Available online at www.sciencedirect.com
ScienceDirect
Contemporary Clinical Trials 28 (2007) 540–547
Contemporary Clinical Trials
www.elsevier.com/locate/conclintrial

The Best Bypass Surgery Trial: Rationale and design of a randomized clinical trial with blinded outcome assessment of conventional versus off-pump coronary artery bypass grafting ☆

Christian H. Møller [a,d,*], Birte Østergaard Jensen [a], Christian Gluud [d], Mario J. Perko [a], Jens T. Lund [a], Lars Willy Andersen [b], Jan Kyst Madsen [c], Pia Hughes [a,d,✠], Daniel A. Steinbrüchel [a]

[a] *Department of Cardiothoracic Surgery, The Heart Center, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark*
[b] *Department of Anesthesiology, The Heart Center, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark*
[c] *Department of Cardiology, The Heart Center, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark*
[d] *Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark*

Received 16 January 2006; accepted 12 November 2006

Abstract

Background: Recent trials suggest that off-pump coronary artery bypass grafting (OPCAB) reduces the risk of mortality and morbidity compared with conventional coronary artery bypass grafting (CCAB) using cardiopulmonary bypass. Patients with a moderate- to high-risk of complications after CCAB may have additional benefit from OPCAB.
Methods: The Best Bypass Surgery Trial is a randomized, single center trial comparing the effects of OPCAB versus CCAB. The inclusion criteria are 3 vessel coronary heart disease affecting one of the marginal arteries, age >54 years, and EuroSCORE ≥5. The primary composite outcome measure consists of all-cause mortality, myocardial infarction, stroke, cardiac arrest, cardiogenic shock, and cardiac revascularization procedure. Follow up involves collection of data of mortality and morbidity via linkage to public registers, quality of life assessment at 3 and 12 months postoperatively and angiographic control at 12 months. The sample size of 330 patients was based on an estimated 75% one-year event free rate of the primary outcome measure in the OPCAB arm and 60% in the control arm with alpha = .05 and beta = .20. Accordingly, the trial will be able to detect an absolute risk reduction of 15% or a relative risk reduction of 37.5%. The median follow-up time is scheduled to 3 years.
Results: Enrollment started in April 2002 and ended March 2006.
Conclusion: The results may have implications on the treatment modality of moderate- to high-risk patients scheduled for coronary artery bypass grafting.

Keywords: Coronary artery bypass surgery; Off-pump coronary artery bypass, OPCAB; Coronary artery bypass grafting, CABG; Randomized clinical trial design; Moderate- and high-risk patients

☆ Supporting grants were received from The Danish Heart Foundation, The Danish Medical Research Council and The Rigshopitalet Research Council.
* Corresponding author. Department of Cardiothoracic Surgery RT 2152, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. Tel.: +45 35457154, +45 35458740 (Dect); fax: +45 35452548.
E-mail address: christian.01.moeller@rh.hosp.dk (C.H. Møller).
✠ Deceased.

1551-7144/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.cct.2006.11.002

1. Introduction

Patients with stenosed or occluded coronary arteries can be treated with coronary artery bypass grafting (CABG). CABG may relieve pain and prolong life [1]. The operation can be performed in different ways. Two of the most common operative techniques are: conventional coronary artery bypass grafting (CCAB), with cardiopulmonary bypass and a heart- and lung machine, aortic cross clamping, and cardioplegic arrest, or off-pump coronary artery bypass grafting (OPCAB), coronary bypass on beating heart without cardiopulmonary bypass, aortic cross clamping, and cardioplegic arrest.

CCAB is associated with cardiac, pulmonary, renal, neurological, and coagulation related complications [1]. To avoid some of these complications, the OPCAB procedure has gained increased interest since the mid 1990s. A number of observational quality-control studies have focused on learning curves, graft patency, feasibility, technical aspects, and patient safety. These studies suggest, that the OPCAB procedure can be performed in selected and possibly also unselected patients with the same mortality as CCAB [2–6]. Further, some studies indicate that the OPCAB procedure may offer benefits especially in patients with a moderate- to high-risk of complications [7]. OPCAB is superior to CCAB in a few small randomized trials with respect to postoperative bleeding and inflammatory response [8–11]. A recent meta-analysis, including 3369 patients, states that randomized trials of the two different surgical procedures are still lacking for patients with 3-vessel disease focusing on clinically relevant long-term outcomes [12].

In the present article we describe the Best Bypass Surgery (BBS) Trial, a randomized trial taking advantage of public registers to facilitate the conduct of a surgical trial with blinded outcome assessment.

2. Objectives

The aims of the BBS Trial are to compare OPCAB versus CCAB with respect to peri and postoperative mortality, morbidity, length of stay in hospital, quality of life, and graft patency in patients with 3-vessel disease and a predicted moderate- to high-risk of complications according to EuroSCORE [13].

3. Rationale

CABG plays an important role in the treatment of patients with ischemic heart disease. Complications seen in conjunction with CCAB can as well be seen in OPCAB patients. Due to the cardiopulmonary bypass of CCAB a number of specific complications have been described in this procedure (i.e., reperfusion damages, cardioplegic damages, emboli after cannulation of the aorta, disturbances of coagulation, and inflammatory response). Known adverse events of the OPCAB procedure, which may occur more often compared with the CCAB procedure might include per procedural hemodynamic instability [14] and risk of postoperative reduced graft patency [15]. The potential risks and benefits of CCAB and OPCAB procedures for patients with 3-vessel disease are summarized in Table 1.

Table 1
Summary of the potential risks and benefits with CCAB and OPCAB procedures for patients with 3-vessel disease

Outcome measures	Incidence after CCAB	Reference	Incidence after OPCAB	Reference
Mortality	According to EuroSCORE	[13]	According to EuroSCORE	[7,13]
Neurological events (type 1)	4%	[27]	Unknown	No data
Neurological events (type 2)	23–90%	[28,29]	0–?%	[28]
Low cardiac output	9%	[30]	Unknown	No data
Perioperative AMI	3%	[30,31]	Unknown	No data
Atrial fibrillation	28–39%	[32–35]	8–18%	[33]
Renal dysfunction	8%	[36]	Unknown	No data
Re-operation	7%	Local data	4%	Local data
Use of homologous blood transfusion	69%	Local data, [37]	57%	Local data
Freedom for angina at 1 year	83%	[38]	Unknown	No data

AMI: Acute myocardial infarction.
Neurological events type 1: Focal stoke, transient ischemic attack, and fatal stroke or hemorrhage.
Neurological events type 2: Global/diffuse brain damage, with disorientation or immediate (and usually reversible) intellectual decline.
Local data: Unpublished observations.

OPCAB may reduce postoperative cardiac, pulmonary, renal, neurological, coagulation related, and infectious complications especially in the group of patients with a moderate- and high-risk mortality according to EuroSCORE [13]. This might lead to a shorter length of stay at the hospital and a shorter rehabilitation period. However, evidence for these statements is poor and mainly based on observational studies, which have a lower ranking in the evidence hierarchy [16].

4. Trial design

BBS is a randomized, observer-blinded, single center, clinical trial, launched April 2002. The primary aim is to assess the long-term effect of OPCAB versus CCAB on peri and postoperative mortality and morbidity in patients with 3-vessel disease and a EuroSCORE within moderate- to high-risk i.e., EuroSCORE ≥ 5 [13].

4.1. Trial organization

The inclusion, operations, and postoperative treatment were carried out at the Department of Cardiothoracic Surgery, Rigshospitalet, Copenhagen University Hospital. Three surgeons conducted all operations. Experience of the three surgeons to the two operative techniques was high. The Copenhagen Trial Unit (CTU), Center for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital carried out protocol and case record form development, randomization, and coordinates follow up. The trial has a Steering Committee, an Event Adjudication Committee, and an Independent Data Monitoring and Safety Committee. Funding was raised from public funds in order to keep our independence [17]. No investigator is profiting from the trial.

4.2. Ethics

The Danish Regional Committee on Biomedical Research Ethics (journal number 01-007/02) and the Danish Data Protection Agency (journal number 2002-41-1968) approved the BBS Trial (internal registration number 2001-11-DP-83-RKF-22). The trial is registered on *ClinicalTrials.gov* (NCT00120991) and is conducted in accordance with the International Conference on Harmonization on Good Clinical Practice Guidelines and The Helsinki Declaration. All participants signed written informed consent forms before randomization.

4.3. Trial population and patient recruitment

Patients who met the inclusion criteria and none of the exclusion criteria (Table 2) were consecutively enrolled in the trial. The investigators screened daily for eligibility of all patients scheduled for elective or sub-acute CABG.

4.4. Randomization

Patients were centrally randomized by a press-button voice response telephone. They were randomized in blocks, 1:1, stratifying for sex, age (55–65 years or more than 65 years), diabetes mellitus (yes or no), and EuroSCORE (5–7;8–10;11–13;14–16) [13].

Table 2
Eligibility criteria

Inclusion criteria	Exclusion criteria
1. Known ischemic 3-vessel heart disease affecting one of the marginal coronary arteries 2. Patients >54 y 3. Scheduled for elective or subacute coronary artery bypass grafting 4. EuroSCORE ≥ 5 5. The patient has signed written informed consent form before randomization and surgery.	1. Previous heart surgery 2. Ejection fraction below 30% 3. Unstable preoperative condition, i.e., continuous infusion of inotropics on the day of the operation 4. Patient unable to give informed consent.

Table 3
Outcome measures

The primary outcome measure is a composite outcome measure defined as the time to
- All-cause mortality
- Acute myocardial infarction
- Cardiac arrest with successful resuscitation
- Low cardiac output syndrome/cardiogenic shock
- Stroke
- Renewed cardiac revascularization procedure.

The secondary outcome measures
- Hyper-dynamic shock
- Atrial fibrillation during index admission
- Need for pacing more than 24 h
- Renal complications, i.e., serum creatinine more than 200 μmol/l
- Re-operation during index admission
- Pneumonia
- Respiratory insufficiency requiring intubation more than 24 h
- Additional serious adverse events (e.g., gastritic ulcer, lung embolus)
- Duration of stay in intensive care unit
- Duration of stay in the hospital
- Quality of life after 3 and 12 months
- Graft patency at one year postoperatively defined by coronary angiography.

The tertiary outcome measures
- Cardiovascular mortality and morbidity
  - Cardiovascular mortality
  - Acute myocardial infarction
  - Cardiac arrest with successful resuscitation
  - Low cardiac output syndrome/cardiogenic shock
- Stroke
- Renewed cardiac revascularization.

4.5. Blinding

The BBS Trial is conducted without blinding after randomization, which leaves ample room for bias [18–20]. Therefore, the primary, secondary, and tertiary outcome measures will be assessed by the Event Adjudication Committee, which is blinded to the intervention performed. The blinding consists in removal of all information related to the type of intervention (OPCAB/CCAB) from the collected patient records and death certificates. Potential demasking of the Event Adjudication Committee will be checked at completion of each outcome assessment.

5. Outcome measures

The primary outcome measure is a composite defined as the time to death, cardiac complications, or cerebral complications. The primary, secondary, and tertiary outcome measures are shown in Table 3. As a sub-study postoperative cognitive function will be evaluated in the first 120 randomized patients.

6. Follow up and outcome validation

All patients are followed after discharge by searching The Danish National Patient Registry and The Danish Civil Registration System. The Danish National Patient Registry contains information about all somatic hospital admissions and The Danish Civil Registration System records the vital status of all inhabitants in Denmark.

A copy of all patient records for each hospital admission as well as all death certificates is obtained and stored. Including the index hospitalization this number is expected to be about 1000–1200 records. After the patient record has been blinded regarding the surgical intervention, the record is presented to two randomly selected adjudicators from the

Event Adjudication Committee. These adjudicators assess the patient record for outcome measures. Their assessments are recorded on case record forms. In case of discrepancy between the assessments of the two adjudicators, the case record forms together with the patient record and death certificate are sent to the third adjudicator who will decide the most likely assessment or request for a reassessment. The data are double entered into an outcome measure database.

Furthermore, each patient is contacted at 3 and 12 months after surgery to fill out a quality of life form [21]. Due to economical constraints, 70 patients will undergo a renewed angiography after 12 months. A random sample of the patients (10% corresponding to about 33 patients) will have their data monitored with source data verification by an impartial monitor.

7. Statistical analysis

7.1. Sample size

The BBS Trial is planned as a superiority trial, aiming to demonstrate that one intervention is better than the other.

Since the primary outcome measure is a binary response, sample size may be estimated using a Chi-square approach with one degree of freedom and a two-sided test and an equal number of patients in each treatment group.

Based on the estimated frequency of complications in the two treatment groups and a chosen power of $1-\beta=80\%$ and $2\alpha=5\%$, an absolute risk reduction of 15% or a relative risk reduction of 37.5% if the proportion of primary outcome measure in the CCAB group is about 40% compared with 25% in the OPCAB group, it has been decided that it is realistic to include 330 patients in the BBS Trial, resulting in approximately 165 patients in each arm.

The sample size calculation for the sub-study of cognitive dysfunction is based on the assumption of a 30% reduction in cognitive dysfunction in the OPCAB group compared with the CCAB group and an expected dropout of 20% ($\alpha=.05$, $\beta=.2$).

7.2. Interim analysis and stopping rules

An interim analysis is planned after the occurrence of the first 100 primary outcomes. The interim analysis is based on the same approach as the final analysis. The Independent Data Monitoring and Safety Committee (IDMSC) conducts the interim analysis. The IDMSC will be presented with all information about patients that suffer from death or cardiac, pulmonary, cerebral, renal, or coagulation related complications. The IDMSC will get the data under code (a,b) and accordingly be unaware of the group to which the patients is randomized. The purpose of the interim analysis is to monitor the efficacy and safety of the trial interventions. The IDMSC may advise early interruption of the trial to the Steering Committee if the interim analysis demonstrate the following, estimated by univariate Cox regression analysis (by intervention):

- Conclusive evidence of a benefit regarding the primary outcome measure of OPCAB with $p<.001$ against CCAB.
- If OPCAB is associated with an increase in the occurrence of the primary outcome measure and the 99% confidence interval excludes the possibility of a hazard ratio of 1.0, i.e., $p<.01$ against CCAB.
- If OPCAB is associated with an increase of the most severe outcomes of the primary composite outcomes measure, i.e., death, acute myocardial infarction or stroke, and the 99% confidence interval excludes the possibility of a hazard ratio of 1.0, i.e., $p<.01$ against CCAB.

The IDMSC will be informed about all serious adverse events occurring in the two intervention arms. Serious adverse events are defined as an untoward medical occurrence that results in death, is life-threatening, results in persistent or significant disability, or any important medical event which may jeopardize the patient or require intervention to prevent it (ICH-GCP1997) [22].

The secondary purpose of the interim analysis is to enable the IDMSC to advise the Steering Committee to continue patient inclusion if data from the interim analysis suggest that an extension of the trial is needed to demonstrate an effect of the intervention. This advice must be based on conditional power calculation [23]. Furthermore, the trial should be stopped if any new information, that may become available during the trial, necessitates early termination of the trial.

OPCAB patients may be converted to CCAB due to hemodynamic instability and CCAB patients may be converted to OPCAB due to heavily calcified aorta. These patients' data are registered and followed like the remaining patients to allow intention-to-treat analysis.

7.3. Analysis of outcome measure

The purpose of the statistical analysis is to evaluate possible differences in clinical outcome between CCAB and OPCAB.

The time to occurrence of the composite primary outcome measure will be analyzed using a log-rank test and Cox's proportional hazard analysis. Covariates chosen before starting data analyses are type of intervention, sex, age, diabetes mellitus, and EuroSCORE. Possible interactions and sub-group effects will be determined according to statistically significant interactions between covariates in the Cox-model at the 5% level. Patients, lost during follow up, will be censored at the time of dropping-out. Number of patients having acquired a primary outcome measure in each group during the observation period will be compared and analyzed with a Chi-square test.

The length of stay in the intensive care unit and in hospital will be analyzed with an unpaired Student *t*-test if data are normally distributed or Mann–Whitney test if not. The analyses of the questions on quality of life are performed according to rules outlined by Ware et al. [21]. All categorical data will be analyzed with Chi-square test or Fishers exact test as appropriate.

8. Results

From April 2002 to December 2006 341 patients have been randomized. Recruitment of patients ended March 2006. Average monthly recruitment for the trial was eight patients.

9. Discussion

The design of the BBS Trial differs from several previous trials investigating OPCAB versus CCAB. First, the trial is including patients with a moderate- to high-risk of 30-days mortality. Second, the existence of both a national register of unique person identification and a national register of data on all somatic hospital admissions in a population of relative demographic stability enable the BBS Trial to provide reliable, comprehensive, and unbiased follow-up data. Third, the blinded Event Adjudication Committee is intended to give an unbiased and objective judgment of the results of surgery. Fourth, the IDMSC ensures a close monitoring of the trial and is able to recommend early termination if unacceptable differences occur. Fifth, the statistical analysis will be performed without unmasking the treatment arm.

We have taken several initiatives in order to minimize bias in data collection and assessment. The consecutive enrollment and the central randomization ensure random allocation and allocation concealment, which minimizes selection bias [18–20,24]. It is of course not possible to blind the operating surgeons. Unblinded trials are at risk of introducing performance, collateral intervention, attrition, and assessment bias [19,20]. Performance and collateral intervention bias cannot be eliminated in the BBS Trial. However, the blinded adjudication may eliminate the risks of assessment bias. Outcome reporting bias has been avoided by publication of the trial protocol prior to analyzing and reporting the data [25].

The Danish National Patient Registry has collected nation wide 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 97–98%. The validity of data concerning treatment and diagnosis is, however, only 66–89% depending on diagnosis [26]. Therefore, copies of all patient records of admissions after randomization will be collected and adjudicated.

The Danish Civil Registration System is a national system of unique person identification and is used, among other things, for achieving information of deaths among the study population. This register has existed in Denmark for more than 37 years and is almost 100% valid. Follow–up on death will therefore be complete.

Data from previous trials have been included in a meta-analysis of 3369 patients randomized to OPCAB versus CCAB [12]. No difference between the groups was found in mortality, stroke, and acute myocardial infarction. The majority of the patients included in the trials are not from the population, which our trial is focusing on. The meta-analysis concludes that data are lacking with respect to long-term clinical, economic, cognitive function, and quality of life outcome associated with the two different surgical techniques. Additionally comparison of the graft patency has not yet been adequately addressed. Finally, trials investigating the older population, females, and high-risk patients are still needed.

10. Conclusion

The BBS Trial is to our knowledge the first trial to compare OPCAB versus CCAB with respect to peri and postoperative mortality, morbidity, length of stay in hospital, quality of life, graft patency, and cognitive function in moderate- to high-risk patients with 3-vessel disease. Further, it is the first trial using blinded long-term outcome assessment, which hopefully enables an unbiased assessment of the benefits and harms of the two interventions. The result of the trial may have implications for which surgical option patients might be offered in the future.

Steering Committee
Steinbrüchel DA, DMSc, Møller CH, MD, Gluud C, DMSc, Andersen LW, DMSc, Madsen JK, DMSc.

The Event Adjudication Committee
Hasenkam JM, DMSc, Hildebrandt P, DMSc, Wetterslev J, PhD.

The Independent Data Monitoring and Safety Committee
Hilden J, MD, Thygesen K, DMSc.

Acknowledgments

This paper is dedicated to the memory of Pia Hughes, who has put a great work in this trial, but has unfortunately passed away. We acknowledge The Danish Heart Foundation, The Danish Medical Research Council, The Copenhagen Hospital Corporation's Medical Research Council and The Rigshospitalet Research Council for economical support. We thank the patients who participate in the BBS Trial and the cardiologists in the Cardiac Catheterization Laboratory for excellent collaboration.

References

[1] Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). Circulation 2004;110:e340–437.
[2] Bull DA, Neumayer LA, Stringham JC, et al. Coronary artery bypass grafting with cardiopulmonary bypass versus off-pump cardiopulmonary bypass grafting: does eliminating the pump reduce morbidity and cost? Ann Thorac Surg 2001;71:170–3.
[3] Czerny M, Baumer H, Kilo J, et al. Complete revascularization in coronary artery bypass grafting with and without cardiopulmonary bypass. Ann Thorac Surg 2001;71:165–9.
[4] Wan S, Izzat MB, Lee TW, et al. Avoiding cardiopulmonary bypass in multivessel CABG reduces cytokine response and myocardial injury. Ann Thorac Surg 1999;68:52–6.
[5] Cartier R, Blain R. Off-pump revascularization of the circumflex artery: technical aspect and short-term results. Ann Thorac Surg 1999;68:94–9.
[6] Calafiore AM, Teodori G, Di Giammarco G, et al. Multiple arterial conduits without cardiopulmonary bypass: early angiographic results. Ann Thorac Surg 1999;67:450–6.
[7] Sergeant P, de Worm E, Meyns B, Wouters P. The challenge of departmental quality control in the reengineering towards off-pump coronary artery bypass grafting. Eur J Cardiothorac Surg 2001;20:538–43.
[8] Ascione R, Lloyd CT, Gomes WJ, et al. Beating versus arrested heart revascularization: evaluation of myocardial function in a prospective randomized study. Eur J Cardiothorac Surg 1999;15:685–90.
[9] Ascione R, Lloyd CT, Underwood MJ, Gomes WJ, Angelini GD. On-pump versus off-pump coronary revascularization: evaluation of renal function. Ann Thorac Surg 1999;68:493–8.
[10] Ascione R, Lloyd CT, Underwood MJ, et al. Inflammatory response after coronary revascularization with or without cardiopulmonary bypass. Ann Thorac Surg 2000;69:1198–204.
[11] Diegeler A, Doll N, Rauch T, et al. Humoral immune response during coronary artery bypass grafting: A comparison of limited approach, "off-pump" technique, and conventional cardiopulmonary bypass. Circulation 2000;102:III95–III100.
[12] Cheng DC, Bainbridge D, Martin JE, Novick RJ. Does off-pump coronary artery bypass reduce mortality, morbidity, and resource utilization when compared with conventional coronary artery bypass? A meta-analysis of randomized trials. Anesthesiology 2005;102:188–203.
[13] Nashef SA, Roques F, Michel P, et al. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16:9–13.
[14] Legare JF, Buth KJ, Hirsch GM. Conversion to on pump from OPCAB is associated with increased mortality: results from a randomized controlled trial. Eur J Cardiothorac Surg 2005;27:296–301.
[15] Khan NE, De Souza A, Mister R, et al. A randomized comparison of off-pump and on-pump multivessel coronary-artery bypass surgery. N Engl J Med 2004;350:21–8.

[16] Guyatt GH, Haynes RB, Jaeschke RZ, et al. Users' guides to the medical literature: XXV. Evidence-based medicine: principles for applying the users' guides to patient care. Evidence-based medicine working group. JAMA 2000;284:1290–6.
[17] Als-Nielsen B, Chen W, Gluud C, Kjaergard LL. Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events? JAMA 2003;290:921–8.
[18] Gluud C. Trials and errors in clinical research. Lancet 1999;354:SIV59 [Suppl].
[19] Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;273:408–12.
[20] Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Ann Intern Med 2001;135:982–9.
[21] Ware Jr JE, Kosinski M, Gandek B, et al. The factor structure of the SF-36 health survey in 10 countries: results from the IQOLA Project. International quality of life assessment. J Clin Epidemiol 1998;51:1159–65.
[22] ICH-GCP. International Conference on Harmonisation Expert Working Group. Code of Federal Regulation and International Conference on Harmonisation Guidelines, vol. 1. Pennsylvania: Parexel/Barnet; 1997.
[23] Whitley E, Ball J. Statistics review 4: sample size calculations. Crit Care 2002;6:335–41.
[24] Altman DG, Schulz KF. Statistics notes: Concealing treatment allocation in randomised trials. BMJ 2001;323:446–7.
[25] DeAngelis CD, Drazen JM, Frizelle FA, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. JAMA 2004;292:1363–4.
[26] Nickelsen TN. Data validity and coverage in the Danish National Health Registry. A literature review. Ugeskr Laeger 2001;164:33–7.
[27] Roach GW, Kanchuger M, Mangano CM, et al. Adverse cerebral outcomes after coronary bypass surgery. Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation Investigators. N Engl J Med 1996;335:1857–63.
[28] Diegeler A, Hirsch R, Schneider F, et al. Neuromonitoring and neurocognitive outcome in off-pump versus conventional coronary bypass operation. Ann Thorac Surg 2000;69:1162–6.
[29] van Dijk D, Keizer AM, Diephuis JC, et al. Neurocognitive dysfunction after coronary artery bypass surgery: a systematic review. J Thorac Cardiovasc Surg 2000;120:632–9.
[30] Rao V, Ivanov J, Weisel RD, et al. Predictors of low cardiac output syndrome after coronary artery bypass. J Thorac Cardiovasc Surg 1996;112:38–51.
[31] Alderman EL, Levy JH, Rich JB. Analyses of coronary graft patency after aprotinin use: results from the International Multicenter Aprotinin Graft Patency Experience (IMAGE) trial. J Thorac Cardiovasc Surg 1998;116:716–30.
[32] Almassi GH, Schowalter T, Nicolosi AC, et al. Atrial fibrillation after cardiac surgery: a major morbid event? Ann Surg 1997;226:501–11.
[33] Ascione R, Caputo M, Calori G, et al. Predictors of atrial fibrillation after conventional and beating heart coronary surgery: A prospective, randomized study. Circulation 2000;102:1530–5.
[34] Cooklin M, Gold MR. Implications and treatment of atrial fibrillation after cardiothoracic surgery. Curr Opin Cardiol 1998;13:20–7.
[35] Svedjeholm R, Hakanson E. Predictors of atrial fibrillation in patients undergoing surgery for ischemic heart disease. Scand Cardiovasc J 2000;34:516–21.
[36] Mangano CM, Diamondstone LS, Ramsay JG, et al. Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes, and hospital resource utilization. The Multicenter Study of Perioperative Ischemia Research Group. Ann Intern Med 1998;128:194–203.
[37] Tobe CE, Vocelka C, Sepulvada R, et al. Infusion of autologous platelet rich plasma does not reduce blood loss and product use after coronary artery bypass. A prospective, randomized, blinded study. J Thorac Cardiovasc Surg 1993;105:1007–13.
[38] Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA Guidelines for Coronary Artery Bypass Graft Surgery: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee to revise the 1991 Guidelines for Coronary Artery Bypass Graft Surgery). American College of Cardiology/American Heart Association. J Am Coll Cardiol 1999;34:1262–347.