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

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Background Recent trials suggest that perioperative β-blockade reduces the risk of cardiac events in patients with a risk of myocardial ischemia who are undergoing noncardiac surgery. Patients with diabetes mellitus are at a high-risk for postoperative cardiac morbidity and mortality. They may, therefore, benefit from perioperative β-blockade.

Methods The Diabetic Postoperative Mortality and Morbidity (DIPOM) trial is an investigator-initiated and -controlled, centrally randomized, double-blind, placebo-controlled, multicenter trial. We compared the effect of metoprolol with placebo on mortality and cardiovascular morbidity rates in patients with diabetes mellitus who were β-blocker naive, ≥40 years old, and undergoing noncardiac surgery. The study drug was given during hospitalization for a maximum of 7 days beginning the evening before surgery. The primary outcome measure is the composite of all-cause mortality, acute myocardial infarction, unstable angina, or congestive heart failure leading to hospitalization or discovered or aggravated during hospitalization. Follow-up involves re-examination of patients at 6 months and collection of mortality and morbidity data via linkage to public databases. The study was powered on the basis of an estimated 30% 1-year event rate in the placebo arm and a 33% relative risk reduction in the metoprolol arm. The median follow-up period was 18 months.

Results Enrollment started in July 2000 and ended in June 2002. A total of 921 patients were randomized, and 54% of these patients had known cardiac disease, hypertension, or both.

Conclusion The results of this study may have implications for reduction of perioperative and postoperative risk in patients with diabetes mellitus who are undergoing major noncardiac surgery. (Am Heart J 2004;147:677–83.)

The leading causes of death in patients undergoing noncardiac surgery are related to cardiac complications.[1] The incidence of both short- (<30 days) and long-term (≥30 days) cardiac events after noncardiac surgery is substantial and ranges from 11% to 34% in patients who are at high risk,[1–6] defined as patients with multiple cardiac risk factors or with established coronary artery disease (CAD).[1–3] Perioperative myocardial ischemia (PMI) is the most likely culprit of postoperative cardiac morbidity and mortality.[4–11] Further, approximately one third of PMI or myocardial infarctions (MIs) are clinically silent.[7,12] Different medical strategies to reduce PMI have therefore been proposed. Studies using intraoperative calcium channel blockers, alpha-2 agonists, and nitroglycerin have been inconclusive.[13–16] Recent randomized clinical trials examined the effects of perioperative adrenergic β-blockade in major noncardiac surgery on PMI, MI, and all-cause mortality.[17–20] The trials demonstrated that β-blockade might reduce the risk of these outcomes. An observational study of 629,877 patients undergoing

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Table I. Inclusion and exclusion criteria of the DIPOM trial

Inclusion criteria
Known diabetes mellitus (insulin dependent diabetes mellitus or noninsulin dependent diabetes mellitus according to the WHO classification 1985)
Age ≥40 years
Scheduled for major noncardiac surgery (surgery presumed to last more than 1 hour)
Exclusion criteria
Refusal or inability to sign written informed consent before surgery
Ongoing systemic β-blocker treatment
Conditions indicating β-blocker treatment
Condition contraindicating β-blocker treatment
Previous inclusion into the DIPOM trial
Congestive heart failure classified by The New York Heart Association class IV (difficulty in breathing or palpitations occurring at rest, and which worsen by any physical activities)
Pregnancy or breast-feeding
Allergic to contents of metoprolol CR/XL, metoprolol or placebo

WHO, World Health Organization.

cardiac surgery supports these findings.[21] The cardioprotective effects of β-blockers might be related to a reduction in heart rate, wall tension, myocardial contractility, reducing myocardial ischemia, and antiarrhythmic effect. The use of β-blockers to reduce perioperative cardiac risk has been recommended by the American College of Physicians[22] and the American College of Cardiology.[23] However, the randomized trials are small and have some design flaws. Additional research is needed to formulate firm treatment recommendations.

The major cause of morbidity and mortality in patients with diabetes mellitus, 90% of whom have type II diabetes mellitus, is CAD.[24,25] The American Heart Association asserts that patients with diabetes mellitus belong to the same high-risk category as patients with known cardiovascular disease.[26] Diabetes mellitus has been shown to be a major predictor of postoperative death. In the Mangano trial, a subgroup analysis showed that the use of β-blockade in patients with diabetes mellitus was associated with a substantial improvement of prognosis (2-year hazard ratio for death, 0.25; $P = .03$).[17] However, the patients in the Mangano trial were characterized as having a minimum of 2 risk factors for CAD. Thus, whether patients with diabetes mellitus generally will benefit from perioperative treatment with a β-blocking agent remains to be established.

Trial design

The Diabetic Postoperative Mortality and Morbidity (DIPOM) trial is a randomized, double-blind, placebo-controlled, multicenter trial, launched on July 1, 2000. Randomization was completed on June 30, 2002 with 921 patients included. The primary aim of the trial was to assess the long-term effect of 7-day perioperative β-blockade on perioperative and postoperative mortality and cardiac morbidity in patients with diabetes mellitus who were undergoing major noncardiac surgery.

Study organization

Thirteen anesthetic centers in 9 hospitals in the Greater Copenhagen area participated. In each center, ≥2 investigators and 1 study nurse were attached to the DIPOM trial. A list of participating sites and investigators is provided in the acknowledgments and appendix. The Copenhagen Trial Unit coordinated the trial. The trial had a steering committee, a data monitoring and safety committee (DMSC), and an event committee, all of which were independent.

Ethics

The Regional Ethics Committees, the Danish Medicines Agency, and the Danish Data Protection Agency approved the DIPOM trial, registered with ISRCTN5845613. The trial was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines[27] and the Helsinki Declaration.[28] All participating patients signed written informed consent.

Patient recruitment

Patients who met the inclusion criteria and had none of the exclusion criteria were enrolled in the trial (Table I). Major surgery was defined as surgery presumed to last >1 hour. The study nurses and the investigators screened all patients scheduled for elective or emergency surgery daily for eligibility.

Randomization

Patients were centrally randomized by an interactive voice-response system. The randomization sequence was computer generated in blocks of 8. The patients were stratified by using the following characteristics: center, degree of expected perioperative stress on the basis of type of surgery (high- and intermediate-risk surgery or low-risk surgery[23]), history of heart disease (yes or no), age (<65 years or ≥65 years), active malignant disease (yes or no), and sex. Patients were randomized in a 1-to-1 ratio to receive perioperative metoprolol or matching placebo.

Blinding

All study personnel and participants were blinded to the packaging of the study drug, and blinding was maintained through monitoring, follow-up, data management, and assessment of outcomes and data analysis.

Study drug

Metoprolol is a selective adrenergic β-1-receptor blocking agent. It was given orally once a day as metoprolol succinate controlled-release/extended-release tablets (metoprolol CR/XL) or, when oral administration was not feasible, as an intravenous administration of metoprolol tartrate. The metoprolol CR/XL releases metoprolol during approximately 20 hours and maintains effective β-blockade in 24-hour dosing interval.[29]

After the patient was randomized, a test dose of 50 mg of the study drug was given the evening before surgery, whenever possible. When the patient tolerated the test dose, 2 50-mg tablets of the study drug was given approximately 2 hours before induction of anesthesia. The study drug was administered once daily observing these precautions: when the heart rate (HR) was >65 beats/min and the systolic blood pressure (SBP) was ≥100 mm Hg, 100 mg of the study drug was given orally; when the HR was 55 to 65 beats/min and the SBP was ≥100 mm Hg, only 50 mg was given; when the HR was <55 beats/min or the SBP was <100 mm Hg, the study drug was withheld. The study drug was also withheld when any of these conditions occurred: atrioventricular block, acute episodes of bronchospasm requiring treatment, or congestive heart failure requiring treatment. When oral administration was not feasible, the study drug was given intravenously every sixth hour (5 mg metoprolol or placebo) until the patient was able to receive oral medication. During intravenous administration, half the dose was infused in a period of 5 minutes. The patient was then observed for 5 minutes according to HR and SBP criteria aforementioned, and, when these criteria were met, the other half was infused. We gave the study drug until the patient was discharged from the hospital or to a maximum of 7 days.

Outcome measures

The primary outcome measure was the composite outcome of all-cause mortality, acute myocardial infarction (AMI), unstable angina, or congestive heart failure, leading to hospitalization or discovered or aggravated during hospitalization at the end of follow-up (Table II). In addition, the in-hospital and 30-day primary outcome was registered. Secondary outcome measures included those shown in Table II. Plasma concentration of troponin T was determined on the third postoperative day. Measures pertaining to safety include hypoglycemia (blood glucose <2.5 mmol/L), hypotension (systolic blood pressure <65 mm Hg), bradycardia (heart rate <45 beats/min), bronchospasm requiring treatment, and any serious adverse event plus any nonserious adverse event leading to discontinuation of the study drug. The safety variables were recorded during study drug administration.

Table II. Major outcome measures*

Primary outcome measure
All-cause mortality, AMI; unstable angina, or congestive heart failure, leading to hospitalization or discovered or aggravated during hospitalization
Secondary outcome measures
All-cause mortality
Cardiac mortality
Noncardiac mortality
AMI, unstable angina, or congestive heart failure, leading to hospitalization or discovered or aggravated during hospitalization
Cardiac mortality, AMI, unstable angina, or congestive heart failure, leading to hospitalization or discovered or aggravated during hospitalization

AMI, Acute myocardial infarction.
*All outcome measures are assessed from the time of randomization.

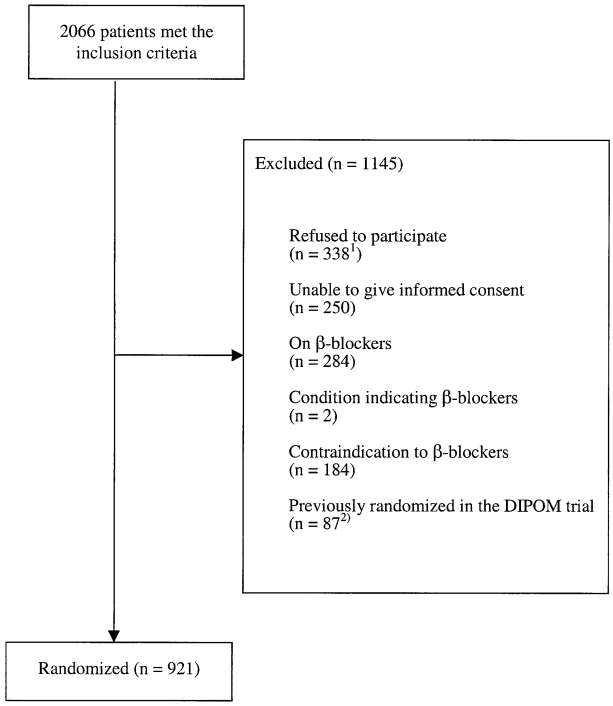
Follow-up and outcome validation

The patients were observed after discharge by linkage to the Danish National Health Register, which contains information about all hospital admissions in Denmark, and the Centralized Civil Register, which records the vital status of all inhabitants in Denmark. Further, each patient was recalled as an outpatient at 6 months. β-blocker use after discharge from hospital was recorded, and an electrocardiogram (ECG) was performed to detect any clinically unrecognized myocardial infarction.[30] The ECGs were classified according to the Minnesota code criteria.[31] All hospital admissions and the MI suspected with ECG were submitted to the Event Committee for evaluation.

Sample size

The expected mortality rate was determined on the basis of a retrospective cohort study of long-term postoperative mortality of patients with diabetes mellitus who were undergoing major noncardiac surgery at KAS Herlev, Copenhagen University Hospital. The all-cause mortality rate was 32% (95% CI, 16%–48%) during the first 15 months postoperatively,[32] which is similar to that of the diabetic population presented in the Mangano trial.[17] In addition, Mangano et al registered an AMI and chronic heart failure proportion of 11 % (95% CI, 8%–17%) at 24 months. We therefore expected a composite outcome incidence of about 43% in the placebo arm during a 15- to 24-month period. In our sample size calculations,[33] the incidence of the composite outcome measure in the placebo group after 12 months was estimated to be 30%, taking into account a shorter follow-up period, a possible reduction because of the inclusion of younger patients, and the wide 95% CIs. The other variables of the sample size calculation were the 2-sided test at $\alpha = .05$; power $(1 - \beta) = 90\%$; effect size considered to be clinically important = 10%. With these figures, the

Figure 1



[1]Five patients after the randomization, but before any medication and surgery. [2]Two patients after erroneous rerandomization.

sample size required 824 patients to detect a difference in the 1-year composite event rates of 20% and 30% in the active versus placebo treated arms. The sample size should be 1274 patients to detect a difference in the 1-year composite event rates of 22% versus 30%. Accordingly, we planned to include approximately 1000 patients.

Interim analyses and stopping rules

The interim analyses were planned to analyze the primary outcome measure and all serious adverse events plus any nonserious adverse event leading to withdrawal of the study drug. Events were presented under the code for the 2 arms of the trial to the DMSC whenever 50 primary outcomes had occurred or as required by the DMSC. The DMSC could advise early interruption of the trial to the Steering Committee if the interim analysis demonstrated:

- conclusive evidence of a benefit in the primary outcome measure of metoprolol, with P value $<.001$ against the placebo arm;
- treatment with metoprolol was associated with an increase in the occurrence of the primary outcome measure, and the 99% CI excluded the possibility of an odds ratio of 1.0 (ie, $P<.01$ against placebo);
- the number and the nature of serious adverse events significantly outweighed any potential beneficial effects.

Until April 2003, the DMSC had not requested a break of the code.

Statistical analysis

All data analysis will be carried out according to a pre-established analysis plan. The composite outcome will be presented as Kaplan-Meyer curves and analyzed with the log-rank test. The outcome measures will be further tested with Cox regression analysis after testing for proportional hazards. A 2-tailed P value $<.05$ is considered to be significant. The influence of the baseline variables on the event rate will be tested with a Cox regression analysis for survival data, including all covariates and all baseline variables with a P value $<.1$ in an univariate analysis. The analysis will include a test for intervention-by-center interaction for homogeneity across centers. Only 2-sided statistical tests will be used. All randomized patients will be included in the intention-to-treat analysis. Patients lost during follow-up will be censored at the time of dropping-out. A per-protocol analysis will be performed, only including patients who received the study drug according to the protocol.

Current status of the trial

From July 2000 to January 2002 (the scheduled period of recruitment), 725 patients were enrolled. The average monthly recruitment for the entire study was 43 patients/month. The DIPOM Steering Committee decided to extend the period of recruitment by 6 months. The last patient was randomized on July 1, 2002. A total of 2066 candidate patients were identified in the 13 centers (Figure 1), and, of these, 921 patients (45%) were randomized (Table III). Baseline characteristics of the randomized patients are listed in Table IV. Of these patients, 485 (53%) had known heart disease, hypertension, or both.

Discussion

Design features

The design of the DIPOM trial differs from that of previous perioperative β-blocker trials. First, it is a large multicenter trial with increased power to measure outcomes after a minimum of 6 months (median, 18 months) of follow-up. In-hospital outcomes and outcomes at 30 days will also be reported. Second, only patients who were β-blocker naive were included, because β-blocker withdrawal may increase the risk of

Table III. Patient recruitment by hospital

Hospital	Patients meeting the inclusions criteria, n	Randomized patients, n (%)*
Herlev	271	126 (45)
Amager	167	70 (42)
Rigshospitalet	361	211 (58)
Frederiksberg	57	45 (79)
Gentofte	390	170 (44)
Glostrup	292	123 (42)
Bispebjerg	300	88 (29)
Hillerød	106	34 (32)
Hvidovre	122	54 (44)
Total	2066	921 (45)

*Number and proportion of randomized patients meeting the inclusion criteria in each hospital.

Table IV. Principal entry characteristics of the 921 patients included in the DIPOM trial

Sex (%)	
Female	382 (41)*
Male	539 (59)
Age (y)	64.9 ± 10.9 (40–94)†
Body mass index (kg/m^2)	27.1 ± 5.3 (15.8–49.8)
History of heart disease (%)	
Congestive heart failure	95 (10)
Atrial fibrillation	73 (8)
Arrhythmia requiring treatment	25 (3)
Angina pectoris	105 (11)
Previous acute myocardial infarction	71 (8)
Previous PTCA/CABG	35 (4)
History of hypertension (%)	
Calcium-channel blockers	151 (16)
Diuretics	48 (5)
Angiotensin-converting enzyme inhibitor	278 (30)
Angiotensin II receptor blocker	57 (6)
Antidiabetic treatment (%)	
Diet alone	57 (6)
Oral hypoglycemic agent	444 (48)
Insulin	369 (40)
Combined insulin and oral hypoglycemic agent	51 (6)
Known duration of diabetes (y)*	11.8 ± 11.7 (0–77)
Diabetic neuropathy (%)	242 (26)
Diabetic retinopathy (%)	178 (19)
Diabetic nephropathy (%)	72 (8)
Current smoker (%)	349 (38)
Former smoker (%)	356 (39)
Excessive alcohol consumption (%)‡	53 (6)
Active malignant disease (%)	176 (19)
Expected high- and intermediate-risk surgery (%)§	563 (61)
Expected low-risk surgery (%)§	362 (39)

PTCA, Percutaneous transluminal coronary angioplasty; *CABG,* coronary artery bypass graft.
*Numbers in parentheses are percent of randomized patients.
†Means ± SD. Ranges are shown in parentheses.
‡More than 60 grams ethanol per day.
§Defined according to the ACC/AHA guideline update (Eagle, Berger, et al. 2002 1470/id).

postoperative cardiovascular morbidity and mortality.[34] Third, patients with diabetes mellitus are easily identified and very likely to benefit from a perioperative cardioprotective regime because they often have more extensive CAD, are at risk for autonomic dysfunction, and have a higher postoperative mortality and morbidity rate than patients without diabetes mellitus. Fourth, blinding is rather difficult to maintain for the clinical effects of β-blockers,[35,36] and special efforts were carried out to maintain blinding through monitoring, follow-up, data management, assessment of outcomes, and data analysis. Fifth, the existence of both a national system of unique person identification and a national register of data on all somatic hospital admissions in a population of relative demographic stability enabled the DIPOM trial to provide reliable, unbiased, and comprehensive follow-up data.

One study[17] demonstrated that perioperative β-blockade reduces the risk of late cardiac events. Consequently, an extended follow-up period was included in our trial. The mechanism of the sustained effect may be that perioperative ischemia and MI could lead to an increased occurrence of late arrhythmia and heart failure.

Of the 2066 eligible patients, only 284 were receiving β-blockers. β-blockers are underprescribed to patients with diabetes mellitus after MI and patients with diabetes mellitus and hypertension, possibly because of the risk of adverse surrogate events (increased insulin resistance and hyperglycemia, prolongation of insulin-induced hypoglycemia, and lipid disturbances).[37] Instead angiotensin-converting enzyme inhibitors are prescribed as first-line therapy in patients with diabetes mellitus and hypertension because of their renoprotective effects.[38]

The Danish National Health Register has collected nationwide data on all somatic hospital admissions since 1977, and on all outpatients and emergency patients since 1995. The validity of the administrative data (data concerning admission, identification, and discharge) is 97% to 98%.[39] The validity of data on treatment and diagnosis is, however, only 66% to 88%, depending on diagnosis.[39] Thus, copies of all patient records of admissions identified after randomization were collected and evaluated by the Event Committee. The Centralized Civil Register is a national system of unique person identification and is used for achieving information of deaths among the study population. This register has existed in Denmark for >35 years, is almost 100% valid, and contains personal data covering approximately 7.7 million persons. Follow-up on death is therefore 100% complete. The Event Committee also assessed death certificates.

Previous studies have shown that industry-funded randomized trials are significantly associated with conclusions favoring the experimental drug.[40–42] The DIPOM trial has received nonrestricted grants from nonprofit and for-profit organizations and is investigator initiated and controlled. This organization should secure unbiased assessment of the effect of metoprolol.

Conclusion

DIPOM is, according to our knowledge, the first trial examining the effects of perioperative β-blocker administration on outcomes, including mortality and cardiac morbidity, in patients with diabetes mellitus. The results of the study may have implications for therapeutic measures in a growing and threatened patient population. If the trial shows that perioperative β-blockade reduces postoperative mortality and morbidity rates in patients with diabetes mellitus, this will be an important advantage to these high-risk patients.

We thank the patients who participated in the DIPOM trial, the surgeons at the surgical departments for their excellent collaboration, AstraZeneca for helpful discussions and excellent collaboration during the design and inclusion phase of the DIPOM trial and for free supply of the study drug, and AstraZeneca, the Danish Heart Foundation, the Danish Diabetes Foundation, the Copenhagen Hospital Corporation's Research Council, and the Danish Medical Research Council's "Program for Strengthening Regional Collaboration within Medical Health Research" for nonrestricted economical support.

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Appendix

The DIPOM group

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