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Secondary prevention with beta-blockers after myocardial infarction

PERSPECTIVES

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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).

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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).

Table 1

Clinical characteristics at randomisation and incidence of endpoints in five contemporary beta-blocker trials (12–16)

	BETAMI-DANBLOCK	REBOOT-CNIC	REDUCE-AMI	CAPITAL-RCT	Abyss
No. of patients, *N*	5 574	8 438	5 020	801	3 698
Country	Norway, Denmark	Spain, Italy	Sweden	Japan	France
Year of publication	2025	2025	2024	2018	2024
Baseline characteristics					
Median age, years (IQR)[1]	65 (57–73)	61 (50–72)	63 (55–71)	63 (55–71)	64 (53–75)
Women (%)	21	19	23	19	17
Median no. of days from myocardial infarction to randomisation (IQR) [1]	2 (1–3)	3.8 ± 2.6	-	-	2.9 years (1.2–6.4)
Prior myocardial infarction (%)	11	10	7	3	100
Prior atrial fibrillation (%)	2.0	2.3	-	-	0.3
Previously used beta-blockers (%)	8.5	12	12	-	100
STEMI (%)[1]	47.5	51	35	100	63
LVEF 40–49 % (%)[1]	15.3	12	-	16	23
Treated with percutaneous coronary intervention (%)	92	92	95	95	97
Aspirin (Albyl-E) at discharge (%)	95	98	97	98	95
Statins at discharge (%)	97	98	99	86	95
Follow-up and endpoints					
Median follow-up, years (IQR)	3.5 (2.2–4.6)	3.7	3.5 (2.2–4.7)	3.9 (3.0–4.6)	3.0 (2.0–4.0)
Incidence of recurrent myocardial infarction, *n* (%)	324 (5.8)	286 (3.4)	229 (4.6)	17 (2.1)	90 (2.4)
Incidence of heart failure, *n* (%)	94 (1.7)	83 (1.0)	42 (0.8)	15 (1.9)	57 (1.5)
Incidence of all-cause mortality, *n* (%)	242 (4.3)	314 (3.7)	200 (4.0)	44 (5.5)	150 (4.0)

[1]IQR: interquartile range; STEMI: ST-elevation myocardial infarction; LVEF: left ventricular ejection fraction

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»

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