Research

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Effect of perioperative β blockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial

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Abstract

Objectives To evaluate the long term effects of perioperative β blockade on mortality and cardiac morbidity in patients with diabetes undergoing major non-cardiac surgery.
Design Randomised placebo controlled and blinded multicentre trial. Analyses were by intention to treat.
Setting University anaesthesia and surgical centres and one coordinating centre.
Participants 921 patients aged >39 scheduled for major non-cardiac surgery.
Interventions 100 mg metoprolol controlled and extended release or placebo administered from the day before surgery to a maximum of eight perioperative days.
Main outcome measures The composite primary outcome measure was time to all cause mortality, acute myocardial infarction, unstable angina, or congestive heart failure. Secondary outcome measures were time to all cause mortality, cardiac mortality, and non-fatal cardiac morbidity.
Results Mean duration of intervention was 4.6 days in the metoprolol group and 4.9 days in the placebo group. Metoprolol significantly reduced the mean heart rate by 11% (95% confidence interval 9% to 13%) and mean blood pressure by 3% (1% to 5%). The primary outcome occurred in 99 of 462 patients in the metoprolol group (21%) and 93 of 459 patients in the placebo group (20%) (hazard ratio 1.06, 0.80 to 1.41) during a median follow-up of 18 months (range 6-30). All cause mortality was 16% (74/462) in the metoprolol group and 16% (72/459) in the placebo group (1.03, 0.74 to 1.42). The difference in risk for the proportion of patients with serious adverse events was 2.4% (−0.8% to 5.6%).
Conclusions Perioperative metoprolol did not significantly affect mortality and cardiac morbidity in these patients with diabetes. Confidence intervals, however, were wide, and the issue needs reassessment.
Trial registration Current Controlled Trials ISRCTN58485613.

Introduction

Cardiac morbidity and mortality after non-cardiac surgery is 11% to 34% in patients with diabetes, recent myocardial infarction, unstable angina, or congestive heart failure.[1–4] Complications are probably due to perioperative myocardial ischaemia.[1 5]

Perioperative β blockade is recommended in patients at cardiac risk undergoing major non-cardiac surgery.[6] The recommendations are based on the results of small trials indicating that patients at cardiac risk should receive perioperative β blockade when they undergo major non-cardiac surgery.[2 5 7 8] Devereaux et al carried out a meta-analysis of trials on perioperative β blockers up to April 2003.[8] They found insufficient evidence for a reduction of major cardiovascular events.[8] Subsequently, the perioperative β blockade (POBBLE) trial failed to show significant effects of perioperative β blockade on mortality and major cardiovascular events in patients undergoing vascular surgery.[9]

The multicentre study group of perioperative ischaemia suggested that diabetes was a significant predictor of postoperative death.[5 7] Perioperative β blockade in patients with diabetes and additional risk factors for coronary artery disease seemed beneficial, with a two year hazard ratio for death of 0.25 (P = 0.03).[7] The American College of Cardiology and the American Heart Association assert that patients with diabetes have the same risk as coronary artery disease patients[6] and therefore may benefit from perioperative β blockade.[10 11] We conducted the diabetes postoperative mortality and morbidity (DIPOM) trial to assess metoprolol versus placebo for patients with diabetes undergoing major non-cardiac surgery.[10]

Methods

The DIPOM trial is an investigator initiated and controlled, randomised placebo controlled, multicentre trial with central randomisation and blinding of all parties in all phases.[10] The code was broken when analyses were completed and a conclusion formulated.

Organisation

Thirteen anaesthesia and surgical centres in nine hospitals in the greater Copenhagen area participated. An independent and blinded event committee adjudicated all reports of outcomes registered in public databases. An independent and blinded data monitoring and safety committee assessed the interim analyses.[10] The Copenhagen trial unit coordinated randomisation, collection, and distribution of patients' records to the event and safety committees, data entry, and data management. Clean files were exported to the department of biostatistics, University of Copenhagen, for analyses.

Patient recruitment

Between 1 July 2000 and 1 July 2002 project nurses contacted eligible patients aged >39 with diabetes who were scheduled for major (that is, expected duration over one hour) non-cardiac surgery. Patients with either insulin or non-insulin dependent diabetes were included.[12] All participants gave written informed consent. Exclusion criteria were: no written informed consent; systemic treatment with β blocker; conditions indicating β blocker treatment; New York Heart Association class IV congestive heart failure; third degree atrioventricular blockade; pregnancy or breast feeding; allergic to metoprolol or placebo; or previously included in the DIPOM trial.[10]

Randomisation

A computer generated the allocation sequence and served a telephone voice response randomisation system. The allocation sequence was in blocks of eight and stratified for centre, age >65, sex, expected perioperative stress (high and intermediate risk or low risk surgery), history of coronary artery disease, and active malignant disease.[10] Patients were randomly assigned to metoprolol succinate controlled/extended release (CR/XL) or matching placebo. When possible patients were given a test dose of 50 mg study drug the evening before surgery (day 1). If it was tolerated, they were given two 50 mg tablets (full daily dose) at least two hours before induction of anaesthesia on the day of surgery (day 2). The study drug was administered once daily until discharge from the hospital or to a maximum of eight days. Half dose was given in patients with a heart rate of 55-65 beats per minute and systolic blood pressure ≥100 mm Hg. The study drug was withheld in patients with a heart rate <55 beats per minute or systolic blood pressure <100 mm Hg. When oral administration was not feasible, 5 mg metoprolol or matching placebo was given intravenously before surgery and every sixth hour. Incorrect dosing of trial drug was considered a protocol violation.

Follow-up

We collected morbidity and mortality data from the Danish national hospital register, which contains information about all somatic hospital admissions in Denmark,[10] and the centralised civil register, which records the vital status of all inhabitants in Denmark.[10] In addition, all patients were recalled six months after discharge, when we recorded use of β blockers after discharge and an electrocardiogram.

Outcome measures

The primary outcome measure was time to the composite outcome of all cause mortality, acute myocardial infarction, unstable angina, or congestive heart failure discovered or aggravated during admission to hospital. Non-fatal myocardial infarction was diagnosed using electrocardiography; concentrations of troponin, CK-MB, or LDH-1 isoenzymes; and pain.[10] The criteria to be fulfilled were a rise in concentrations of troponin, LDH-1, or CK-MB at or above double the upper normal concentration and presence of angina, equivalent of angina, respiratory distress, palpitations, atypical pain, sickness, or development of Q wave, ST elevation, ST depression, or T wave abnormalities. At the outpatient visit we recorded the presence of new Q waves according to the Minnesota Code Criteria[10] as myocardial infarction. Cardiac heart failure was defined as start of medication, increased dose of existing medication, or new class of medication for cardiac heart failure. Unstable angina pectoris was diagnosed

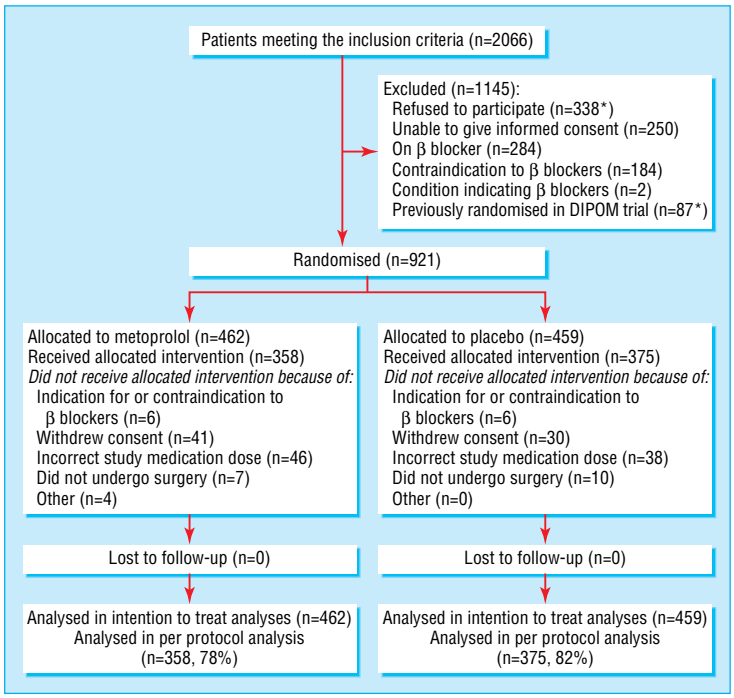

Fig 1 Flow of patients through study (*includes five patients who refused to take part after randomisation but before any medication and surgery; †includes two patients who had previously been randomised in the DIPOM trial)

if the patient had a record of typical pain and no detectable rise in coronary enzymes along with a specific medical intervention for unstable angina pectoris or ST depression or inversion of T wave. Secondary outcomes were all cause mortality, cardiac mortality, non-cardiac mortality, and cardiac morbidity.[10] We registered serious adverse events and adverse events leading to withdrawal of the study drug.

Statistical analysis

We estimated that 30% of patients in the placebo group would have a primary outcome due to a shorter follow-up, inclusion of younger patients, and the wide 95% confidence interval in previous studies.[7 11] To detect a 33% relative risk reduction in the metoprolol group we needed a sample size of 824 patients with a two sided $\alpha = 0.05$ and power $(1-\beta) = 0.90$. We aimed to randomise 1000 patients.[10]

We compared Kaplan-Meier survival curves by log rank test. To estimate the intervention effect, we used univariate Cox regression models as the primary analyses. Adjusted intervention effects were calculated with all variables used for stratification during randomisation in a multivariate Cox regression analysis.[13] We also calculated cumulated intensities, time dependent effects, and residual plots substantiating proportional hazards. We performed a prespecified subgroup analysis of the patients fulfilling the inclusion criteria in the trial of Mangano et al (having at least one risk factor for coronary artery disease besides diabetes and undergoing high risk or intermediate risk surgery[7 11]). $P < 0.05$ was considered significant.

Results

We randomised 921 patients: 462 to metoprolol and 459 to placebo. All patients were followed up until 1 January 2003 and analysed in intention to treat analyses; 733 patients (80%) were analysed in per protocol analyses (fig 1). Baseline and surgical characteristics were comparable in the two groups (table 1). In addition to diabetes, 496 of the patients (54%) had a history of, or an additional risk factor for, coronary artery disease and were undergoing high risk or intermediate risk surgery. The median follow-up was 18 months (range 6-30 months). At six months, 720 patients (78%) had an outpatient follow-up, and 713 patients (77%) underwent electrocardiography. Seven patients in the metoprolol group and five in the placebo group had received β blockers during follow-up.

Primary outcome

Overall 99 of 462 patients in the metoprolol group (21%) and 93 of 459 patients in the placebo group (20%) had a primary outcome. Figure 2 shows the Kaplan-Meier estimates of the primary outcome measure in the two groups (log rank test $P = 0.66$). Within 30 days postoperatively 27 of 462 patients in the metoprolol group (6%, 95% confidence interval 4% to 8%) and 21 of 459 patients in the placebo group (5%, 3% to 7%) had a primary outcome.

Table 2 shows predictors of the primary outcome in univariate Cox regression models. We found no significant effect of metoprolol compared with placebo (hazard ratio 1.06, 0.80 to 1.41, $P = 0.66$) and no evidence of significant variation in treatment effect according to centre or baseline characteristics. Presence of coronary artery disease or malignant disease contained significant prognostic information. Multivariate analysis with all variables used for stratification in the model showed no significant effect of metoprolol (1.05, 0.79 to 1.40) (table 2). Metoprolol still had no significant effect even when we added preoperative insulin treatment to the multivariate model (1.07, 0.80 to 1.42) (table 2). The effect of preoperative insulin treatment was not significant in a univariate analysis ($P = 0.46$). In the subgroup of 496 patients fulfilling the criteria of Mangano et

Table 1 Entry characteristics of patients randomised to metoprolol or placebo. Figures are number (percentage) of patients unless stated otherwise

	Metoprolol (n=462)	Placebo (n=459)
Demographics		
Mean (SD) age (years)	64.9 (11.1)	64.8 (110.8)
Mean (SD) body mass index	27.2 (5.4)	26.9 (5.2)
No (%) of women	191 (41)	191 (42)
Cardiovascular disease		
Congestive heart failure	47 (10)	48 (11)
Atrial fibrillation	34 (7)	38 (8)
Arrhythmia requiring treatment	12 (3)	13 (3)
Angina pectoris	56 (12)	48 (11)
Previous acute myocardial infarction	36 (8)	34 (7)
Previous PTCA/CABG	20 (4)	15 (3)
History of hypertension	254 (55)	288 (58)
Calcium channel blockers	70 (15)	81 (18)
Diuretics	155 (34)	170 (37)
ACE inhibitor	130 (28)	148 (32)
Anticoagulants	114 (25)	99 (22)
Statins	53 (12)	46 (10)
Angiotensin II receptor blocker	29 (6)	27 (6)
History of coronary artery disease and hypertension	279 (61)	286 (62)
Antidiabetic treatment		
Diet alone	81 (18)	80 (17)
Oral hypoglycaemic agent	201 (44)	191 (42)
Insulin	153 (33)	164 (36)
Insulin and oral hypoglycaemic agent	26 (6)	24 (5)
Diabetes duration and complications		
Mean (SD) duration of diabetes (years)	12.0 (11.8)	11.6 (11)
Diabetic neuropathy	116 (25)	124 (27)
Diabetic retinopathy	92 (20)	85 (19)
Diabetic nephropathy	35 (8)	37 (8)
Concurrent diseases and surgical risk		
Current smoker	179 (39)	171 (38)
Former smoker	183 (40)	169 (37)
Excessive alcohol consumption	25 (5)	28 (6)
Active malignant disease	86 (19)	88 (19)
Surgical risk		
Expected high or intermediate risk	283 (61)	278 (61)
Expected low risk surgery	179 (39)	181 (39)
Type of surgery		
Orthopaedic	154 (33)	149 (32)
Intra-abdominal	126 (27)	129 (28)
Neurological	40 (9)	32 (7)
Vascular	30 (7)	32 (7)
Gynaecological	23 (5)	24 (5)
Thoracic	20 (4)	17 (4)
Other*	69 (15)	76 (17)
Type of anaesthesia		
General	269 (58)	295 (64)
Combined epidural and general	85 (18)	78 (17)
Epidural or spinal	91 (20)	69 (15)
Unknown	17 (4)	17 (4)
Duration of surgery		
Mean hours (range)†	2.6 (0.5-9.8)	2.6 (0.4-9.8)
Blood transfusion		
No transfused	33 (8)	38 (9)
Mean (SD) amount transfused (ml)	809 (735)	825 (528)

ACE inhibitor=angiotensin converting enzyme inhibitor; PTCA/CABG=percutaneous transluminal coronary angioplasty/coronary artery bypass graft.
*Includes head and neck surgery, plastic surgery, eye surgery, or general surgery.
†Measured from induction of anaesthesia to time of final blood pressure measurement.

al[7] there was no significant effect of metoprolol (1.03, 0.71 to 1.50). The per protocol analysis and analyses of risk of type of surgery yielded similar results.

Mortality and cardiac morbidity

There were no significant differences between the intervention groups in any of the secondary outcomes. Seventy four of 462 patients (16%) in the metoprolol group and 72 of 459 in the placebo group (16%) died (1.03, 0.74 to 1.42). In a multivariate analysis with all stratification variables in the model the hazard ratio of death was 1.01 (0.72 to 1.41). Addition of preoperative insulin treatment to the multivariate analysis changed the hazard ratio of the intervention effect to 1.03 (0.74 to 1.42), and the effect of preoperative insulin treatment was not significant (P = 0.068). Forty six of 462 patients in the metoprolol group and 45 of 459 in the placebo group had a cardiac outcome (1.02, 0.67 to 1.67), with an adjusted hazard ratio of 1.03 (0.69 to 1.54). We found similar non-significant effects of metoprolol on cardiac mortality, non-fatal cardiac morbidity, or non-cardiac mortality (table 3).

Safety outcomes

The administration of metoprolol was associated with a significant increase in low heart rate and blood pressure; 147 of 462 patients in the metoprolol group (32%) and 80 of 459 in the placebo group (17%) had episodes of heart rate <65 beats per minute or systolic blood pressure <100 mm Hg (table 4). Serious adverse events occurred in 8% in the metoprolol group and 5% in the placebo group, a risk difference of 2.4% (−0.8% to 5.6%) (table 5).

Compliance and haemodynamics

In total 358 patients in the metoprolol group and 375 in the placebo group received the as intended intervention; one or more minor protocol violations occurred in 104 patients in the metoprolol group and 84 in the placebo group (fig 1).

The test dose was administered the day before surgery in 678 patients (74%). The target dose thereafter was 100 mg metoprolol or placebo daily. Several patients received either half the dose or no study drug because of low blood pressure or low heart rate (table 4). The mean duration of drug administration was 4.6 (range 0 to 8) days in the metoprolol group and 4.9 (0 to 8) days in the placebo group.

The heart rate and blood pressure were measured immediately before the next dose of study drug (table 6). Before the first dose of study drug, the mean heart rate and mean arterial pressure did not differ between the two groups. Thereafter, patients in the metoprolol group had significantly lower mean

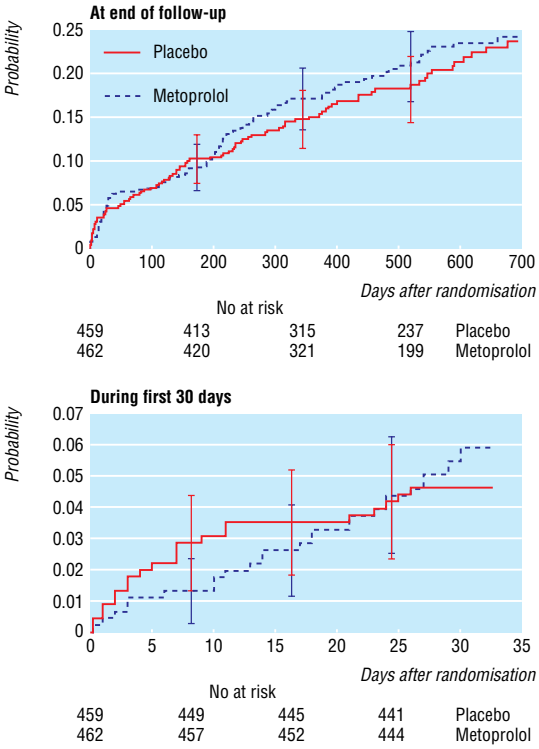

Fig 2 Kaplan-Meier plot of time to primary outcome measure during maximum follow-up and during first 30 days (with 95% confidence intervals)

Table 2 Intention to treat analysis. Predictors of primary outcome (all cause mortality, acute myocardial infarction, unstable angina, and congestive heart failure) among patients with diabetes undergoing non-cardiac surgery

	Hazard ratio (95% CI)	P value
Univariate analyses		
Metoprolol	1.06 (0.80 to 1.41)	0.66
Age (>65 or ≤65 years)	2.62 (1.91 to 3.58)	<0.001
Sex	1.25 (0.93 to 1.68)	0.13
Coronary artery disease	1.60 (1.18 to 2.17)	0.002
Malignant disease	1.90 (1.40 to 2.59)	<0.001
Expected surgical stress	1.31 (0.98 to 1.77)	0.07
Centre	Not shown†	0.08
Multivariate analyses*		
Metoprolol	1.05 (0.79 to 1.40)	0.53
Age (>65 or ≤65 years)	2.48 (1.79 to 3.43)	<0.001
Sex	1.17 (0.86 to 1.57)	0.31
Coronary artery disease	1.35 (0.99 to 1.85)	0.056
Malignant disease	1.55 (1.09 to 2.19)	0.014
Expected surgical stress	1.02 (0.39 to 1.41)	0.89
Centre	Not shown†	0.14
Multivariate analyses including preoperative insulin treatment		
Metoprolol	1.07 (0.80 to 1.42)	0.65
Age (>65 or ≤65 years)	2.56 (1.85 to 3.55)	<0.001
Sex	1.17 (0.87 to 1.59)	0.30
Coronary artery disease	1.38 (1.01 to 1.88)	0.04
Malignant disease	1.57 (1.10 to 2.22)	0.01
Expected surgical stress	1.04 (0.75 to 1.44)	0.83
Centre	Not shown†	0.11
Preoperative insulin treatment	1.36 (1.02 to 1.83)	0.04

*Based on a Cox proportional hazards model including all variables used for stratification at randomisation and trial drug as mandatory covariates.
‡Data not reported from all 13 centres.

Table 3 Intention to treat analysis. Hazard ratios of effect of perioperative β blockade on secondary outcomes among patients with diabetes undergoing non-cardiac surgery

	Hazard ratio* (95% CI)	P value
Univariate analyses		
All cause mortality	1.03 (0.74 to 1.42)	0.88
Cardiac events	1.02 (0.67 to 1.57)	0.91
Cardiac death	0.85 (0.45 to 1.60)	0.61
Non-fatal cardiac events	1.24 (0.70 to 2.17)	0.46
Non-cardiac death	1.10 (0.75 to 1.61)	0.63
Multivariate analyses		
All cause mortality	1.01 (0.72 to 1.41)	0.79
Cardiac events	1.03 (0.69 to 1.54)	0.87
Cardiac death	0.84 (0.46 to 1.52)	0.56
Non-fatal cardiac events	1.23 (0.68 to 2.23)	0.44
Non-cardiac death	1.13 (0.75 to 1.70)	0.65

*Adjusted in multivariate analysis for all variables used for stratification at randomisation and trial drug as mandatory covariates.

Table 4 Daily dose of metoprolol (M) and placebo (P). Figures are number (percentage) of patients

Variable	Day 2*		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8	
	M	P	M	P	M	P	M	P	M	P	M	P	M	P
Full dose	294 (64)	357 (78)	311 (67)	358 (78)	235 (51)	304 (66)	192 (42)	267 (58)	167 (36)	231 (50)	145 (31)	202 (44)	123 (27)	173 (38)
Half dose†	122 (26)	70 (15)	65 (14)	32 (7)	58 (13)	31 (7)	57 (12)	14 (3)	46 (10)	17 (4)	34 (7)	15 (3)	24 (5)	13 (3)
Not treated‡	46 (10)	32 (7)	86 (19)	69 (15)	169 (37)	124 (27)	213 (46)	178 (39)	249 (54)	211 (46)	283 (61)	283 (53)	315 (68)	273 (59)

*Day 1 defined as day before surgery. Day 2 is day of surgery before induction of anaesthesia. Days 3-8 are postoperative days.
†Because of heart rate between 55-65 beats per minute and systolic blood pressure ≥100 mm Hg.[26]
‡Because of contraindications (heart rate <55 beats per minute or systolic blood pressure <100 mm Hg), discharge, or death.[26]

Table 5 No of reported serious adverse events

	Metoprolol	Placebo
Cardiovascular:		
Myocardial infarction	3	4
Myocardial ischaemia	0	1
Congestive heart failure	2	1*
Atrial fibrillation	6	2
Atrioventricular dissociation	2	1*
Bradycardia	4	0
Hypotension	2	1
Cardiac arrest	2	1
Sudden death	2	3
Pulmonary:		
Respiratory failure	1	0
Pneumonia	1	1
Gastrointestinal:		
Ileus	1	1
Anastomosis leakage	1	0
Gastrointestinal haemorrhage	2	1
Perforated intestine	0	1
Peritonitis	1	0
Necrotising fasciitis	0	1
Reoperation	0	1
Cerebral:		
Stroke	2	0
Psychosis	1	0
Delirium	0	2
Dizziness	0	1
Intoxication	0	1
Metabolic:		
Ketoacidosis	1	0
Nephrological:		
Acute tubular interstitial nephropathy	1	1
Extremities:		
Amputation	0	1
Systemic:		
Allergic reaction	1	0
All	36†	26†

*One patient having two reported serious adverse events.
†No significant difference between metoprolol and placebo group, P=0.2.

heart rate by 11% (9% to 13%, P < 0.001) and mean arterial pressure by 3% (1% to 5%, P < 0.02). In two patients in the metoprolol group and five in the placebo group we discontinued the trial drug because treatment with β blockers was indicated.

Discussion

The results of this trial showed that compared with placebo, metoprolol has no significant effect on short or long term outcomes in patients with diabetes undergoing major non-cardiac surgery. This finding was consistent across the intention to treat and per protocol analyses as well as in analyses of the 496 patients with additional risk factors for coronary artery disease.

Strengths and limitations

This trial was a multicentre trial of the long term effects of metoprolol. We used adequate methods for generation of the allocation sequence and allocation concealment.[14] We made efforts to maintain blinding through selection, treatment, monitoring, data management, and data analyses. Blinding is difficult in β blocker trials because of changes in pulse and blood pressure, but the event committee performed blinded outcome assessment.[10] We used metoprolol in a sustained release formulation, comparable with atenolol,[15] as long acting β blockers offer better protection than short acting ones.[16] Our trial is comparable with previous trials[8] regarding intervention, dose, duration, the inclusion of patients at intermediate and high risk, surgery, and outcome measures, but we excluded patients already taking β blockers.[17] A total of 496 of our patients met the inclusion criteria used by Mangano et al,[7] nearly two and a half times the sample size in that trial.[7]

The potential limitations of this trial are that we included only patients with diabetes and we may not have included enough patients. However, 21% in the placebo group developed a primary outcome, enabling us to detect a hypothetical 7% absolute risk reduction with a power of 80%, making our trial far more sensitive than previous trials.[8] A daily dose of 100 mg metoprolol controlled/extended release may not have ensured sufficient β blockade, but heart rates and reductions in blood

Table 6 Means of heart rates and arterial pressures

Day*	Mean (SD, range) heart rate (beats/min)		Mean (SD, range) arterial pressure (mm Hg)	
	Metoprolol	Placebo	Metoprolol	Placebo
1	78 (12, 47-120)	79 (12, 50-128)†	103 (14, 58-150)	104 (14, 61-145)†
2	72 (12, 40-122)	77 (13, 50-128)‡	99 (14, 58-147)	102 (14, 63-145)§
3	74 (12, 40-120)	83 (14, 48-132)‡	91 (16, 56-139)	94 (16, 50-149)§
4	75 (12, 49-120)	84 (14, 52-120)‡	92 (15, 51-149)	95 (15, 47-132)§
5	75 (13, 44-124)	84 (14, 50-136)‡	92 (14, 58-140)	96 (14, 58-142)§
6	75 (14, 44-135)	82 (13, 46-124)‡	93 (14, 55-144)	96 (14, 63-148)§
7	75 (12, 50-112)	83 (13, 47-124)‡	94 (14, 53-127)	97 (15, 50-167)§
8	76 (14, 44-131)	83 (13, 52-123)‡	92 (14, 51-149)	97 (15, 57-140)§

*Day 1 is first day of study drug administration on day before surgery. Day 2 is day of surgery. Days 3-8 are six postoperative days. Values days 1-8 are from just before next dose of study drug was to be given.
†P=0.7 at day 1 for comparison of mean heart rates and mean arterial pressures.
‡P<0.001 at day 2-8 for comparison of mean heart rates.
§P<0.02 at day 2-8 for comparison of means of mean arterial pressures.

What is already known on this topic

Guidelines recommend perioperative β blockers for patients at cardiac risk who are undergoing major non-cardiac surgery, including those with diabetes

A meta-analysis of randomised trials concluded that perioperative β blockade significantly reduces the perioperative burden of ischaemia but increases the number of episodes of bradycardia and hypotension compared with placebo

What this study adds

Compared with placebo, sustained release metoprolol (100 mg a day for up to eight perioperative days) given to patients with diabetes undergoing non-cardiac surgery does not affect long term mortality and cardiac morbidity

pressure were similar to those seen in previous trials.[2 8] Initiating β blockade with a higher dose in patients with cardiac risks before surgery may jeopardise the patients. In fact, several patients in this trial did not tolerate the full dose. Our intervention lasted longer than most of the trials included in the meta-analysis by Devereaux et al.[8] We experienced fewer primary outcomes than expected during follow-up. Our analyses indicate that we cannot exclude a beneficial effect of 20% or less or a detrimental effect of 40% or less (table 2). Confounding by patients with a β_2 adrenergic receptor genotype[18] is unlikely but possible.

Comparison with related research

Previous trials that showed a positive effect of perioperative β blockers on morbidity and mortality may have overestimated the effect.[8] These trials had several methodological problems.[8 14] Pooling the trials with low bias risk from the meta-analysis of Devereaux et al,[8] the POBBLE trial,[9] and the current trial showed no significant effect of β blockers on 30 day perioperative myocardial infarction (relative risk 0.85, 0.49 to 1.46) or on 30 day mortality (1.15, 0.68 to 1.95). Even when we included a high bias risk trial[2] in the analysis β blockers did not significantly reduce 30 day mortality (0.89, 0.55 to 1.43). Admittedly, the 95% confidence interval leaves room for both benefit and harm. With 2112 patients randomised to perioperative β blockade for non-cardiac surgery we may still observe both beneficial or harmful effects.[19] In a retrospective study of 663 635 patients, Lindenauer et al found that patients with the highest cardiac risk scores might benefit from perioperative β blockade.[20] Patients with the lowest cardiac risk score and diabetes, however, might be harmed by β blockade (odds ratios for death 1.28, 1.10 to 1.50).[20] Our trial shows significant mortality and morbidity in patients with diabetes undergoing non-cardiac surgery, confirming previous observations.[7 11 21] Adjusment for preoperative insulin treatment in the multivariate analysis did not significantly affect the hazard ratio of metoprolol in our trial.

Conclusions

Our results show no significant effect of perioperative metoprolol on cardiac morbidity and mortality in patients with diabetes undergoing major non-cardiac surgery. The evidence is insufficient to recommend perioperative β blockers for patients at risk of cardiac morbidity. It is premature for policy making organisations to use treatment with perioperative β blocker as a measure of hospital quality.[22 23] Therapeutic actions ought to await the perioperative ischemic evaluation study (POISE)[24] and systematic reviews.

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Contributors: The DIPOM Trial Group consists of investigators from public hospitals in the greater Copenhagen area. Principal investigators were PN, KF, JW, RV, JJ, YM, PS, TC, LJ, JJ, GJ, NBF, KB, JBM, TB, and SY. Clinical investigators were MB, ABJ, AM, JR, M-BM, M-LR, PLP, RA, FP, MH, LLN, JE, BD, DZ, AM, BØ, LPW, BK, GP, JW, and PW. NS developed the data management systems and was responsible for data management. PJ and JH carried out statistical analyses. ABJ (coordinating investigator and guarantor), CG, JW, AKE, GJ, and TC formed the steering committee.

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