Is the evidence base for post-myocardial infarction beta-blockers outdated?

Post-myocardial infarction beta-blocker therapy is based on studies from the early 1980s. Since then, the diagnostics for myocardial infarction have become more sensitive, revascularisation has improved survival and there are now improved secondary prophylaxis drugs. We therefore believe it is time for new research, and that the indication for routine beta-blocker therapy following myocardial infarction should be reviewed.

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It was pointed out as early as in 2007 that (1) post-myocardial infarction beta-blocker therapy is based on three studies from 1981–1982 (2–4) (Table 1). The clinical manifestations of myocardial infarction are the same now as in the early 1980s, but the diagnostics, treatment and patient population have all changed. The introduction of high-sensitivity troponin assays has changed the diagnostics. The pathogenesis and therapeutic effect may both be different now from in the past, because the relative distribution of various causal factors has changed. A patient with acute myocardial infarction in the 1970s was often a smoker, slender and with high total cholesterol. In 2015, the patient is an overweight, prediabetic non-smoker with low HDL cholesterol and high triglyceride levels. In the past, left-ventricular remodelling after severe myocardial infarction was a major problem and involved loss of contractile tissue followed by dilation of the left ventricle, a reduced ejection fraction and heart failure development. Today such infarctions are less common, as most patients are revascularised early and survive the infarction with a well preserved heart function. Are we actually looking at the same disease?

The efficacy of any treatment depends on the point of departure in relation to the maximum that can be achieved, and the lower limit for a clinically relevant result. Reduced efficacy may be due to the treatment only working when there is a certain relative distribution of causal factors, or to the factors that are affected being already almost maximally reduced.

New prevalence data show that a large number of coronary patients remain on beta-blocker therapy for several years after an infarction. This applies to both genders of all ages, with and without heart failure.

In the NOR-COR Study for Coronary Prevention, the use of beta-blockers after myocardial infarction, percutaneous coronary intervention (PCI) or aortocoronary bypass surgery was registered on discharge and after a follow-up period of 1.7 years (5) (Table 2). The figures for prescription of beta-blockers were 85 % on discharge and 72 % after 1.7 years, which correspond to figures from the big European registry survey EUROASPIRE IV (6). Is the evidence base for routine beta-blocker treatment following myocardial infarction good enough?

What do new studies indicate?

A single literature search revealed no major studies with follow-up of ≥ three months of patients with a normal left ventricular ejection fraction.

The Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) (n = 45 852 patients, metoprolol versus placebo within 24 hours, four-week follow-up) revealed no effect on total mortality, and a reduction of reinfarction and ventricular fibrillation was counterbalanced by increased risk of cardiogenic shock (7). Nor have beta-blockers been found to influence cardiovascular events in patients with stable coronary disease (8).

Two new registry studies have brought the problem to the fore:

In the biggest study, based on the Reduction of Atherothrombosis for Continued Health (REACH) Registry, 44 708 patients from general practice were included in the period 2003–2004 (9) (Table 3). The patients were from 44 countries worldwide, and 31 % had suffered myocardial infarction. After a follow-up period of 3.6 years, there was no difference in cardiovascular mortality between patients with and without beta-blockers when propensity score matching was used. In this analysis, attempts are made retrospectively to eliminate bias factors in the two groups (Table 4).

CORonariens stables en region NORd-Pas-de-Calais (the CORONOR study) included 4 184 patients from northern France, 2 612 (62 %) of whom had suffered infarctions (10). The follow-up time was two years, and a statistically significant reduction in cardiovascular mortality was seen. There were few events, and type 2 errors therefore cannot be excluded. The same statistical method was used as for the study based on REACH.

The CORONOR and REACH studies are accompanied by commentaries by, respectively, Floyd (11) and Danchin & Laurent (12), who examine some weaknesses of the studies. Non-beta-blocker users may have stopped because of side effects or because of contraindications that affected their prognosis. The type of beta-blocker and indication for treatment are not known, and no information is provided about left ventricular function. The conclusion is that more research is needed.

A meta-analysis of randomised, controlled studies included 102 003 patients from 60 studies, 12 of which were published in the revascularisation period (1991–2013) (13). Beta-blockers had no effect on mortality, whereas the 30-day incidence of reinfarction and angina were reduced at the expense of increased incidence of heart failure and cardiogenic shock. The other 48 studies were published during the pre-revascularisation period (1966–1999), when beta-blockers reduced mortality, infarction and angina alike.

Another, recent meta-analysis included 10 observational studies of treatment with beta-blockers after PCI-treated infarction (14). Of the patients in this analysis, 25 168 had been given beta-blockers and 15 705 had not. The primary endpoint was total mortality. In adjusted analyses, this was reduced with beta-blockers, but the effect was only present in study populations with a reduced ejection fraction and low consumption of other medicinal secondary

Table 1 Long-term studies of post-infarction beta-blocker therapy. GMT = Gothenburg Metoprolol Trial; NTS = Norwegian Timolol Study; BHAT = The β-blocker Heart Attack Trial; LVEF = Left ventricular ejection fraction ; n.a. = not available; mo. = months CAPRICORN = Carvedilol Post-infarct Survival Control in LV dysfunction study; RR = Relative risk

	GMT, n = 1 395 from 1981 (3)	NTS, n = 1 884 from 1981 (2)	BHAT, n = 3 838 from 1982 (4)	CAPRICORN, n = 1 959 from 2001 Patients with LVEF < 40 % (5)
Therapy/follow-up				
Drug	Metoprolol	Timolol	Propranolol	Carvedilol
Time from infarction to inclusion (average)	< 48 hours (11 ± 3)	6–27 days (14)	5–12 days (14)	3–21 days (n.a.)
Initially intravenously	15 mg on admission	no	no	no
Post-infarction target dose	100 mg × 2	10 mg × 2	60–80 mg × 3[1]	25 mg × 2
Time to target dose	2 days	2 days	2 days	4–6 weeks
Average follow-up (min–max)	3 mo. (n.a.)	17 mo. (12–33)	25 mo. (n.a.)	15 mo. (n.a.)
Concomitant therapy				
Thrombolysis/primary PCI	no	no	no	45 %
Acetyl salicylic acid	n.a.	n.a.	22 %	86 %
Anticoagulation	n.a.	n.a.	9 %	n.a.
ACE inhibitor	no	no	no	98 %
Statin	no	no	no	n.a.
Mortality reduction	RR 36 % (p < 0.03)	RR 45 % (p < 0.001)	RR 27 % (p < 0.005)	HR 0.77 (0.60–0.98) (p = 0.03)

[1] Patients with serum propranolol ≥ 20 mg/l at 80 mg × 3 had the dose reduced to 60 mg × 3 at 4-week visit (82 %)

prophylaxis. There was no effect on cardiac mortality, reinfarction or hospitalisations for heart failure. The authors conclude that there is now no evidence for routine beta-blocker therapy for sufferers of myocardial infarction, and that new studies are necessary for further clarification.

International guidelines

The European guidelines of 2013 on treatment of stable coronary disease argue that the efficacy of beta-blockers is uncertain because the studies on post-infarction patients were conducted prior to the implementation of other secondary prophylactic therapy (15).

That same year it was pointed out in similar guidelines for ST elevation infarction that long-term beta-blocker therapy is well established, but that the uncertainties referred to above were recognised (16).

In the 2015 guidelines for non-ST-elevation infarction, early beta-blocker therapy is recommended for patients with persistent ischaemic symptoms, provided this is not contraindicated (17). Patients without severe heart failure can be offered long-term therapy.

In the American guidelines of 2012, it is pointed out that beta-blockers are efficacious in patients who have suffered myocardial infarction in the last three years and/or have left ventricular dysfunction (18).

Adverse effects

Frequently reported adverse effects of beta-blockers are fatigue, impaired exercise capacity, sleeping problems, life-threatening bradyarrhythmia and hypotension (15). However, a recent critical review showed that only five of 33 described adverse effects (hyperglycaemia, diarrhoea, dizziness, intermittent claudication and bradycardia) were more prevalent in patients treated with beta-blockers than in others (19).

Side effects are disagreeable nonetheless, and their nature may be such as to mask another disease, which may remain undiagnosed for a long time as a result.

Should patients today have beta-blockers?

Diagnostic criteria, initial treatment and follow-up of myocardial infarction have changed drastically since the 1980s. In view of the large numbers who use beta-blockers, the problems associated with side effects and masking of other disease are highly relevant. Therapy must therefore be based on the results of prospective, randomised studies performed on a relevant patient population.

No such documentation exists for today's post-infarction patients. The time is ripe for performing a study on patients who have been optimally treated by present standards. A central exclusion criterion must be severe infarctions that predispose the patient to left ventricular remodelling, where both an angiotensin convertase inhibitor and beta-blocker are indicated regardless.

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Table 2 Percentage of patients in the NOR-COR study who were using beta-blockers on discharge and at the follow-up visit. NSTEMI = non-ST-segment elevation myocardial infarction, STEMI = ST-segment elevation myocardial infarction

	Discharge, %[1]	Follow-up, %[1]
All, N = 1 127	85	72
Gender		
Men, n = 890	85	72
Women, n = 237	84	73
Age, years		
< 60, n = 364	85	71
60–75, n = 625	85	73
> 75, n = 138	86	74
Time since index hospitalisation		
8 weeks–6 mo., n = 233		72
6–12 mo., n = 242		74
12–24 mo., n = 347		74
24–36 mo., n = 305		71
Diagnosis on discharge		
NSTEMI, n = 561	83	70
STEMI, n = 335	89[2]	74
Stable coronary disease, n = 231	82	75
Angiography during index hospitalisation		
Open vessels/wall changes, n = 69	74[2]	61[2]
Single-vessel disease, n = 622	84	72
Multiple-vessel disease, n = 435	88	75
Revascularisation during index hospitalisation		
Percutaneous coronary intervention, n = 748	84	72
Aortocoronary bypass, n = 147	91[2]	81[2]
Patients without heart failure		
All, N = 979	83	70
Drammen Hospital, n = 496	86[2]	77[3]
Vestfold Hospital, n = 483	81	63
Percutaneous coronary intervention, n = 816	83	69
Aortocoronary bypass, n = 126	90[2]	79[2]

[1] All p values for differences at time of discharge versus at time of inclusion were significant (< 0.001)
[2] Differences in sub-groups at time of discharge and time of inclusion: p < 0.05
[3] Differences in sub-groups at time of discharge and time of inclusion: p < 0.01

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References

1. Otterstad JE, Platou ES, Mangschau A et al. Hjerteinfarkt. Diagnostikk og behandling. Hjerteforum 2007; 20 (suppl 1): 51–2.
2. The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981; 304: 801–7.
3. Hjalmarson A, Elmfeldt D, Herlitz J et al. Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial. Lancet 1981; 2: 823–7.
4. B-blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. JAMA 1982; 247: 1707–14.
5. Munkhaugen J, Sverre E, Peersen K et al. The role of medical and psychosocial factors for unfavourable coronary risk factor control. Scand Cardiovasc J 2016; 50: 1–8.
6. Kotseva K, Wood D, De Bacquer D et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. Eur J Prev Cardiol 2015; 0: 1–13.

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7. COMMIT (CLOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Early intravenous then oral metoprolol in 45 852 patients with acute myocardial infarction: randomized placebo-controlled trial. Lancet 2005; 366: 1622–32.
8. Huang HL, Fox KAA. The impact of beta-blockers on mortality in stable angina: a meta-analysis. Scott Med J 2012; 57: 69–75.
9. Bangalore S, Steg G, Deedwania P et al. β-Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. JAMA 2012; 308: 1340–9.
10. Bauters C, Lemesle G, Meurice T et al. Prognostic impact of β-blocker use in patients with stable coronary artery disease. Heart 2014; 100: 1757–61.
11. Floyd JS. β-blockers for secondary prevention in stable coronary artery disease: can observational studies provide valid answers? Heart 2014; 100: 1741–2.
12. Danchin N, Laurent S. Coronary artery disease. Are β-blockers truly helpful in patients with CAD? Nat Rev Cardiol 2013; 10: 11–2.
13. Bangalore S, Makani H, Radford M et al. Clinical outcomes with β-blockers for myocardial infarction: a meta-analysis of randomized trials. Am J Med 2014; 127: 939–53.
14. Huang B-T, Huang FY, Zuo Z-L et al. Meta-analysis of relation between oral β-blocker therapy and outcome in patients with acute myocardial infarction who underwent percutaneous coronary intervention. Am J Cardiol 2015; 115: 1529–38.
15. The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. 2013 ESC guidelines on the management of stable coronary artery disease. Eur Heart J 2013; 34: 2949–3003.
16. Steg PG, James SK, Atar D et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012; 33: 2569–619.
17. Roffi M, Patrono C, Collet JP et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016; 37: 267–315.
18. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guidelines for the diagnosis and management of patients with stable ischemic heart disease. Circulation 2012; 126: 354–471.
19. Barron AJ, Zaman N, Cole GD et al. Systematic review of genuine versus spurious side-effects of beta-blockers in heart failure using placebo control: recommendations for patient information. Int J Cardiol 2013; 168: 3572–9.

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