Beta-Blockers after Myocardial Infarction and Preserved EF

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- The efficacy of beta-blockers in patients with heart failure and reduced EF is well documented.
- Trials have also shown that long-term beta-blocker therapy after MI reduces mortality by approximately 20%.
- A meta-analysis suggested that in the era of modern reperfusion strategies, beta-blockers did not significantly reduce mortality.
- Data on the effect of long-term beta-blocker therapy in patients with acute MI and preserved EF are lacking from contemporary, sufficiently powered, randomized clinical trials.

- We conducted a trial (Randomized Evaluation of Decreased Usage of Beta-Blockers after Acute Myocardial Infarction [REDUCE AMI]) to investigate whether long-term oral beta blocker treatment in patients with acute MI and preserved LVEF would lead to a lower risk of a composite end point of death of any cause or new MI than no beta-blocker use.

Methods

- **Trial Design and Oversight**
  - We conducted this registry-based, prospective, open-label, parallel-group, randomized clinical trial in three countries: Sweden (38 centers), Estonia (1 center), and New Zealand (6 centers).

- **Patients**
  - Adult patients who provided written informed consent 1 to 7 days after MI and who had undergone CAG and echocardiography with a preserved LVEF (≥50%) were eligible.
    - Patients were also required to have obstructive coronary artery disease as documented by CAG (i.e., stenosis of ≥50%, a FFR of ≤0.80, or an iFR of ≤0.89 in any segment) at any time point before randomization.

- Major exclusion criteria were an indication for or contraindication to beta-blocker treatment.
  - To ensure completeness of follow-up, nonresidents of the three trial countries could not undergo randomization.

Trial Treatments and Procedures

- Patients who were randomly assigned to the beta blocker group were administered metoprolol (first choice) or bisoprolol (alternative) during the remaining hospital stay and received a prescription for continued use after discharge.
  - The treating physician was encouraged to aim for a dose of at least 100 mg daily for metoprolol and at least 5 mg daily for bisoprolol.

- Patients were encouraged to continue the use of beta-blockers after discharge until the occurrence of a contraindication.

- Patients who were randomly assigned to the no–beta-blocker group were discouraged from using beta-blockers as long as there was no other indication than secondary prevention after MI.

- **Clinical End Points**

  - The **primary end point** was:
    - a composite of death from any cause or
    - new MI.

  - **Secondary end points** were
    - death from any cause,
    - death from cardiovascular causes,
    - MI,
    - hospitalization for AF (as a primary diagnosis),
    - hospitalization for heart failure (as a primary diagnosis).

- **Safety end points** were
  - hospitalization for bradycardia,
  - second- or third-degree AV block,
  - hypotension,
  - syncope,
  - implantation of a pacemaker;
  - hospitalization for asthma or COPD (as a primary diagnosis);
  - hospitalization for stroke.

- Angina pectoris and dyspnea after 6 to 10 weeks and after 11 to 13 months were also end points.

Results

- **Characteristics of the Patients**
  - From the start of the trial in September 2017 to the end of enrollment in May 2023, a total of 5020 patients underwent randomization, with
    - 4788 patients (95.4%) in Sweden,
    - 32 (0.6%) in Estonia, and
    - 200 (4.0%) in New Zealand.

Table 1. Characteristics of the Patients.*

Characteristic	Beta-Blockers (N=2508)	No Beta-Blockers (N=2512)
Median age (IQR) — yr	65 (57–73)	65 (57–73)
Female sex — no. (%)	563 (22.4)	568 (22.6)
Country — no. (%)		
Sweden	2392 (95.4)	2396 (95.4)
Estonia	16 (0.6)	16 (0.6)
New Zealand	100 (4.0)	100 (4.0)
Risk factors — no./total no. (%)		
Current smoking	478/2466 (19.4)	530/2483 (21.3)
Hypertension	1155/2507 (46.1)	1163/2509 (46.4)
Diabetes mellitus	346/2506 (13.8)	354/2509 (14.1)
Previous cardiovascular disease — no./total no. (%)		
Previous myocardial infarction	165/2503 (6.6)	192/2507 (7.7)
Previous PCI	147/2504 (5.9)	175/2505 (7.0)
Previous CABG	33/2504 (1.3)	36/2507 (1.4)
Previous stroke	52/2506 (2.1)	67/2507 (2.7)
Previous heart failure	13/2486 (0.5)	22/2481 (0.9)

Characteristic at presentation		
Chest pain as main symptom — no./total no. (%)	2421/2507 (96.6)	2417/2512 (96.2)
CPR before hospital arrival — no./total no. (%)	10/2483 (0.4)	11/2485 (0.4)
Pulmonary rales — no./total no. (%)	29/2445 (1.2)	42/2462 (1.7)
Median heart rate (IQR) — beats/min†	74 (65–85)	73 (64–84)
Median systolic blood pressure (IQR) — mm Hg‡	150 (135–170)	151 (136–170)
Atrial fibrillation — no./total no. (%)	21/2502 (0.8)	23/2504 (0.9)
ST-segment elevation myocardial infarction — no./total no. (%)	877/2507 (35.0)	892/2512 (35.5)
Current oral beta-blocker treatment — no./total no. (%)	269/2468 (10.9)	302/2472 (12.2)
Median no. of days from hospital admission to randomization (IQR)	2 (1–3)	2 (1–3)
In-hospital course — no./total no. (%)		
Coronary angiography		
No stenosis	26/2484 (1.0)	25/2491 (1.0)
One-vessel disease	1378/2484 (55.5)	1378/2491 (55.3)
Two-vessel disease	676/2484 (27.2)	668/2491 (26.8)
Left main or three-vessel disease	404/2484 (16.3)	420/2491 (16.9)
PCI	2387/2491 (95.8)	2376/2496 (95.2)
CABG	92/2491 (3.7)	103/2496 (4.1)

Table 1. (Continued.)

Characteristic	Beta-Blockers (N=2508)	No Beta-Blockers (N=2512)
Medication at discharge — no./total no. (%)		
Aspirin	2450/2507 (97.7)	2440/2512 (97.1)
P2Y12 receptor blocker	2411/2507 (96.2)	2398/2512 (95.5)
Beta-blocker	2399/2505 (95.8)	247/2512 (9.8)
ACE inhibitor or ARB	1985/2507 (79.2)	2040/2512 (81.2)
Statin	2481/2507 (99.0)	2461/2510 (98.0)
Diuretic agent	211/2507 (8.4)	191/2512 (7.6)
Calcium-channel blocker	416/2508 (16.6)	496/2511 (19.8)

* Patients in the beta-blocker group were given metoprolol (first choice) or bisoprolol (alternative). Data on race and ethnic group were not collected. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, CABG coronary-artery bypass grafting, CPR cardiopulmonary resuscitation, IQR interquartile range, and PCI percutaneous coronary intervention.
† Data on heart rate were missing for 19 patients in the beta-blocker group and for 17 in the no–beta-blocker group.
‡ Data on systolic blood pressure were missing for 23 patients in the beta-blocker group and for 22 in the no–beta-blocker group.

- **Follow-up and Treatment Adherence**
  - Patients were followed until November 16, 2023. Four patients withdrew consent, and 8 emigrated.
  - Of the 4788 patients in Sweden, 4388 (91.6%) were invited to the SWEDEHEART registry follow-up visits;
    - 3836 of these patients (87.4%) attended a follow-up visit in the period from 6 to 10 weeks and
    - 3720 (84.8%) attended a visit in the period from 11 to 13 months.

- Of the 2508 patients who had been assigned to the beta-blocker group,
  - 1560 (62.2%) were treated with metoprolol and
  - 948 (37.8%) with bisoprolol.

- For metoprolol, the median starting dose was 50 mg , and the median target dose was 100 mg;

- for bisoprolol, the median starting dose was 2.5 mg, and the median target dose was 5.0 mg.

- Among the patients who attended the SWEDEHEART registry follow-up visits and had their data regarding beta-blocker treatment recorded,
  - 1726 of 1906 (90.6%) in the beta-blocker group were still taking beta-blockers after 6 to 10 weeks and
  - 1500 of 1831 (81.9%) were still taking beta blockers after 11 to 13 months;

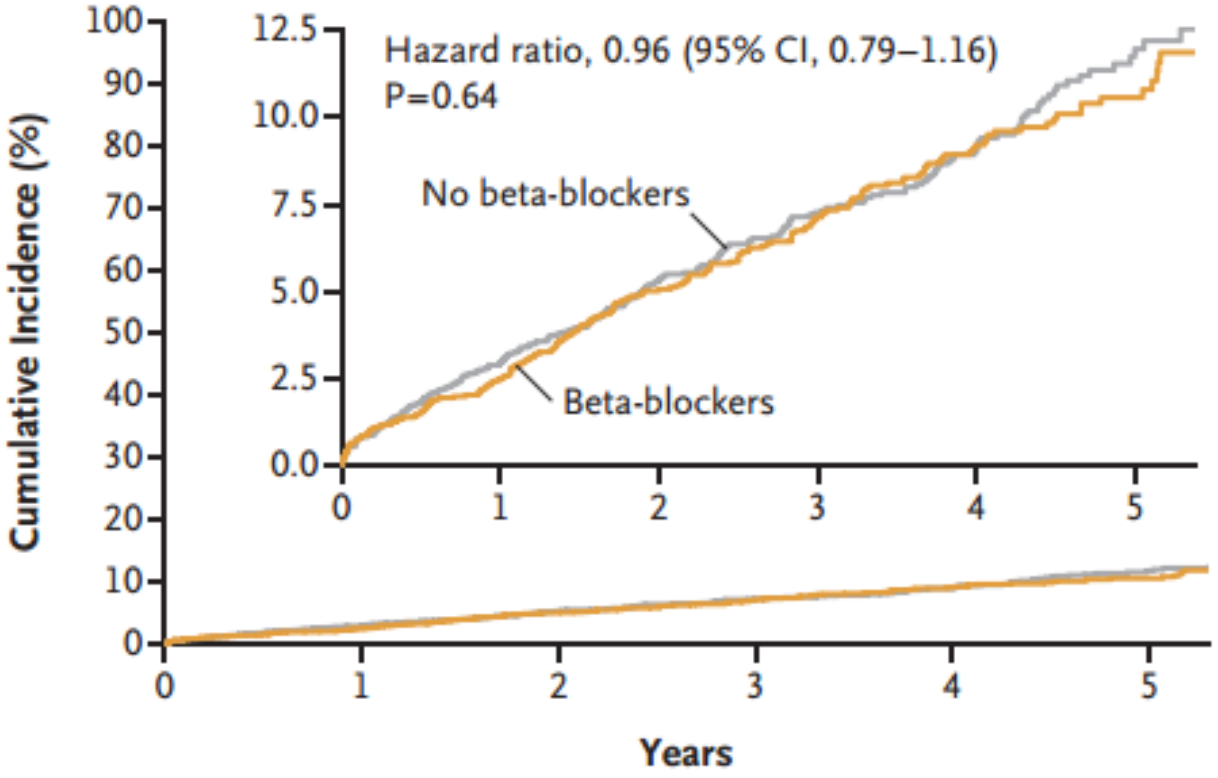
- in the no–beta blocker group,
  - 217 of 1924 (11.3%) were taking beta-blockers after 6 to 10 weeks and
  - 269 of 1886 (14.3%) were taking beta-blockers after 11 to 13 months.

- **End Points**

Table 2. Primary and Secondary End Points.*

End Point	Beta-Blockers (N=2508)	No Beta-Blockers (N=2512)	Hazard Ratio (95% CI)†	P Value
	number (percent)			
Primary end point				
Death from any cause or myocardial infarction	199 (7.9)	208 (8.3)	0.96 (0.79 to 1.16)	0.64
Secondary end points				
Death from any cause	97 (3.9)	103 (4.1)	0.94 (0.71 to 1.24)	
Death from cardiovascular causes	38 (1.5)	33 (1.3)	1.15 (0.72 to 1.84)	
Myocardial infarction	112 (4.5)	117 (4.7)	0.96 (0.74 to 1.24)	
Hospitalization for atrial fibrillation	27 (1.1)	34 (1.4)	0.79 (0.48 to 1.31)	
Hospitalization for heart failure	20 (0.8)	22 (0.9)	0.91 (0.50 to 1.66)	
Safety end points				
Hospitalization for bradycardia, second- or third-degree atrioventricular block, hypotension, syncope, or implantation of a pacemaker	86 (3.4)	80 (3.2)	1.08 (0.79 to 1.46)	
Hospitalization for asthma or COPD	15 (0.6)	16 (0.6)	0.94 (0.46 to 1.89)	
Hospitalization for stroke	36 (1.4)	46 (1.8)	6.80 (–7.11 to 20.72)†	

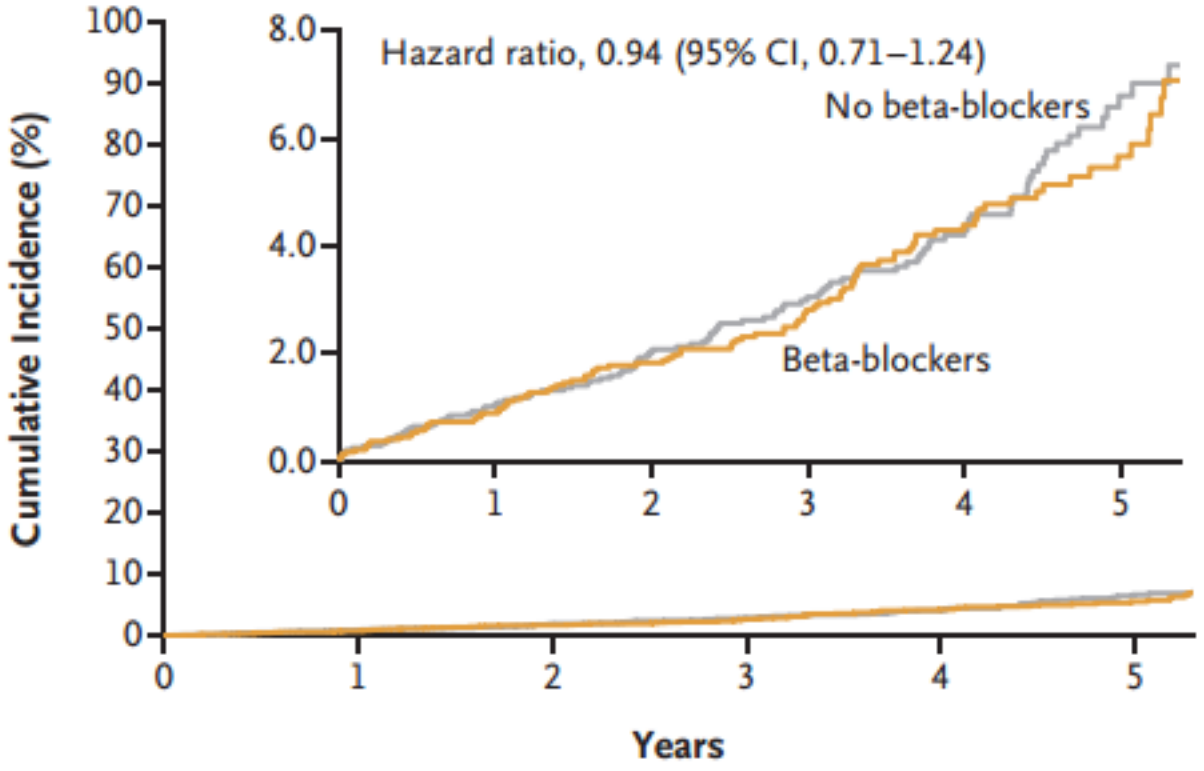
A **Death from Any Cause or New Myocardial Infarction (primary end point)**



No. at Risk

No beta-blockers	2512	2299	1898	1417	963	416
Beta-blockers	2508	2311	1911	1422	975	422

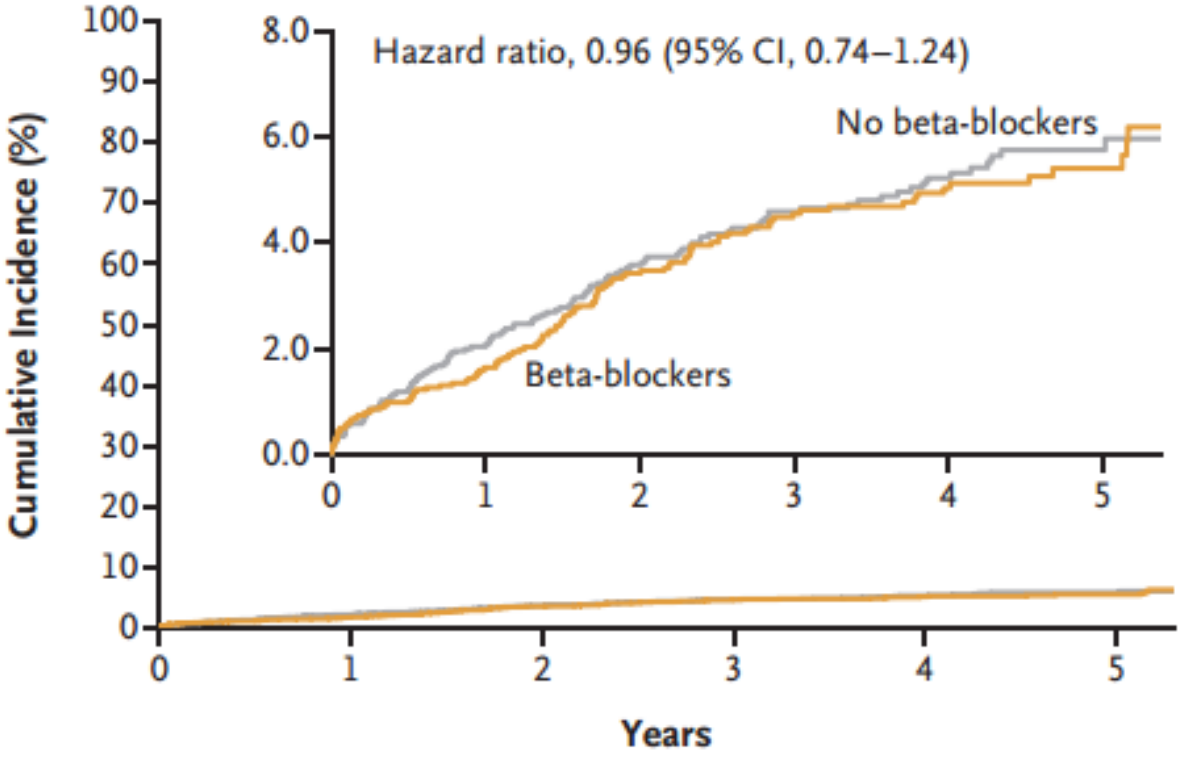
B **Death from Any Cause**



No. at Risk

No beta-blockers	2512	2342	1965	1482	1017	437
Beta-blockers	2508	2351	1976	1495	1026	444

C **New Myocardial Infarction**



No. at Risk

No beta-blockers	2512	2320	1932	1465	1008	452
Beta-blockers	2508	2331	1945	1468	1023	456

Discussion

- In this registry-based, prospective, randomized, open-label, parallel-group trial conducted across 45 centers, most of which were in Sweden, the early initiation of oral beta-blocker treatment after an acute MI in patients with a preserved LVEF did not lead to a lower cumulative incidence of death from any cause or new MI (composite primary end point).

- In addition, no appreciable between-group differences were observed in the analyses of secondary efficacy and safety end points.

- After 1 year, the incidence and severity of symptoms appeared to be similar in the two groups among the patients in Sweden who attended registry follow-up visits and had symptoms assessed.

- The absence of an effect of beta-blocker treatment on the cumulative incidence of death or myocardial infarction appeared to be consistent across all prespecified subgroups.

- The baseline characteristics indicated that the patients who were included in the trial were representative of the population of patients with MI and preserved EF in the trial countries and were generally at low risk for new cardiac events.

- The patients were well treated with early revascularization procedures and received evidence-based medications at discharge.

- Our trial included only patients who had a LVEF of at least 50%. During the planning phase, many potential investigators were hesitant to include patients who had a mid-range LVEF (40 to 49%).
- We also wanted to keep the trial population as homogeneous as possible, since any interaction between trial group and a subgroup makes the trial results more difficult to interpret and generalize.
- A later meta-analysis of clinical trials involving patients with a midrange LVEF suggested a beneficial effect of beta-blockers generally, and a large Korean registry suggested a benefit specifically after MI.

- We allowed only beta-1–receptor selective blockers (metoprolol and bisoprolol) because these drugs had the best documentation for long-term treatment and had been used extensively in the countries involved in the trial.
- Indications for beta-blockers other than secondary prevention was an exclusion criterion.
- We also mandated an early invasive strategy because it reflects a contemporary treatment strategy — that is, the basis for reevaluation of beta-blockers in a new trial.

- Three other large, ongoing trials examining long-term treatment with beta blockers in patients with MI and preserved fraction have defined a preserved EF of at least 40% and also are allowing the use of nonselective beta-blockers.
- Two of the trials also include patients being treated without an early invasive approach.

- The doses of beta-blockers that were used in our trial were lower than those in previous trials. However, the doses that were used in our trial mirror the current practice of beta-blocker treatment, and no apparent association between the planned target dose of beta-blocker treatment and the primary end point was observed.

- Results from contemporary observational studies comparing various doses of beta-blockers have not shown any clear association with outcome.

- A study from the SWEDEHEART registry that compared 33,126 patients who received a prescription for at least 50% of the target beta-blocker dose at discharge with 64,449 patients who received a prescription for less than 50% of that dose did not show a between-group difference in outcome.

- Our trial has several limitations.
  - **First**, it was an open-label trial, because blinding was not judged to be feasible.
  - Data on clinical end points were obtained from the SWEDEHEART registry and the Swedish Population Registry and were not centrally adjudicated.
  - However, this approach should have had a limited effect on the hard composite primary end point, whereas results regarding softer end points such as symptoms need to be interpreted more cautiously.

- During follow-up, investigators reviewed electronic health records to confirm that reported new MIs in the SWEDEHEART registry fulfilled the criteria for a MI according to the treating physician, and any misclassification should have been equally distributed over the two randomized trial groups.

- **Second,** only safety end points that are associated with hospitalization were assessed.

- **Third**, a limitation of pragmatic trials of routinely used therapy is the potential for crossovers. Despite strategies to mitigate this issue, among patients with available information, 14% of those who had been assigned to the no–beta-blocker group were taking beta-blockers after 1 year of follow-up, and we do not yet have information about beta-blocker use after the first year.
- The adherence to the assigned beta-blocker regimen mirrored patterns that are observed in everyday clinical practice; however, we cannot rule out the possibility that the use of beta blockers in the no–beta-blocker group contributed to our null finding.

نتیجه گیری

در بیماران سکته قلبی که تحت آنژیوگرافی زودهنگام قرار گرفتند و EF>50% داشتند، استفاده طولانی مدت از داروهای بتا بلاکر موجب کاهش مرگ به هر علت یا سکته مجدد نشد.