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Jarmo Lahtinen

PREDICTORS OF IMMEDIATE OUTCOME AFTER CORONARY ARTERY BYPASS SURGERY

FACULTY OF MEDICINE,
DEPARTMENT OF SURGERY,
DIVISION OF CARDIO-THORACIC AND VASCULAR SURGERY,
UNIVERSITY OF OULU

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Abstract

The identification of risk factors for major adverse events after coronary artery bypass surgery is of main importance as it allows outcome prediction, facilitates preoperative patient selection and improves the quality of care. In the present clinical studies we have evaluated the impact of preoperative angiographic severity of a coronary artery disease and preoperative C-reactive protein (CRP) on the immediate outcome after coronary artery bypass surgery. We have reviewed the results of off-pump (OPCAB) versus conventional on-pump coronary artery bypass surgery (CCAB) in high risk patients. We have evaluated the impact of postoperative pulmonary artery blood temperature on the immediate outcome as well. In addition, we have investigated the incidence, timing and outcome of an atrial fibrillation (AF) related stroke after surgery.

The multivariate analysis showed that among 2233 patients, the overall coronary angiographic score was predictive of postoperative death ($p = 0.03$; OR 1.027, 95% CI: 1.003–1.052) and of a low cardiac output syndrome ($p = 0.04$; OR 1.172, 95% CI: 1.010–1.218). The poor status of the proximal segment of the left circumflex coronary artery, the diagonal branches and the left obtuse marginal artery were most closely associated with adverse postoperative outcome.

Patients (114/764) with a preoperative serum concentration of CRP≥1.0 mg/dL had a higher risk of overall postoperative death (5.3% vs. 1.1%, $p = 0.001$), cardiac death (4.4% vs. 0.8%, $p = 0.002$), a low cardiac output syndrome (8.8% vs. 3.7%, $p = 0.01$).

Among 179 high risk patients with an additive EuroSCORE6, the 30-day postoperative death and stroke rates were 7.5% and 6.0% in the OPCAB group, and 5.4% ($p = 0.75$) and 8.0% ($p = 0.77$) in the CCAB group, respectively. No significant differences were observed in other major outcome end-points between these non-randomised groups either.

High pulmonary artery blood temperature on admission to the ICU among 1639 patients was significantly associated with an increased risk of overall postoperative death ($p = 0.002$), cardiac death ($p = 0.03$), and a low cardiac output syndrome ($p < 0.0001$), and was significantly correlated with prolonged length of the ICU stay ($r = 0.095$; $p < 0.0001$), and postoperative bleeding ($\rho = -0.091$; $p = 0.001$).

Among 2,630 patients who underwent coronary artery bypass grafting (CABG), 52 (2.0%) experienced a postoperative stroke. Twelve out of these 52 patients (23.1%) died postoperatively. The ischemic cerebral event occurred after a mean of 3.7 days (0–33). In 19 patients (36.5%), atrial fibrillation preceded the occurrence of neurological complication.

The angiographic severity of the coronary artery disease and the preoperative serum concentration of CRP predict postoperative outcome after a CABG operation. OPCAB can be performed safely in high-risk patients with results as satisfactory as those achieved with CCAB. CABG patients with a high pulmonary artery blood temperature on admission to the ICU seem to have a higher risk of postoperative adverse events. Atrial fibrillation occurring after coronary artery bypass grafting is a major determinant of a postoperative stroke.

Keywords: atrial fibrillation, C-reactive protein, coronary artery bypass surgery, off-pump coronary artery bypass surgery, stroke, temperature

To my family

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Jarmo Lahtinen

Abbreviations

AF	atrial fibrillation
CABG	coronary artery bypass surgery
CCAB	conventional coronary artery bypass surgery
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPB	cardiopulmonary bypass
CRP	C-reactive protein
CX	circumflex coronary artery
EuroSCORE	European System for Cardiac Operative Risk Evaluation
IABP	intra-aortic balloon pump
ICU	intensive care unit
LAD	left anterior descending coronary artery
LOM	left obtuse marginal coronary artery
LV	left ventricle
LVEF	left ventricular ejection fraction
NYHA	New York Heart Association
OPCAB	off-pump coronary artery bypass surgery
OR	odds ratio
RCA	right coronary artery
SE	standard error
TIA	transient ischemic attack
VSD	ventricular septal defect

List of original publications

This thesis is based on the following articles, referred to in the text by their Roman numerals:

I Biancari F, Lahtinen J, Salmela E, Niemelä M, Pokela R, Rainio P, Lepojärvi M, Satta J, Juvonen T (2003) Does angiographic severity of coronary artery disease predict postoperative outcome after coronary artery bypass surgery? Scand Cardiovasc J 37:275–82.

II Biancari F, Lahtinen J, Lepojärvi S, Rainio P, Salmela E, Pokela R, Lepojärvi M, Satta J, Juvonen T (2003) Preoperative C-reactive protein and outcome after coronary artery bypass surgery. Ann Thorac Surg 76:2007–12.

III Lahtinen J, Biancari F, Rimpiläinen J, Kytökorpi R, Mosorin M, Rainio P, Cresti R, Juvonen T, Lepojärvi M (2007) Off-pump versus on-pump coronary artery bypass surgery in high-risk patients (EuroSCORE≥6). Thorac Cardiovasc Surg 54:13–8.

IV Lahtinen J, Biancari F, Ala-Kokko T, Rainio P, Salmela E, Pokela R, Satta J, Lepojärvi M, Juvonen T (2004) Pulmonary artery blood temperature on admission to the intensive care unit is predictive of outcome after coronary artery bypass surgery. Scand Cardiovasc J 38:104–12.

V Lahtinen J, Biancari F, Mosorin M, Satta J, Rainio P, Lepojärvi M, Juvonen T (2004) Postoperative atrial fibrillation is a major course of stroke after on-pump coronary artery bypass surgery. Ann Thorac Surg 77:1241–4.

Contents

1 Introduction

As a result of continually improving surgical strategy and technology which supports it, coronary artery surgery is now possible in an increasingly high-risk population (Warner *et al.* 1997). At the same time the quality of medical care and risk factors associated with coronary artery bypass surgery are increasingly scrutinazed (Nugent *et al.* 1994). The demand for these data comes from patients who desire to know the "track record" of their doctor and hospital, physicians and hospitals pursuing quality improvement; and purchasers of health care who are searching for the best value (Green *et al.* 1990, Higgins *et al.* 1991, Hammermeister *et al.* 1995, Higgins 1998, Sherlaw-Johnson *et al.* 2000).

Crude mortality rates have initially been used as an indicator of the quality of care, but their value is limited without knowledge of the risk profile of the patients. Institutional data management has gradually been replaced by multi-institutional databases to monitor outcomes following cardiac surgery (Grover *et al.* 2001). There has been a progressive increase in their sophistication, with the building of risk models based on preoperative variables, which quite accurately predict the risk of adverse outcomes (Grover *et al.* 1993*)*. In addition to mortality, other outcomes of cardiac surgery have gained importance in assessing the quality of care. Postoperative morbidity, critical events, resource utilization, costs, postoperative functional status and patient satisfaction as well as long term results and freedom from repeat revascularization are other important outcome end-points after coronary artery bypass grafting (CABG).

Mortality is an outcome measure that is almost universally reported. The advantages of mortality as an outcome measure include lack of ambiguity and availability of mortality data from a variety of sources. The limitations of mortality as a sole outcome measure are especially apparent in the cardiac surgery population, where the unadjusted mortality rates are very low, ranging from 1% to 5% (Vogt *et al.* 2000).

Morbidity is a much more convenient endpoint for outcome analysis as it occurs more frequently than mortality, allowing statistical inferences to be drawn from smaller populations. Typical morbidity rates range from 2% for a stroke to 6% for respiratory complications. About 18% to 43% of patients have one or more complications after CABG (Shroyer *et al.* 2003). Unfortunately, morbidity data is more difficult to collect and there has been a lack of standardization of morbidity definitions. Because of this, morbidity data is not so reliable.

The identification of factors associated with an increased risk to develop complications after surgery is of main importance for an adequate preoperative patient selection, indicating the need of optimization of patients' condition before surgery or cancellation of the operation for those with an excessively high operative risk. Furthermore, the identification of such risk factors and their inclusion in specific methods of risk stratification permits evaluation of the quality of treatment. Major efforts have been made to develop scoring methods for patients undergoing cardiac surgery. However, the complexity of surgical and anesthesiologic management of these patients along with the burden of extracardiac comorbidities makes any attempt to preoperative risk stratification rather difficult.

Although a few scoring systems have been shown to be quite good predictors of outcome after cardiac surgery, they unfortunately still variably suffer from certain inaccuracy in predicting the individual risk of postoperative complications (Orr *et al.* 1995, Pons *et al.* 1998, Geissler *et al.* 2000, Kurki *et al.* 2002, Pinna-Pintor *et al.* 2002, Baretti *et al.* 2002). This leads to continuous efforts to identify those risk factors and stratifying risk models which better predict the risk of postoperative adverse events.

In the present clinical studies we have focused on a few risk factors predicting the outcome after CABG, which have previously not been extensively investigated. We have evaluated the impact of preoperative angiographic severity of a coronary artery disease and preoperative C-reactive protein (CRP) on the immediate outcome after coronary artery bypass surgery (I,II). We have reviewed the results of off-pump (OPCAB) versus conventional on-pump coronary artery bypass surgery (CCAB) in high risk patients (III). We have evaluated the impact of postoperative pulmonary artery blood temperature on the immediate outcome as well (IV). In addition, we have investigated the incidence, timing and outcome of an atrial fibrillation (AF) related stroke after surgery (V).

2 Review of the literature

2.1 Risk indices

A number of different preoperative risk indices have been developed over the years for the prediction of postoperative mortality and morbidity in cardiac surgery (Hannan *et al.* 1990, O'Connor *et al.* 1992, Higgins *et al*. 1992, Tuman *et al.* 1992, Tremblay *et al*. 1993, Edwards *et al.* 1994, Roques *et al.* 1995, Tu *et al*. 1995, Pons *et al*. 1997, Gabrielle *et al.* 1997). In 1989, Parsonnet and collaborators proposed a simple preoperative scoring system for adult cardiac surgery, which graded the severity of illness of patients into five groups (Parsonnet *et al.* 1989). This useful score was rapidly taken up by several cardiac surgery teams and it confirmed its value in predicting hospital mortality and morbidity. Two risk factors of this initial Parsonnet´s score were, however, imprecise and their weights were arbitrarily chosen by the surgeon (catastrophic states, other rare circumstances). Thus the reliability of the score decreased when these two risk factors were present (Wynne-Jones *et al.* 2000). This original score was later modified, including thirty new risk factors according to the SUMMIT system replacing the former two imprecise factors (Parsonnet *et al.* 1996). This new score, referred to as the modified Parsonnet´s score, is since considered the golden standard of risk score indices predicting postoperative outcome after cardiac surgery (Table 1).

Between 1987 and 1989, the Department of Veterans Affairs (VA) and the Society of Thoracic Surgeons (STS) developed national cardiac surgical databases in the USA to risk-adjust outcomes as a preliminary screening tool for evaluating and improving the quality of care (Table 1). More than 74,000 and 1.6 million cardiac surgical patients have already been entered into the VA and STS databases, respectively, and ongoing data collection continues (Edwards *et al.* 1994, Hattler *et al*. 1994, Grover *et al.* 2001**)**.

In order to enlighten the risk profile of the European cardiac surgery patients a risk stratification method called European system for cardiac operative risk evaluation (EuroSCORE) was developed and the results were published in 1999 (Table 1 and 2) (Roques *et al.* 1999, Nashef *et al.* 1999). It was essential from the beginning that this risk stratification system should have been objective and resistant to manipulation and that as few risk factors as possible would be determined by surgical decision-making. This was achieved by the selection of real, measurable and easily available risk factors. Despite epidemiological differences between European countries, the discriminative power of EuroSCORE has been found to be good or excellent in all European countries (Roques *et al.* 2000) as well as in North America (Nashef *et al.* 2002) and in Japan (Kawachi *et al.* 2001). The new full logistic EuroSCORE is superior to the standard additive EuroSCORE in predicting mortality, especially among high risk cardiac surgical patients (Michel *et al.* 2003).

However, it was also realized that preoperative factors alone could not predict the outcome after cardiac surgery. Operating room and ICU events can neutralize or amplify the risk present based on preoperative status (Reich *et al.* 1999, Turner *et al.* 1995). The altered physiologic values of a CABG patient were used as a marker of risk by ICU outcome stratification systems such as Acute Physiology and Chronic Health Evaluation (APACHE), Simplified Acute Physiology Score (SAPS), Mortality Probability Model (MPM), the Edinburgh Cardiac Surgery Score (ECS) and ICU admission score (Knaus *et al.* 1991, Lemeshow *et al.* 1993, Le Gall *et al.* 1993, Thompson *et al.* 1995, Becker *et al.* 1995, Higgins *et al.* 1997, Martinez-Alario *et al.* 1999, Capuzzo *et al.* 2000). They took intraoperative effects such as surgical and anesthetic techniques into consideration in addition to preoperative condition of patient. These scores also provided a tool with which to judge the effects of ICU quality of care on outcome.

Table 1. Predictive risk factors included in four major cardiac surgery risk indices

Variable	Risk score items	Parsonnet	VA	STS	EuroSCORE
Patient data	Age	+	+	+	+
	Gender	+		+	+
	Body weight	+		+	
Cardiac	Unstable angina		+*	+	+
	Aortic stenosis	+		+	
	Active endocarditis				+
	Congenital heart defect	+			
	Cardiomegaly		+		
	Hypertension, arterial	+		+	
	Hypertension, pulmonary	+			+
	LV aneurysm	+		+	
	LV ejection fraction	+		+	+
	Mitral insufficiency	+		+	
	Myocardial infarction (MI)		+	+	+
	NYHA		+		
	Post MI VSD				+
	Ventricular tachycardia				+
Pulmonary	Asthma	+			+
	COPD			+	+
Renal	Dialysis	+			
	Creatinine		+		+
	Acute renal failure	+		+	+
Other	Anemia				
	Diabetes	+		+	
	Liver disease				
	History of TIA, stroke			+	+
	Paraplegia	+			
	Pacemaker	+			
Vascular	Aortic dissection, acute				
	Peripheral arterial disease		+		+
	History of vascular surgery				+
Preoperative	Ventilation				+
	IABP	+	+		+
	Inotropes			+	+
	Resuscitation				+
	Cardiogenic shock	+		+	
Operation	Combined surgery	+			+
	Urgent/emergency	+		+	+
	Reoperation	+	+	+	+

LV, left ventricular; NYHA, New York Heart Association class; VSD, ventricular septal defect; COPD, chronic obstructive pulmonary disease; IABP, intra-aortic balloon pump; *: resting ST depression.

Table 2. Additive model of the European system for cardiac operative risk evaluation (EuroSCORE) with related scores.

Risk factor	Criteria	Score
Age	per 5 years or part thereof over 60 years	1
Sex	female	1
Chronic pulmonary disease	long-term use of bronchodilators or steroids for lung disease	1
Extracardiac arteriopathy	one or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta,limb arteries or carotids	2
Neurological dysfunction disease	severely affecting ambulation or day-to-day functioning	2
Previous cardiac surgery	requiring opening of the pericardium	3
Serum creatinine	>200m micromol/L preoperatively	2
Active endocarditis	patient still under antibiotic treatment for endocarditis at the time of surgery	3
Critical preoperative state	one or more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anaesthetic room,preoperative inotropic support, intraaortic balloon counterpulsation or preoperative acute renal failure (anuria or oliguria<10 ml/hour)	3
Unstable angina	rest angina requiring iv nitrates until arrival in the anaesthetic room	2
LV dysfunction	moderate or LVEF30-50%	1
	poor or LVEF <30%	3
Recent myocardial infarct	<90 days	2
Pulmonary hypertension	Systolic PA pressure>60 mmHg	2
Emergency	carried out on referral before the beginning of the next working day	2
Other than isolated CABG	major cardiac procedure other than or in addition to CABG	2
Surgery on thoracic aorta	for disorder of ascending, arch or descending aorta	3
Postinfarct septal rupture		4

Table 3. Beta coefficients for the logistic model of the European system for cardiac operative risk evaluation (EuroSCORE).

Risk factor	Beta coefficients
Age	0.0666354
Sex	0.3304052
Chronic pulmonary disease	0.4931341
Extracardiac arteriopathy	0.6558917
Neurological dysfunction disease	0.841626
Previous cardiac surgery	1.002625
Serum creatinine	0.6521653
Active endocarditis	1.101265
Critical preoperative state	0.9058132
Unstable angina	0.5677075
Left ventricular ejection fraction 30–49%	0.4191643
Left ventricular ejection fraction <30%	1.094443
Recent myocardial infarct	0.5460218
Pulmonary hypertension	0.7676924
Emergency	0.7127953
Other than isolated CABG	0.5420364
Surgery on thoracic aorta	1.159787
Postinfarct septal rupture	1.462009

Logistic EuroSCORE = $e^{(o + \Sigma\beta i \ Xi)} / 1 + e^{(o + \Sigma\beta i \ Xi)}$
e is the natural logarithm = 2.718281828; β**o** is the constant of the logistic regression equation = –4.789594; β**i** is the coefficient of the variable Xi; **Xi** = 1 if a categorical risk factor is present and 0 if it is absent; For age, **Xi** = 1 if patient age < 60; Xi increase by one point per year thereafter.

2.2 Preoperative factors

Independent preoperative variables that affect postoperative outcome can be categorized as patient demographics, preexisting health problems or comorbidities, measurements of physiological reserve, and priority of care.

2.2.1 Demographic variables

Age

Patients' age in cardiac surgery is significantly associated with mortality and morbidity (Nashef *et al.* 1999, Hirose *et al.* 2000, Grover *et al.* 2002). However, the relationship between advanced age and poor outcome is neither linear nor consistent from one patient to another. Traditionally, the age of 65 years has been used as a cut-off value dividing the elderly from the nonelderly patients, but with the advancement in the general health of the population, this particular cut-off value may no longer be valid. At a recent meta-analysis, age over 70 years was a clear predictor of 30-day mortality after CABG (OR 2.42, 95% CI: 2.00–2.80) (Nalysnyk *et al.* 2003).

Gender

Several authors have found out that female gender is a predictive risk factor for mortality, but its predictive value was always low (Loop *et al.* 1983, Weintraub *et al.* 1993, O'Connor *et al.* 1993, Philippides *et al.* 1995, Vogt *et al.* 2000). Many studies also quote female sex as a risk factor for morbidity (Tuman *et al*. 1992, O'Connor *et al.* 1992, Hogue *et al.* 2001). Other studies, however, have examined both sex and body size in the same population, and determined that it is the small body size, and not the sex, that increases the risk (Loop *et al.* 1983, Higgins *et al.* 1992, O'Connor *et al.* 1993). Without adjustment for body size, women do appear to be at higher risk, because they commonly have smaller body size or smaller body surface area compared with that of men.

A risk by sex may also be affected by referral bias resulting in diagnosis and treatment of women at a later stage of illness (Khan *et al.* 1990). Another study has confirmed that women have a higher crude mortality rate after cardiac surgery, but this discrepancy is entirely due to a higher baseline risk resulting from the presence of more concurrent risk factors (Koch *et al.* 1996). However, a recent study, in which data of 345,000 patients from STS database was retrospectively analyzed, concluded that female gender is an independent predictor of operative mortality except for patients in very high-risk categories (Edwards FH *et al.* 1998). There is also evidence showing that younger women undergoing CABG surgery are at higher risk of in-hospital mortality than men, in the same way as after myocardial infarction, but this difference in risk decreases with advanced age (Vaccarino *et al.* 2002).

Body mass index

Obese patients generally carry a higher risk of death (Manson *et al.* 1995). Although there is little evidence in the literature, obesity is often thought to be a risk factor also for postoperative morbidity and mortality with cardiac surgical patients (Parsonnet *et al*. 1989). The factors predisposing and contributing to severity of a coronary artery disease, such as hypertension, hypercholesterolemia, and diabetes, which are more common among obese patients, likely contribute to these perceptions (Prasad *et al.* 1991).

A recent study by Järvinen *et al.* (2006) has shown a significant association between obesity and postoperative complications such as wound and renal complications. Obese patients also had a longer in-hospital stay (Jarvinen *et al.* 2006). Previously, other authors also reported a significant association between obesity and postoperative complications such as dysrhythmias, superficial wound infections and respiratory complications (Moulton *et al*. 1996, Birkmeyer *et al.* 1998, Akdur *et al.* 2006). Diabetes seems to increase the risk of postoperative adverse outcome in obese patients (Pan *et al.* 2006) However, other studies have failed to show any statistically significant association between obesity and serious adverse outcomes, such as postoperative death, deep infections, myocardial infarction, stroke and pulmonary complications (Prasad *et al.* 1991, Moulton *et al*. 1996, Birkmeyer *et al.* 1998). Interestingly, quality of life after surgery improves in both obese and non-obese patients even if obese patients have worse preoperative scores in quality of life (Järvinen *et al.* 2006).

In other studies, however, patients with very low body weight or small body surface area have been shown to be at increased risk of morbidity and mortality (O'Connor *et al.* 1991, Higgins *et al.* 1992).

These controversial findings have partly been explained by the results of a study by Jin and colleagues (Jin *et al*. 2005) as they have shown that only severely obese and underweight patients have an increased risk of in-hospital mortality compared to high-normal and overweight patients. This observation couples that by a recent meta-analysis which showed that among patients with a coronary artery disease only those with severe obesity and those underweight have an increased risk of long-term total and cardiovascular mortality (Romero-Corral *et al.* 2006). The authors suggested that the evidently protective effect of slight obesity can be explained by the lack of data to distinguish a real excess of body fat from a better preserved muscle mass in patients with a normal/slightly increased body mass index (Romero-Corral *et al*. 2006).

2.2.2 Comorbidities

Extracardiac arteriopathy

Several authors have noted that a peripheral arterial disease increases the risk of postoperative mortality and morbidity of cardiac surgery (Higgins *et al.* 1992, Geissler *et al.* 2000, Hill SE *et al.* 2000, Naylor *et al.* 2002, Loponen *et al.* 2003). Above all, history of stroke is strongly and independently associated with susceptibility for stroke after cardiac surgery (Hogue *et al.* 2003). However, a carotid artery disease alone has not shown to be statistically associated with mortality (Gabrielle *et al.* 1997).

A lower limb arterial disease seems to be a better indicator for the severity and the extent of an atherosclerotic disease, and it has been shown to be an independent risk factor for postoperative mortality in patients undergoing CABG surgery (OR 2.3, 95% CI: 1.5–3.7) (Gabrielle *et al.* 1997). Yet, the association of a carotid stenosis with a lower limb arterial disease significantly increases the frequency of postoperative neurologic events after CABG (Salasidis *et al.* 1995). The intracranial cerebral artery disease has also been suggested of being an independent risk factor for neurologic complications after CABG surgery (Yoon *et al.* 2001).

Chronic renal failure

Chronic renal failure is an important preoperative risk factor in cardiac surgery (Liu *et al.* 2000, Szczech *et al.* 2002). Higgins reported a significantly higher mortality and morbidity among patients in North America with serum creatinine 168µmol/L (OR 7.39 and OR 4.27, respectively) (Higgins *et al.* 1992). Similar results have been observed in Europe, where multivariate analysis identified serum creatinine >200µmol/L as a predictor of postoperative mortality (OR 1.9) (Roques *et al.* 1999). Such an increased risk is further raised by the need of chronic dialysis (Parsonnet *et al.* 1989, Hannan *et al.* 1990, Gabrielle *et al.* 1997). A recent study has shown that the use of cardiopulmonary bypass is significantly associated with adverse renal outcome in patients with preoperative non-dialysis dependent renal insufficiency (Sajja *et al.* 2007).

Holzmann and colleagues (Holzmann *et al.* 2005) have demonstrated that preoperative creatinine clearance calculated by the Cockroft-Gault method is a better predictor of postoperative death compared to preoperative creatinine after

CABG. This is due to the fact that serum creatinine levels are greatly dependent on dietary intake, total muscle mass, the use of certain medications that can interfere with renal creatinine handling, and renal and extrarenal excretion, all of which might be altered in a chronic kidney disease (Bostom *et al.* 2002). Interestingly, it has been demonstrated a survival benefit among patients with an end stage renal disease undergoing CABG surgery as compared with percutaneous coronary angioplasty (Szczech *et al.* 2001, Herzog *et al.* 2002).

Hematocrit, albumin

Preoperative anemia, hematocrit 0.34, has been identified as an independent risk factor (Higgins *et al*. 1992). Habib and colleagues have shown that also increased hemodilution significantly affect the immediate and long-term outcome (Habib *et al*. 2003). However, controversial results on the predictive importance of hematocrit have also been reported in the literature (Hill SE *et al*. 2000).

Low albumin levels, perhaps reflecting a chronic illness, have been identified as an important risk factor for adverse postoperative outcome after cardiac surgery (Engelman *et al*. 1999, Gibbs *et al.* 1999, Higgins *et al.* 1997). Indeed, intraoperative administration of albumin has been shown to improve the outcome of patients undergoing CABG (Sedrakyan *et al.* 2003).

It has been shown that hypoalbuminemia is significantly associated with coexistence of a coronary artery disease and a peripheral artery disease in patients on chronic dialysis (Beddhu *et al.* 2002). Savage and colleagues showed that hypoalbuminemia is significantly inversely correlated with the degree of carotid and femoral artery intima media thickness and the severity of arterial stenosis (Savage *et al.* 1998). Kim and colleagues demonstrated that serum albumin is inversely correlated with C-reactive protein, D-dimer and von Willebrand factor levels, and that hypoalbuminemia increases thrombocyte aggregation in dialysis patients (Kim *et al.* 1999). The authors showed that the former parameters are not affected by infusion of albumin, but this treatment decreased the platelet aggregability.

It is likely that also in non-uremic patients the serum concentration of albumin is an important parameter of poor general conditions and possibly associated with other risk factors leading to accelerated atherosclerosis.

C-reactive protein

Atherosclerosis is, nowadays, considered a chronic low-grade inflammatory disease. The degree of such an inflammatory process strongly correlates with the extent and severity of an atherosclerotic disease (Yamashita *et al.* 2003, Erren *et al.* 1999). C-reactive protein (CRP) has emerged not only as a relevant marker of this inflammatory process underlying the development of atherosclerosis, but also as one of the engines of the inflammatory cascade (Ablij *et al.* 2002). Modern high-sensitivity C-reactive protein (hs-CRP) analysing methods have increased the clinical value of CRP especially in predicting the risk of vascular events.

There is a burden of evidence showing that CRP is an independent predictor of long-term cardiovascular events in healthy subjects (Koenig *et al.* 1999, Ablij *et al.* 2002, Ridger *et al.* 2003). Furthermore, increased serum levels of CRP have been shown to predict poor outcome in patients with unstable angina (Rallidis *et al.* 2002) and myocardial infarction (Zairis *et al.* 2002) as well as with ischemic stroke (Di Napoli *et al.* 2001). Similarly, a number of studies have shown that CRP predicts early and late cardiac events after coronary angioplasty (Buffon *et al.* 1999, Versaci *et al.* 2000, Walter *et al.* 2001, Chew *et al.* 2001, de Winter *et al.* 2002, Honq *et al.* 2005), but scanty data exists on its impact on the outcome after coronary artery bypass grafting (Milazzo *et al.* 1999, Gaudino *et al.* 2002). It has recently been shown that preoperative CRP also predicts late mortality after CABG (Kangasniemi *et al*. 2006, Palmerini *et al.* 2007).

Chronic pulmonary disease

Asthma is not statistically associated with postoperative mortality, in contrast to a chronic obstructive pulmonary disease. It is, in fact, difficult to estimate the degree of severity of asthma, and severe asthma may often evolve into a chronic obstructive disease. Both mortality and morbidity rates are higher among CABG patients with a significant chronic obstructive pulmonary disease (COPD) (Higgins *et al*. 1992, Gabrielle *et al.* 1997).

Especially arrhythmias and arrhythmia-related deaths are more common among patients with severe COPD (Cohen *et al.* 1995). On the contrary, patients with mild-to-moderate COPD undergoing coronary artery surgery have quite similar mortality and morbidity rates to those patients with no COPD (Samuels *et al.* 1998, Michalopoulos *et al.* 2001).

Diabetes

The association between diabetes and mortality at coronary surgery has been inconsistent, with some studies supporting and other studies not supporting such an association (Barzilay *et al.* 1994, Tu *et al.* 1995, Herlitz *et al.* 1996, Geissler *et al.* 2000, Nalysnyk *et al.* 2003, Rajakaruna *et al.* 2006). Diabetics are believed to have more extensive and diffuse lesions of the coronary arteries in the presence of a coronary arterial disease than non-diabetics, this explaining the possible differences in postoperative outcomes. However, a prospective study failed to confirm a significant difference in the extent and severity of the coronary artery disease in diabetics and nondiabetics as assessed by angiography and at surgery (Bhan *et al.* 1991). Diabetics seem to have increased postoperative morbidity after CABG in comparison with nondiabetic patients, particularly with regard to renal function, cerebral complications, and infections (Szabo *et al.* 2002). They have, however, a risk of immediate postoperative death similar to non-diabetics (Rajakaruna *et al.* 2006).

Hypertension

Hypertension is certainly the most common comorbid condition in patients undergoing CABG, its prevalence ranging from 35% to 65% (Gabrielle *et al*. 1997, Nalysnyk *et al.* 2003). Most studies, however, did not find any significant association between in-hospital mortality and hypertension (Tu *et al.* 1995, Clough *et al.* 2002) with a couple of exceptions (Parsonnet *et al.* 1989, Edwards *et al.* 1994, Hill SE *et al.* 2000).

It has recently been shown that it is the isolated systolic hypertension (systolic blood pressure >140 mmHg) only, not the diastolic hypertension (diastolic blood pressure >90 mmHg) nor the combination of these, that is associated with adverse outcomes after CABG, causing a 40% increase in the likelihood of postoperative morbidity (Aronson *et al.* 2002).

2.2.3 Physiological reserve

Coronary artery disease

Left main coronary artery stenosis is a risk that may have been neutralized in recent studies by improved anesthetic and surgical techniques. Still some evidence on the association between this risk factor and mortality has been reported (Kennedy *et al.* 1981, Ringqvist *et al.* 1983, Gersh *et al.* 1983, Gabrielle *et al.* 1997). Among CABG patients with left main coronary artery stenosis in the Collaborative Study in Coronary Artery Surgery (CASS), postoperative mortality ranged from 1.6% in patients with mild stenosis and a right-dominant system to 25% in patients with severe (90%) stenosis and left dominance (Kennedy *et al.* 1981). In the same study, the overall postoperative mortality was 1.4% in a one-vessel, 2.1% in a two-vessel and 2.8% in a three-vessel disease. The three-vessel coronary disease has been identified as a predictor of mortality by multivariate analysis (Vogt *et al.* 2000).

However, the presence and degree of the left main stenosis as well as the distribution of atherosclerotic lesions throughout the coronary tree have been considered too subjective and unreliable and thus excluded from most of the risk indices (Parsonnet *et al.* 1989). There is some evidence that a diffuse distal coronary artery disease could be quantified by a structural reading of the coronary angiogram and it is a powerful independent predictor of death after coronary artery bypass surgery (Graham *et al.* 1999). However, it is not clear so far which the coronary arteries and their segments are whose extent of atherosclerosis is associated with poor postoperative outcome.

Unstable angina

Unstable angina is one of those subjectively assessed parameters which are causing problems by definitional variability and uncertainty. Because of this, most risk indices have not qualified it as a predictor of mortality (Geissler *et al*. 2000). There are some exceptions such as the modified Parsonnet's score and the EuroSCORE, which consider this particular variable significant, yet its odds ratio is fairly low (Parsonnet *et al.* 1996, Gabrielle *et al.* 1997, Roques *et al.* 1999).

Previous myocardial infarction

Meta-analyses showed that the history of previous myocardial infarction is usually associated with increased morbidity and mortality after CABG (OR 1.3–2.4) (Higgins *et al.* 1997, Gabrielle *et al.* 1997, Geissler *et al.* 2000, Nalysnyk *et al.* 2003). Unfortunately, definitional variability and uncertainty has been encountered in many studies also with preoperative myocardial infarction, thus decreasing its value in risk assessment (Nalysnyk *et al.* 2003). It is nevertheless one of the most common risk factors encountered and it has been recognised as a major prognostic factor in most risk scoring methods.

Left ventricular ejection fraction

Left ventricular ejection fraction (LVEF) as a preoperative risk factor is rather imperfect as its estimation is potentially affected by the method of assessment (catheterisation, scintigraphy, ultrasonography), and the conditions of measurement (volume load, arrhythmias, valvular diseases). However, this risk factor has been recognised as a relevant predictor of postoperative mortality and morbidity (Parsonnet *et al.* 1989, Geissler *et al.* 2000, Nashef *et al.* 1999, Higgins *et al.* 1992).

In a recent study by Nalysnyk and colleagues preoperative LVEF≤50% was associated with an increased risk as twice for postoperative adverse events such as myocardial infarction, stroke and renal failure as compared with patients with preoperative LVEF>50% (Nalysnyk *et al.* 2003). For patients with severe left ventricular systolic dysfunction (LVEF≤25%) undergoing CABG, preoperative simultaneous right ventricular dysfunction is associated with even poorer outcome (Maslow *et al.* 2002).

2.2.4 Priority of care

Previous cardiac surgery

Reoperation is indisputably a major risk factor for hospital mortality, as shown in most large cardiac surgery risk studies, the related odds ratios ranging from 1.32 to 7.05 (Tu *et al.* 1995, Nalysnyk *et al.* 2003). Such an increased risk is likely to be related to increased technical difficulties encountered in a scarred field. However, it is also likely that patients requiring redo CABG have a more severe coronary artery disease and possibly also an underlying prothrombotic status (Moor *et al.* 1998, Moor *et al.* 2000, Curi *et al.* 2003, Siren *et al.* 2003).

Emergency, critical state

In the Parsonnet’s (Parsonnet *et al.* 1989), Higgins´ (Higgins *et al.* 1992), and O’Connor’s scores (O’Connor *et al.* 1992), emergency surgery is neither defined nor detailed. Furthermore, in the Parsonnet´s score the weight of the risk factors “catastrophic states and other rare circumstances” are decided by the surgeon, thus the level and the severity of emergency are subjective.

Nevertheless, emergency is clearly associated with a critical preoperative status which inevitably leads the surgeon and anesthesiologist to face with unstable, severe conditions and it is considered in the EuroSCORE as having a great prognostic value (Roques *et al.* 1999, Nashef *et al.* 1999).

2.3 Operative technique

Recent meta-analyses of randomized studies failed to demonstrate a significant reduction of immediate postoperative mortality in patients undergoing off-pump coronary artery bypass surgery (OPCAB) as compared with conventional, on-pump coronary artery bypass surgery (CCAB) (Wijeysundera *et al.* 2005, Cheng *et al.* 2005). However, OPCAB has been shown to significantly reduce postoperative morbidity (Wijeysundera *et al.* 2005, Cheng *et al.* 2005) and it is associated with markedly lower costs (Cheng *et al.* 2005, Puskas *et al.* 2004). Unfortunately, we do not have randomized trials with Finnish patients yet. Because of the minimally invasive nature and the lessened inflammatory reaction associated with the use of off-pump technique, the latter has been suggested to be of particular benefit in high-risk patients (Stamou & Corso 2001). Indeed, a growing amount of evidence indicates that avoidance of cardiopulmonary bypass is associated with better immediate postoperative outcome in these patients (Sharoni *et al.* 2005, Sharony *et al.* 2003, Srinivasan *et al.* 2004, Stamou *et al.* 2005, van Belleghem *et al.* 2003, Yokohama *et al.* 2000, Akpinar *et al.* 2001, Al-Ruzzeh *et al.* 2003, Chamberlain *et al.* 2002, D’Ancona *et al.* 2001, Deuse *et al.* 2003, Dewey *et al.* 2004, Goldstein *et al.* 2003, Mack *et al.* 2004, Meharwal *et al.* 2002, Meharwal & Trehan 2002, Nishimura *et al.* 2004, Oo *et al.* 2003, Ascione *et al.* 2003). However, none of these reported studies was randomized and this prevents any definitive conclusion on this important issue. On the basis of a meta-analysis of five recently published prospective randomized trials that compare the results of OPCAB versus CCAB, Takagi and his coauthors (Takagi *et al.* 2007) claimed that OPCAB resulted in a significant increase in overall graft occlusion. Lim and colleagues (Lim *et al.* 2006) got very much the same results. This statistical conclusion, however, included several limitations (Gardner 2007) and we are still lacking large, multicenter, randomized studies.

2.4 Intensive care unit admission factors

In cardiac surgery, most predictive models only take preoperative risk factors into account as determinants of outcome. This is sound as a risk scoring method would, thus, enable preoperative risk stratification by which to identify those patients at highest risk of postoperative adverse outcome. Furthermore, this enables a comparative analysis of patients' conditions between different institutions.

There is, nevertheless, evidence of a certain impact of intraoperative and ICU admission variables on patient's outcome after cardiac surgery. The observation that increased surgeons' volume (Bridgewater *et al.* 2003, Hannan *et al.* 2003) along with increased hospital volume (Hannan *et al*. 2003) is associated with lower mortality rates in patients undergoing cardiac surgery, indirectly indicates that the surgeon and anesthesiologist's experience has a marked impact on the postoperative outcome. Whether this is due to different individual techniques is far from being ascertained, but it seems that the duration of cardiopulmonary bypass, the use of intra-aortic balloon pump, the completeness of revascularization, the adequacy of myocardial protection as well as hemodynamic management are significantly affecting the immediate postoperative results (Higgins *et al.* 1997, Michalopoulos *et al.* 1999). In particular, identification of variables associated with poor outcome at ICU admission is of great importance as they may reflect different intraoperative strategies and thus they can be assumed as potential therapeutic targets. Higgins and colleagues (1997) provided the most extensive analysis of ICU admission variables associated with adverse outcome after cardiac surgery. The univariate analysis showed that the use of intraaortic balloon pump after cardiopulmonary bypass, heart rate, mean arterial pressure, central venous pressure, pulmonary artery pressure, low cardiac index, use of inotropes, vasopressors and antiarrythmics, fraction of inspired oxygen, alveolar-arterial gradient, hematocrit, glucose, arterial pH, arterial HCO_3, core temperature and white blood cell count at admission to the ICU were significantly associated with postoperative mortality and morbidity (Higgins *et al.* 1997). Logistic regression showed, however, that among the ICU admission risk factors, only heart rate more than 100 beats/min (OR 2.27, 95% CI: 1.36–3.85) and arterial bicarbonate (OR 0.85, 95% CI: 0.76–0.94) were independent predictors of postoperative mortality. This study provides evidence that further research is needed to ascertain which intraoperative and ICU admission risk factors are associated with poor outcome as they may represent important therapeutic targets.

2.4.1 Pulmonary artery blood temperature

The patient's core temperature at admission in the intensive care unit has been found to be an important determinant of outcome after coronary artery bypass surgery, however its role still being far from established (Insler *et al.* 2000, Grocott *et al.* 2002, Nesher *et al.* 2003). Hypothermia is known to have protective effects on tissues undergoing a period of ischemia mainly by decreasing metabolic activity, reducing oxygen demand and preserving ATP storage (Ergin 2000, Wang *et al.* 2000). Furthermore, there are many other beneficial effects found to be in association with hypothermic strategies during and/or after hypothermic events, such as reduced release of excitotoxin in the brain (Thoresen *et al.* 1997), inhibition of apoptosis (Lin *et al.* 2001, Xu *et al.* 2002), suppression of inflammatory cytokine release (Vazquez-Jimenez *et al.* 2001, Kimura *et al.* 2002), decreased complement and neutrophil activation (Chello *et al.* 1997), suppression of protein kinase C (Cardell *et al.* 1991), reduction of enhanced cerebrovascular permeability and amelioration of postischemic hyper- and hypoperfusion (Karibe *et al.* 1994).

Recent clinical studies provided also evidence of a certain neuroprotective efficacy of mild or moderate hypothermia in the setting of ischemic stroke (Schwab *et al.* 1998, Kammersgaard *et al.* 2000), neonatal asphyxia (Edwards AD *et al.* 1998, Gunn *et al.* 1998), cardiac arrest (Bernard *et al.* 2002, Hypothermia after Cardiac Arrest Study Group 2002) and traumatic brain injury (Marion *et al.* 1997, Bernard *et al.* 1999, Chen *et al.* 2001). However, there are studies failing to confirm the beneficial effects of hypothermia in patients with traumatic brain injury as well (Clifton *et al.* 2001, Gadkary *et al.* 2002). Indeed, hypothermia has also been demonstrated to be in association with such deleterious effects as acidosis (Romsi *et al.* 2002), coagulopathy (Krause *et al.* 2000), hemodynamic instability (Schwab *et al.* 1998, Mizushima *et al.* 2000, Georgiadis *et al.* 2001, Krieger *et al.* 2001, Romsi *et al.* 2002), cardiac arrhythmias (Sun *et al.* 1997, Schwab *et al.* 1998, Georgiadis *et al.* 2001, Krieger *et al.* 2001), ventilatory instability (Sladen 1985, Mills *et al.* 1997, McCormick *et al.* 1998), reduction of leukocytes and neutrophils (Shiozaki *et al.* 2001, Romsi *et al.* 2002), thrombocytopenia (Schwab *et al.* 1998, Georgiadis *et al.* 2001, Shiozaki *et al.* 2001), endotoxemia (Gercekoglu *et al.* 1997), infectious complications (Schwab *et al.* 1998, Ishikawa *et al.* 2000, Georgiadis *et al.* 2001, Krieger *et al.* 2001, Shiozaki *et al.* 2001) and increase of amylase and lipase levels (Metz *et al.* 1996, Schwab *et* *al.* 1998, Shiozaki *et al.* 2001). However, most of these adverse effects have only been reported in association with prolonged mild hypothermia.

In a large series of patients having undergone CABG operation, a bladder temperature less than 36ºC at the time of admission to the ICU was shown to be in association with increased mortality, prolonged mechanical ventilation, increased red blood cell transfusion and longer hospital stay (Insler *et al.* 2000). In an experimental setting in our institution, we have demonstrated that a period of mild hypothermia also after a hypothermic circulatory arrest has detrimental effects on animals' outcome, thus confirming the observation made by Insler and colleagues (Romsi *et al.* 2002, Pokela *et al.* 2003).

Bar-Yosef *et al.* (2004) have shown that a strategy of limited rewarming to 35.0ºC and then slowly to 36.8ºC compared with prompted rewarming to 37.0 ºC is associated with a lower risk of postoperative hyperthermia and its associated risk of cerebral injury, and, at the same time, it minimizes the risk of postoperative hypothermia.

However, so far the impacts of intraoperative temperature management as well as the core temperature itself during the early postoperative hours after CABG have not been adequately evaluated.

2.5 Postoperative atrial fibrillation

After admission to the intensive care unit, coronary artery bypass patients still have risks to face, which can negatively affect their early clinical outcome. Among these factors, atrial fibrillation (AF), the most common arrhythmias occurring after conventional CABG, is by far the most important one (Aranki *et al.* 1996, Mathew *et al* 1996, Almassi *et al.* 1997).

Postoperative AF, its incidence ranging from 5 % to 40 %, has been associated with increased morbidity and prolonged hospitalization (Bietz 1997, Kowey *et al.* 1997, Stamou *et al.* 2000, Hravnak *et al.* 2002). The onset of AF usually occurs between the second and the third postoperative days (Maisel *et al.* 2001). The onset mechanisms of AF are dominated by atrial extrasystoles with multiple atrial extrasystoles and short runs of AF preceding the main AF onset in the majority of cases (Taylor *et al.* 2002). It has been suggested that surgical manipulation of the right atrium, surgical thoracic trauma, the use of cardioplegic solutions and cross-clamping of the aorta could trigger AF in patients undergoing coronary artery bypass surgery (Creswell *et al.* 1993, Asamura *et al.* 1993, Mathew *et al.* 1996, Aranki *et al.* 1996). Prophylactic β-blockers and amiodarone all reduce the risk of postoperative AF without any significant difference between them (Hogue *et al.* 2000, Maisel *et al.* 2001, Crystal *et al.* 2002). A recent Finnish study suggested that intravenous metoprolol is well-tolerated and more effective than oral metoprolol in the prevention of AF after cardiac surgery (Halonen *et al.* 2006). Also biatrial overdrive pacing has been shown to prevent post-CABG AF (Fan *et al.* 2000, Levy *et al.* 2000). Although there is some evidence that OPCAB surgery may reduce the incidence of post-operative AF, this finding is not clearly supported by high quality randomized trials (Athanasiou *et al.* 2004).

The most devastating complication caused by AF is a stroke (Naylor *et al.* 2002). In fact, the occurrence of AF after cardiac surgery has been increasingly recognized as a condition underlying the development of the stroke (Taylor *et al.* 1987, Reed *et al.* 1988, Creswell *et al.* 1993, Almassi *et al.* 1997, Fan *et al.* 2000, Stamou *et al.* 2000, Stamou *et al.* 2001). A recent meta-analysis showed that antiarrythmic therapy for the prevention of postoperative AF is also associated with marked reduction of the incidence of postoperative cerebrovascular accidents (Zimmer *et al.* 2003). However, the incidence of a postoperative AF-related stroke, the timing of its occurrence and the related outcome are not yet clear.

3 Aims of the research

The aims of the present research were

1. to evaluate the impact of the severity of a coronary artery disease as assessed at preoperative angiography on the postoperative outcome after conventional coronary artery bypass surgery (I),
2. to find out whether preoperative serum level of CRP is predictive of the outcome after conventional coronary artery bypass surgery (II),
3. to review the results of off-pump (OPCAB) versus conventional on-pump coronary artery bypass surgery (CCAB) in high risk patients (III),
4. to assess whether pulmonary artery blood temperature on admission to the intensive care unit is predictive of postoperative outcome after conventional coronary artery bypass surgery (IV),
5. to evaluate the impact of postoperative atrial fibrillation as a cause of a postoperative stroke on the outcome after conventional coronary artery bypass surgery (V).

4 Patients and methods

4.1 Patients

From January 1997 to December 2001, 2630 patients underwent isolated on-pump CABG at our institution. Data on pre-, intra- and postoperative variables as well as on the angiographic status of the coronary artery were available in 2233 patients, whose results are reported in study I. Forty-five of these 2630 patients (1.7%) died during the in-hospital stay. Eighty-five patients (3.2%) experienced neurological complications ranging from disorientation to unconsciousness. Among these patients, 52 (2.0%) had a stroke and they form the basis of the study V.

All patients who underwent isolated on-pump CABG at our institution between January 2000 and December 2001 were identified using our institutional database. Of these, 764 patients had data on preoperative serum concentration of CRP as well as pre-, intra- and postoperative variables available and were included in study II.

From January 2003 to March 2004, 703 consecutive patients underwent isolated coronary artery bypass surgery. It was calculated that the best cut-off value for an additive EuroSCORE in predicting in-hospital death was 6. The mortality rate during the stay in our institution in the overall series was 1.7% (12/703). Patients with an additive EuroSCORE<6 had an in-hospital mortality rate of 0.8%, whereas for those with an additive EuroSCORE≥6 it was 6.6% ($p<0.0001$, sensitivity 80.0%, specificity 75.1%, accuracy 75.2%). Among these 703 patients, 179 had an additive EuroSCORE<6 and they were included in study III. One-hundred and twelve patients were operated with CCAB technique and 67 patients with OPCAB technique.

Study IV comprised of a retrospective analysis of 1639 patients who underwent, from January 1998 to December 2001, an isolated on-pump CABG operation and of whom we had data on pulmonary artery blood temperature at the time of admission to the ICU.

4.2 Methods

All patients underwent CCAB under mild hypothermic cardiopulmonary bypass (CPB). The degree of core temperature was assessed by a pulmonary artery thermodilution catheter. Intermittent cold blood ante- and retrograde perfusion cardioplegia was used for myocardial protection in almost all the cases. CPB rewarming was started on completion of proximal anastomoses and discontinued when pulmonary artery blood temperature reached about 36ºC. A single aortic cross-clamping technique was used in all the cases. The patients were actively rewarmed by using a forced-air convective warmer if the pulmonary artery blood temperature was lower than 36ºC.

The data concerning preoperative factors and postoperative outcome were collected retrospectively (Table 4), whereas angiographic findings of the status of the coronary arteries as well as all the intraoperative variables were collected prospectively. Left heart catheterisation was performed by Judkins´ technique. The left coronary artery was examined in six projections and the right coronary artery at least in two projections to obtain optimal assessment of each specific coronary segment.

The angiographic status of the coronary arteries was graded according to the following criteria: 1, no stenosis; 2, stenosis <50%; 3, stenosis of 50–69%; 4, stenosis of 70–89%; 5, stenosis of 90–99%; 6, vessel occlusion; and 7, the vessel is not visualized by contrast media. These scores were assigned to the following vessels/segments: on the left side, the left main coronary artery, the anterior descending artery divided into proximal, middle and distal segments, the first and second diagonal arteries, the ramus intermedius, the circumflex artery divided into proximal, middle and distal segments, and the first obtuse and second marginal branches; and on the right side, the right coronary artery divided into proximal, middle and distal segments. The overall angiographic score was calculated by summing the score of each coronary segment, the overall score varying from a minimum of 15 to a maximum of 105.

Serum concentrations of C-reactive protein were quantified using Cobas Integra 700 (Latex, Roche Diagnostics). Since in our institution serum levels of CRP <1.0mg/dL are considered normal, in most cases this parameter is not reported in patients´ laboratory records with specific values under 1.0mg/dL. Because of this, our analysis was done considering CRP as a categorical variable (CRP< or ≥1.0 mg/dL).

In all patients, the additive EuroSCORE (Nashef *et al.* 1999) was prospectively calculated by one of the staff surgeons in the operating room. These scores were then retrospectively recalculated. Since we only took the mean pulmonary artery pressure as reported in the anesthesiologists' report in our retrospective calculation into account, the systolic pulmonary pressure was calculated according to the formula proposed by Chemla (Chemla *et al.* 2004). The correlation between the initially calculated scores and the reviewed scores was statistically significant (ρ: 0.923; $p<0.0001$). The receiver operating characteristic curve (ROC) analysis showed that both the initially calculated additive EuroSCORE ($p<0.0001$; area under the curve: 0.821; 95%CI: 0.710–0.932; SE 0.057) and the recalculated additive EuroSCORE ($p<0.0001$; area under the curve: 0.849; 95%CI: 0.758–0.941; SE 0.047) were significant predictors of in-hospital mortality.

The best cut-off value of EuroSCORE in predicting in-hospital death was 6. According to the initially calculated score, patients with an additive EuroSCORE<6 had an in-hospital mortality rate of 0.6% whereas in those with an additive EuroSCORE≥6 was 5.9% ($p<0.0001$, sensitivity 80.0%, specificity 72.1%, accuracy 72.3%). According to the recalculated score, patients with an additive EuroSCORE<6 had an in-hospital mortality rate of 0.8% whereas in those with an additive EuroSCORE≥6 was 6.6% ($p<0.0001$, sensitivity 80.0%, specificity 75.1%, accuracy 75.2%). We chose the recalculated score as in the primarily calculated additive EuroSCORE we had observed, in a few cases, an overestimation of the variable unstable angina pectoris. Thus, in the present study we have only included patients with a recalculated EuroSCORE≥6. The records of these patients have been retrospectively reviewed and patients contacted by phone. The causes of death in patients who died in other institutions have been retrieved from the latter centres.

The data on those patients having suffered a postoperative stroke were retrospectively collected to evaluate those variables not originally included in the registry, in order to determine the exact number of AF events as well as the timing of occurrence of neurological event. The diagnosis of a stroke was made on the basis of neurological signs and symptoms and of imaging findings. In case of missing or negative computed tomography, the diagnosis of a stroke was solely made on the basis of clinical findings. Atrial fibrillation events having occurred during the postoperative period have been identified by continuous electrocardiographic monitoring during the intensive and subintensive care unit stay and confirmed by a 12-lead electrocardiogram. When patients were moved to the recovery rooms, usually 2–4 days after operation, the occurrence of arrhythmia was detected on the basis of patients’ complaints. Only atrial fibrillations lasting more than a few minutes were reported in the patient records.

Only a small number of stroke patients had their carotid arteries examined preoperatively, because in our institution preoperative carotid duplex examination is only performed in patients having carotid bruit in preoperative auscultation or history of transient ischemic attack or stroke. The intraoperative findings of calcification in ascending aorta have been assessed only by palpation. In our institution we prefer the use of amiodarone in the management of postoperative AF. In a few cases in this series we also used electrical cardioversion as well as β-blockers, ibutilide, quinidine and digoxin. Anticoagulation treatment with enoxaparin (Klexane) was started with those patients with prolonged or repeating AF.

4.3 Statistical analysis

The statistical analysis was performed using SPSS software (SPSS v. 10.0.5, SPSS Inc., Chicago, Ill., USA). The Chi-square test and the Fisher's exact test were used for the univariate analysis of categorical data. The Mann-Whitney test and the Kruskal-Wallis test were used to assess the distribution of continuous variables in different subgroups. The Spearman's test was used to evaluate the correlation between variables. The area under the receiver-operating characteristic (ROC) curve was calculated to depict the relationship between the postoperative end-points and coronary angiographic score, and to identify the related cut-off points. These cut-off points were then determined by choosing the value with the highest sensitivity, specificity and accuracy. Logistic regression with the help of backward selection was used for a multivariate analysis. Unless otherwise indicated, the multivariate analysis included only the preoperative variables shown to be significantly associated with the outcome in the univariate analysis. Odds ratios for overall coronary angiographic score, cardiac ejection fraction, patient's age and pulmonary artery blood temperature are reported for an increase of ten units. We have used a propensity score-matching analysis in order to compensate for differences in patient characteristics between the OPCAB and CCAB study groups. Nonparsimonious logistic regression including pre- and operative variables (additive and logistic EuroSCOREs were excluded) was performed to predict the probability that the patient would be assigned to one of the study groups. Only variables with $p<0.2$ were entered into the final regression model. This final model included age, gender, neurological dysfunction, preoperative intraaortic balloon pump, number of proximal anastomoses, preoperative level of creatinine, and calcified ascending aorta. The Hosmer and Lemeshow test for the final regression model was $p=0.314$. Then, the receiver operating characteristics (ROC) analysis was used to assess the validity of propensity score model. A $p<0.05$ was considered statistically significant.

5 Results

The distributions of demographic variables, comorbidities and other preoperative risk factors in studies I, II, IV and V have been summarized in Table 4.

Table 4. Preoperative risk factors in studies I, II, IV and V.

Risk factor	Study I (%)	Study II (%)	Study IV (%)	Study V (%)
Age	63.5±9.3	64.0±9.2	63.8±9.2	67.7±8.0
Sex				
Male	1669 (74.7)	574 (75.1)	1221 (74.5)	35 (67.3)
Female	564 (25.3)	190 (24.9)	418 (25.5)	17 (32.7)
History of myocardial infarction	1001 (44.8)	334 (43.7)	727 (44.4)	33 (63.5)
History of stroke	108 (4.8)	32 (4.2)	73 (4.5)	10 (19.2)
Diabetes	524 (23.5)	180 (23.6)	396 (24.2)	22 (42.3)
Lower limb ischemia	162 (7.3)	44 (5.8)	118 (7.2)	12 (23.1)
NYHA class				
I	28 (1.3)	8 (1.0)	24 (1.5)	0
II	511 (22.9)	182 (23.8)	378 (23.1)	3 (5.8)
III	1118 (50.1)	363 (47.5)	798 (48.7)	27 (51.9)
IV	576 (25.8)	211 (27.6)	439 (26.8)	22 (42.3)
Left ventricular ejection fraction (%)	66±16	67±16	66±12	56±2
Type of operation				
Elective	1567 (70.2)	491 (64.3)	1118 (68.2)	25 (48.1)
Urgent	532 (23.8)	222 (29.1)	414 (25.3)	22 (42.3)
Emergent	134 (6.0)	51(6.7)	107 (6.5)	5 (9.6)
Redo operation	53 (2.4)	16 (2.1)	42 (2.6)	0

Values in parenthesis are percentages; Continuous variables are reported as the mean ± standard deviation; NYHA, New York Heart Association.

5.1 Preoperative angiographic status of coronary arteries

The mean overall coronary angiographic score was 39.0±12.1, and the details on its distribution as well as the score of each coronary artery/segment distribution among different preoperative risk factors and postoperative outcome end-points are reported in Table 5. Data on coronary artery dominance was available in 2194 cases. A right dominance was present in 1427 patients (65.0%), a left dominance in 369 (16.8%) and there was a balance in 398 cases (18.1%). The mean number of the distal anastomoses performed was 3.8±1.0.

During the postoperative period, 108 patients (4.8%) developed a low cardiac output syndrome, which required a prolonged vasoactive treatment in 84 cases (3.8%), an intra-aortic balloon pump in 21 cases (0.9%), redo coronary artery bypass grafting in two cases (0.1%) and mitral valve replacement in one case

(0.05%). Thirty-seven patients (1.7%) died during the in-hospital stay. Cardiac complication was the primary cause of death in 25 patients, neurological complication in 10 patients, bleeding in one case and multiorgan failure in another case. In almost all the cases, the clinical course of these patients was complicated by a cardiac and/or multiorgan failure.

5.1.1 Impact of preoperative variables on postoperative death

The univariate analysis showed that the preoperative NYHA class ($p<0.0001$), history of myocardial infarction ($p=0.005$), diabetes ($p=0.04$), lower limb ischemia ($p=0.04$), the emergency and urgency nature of the procedure ($p<0.0001$), patient's age ($p<0.0001$), cardiac ejection fraction ($p<0.0001$), and the overall coronary angiographic score ($p=0.016$) were predictive of postoperative death. Among the operative variables, intraoperative bleeding ($p=0.04$) and the length of perfusion ($p<0.0001$), but not the aortic cross-clamping time ($p=0.07$), were predictors of postoperative death.

The multivariate analysis including only the preoperative variables showed that cardiac ejection fraction ($p<0.0001$, OR 0.505, 95% CI: 0.385–0.671) and history of lower limb ischemia ($p=0.008$, OR 4.243, 95% CI: 1.458–12.352) were predictors of postoperative death. However, the inclusion of cardiac ejection fraction restricted the analysis only to 1290 patients. When the analysis was extended to all the patients by excluding preoperative cardiac ejection fraction from the model, the multivariate analysis showed that patient's age ($p=0.01$, OR 1.174, 95% CI: 1.130–2.665), the preoperative NYHA class ($p=0.001$) and the coronary angiographic score ($p=0.03$, OR 1.027, 95% CI: 1.003–1.052) were predictors of postoperative death.

The best cut-off value for coronary angiographic score in predicting postoperative death was 39.5 (sensitivity: 54.5%, specificity: 61.6%, area under the curve: 0.615, SE 0.049, $p=0.016$). Postoperative death occurred in 15 patients (1.1%) having an angiographic score of <40 and in 22 patients (2.5%) having a score ≥40 ($p=0.004$, OR 2.354, 95% CI: 1.214–4.562).

5.1.2 Impact of preoperative variables on the development of postoperative low-output syndrome

The univariate analysis showed that female sex ($p=0.01$), the preoperative NYHA class ($p<0.0001$), history of myocardial infarction ($p<0.0001$), the emergency and urgency condition of the procedure ($p<0.0001$), redo operation ($p=0.004$), age ($p<0.0001$), preoperative cardiac ejection fraction ($p<0.0001$), and the overall coronary angiographic score ($p=0.001$) were predictive of the development of a postoperative low-output syndrome. Among the intraoperative variables, blood loss ($p=0.02$), the length of perfusion ($p<0.0001$) and the aortic cross-clamping time ($p=0.01$) were predictors of a postoperative low-output syndrome.

The multivariate analysis of the preoperative variables showed that cardiac ejection fraction ($p<0.0001$, OR 0.693, 95% CI: 0.580–0.0.817) and the urgent/ emergent nature of the operation ($p=0.001$) were predictors of a postoperative low-output syndrome. The inclusion of cardiac ejection fraction restricted the analysis only to 1290 patients. When the analysis was extended to all the patients by excluding preoperative cardiac ejection fraction from the model, the multivariate analysis showed that patient's age ($p<0.0001$, OR 1.582, 95% CI: 1.243–2.004), the urgent/emergent nature of the operation ($p<0.0001$), redo operation ($p=0.003$, OR 3.763, 95% CI: 1.571–9.013), history of myocardial infarction ($p=0.01$, OR 1.616, 95% CI: 1.063–2.456), and the coronary angiographic score ($p=0.04$, OR 1.172, 95% CI: 1.010–1.218) were predictors of a postoperative low-output syndrome.

The best cut-off value for coronary angiographic score in predicting a postoperative low-output syndrome was 39.5 (sensitivity: 53.7%, specificity: 62.0%, area under the curve: 0.593, SE 0.029, $p=0.001$). The postoperative low-output syndrome occurred in 50 patients (3.6%) having an angiographic score of <40 and in 58 patients (6.7%) having a score ≥40 ($p=0.001$, OR 1.894, 95% CI: 1.285–2.793).

5.1.3 Coronary angiographic score and preoperative ejection fraction

The coronary angiographic score was significantly correlated with the preoperative value of cardiac ejection fraction ($\rho=0.122$, $p<0.0001$). The mean angiographic score was 38.7±11.4 among patients with an ejection fraction ≥50% and 42.7±13.2 among those with an ejection fraction <50% ($p<0.0001$).

5.1.4 Angiographic status of each coronary artery/segment and postoperative outcome

The results of the univariate analysis for prediction of postoperative outcome according to the angiographic status of each coronary artery/segment are reported in Table 5. The multivariate analysis including only the coronary artery/segments which were found to be significantly associated with postoperative outcome in the univariate analysis, showed that the angiographic status of the first diagonal artery ($p=0.01$, OR 1.256, 95% CI: 1.057–1.492) and of the first left obtuse marginal artery ($p=0.002$, OR 1.278, 95% CI: 1.090–1.498) were predictive of postoperative death, whereas the angiographic status of the second diagonal artery ($p=0.001$, OR 1.140, 95% CI: 1.052–1.232) and of the proximal segment of the left circumflex artery ($p=0.002$, OR 1.201, 95% CI: 1.072–1.345) were predictive of a postoperative low cardiac output syndrome.

5.1.5 Angiographic status of the proximal segment of the left circumflex coronary artery and postoperative outcome

The degree of stenosis of the proximal segment of the left circumflex coronary artery was significantly associated with most of the preoperative risk factors and with the postoperative outcome end points (Table 5). There was a correlation between the angiographic status of this artery segment and the overall angiographic score ($p<0.0001$), in particular, there was a relevant increase in the overall angiographic score in case of its occlusion or not visualization (Fig. 1). Indeed, the angiographic score of the proximal segment of the left circumflex coronary artery was shown to be significantly associated with the postoperative outcome (Figs 2,3). In particular, the postoperative mortality and the low cardiac output syndrome rates, when the proximal segment of the left circumflex coronary artery was visualized as open were 1.4% and 4.3%, respectively, whereas they were 4.2% and 10.8%, respectively, when it was occluded or not visualized ($p=0.02$, $p=0.001$). When the degree of stenosis of the proximal segment of the left circumflex artery was included in the multivariate analysis substituting the overall angiographic score (preoperative cardiac ejection fraction excluded), patient's age ($p=0.005$, OR 1.825, 95% CI: 1.195–2.788), the preoperative NYHA class ($p=0.001$) and the degree of stenosis involving the proximal segment of the left circumflex artery ($p=0.03$, OR 1.245, 95% CI: 1.025–1.512) were predictors of postoperative death.

Similarly, when the variable LCXa was included in the multivariate analysis substituting the overall angiographic score, patient's age ($p<0.0001$, OR 1.582, 95% CI: 1.243–2.023), the emergent and urgent nature of the operation ($p<0.0001$), redo operation ($p=0.003$, OR 3.841, 95% CI: 1.613–9.144), history of myocardial infarction ($p=0.02$, OR 1.624, 95% CI: 1.069–2.468), and the degree of stenosis involving the proximal segment of the left circumflex artery ($p=0.03$, OR 1.141, 95% CI: 1.015–1.282) were predictors of a postoperative low-output syndrome.

5.1.6 Coronary artery dominance and postoperative outcome

The postoperative mortality rate among patients with right, balanced and left coronary dominance was 1.3%, 1.3% and 3.2%, respectively ($p=0.04$), while the postoperative rate of a low cardiac output syndrome was 3.8%, 6.5% and 7.3%, respectively ($p=0.003$). The overall coronary angiographic score was similar in each of the dominance patterns ($p=0.38$). The angiographic scores for each coronary artery/segment in patients who died or developed a low cardiac output syndrome postoperatively according to the pattern of coronary dominance are reported in Table 6.

The multivariate analysis including the angiographic scores of all the coronary artery/segments and the coronary dominance pattern, showed that the angiographic status of the first diagonal artery ($p=0.003$, OR 1.312, 95% CI: 1.096–1.572), the first left obtuse marginal artery ($p=0.004$, OR 1.268, 95% CI: 1.078–1.490), and coronary dominance pattern ($p=0.05$) were predictive of postoperative death.

The angiographic status of the second diagonal artery ($p=0.001$, OR 1.141, 95% CI: 1.055–1.234) and of the proximal segment of the left circumflex artery ($p=0.002$, OR 1.200, 95% CI: 1.069–1.347), and coronary dominance pattern ($p=0.003$) were predictive of a postoperative low cardiac output syndrome. These results are rather similar to those of the multivariate analysis including only the coronary artery/segments which were found to be significantly associated with postoperative outcome in the univariate analysis.

In order to better evaluate the impact of the severity of coronary artery disease affecting the major arteries according to the coronary dominance pattern, the angiographic score of each segment of the right coronary, left anterior descending and circumflex artery as well as their branches (the first and second diagonal for the left anterior descending artery, and the first and second obtuse marginal for the circumflex artery) were summed to get the overall angiographic score of three major myocardial territories. These three regional angiographic scores as well as the angiographic score of the left main coronary artery and the coronary dominance pattern were included in the regression model in order to identify the coronary territory having the major impact on the postoperative outcome. The multivariate analysis showed that the left circumflex coronary artery territory ($p=0.002$, OR 1.070, 95% CI: 1.025–1.116) and the coronary dominance pattern ($p=0.02$) were predictive of postoperative death, whereas the left anterior descending coronary artery territory ($p=0.02$, OR 1.034, 95% CI: 1.006–1.063), the left circumflex coronary artery territory ($p=0.02$, OR 1.036, 95% CI: 1.006–1.066) and the coronary dominance pattern ($p=0.002$) were predictive of a postoperative low cardiac output syndrome.

5.1.7 Coronary angiographic score and adequacy of coronary revascularization

The mean number of distal anastomoses in patients who died postoperatively was 3.7 ± 1.0, whereas it was 3.8 ± 0.8 among survivors ($p=0.38$). The mean number of distal anastomoses was the same among patients who suffered postoperatively from a low cardiac output syndrome and in those who did not (3.8, $p=0.8$). No statistically significant differences were observed in each tertile of the overall coronary angiographic score between patients who died ($p>0.11$) or developed a low cardiac output syndrome postoperatively ($p>0.28$) and those who were not affected by such adverse events.

Table 5. Coronary angiographic scores according to different risk factors and postoperative outcome end-points (Study I).

Variable	n	Left main	LADa	LADb	LADc	Diag. 1	Diag. 2	IM	CXa	CXb	CXc	LOM1	LOM2	RCAa	RCAb	RCAc	Overall angio-graphic score
Preoperative risk factors																	
Myocardial infarction																	
No	1232 (55.2)	1.8**	3.6**	2.8	1.8	2.8**	2.0	2.0**	2.7**	2.6	1.8	2.6	2.0	3.2*	3.1***	2.7**	37.7***
Yes	1001 (44.8)	1.6	3.7	3.0	2.1	3.1	2.2	2.2	2.9	2.6	1.9	2.7	2.2	3.4	3.6	3.1	40.5
Diabetes																	
No	1709 (76.5)	1.8*	3.7	2.9	2.0	2.9	2.1	2.0*	2.7**	2.5**	1.8	2.6	2.1	3.2**	3.3	2.9	38.6**
Yes	524 (23.5	1.6	3.6	2.9	2.0	3.0	2.1	2.2	3.0	2.8	2.0	2.8	2.2	3.5	3.5	2.9	40.2
Stroke																	
No	2125 (95.2)	1.7	3.6	2.9	2.0	2.9**	2.1	2.1	2.8**	2.6	1.9	2.6	2.1	3.3*	3.3	2.9*	38.8**
Yes	108 (4.8)	1.8	3.5	3.2	2.2	2.9	2.5	2.2	3.2	2.6	2.1	2.8	2.4	3.6	3.7	3.3	41.9
Lower limb ischemia																	
No	2071 (92.7)	1.7**	3.7	2.9	2.0	2.9	2.1	2.1	2.8*	2.6	1.9	2.7	2.1	3.2***	3.3***	2.9	38.9
Yes	162 (7.3)	1.9	3.4	2.7	1.8	2.9	1.9	1.9	3.1	2.6	2.0	2.6	2.0	4.0	4.0	3.0	40.0
NYHA class																	
I	28 (1.3)	1.3**	3.5***	2.3	1.6	2.7	2.1*	1.9	2.6**	2.4	1.5*	2.4	1.7	2.8*	2.8	2.5	34.2***
II	511 (22.9)	1.6	3.4	2.9	1.9	2.9	2.0	2.0	2.6	2.5	1.8	2.6	2.1	3.1	3.2	2.8	37.4
III	1118 (50.1)	1.7	3.7	2.9	2.0	2.9	2.0	2.0	2.8	2.6	1.9	2.6	2.1	3.4	3.4	2.9	38.9
IV	576 (25.8)	1.8	3.8	3.0	2.1	3.1	2.4	2.3	3.0	2.6	1.8	2.8	2.1	3.3	3.4	3.0	40.6
Type of operation																	
Elective	1567 (70.2)	1.6***	3.6**	3.0	2.0	2.9	2.1	2.1	2.7	2.6	1.9	2.6	2.1	3.3	3.3	2.9	38.7
Urgent	532 (23.8)	2.0	3.8	2.8	1.9	3.0	2.1	2.0	2.9	2.6	2.0	2.6	2.0	3.3	3.3	2.9	39.4
Emergent	134 (6.0)	1.8	3.9	3.0	2.0	2.9	2.5	2.4	3.0	2.5	1.8	2.8	2.1	3.4	3.2	2.8	40.1
First CABG	2180 (97.6)	1.7	3.6***	2.9	2.0	2.9**	2.1*	2.1	2.8***	2.6	1.9	2.6**	2.1	3.3***	3.3	2.9	38.8***
Redo CABG	53 (2.4)	1.9	4.7	3.1	2.1	3.9	2.9	2.5	3.8	2.7	2.3	3.7	2.6	4.4	3.8	2.9	47.5
Coronary dominance																	
Balanced	398 (18.1)	1.7	3.3***	2.8	1.8	2.9	2.0	2.0	2.6	2.6*	1.9	2.6	2.1	3.5***	3.7**	3.2***	38.9
Right	1427 (65.0)	1.8	3.7	3.0	2.0	2.9	2.1	2.1	2.9	2.7	1.9	2.6	2.1	3.1	3.3	2.9	39.0
Left	369 (16.8)	1.7	3.9	2.9	2.1	3.1	2.4	2.2	2.8	2.3	1.9	2.7	2.1	3.5	3.2	2.5	39.2
Outcome																	
Postoperative death																	
No	2196 (98.3)	1.7	3.6	2.9	2.0	2.9*	2.1*	2.1	2.8**	2.6	1.9	2.6**	2.1	3.3	3.3	2.9	38.9*
Yes	37 (1.7)	1.5	3.9	2.6	2.3	3.9	3.0	2.5	3.6	3.0	2.2	3.8	2.6	3.7	3.4	2.9	44.8
Low-output syndrome																	
No	2125 (95.2)	1.7	3.6**	2.9	2.0	2.9**	2.1**	2.0*	2.8**	2.6	1.9	2.6	2.1	3.3*	3.3	2.9	38.7**
Yes	108 (4.8)	1.7	4.0	2.9	2.1	3.5	2.9	2.6	3.4	2.7	1.9	3.1	2.4	3.7	3.3	2.7	42.9

LAD: left anterior descending coronary artery; a: proximal segment; b: middle segment; c: distal segment; Diag.: diagonal artery; CX: left circumflex coronary artery; LOM: left obtuse marginal artery; RCA: right coronary artery; *p<0.05; **p<0.01; ***p<0.0001.

Table 6. Mean coronary angiographic scores in patients who died or developed low cardiac output syndrome postoperatively according to coronary dominance (Study I).

Postoperative outcome	n (%)	Left main	LADa	LADb	LADc	Diag. 1	Diag. 2	IM	CXac	CXb	CXc	LOM1	LOM2	RCAa	RCAb	RCAc	Overall angio-graphic score
Postoperative death																	
Right dominance																	
Alive	1408 (98.7)	1.8*	3.7	3.0	2.0	2.9	2.1	2.1*	2.8	2.6	1.9	2.6	2.1*	3.1	3.3	2.9	38.9
Dead	19 (1.3)	1.2	3.8	2.8	2.1	3.8	2.7	2.9	3.4	3.2	2.0	3.6	3.1	3.8	3.6	2.9	44.9
Balanced dominance																	
Alive	393 (98.7)	1.7	3.3	2.8	1.8	2.9	2.0	2.0	2.6*	2.6	1.9	2.6	2.1	3.5	3.7	3.1	38.8
Dead	5 (1.3)	2.0	3.0	1.6	1.6	3.8	2.2	1.8	4.4	3.6	2.2	4.4	3.4	4.2	3.6	3.8	45.6
Left dominance																	
Alive	357 (96.7)	1.6	3.9	2.9	2.1	3.0	2.3*	2.2	2.7	2.3	1.9	2.7*	2.1	3.5	3.2	2.5	39.1
Dead	12 (3.3)	1.8	4.4	2.8	2.8	4.2	4.0	2.2	3.4	2.2	2.7	3.7	2.5	3.1	3.2	2.7	44.7
Postoperative low cardiac output syndrome																	
Right dominance																	
No	1375 (93.5)	1.8	3.6**	3.0	2.0	2.9	2.1	2.1	2.9	2.7	1.9	2.6	2.1	3.1	3.3	2.9	38.9
Yes	52 (6.5)	1.5	4.2	2.7	1.9	3.5	2.5	2.3	3.3	2.7	1.7	3.0	2.5	3.4	3.3	2.5	40.9
Balanced dominance																	
No	372 (96.4)	1.7	3.3	2.8	1.8	2.8	2.0	2.0	2.6	2.6	1.9	2.6	2.0	3.5	3.7	3.1	38.4*
Yes	26 (3.6)	1.8	3.6	2.8	2.0	3.5	2.8	2.6	3.0	3.1	2.6	3.2	2.9	3.9	3.7	3.5	45.2
Left dominance																	
No	342 (92.7)	1.6	3.9	2.9	2.1	3.0	2.3**	2.1*	2.7**	2.3	1.9	2.7	2.1	3.5	3.2	2.5	38.8*
Yes	27 (7.3)	2.0	4.1	3.1	2.4	3.7	3.9	3.4	3.6	2.6	1.9	3.2	2.0	3.7	3.1	2.7	45.1

LAD: left anterior descending coronary artery; a: proximal segment, b: middle segment; c: distal segment; Diag.: diagonal artery; CX: left circumflex coronary artery; LOM: left obtuse marginal artery; RCA: right coronary artery; *p<0.05; **p<0.01.

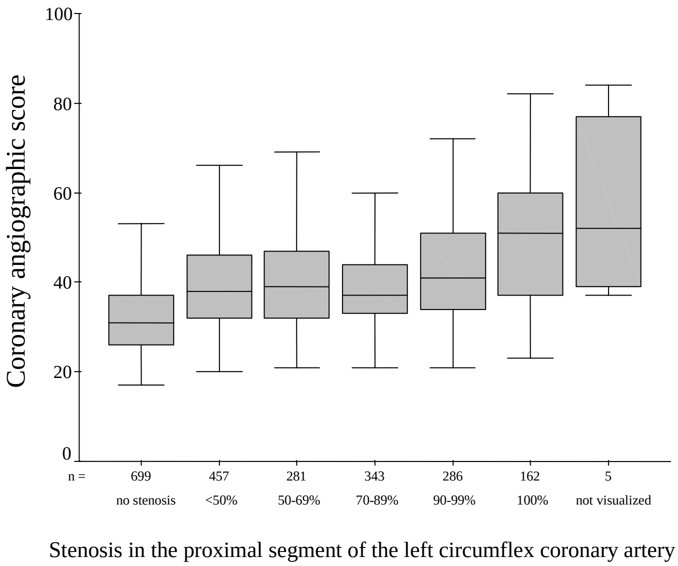


Fig. 1. Coronary angiographic score among patients with different degrees of stenosis involving the proximal segment of the left circumflex coronary artery (p<0.0001).

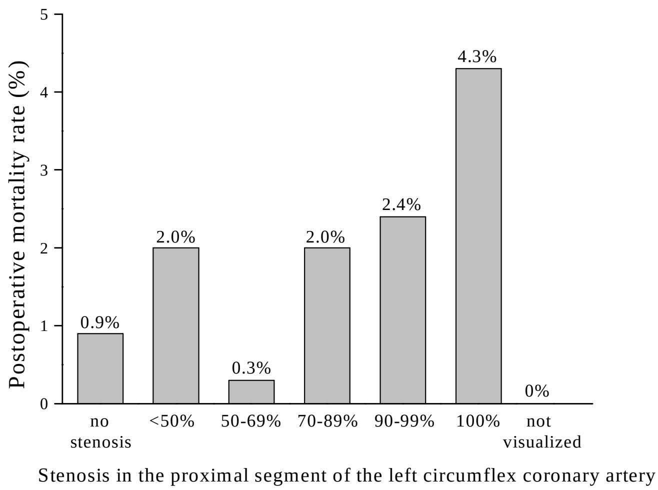


Fig. 2. Postoperative mortality rates according to different degrees of stenosis involving the proximal segment of the left circumflex coronary artery (p=0.02). The number of patients for each degree of stenosis is reported in Fig. 1.

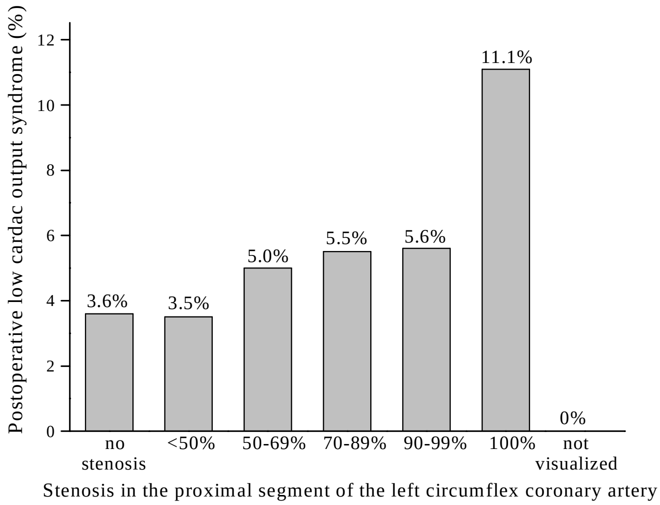


Fig. 3. Postoperative low cardiac output syndrome rates according to different degrees of stenosis involving the proximal segment of the left circumflex coronary artery (p=0.01). The number of patients for each degree of stenosis is reported in Fig. 1.

5.2 Preoperative C-reactive protein

In study II, during the in-hospital stay, 13 patients (1.7%) died, 34 (4.5%) developed a low cardiac output syndrome, and 28 (3.7%) suffered from any minor or major cerebrovascular complications. The impact of clinical variables, according to the univariate analysis, on postoperative death, low cardiac output syndrome and any postoperative cerebrovascular complications is summarized in Table 7.

114 patients had a preoperative serum concentration of CRP≥1.0 mg/dL. The distribution of the preoperative serum concentration of CRP is shown in Fig. 4.

Patients with a preoperative serum concentration of CRP≥1.0 mg/dL had a higher risk of overall postoperative death (5.3% vs. 1.1%, p=0.001), cardiac death (4.4% vs. 0.8%, p=0.002), low cardiac output syndrome (8.8% vs. 3.7%, p=0.01), and any cerebrovascular complication (4.4% vs. 3.5%, p=0.66). The preoperative serum concentration of CRP≥1.0 mg/dL was significantly more frequent among patients with history of myocardial infarction, diabetes, lower limb ischemia, low left ventricular ejection fraction, NYHA class IV and in those undergoing an urgent or emergent operation (Table 8). In the multivariate analysis, the preoperative serum concentration of CRP≥1.0 mg/dL (p=0.01, OR 6.97) and the left ventricular ejection fraction (p=0.01, OR 0.95) were independent predictors

Table 7. Distribution of pre- and intraoperative risk factors according to postoperative outcome end-points (Study II).

Risk factor	Overall	Postoperative death[a]	Postoperative low cardiac output syndrome[a]	Postoperative cerebrovascular complications[a]
Patient's age	64.0±9.2			
No adverse event		63.8±9.2**	63.8±9.2*	63.8±9.2*
With adverse event		71.8±5.7	66.7±9.7	67.6±9.4
Sex				
Males	574 (75.1)	8 (1.4)	23 (4.0)	21 (3.7)
Females	190 (24.9)	5 (2.6)	11 (5.8)	7 (3.7)
Preoperative serum C-reactive protein concentration				
<1.0 mg/dL	650 (85.1)	7 (1.1)**	24 (3.7)*	23 (3.5)
≥1.0 mg/dL	114 (14.9)	6 (5.3)	10 (8.8)	5 (4.4)
NYHA classes				
I	8 (1.0)	1 (12.5)***	1 (12.5)*	0 (0)
II	182 (23.8)	2 (1.1)	5 (2.7)	8 (4.4)
III	363 (47.5)	1 (0.3)	12 (3.3)	11 (3.0)
IV	211 (27.6)	9 (4.3)	16 (7.6)	9 (4.3)
Myocardial infarction				
No	430 (56.3)	5 (1.2)	14 (3.3)	10 (2.3)*
Yes	334 (43.7)	8 (2.4)	20 (6.0)	18 (5.4)
Diabetes				
No	584 (76.4)	10 (1.7)	28 (4.8)	19 (3.3)
Yes	180 (23.6)	3 (1.7)	6 (3.3)	9 (5.0)
Stroke				
No	732 (95.8)	13 (1.8)	33 (4.5)	28 (3.8)
Yes	32 (4.2)	0 (0)	1 (3.1)	0 (0)
Lower limb ischemia				
No	720 (94.2)	12 (1.7)	32 (4.4)	23 (3.2)**
Yes	44 (5.8)	1 (2.3)	2 (4.5)	5 (11.4)
Coronary angiographic score	39.0±11.4			
No adverse event		39.0±11.4	38.9±11.3	38.9±11.3
With adverse event		42.7±13.1	42.7±13.2	42.5±12.9
Coronary dominance (748 pts.)				
Right	457 (61.1)	6 (1.3)	11 (2.4)**	14 (3.1)
Balanced	161 (21.5)	3 (1.9)	11 (6.8)	8 (5.0)
Left	130 (17.4)	4 (3.1)	10 (7.7)	5 (3.8)
Left ventricular ejection fraction (%) (443 pts.)	67.4±15.5			
No adverse event		67.7±15.3**	68.1±14.9***	67.7±15.5*
With adverse event		49.1±18.4	50.2±20.2	57.2±11.4
Operation				
Elective	491 (64.3)	5 (1.0)	12 (2.4)**	18 (3.7)
Urgent	222 (29.1)	6 (2.7)	17 (7.7)	9 (4.1)
Emergent	51 (6.7)	2 (3.9)	5 (9.8)	1 (2.0)
Type of operation				
Primary	748 (97.9)	12 (1.6)	31 (4.1)**	27 (3.6)
Redo	16 (2.1)	1 (6.3)	3 (18.8)	1 (6.3)
Intraoperative bleeding (ml)	727±443			
No adverse event		721±430	719±430	726±446
With adverse event		1038±911	900±650	737±346
Aortic cross-clamping time (min)	91.0±39.6			
No adverse event		90.8±39.7	90.3±39.8**	90.8±40.0
With adverse event		103.1±26.4	100.6±29.7	96.4±25.3
CPB time (min)	118.2±33.0			
No adverse event		117.3±31.0**	116.6±30.4***	117.4±32.5**
With adverse event		169.2±76.1	151.6±50.1	138.2±40.3

Values in parentheses are percentages; Continuous variables are reported as the mean±standard deviation; [a]: Continuous variables are reported for those who did not versus those who had adverse outcome; NYHA: New York Heart Association; CPB: cardiopulmonary bypass; *: p<0.05; **: p<0.01; ***: p<0.0001.

Table 8. Distribution of C-reactive protein < or ≥1.0 mg/dL among other preoperative risk factors (Study II).

Risk factor	<1.0 mg/dL (650 pts.)	≥1.0 mg/dL (114 pts.)	p-value
Patient's age	63.7±9.1	65.1±9.6	p=0.15
Sex			p=0.18
Males	494 (76.0)	80 (70.2)	
Females	156 (24.0)	34 (29.8)	
NYHA classes			p<0.0001
I	7 (1.1)	1 (0.9)	
II	168 (25.8)	14 (12.3)	
III	335 (51.5)	28 (24.6)	
IV	140 (21.5)	71 (62.3)	
Myocardial infarction			p<0.0001
No	389 (59.8)	41 (36.0)	
Yes	261 (40.2)	73 (64.0)	
Diabetes			p=0.05
No	505 (77.7)	79 (69.3)	
Yes	145 (22.3)	35 (30.7)	
Stroke			p=0.26
No	625 (96.2)	107 (93.9)	
Yes	25 (3.8)	7 (6.1)	
Lower limb ischemia			p=0.02
No	618 (95.1)	102 (89.5)	
Yes	32 (4.9)	12 (10.5)	
Coronary angiographic score	38.8±11.4	40.6±11.4	p=0.07
Coronary dominance (748 pts.)			p=0.07
Right	399 (62.7)	58 (51.8)	
Balanced	129 (20.3)	32 (28.6)	
Left	108 (17.0)	22 (19.6)	
Left ventricular ejection fraction (%) (443 pts.)	68.2±15.2	62.1±16.6	p=0.006
Operation			p<0.0001
Elective	456 (70.2)	35 (30.7)	
Urgent	159 (24.5)	63 (55.3)	
Emergent	35 (5.4)	16 (14.0)	
Type of operation			p=0.66
Primary	637 (98.0)	111 (97.4)	
Redo	13 (2.0)	3 (2.6)	

Values in parentheses are percentages; Continuous variables are reported as the mean±standard deviation; NYHA: New York Heart Association.

of postoperative death. The postoperative mortality rate was 0.3% among patients with a preoperative CRP<1.0 mg/dL and an ejection fraction ≥50%, whereas it was 21.4% among those with a preoperative CRP≥1.0 mg/dL and an ejection fraction <50% (p<0.0001). Figure 5 depicts the increase in risk of postoperative death by increasing the preoperative serum concentration of C-reactive protein and decreasing preoperative left ventricular ejection fraction.

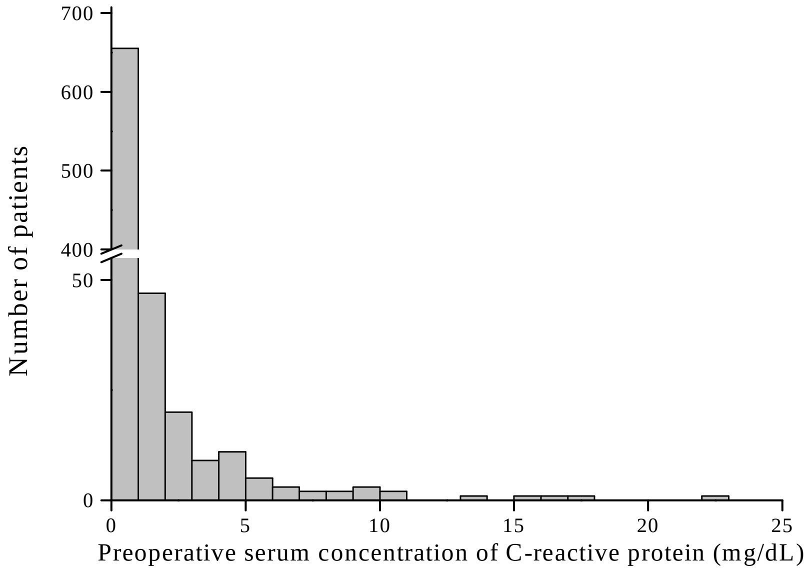


Fig. 4. Distribution of preoperative serum concentration of C-reactive protein.

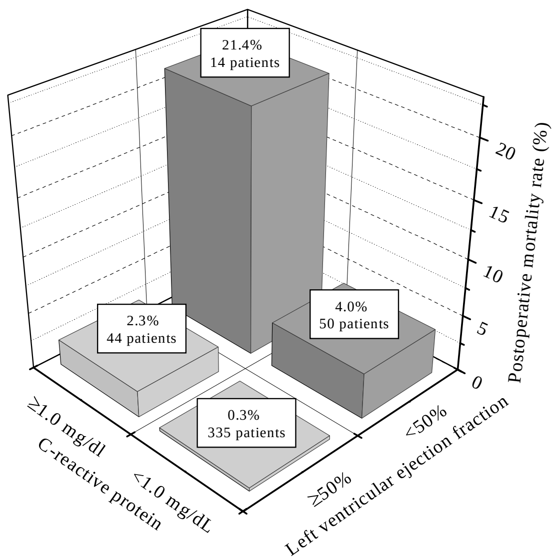


Fig. 5. Progressive increase of postoperative mortality rate by increasing preoperative serum concentration of C-reactive protein and decreasing preoperative left ventricular ejection fraction in 443 patients (p<0.0001).

5.3 Operative technique

In paper V during the study period, 183 patients with a EuroSCORE≥6 (26.0% of all the patients) underwent coronary artery bypass surgery at our institution. Four patients underwent pump-supported beating heart coronary surgery without aortic cross-clamp and were excluded from this analysis. In three of these patients, having an additive EuroSCORE ranging from 9 to 16, OPCAB was performed by a surgeon not entirely committed to off-pump coronary surgery (out of 14 operations belonging to this series he performed 2 employing the off-pump technique). Another patient with an additive EuroSCORE of 11 was operated by a surgeon "half committed" to OPCAB (out of 28 operations belonging to this series he performed 12 employing the off-pump technique) (Table 9). One of these patients died during the immediate postoperative period of pulmonary embolism.

The clinical and operative variables of 179 patients included in this analysis are summarized in Table 10. The risk factors of 40 propensity-matched pairs are also reported in the same Table 10. Only one conversion to CCAB occurred in this series, and this patient was considered in the analysis as belonging to the OPCAB group. In this patient, CCAB was required because of hemodynamic instability during completion of the last distal anastomosis. This 81-year-old woman underwent an urgent operation for unstable angina. Her additive EuroSCORE was 10 and logistic EuroSCORE of 14.0%, preoperative left ventricular function was normal, baseline cardiac index was 2.27 L/min/m^2. Her postoperative recovery was uneventful. The 30-day postoperative mortality rate was 6.1% and the in-hospital mortality rate was 6.7%. Table 11 summarizes the postoperative complications in the entire series and among propensity-matched pairs.

Table 9. Distribution of OPCAB and CCAB operations according to surgeons (p<0.0001) (Study III).

Surgeon	OPCAB (%)	CCAB (%)	n
A	5 (50.0)	5 (50.0)	10
B	0 (0)	23 (100)	23
C	2 (14.3)	12 (85.7)	14
D	0 (0)	3 (100)	3
E	0 (0)	12 (100)	12
F	12 (42.9)	16 (57.1)	28
G	14 (93.3)	1 (6.7)	15
H	23 (100)	0 (0)	23
I	3 (27.3)	8 (72.7)	11
L	3 (12.0)	22 (22.0)	25
M	4 (40.0)	6 (60.0)	10
N	1 (20)	4 (80)	5
Total	67 (37.4)	112 (62.6)	179

5.3.1 OPCAB versus CCAB

Table 11 summarizes the immediate postoperative outcome in the entire series and in 40 propensity-matched pairs according to the surgical strategy. In both comparative analyses, the outcome in the OPCAB was similar to that of patients of the CCAB group. No major difference was observed both in terms of mortality and major morbidity. This occurred despite some differences in the preoperative and operative variables noted among the study groups in the entire series, still having similar additive and logistic EuroSCORE. Although the amount of propensity-matched pairs was relatively small, the results of this analysis further confirm that OPCAB achieved results comparable to CCAB. The incidence of a postoperative stroke was also similar despite a higher incidence of diseased ascending aorta encountered in the OPCAB group.

Higher cardiac troponin I levels have been detected postoperatively in the OPCAB group. This parameter has not been associated with 30-day postoperative mortality (Mann-Whitney test: p=0.19, area under the ROC curve 0.62). Two patients who underwent OPCAB had a marked increase in cardiac troponin I and a massive myocardial infarction preoperatively. They had an intra-aortic balloon pump inserted preoperatively and their left ventricular ejection fraction was 25%

and 20%, respectively. Their additive and logistic EuroSCOREs were 18 and 73.7%, and 16 and 62.9%, respectively. On the first postoperative day, cardiac troponin levels were 1401 and 3408 ng/ml, respectively. One of these two patients died of multiorgan failure. Since diagnosis of myocardial infarction in most cases was made before admission to our hospital employing in some cases measurement of troponin T, we do not have the possibility to stratify the severity of preoperative myocardial infarction according to this parameter. Fifty percent of patients in the CCAB and 39% of patients in the OPCAB group had a maximum postoperative level of troponin I20 ng/ml (p=0.19).

5.3.2 Predictors of immediate postoperative death

Risk factors associated with significantly increased risk of 30-day postoperative death at univariate analysis are listed in Table 12. Logistic regression showed that congestive heart failure (p=0.006, OR 6.366, 95% CI: 1.682–24.093) and baseline cardiac index (p=0.018, OR 0.171, 95% CI: 0.040–0.735) were independent predictors of 30-day postoperative death. These results were not affected by entering the propensity score as a covariate in the final logistic regression analysis.

The area under the ROC curve for baseline cardiac index in predicting 30-day postoperative death was 0.772 (SE 0.090, p=0.003, 95% CI: 0.596–0.949). Thirty-day postoperative mortality was 20.6% (7/34) in patients with baseline cardiac index <2.00 L/min/m^2 and 2.8% (4/145) in those with higher baseline cardiac index (sensitivity 63.6%, specificity 83.9%, accuracy 82.7%; at logistic regression: p=0.006, OR 6.762, 95% CI: 1.751–26.111). Eleven patients (16.4%) in the OPCAB group had a baseline cardiac index <2.00 L/min/m^2 versus 23 patients (20.5%) in the CCAB group (p=0.50).

Congestive heart failure was the only predictor of in-hospital death (p=0.009, OR 5.238, 95% CI: 1.524–18.002), whilst baseline cardiac index tended to be an independent predictor of this endpoint (p=0.061, OR 0.307, 95% CI: 0.090–1.055). These results were not affected by entering the propensity score as a covariate in the final logistic regression analysis.

Table 10. Baseline characteristics in the entire series and in propensity matched pairs (Study III).

Risk factor	Entire series						Propensity-matched pairs					
	Overall	OPCAB (67 patients)	CCAB (112 patients)	p-value	F-statis-tics	Initial bias	Overall	OPCAB (40 patients)	CCAB (40 patients)	p-value	F-statis-tics	Bias after matching
Age	72.7±7.4	74.1±6.2	71.9±7.9	0.08	1.399	–2.183	73.9±5.2	74.1±5.3	73.6±5.1	0.74	0.796	0.441
Females	69 (38.5)	20 (29.9)	49 (43.8)	0.06	14.751	0.139	24 (30.0)	14 (35.0)	10 (25.0)	0.33	3.706	0.335
Pulmonary disease	28 (15.6)	15 (22.4)	13 (11.6)	0.055	14.555	–0.108	13 (16.3)	7 (17.5)	6 (15.0)	1.00	0.360	0.025
Extracardiac arteriopathy	55 (30.7)	22 (32.8)	33 (29.5)	0.63	0.846	–0.034	26 (32.5)	14 (35.0)	12 (30.0)	0.63	0.883	0.050
Neurological dysfunction	12 (6.7)	7 (10.4)	5 (4.5)	0.12	9.758	–0.060	4 (5.0)	3 (7.5)	1 (2.5)	0.61	4.380	0.050
Unstable angina pectoris	76 (42.5)	30 (44.8)	46 (41.1)	0.63	0.781	–0.037	32 (40.0)	16 (40.0)	16 (40.0)	1.00	0	0
Urgent operation	104 (58.1)	42 (62.7)	62 (55.2)	0.33	3.913	–0.073	47 (58.8)	22 (55.0)	25 (62.5)	0.50	1.569	–0.075
Emergency operation	14 (7.8)	5 (7.5)	9 (8.0)	0.89	0.076	0.006	2 (2.5)	1 (2.5)	1 (2.5)	1.00	0	0
Recent myocardial infarction	152 (84.9)	53 (79.1)	99 (88.4)	0.09	11.081	0.093	65 (81.3)	31 (77.5)	34 (85.0)	0.57	2.975	–0.075
Previous cardiac surgery	8 (4.5)	3 (4.5)	5 (4.5)	1.00	0	0	5 (6.3)	1 (2.5)	4 (10.0)	0.36	8.440	–0.075
Congestive heart failure	40 (22.3)	14 (20.9)	26 (23.2)	0.72	0.526	0.023	17 (21.3)	7 (17.5)	10 (25.0)	0.59	2.689	–0.075
Critical preoperative status	28 (15.6)	10 (14.9)	18 (16.1)	0.83	0.167	0.011	9 (11.3)	4 (10)	5 (12.5)	0.72	0.492	–0.025
Intra-aortic balloon pump	4 (2.2)	2 (3.0)	2 (1.8)	0.63	1.093	–0.012	1 (1.3)	1 (2.5)	0 (0)	0.31	4.213	0.025
Ventricular septal rupture	0	0	0	–	–	–	0	0	0	–	–	–
Calcified ascending aorta	26 (14.8)	15 (22.4)	11 (10.1)	0.03	20.209	–0.123	13 (16.3)	8 (20.0)	5 (12.5)	0.55	3.356	0.075
Creatinine (mg/dL)	90±54	84±25	93±65	0.77	1.994	9.052	86.2±26.5	86.5±27.8	85.9±25.4	0.74	0.092	0.650
Renal failure	2 (1.1)	0	2 (1.8)	0.53	4.998	0.018	0	0	0	–	–	–
Left ventricular ejection fraction												
≥ 50%	113 (63.1)	42 (62.7)	71 (63.4)	1.00	0.35	0.007	45 (56.3)	25 (62.5)	20 (50)	0.26	2.600	0.125
30–49%	50 (27.9)	21 (31.3)	29 (25.9)	0.49	2.302	–0.055	29 (36.3)	12 (30.0)	17 (42.5)	0.24	4.715	–0.125
< 30%	16 (8.9)	4 (6.0)	12 (10.7)	0.42	4.865	0.047	6 (7.5)	3 (7.5)	3 (7.5)	1.00	0	0
Baseline cardiac index (L/min/m^2)	2.5±0.6	2.5±0.5	2.5±0.6	0.96	0.152	–0.024	2.5±0.6	2.5±0.6	2.4±0.6	0.67	0.111	0.050

Table 10. Continued

Risk factor	Entire series						Propensity-matched pairs					
	Overall	OPCAB (67 patients)	CCAB (112 patients)	p-value	F-statistics	Initial bias	Overall	OPCAB (40 patients)	CCAB (40 patients)	p-value	F-statistics	Bias after matching
Baseline oxygen delivery (mL/min/m^2)	396±101	402±111	393±96	0.82	1.168	–8.986	387±100	389±101	386±99	0.85	0.117	3.722
Mean pulmonary artery pressure (mmHg)	21±7	20±7	21±8	0.72	0.294	0.504	20.9±6.9	20±7	22±6	0.12	2.888	–2.025
Systolic pulmonary artery pressure> 60 mmHg	5 (2.8)	2 (3.0)	3 (2.7)	1.00	0.057	–0.003	1 (1.3)	1 (2.5)	0 (0)	0.31	4.213	0.025
n distal anastomoses	3.6±0.9	3.4±0.8	3.8±0.9	0.006	0.28	0.377	3.7±0.7	3.7±0.8	3.7±0.8	1.00	0.706	0.025
n proximal anastomoses	1.9±0.7	1.6±0.7	2.1±0.6	<0.0001	11.247	0.480	1.9±0.4	2.0±0.4	1.9±0.4	0.39	2.714	0.075
Additive EuroSCORE	8.3±2.5	8.5±2.6	8.3±2.4	0.65	0.343	–1.719	8.1±2.2	7.9±2.2	8.3±2.2	1.00	0.411	–0.325
Logistic EuroSCORE (%)	13.0±12.0	13.8±13.4	12.4±11.1	0.29	0.304	–0.296	11.6±0.10	11.6±11.1	11.7±8.3	0.50	0.005	–0.0001
Propensity score	0.54±1.35	–0.21±1.35	0.99±1.14	0.006	3.994	1.207	0.45±0.86	0.44±0.86	0.45±0.87	0.95	0.001	–0.007

Continuous variables are reported as the mean ± standard deviation. Risk factors are reported according to the EuroSCORE criteria.

Table 11. Postoperative complications in the overall series and in propensity-matched pairs (Study III).

Outcome end-point	Entire series				Propensity-matched pairs			
	Overall	OPCAB (67 patients)	CCAB (112 patients)	p-value	Overall	OPCAB (40 patients)	CCAB (40 patients)	p-value
In-hospital mortality	12 (6.7)	4 (6.0)	8 (7.1)	1.00	7 (8.8)	3 (7.5)	4 (10.0)	1.00
30-day postoperative mortality	11 (6.1)	5 (7.5)	6 (5.4)	0.75	8 (10.0)	4 (10.0)	4 (10.0)	1.00
Atrial fibrillation	80 (44.7)	30 (44.8)	50 (44.6)	0.99	37 (46.3))	17 (42.5)	20 (50.0)	0.50
Pneumonia	28 (15.6)	10 (14.9)	18 (16.1)	1.00	15 (18.8)	6 (15.0)	9 (22.5)	0.57
Stroke	13 (7.3)	4 (6.0)	9 (8.0)	0.77	6 (7.5)	3 (7.5)	3 (7.5)	1.00
Transient ischemic attack	2 (1.1)	2 (3.0)	0 (0)	0.14	2 (2.5)	2 (5.0)	0 (0)	0.49
Renal failure requiring dialysis	7 (3.9)	1 (1.5)	6 (5.4)	0.26	3 (3.8)	1 (2.5)	2 (5.0)	1.00
Postoperative bleeding requiring reoperation	10 (5.6)	4 (6.0)	6 (5.4)	0.86	2 (2.5)	2 (5.0)	0 (0)	0.49
Low cardiac output	28 (15.6)	9 (13.4)	19 (17.0)	0.67	12 (15.0)	5 (12.5)	7 (17.5)	0.75
Postoperative intraaortic balloon pump	8 (4.5)	2 (3.0)	6 (5.4)	0.71	4 (5.0)	1 (2.5)	3 (7.5)	0.61
Postoperative cardiac index (L/min/m^2)	2.57±0.53	2.46±0.51	2.63±0.53	0.57	2.6±0.55	2.50±0.51	2.70±0.59	0.26
Postoperative oxygen delivery (mL/min/m^2)	320±76	334±79	311±73	0.051	333±88	335±88	330±90	0.74
Troponin I on the 1st postop. day (ng/ml)	72±265	102±416	54±95	0.009	73±354	100±485	43±63	0.04
Highest level of troponin I (ng/ml)	81±273	117±428	58±99	0.028	85±360	117±493	48±69	0.18
Creatinine level on the 1st postoperative day	95±103	96±147	93±66	0.38	101±141	109±188	92±52	0.43
Highest level of creatinine	124±131	121±154	126±117	0.73	131±160	137±195	123±110	0.51

In parentheses are reported percentages. Continuous variables are reported as the mean ± standard deviation.

Table 12. Risk factors significantly associated with 30-day postoperative mortality in univariate analysis in the entire series (Study III).

Risk factor	p-value	Rates*
Left ventricular ejection fraction<30%	*p*=0.028	18.8% vs. 4.9%
Congestive heart failure	*p*=0.003	17.5% vs. 2.9%
Critical preoperative state	p=0.002	17.9% vs. 4.0%
Baseline mean pulmonary artery pressure	p=0.035	–
Baseline cardiac index	p=0.003	–
Baseline oxygen delivery	p=0.028	–

*: Risk factor present vs. absent.

5.3.3 Long-term outcome

During the study period (mean follow-up: 1.2±0.6 years) (Study III), 20 patients died. In two years time, the overall survival was 87.7%. Patients in the OPCAB group had a 2-year survival rate of 84.9%, whereas it was 89.2% in the CCAB group (log-rank: p=0.45). Such a difference remained non significant also when adjusted to propensity score (p=0.79). Among the propensity-matched pairs, the 2-year overall survival rate was 89.7% in the OPCAB group and 84.9% in the CCAB group (log-rank: p=0.53).

5.4 Pulmonary artery blood temperature

In study IV 33 patients (2.0%) died during the in-hospital stay; 23 patients died of cardiac complications, eight of neurological complications, one of bleeding and another of multiorgan failure. Eighty-seven patients (5.3%) developed a low cardiac output syndrome and in 19 cases the use of an intra-aortic balloon pump was required. The distribution of pre-, intra- and postoperative risk factors according to the main outcome end-points is summarized in Table 13.

The mean pulmonary artery blood temperature on admission to the ICU was 36.2°C (median: 36.2, SD: 0.60, range: 33.4–38.7). According to the univariate analysis, increased patient’s age (p=0.001), female sex (p<0.001), left ventricular ejection fraction (p=0.02), high New York Heart Association classes (p<0.0001), diabetes (p=0.001), history of myocardial infarction (p=0.004), lower limb ischemia (p=0.005), emergency/urgent operation (p<0.0001), redo operation (p<0.0001), high intraoperative pulmonary artery blood temperature (p<0.0001), prolonged aortic cross clamping time (p=0.005) and prolonged CPB time (p<0.0001) were significantly associated with high pulmonary artery blood temperature on admission to the ICU. Since the left ventricular ejection fraction was not shown in the linear logistic regression to be a predictor of postoperative pulmonary artery blood temperature, this variable was excluded from the model to extend the analysis to a larger number of patients. The linear regression analysis showed that age (p=0.004), gender (p<0.0001), New York Heart Association class (p=0.03), diabetes (p=0.002), lower limb ischemia (p=0.03), emergency/urgent operation (p<0.0001), CPB time (p<0.0001) and intraoperative pulmonary artery blood temperature (p<0.0001) were predictors of pulmonary artery blood temperature on admission to the ICU.

Pulmonary artery blood temperature on admission to the ICU was significantly associated with an increased risk of overall postoperative death (p=0.002), cardiac death (p=0.03), and a low cardiac output syndrome (p<0.0001). The pulmonary artery blood temperature on admission to the ICU was significantly correlated with prolonged length of the ICU stay (ρ=0.095, p<0.0001), and postoperative bleeding (ρ= –0.091, p=0.001), but correlation coefficients were rather low.

The ROC curve analysis showed that the pulmonary artery blood temperature on admission to the ICU in predicting postoperative death had an area under the curve of 0.660 (95% CI: 0.562–0.758, SE 0.050, p=0.002). Such a significant finding also persisted when patients with pulmonary artery blood temperature on admission to the ICU <35.0°C and >37.5°C were excluded from the analysis (AUC: 0.652). The best cutoff-value was 36.4°C (sensitivity: 63.6%, specificity: 65.2%). When the pulmonary artery blood temperature on admission to the ICU was ≥36.4°C, the overall postoperative mortality rate was 3.6%, whereas it was 1.1% when the pulmonary artery blood temperature on admission to the ICU was <36.4°C (p=0.001). In Figure 6 the postoperative mortality rates are reported according to different pulmonary artery blood temperature quintiles. Similarly, the postoperative cardiac mortality rate was 2.4% among patients with a pulmonary artery blood temperature on admission to the ICU ≥36.4°C, whereas it was 0.8% among those with a pulmonary artery blood temperature on admission to the ICU <36.4°C (p=0.01).

The ROC curve analysis showed that the pulmonary artery blood temperature on admission to the ICU in predicting a postoperative cardiac low-output syndrome had an area under the curve of 0.650 (95% CI: 0.586–0.715, SE 0.033, p<0.0001). Such a significant finding also persisted when patients with a pulmonary artery blood temperature on admission to the ICU <35.0°C and

>37.5°C were excluded from the analysis (AUC: 0.629). The best cutoff-value was 36.4°C (sensitivity: 52.2%, specificity: 65.7%). When the pulmonary artery blood temperature on admission to the ICU was ≥36.4°C, the postoperative low cardiac output syndrome rate was 8.3%, whereas it was 3.7% when the pulmonary artery blood temperature on admission to the ICU was <36.4°C (p<0.0001). In Figure 6 the low cardiac output syndrome rates are reported according to different pulmonary artery blood temperature quintiles.

The distribution of preoperative and intraoperative variables among patients with a pulmonary artery blood temperature on admission to the ICU < or ≥36.4°C is reported in Table 14. Although the pulmonary artery blood temperature on admission to the ICU, tested as a continuous variable, was not predictive of a postoperative stroke or transient ischemic attacks (p=0.25), a tendency for an increased risk of such complications was observed among those patients with a pulmonary artery blood temperature on admission to the ICU ≥36.4°C.

The results of multivariate analysis are reported in Table 15. The left ventricular ejection fraction and CPB duration were independent predictors of postoperative death and a cardiac low-output syndrome. A pulmonary artery blood temperature on admission to the ICU was an independent predictor of a cardiac low-output syndrome, but not of postoperative death. However, the inclusion of the left ventricular ejection fraction in the model restricted greatly the number of patients included into the analysis. When the latter variable was excluded from the model, thus extending the analysis to 1526 patients, logistic regression showed that the pulmonary artery blood temperature on admission to the ICU was an independent predictor of postoperative death (p<0.0001, OR 2.343, 95% CI: 1.529–3.591) and of a postoperative low cardiac output syndrome (p=0.016, OR 2.235, 95% CI: 1.162–4.297).

Figure 7 depicts the increased risk of postoperative death by increasing the pulmonary artery blood temperature on admission to the ICU and decreasing the preoperative left ventricular ejection fraction (p<0.0001).

Table 13. Distribution of pre-, intra- and postoperative risk factors according to the main outcome end-points (Study IV).

Risk factor	Postoperative death[a]	Postoperative low cardiac output syndrome[a]
Patient's age		
No adverse event	63.7±9.2**	63.6±9.2***
With adverse event	68.3±8.5	67.1±9.3
Gender		
Males	24 (2.0)	56 (4.6)*
Females	9 (2.2)	31 (7.4)
NYHA classes		
I	1 (4.2)***	1 (4.2)***
II	4 (1.1)	8 (2.1)
III	8 (1.0)	35 (4.4)
IV	20 (4.6)	43 (9.8)
Myocardial infarction		
No	12 (1.3)*	32 (3.5)***
Yes	21 (2.9)	55 (7.6)
Diabetes		
No	20 (1.6)*	65 (5.2)
Yes	13 (3.3)	22 (5.6)
Stroke		
No	30 (1.9)	83 (5.3)
Yes	3 (4.1)	4 (5.5)
Lower limb ischemia		
No	26 (1.7)**	77 (5.1)
Yes	7 (5.9)	10 (8.5)
Coronary angiographic score	38.4±11.7	38.3±11.6**
	43.7±14.8	42.5±13.5
Coronary dominance		
Balanced	4 (1.3)*	22 (7.0)**
Right	17 (1.7)	39 (3.8)
Left	11 (4.1)	23 (8.6)
Cardiac ejection fraction (%)	66±15***	67±15***
	48±19	54±20
Operation		
Elective	13 (1.2)***	34 (3.0)***
Urgent	13 (3.1)	33 (8.0)
Emergent	7 (6.5)	20 (18.7)
Type of operation		
Primary	31 (1.9)	80 (5.0)**
Redo	2 (4.8)	7 (16.7)
Intraoperative bleeding (ml)	739±389*	736±388***
	1310±1311	1018±899
Aortic cross-clamping time (min)	91.7±37.3	91.4±37.5**
	97.1±28.0	100.1±26.9
CPB time (min)	118.6±32.7***	117.8±31.9***
	167.9±72.1	151.1±59.1
Lowest intraoperative PA temperature (°C)	32.73±1.98*	32.74±2.00
	32.12±1.59	32.39±1.35
PABT on admission to the ICU (°C)	36.16±0.60**	36.15±0.59***
	36.48±0.58	36.50±0.70

[a]: Continuous variables are reported for those who did not versus those who had adverse outcome; NYHA: New York Heart Association; CPB: cardiopulmonary bypass; PA: pulmonary artery; ICU: intensive care unit. *: p<0.05; **: p<0.01; ***: p<0.0001

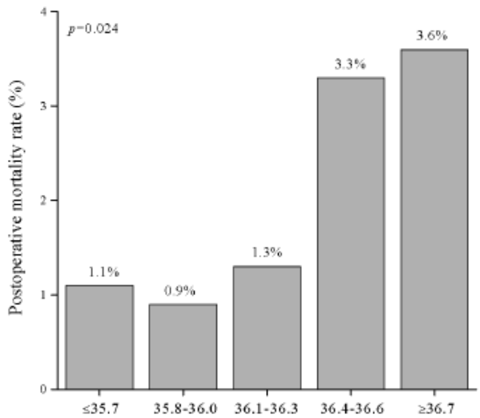
Table 14. Distribution of pre- and intraoperative risk factors and postoperative adverse events according to pulmonary artery blood temperature on admission to the ICU cut-off (Study IV).

Risk factor or outcome end-point	PA Temperature < 36.4 °C (1059 patients)	PA Temperature ≥ 36.4 °C (580 patients)	*p*-value
Preoperative risk factors			
Patient's age	64±9	63±9	0.02
Males	763 (72)	458 (79)	0.002
Females	296 (28)	122 (21)	
Ejection fraction (%)	66±15	65±16	0.22
New York Heart Association classes			<0.0001
I	17 (2)	7 (1)	
II	253 (24)	125 (22)	
III	545 (51)	253 (43)	
IV	244 (23)	195 (34)	
Diabetes	231 (22)	165 (28)	0.003
Myocardial infarction	450 (42)	277 (48)	0.04
Stroke	45 (4)	28 (5)	0.59
Lower limb ischemia	60 (6)	58 (10)	0.001
Preoperative serum concentration of creatinine (μmol/l)	92±47	89±20	0.92
Coronary angiographic score	38±12	39±12	0.59
Coronary dominance			0.52
Balanced	198 (19)	116 (20)	
Right	656 (63)	370 (65)	
Left	179 (17)	87 (15)	
Operation			<0.0001
Elective	752 (71)	366 (63)	
Urgent	261 (25)	153 (26)	
Emergent	46 (4)	61 (10)	
Redo operation	20 (2)	22 (4)	0.02
Intraoperative data			
Intraoperative bleeding (ml)	739±388	772±511	0.20
Aortic cross-clamping time (min)	90±33	95±43	0.005
Cardiopulmonary bypass time (min)	116±33	125±36	<0.0001
Lowest intraoperative PA temperature (°C)	32.6±1.0	32.9±1	<0.0001
Postoperative endpoints			
Postoperative death	12 (1)	21 (4)	0.001
Postoperative cardiac death	9 (1)	14 (2)	0.01
Postoperative cardiac low-output syndrome	39 (4)	48 (8)	<0.0001
Need of intra-aortic balloon pump during the postoperative period	7 (1)	12 (2)	0.01
Postoperative stroke or transient ischemic attack	19 (2)	20 (3)	0.04
Postoperative blood loss (ml)	747±659	720±825	0.002
Blood units transfused	2.8±3.0	2.9±3.5	0.74
Length of stay in intensive care unit	1.7±1.8	2.1±2.8	0.01

Values in parentheses are percentages. Continuous variables are reported as the mean±standard deviation.

Table 15. Results of logistic regression analysis (Study IV).

Outcome end-point and independent predictor	p-value	Odds ratio	95% Confidence interval
Postoperative mortality (882 pts.)			
Lower limb ischemia	p=0.003	5.840	1.820–18.734
Left ventricular ejection fraction	p<0.0001	0.938	0.907–0.970
Cardiopulmonary bypass time	p=0.002	1.024	1.009–1.40
Postoperative cardiac low-output syndrome (886 pts.)			
Pulmonary artery blood temperature on admission to the ICU	p=0.001	2.530	1.464–4.373
Cardiopulmonary bypass time	p<0.0001	1.018	1.008–1.028
Left ventricular ejection fraction	p<0.0001	0.957	0.938–0.975
Female sex	p=0.001	3.262	1.605–6.631



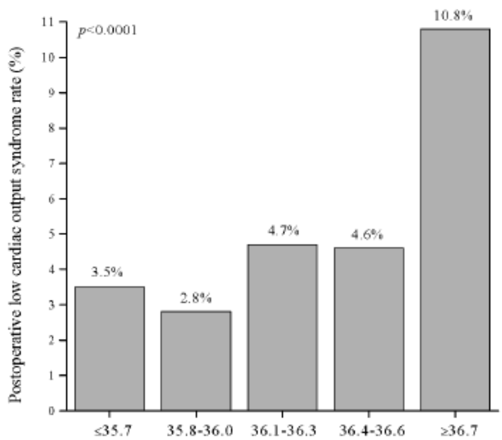


Fig. 6. Postoperative rates of death and low cardiac output syndrome after coronary artery bypass surgery according to different quintiles of pulmonary artery blood temperature at admission to the intensive care unit.

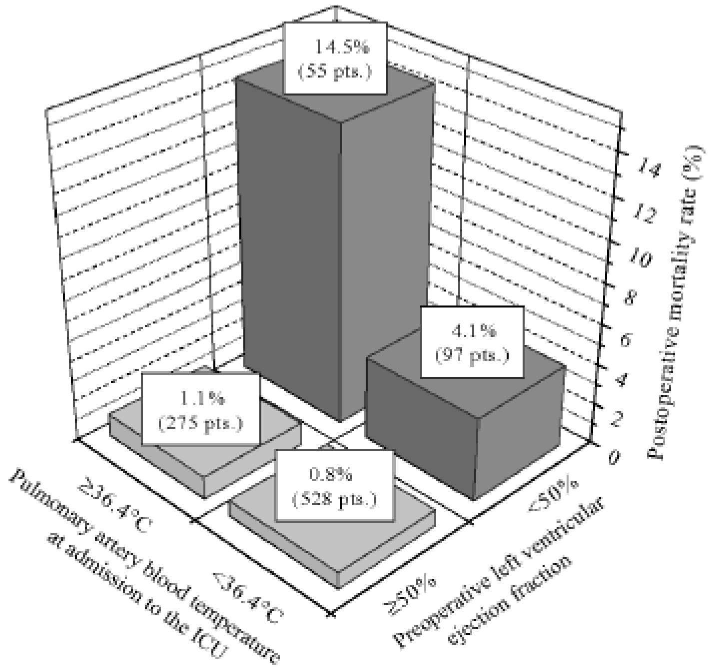


Fig. 7. Postoperative mortality rates by increasing pulmonary artery blood temperature on admission to the intensive care unit and decreasing preoperative left ventricular ejection fraction in 955 patients having undergone coronary artery bypass surgery ($p<0.0001$).

5.5 Postoperative atrial fibrillation and stroke

Study V included 52 patients (2.0%) who experienced a postoperative stroke out of 2630 CABG patients. Twelve of these patients (23.1%) died during the in-hospital stay in our institution or later on in other central hospitals. The mean intensive care unit length of stay was 5.0 days (1–36). Only one of these patients (1.9%) had a postoperative myocardial infarction and seven patients (13.5%) experienced a low cardiac-output syndrome. The ischemic cerebral event occurred after a mean of 3.7 days (0–33). Thirty-six patients had hemiplegia, 17 had aphasia/dysphasia and 17 had unconsciousness.

Forty-seven patients (90.4%) were evaluated postoperatively by a computed tomography scan. In one patient in whom the computed tomography was not performed, the diagnosis of cerebral infarction was done at autopsy. Other four patients did not have a computed tomography scan of the brain in this hospital, and one of them died during the postoperative period but the autopsy was not performed. Among those patients evaluated by the computed tomography, 24 patients had a focal, unilateral brain infarction, nine patients had multifocal unilateral focal infarctions, 10 had bilateral cerebral infarctions, and in other four there were no signs of a brain infarction on imaging. These latter four patients had hemiplegia and three of them also dysphasia/aphasia. Among those patients with a diagnosis of a brain infarction confirmed at the autopsy or at the computed tomography, bilateral brain infarctions were more frequent than an unilateral brain infarction in patients with a calcified ascending aorta (p=0.006) (Table 16).

Four patients having a calcified ascending aorta experienced a stroke after atrial fibrillation. In these patients the cerebral ischemic event occurred between the third and the eighth postoperative days, 8 hours to 28 hours after the onset of atrial fibrillation, thus suggesting that the latter was the main cause of the stroke. The outcome of patients with probable stroke pathogenesis is reported in Table 17.

Twenty patients awoke with signs and symptoms of a stroke, 10 patients (76.9%) with a calcified ascending aorta and 10 (50%) without a calcified ascending aorta or in whom atrial fibrillation did not precede the cerebrovascular complication (p=0.12). The cerebrovascular event occurred after a mean of 6.0 days (2–33) in those patients in whom atrial fibrillation preceded it, after 1.2 days (range: 0–3) in those with a calcified ascending aorta, and after 3.1 days (range: 1–16) in those without a calcified ascending aorta or in whom atrial fibrillation did not precede the cerebrovascular complication ($p<0.0001$).

Among those 30 patients in whom the status of the carotid arteries was known, a stenosis of the internal carotid artery ≥70% was more frequently present in patients without a calcified ascending aorta or who did not have postoperatively atrial fibrillation.

A mean of 2.6 postoperative atrial fibrillation episodes (range, 0–20) occurred in the overall series. In 19 patients (36.5%), atrial fibrillation preceded the occurrence of neurological complication with a mean interval of 21.3 hours (0–40). These patients experienced a mean of 2.5 episodes of atrial fibrillation (1–6) before the occurrence of neurological complication, whilst the mean overall number of atrial fibrillations in these 19 patients was 5.1 (1–20). In only eight of these patients, an anticoagulation therapy was on-going on the day of occurrence of a stroke. Warfarin was on-going in six patients, but only in two of them the TT-INR value was at the therapeutic range (2.04 and 2.32), in one patient the TT-INR value having been far above the therapeutic range (5.70).

In the univariate analysis preoperative serum concentration of C-reactive protein >1.0 mg/dL (in overall 34 patients: 50.0% vs. 12.5%, $p=0.02$), serum concentration of creatinine on the day of occurrence of neurological complication (in overall 42 patients: $p=0.002$), and cardiopulmonary bypass time (all patients: $p=0.03$) were predictive of postoperative death. The multivariate analysis showed that the preoperative left ventricular ejection fraction ($p=0.08$) and cardiopulmonary bypass time ($p=0.06$) tended to be predictors of postoperative death.

Table 16. Postoperative outcome in groups of patients with probable different stroke pathogenesis (Study V).

Risk factor	n of patients (%)	n of patients with ICA stenosis > 70% (%)[a]	n of patients awoken with stroke	Mean overall no. of AF episodes	Mean delay of stroke occurrence (days)	Bilateral brain infarction (%)	Postoperative death (%)	Improvement at discharge[b] (%)
AF preceding stroke	19 (36.5)	3 (30.0)	0	5.1 (1–20)	6.0 (2–33)	1 (6.7)	5 (26.3)	14 (100)
Calcified ascending aorta	13 (25.0)	2 (33.3)	10 (76.9)	1.5 (0–5)	1.2 (0–3)	6 (54.5)	3 (23.1)	9 (90.0)
Neither AF preceding stroke nor calcified ascending aorta	20 (38.5)	9 (64.3)	10 (50.0)	1.0 (0–5)	3.1 (1–16)	3 (16.7)	4 (20.0)	14 (87.5)

Continuous variables are reported as the mean and range; [a]: 30 patients included; [b]: only surviving patients included; AF: atrial fibrillation

6 Discussion

6.1 Risk assessment

The identification of the risk factors which the cardiac surgical patient has to face is extremely important in order to estimate the individual operative risk and to assess the quality of care. This also allows us to understand the causes and mechanisms resulting in adverse postoperative events better, thus offering the possibility for therapeutic interventions. In cardiac surgery, the identification of such risk factors is complicated by a multitude of factors intrinsically related to the high risk nature of the procedure and its related technical aspects as well as the complexity of both the surgical procedure and the anesthesiologic management.

Although a few scoring systems have been shown to be reasonable good predictors of outcome after cardiac surgery, they variably suffer from a certain inaccuracy (Orr *et al.* 1995, Baretti *et al.* 2002, Pinna-Pintor *et al.* 2002). Scoring systems and logistic regression models cannot include every risk factor, especially a factor with low incidence, so physician knowledge should temper outcome prediction in the individual. Also the simplification of continuous variables into scoring categories introduces large increments or steps of risk in the clinical model that contrasts with the gradual increases apparent in the logistic regression models.

Patient material as well as operative and anesthetic methods are in constant change. Improvements in severity-adjusted outcome have been documented, which causes pressure to the scoring systems to be revised every now and then in order to keep them up with time (Castella *et al.* 1995, Ivanov *et al.* 1999). Although valid when comparing outcomes in large numbers of unselected patients, these risk models can be inaccurate when applied to subpopulations or individuals (Schafer *et al.* 1990). Probabilities are not prediction, however, and caution must be exercised when applying scores to individuals. Common sense dictates that a patient's prognosis be assessed one day at a time. The study by Rue and colleagues supports the concept that regardless of condition at admission, it is the patient's response to therapy and daily assessments that best predict outcome (Rue *et al.* 2001, Higgins *et al.* 2001). Thus, decisions to limit therapy cannot be supported by any of the current scoring systems. Nonetheless, scoring for risk factors is of main importance.

6.2 Preoperative angiographic status of coronary arteries

The optimization of the anesthesiologic management and of the operative strategy is of key importance in cardiac surgery. This is particularly true in patients undergoing CABG as the optimal surgical strategy for a coronary artery disease is still a matter of debate (van den Brand *et al.* 2002, Vander Salm *et al.* 2002). It is objectively difficult to establish what a complete or effective revascularization is, as it is not clear what the impact of the severity of a coronary artery disease on the immediate and long-term outcome is. A few large studies have addressed this topic and concluded that the angiographic status of the coronaries is of major prognostic importance (Kennedy *et al.* 1981, Gersh *et al.* 1983, Ringqvist *et al.* 1983, Jones *et al.* 1996, Graham *et al.* 1999, Kurbaan *et al.* 2000), irrespective of the type of treatment (Jones *et al.* 1996, Kurbaan *et al.* 2000). Because of this, one of these coronary angiographic scores, the Duke score, has been used to define at which extent of coronary artery disease CABG provides better results than percutaneous transluminal angioplasty (Jones *et al.* 1996, Kurbaan *et al.* 2000).

Herein, we employed a rather descriptive scoring method that grades the degree of stenosis in the same fashion for all the vessels. This permitted the evaluation of the impact of the overall angiographic score and the identification of those vessels and their segments being associated with a poor prognosis. In this sense, the present scoring method is less restrictive than others previously used which are somewhat weighted toward the severity of the left main coronary artery (Kennedy *et al.* 1981, Gersh *et al.* 1983) or the left anterior descending coronary artery (Jones *et al.* 1996). Furthermore, angiographic scoring methods taking only the main coronary arteries into account and those falling into the one-, two- and three vessel disease classifications are not descriptive enough as they do not consider important branches such as the diagonal arteries, the ramus medianus and the left obtuse marginal arteries. Indeed, in this study the latter vessels were found to be of great prognostic importance at much larger extent than the left main and the left anterior descending coronary artery.

This observation along with the findings of the impact of the angiographic status of the proximal segment of the left circumflex coronary artery on the immediate postoperative outcome brought some indirect evidence on the importance of the territory of myocardium supplied by these vessels. Although we do not have data regarding the presence and the degree of mitral regurgitation in this patient series, the prognostic value of the diagonal, left obtuse marginal and proximal segment of the left circumflex artery suggests that a severe coronary artery disease affecting these vessels might likely have affected the function of the mitral apparatus, i.e., the left ventricle, papillary muscles and annulus. Ischemic mitral regurgitation is particularly associated with posterior infarction rather than anterior infarction (Heikkilä 1967, Sharma *et al.* 1992, Edmunds 1997, Gorman *et al.* 1997, Gorman *et al.* 1998). Sharma and colleagues observed that 80% of the patients with acute severe ischemic mitral regurgitation had a stenosis >70% of the right and left circumflex coronary arteries with or without stenosis of the left anterior descending coronary artery (Sharma *et al.* 1992). Ko and colleagues showed that in patients with a stenosis ≥60% of the left main coronary artery undergoing coronary angiography, a severe left circumflex coronary artery disease and NYHA class III–IV were independent predictors of death after angiography (Ko *et al.* 1991). However, also these authors did not provide data on mitral valve function which may support the hypothesis that significant changes in the mitral valve competence, likely associated with severe stenosis of the left circumflex coronary artery, may have adversely affected the mitral apparatus.

Elhendy and colleagues showed that myocardial viability and functional recovery after CABG are not related to the severity of coronary stenosis or the grade of collateral circulation (Elhendy *et al.* 1997). Their results suggest that surgical revascularization distally to an occluded coronary artery is associated with good functional outcome. However, other authors observed that non viable segments were more likely to be located distally to an occluded vessel and less collateralized than viable segments (Di Carli *et al.* 1994, Marzullo *et al.* 1995). The present finding of a significantly increased risk of postoperative death and a low cardiac output syndrome (i.e. prolonged need of inotropes and decreased cardiac index) after CABG in patients with occluded proximal segment of the left circumflex coronary artery is more in line with the latter point of view. Although we do not have any data to quantify the amount of collateral vessels, the association of significantly increased overall coronary angiographic score in patients with occluded proximal segment of the left circumflex coronary artery indirectly suggests a poorer collateral circulation in this coronary artery disease pattern. It is likely that our rather aggressive revascularization strategy as suggested by the relatively high mean number of distal anastomoses, despite attempting to achieve complete myocardial revascularization, was not associated with adequate recovery of myocardial function in critical territories as supplied by the left circumflex, left obtuse marginal and diagonal arteries.

6.3 Preoperative C-reactive protein

During the last decade, CRP has emerged as an important predictor of cardiovascular events in healthy subjects and in those with a known coronary artery disease. Interestingly, CRP has been shown to be a strong predictor of early and long-term outcome after percutaneous coronary intervention (Buffon *et al.* 1999, Versaci *et al.* 2000, Walter *et al.* 2001, Chew *et al.* 2001, de Winter *et al.* 2002). Furthermore, it is also an important predictor of outcome after peripheral vascular surgery (Satta *et al.* 1996, Biancari *et al.* 2000, Schillinger *et al.* 2002). A few studies showed an increased risk of adverse postoperative events in children and adults with increased preoperative serum levels of CRP undergoing cardiac surgery (Borolessa *et al.* 1986, Aronen 1990, Boeken *et al.* 1998, Fransen *et al.* 1999). However, only two recent small studies have specifically addressed this topic in patients undergoing CABG. Gaudino et al. showed in a series of 113 patients that those with preoperative levels of CRP>0.5 mg /dL did not have an increased risk to develop postoperative adverse events (Gaudino *et al.* 2002). Milazzo et al. showed in a series of 86 patients who underwent CABG that patients with a preoperative serum level of CRP 0.3 mg/dL had a significantly increased risk to experience late ischemic events (Milazzo *et al.* 1999). Still, also this small series showed that preoperative CRP levels did not have any impact on the immediate outcome of these patients.

The present study showed that the preoperative serum concentration of CRP≥1.0 mg/dL is associated with a significantly increased risk of overall postoperative death, cardiac death and a low cardiac output syndrome. Interestingly, the preoperative serum concentration of CRP was an independent predictor of postoperative death along with the left ventricular ejection fraction. It is worth noting that preoperative serum level of CRP≥1.0 mg/dL was particularly associated with a lower left ventricular ejection fraction, New York Heart Association class IV and the need of urgent/emergent operation. This observation suggests that besides the well recognized association between CRP and the coronary artery disease, the former may also be a marker of depressed ventricular function in these patients.

Peripheral levels of proinflammatory cytokines have been shown to increase in direct relation to increasing heart failure symptoms (Torre-Amione *et al.* 1996, Alonso-Martinez *et al.* 2002). Also CRP is significantly increased in the serum of patients with chronic heart failure (Pye *et al.* 1990, Niebauer *et al.* 1999, Sato *et al.* 1999, Alonso-Martinez *et al.* 2002) and it is an independent predictor of readmission to the hospital and of mortality (Boralessa *et al.* 1986). Niebauer and colleagues observed an increase in endotoxin levels in patients with chronic heart failure during acute edematous exacerbations events, which was associated with significantly increased concentrations of inflammatory markers such as CRP (Niebauer *et al.* 1999). The authors suggested that this increase in plasma endotoxin is likely due to bacterial translocation from the bowel as a result of altered gut permeability secondary to mesenteric venous congestion. Activation of immune system can also be related to peripheral hypoxia occurring in chronic heart failure, but this mechanism does not seem to be the most important trigger of cytokine production (Anker *et al.* 1998). However, the exact sites and mechanisms of production of inflammatory mediators in patients with chronic heart failure are not yet clearly identified.

The lack of specified CRP values below 1.0 mg/dL in most of the patients of this series is a study limitation. In fact, this prevented the analysis of the data considering CRP as a continuous variable and the identification of a cutoff-value for the prediction of postoperative adverse outcome. Because of this, CRP was, herein, necessarily considered as a categorical variable. Nonetheless, a cutoff value of 1.0 mg/dL demonstrated a good specificity and accuracy for the prediction of postoperative adverse events, but its sensitivity was unsatisfactory. A large prospective study by Chew and colleagues showed that the 30-day mortality rate after percutaneous coronary intervention was 4.1% among patients with preprocedural serum levels of CRP>1.01 mg/dL, whereas it was 0.2% among those with CRP≤1.00 mg/dL, thus, it somewhat substantiates the value of a cut-off level of CRP of 1.0 mg/dL as herein used (Chew *et al.* 2001).

6.4 Operative technique

The results of this study reflect those reported by Gaudino and collaborators (Gaudino *et al.* 2004), one of the few studies showing that fairly similar results can be achieved by CCAB and OPCAB. These findings, however, cannot be considered “negative” as they provide support for continuing to perform OPCAB also in high-risk patients. In fact, the present results suggest that avoidance of cardiopulmonary bypass can be attained safely also in patients with depressed ventricular function and hemodynamic instability. Certainly, the retrospective nature of this study is a major weakness for the correct interpretation of the data. We attempted to overcome this by employing the propensity score analysis. The latter is increasingly used in clinical studies since the lack of randomization affects a large number of otherwise well conducted studies. Indeed, in several cases randomization is difficult to obtain and still it can be affected by dissimilarities in the study groups. In the specific case of high-risk patients undergoing OPCAB, we believe that “true” randomization is not possible. In fact, assigning a high-risk patient to an entirely committed OPCAB or CCAB surgeon offers a potential for major treatment bias. It would be appropriate to prospectively assess in a randomized fashion the results of OPCAB surgeons to those of CCAB surgeons. This would lead to optimization of the results of OPCAB performed by experienced surgeons in beating heart surgery, avoiding the bias of CCAB surgeons who, by attitude and/or by lack of experience, are not so familiar with beating heart surgery. In this view, it would have been herein appropriate to compare the results of CCAB surgeons to OPCAB surgeons, but this was prevented by the small size of this series.

The present results have encouraged many surgeons of our team to perform OPCAB in all cases and, thus, to further increase the overall proportion of off-pump coronary surgery in our institution. This means that in the present series a certain effect of learning curve for OPCAB could have affected the results, and that likely in the near future better outcome could be expected as reported by other authors. Besides, only a few previous studies have considered those patients with an additive EuroSCORE6 as high-risk cases. In our series, in fact, patients with lower scores than 6 had an extremely low rate of postoperative death (0.6%), in patients with an additive EuroSCORE of 5 the in-hospital mortality rate having been 2.6%. Thus, we believe that a cut-off of 6 better qualifies patients at high risk.

Although the outcome in the OPCAB and CCAB groups is similar, the results of two outcome end-points require some comments. There is a burden of evidence suggesting that OPCAB is associated with decreased postoperative levels of cardiac troponin. This was not the case in the present series, likely because two patients belonging to the OPCAB group suffered preoperatively from a massive myocardial infarction and the related depressed ventricular function required preoperatively insertion of an intra-aortic balloon pump. Consequently, they had extremely high levels of cardiac troponin I during the postoperative period. The second point is the higher incidence of a diseased ascending aorta in the OPCAB group. This was likely due to conversion from intended CCAB to OPCAB in case of intraoperatively observed severely calcified ascending aorta and the anticipated increased risk of embolization. This has led to leave the ascending aorta untouched in 5 cases, to use an aortic connector in 6 cases, whereas in the other 4 cases grafts were anastomosed to the ascending aorta by hand-sewn technique. One patient with hand-sewn proximal anastomoses experienced a stroke postoperatively (6.7%). Also in the CCAB group, among 11 patients with a diseased ascending aorta, one patient had a stroke postoperatively (11.1%). However, herein we do not have routine data of all patients regarding intraoperative epiaortic ultrasound findings to establish whether, despite being calcified, the ascending aorta at the clamping and cannulation sites was free of disease. We must believe that in most cases with a calcified ascending aorta, the surgeon appropriately established whether the aorta was safe to cross-clamp or not.

What we have learned from previous studies and from our results is that OPCAB can be safely performed in high-risk patients with results as satisfactory as those achievable with CCAB. This should encourage surgeons to perform more frequently OPCAB in order to optimize the results of this technique. Larger, and possibly, prospective, randomized studies are likely to better assess the value of OPCAB in high-risk patients or, more likely, to identify specific conditions in which OPCAB can achieve better results than CCAB.

6.5 Pulmonary artery blood temperature

Controversial results have been reported regarding the use of hypothermic strategies for myocardial (Martin *et al.* 1994, The Warm Heart Investigators 1994, Kaukoranta *et al.* 1995, Rainio *et al.* 1998, Jones *et al.* 1999, Vazquez-Jimenez *et al.* 2001, Nappi *et al.* 2002, Nesher *et al.* 2003) and cerebral protection (Martin *et al.* 1994, Jones *et al.* 1999, Nathan 1999, Engelman *et al.* 2000, Grimm *et al.* 2000, Rees *et al.* 2001, Grigore *et al.* 2001) during adult cardiac surgery. Up to now, no study has provided conclusive results on the benefits or harmful effects of mild/ moderate hypothermia during CPB. The main problem in extrapolating the results of different studies is the fact that both hypothermia and normothermia can be administered and managed during and after CPB according to different strategies guided by target temperatures monitored at different sites (Jones *et al.* 1999).

The good results of our clinical experience led us to continue the use of mild hypothermic CPB associated with a non aggressive rewarming policy, which results in most patients in a slight systemic hypothermic status on arrival to the ICU. This study seems to confirm the advantages of this perfusion strategy, but our clinical results seem to conflict with those reported by Insler and colleagues (Insler *et al.* 2000). They showed that a bladder core temperature of less than 36°C was associated with an increased postoperative mortality rate, prolonged mechanical ventilation, increased red blood cell transfusion and a longer hospital stay. They referred to the bladder temperature as the core temperature, but this does not necessarily reflect the pulmonary artery blood temperature, which is generally considered as the core temperature. It has been observed that the correlation coefficient between pulmonary artery blood temperature and other core (nasopharynx or esophagus) or peripheral (urinary bladder or rectum) temperature as measured at the time of separation from CPB was somewhat low (El-Rahmany *et al.* 2000). Interestingly, they also observed that the pulmonary artery blood temperature on admission to the ICU can be rather low despite an aggressive rewarming in the operating room. However, the authors did not provide any information on differences in temperatures from different body sites on admission to the ICU, thus preventing the analysis of postoperative temperature afterdrop (El-Rahmany *et al.* 2000).

Insler and colleagues considered a urinary bladder temperature as the core temperature and they did not discontinue the CPB unless the bladder temperature was ≥37°C (Insler *et al.* 2000). Since 28% of their patients had a bladder temperature <36°C, it is likely that a large number of patients in their series experienced a significant afterdrop despite an aggressive, complete rewarming. On the contrary, it is possible that in our series the afterdrop phenomenon was less severe as patients were left to a passive, slow rewarming during the first postoperative hours. Indeed, in our material the lowest pulmonary artery blood temperature on admission to the ICU was only slightly lower than the rewarming target temperature.

Herein, the occurrence of high pulmonary artery blood temperatures on admission to the ICU can be viewed, in our experience, as a result of mechanisms leading to hyperthermia such as postoperative inflammatory reaction. Contrary to the report by Insler and colleagues (Insler *et al.* 2000), patients with a pulmonary artery blood temperature ≥36.4°C had significantly more comorbidities than those with a lower pulmonary artery blood temperature on admission to the ICU. Furthermore, it is worth noting that among other important preoperative risk factors, CPB time was shown to be predictive in the linear regression analysis of the pulmonary artery blood temperature on admission to the ICU. This may suggest that prolonged CPB time can be associated with a better rewarming, but also with a more pronounced CPB-related inflammatory reaction. The latter hypothesis seems to be confirmed by the fact that longer aortic cross clamping time, despite being significant only in the univariate analysis, was associated with an increased early postoperative pulmonary artery blood temperature.

6.6 Postoperative atrial fibrillation and stroke

Atherosclerotic lesions of the ascending aorta and of the carotid arteries have been suggested to be the main sources of embolism after cardiac surgery (Saimanen 1998, Wolman *et al.* 1999, Hogue *et al.* 1999, Biancari *et al.* 2007). Indeed, some authors suggest that preoperative screening of carotid arteries should definitely be performed in all patients with carotid bruit and history of stroke (Hill *et al.* 1999, Archbold *et al.* 2001). Asymptomatic cervical bruit has proved a highly specific clinical sign for detection of internal carotid artery stenosis, whether haemodynamically significant (> or = 50%) or otherwise, in patients undergoing myocardial revascularisation. Yet, steering carotid investigations on the basis of cervical bruit alone would result in > or = 80% internal carotid artery stenosis remaining undetected in 3% of overall patients, in whom cervical bruit is absent (Sonecha *et al.* 2006).

No touch technique to prevent dislodgement of plaques from a calcified ascending aorta and prophylactic carotid endarterectomy are expected to reduce the risk of a postoperative stroke. Major expectations are especially reserved to the role of synchronous or staged carotid endarterectomy and coronary artery bypass grafting. However, it seems that prophylactic carotid endarterectomy, which by itself carries some further operative risk, could only prevent about 40 to 50% of postoperative strokes after coronary artery bypass grafting (Naylor *et al.* 2002, Brown *et al.* 2003, Ricotta *et al.* 2003). A recent population-based study strongly questioned the benefits of combined carotid endarterectomy and coronary artery bypass grafting as the overall stroke and mortality rate was 17.7% (Brown *et al.* 2003), a rate much higher than the one calculated in a systematic review of the literature (Naylor *et al.* 2003). Certainly the finding of most importance is that in logistic regression proximal aortic atherosclerosis was the only independent risk factor for a postoperative stroke (adjusted OR 5.35) (Brown *et al.* 2003). It was also observed that in most cases, a stroke after combined carotid endarterectomy and coronary artery bypass grafting occurred beyond the first 24 postoperative hours, an observation which claims for a further etiology of a postoperative stroke other than arterial embolism (Libman *et al.* 1997, Brown *et al.* 2003). A recent large propensity score analysis did not show any increased risk of stroke, death or combined end-point with the use of combined carotid endarterectomy plus CABG versus isolated CABG (Ricotta *et al.* 2005). An absolute increased risk of adverse outcome has been, nevertheless, reported in the overall study population (Ricotta *et al.* 2005).

The lack of data on the preoperative status of the carotid arteries of all the patients is a major limitation of this study. However, our current clinical practice to perform selective preoperative carotid artery screening with duplex scanning in all patients with a history of a stroke or TIA and all patients with carotid bruit will reveal, in accordance with the literature, 80–90% of the patients with severe carotid stenosis (Hill *et al.* 1999, Archbold *et al.* 2001).

In fact, the occurrence of atrial fibrillation after cardiac surgery has been increasingly recognized as a condition underlying the development of a stroke (Taylor *et al.* 1987, Reed *et al.* 1988, Creswell *et al.* 1993, Almassi *et al.* 1997, Fan *et al.* 2000, Stamou *et al.* 2000, Stamou *et al.* 2001). The present study confirmed that atrial fibrillation may cause one third of postoperative strokes after CABG. This observation may explain why prophylactic endarterectomy provides protection only in a limited number of patients and why in most cases a stroke develops later than the first 24 postoperative hours (Naylor *et al.* 2002). In fact, atrial fibrillation usually occurs far beyond the first postoperative day.

The finding of an association between atrial fibrillation and a postoperative stroke seems to be rather strong. It has a major clinical importance as AF regards about one third of the patients undergoing CABG, and as these strokes can be potentially prevented. In fact, as we have seen in our own clinical practice, a reduction of a postoperative atrial fibrillation-related stroke can be achieved by strategies preventing postoperative atrial fibrillation as well as by reducing the risk of clot formation into the left atrium by prompt administration of anticoagulation during the postoperative period. Whether the latter strategy can be associated with an increased risk of postoperative bleeding is unknown, but the administration of anticoagulants at least at the onset of atrial fibrillation may be useful in preventing clot formation and in reducing the risk of embolism. The fact that herein a few patients had a stroke despite on-going anticoagulation is not conclusive against such a treatment approach. In fact, a mean of 2.5 episodes of atrial fibrillation preceded the occurrence of a stroke in this series, thus potentially reducing the efficacy of the anticoagulation therapy not started at the onset of the first arrhythmia episode.

Prophylactic obliteration of the left atrial appendage at cardiac surgery has been suggested as a potential method to reduce a postoperative stroke (Odell *et al.* 1996, Feinglass *et al.* 1998, Johnson *et al.* 2000). Some patients, however, develop atrial thrombi in regions other than the appendage (Blackshear *et al.* 1996). A recent trial designed to evaluate whether atrial appendage occlusion performed during coronary artery bypass grafting may reduce the long-term risk of a stroke and systemic embolism associated with atrial fibrillation has provided inconclusive results (Healey *et al.* 2005).

7 Conclusions

With reference to the purpose of the present investigation, the results can be summarised as follows:

1. The angiographic severity of the coronary artery disease predicts postoperative outcome after a CABG operation. In particular, the status of the proximal segments of the left side arteries (diagonal, obtuse marginal and circumflex arteries) are significantly associated with the immediate outcome.
2. The high preoperative serum concentration of CRP in patients undergoing CABG is an important determinant of immediate postoperative adverse outcome.
3. OPCAB can be performed safely in high-risk patients with results as satisfactory as those achieved with CCAB.
4. CABG patients with high pulmonary artery blood temperature on admission to the ICU have a higher risk of postoperative adverse events.
5. Atrial fibrillation occurring after coronary artery bypass grafting is a major determinant of a postoperative stroke.

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Original publications

This thesis is based on the following articles, referred to in the text by their Roman numerals:

I Biancari F, Lahtinen J, Salmela E, Niemelä M, Pokela R, Rainio P, Lepojärvi M, Satta J, Juvonen T (2003) Does angiographic severity of coronary artery disease predict postoperative outcome after coronary artery bypass surgery? Scand Cardiovasc J 37:275–82.

II Biancari F, Lahtinen J, Lepojärvi S, Rainio P, Salmela E, Pokela R, Lepojärvi M, Satta J, Juvonen T (2003) Preoperative C-reactive protein and outcome after coronary artery bypass surgery. Ann Thorac Surg 76:2007–12.

III Lahtinen J, Biancari F, Rimpiläinen J, Kytökorpi R, Mosorin M, Rainio P, Cresti R, Juvonen T, Lepojärvi M (2007) Off-pump versus on-pump coronary artery bypass surgery in high-risk patients (EuroSCORE≥6). Thorac Cardiovasc Surg 54:13–8.

IV Lahtinen J, Biancari F, Ala-Kokko T, Rainio P, Salmela E, Pokela R, Satta J, Lepojärvi M, Juvonen T (2004) Pulmonary artery blood temperature on admission to the intensive care unit is predictive of outcome after coronary artery bypass surgery. Scand Cardiovasc J 38:104–12.

V Lahtinen J, Biancari F, Mosorin M, Satta J, Rainio P, Lepojärvi M, Juvonen T (2004) Postoperative atrial fibrillation is a major course of stroke after on-pump coronary artery bypass surgery. Ann Thorac Surg 77:1241–4.

Original publications are not included in the electronic version of the dissertation.

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