Investigators. Beta-blockers after myocardial infarction and preserved ejection fraction. N Engl J Med 2024; 390: 1372–81. [PubMed][CrossRef]
14. ABYSS Investigators of the ACTION Study Group. Beta-blocker interruption or continuation after myocardial infarction. N Engl J Med 2024; 391: 1277–86. [PubMed][CrossRef]
15. REBOOT-CNIC Investigators. Beta-Blockers after Myocardial Infarction without Reduced Ejection Fraction. N Engl J Med 2025; 393: 1889–900. [PubMed] [CrossRef]
16. BETAMI–DANBLOCK Investigators. Beta-blockers after myocardial infarction in patients without heart failure. N Engl J Med 2025; 393: 1901–11. [PubMed] [CrossRef]
17. Jernberg T, Hasvold P, Henriksson M et al. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. Eur Heart J 2015; 36: 1163–70. [PubMed] [CrossRef]
18. 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. [PubMed] [CrossRef]
19. Kristensen AMD, Rossello X, Atar D et al. Beta-Blockers after Myocardial Infarction with Normal Ejection Fraction. N Engl J Med 2025; NEJMoa2512686.
20. Mars K, Humphries S, Leissner P et al. Effects of beta-blockers on quality of life and well-being in patients with myocardial infarction and preserved left ventricular function-a prespecified substudy from REDUCE-AMI. Eur Heart J Cardiovasc Pharmacother 2025; 10: 708–18. [PubMed][CrossRef]
21. Leissner P, Mars K, Humphries S et al. Short- and long-term effects of beta-blockers on symptoms of anxiety and depression in patients with myocardial infarction and preserved left ventricular function: a pre-specified quality of life substudy from the REDUCE-AMI trial. Eur Heart J Acute Cardiovasc Care 2024; 13: 789–97. [PubMed][CrossRef]

Publisert: 2. February 2026. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.25.0735
Received 24.11.2025, first revision submitted 18.12.2025, accepted 5.1.2026.

