

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

DIPOM Trial Group

Correspondence to:  
A B Juul  
anne.j@ctu.rh.dk

BMJ 2006;332:1482-5

## Abstract

**Objectives** To evaluate the long term effects of perioperative  $\beta$  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

Perioperative  $\beta$  blockade is recommended in cardiac risk patients undergoing major non-cardiac surgery.<sup>1</sup> The recommendations are based on the results of small trials indicating that patients at cardiac risk should receive perioperative  $\beta$  blockade when they undergo major non-cardiac surgery. A meta-analysis of perioperative  $\beta$  blockers up to April 2003 found insufficient evidence for a reduction of major cardiovascular events.<sup>2</sup> Subsequently, the perioperative  $\beta$  blockade (POBBLE) trial failed to show significant effects of perioperative  $\beta$  blockade on mortality and major cardiovascular events.<sup>3</sup>

The multicentre study group of perioperative ischaemia suggested that diabetes was a significant predictor of postoperative death.<sup>4</sup> Perioperative  $\beta$  blockade in patients with diabetes and additional risk factors for coronary artery disease seemed beneficial.<sup>4</sup> The American College of Cardiology and the American Heart Association assert that patients with diabetes have the same risk as coronary artery disease patients<sup>1</sup> and may benefit from perioperative  $\beta$  blockade.<sup>5,6</sup> We conducted the diabetes postoperative mortality and morbidity (DIPOM) trial to assess metoprolol versus placebo for patients with diabetes undergoing major non-cardiac surgery.<sup>5</sup>

## Methods

The DIPOM trial was a randomised placebo controlled, multicentre trial with central randomisation and blinding of all parties in all phases.<sup>5</sup> Thirteen anaesthesia and surgical centres in nine hospitals in the greater Copenhagen area participated.

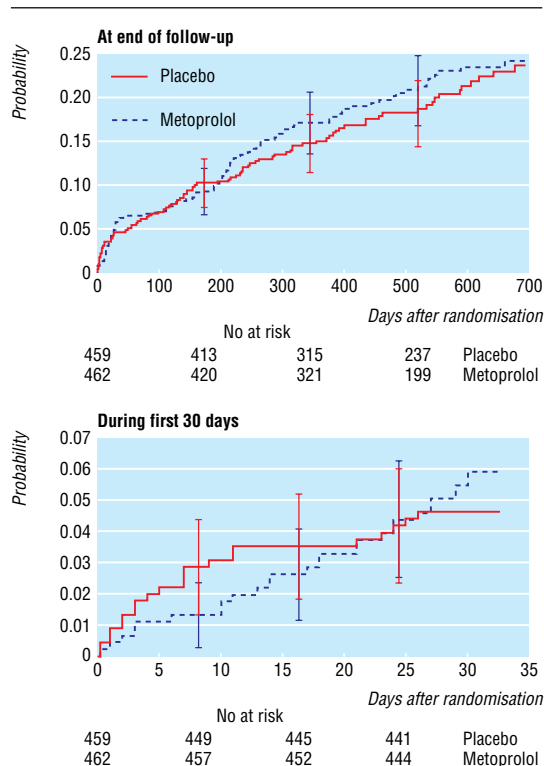
**Recruitment**—Between 1 July 2000 and 1 July 2002 project nurses contacted eligible patients aged  $> 39$  with diabetes who were scheduled for major (that is, expected duration over one hour) non-cardiac surgery. Patients with either insulin or non-insulin dependent diabetes were included. See [bmj.com](http://bmj.com) for exclusion criteria.

**Randomisation**—Randomisation was 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.<sup>5</sup> 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  $\geq 100$  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 administered 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, and the centralised civil register, which records the vital sta-



This is the abridged version: the full version is on [bmj.com](http://bmj.com)



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

tus of all inhabitants in Denmark. In addition, all patients were recalled six months after discharge, and we recorded use of  $\beta$  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. See *bmj.com*. Secondary outcomes were all cause mortality, cardiac mortality, non-cardiac mortality, and cardiac morbidity.<sup>5</sup>

**Statistical analysis**—From our power calculation we aimed to randomise 1000 patients. We compared Kaplan-Meier survival curves. 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 analyses. We also calculated cumulated intensities, time dependent effects, and residuals plots substantiating proportional hazards. We performed a prespecified subgroup analysis of the patients undergoing high risk or intermediate risk surgery having at least one risk factor for coronary artery disease besides diabetes.<sup>4 5</sup>

## 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. Baseline and surgical characteristics were comparable in the two groups. See *bmj.com*. In

addition to diabetes, 496 of the patients (54%) had a history of, or an additional risk factor for, coronary artery disease. The median follow-up was 18 months (range 6-30 months). At six months 720 patients (78%) visited outpatients for follow-up, and 713 patients (77%) underwent electrocardiography. Seven patients in the metoprolol group and five in the placebo group had received  $\beta$  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. The figure 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.

In univariate Cox regression models we found no significant effect of metoprolol compared with placebo and no evidence of significant variation in treatment effect according to centre or baseline characteristics (table 1). Multivariate analysis with all variables used for stratification in the model showed no significant effect of metoprolol. In the subgroup of 496 patients undergoing high risk or intermediate risk surgery having at least one risk factor for coronary artery disease besides diabetes there was no significant effect of metoprolol (1.03, 0.71 to 1.50).

### Mortality and cardiac morbidity

There were no significant differences between the intervention groups in any of the secondary outcomes (table 2).

**Table 1** Intention to treat analysis. Predictors of primary outcome (all cause mortality, acute myocardial infarction, unstable angina, or congestive heart failure) among patients with diabetes undergoing non-cardiac surgery

	Hazard ratio (95% CI)	P value
<b>Univariate analyses</b>		
Metoprolol	1.06 (0.80 to 1.41)	0.66
Age (>65 or $\leq$ 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
<b>Multivariate analyses*</b>		
Metoprolol	1.05 (0.79 to 1.40)	0.53
Age (>65 or $\leq$ 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
<b>Multivariate analyses including preoperative insulin treatment</b>		
Metoprolol	1.07 (0.80 to 1.42)	0.65
Age (>65 or $\leq$ 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 2** Intention to treat analysis. Hazard ratios of effect of perioperative  $\beta$  blockade on secondary outcomes among patients with diabetes undergoing non-cardiac surgery

	Hazard ratio* (95% CI)	P value
<b>Univariate analyses</b>		
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
<b>Multivariate analyses</b>		
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.

### 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. 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%).

### Compliance and haemodynamics

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

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. 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.

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 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  $\beta$  blockers was indicated.

### Discussion

Results of this trial show 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 and analyses of 496 patients undergoing high risk or intermediate risk surgery with additional risk factors for coronary artery disease.

### Strengths and limitations

Blinding is difficult in  $\beta$  blocker trials because of changes in pulse and blood pressure, but the event

committee performed blinded outcome assessment.<sup>5</sup> We used metoprolol in a sustained release formulation. Our trial is comparable with previous trials,<sup>2</sup> but we excluded patients already taking  $\beta$  blockers. A total of 496 of our patients met the inclusion criteria used of Mangano et al,<sup>4</sup> nearly two and a half times the sample size in that trial.

Potential limitations are that we included only patients with diabetes and we might 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.<sup>2</sup> A daily dose of 100 mg metoprolol controlled/extended release may not have ensured sufficient  $\beta$  blockade, but heart rates and reductions in blood pressure were similar to those seen in previous trials.<sup>2</sup> Our intervention lasted longer than most of the trials included in the meta-analysis by Devereaux et al.<sup>2</sup> 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 1). Confounding by patients with a  $\beta_2$  adrenergic receptor genotype<sup>7</sup> is unlikely but possible.

### Comparison with related research

Previous trials that showed a positive effect of perioperative  $\beta$  blockers on morbidity and mortality may have overestimated the effect.<sup>2</sup> These trials had several methodological problems. Pooling the trials with low bias risk from the meta-analysis of Devereaux et al,<sup>2</sup> the POBBLE trial,<sup>3</sup> and our current trial showed no significant effect of  $\beta$  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<sup>8</sup> in the analysis  $\beta$  blockers did not significantly reduce 30 day mortality (0.89, 0.55 to 1.43). The 95% confidence interval leaves room for both benefit and harm. In a retrospective study of 663 635 patients, patients with the highest cardiac risk scores might have benefited from perioperative  $\beta$  blockade.<sup>9</sup> Patients with the lowest cardiac risk score and diabetes, however, might have been harmed by  $\beta$  blockade (odds ratios for death 1.28, 1.10 to 1.50).

### Conclusions

Evidence is insufficient to recommend perioperative  $\beta$  blockers for patients at risk of cardiac morbidity. It is premature for policy making organisations to use treatment with perioperative  $\beta$  blocker as a measure of hospital quality. Therapeutic actions ought to await the perioperative ischemic evaluation study (POISE) and systematic reviews.

We thank the patients who participated in the trial; our colleagues at the surgical departments for excellent collaboration; AstraZeneca for helpful discussions and excellent collaboration during the design and inclusion phase of the DIPOM trial and for supplying metoprolol and placebo; and John Wikstrand and Björn Karlson, AstraZeneca, Sweden, and Birgit Springer, AstraZeneca, Denmark, for helpful comments on an earlier draft. This trial was presented at the 2004 American Heart Association Scientific Sessions as a late breaking clinical trial and published as an abstract in *Circulation* 2005;111:1725. A full list of the DIPOM Trial Group is with the full version of this paper on bmj.com.

Contributors: See bmj.com.

Funding: AstraZeneca, Danish Heart Foundation, Danish Diabetes Foundation, Copenhagen Hospital Corporation's

### What is already known on this topic

Guidelines recommend perioperative  $\beta$  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  $\beta$  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

Research Council, Danish Medical Research Council's "Program for Strengthening Regional Collaboration within Medical Health Research," and Copenhagen Hospital Corporation.

Competing interests: None declared.

Ethical approval: The trial was approved by the local ethics committee (journal No AGF/USS KA 99077ms), the Danish Medicines Agency (journal No AD-MET-0003), and the Danish Data Protection Agency.

- 1 Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for non-cardiac surgery—executive summary. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee to update the 1996 guidelines on perioperative cardiovascular evaluation for noncardiac surgery). *Circulation* 2002;105:1257-67.
- 2 Devereaux PJ, Scott Beattie W, Choi PFL, Badner NH, Guyatt G, Villar JC, et al. How strong is the evidence for the use of perioperative  $\beta$  blockers in non-cardiac surgery? Systematic review and meta-analysis of randomised controlled trials. *BMJ* 2005;331:313-21.
- 3 POBBLE Trial investigators. Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. *J Vasc Surg* 2005;41:602-9.
- 4 Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. *N Engl J Med* 1996;335:1713-20.
- 5 Juul AB, Wetterslev J, Kofoed-Enevoldsen A, Jensen G, Callesen T, Gluud C, The DIPOM Group. The diabetic postoperative mortality and morbidity (DIPOM) trial: rationale and design of a multicenter, randomised, placebo-controlled, clinical trial of metoprolol for patients with diabetes mellitus who are undergoing major noncardiac surgery. *Am Heart J* 2004;147:677-83.
- 6 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.
- 7 Lanfear DE, Jones PG, Marsh S, McLeod HL, Spertus JA. Beta<sub>2</sub>-adrenergic receptor genotype and survival among patients receiving beta-blocker therapy after an acute coronary syndrome. *JAMA* 2005;294:1526-33.
- 8 Poldermans D, Boersma E, Bax JJ. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med* 1999;341:1789-94.
- 9 Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med* 2005;353:349-61.

(Accepted 13 March 2006)

doi 10.1136/bmj.38835.648194.4F

## Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial

Etelka Moll, Patrick M M Bossuyt, Johanna C Korevaar, Cornelis B Lambalk, Fulco van der Veen

### Abstract

**Objective** To compare the effectiveness of clomifene citrate plus metformin and clomifene citrate plus placebo in women with newly diagnosed polycystic ovary syndrome.

**Design** Randomised clinical trial.

**Setting** Multicentre trial in 20 Dutch hospitals.

**Participants** 228 women with polycystic ovary syndrome.

**Interventions** Clomifene citrate plus metformin or clomifene citrate plus placebo.

**Main outcome measure** The primary outcome measure was ovulation. Secondary outcome measures were ongoing pregnancy, spontaneous abortion, and clomifene resistance.

**Results** 111 women were allocated to clomifene citrate plus metformin (metformin group) and 114 women were allocated to clomifene citrate plus placebo (placebo group). The ovulation rate in the metformin group was 64% compared with 72% in the placebo group, a non-significant difference (risk

difference -8%, 95% confidence interval -20% to 4%). There were no significant differences in either rate of ongoing pregnancy (40% v 46%; -6%, -20% to 7%) or rate of spontaneous abortion (12% v 11%; 1%, -7% to 10%). A significantly larger proportion of women in the metformin group discontinued treatment because of side effects (16% v 5%; 11%, 5% to 16%).

**Conclusion** Metformin is not an effective addition to clomifene citrate as the primary method of inducing ovulation in women with polycystic ovary syndrome.

**Trial registration** Current Controlled Trials ISRCTN5590681.

### Introduction

Polycystic ovary syndrome is characterised by any of oligoanovulation, clinical or biochemical hyperandro-

Editorial by  
Al-Inany and  
Johnson

Centre for Reproductive Medicine,  
Department of Obstetrics and Gynaecology,  
Academic Medical Centre, PO Box 22700, 1100 DE, Amsterdam, Netherlands  
Etelka Moll  
registrar obstetrics and gynaecology  
Fulco van der Veen  
professor in reproductive medicine  
continued over

BMJ 2006;332:1485-8



This is the abridged version of an article that was posted on bmj.com on 13 June 2006: <http://bmj.com/cgi/doi/10.1136/bmj.38867.631551.55>