

**Long-term postoperative mortality and
morbidity of diabetic patients undergoing
non-cardiac surgery:
Intervention effects of metoprolol**

PhD Thesis

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Original papers

This PhD thesis is based on the following papers:

1. Juul AB, Wetterslev J, Kofoed-Enevoldsen A. Long-term postoperative mortality in diabetic patients undergoing major non-cardiac surgery. *Eur J Anaesthesiol* 2004;21:523-9.⁶⁰
2. Juul AB, Wetterslev J, Kofoed-Enevoldsen A, Callesen T, Jensen G, Gluud C and the DIPOM Trial Group. The Diabetic Postoperative Mortality and Morbidity (DIPOM) trial: rationale and design of a multicenter, randomized, placebo-controlled, clinical trial of metoprolol for patients with diabetes mellitus who are undergoing major noncardiac surgery. *Am Heart J* 2004;147:677-83.⁶¹
3. Juul AB, Wetterslev J, Gluud C, Kofoed-Enevoldsen A, Jensen G, Callesen T, Peter Nørgaard, Kim Fruergaard, Morten Bestle, Rune Vedelsdal, André Miran, Jon Jacobsen, Jakob Roed, Pia Stjernholm, Yvonne Mølgaard, Maj-Britt Mortensen, Lise Jørgensen, Jørgen Jørgensen, Marie-Louise Rovsing, Pernille Lykke Petersen, Frank Pott, Merete Haas; Rikke Albret, Lise Lotte Nielsen, Gun Johansson, Nikolai Bang Foss, Jeanie Elkjær, Bjørn Dehlie, Klavs Boysen, Dusanka Zaric, Anne Munksgaard, Jørn Bo Madsen, Bjarne Øberg, Tine Blemmer, Grazyna Perko, Allan Horn, Lars Peter Wang, Stig Yndgaard, Boris Khanykin, Jørgen Hilden, Per Jensen, Nader Salas, and the DIPOM Trial Group. Randomized blinded trial on perioperative metoprolol vs. placebo for diabetic patients undergoing major noncardiac surgery. *JAMA* 2005; submitted.⁶²

Abstract

Introduction Perioperative ischaemic cardiac events in patients undergoing noncardiac surgery present a significant clinical problem with consequences for both short- and long-term postoperative prognosis. Diabetic patients experience an excess risk of developing ischaemic heart disease and are also more often in need for surgery compared to non-diabetic patients. Recent trial results suggest that perioperative beta-blockade reduces the risk of cardiac events in patients with risk of myocardial ischemia undergoing noncardiac surgery.

Objectives To examine the long-term postoperative mortality among diabetic patients undergoing major noncardiac surgery and to evaluate the beneficial and harmful effects of perioperative intervention with metoprolol versus placebo on long-term postoperative mortality and cardiac events in diabetic patients undergoing major noncardiac surgery.

Material and methods We studied the long-term postoperative mortality in a retrospective observational study. Data from all consecutive diabetic patients, who underwent major non-cardiac surgery from September 1996 to September 1997 at KAS Herlev hospital, were analysed. The data were obtained from patient records and from the Causes of Death Registry. We studied the effects of metoprolol in the Diabetic Postoperative Mortality and Morbidity (DIPOM) trial. The DIPOM trial is an investigator-controlled, centrally randomised, placebo-controlled, blinded, multicenter trial. Thirteen centers in the Copenhagen Area participated. We compared metoprolol 100 mg daily versus placebo on mortality and cardiovascular morbidity in beta-blocker naive diabetic patients above 39 years undergoing non-cardiac surgery. The study drug was given during hospitalisation to a maximum of 8 days beginning the evening before surgery. The primary outcome measure was a composite of all-cause mortality, acute myocardial infarction, unstable angina, or congestive heart

failure. Follow-up involved re-examination of patients at 6 months and collection of data by linkage to the Danish National Hospital Register and the Centralised Civil Register.

Results The observational study indicated a 12-months overall postoperative mortality of 24% (95% confidence interval (CI) 17 to 31%). One third of the fatalities occurred 30 days postoperatively. Ischaemic heart disease diagnosed before surgery was associated with an overall postoperative mortality of 44% (95% CI 29 to 58%), which was significantly higher ($P<0.03$) than in diabetic patients without a history of ischaemic heart disease. In the DIPOM trial a total of 921 patients were randomised (462 to metoprolol and 459 to placebo). Baseline patient characteristics were similar in the two groups. The median follow-up was 18 (range 6 to 30) months. Patients received metoprolol for a mean of 4.6 days versus placebo 4.9 days. Metoprolol significantly reduced the mean heart rate by 11% and mean arterial blood pressure by 3%. The primary outcome measure frequency was 99/462 (21%) in the metoprolol versus 93/459 (20%) in the placebo group. Intention-to-treat analysis demonstrated a hazard ratio of 1.10 (95% CI 0.82 to 1.46). The all-cause mortality frequency was 16% (74/462) in the metoprolol group and 16% (72/459) in the placebo group (logrank test, $P=0.88$). Per-protocol and secondary outcomes analyses showed similar results. The proportion of reported serious adverse events in the metoprolol group was 7.8% (36/462 patients) versus 5.7% (26/459 patients) in the placebo group ($P=0.20$).

Conclusions The long-term mortality of diabetic patients undergoing non-cardiac surgery is substantial. Short-term perioperative metoprolol did not significantly affect mortality and cardiac morbidity or adverse events in diabetic patients undergoing non-cardiac surgery. The doses, duration, and drug need reconsideration. Larger, blinded, placebo-controlled trials are warranted. Until such trials have demonstrated convincing effects of beta-blockers international, national, and local guidelines should not recommend its use for this indication.

Introduction

Epidemiology

Diabetes is a progressive endocrinopathy associated with carbohydrate intolerance and insulin dysregulation. Especially type II diabetes has become more common.^{1,2} Factors explaining this increase in prevalence include an increased age of the population, decreased physical activity, increase in body fat, and adoption of stricter diagnostic criteria.^{3,4} The prevalence of patients with a diagnosis of type II diabetes is between 100,000 to 150,000 and with type I diabetes about 25,000 patients out of 5.4 million inhabitants in Denmark.⁵ Further, another 50,000 to 75,000 type II diabetic patients are expected to be unaware of their disease.⁶⁻⁸ The total number of diabetic patients is therefore about 250,000 in Denmark. The number of patients with type II diabetes is estimated to increase rapidly within the next 25 years with estimated 42% increase in developed countries.⁹

Diabetes and postoperative mortality

Diabetes is a well-established risk factor for coronary artery disease (CAD),¹⁰ which tends to be more extensive, involve multiple vessels, and be more progressive than in non-diabetic patients.¹¹ The defective insulin secretion and insulin resistance in diabetic patients increase the metabolic effects of surgical stress-response (hyperglycaemia, increased insulin resistance, and reduction of trans-membrane glucose transport).¹² Autonomic neuropathy, which is an important risk factor per se of cardiac death,^{13,14} interferes with the perception of cardiac pain and myocardial ischaemia,¹⁵ leading to a high prevalence of clinically silent CAD in the diabetic population.

There are a number of possible explanations for a relation between diabetes and increased mortality and morbidity after high- and intermediate risk surgery. The most obvious explanation is that patients with diabetes have more comorbidity and/or more

advanced CAD at the time of surgery. However, the metabolic abnormalities associated with diabetes could also be responsible for an increased mortality and morbidity. Dehydration and electrolyte disturbances as a result of uncontrolled hyperglycaemia could contribute, free fatty acids levels are elevated after major surgery and may suppress cardiac function, and increased myocardial oxygen demand could be arrhythmogenic.¹⁶⁻¹⁹ Hyperglycaemia per se may also directly impact perioperative mortality and morbidity by different mechanisms. Hyperglycaemia interferes with the function of polymorphonuclear leukocytes predisposing to infection and may impair wound healing.^{20,21} Further, hyperglycaemia may contribute to increased platelet activity and disordered coagulation and fibrinolytic function,²² and may adversely affect endothelial function.²³ Some studies have also indicated a relation between improved glucose control in the perioperative period and lower rates of wound infection and dehiscence.²⁴⁻²⁶ A recent observational study²⁷ indicates that metabolic control improves myocardial diastolic function and perfusion in NIDDM patients. All these risk factors may contribute significantly to the postoperative mortality and morbidity in diabetic patients. The American Heart Association has stated that diabetic patients belong to the same high-risk category previously reserved for patients with known cardiovascular disease.²⁸

However, the postoperative prognosis of diabetic patients remains controversial. Many studies indicate that diabetes still constitutes a major risk factor for both short-term (≤ 30 days) and long-term (> 30 days) increased postoperative mortality and morbidity, especially after major cardiac surgery.^{26,29-35} Other studies indicate that the rates of death and complications today are nearly identical in diabetic and nondiabetic patients both within hospital-stay and after discharge from hospital.³⁶⁻⁴¹

Effect of perioperative beta-blockade on cardiac morbidity

The benefits of perioperative beta-blockade in reducing perioperative myocardial ischaemia in cardiac risk patients undergoing vascular surgery have been demonstrated in

non-randomised studies^{42,43} as well as randomised trials.^{44,45} There is also evidence from several randomised trials that perioperative beta-blockade in cardiac risk patients undergoing non-cardiac surgery reduces the occurrence of perioperative cardiovascular morbidity, as determined by blood pressure and heart rate (HR) responses as well as ECG changes associated with ischaemia.⁴⁵⁻⁴⁸ However, these are surrogate outcome measures. Hard outcome measures (such as all-cause mortality, cardiac death, acute myocardial infarction (AMI), unstable angina, or congestive cardiac failure) have only been directly addressed in two small randomised clinical trials.^{49,50}

The effect of short-term perioperative beta-blockade on postoperative mortality in patients undergoing non-cardiac surgery

The trial by Mangano and colleagues⁴⁹ indicated a substantial long-term postoperative mortality among diabetic patients undergoing noncardiac surgery. It indicated also that short-term (seven days) perioperative beta-blocker treatment could reduce the long-term postoperative mortality and cardiac morbidity in patients with or at risk of CAD, and especially diabetic patients seemed to benefit from this treatment. Two hundred male patients undergoing elective major noncardiac surgery were randomised to seven days perioperative atenolol or placebo treatment. The patients either had or were at risk for CAD (having at least two of the following cardiac risk factors: age above 65 years, hypertension, current smoking, serum cholesterol above 6.2 mmol/l, or diabetes mellitus). Event-free survival after discharge from hospital at two years was 83 percent in the atenolol group versus 68 percent in the placebo group (P=0.008).

The trial by Poldermans and colleagues⁵⁰ added evidence for the preventive effect of perioperative beta-blockade on postoperative cardiac mortality and morbidity. A total of 112 patients undergoing high-risk vascular surgery were randomised to bisoprolol or standard

perioperative care (i.e., where beta-blockers were used if symptoms or signs of perioperative myocardial ischaemia accompanied by tachycardia developed). Fifty-nine patients received bisoprolol and 53 patients the standard treatment. Beta-blocker treatment was initiated minimum one week before surgery and lasted until 30 days postoperatively. The patients were a high-risk subpopulation with abnormal results on stress echocardiography with dobutamine chosen among 1,351 patients undergoing elective abdominal aortic or infrainguinal arterial reconstruction. The number of deaths and of non-fatal AMI in the group receiving bisoprolol treatment was 2 (3.4%) compared to 18 (34%) in the group receiving standard treatment 30 days postoperatively. Hereafter the trial was stopped.

Due to the results of these trials, both the American College of Physicians and the American College of Cardiology/American Heart Association have recommended perioperative use of atenolol in patients with CAD.^{51,52} However, they also state that further research is needed.

Perioperative beta-blockade – beneficial effects

The mechanisms of the potential beneficial effects of perioperative beta-blockade remain to be established. Sympatholytic effects of beta-blockade may reduce the incidence of perioperative cardiac complications. Several trials have demonstrated that perioperative beta-adrenergic blockade reduces the incidence of perioperative myocardial ischaemia.⁴⁴⁻⁴⁶ Perioperative cardiac events may be a result of a supply–demand imbalance in the delivery of oxygen to the myocardium, thus a reduction in heart rate produced by beta-blockers could minimise this imbalance. However, perioperative myocardial infarction could also be a result of an acute coronary event precipitated by the rupture of an atheromatous plaque.⁵³ Beta-blockers may reduce the shear stress across atheromatous plaques by inducing haemodynamic changes, hereby reducing the incidence of plaque rupture and consequent acute coronary thrombosis.⁵⁴ Another possible mechanism of perioperative beta-adrenergic

blockade is a reduction in the neuroendocrine stress response to surgery. Beta-blockers may also improve myocardial metabolism independently of their effects on heart rate, by reducing myocardial contractility or overall oxygen consumption of the heart.^{55,56}

Perioperative beta-blockade – harmful effects

The most common adverse effects of beta-adrenoceptor blockers are bradycardia, hypotension, congestive heart failure, and bronchospasm. The currently available studies suggest that the use of beta-blockers in the perioperative period is not associated with significant risk as long as they are withheld if there is evidence of bradycardia or hypotension.^{44,45,49,50,57,58} However, this finding is based on relatively small studies and most of them have been carried out in intensive care wards where the adverse effects are easily detected and corrected. In an ordinary ward monitoring these patients intensively may cause logistic problems and the risk of experiencing serious adverse events may increase.

The use of perioperative beta-blockade may also pose an additional risk as withdrawal of beta-blockers may lead to adrenergic hypersensitivity and possibly worsen outcomes.⁵⁹ A particular concern is how long the treatment should last avoiding withdrawal effects. Neither Mangano and colleagues,⁴⁹ where patients were beta-blocked for a maximum of seven days, nor Poldermans and colleagues,⁵⁰ where patients were treated for a minimum of 37 days, have reported adverse effects from discontinuing beta-blockade. However, it remains possible that larger trials with increased power detect adverse effects when the beta-blockers are withdrawn.

Diabetic patients and perioperative beta-blockade

Diabetes mellitus was a major predictor of postoperative mortality in the trial by Mangano and colleagues.⁴⁹ The results of the trial showed that perioperative beta-blocker treatment of patients with diabetes had survival rates similar to those of patients without

diabetes, whereas diabetic patients receiving placebo had a 4-fold increase in mortality. However, diabetic patients constituted only a subgroup in the study (n=63/200 patients). The trial by Poldermans and colleagues⁵⁰ only included 17 diabetic patients and did not specify the course of this subpopulation. No data concerning quality of perioperative metabolic control or autonomic neuropathy status were presented in any of the trials. In the Mangano trial patients were characterised by having a minimum of two risk factors of CAD. Therefore, further research of the effect of perioperative beta-blockade in diabetic patients would be needed to demonstrate, whether diabetic patients would benefit from the intervention.

Evaluation of the evidence in the year 2000

The implications of the two randomised trials^{49,50} may be confusing. It seems appropriate that patients undergoing major surgery and having evidence of inducible myocardial ischaemia on stress testing should receive beta-blockers perioperatively, but we do not know if patients with a history of CAD presenting for major surgery should be given beta-blockers on the basis of this history alone. Mangano and colleagues studied patients who either had a history of CAD or who had two or more cardiac risk factors. Thus, the patients in his study could both be subject to intermediate or high risk of adverse cardiac events. And what is the optimal duration and dosage of perioperative beta-blocker treatment? Is it a short-term treatment beginning immediately prior to surgery as in the Mangano trial or must the therapy be initiated at least one week before surgery and continued for 30 days postoperatively as in the Poldermans trial? It is not clear what degree of sympathetic blockade is required to offer cardiac protection. In addition, the perioperative introduction of beta-blockers and the associated adverse effects have not been extensively studied, and the safety of the deliberate addition of beta-blocker shortly before surgery needs to be established. For example, both the Mangano and the Poldermans trials were

carried out in intensive care environments where adverse effects easily could be detected and corrected, but this may not be the case in an ordinary ward. And the abrupt interruption after perioperative beta-blockade also poses an additional risk as withdrawal of beta-blockers may lead to adrenergic hypersensitivity and possibly worsen outcomes.⁵⁹ Randomised trials are therefore required to answer questions on optimal duration and dosage of therapy, to identify populations in which beta-blocker use is cost-effective, and to investigate the incidence and degree of adverse reactions to perioperative beta-blockade.

The observational study⁶⁰ and the DIPOM trial^{61,62} were initiated because the current evidence only included two small randomized trials of perioperative beta-blocker intervention to prevent postoperative cardiac morbidity and mortality.^{49,50} These trials did not provide enough data from which to draw firm conclusions or recommendations. Further, a subgroup analysis in the trial by Mangano and colleagues indicated that especially diabetic patients would benefit from the treatment (hazard ratio=0.25, no confidence interval provided). In order to improve the postoperative mortality and morbidity in diabetic patients undergoing noncardiac surgery, it seemed a rational strategy to examine the effects of a cardio-protective regimen involving perioperative beta-blockade.

Objectives

Long-term postoperative mortality in diabetic patients undergoing major non-cardiac surgery

The aim of the observational study⁶⁰ was to examine the long-term postoperative mortality of diabetic patients undergoing major (high and intermediate risk) noncardiac surgery, to identify possible perioperative risk factors, and to examine the causes of death.

Randomised, blinded trial on perioperative metoprolol versus placebo for diabetic patients undergoing major noncardiac surgery

The aim of the DIPOM trial was to conduct a well-designed randomised, placebo-controlled, double-blind, multicentre clinical trial in order to study the beneficial and harmful effects of short-term perioperative beta-blockade in diabetic patients undergoing non-cardiac high- or intermediate-risk surgery. The primary outcome measure included peri- and postoperative mortality and cardiac morbidity.

Methods

Long-term postoperative mortality in diabetic patients undergoing major non-cardiac surgery – the observational study

The observational study is a retrospective cohort study based on hospital records and follow-up by linkage to the Causes of Death Registry. Data from 179 consecutive diabetic patients, who underwent major (defined as surgery lasting more than one hour) noncardiac surgery at Herlev Hospital from September 1996 to September 1997, were analysed. The main outcome measure was long-term postoperative mortality.

Randomised, blinded trial on perioperative metoprolol versus placebo for diabetic patients undergoing major noncardiac surgery – the DIPOM trial

The DIPOM trial is an investigator-initiated, centrally randomized, double blind, placebo-controlled, multicenter trial. We compared the effect of metoprolol versus placebo on peri- and postoperative cardiac morbidity and mortality in beta-blocker naive diabetic patients more than 39 years old scheduled to undergo major (defined as surgery presumed to last more than one hour) intermediate- and high-risk noncardiac surgery. The study drug was given during hospitalisation to a maximum of 8 days beginning the evening before surgery. The primary outcome measure was the composite of all-cause mortality, AMI, unstable angina, or congestive heart failure leading to hospitalisation or discovered or aggravated during hospitalisation. The study was powered on the basis of an estimated 30% one-year event rate in the placebo group and a 33% relative risk reduction in the metoprolol group. In order to study the withdrawal symptoms after short-term beta-blocker therapy an interview 3 days after discontinuing the trial drug was carried through. Follow-up involved re-examination of patients at 6 months and collection of mortality and morbidity data by linkage to the Danish National Hospital Register and the Centralised Civil Register.⁶¹

Results

Long-term postoperative mortality in diabetic patients undergoing major non-cardiac surgery – the observational study

Patient records could be obtained from 170/179 patients (86 males and 84 females).⁶⁰ Their median age was 65 (range 26 to 96) years. The median postoperative observation period was 10 (range 0 to 18) months. One-year overall postoperative mortality was 24% (95% CI 17 to 31%). One third of the fatalities occurred during the first 30 days. A history of CAD was associated with an overall postoperative mortality of 44% (95% CI 29-58%), which was significantly ($P<0.03$) higher than in diabetic patients without known CAD. The major causes of death in 18/39 (46%) patients were diseases of the cardiovascular system. A history of hypertension or ongoing beta-blocker treatment had no significant effects on mortality.

Randomised, blinded trial on perioperative metoprolol versus placebo for diabetic patients undergoing major noncardiac surgery – the DIPOM trial

We included 921 patients, 462 to metoprolol and 459 to placebo.^{61,62} All patients were analysed in the intention-to-treat analysis (ITT) and 733 patients (358 in the metoprolol group versus 375 patients in the placebo group) were analysed in the per-protocol (PP) analysis. Baseline patient characteristics were similar in the two groups. The mean age was 65 years. In addition to diabetes 496 (54%) patients had a history of CAD and/or an additional risk factor risk for CAD, meeting the inclusion criteria in the trial by Mangano and colleagues. The median follow-up time was 18 (range 6 to 30) months. No patients were lost to follow up. Twelve patients were receiving beta-blockers at the time of 6-month follow-up.

Patients received metoprolol for a mean of 4.6 days versus placebo 4.9 days. Metoprolol significantly reduced the mean heart rate by about 11% and mean arterial blood pressure by 3%. The primary outcome measure frequency was 99/462 (21%) in the metoprolol versus 93/459 (20%) in the placebo group. The intention-to-treat analysis demonstrated a hazard ratio of 1.10 (95% CI 0.82 to 1.46). The all-cause mortality frequency was 16% (74/462) in the metoprolol group and 16% (72/459) in the placebo group (logrank test, $P=0.88$). The per-protocol analyses and analyses of secondary outcomes showed similar results.

The administration of metoprolol was associated with a significant increase in the incidence of low heart rate or blood pressure. One hundred and forty seven patients (32%) in the metoprolol group versus 80 (17%) ($P<0.001$) in the placebo-group experienced one or more episodes of heart rate below 65 beats per minute or systolic blood pressure below 100 mm Hg. We did not observe a statistically significant increased occurrence of other adverse events in the metoprolol group. The proportion of reported serious adverse events in the metoprolol group was 7.8% (36/462 patients) versus 5.7% (26/459 patients) in the placebo group ($P=0.20$). Three days after we stopped the short-term beta-blockade, we did not observe any significant increase in proportion of withdrawal symptoms. These were measured as tachycardia (26 patients (5.6%) in the metoprolol group versus 24 patients (5.2%) in the placebo group) and angina pectoris (20 patients (4%) in the metoprolol group versus 15 patients (3%) in the placebo group) (unpublished results).

Table 1. Intention-to-treat analyses**Predictors of the primary outcome (proportional hazards model)**

Predictors	Hazard ratio (95% confidence interval)	P-value
Univariate model		
Metoprolol	1.06 (0.80 to 1.41)	0.66
Age (>65 years vs. <65 years)	2.62 (1.91 to 3.58)	<0.001
Sex (man vs. woman)	1.25 (0.93 to 1.68)	0.13
Coronary artery disease	1.60 (1.18 to 2.17)	<0.001
Malignant disease	1.90 (1.40 to 2.59)	<0.001
Multivariate model		
Metoprolol	1.10 (0.82 to 1.46)	0.53
Age (>65 years vs. ≤65 years)	1.59 (0.96 to 2.65)	0.07
Coronary artery disease	2.18 (1.52 to 3.11)	<0.001
Malignant disease	2.62 (1.77 to 3.80)	<0.001

Table 2. Per-protocol and subgroup analyses**Predictors of the primary outcome (proportional hazards model)**

Predictors	Hazard ratio (95% confidence interval)	P-value
Multivariate model (per protocol analyses)		
Metoprolol	1.04 (0.74 to 1.47)	0.82
Age (>65 years vs. ≤65 years)	2.25 (1.53 to 3.29)	<0.001
Coronary artery disease	2.26 (1.51 to 3.73)	<0.001
Malignant disease	2.35 (1.48 to 3.39)	<0.001
Multivariate model (Mangano et al population⁴⁹)		
Metoprolol	1.01 (0.68 to 1.49)	0.97
Age (>65 years vs. <65 years)	1.92 (1.19 to 3.10)	0.01
Coronary artery disease	2.42 (1.47 to 3.97)	<0.001
Malignant disease	3.74 (2.28 to 6.18)	<0.001

Discussion

Long-term postoperative mortality in diabetic patients undergoing major non-cardiac surgery – the observational study

Before initiating a large randomised clinical trial on perioperative beta-blockade in diabetic patients, it was important to examine whether diabetic patients generally had a high postoperative mortality after noncardiac surgery. Unfortunately, the literature regarding postoperative cardiac adverse events in diabetic patients was sparse and conflicting. The observational study was therefore conducted to assess the extent of postoperative mortality in diabetic patient undergoing major noncardiac surgery in a hospital in the Greater Copenhagen area.

The results of the observational study indicate that diabetic patients undergoing major non-cardiac surgery have a substantial one-year postoperative mortality of 24%. Not unexpectedly, a history of CAD, high risk ASA grade (the preoperative classification system of physical status by the American Society of Anaesthesiologists⁶³), and urgent surgery were important risk factors of long-term postoperative mortality. Cardiovascular diseases were the major causes of death. About one third of the deaths occurred within 30 days postoperatively indicating that the surgical and anaesthetic procedures contributed to a high risk in those patients.

The external validity of the observational study is, however, limited, as it is a single-centre, retrospective, cohort study. In order to assess the scientific knowledge regarding efficacy of treatment, a hierarchy of evidence has been developed.⁶⁴ The construction of this hierarchy is mainly based on the risk of systematic errors (i.e, bias) associated with different research designs. Randomised trials and systematic reviews of randomised trials are placed

as category 1 of evidence (table 3), due to their ability to control bias. A retrospective cohort study is placed as category 3 (table 3), and caution must be used in

Table 3. Categories of evidence regarding the effects of interventions⁶⁴

1a	Evidence from meta-analysis of randomised clinical trials
1b	Evidence from at least one randomised clinical trial
2a	Evidence from at least one controlled study without randomisation
2b	Evidence from at least one other type of quasi-experimental study
3	Evidence from descriptive studies, such as comparative studies, correlation studies, and case-control studies
4	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

extrapolating the results from an observational study to a surgical diabetic population. As a consequence of the retrospective design, important information of, for example, the frequency of late diabetic complications, perioperative haemodynamic variations, or postoperative treatment could not be obtained. We did also not include a group of matched non-diabetic patients, and a specific diabetes-related mortality could not be calculated. The reason for not including a group of matched non-diabetic patients is that we find it very difficult to classify such patients correctly in a retrospective design.

Despite the limitations mentioned above, the results of the observational study are in accordance with other studies demonstrating that diabetic patients undergoing surgery have an increased long-term postoperative mortality compared to non-diabetic patients.^{29,30,32,33,35}

Most of the studies finding no association of diabetes mellitus with increasing postoperative mortality are only reporting short-term follow-up.³⁶⁻⁴⁰ Diabetic patients have more extensive and progressive CAD⁶⁵⁻⁶⁹ and a higher incidence of silent myocardial infarction than the general population.⁷⁰⁻⁷⁴ Surgery in this patient group not causing immediate mortality may start a sequence of events leading to cardiac morbidity or death beyond 30 days postoperatively, and a long-term follow-up may therefore be required.

Randomised, blinded trial on perioperative metoprolol versus placebo for diabetic patients undergoing major noncardiac surgery – the DIPOM trial

The principal finding of the DIPOM trial is that among diabetic patients undergoing major noncardiac surgery, short-term perioperative beta-blockade does not seem to improve long-term event-free survival. This finding was consistent across the ITT analyses (table 1), the PP analyses, and subgroup analyses (table 2). We found a significant difference in mean heart rate and mean arterial pressure between the two groups, in spite of the fact that 33% of the patients in the metoprolol group received half dose or no treatment due to the low heart rate and/or low blood pressure compared to 17% in the placebo group. The dose reductions were in accordance with the safety criteria. There was also no reduction in 30 days postoperative primary outcomes including death, MI, unstable angina pectoris, and congestive heart failure.

The design of the DIPOM trial has several advantages over previous perioperative beta-blocker trials. First, it is the largest randomised clinical trial on perioperative beta-blocker treatment with 921 randomised patients designed to measure long-term postoperative outcomes until present. Hereby we aimed at reducing random errors. Further, the DIPOM trial is the first trial to examine the effects of perioperative beta-blockade in diabetic patients, which raises the external validity, as this patient group is relatively easy to identify. Second, the methods used for generation of the allocation sequence and for allocation concealment were adequate.⁷⁵⁻⁷⁷ Third, it is a double-blind, multicenter trial where both in-hospital outcomes and outcomes after 30 days postoperatively are reported. And as blinding for the clinical effects of beta-blockers is rather difficult to maintain,^{78,79} additional efforts to sustain blinding have been carried out during selection, treatment, monitoring, data management, assessment of outcomes, data analyses, and conclusion drawing. Additionally, copies of patient records from all hospital admissions after randomisation were

sent strictly blinded to the Adjudication Committee.⁶¹ Fourth, the existence of both a national system of person identification and a national register of data on all somatic hospital admissions in a population of relative demographic stability provided reliable and unbiased follow-up data.⁸⁰ Fifth, only beta-blocker naive patients were included, eliminating the risk of beta-blocker withdrawal symptoms in the patients randomised to placebo.⁵⁹ Sixth, metoprolol CR/XL was preferred since it is a beta-1 selective beta-receptor-blocking agent and provides low risk of induction of hypoglycaemia and bronchospasm. In addition, it provides a steady diurnal pharmacokinetics (plasma level) and pharmacodynamic (heart rate and blood pressure) effects.⁸¹ The extended-release tablet (metoprolol CR/XL 100 mg) allows convenient once-daily dosing; and it produces an even and consistent beta-blockade throughout the 24-hour dosing interval, with small fluctuation in metoprolol plasma concentrations.⁸² The dose-regimen would also be easy to implement in both intensive care wards and in ordinary wards improving the external validity of the trial.

The results of the DIPOM trial in relation to current evidence of the effect of perioperative beta-blockade on postoperative cardiac morbidity and mortality

The results of the DIPOM trial differ from the findings of the two previous randomised clinical trials,^{49,50} which indicated a survival benefit associated with short-term perioperative beta-blockade in intermediate- and high-risk patients undergoing major non-cardiac surgery after respectively 30 days⁵⁰ and eight months⁴⁹ postoperatively. However, these two trials have been criticised on a number of grounds. Primarily, because they are relatively small (a total number of 312 randomised patients) and have some design flaws.

In the trial by Mangano and colleagues,⁴⁹ patients who were already receiving beta-blockers had them discontinued on entry to the study and were thereafter randomised to beta-blockade or placebo. The patients receiving placebo were therefore at risk of beta-

blocker withdrawal symptoms.⁵⁹ Deaths and adverse events in hospital were ignored in the analyses, and it appeared that the statistically significant effect of beta-blockade on survival analysis disappeared when outcomes were assessed on an intention-to-treat analysis where both in-hospital and long-term outcomes were included.⁴⁹ In addition, the trial was underpowered to detect 30 days treatment effects. On balance the trial presents some evidence for a beneficial effect of perioperative beta-blockade in patients undergoing intermediate and high-risk non-cardiac surgery, but it is definitely not conclusive.²⁸

In the trial by Poldermans and colleagues⁵⁰ the only patients being studied were high-risk patients, whom it would be difficult to identify in many centres, as most hospitals do not have the resources to include cardiac stress testing in the preparation of patients for major surgery. All patients also received a minimum of 7 days beta-blocker therapy preoperatively. And there was no information on patient compliance. Further, the trial was unblinded^{76,77} and stopped early after the first interim analysis in accordance with the O'Brien and Fleming criteria⁸³ finding a significant difference in the rate of the primary outcome measure between the intervention and control group ($P=0.001$). Although this seems to be in accordance with internationally accepted stopping of trials, the small sample size leaves room for a type I error leading to spurious overestimation of intervention effect due to imbalance of known or unknown prognostic variables at entry.⁸⁴

The DIPOM trial is comparable to the Mangano et al trial⁴⁹ regarding intervention (dosage and duration), the inclusion of intermediate- and high-risk patients, types of surgery, outcome measures, and follow-up. We obtained similar reduction of heart rate in the intervention group (72⁶² and 75⁴⁹ beats per minute, respectively). Besides we performed both ITT and PP analyses. We only randomised diabetic patients, as this patient group seemed to benefit most from the treatment according to a subgroup analysis in the Mangano trial. In addition, 496 of all randomised diabetic patients also met the inclusion criteria of the Mangano et al trial.⁴⁹ We included an analysis of this subgroup in our proportional hazards

model (table 2), but despite of these efforts, we could not reproduce anything similar to the favourable effect of perioperative beta-blockade previously reported.

We experienced fewer primary outcomes in the DIPOM trial than anticipated. This may be a reflection of the facts that some of the patients in the DIPOM trial may have been low-risk patients without CAD or other diabetic complications and that some patients underwent low-risk surgical procedures. Further, patients undergoing emergency surgery and patients unable to give written informed consent were not randomised. Thus, a group of patients with high baseline risk and large event rate were excluded. As a consequence, the 95% CI of 0.82 to 1.46 in the multivariate analysis is wide. We cannot exclude either a beneficial effect of 18% or less or a detrimental effect of 46% or less of metoprolol. However, we can exclude a relative risk reduction of 50% or more as reported by Mangano et al and Poldermans et al.

A daily dose of 100 mg metoprolol CR/XL during a mean of 4½ days may not have been the optimal duration and dosage of therapy to ensure sufficient beta-blockade in all patients. However, the duration of treatment in the DIPOM trial seems to be longer than in most of the trials included in the meta-analysis by Stevens and colleagues⁸⁵ and certainly comparable to the duration of treatment in the trial by Mangano and colleagues. Moreover, our dose regimen matches the dose regimen of Mangano and colleagues. A number of patients in the DIPOM trial only tolerated half the target dose or no dose at all due to hypotension and/or bradycardia. As a result, initiating beta-blockade with a higher dose of metoprolol than 100 mg in cardiac risk patients prior to surgery may jeopardise the patients. Administering the trial drug after discharge from hospital also causes difficulties in ensuring that the safety criteria are met.

Our findings are in accordance with a very recent randomised placebo-controlled clinical trial by Yang and colleagues (the MaVS trial),⁸⁶ who randomised 497 patients undergoing vascular surgery to either five days perioperative beta-blockade or placebo. The

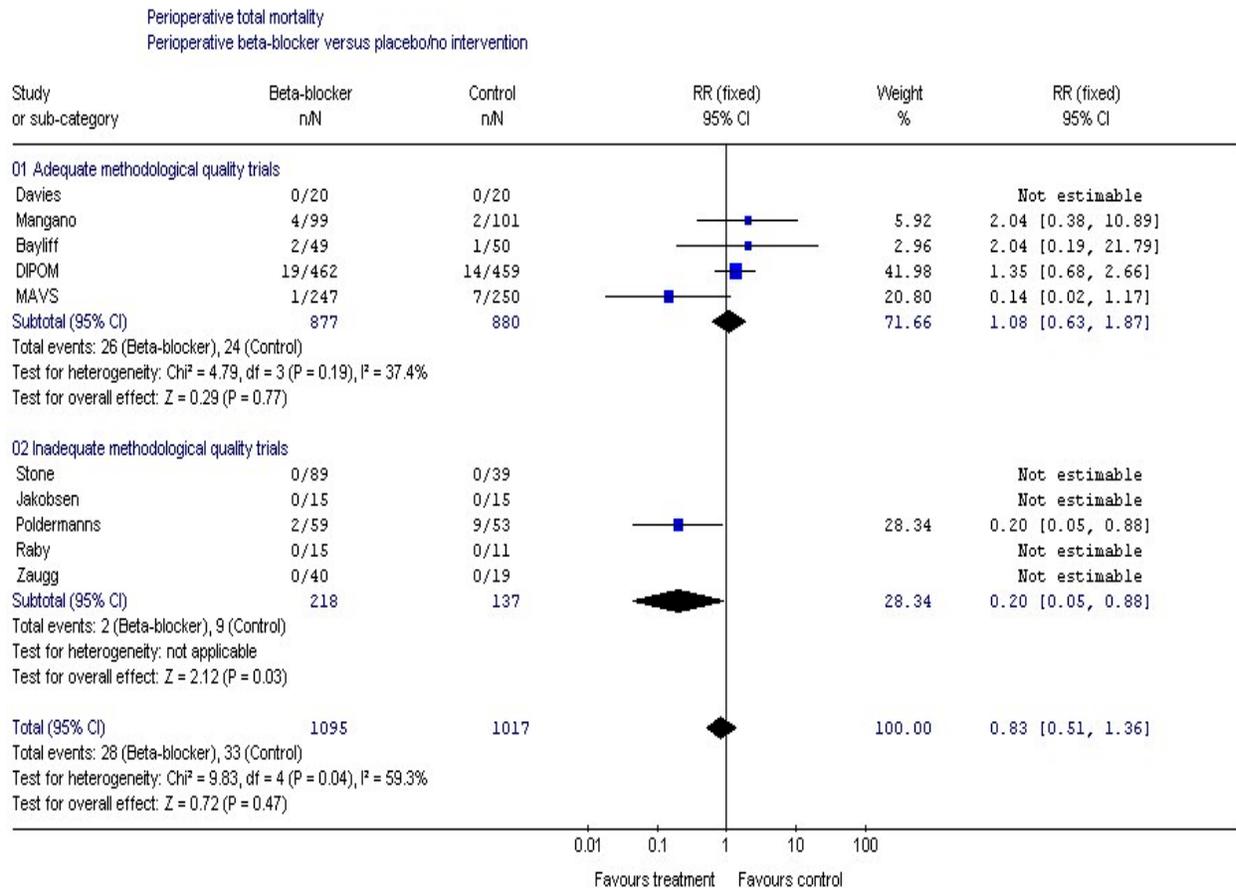
primary outcome was 30-day composite incidence of postoperative cardiac morbidity and mortality. Yang and colleagues did not find a significant difference in the primary outcome (25/247 patients on metoprolol versus 30/250 patients on placebo).

We combined the data from the DIPOM trial⁶² and the MaVS trial⁸⁶ with the data in the meta-analysis by Stevens and colleagues⁸⁵ on total mortality and non-fatal MI within 30 days postoperatively. The meta-analysis included data from eight trials assessing the effect of beta-blockade on peri- or post-operative (≤ 30 days postoperatively) cardiac morbidity and mortality in patients undergoing non-cardiac surgery (386 patients were in the beta-blocker group versus 308 patients in the placebo group).^{44,46,49,50,58,62,86-89}

Among the trials having adequate methodology⁷⁵⁻⁷⁷ the effect of perioperative beta-blockade versus placebo on short-term (≤ 30 days), postoperative all-cause mortality was not significant (RR 1.08 (95% CI 0.63 to 1.87)^{44-46,50,58,89} (fig. 1). There was only modest heterogeneity ($I^2 = 37.4\%$). Among the trials having inadequate or unclear methodology the effect of perioperative beta-blockade versus placebo on short-term (≤ 30 days), postoperative all-cause mortality was significant (RR 0.20 (95% CI 0.05 to 0.88)^{44-46,50,58,89} (fig. 1). Only the Poldermans and colleagues trial provided data. Even when we added the trials having one or more inadequate quality component to the adequate trials there was no significant effect of beta-blockade on mortality (RR 0.83 (95% CI 0.51 to 1.36). Now there was more heterogeneity among the trial results ($I^2 = 59.3\%$)^{44,50,58,58,89} (fig. 1).

Figure 1

Meta-analysis of all-cause mortality in randomized trials comparing perioperative beta-blocker versus placebo/no intervention included in the meta-analysis by Stevens et al⁸⁵ plus the data from the DIPOM trial⁶² and the MaVS trial.⁸⁶ Trials were subdivided into those with adequate methodology (i.e., adequate generation of the allocation sequence, adequate allocation concealment, and adequate blinding) and those being inadequate or unclear regarding one or more of these components.



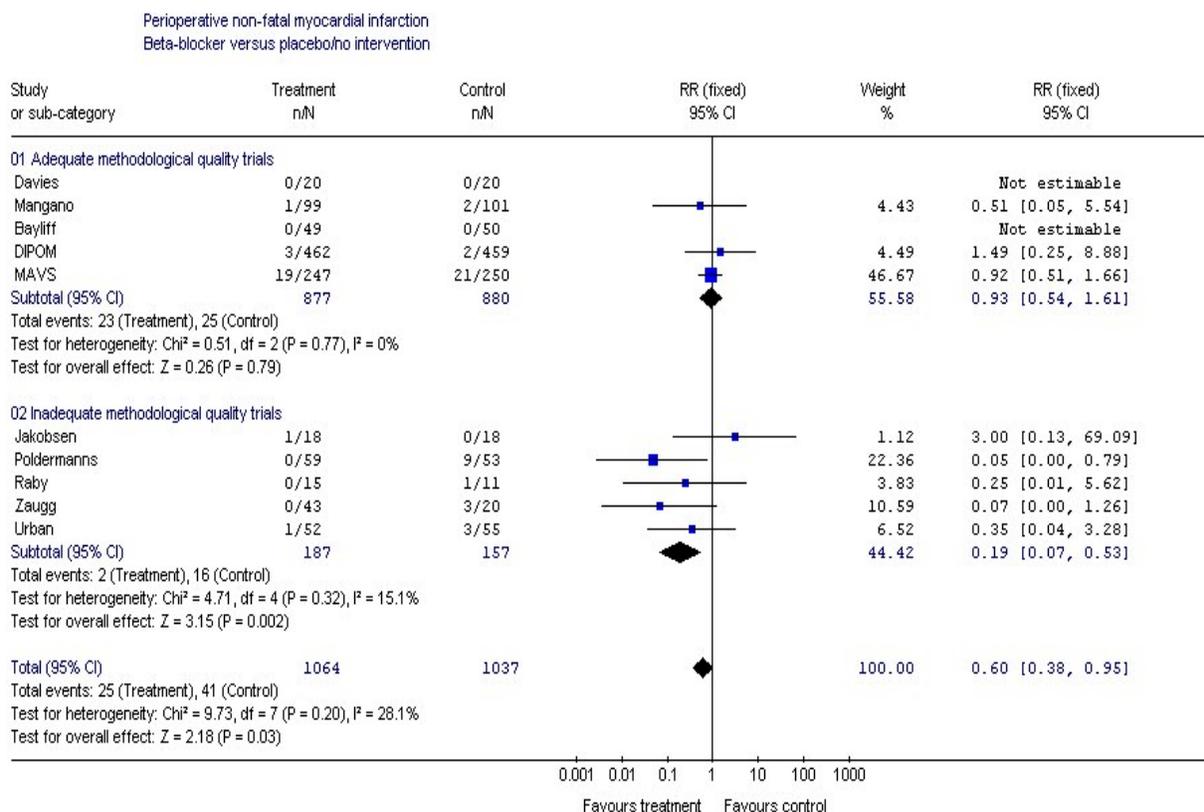
Among the trials having adequate methodology the effect of perioperative beta-blockade versus placebo on short-term (≤ 30 days) postoperative non-fatal MI was not significant (RR 0.93 (95% CI 0.54 to 1.61)^{44-46,50,58,89} (fig. 2). There was no heterogeneity ($I^2 = 0\%$). Among the trials having inadequate or unclear methodology the effect of perioperative beta-blockade versus placebo on short-term (≤ 30 days) postoperative non-fatal MI was significant (RR 0.19 (95% CI 0.07 to 0.53)^{44-46,50,58,89} (fig 2). There was no substantial heterogeneity ($I^2 = 15.1\%$). When combining the results of the trials having one

or more inadequate quality component to the adequate trials we also observed a significant effect of beta-blockade on non-fatal MI (RR 0.60 (95% CI 0.38 to 0.95). But, now the heterogeneity among the trial results ($I^2 = 28.1\%$) (fig. 2) was bigger.

Caution should be exercised in interpreting these results because of the inherent differences in patient population, types and dosages of beta-blocker used, and time of initiation and duration of treatment.^{44,50,58,58,89}

Figure 2

Meta-analysis of perioperative non-fatal myocardial infarction in randomized trials comparing perioperative beta-blocker versus placebo/no intervention included in the meta-analysis by Stevens et al⁶⁵ plus the data from the DIPOM trial⁶² and the MaVS trial.⁸⁶ The trials were subdivided into those with adequate methodology (i.e., adequate generation of the allocation sequence, adequate allocation concealment, and adequate blinding) and those being inadequate or unclear regarding one or more of these components.



Implications for clinical practice

On the basis of the DIPOM results a beneficial effect of 18% or less of perioperative beta-blockade on our primary outcome in diabetic patients cannot be excluded (table 1). This is also the case with a detrimental effect of 46% or less (table 1). These figures are supported by our meta-analyses taking methodological quality into consideration. Thus, there is no valid evidence to recommend perioperative beta-blocker treatment on the sole indication of diabetes mellitus. A possibly beneficial effect of perioperative beta-blockade in high-risk patients having evidence of myocardial ischaemia on stress testing cannot be excluded.⁵⁰

However, the DIPOM and the MaVS trials did not find any significant beneficial effects from perioperative beta-blockade in cardiac-risk patients. In addition, the meta-analyses were unable to demonstrate a statistically significant difference in fatal events (fig. 1) or in non-fatal MI (fig 2) when trials with inadequate or unclear methodology had been excluded. Therefore, considering the design flaws in the two randomized clinical trials by Mangano and colleagues and Poldermans and colleagues,^{45,49,50} there is not evidence to recommend perioperative beta-blockade in intermediate- or high-risk patients. International, national, and local guidelines therefore need to be updated accordingly.

Implications for research

Short-term perioperative metoprolol (100 mg/day) does not significantly effect mortality and cardiac morbidity in diabetic patients undergoing non-cardiac major surgery. But it is possible that a larger dose of and/or longer treatment duration with beta-blockers may provide a beneficial effect on important clinical outcomes.

Until now the use of perioperative beta-blockade has not been associated with significant risk as long as the treatment is withheld if in case of relative bradycardia or hypotension. However, this is based on small trials in intensive wards. In future trials a larger

number of patients may have to be treated to prevent one non-fatal myocardial infarction or fatal event. And the treatment may have to be continued after discharge from the intensive care ward or the hospital. This makes heavy demands on the examination of the safety of the treatment, and it is extremely important to quantify the benefits of perioperative beta-blockade against any risk of harm, both in ordinary wards and after discharge from the hospital.

Future trials must be adequately powered, as it is very likely that the effect of perioperative beta-blockade in cardiac-risk patients has been overestimated. The size of intervention effects is often overestimated in early, small trials compared with later, equally rigorous but larger trials.⁹⁰ This pattern may arise from publication bias, but it may also be related to a shift in setting from trials testing efficacy under ideal condition to those that assess effectiveness in daily clinical practice.⁹¹ In long-term prevention trials on beta-blockade for survivors of myocardial infarction⁹² a relative risk reduction of 22% can be calculated in non-fatal reinfarction or for fatal events respectively. It is probably more realistic to expect this effect size from short-term perioperative beta-blocker treatment. To detect a 20% relative risk reduction in the primary composite outcome with a 5% type 1 error rate, 80% power, and a control outcome rate of 10%, we need a sample size of 6,626 patients. The meta-analyses (fig. 1 and 2) on peri-and postoperative mortality and non-fatal MI included only about 20% of this minimal sample size. The evidence from the meta-analyses is therefore inconclusive.

Large randomized trials using larger dose and/or longer duration of treatment than were used in the DIPOM trial are therefore needed to answer questions regarding optimal duration, dosage and safety of therapy, and identify populations in which beta-blocker use is cost-effective. Such a trial is presently on its way.⁹³⁻⁹⁵

Dansk resumé

Introduktion Perioperative myokardielle iskæmiske episoder hos patienter, der gennemgår et større operativt indgreb, er et betydeligt klinisk problem med konsekvenser for den postoperative prognose i form af øget risiko for kardiell morbiditet og mortalitet. Diabetes patienter har en øget forekomst af iskæmisk hjertesygdom sammenlignet med ikke-diabetikere. Flere mindre forsøg har indikeret at perioperativ betablokade kan mindske den postoperative kardielle morbiditet og mortalitet.

Formål At belyse langtids mortalitet og undersøge effekten af perioperativ intervention med metoprolol CR/XL versus placebo på langtids mortalitet og kardiell morbiditet hos diabetes patienter, der skulle gennemgå et større ikke-kardielt operativt indgreb.

Materialer og metoder Langtids mortaliteten belystes i en retrospektiv kohorteundersøgelse. Kohorten består af alle diabetes patienter, som på KAS Herlev fra september 1996-1997 havde gennemgået en større ikke-kardiell operation. Alle data blev tilvejebragt ved journalgennemgang og via Dødsårsagsregistret. DIPOM forsøget er et randomiseret, dobbelt blindt, placebokontrolleret, multicenter klinisk forsøg. Tretten centre i Storkøbenhavn deltog. Patienter, der opfyldte inklusionskriterierne diabetes mellitus hos patienter ældre end 39 år, der skulle gennemgå en større ikke-kardiell operation og ingen af eksklusionskriterierne (igangværende betablokkerbehandling, indikation eller kontraindikation for betablokkerbehandling eller i NYHA gruppe IV) blev randomiseret til en af to grupper ved brug af et tryknapstelefon randomiseringssystem (central randomisering). Det primære sammensatte effektmål var den samlede mortalitet, AMI, ustabil angina pectoris, eller kardiell inkomensation, der medførte hospitalsindlæggelse. Metoprolol CR/XL eller placebo blev administreret under indlæggelsen fra aftenen før operation til et maksimum af 8 dage. En ambulant kontrol gennemførtes seks måneder postoperativt. Øvrige effektmål blev indhentet via Landspatientregisteret og CPR-registeret.

Resultater Det observationelle studie viste at den postoperative 12 måneders dødelighed hos diabetes patienter var 24% (95% sikkerhedsgrænser 17 til 31%). En tredjedel af dødsfaldene forekom i de første 60 dage postoperativt. Kendt iskæmisk hjertesygdom var associeret med en postoperativ dødelighed på 44% (95% sikkerhedsgrænser 29 til 58%), hvilket var signifikant ($P < 0.03$) højere end hos diabetes patienter uden kendt iskæmisk hjertesygdom. I alt 921 patienter blev inkluderet i DIPOM forsøget, 462 fik metoprolol and 459 fik placebo. Patient karakteristika var sammenlignelige i de to grupper. Gennemsnitlig opfølgningstid var 18 (spændvidde 6 til 30) måneder. Patienterne fik metoprolol gennemsnitligt i 4.6 dage versus placebo i 4.9 dage. Metoprolol reducerede signifikant den gennemsnitlige hjerte aktion med 11% og det gennemsnitlige arterielle blodtryk med 3%. Det primære effektmål forekom hos 99/462 (21%) i metoprolol gruppen versus 93/459 (20%) i placebo gruppen. Intention-to-treat analyserne viste en risiko rate på 1.10 (95% sikkerhedsgrænser 0.82 til 1.46). Den samlede mortalitet var 16% (74/462) i metoprolol gruppen versus 16% (72/459) i placebogruppen (logrank test, $P = 0.88$). Per-protokol og sekundære effektmålsanalyser viste lignende resultater. Der blev ikke observeret signifikant forskel i forekomsten af alvorlige uønskede begivenheder (metoprololgruppen: 7.8% (36/462 patienter) versus 5.7% (26/459 patienter) i placebogruppen ($P > 0.20$)).

Konklusion Kortvarig perioperativ metoprolol behandling reducerer ikke den samlede mortalitet og kardielle morbiditet hos diabetes patienter, der gennemgår en større ikke-kardiel operation. Muligvis kan større dosis og/eller længere behandlingsvarighed have en gavnlige effekt. Dette bør undersøges via store randomiserede kliniske forsøg. Indtil der foreligger resultater der overbevisende støtter perioperativ beta-blokade bør internationale, nationale og lokale kliniske retningslinjer ikke anbefale beta-blokade på den undersøgte indikation.

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