

*Matti-Alexsi Mosorin*

PROGNOSTIC IMPACT OF  
PREOPERATIVE AND  
POSTOPERATIVE CRITICAL  
CONDITIONS ON THE  
OUTCOME OF CORONARY  
ARTERY BYPASS SURGERY

UNIVERSITY OF OULU GRADUATE SCHOOL;  
UNIVERSITY OF OULU,  
FACULTY OF MEDICINE;  
MEDICAL RESEARCH CENTER OULU;  
OULU UNIVERSITY HOSPITAL





ACTA UNIVERSITATIS OULUENSIS  
D Medica 1369

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BYPASS SURGERY**

Academic Dissertation to be presented with the assent of  
the Doctoral Training Committee of Health and  
Biosciences of the University of Oulu for public defence in  
Auditorium I of Oulu University Hospital, on 26 August  
2016, at 12 noon

UNIVERSITY OF OULU, OULU 2016

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Acta Univ. Oul. D 1369, 2016

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ISBN 978-952-62-1250-0 (Paperback)  
ISBN 978-952-62-1251-7 (PDF)

ISSN 0355-3221 (Printed)  
ISSN 1796-2234 (Online)

Cover Design  
Raimo Ahonen

JUVENES PRINT  
TAMPERE 2016

## **Mosorin, Matti-Aleks, Prognostic impact of preoperative and postoperative critical conditions on the outcome of coronary artery bypass surgery.**

University of Oulu Graduate School; University of Oulu, Faculty of Medicine; Medical Research Center Oulu; Oulu University Hospital

*Acta Univ. Oul. D 1369, 2016*

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### ***Abstract***

Coronary artery disease is the leading cause of death in the world. The outcome of patients at a very high operative risk undergoing coronary artery bypass surgery has not been thoroughly investigated.

Cohorts of patients underwent coronary surgery between January 1997 and December 2013 at the Oulu University Hospital, Finland. Data was acquired from electronic patient records. Statistical analysis was performed on the collected data to evaluate outcome and identify predictors of adverse events.

Very high-risk patients who underwent isolated coronary artery bypass surgery had a high 30-day mortality (16.2%), but their 5-year survival was satisfactory (66.8%).

Survivors of out-of-hospital cardiac arrest were compared to a control group. Immediate postoperative mortality was slightly higher in out-of-hospital cardiac arrest patients (6.3% vs. 0%,  $p = 0.24$ ), but the overall 5-year survival rates were similar (80.7% vs. 84.5%).

Patients with preoperative stage 3 chronic kidney disease have a higher mortality than patients with stage 1-2 chronic kidney disease. Kidney function decline/year was predictive of all-cause mortality, cardiovascular mortality and also tended to predict fatal and non-fatal cardiovascular events.

The E-CABG postoperative complication grading system was used to stratify the severity and prognostic impact of postoperative complications and was shown to predict early and late mortality for these patients.

The outcome of emergency coronary artery bypass surgery was studied in a multi-center setting. Increasing emergency classes, left ventricular ejection fraction  $\leq 30\%$ , on-pump surgery, and participating centers were independent predictors of in-hospital mortality. Survival rates at 1, 3 and 5 years were 86.4%, 81.6%, and 76.1%.

Despite the high preoperative risk of these patients, the long-term outcome for coronary surgery is satisfactory. Patients with stage 3 chronic kidney disease may experience a significant decline in kidney function and poor outcome. Early referral to a nephrologist may be beneficial for these patients. The E-CABG complication grading system seems to be a promising tool for stratifying the severity and prognostic impact of complications occurring after coronary surgery.

**Keywords:** cardiac arrest, cardiac surgery, chronic kidney disease, complication, coronary artery bypass surgery, emergency operation



## **Mosorin, Matti-Alexi, Ohitusleikkattujen potilaiden leikkausta edeltävän ja leikkausta seuraavan kriittisen tilanteen vaikutus ennusteeseen.**

Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Medical Research Center Oulu; Oulun yliopistollinen sairaala

*Acta Univ. Oul. D 1369, 2016*

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### ***Tiivistelmä***

Sepelvaltimotauti on johtavia kuolinsyitä Maailmassa. Ohitusleikkauksen tuloksia ei ole täysin selvitetty erittäin korkean riskin potilailla.

Potilaat leikattiin vuosina 1997-2013. Potilastiedot hankittiin sairauskertomuksista ja kuolin-syytiedot kansallisista rekistereistä.

Erittäin korkean riskin potilaiden välitön kuolleisuus ohitusleikkauksen jälkeen on korkea (30 päivän kuolleisuus 16,2 %). Viiden vuoden kuluttua leikkauksesta elossa oli 66,8% leikatuis-ta.

Ohitusleikkausta edeltävästi elvytettyjä potilaita verrattiin kontrolliryhmään. Välittömät leik-kauksen jälkeinen kuolleisuus oli 6,3% vs. 0% ( $p = 0,24$ ). Viiden vuoden kuluttua leikkauksesta elossa oli tutkimusryhmästä 80,7% ja kontrolliryhmästä 80,7%.

Leikkausta edeltävästi keskivaikean munuaisten vajaatoiminnan omaavilla potilailla on kor-keampi kuolleisuus verrattuna potilaisiin, joiden munuaistoiminta on normaalia tai lievästi hei-kentynyt. Munuaisten vajaatoiminnan eteneminen ennusti kokonaiskuolleisuutta, sydän- ja veri-suonikuolleisuutta ja enteili sydän- ja verisuonitapahtumia.

E-CABG leikkauksen jälkeisten komplikaatioiden luokittelujärjestelmällä luokiteltiin leikka-uksen jälkeisten komplikaatioiden vaikeusastetta ja ennusteellista vaikutusta. E-CABG luokat ja pisteytys ennustivat 1kk, 3kk kuolleisuutta ja kuolleisuutta pidemmällä aikavälillä.

Päivystysohitusleikkauksen tuloksia tutkittiin monikeskusasetelmassa. Sairaalakuolleisuutta ennustivat päivystysleikkausluokitteluluokan vakavuus, vasemman kammion ejektiofraktio  $\leq 30\%$ , perfuusiossa tehty leikkaus ja leikkaava keskus. Potilaiden elossaololuvut olivat 1, 3 ja 5 vuoden kohdalla 86,4%, 81,6%, and 76,1%.

Leikkaustulokset erittäin korkean riskin potilailla ohitusleikkauksesta ovat kohtuullisia leik-kausta edeltävään riskiarvioon suhteutettuna. Näin ollen tämän potilasryhmän sepelvaltimo-taudin hoito leikkaamalla on perusteltua. Keskivaikean munuaisten vajaatoiminnan omaavien potilaiden munuaissairauden etenemiseen seuranta-aikana liittyy kuolleisuutta ja sydän- ja veri-suonitapahtumia. Aikaisessa vaiheessa tehty nefrolgin konsultaatio voi parantaa näiden potilai-den munuaisfunktioita. E-CABG komplikaatioiden luokittelujärjestelmä vaikuttaa lupaavalta työ-kalulta ohitusleikkauksen jälkeisten komplikaatioiden luokitteluun ja ennustevaikutuksien arvi-ointiin.

*Asiasanat:* komplikaatio, krooninen munuaissairaus, päivystysleikkaus, sepelvaltimo-ohitusleikkaus, sydänkirurgia, sydänpysähdys



*To my family*



## Acknowledgements

This work was carried out at the Department of Surgery, Division of Cardiothoracic and Vascular Surgery, University of Oulu during the years 2008 to 2015.

First and foremost, I wish to express to my deepest gratitude to my supervisor, Professor Fausto Biancari. His enthusiasm towards medicine and science inspired me to start this whole project back in 2008. His ideas, support and criticism during the project have made this project what it is. I am also grateful for his excellent skills in biostatistics. I am also grateful to my second supervisor, Professor Tatu Juvonen for his support towards this project.

Scientific research is always the result of co-operation between researchers. I owe my warmest thanks to my co-workers in this project for offering their valuable time during my project. And I also want to express my gratitude to all the fellow scientists with whom I have been able to share my thoughts and ideas with over the different stages of my project.

I am grateful to Docent Antti Vento, M.D., Ph.D, and Docent Otso Järvinen M.D., Ph.D, for reviewing the present manuscript.

My most sincere thanks to Michael Spalding, M.D., Ph.D., for his efficient and thorough English revision of this thesis.

My warmest thanks to the staff of the Department of Surgery. I have felt deeply honored to be able to co-operate with you and carry my research project through.

I owe my gratitude to my friends too many to name all for their support. My warmest thanks to Timo for the moments of sharing thoughts towards medicine, science and life.

Despite my as yet short career as a doctor, I have had the opportunity to work with great colleagues, learn from them as well as share my thoughts with them. My warmest thanks to Reetta Kukkonen, M.D., Pirkko Saari, M.D., and Kimmo Karjalainen, M.D. for their guidance during my work at the Health Center in the city of Oulu. And my most sincere thanks to Docent Merja Koivuranta, M.D., Ph.D, Pirjo Ranta, M.D., Voitto Järvimäki M.D., Ph.D, Michael Spalding, M.D., Ph.D. and Tuukka Toivio, M.D. for their brief but thorough guidance in the basics of anesthesiology.

I am deeply grateful to my mother and father, Aila and Martti Mosorin for their continuous love, support and encouragement during my whole life. I also want to thank all my relatives for their endurance and charity.

Finally, at the last I am most sincerely grateful to my wife Päivi and our precious daughter Amanda. You are the light of my life and the main reason for me to keep going.

This work was financially supported by the Finnish Foundation for Cardiovascular Research and EVO grants from the Oulu University Hospital, both of which are gratefully acknowledged.

*Oulu March 2016*

*Matti-Alexsi Mosorin*

## Abbreviations

AF	atrial fibrillation
ACCF	American College of Cardiology Foundation
AHA	American Heart Association
AKI	acute kidney injury
BHCAB	beating heart coronary artery bypass surgery
CAD	coronary artery disease
CABG	coronary artery bypass surgery
CCAB	conventional coronary artery bypass surgery
CI	confidence interval
CKD	chronic kidney disease
CPB	cardiopulmonary bypass
CPR	cardiopulmonary resuscitation
CS	cardiogenic shock
ECMO	extracorporeal mechanical oxygenation
eGFR	estimated glomerular filtration rate
EuroSCORE	European System for Cardiac Operative Risk Evaluation
FFP	fresh frozen plasma
IABP	intra-aortic balloon pump
ICU	intensive care unit
IRA	infarct related artery
LVEF	left ventricular ejection fraction
NSTEMI	non ST-segment elevating myocardial infarction
NYHA	New York Heart Association
OHCA	out-of-hospital cardiac arrest
OPCAB	off-pump coronary artery bypass surgery
OR	odds ratio
PA	pulmonary artery
PCI	percutaneous coronary intervention
RBC	red blood cell
SD	standard deviation
STEMI	ST-segment elevating myocardial infarction



## List of original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

- I Mosorin MA, Heikkinen J, Pokela M, Anttila V, Mosorin M, Lahtinen J, Juvonen T & Biancari F (2011) Immediate and 5-year outcome after coronary artery bypass surgery in very high-risk patients (additive EuroSCORE  $\geq 10$ ). (2011) *J Cardiovasc Surg (Torino)* 52:271–276.
- II Mosorin MA, Lantos M, Juvonen T & Biancari F. (2015) Five-year outcome after coronary artery bypass graft surgery in survivors of out-of-hospital cardiac arrest. *Front Surg* 21;2:2
- III Mosorin MA, Kangasniemi O-P, Mahar AAM & Biancari F (2010) Decline of renal function and outcome in patients with moderate chronic kidney disease after coronary artery bypass surgery. Manuscript
- IV Kinnunen EM, Mosorin MA, Perotti A, Ruggieri VG, Svenarud P, Dalén M, Onorati F, Faggian G, Santarpino G, Maselli D, Dominici C, Gherli R, Mariscalco G, Masala N, Rubino AS, Mignosa C, De Feo M, Della Corte A, Bancone C, Chocron S, Gatti G, Juvonen T & Biancari F (2015) Validation of a new classification method of postoperative complications in patients undergoing coronary surgery. *J Cardiothorac and Vasc Anesth*. In press.  
Biancari F, Onorati F, Rubino AS, Mosorin MA, Juvonen T, Ahmed N, Faggian G, Mariani C, Mignosa C, Cottini M, Berghi C & Mariscalco G (2015) Outcome of emergency coronary artery bypass grafting. *J Cardiothorac Vasc Anesth* 29:275–282



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# 1 Introduction

Coronary artery disease (CAD) is the leading cause of death (Lopez *et al.* 2006) worldwide. In the 1960s, Finland had the highest mortality due to CAD in the world (Vartiainen *et al.* 2010). Since then, CAD-related mortality has decreased (Vartiainen *et al.* 2010). In 2013, however, CAD caused every fifth death in Finland and was the most common cause of death resulting in over 10 000 deaths (Statistics Finland). CAD also has a remarkable socio-economical impact. According to the Kelasto-database, in 2013 171,439 out of 5,488,376 inhabitants of Finland (Väestörekisterikeskus, accessed on 5.10.2015) were on medication for chronic CAD. This resulted in a 32,230,532 euros/year expenditure for cardiovascular medication (Kelasto-database, Kela, accessed on 5.10.2015).

Among treatment methods for CAD, coronary artery bypass graft surgery (CABG) has been widely shown to be effective and produce durable long-term results as compared with percutaneous coronary intervention (PCI) (Deb S *et al.* 2013, Sipahi I *et al.* 2014). Technological improvements and its minimally invasive nature have, however, made PCI the most common invasive method in the treatment of CAD. Indeed, in 2014 in Finland, approximately 27 000 coronary angiograms, 12 000 PCI and 1700 CABGs were performed according to a yearly survey of the Finnish Cardiac Society (Suomen Kardiologinen Seura 2015). Despite these figures, CABG continues to be a durable and superior method of treatment in certain subsets of patients, such as diabetics (Deb S *et al.* 2013, Fanari *et al.* 2014, Verma S *et al.* 2013), those with multivessel disease (Deb S *et al.* 2013, Fanari *et al.* 2014, Krenn *et al.* 2014, Sipahi I *et al.* 2014), or those with renal failure (Zheng *et al.* 2013).

The benefits and durability of CABG in subsets of patients with critical preoperative conditions or who have suffered severe postoperative complications are largely unknown and were the topics of the present studies. The aim of the first study was to investigate the results of beating heart (BHCAB) versus conventional on-pump coronary artery bypass surgery (CCAB) in very high-risk patients (I). The outcome after CABG in survivors of out-of-hospital cardiac arrest was investigated in study II. The prognosis of preoperative moderate kidney dysfunction after CABG was the topic of study III. A new classification method of postoperative complications in patients undergoing coronary surgery was validated in study IV. Study V evaluated the outcome of emergency CABG in a multicenter setting.



## 2 Review of the literature

Over the last decade, the preoperative risk of mortality in patients undergoing CABG has increased, whilst early postoperative mortality has decreased, this likely being due to improvements in methods of anaesthesia and the perioperative care of CAD patients (Biancari *et al.* 2009).

Mortality is largely used as an indicator of quality of care and a number of different stratifying tools have been developed for the prediction of the postoperative risk of mortality in patients undergoing cardiac surgery (Hannan *et al.* 1990, Higgins *et al.* 1992, Nashef *et al.* 2012, Nashef *et al.* 1999, Nilsson *et al.* 2006). These risk-stratification methods have been used successfully as research tools for the adjustment of differences in the baseline characteristics of patients undergoing cardiac surgery. The additive (Nashef *et al.* 1999) and logistic EuroSCORE (Roques *et al.* 2003) were the most frequently used risk-stratification methods during the last decade. This has proven to be an accurate method of predicting postoperative mortality (Geissler *et al.* 2000, Nilsson *et al.* 2006). The predictive ability of the original EuroSCORE has been recently improved by the recent EuroSCORE II (Nashef *et al.* 2012). Importantly, EuroSCORE identified a few subsets of patients with critical baseline conditions such as critical preoperative state, renal failure and urgency of the procedure (Tables 1 and 2). It must be recognized, however, that adverse events occurring during or immediately after surgery may have a significant impact on prognosis (Reich *et al.* 1999, Turner *et al.* 1995), even in low risk patients (Freed *et al.* 2009)

**Table 1. 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 of 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	>200µm 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<10ml/h)	3
Unstable angina	Rest angina requiring iv nitrates until arrival in the anaesthetic room	2
LV dysfunction	Moderate or LVEF 30-50%	1
	Poor or LVEF <30%	3
Recent myocardial infarct	<90 days	2
Pulmonary hypertension	Systolic PA pressure>60mmHg	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

LV, left ventricle; LVEF, left ventricular ejection fraction; PA, pulmonary artery

**Table 2. Urgency classes and definitions according to EuroSCORE II**

Urgency class	Definition of urgency class
Elective	Routine admission for operation
Urgent	Patients who have not been electively admitted for the operation but who require intervention or surgery on the current admission for medical reasons. These patients cannot be sent home without a definitive procedure.
Emergency	Operation before the beginning of the next working day after the decision to operate.
Salvage	Patients requiring CPR (external cardiac massage) en route to the operating theatre or prior to induction of anaesthesia. This does not include CPR following induction of anaesthesia

CPR, cardiopulmonary resuscitation

## 2.1 Critical preoperative status

EuroSCORE and EuroSCORE II define the preoperative status as critical when one or more of the following conditions are met: ventricular tachycardia or ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before anaesthetic room, preoperative inotropes or IABP, preoperative acute renal failure (anuria or oliguria <10ml/hr) (Nashef *et al.* 2012, Nashef *et al.* 1999, Roques *et al.* 2003). In other risk indices, a preoperative status of critical is neither defined nor detailed.

### 2.1.1 Out-of-hospital cardiac arrest

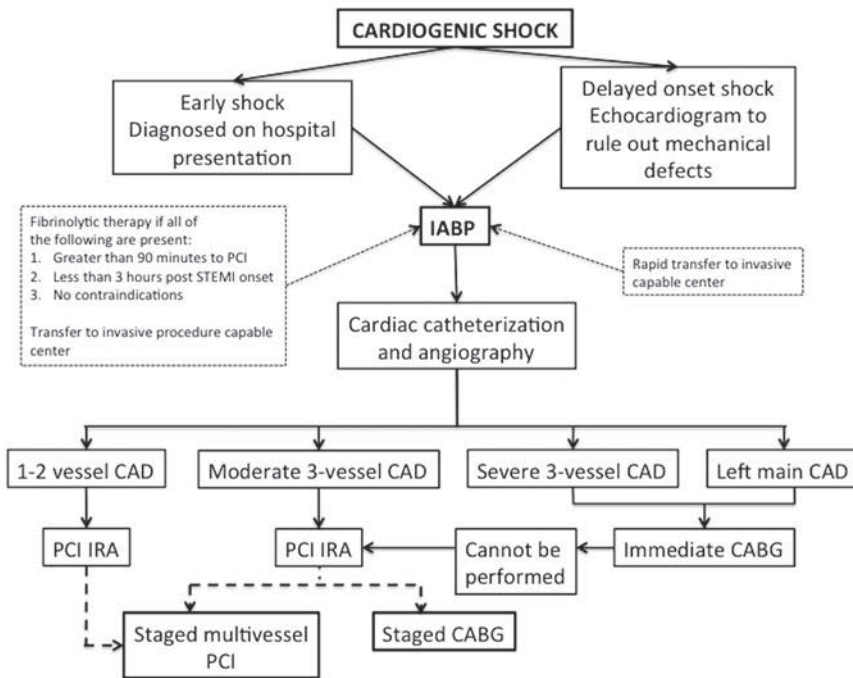
The most frequent cause of sudden cardiac death or cardiac arrest is CAD (Kuriachan *et al.* 2015, Lindner *et al.* 2014, Papadakis & Sharma 2010, Turakhia & Tseng 2007). Indeed, cardiac arrest can be the first symptom of CAD. Lindner and colleagues studied out-of-hospital cardiac arrest survivors' survival over an extended period of time. Only 16% of all OHCA patients survived to hospital discharge in their study population (Lindner *et al.* 2014). Dumas and colleagues reported similar results in their study including about 6 000 patients (Dumas *et al.* 2012).

Most studies investigated the impact of PCI in the prognosis of patients with OHCA (Dumas *et al.* 2012, Lim *et al.* 2013, Zimmermann *et al.* 2013). In contrast to this, the efficacy of CABG in this patient population has not been thoroughly investigated and results are based on small size series. The available data

suggests, however, that encouraging results can be achieved through surgical revascularization. (Every *et al.* 1992, Kelly *et al.* 1990, Mangi *et al.* 2002).

### **2.1.2 Cardiogenic shock**

Cardiogenic shock (CS) is secondary to severely depressed hemodynamics. It is caused by serious injury of the heart muscle causing insufficient end-organ tissue perfusion as well as decreasing the perfusion of the heart muscle itself. CS is a severe complication of myocardial infarction and is associated with high in-hospital mortality (Berger *et al.* 1997, Carnendran *et al.* 2001, Goldberg *et al.* 1999, Goldberg *et al.* 2001). The incidence of cardiogenic shock has been reported to range from 6% to 10% of cases after acute myocardial infarction (Goldberg *et al.* 1999, Goldberg *et al.* 2001, Hochman *et al.* 1999). The in-hospital mortality associated with CS varies between 55 to 80% among those patients whose CS is managed medically (Berger *et al.* 1997, Carnendran *et al.* 2001, Goldberg *et al.* 1999, Goldberg *et al.* 2001). Aggressive invasive revascularization in the treatment of CS has been reported to significantly improve the outcome of these patients (Carnendran *et al.* 2001, Hochman *et al.* 2001, Mehta *et al.* 2008). Based on current evidence, the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) has suggested primary PCI of the infarct-related artery for patients with 1 or 2 vessel CAD or moderate 3-vessel CAD and immediate CABG for patients with severe 3-vessel CAD or diseased left main (Hillis *et al.* 2011, O'Gara *et al.* 2013, Reynolds & Hochman 2008). White and colleagues reported results from acutely treated patients in CS by either PCI or CABG (White *et al.* 2005). Patients treated with CABG had a higher prevalence of diabetes and 3-vessel disease. Despite the differences between the CABG group and the PCI group, survival rates were similar.



**Fig. 1. Revascularization of patients with an acute myocardial infarction complicated with cardiogenic shock according to AHA/ACCF guideline.**

### *Intra-aortic balloon pump*

The intra-aortic balloon pump (IABP) is a mechanical assistive device, which improves coronary and peripheral perfusion via diastolic balloon inflation and augments left ventricular performance via systolic balloon deflation, increasing coronary artery perfusion. IABP increases cardiac output by 10%-30% (Krishna & Zacharowski 2009, Werdan *et al.* 2014). Complications and mortality associated with the insertion of IABP is low, although mortality associated with the use of IABP has remained relatively high (Christenson *et al.* 2002, Cohen *et al.* 2004, Urban *et al.* 2004). IABP has not been shown to reduce 30-day mortality in patients with AMI complicated with CS (Thiele *et al.* 2012).

The reported use of IABP in cardiac surgery varies between 5% and 10% (Arafa *et al.* 1998, Christenson *et al.* 2002, Kucuker *et al.* 2014, Lavana *et al.* 2010, Saura *et al.* 2015). The results of CABG with the use of IABP may depend

on the timing of its insertion (Arafa *et al.* 1998, Christenson *et al.* 2002, Kucuker *et al.* 2014, Lavana *et al.* 2010).

The preoperative use of IABP has been studied quite systematically, in particular by Christenson and colleagues. They received promising results with preoperatively inserted IABP in high-risk patients (Christenson *et al.* 1999, Christenson *et al.* 2001). Canadian colleagues went through a large retrospective study population using the same kind of setting and there were no significant differences in patient survival (Baskett *et al.* 2005). In a study performed by Kucuker and colleagues (Kucuker *et al.* 2014), the preoperative insertion of IABP remarkably resulted in a higher mortality when compared to patients who received IABP intraoperatively (33% vs. 19%). The number of patients who received IABP preoperatively was quite small and their institutional policy was to only insert IABP preoperatively in patients with CS (Kucuker *et al.* 2014). Other studies using matched controls demonstrated encouraging results with the prophylactic use of IABP (Lorusso *et al.* 2010, Santarpino *et al.* 2009).

The intraoperative placement of the IABP has been reported to be associated with encouraging results (Arafa *et al.* 1998, Kucuker *et al.* 2014, Lavana *et al.* 2010, Rubino *et al.* 2008). On the contrary, postoperative insertion of the IABP has been associated with the worst outcome in the previous studies (Arafa *et al.* 1998, Christenson *et al.* 2002, Kucuker *et al.* 2014, Lavana *et al.* 2010), this likely being due to its use being limited to patients with highly depressed hemodynamic conditions.

### **2.1.3 Emergency operation**

According to the EuroSCORE criteria, emergency cardiac surgery is a procedure carried out on referral before the beginning of the next working day (Nashef *et al.* 1999). This definition is probably not sufficient to adequately stratify the preoperative conditions requiring a prompt cardiac procedure, but within its limitation, identifies those with a significantly higher risk of mortality as compared with those undergoing non-emergency surgery (Christiansen & Autschbach 2010). EuroSCORE investigators recognized the high risk profiles of salvage surgery and demonstrated its prognostic significance in the EuroSCORE II (Nashef *et al.* 2012). Biancari and colleagues have provided a more detailed definition of emergency conditions and divided emergency procedures into four categories (Biancari *et al.* 2015).

## 2.2 Preoperative chronic kidney disease

Chronic kidney disease (CKD) is a determinant of cardiovascular disease and mortality (Gradaus *et al.* 2001). Indeed, CKD is also an important preoperative risk factor in cardiac surgery. An elevated level of serum creatinine is a risk factor for immediate adverse outcome in patients undergoing cardiac surgery and it is also included in most risk scoring methods (Nilsson *et al.* 2006). The guideline of National Kidney Foundation divides chronic kidney disease into five stages (Table 3)(National Kidney Foundation. 2002).

**Table 3. Stages of CKD according to KDOQI CKD classification**

SStage	Description	GFR (ml/min/1.73m <sup>2</sup> )
1	Kidney damage with normal or elevated GFR	≥90
2	Kidney damage with mild renal dysfunction	60–89
3	Kidney damage with moderate renal dysfunction	30–59
4	Kidney damage with severe renal dysfunction	15–29
5	Kidney failure or end stage renal disease	<15

Even mild preoperative renal dysfunction has been recognized as a predictor of long-term mortality in patients undergoing CABG (Holzmann *et al.* 2007, Kangasniemi *et al.* 2008, Wal *et al.* 2005). In a Japanese study, stage 4 CKD (eGFR less than 30 mL/min/1.73 m<sup>2</sup>) was found to be a strong predictor of postoperative infection, AKI and in-hospital death (Minakata *et al.* 2014). Even in lower stages of preoperative CKD, the risk for postoperative infections was 2-3 fold when compared to patients with normal estimated kidney function.

In the general population, the identification and referral of subjects with moderate CKD, i.e. stage 3 disease, to a nephrologic clinic has been shown to reduce the decline of kidney function and a significant number of patients may even experience an improvement in kidney function (Taskapan *et al.* 2008).

## 2.3 Operative technique

Robert H. Goetz was the surgeon who performed the first successful CABG in a patient in 1960 by anastomosing the right mammary artery to the right coronary artery using an anastomosis device (Konstantinov 2000). In Russia, Kolesov reported the first series of successful CABG without cardiopulmonary bypass (CPB) by anastomizing the left mammary artery to the left anterior descending

artery. The development and utilization of the CPB led to the development of on-pump surgery and off-pump surgery was nearly forgotten until the 1980s.

At present, CABG is performed either with or without the use of CPB. The off-pump technique has been of remarkable interest in studies previously. Meta-analyses have shown that off-pump is as safe as the on-pump technique (Afilalo *et al.* 2012, Takagi *et al.* 2014) but it is associated with fewer strokes (Kowalewski *et al.* 2015, Vasques *et al.* 2013). In cases of porcelain aorta, the off-pump technique makes revascularization possible using the no-touch technique (Bittner *et al.* 2003). The off-pump technique also provides some benefit when postoperative kidney injury is taken into consideration as compared to on-pump, but according to recent meta-analyses there is no decline in the incidence of acute kidney injury requiring dialysis (Cheungpasitporn *et al.* 2015, Seabra *et al.* 2010). In a Japanese study, the off-pump technique was associated with fewer postoperative infections in patients with preoperative CKD (Minakata *et al.* 2014).

The off-pump approach in patients with recent MI is considered safe (Davierwala *et al.* 2015, Ferrari *et al.* 2008, Kerendi *et al.* 2005). Some studies have even reported lower mortality rates among patients that have been operated on using beating heart techniques (Ferrari *et al.* 2008, Rastan *et al.* 2006).

## **2.4 Grading of postoperative complications**

Postoperative complications are a significant burden to the health care system, as well as socio-economically. Complications bring discomfort to patients suffering from them, but also significantly increase the cost of their treatment (Brown *et al.* 2008). Several grading methods have been developed and approved for a wide range of operations (Dindo *et al.* 2004, Strasberg *et al.* 2009). These grading systems have been developed for non-cardiac surgery procedures and therefore consider many minor complications as significant complications. Adult cardiac surgery is associated with significant morbidity and mortality, and minor complications are frequent and do not necessarily have any significant prognostic impact. A postoperative complication grading method has been developed for adult cardiac surgery and it is in the process of being validated in a multicentre study (Biancari *et al.* 2015).

### **2.4.1 Postoperative critical complications**

Biancari and colleagues graded postoperative complications or interventions according to their severity (Table 4) (Biancari *et al.* 2015). Some of these complications have been reported to also have a significant impact on late survival (Filsoufi *et al.* 2007, Hansen *et al.* 2015, Hobson *et al.* 2009, Liotta *et al.* 2013, Mangi *et al.* 2005, Phan *et al.* 2015, Rydén *et al.* 2014, Toumpoulis *et al.* 2005).

Grade 1 complications are considered as minor, grade 2 intermediate and grade 3 of critical level. Many of these listed complications or interventions for their treatment have been documented to have a remarkable impact on the short-term survival of patients (Anthi *et al.* 1998, Arafa *et al.* 1998, Filsoufi *et al.* 2007, Glance *et al.* 2007, Kucuker *et al.* 2014, Mangi *et al.* 2005, Rahmanian *et al.* 2013, Risnes *et al.* 2010). Interactions between different complications have also been reported (Ang *et al.* 2012, Bahrainwala *et al.* 2011, Dorneles *et al.* 2011, Filsoufi *et al.* 2007, Koch *et al.* 2009, Kollar *et al.* 2006, Lahtinen *et al.* 2004, Mikkola *et al.* 2012, Risnes *et al.* 2010, Vivacqua *et al.* 2011). Complications prolong the ICU stays of the operated patients and significantly increase the cost of their treatment (Biancari & Mahar 2010, Brown *et al.* 2008, Filsoufi *et al.* 2007, Kaw *et al.* 2011, Mostafa *et al.* 2012).

Most of the previous studies have focused on one complication or complications that are connected with each other. Some complications are very rare and only appear in a few patients, so patient data is not so easily collectable. Furthermore, studies may not be very comparable due to the lack of standardization of complication definitions.

**Table 4. Grading and additive score for postoperative complication or intervention for their treatment according to the E-CABG**

Grade	Postoperative complications or interventions	Additive score
Grade 0	None of the below mentioned complications or interventions	0
Grade 1	Postoperative use of antibiotics for proven or suspected infection	2
	Atrial fibrillation	2
	Transfusion of platelets	2
	Transfusion of fresh frozen plasma or Octaplas	3
	Transfusion of 2-4 units of RBC	3
	Deep wound infection of the leg within 3 months of the surgery	3
	Permanent pace-maker implantation	3
Grade 2	Pericardial effusion requiring pericardial fenestration	4
	Acute kidney injury not requiring renal replacement therapy	4
	Transfusion of 5-10 units of RBC	5
	Reoperation for bleeding	5
	Deep sternal wound infection within 3 months of the surgery	5
	Postoperative insertion of IABP	5
Grade 3	Transfusion of >10 units of RBC	7
	Renal failure requiring renal replacement therapy	7
	Mediastinitis within 3 months of the surgery	7
	Stroke	7
	Surgical or percutaneous procedure for technical failure	7
	Reoperation for hemodynamic instability	8
	Ventricular fibrillation/asystole	8
	Surgery for gastrointestinal complications	9
	Postoperative ECMO	9
Grade 4	In-hospital death	10

RBC, red blood cells; IABP, intra-aortic balloon pump; ECMO, extracorporeal mechanical oxygenation.

### **3 Aims of the research**

The aims of the present research were

1. to evaluate the outcome of off-pump and on-pump CABG in very high risk patients (additive EuroSCORE $\geq$ 10) (I),
2. to investigate the prognosis of patients who undergo CABG after surviving an out-of-hospital cardiac arrest (II),
3. to evaluate whether subclinical renal dysfunction affects patients survival and renal failure-related cardiovascular complications (III),
4. to validate a new classification method of postoperative complications in patients undergoing CABG (IV),
5. to assess the immediate and late outcome of emergency CABG in a multicenter setting (V).



## **4 Material and methods**

All the studies included have a retrospective design. Study population in studies I-IV consists of patients who underwent an isolated CABG at the Department of Surgery, Oulu University Hospital, Oulu, Finland from January 2000 to December 2013. Study V consists of patients who underwent an emergency CABG in either the Oulu University Hospital; the Catania University Hospital, Italy; the Varese University Hospital, Italy; or the Verona University Hospital, Italy from 2004 to 2014 during different time periods. Data was retrieved retrospectively from the patient records. All patient data in the study database was entered so that individual patients are unidentifiable. In our institution, the Institutional Review Board did not require any permission for the retrospective collection of patients' data at the time of data collection for studies I, II and III. For the fourth study, permission was applied for and approved in February 2015. The fifth study was approved by the institutional review board at each participating center. Data on time and mode of death were acquired from Statistics Finland in studies I-IV. Late death was recorded by contacting the patients, their relatives, and/or their general practitioner and by checking the patients' records. National registries were also utilised when available for study V.

The studies include elective, urgent and emergency operations carried out with either an off-pump or on-pump technique. Intermittent antegrade and retrograde blood cardioplegia with KCl and MgCl at a temperature ranging from 10 to 16°C was delivered during on-pump CABG. Epiaortic ultrasound was performed according to the surgeon's preference before touching the aorta. The ascending aorta was clamped in case of atherosclerotic lesion involving the lateral and/or anterior wall of the ascending aorta. Proximal anastomoses were sutured to the ascending aorta during side clamping or cross-clamping when it was considered safe. Octopus stabilizer (Medtronic, Minneapolis, MN) as well as intracoronary shunts were routinely used in patients who underwent off-pump CABG.

### **4.1 Study I**

The first study included high-risk patients who underwent isolated CABG at the Oulu University Hospital from January 2003 to May 2008. 2918 patients underwent isolated CABG during that time period. Of these patients, 160 had an

additive EuroSCORE $\geq$ 10. Sixty-one patients underwent CCAB and 99 underwent OPCAB. Patients with a EuroSCORE $\geq$ 10 were included in study I.

The decision to perform either OPCAB/BHCAB or CCAB was made by the surgeon based on his preferred technique and the patient's conditions. Of the 13 surgeons who operated on these patients, four surgeons treated most of their patients (94.4% of 72 patients) using the OPCAB/BHCAB technique while another four surgeons employed the CCAB technique in most cases (86.0% of 41 patients). The other surgeons used both techniques variably. The decision as to the vessels to be revascularized was made by the operating surgeon. In all cases, the revascularization was assumed to be complete according to angiographic and operative findings. During OPCAB, if the target vessels were considered to not be "reachable" using the standard technique, the procedure was converted to BHCAB on perfusion without aortic cross-clamping or CCAB.

## 4.2 Study II

The second study included a series of consecutive patients who survived a recent out-of-hospital cardiac arrest and who underwent CABG at the Department of Surgery, Oulu University Hospital, Finland, from January 1997 to December 2009. A control series of patients with recent myocardial infarction (<3 months prior to CABG) has been randomly chosen from our database and matched in a 1:1 fashion for age ( $\pm$ 1 year), gender and date ( $\pm$ 1 month) of operation.

Study design and data retrieval were planned according to the Newcastle–Ottawa scale criteria ([http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.htm](http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm)) regarding representativeness of the exposed cohort (consecutive series representative of survivors of OHCA without any exclusion criteria), selection of the non-exposed cohort (random, matched sample of patients without any other exclusion criteria than recent myocardial infarction, same age, same gender, and operation carried out during the same period), ascertainment of exposure (data retrieval from electronic records), demonstration that outcome of interest was not present at the start of the study, comparability of cohorts (cohorts matched for more than two important factors), assessment of outcome (blind assessment of the outcome), follow-up length (a 5-year period is likely enough to detect any difference in outcome), and adequacy of follow-up (follow-up data retrieved from an official national registry).

These patients were identified from our institutional database and data was reviewed to collect variables of interest. Patients who suffered an in-hospital cardiac arrest were excluded from this analysis. Follow-up data were retrieved from our institutional records for those patients residing in our catchment area, otherwise from central hospitals' records for those residing outside the Oulu University Hospital's catchment area

### **4.3 Study III**

The third study included 783 patients who were residents of the City of Oulu, Finland and underwent an isolated CABG at the Oulu University Hospital from January 1997 to December 2006. Patients were divided into groups according to their estimated kidney function. All-cause mortality, freedom from fatal cardiovascular events, freedom from any fatal or non-fatal cardiovascular event, freedom from chronic dialysis and decline in estimated glomerular filtration rate (eGFR) were the main outcome end-points. Cardiovascular mortality is defined as any cardiac related death as well as fatal ischemic stroke. Cardiovascular morbidity is defined as any fatal or non-fatal cardiac event, ischemic stroke, any peripheral vascular revascularization, and any major or minor lower limb amputation. Decline of eGFR was calculated according to the change in eGFR from baseline to the last control.

### **4.4 Study IV**

The fourth study included 2764 consecutive patients who underwent isolated CABG from June 2006 to December 2013 at the Oulu University Hospital. Postoperative data was collected according to the E-CABG postoperative complication grading system (Biancari *et al.* 2015). The main outcome measures of this study were all-cause 30-day, 90-day and long-term mortality. The secondary outcome end-point was the length of intensive care unit stay.

### **4.5 Study V**

The fifth study included patients from 4 European centers of cardiac surgery. The study included 596 patients who underwent emergency CABG. Centers participating in the study were the Catania University Hospital, Italy, the Oulu

University Hospital, Finland, the Varese University Hospital, Italy and the Verona University Hospital, Italy.

Eligible study participants were patients of any age who received a diagnosis of unstable angina, non-ST-elevation myocardial infarction or ST-elevation myocardial infarction and underwent emergency CABG. Data on preoperative and procedural variables, as well as on the immediate outcome, were retrieved from patients' records.

Emergency surgery was defined according to the EuroSCORE II definition criterion (Samer A M Nashef *et al.* 2012). The severity of the emergency condition was further graded into four classes according to the definition criteria summarized in Table 5.

**Table 5. Classification of severity of emergency surgery**

Class	Definition of severity class
Class 1	persistent angina, persistent changes in the electrocardiogram, and/or increasing levels of cardiac enzymes despite the best medical treatment but no need for inotropes
Class 2	hemodynamic instability responsive to inotropes
Class 3	hemodynamic instability unresponsive to inotropes and/or requiring intra-aortic balloon pump
Class 4	salvage CABG: patients requiring cardiopulmonary resuscitation (external cardiac massage) en route to the operating theater or before induction of anaesthesia. This does not include cardiopulmonary resuscitation after the induction of anaesthesia.

Neurological status immediately before surgery was defined as (1) no acute neurological problem; (2) acute stroke, responsive; (3) coma/ unresponsive (stroke not assessed preoperatively); and (4) coma/ unresponsive after diagnosed acute stroke.

Failure of primary PCI was defined as a failed attempt, but not a direct complication, of PCI to successfully restore coronary flow; PCI-related complication was defined as an emergency state secondary to complication after elective/urgent PCI. Patients who underwent emergency PCI were excluded from this category. Ischemia despite successful PCI was defined as persistent ischemia despite successful PCI.

Heart failure was defined as any acute heart failure episode within 2 weeks of the operation. All other baseline variables were defined according to the EuroSCORE II criteria. The outcome end-points of this study were in-hospital mortality and late all-cause mortality after surgery. Secondary outcome end-points are listed in Table 15.

## **4.6 Statistical analysis**

All statistical analyses were performed using the SPSS statistical software (SPSS v. 15.0.1-22.0, IBM Corporation, 1 New Orchard Road Armonk, New York 10504-1722, United States).

### **4.6.1 Study I**

Continuous variables were reported as the mean±standard deviation. Pearson's test, the Fisher exact test, and the Mann-Whitney test were used for univariate analysis. Receiver operating characteristic curve (ROC) analysis was used to estimate the impact of continuous variables on 30-day mortality. Logistic regression with the use of backward selection was performed to calculate the risk of these patients to be assigned either OPCAB/BHCAB or CCAB study group and to calculate the propensity score. Logistic regression was used to identify independent predictors of 30-day mortality (only variables with  $p < 0.05$  were entered into the regression model). Intermediate outcome was assessed by the Kaplan-Meier method (log-rank test) and Cox regression analysis. A  $p < 0.05$  was considered statistically significant.

### **4.6.2 Study II**

Continuous variables are reported as the mean ± SD. The Fisher exact' test and the Mann–Whitney tests were used for univariate analysis. The intermediate outcome was assessed by the Kaplan–Meier (log-rank test) and Cox proportional hazards methods. Non-parsimonious logistic regression was performed to estimate a propensity score and to assess the risk of assignment to these study groups, i.e., OHCA vs. control group. Receiver operating characteristics (ROC) analysis was performed to assess the predictive ability of this regression model. The estimated propensity score was employed for adjusted analyses evaluating the immediate and late outcome of these patients. A  $p < 0.05$  was considered statistically significant.

### **4.6.3 Study III**

As the change in eGFR did not correlate with the length of follow-up ( $r^2$  linear 0.002,  $\rho$  0.045), the regression coefficient of time against eGFR was not used to

estimate the decline of eGFR. Thus, the change of eGFR during time was calculated as a change of egFR per year by dividing the absolute change of baseline eGFR value to the last eGFR value divided by the length of follow-up for creatinine measurement. Continuous variables are reported as the mean±standard deviation. Univariate analysis was performed using the Mann-Whitney's test and the Fisher's exact test. Late survival was estimated by the Kaplan-Meier test with the log-rank test and with the Cox regression analysis. Linear regression with backward selection was used to identify predictors of change in eGFR per year. Only variables with a  $p < 0.2$  at univariate analysis were included into the regression analysis. A  $p < 0.05$  was considered statistically significant.

#### **4.6.4 Study IV**

Fisher's exact, chi-square, Mann-Whitney-U, and Kruskal- Wallis tests were used for univariate analysis. Correlation between continuous and ordinal variables was estimated using the Spearman's rank correlation. Survival analysis at 90 days included only patients with a potential follow-up longer than 3 months. C-statistics were calculated to assess the predictive ability of the E-CABG complication classification either as an additive score or grades. The Kaplan-Meier method was used to estimate late survival. Cox proportional hazards analysis was performed to adjust the E-CABG complication grades for baseline and operative variables potentially associated with poor late survival. These variables were age, estimated glomerular filtration rate, sex, diabetes, hypertension, prior stroke, neurologic dysfunction, extracardiac arteriopathy, previous percutaneous coronary intervention, previous cardiac surgery, recent myocardial infarction, pulmonary disease, left ventricular ejection fraction classes, dialysis, elective/urgent/emergency surgery, unstable angina requiring nitrates at operating room arrival, critical preoperative status, systolic pulmonary pressure, off-pump surgery, number of distal anastomoses, and any mammary artery graft. Because of an imbalance between baseline and operative characteristics of patients in the different E-CABG classification grades, probabilities (propensity scores) estimated using multinomial regression analysis were used to adjust the risk of early and late mortality in these patients with different E-CABG grades (multiple propensity score adjusted analysis). Propensity scores were calculated using a regression model in which all of aforementioned baseline and operative variables were entered. All tests were 3-sided, with the alpha level set at 0.05 for statistical significance.

#### **4.6.5 Study V**

There were no missing data in this dataset. Group differences were evaluated by the Mann-Whitney U test, Kruskal-Wallis test, Pearson's chi-square test, and Fisher's exact tests. Logistic regression and Cox proportional hazards method were used to identify independent predictors of immediate and late outcome. Only variables with a p value  $<0.05$  at univariate analysis were included in the regression models to avoid overfitting. Different institutions were included in the regression models as a multinomial variable, and the institution with the lowest mortality was considered the reference category. The regression models were calibrated by the Hosmer-Lemeshow goodness-of-fit test. Regression model discrimination was evaluated using the area under the receiver operating characteristic curve. All tests were two-sided with the alpha level set at 0.05 for statistical significance.



## 5 Results

### 5.1 Outcome of isolated coronary artery bypass grafting in very high risk patients

**Table 6. Clinical and operative data of patients who underwent isolated off-pump/beating heart and conventional coronary artery bypass surgery.**

Patient characteristic	CCAB <i>61 patients</i>	BHCAB <i>99 patients</i>	<i>p</i> -value
Age (years)	70.9±8.9	71.6±9.0	0.58
Female gender	20 (32.8)	32 (32.3)	1.00
Dyslipidemia	21 (34.4)	45 (45.5)	0.19
Pulmonary disease	13 (21.3)	21 (21.2)	1.00
Diabetes	20 (32.8)	24 (24.2)	0.28
Hypertension	34 (55.7)	55 (55.6)	1.00
Renal failure	2 (3.3)	5 (5.1)	0.71
Dialysis	1 (1.6)	2 (2.0)	1.00
Atrial fibrillation	9 (14.8)	17 (17.2)	0.83
Stroke	11 (18.0)	11 (11.1)	0.24
Neurological dysfunction	9 (14.8)	9 (9.1)	0.31
Myocardial infarction<3 months	57 (93.4)	95 (96.0)	0.48
Extracardiac arteriopathy	18 (29.5)	24 (24.2)	0.47
Previous vascular/endovascular surgery	10 (16.4)	10 (10.1)	0.32
Previous cardiac surgery	4 (6.6)	6 (6.1)	1.00
Previous PCI	8 (13.1)	20 (20.2)	0.29
on the same day of surgery	4 (6.6)	13 (13.1)	0.29
Left main stenosis>50%	30 (49.2)	45 (45.5)	0.75
LVEF>50%	10 (16.4)	24 (24.2)	0.41
30-50%	34 (55.7)	46 (46.5)	
<30%	17 (27.9)	29 (29.3)	
Critical preoperative status	36 (59.0)	65 (65.7)	0.40
Congestive heart failure	29 (47.5)	36 (36.4)	0.17
Intraaortic balloon pump	6 (9.8)	15 (15.2)	0.47
Preoperative VT/VF	16 (26.2)	30 (30.3)	0.58
Preoperative inotropic support	24 (39.3)	38 (38.4)	0.90
Preoperative tracheal intubation	10 (16.4)	15 (15.2)	0.83
Preoperative resuscitation	5 (8.2)	20 (20.2)	0.046
Nitrates infusion at operating room arrival	42 (68.9)	65 (65.7)	0.73
Systolic pulmonary a. pressure>60 mmHg	12 (19.7)	7 (7.1)	0.023
Cardiac index (L/min/m <sup>2</sup> ) (141 patients)	2.38±0.70	2.47±0.66	0.25
Emergency operation	25 (41.0)	43 (43.4)	0.76

Patient characteristic	CCAB	BHCAB	<i>p</i> -value
	61 patients	99 patients	
Beating heart surgery on perfusion	-	11 (11.1)	-
Epiaortic ultrasound	6 (9.8)	58 (58.6)	<0.0001
Calcified ascending aorta	2 (3.3)	21 (21.2)	0.001
Untouched ascending aorta	1 (1.6)	13 (13.1)	0.018
Radial a. graft	3 (4.9)	6 (6.1)	1.00
Bilateral mammary a. grafts	1 (1.6)	8 (8.1)	0.16
Only vein grafts	19 (31.1)	10 (10.1)	0.001
No. distal anastomoses	3.8±1.0	3.5±1.0	0.036
Operation length (min)	273±62	250±66	0.058
Additive EuroSCORE	12.1±2.3	12.0±2.1	0.72
Logistic EuroSCORE (%)	30.9±16.5	29.1±14.7	0.58
NNECVDSG stroke risk score	8.4±1.8	8.2±1.6	0.32

Continuous variables are reported as means±standard deviation; PCI: percutaneous coronary intervention; LVEF: left ventricular ejection fraction; VT/VF: ventricular tachycardia/ventricular fibrillation; NNECVDSG: Northern New England Cardiovascular Disease Study group; Definition criteria for preoperative variables are according to EuroSCORE. Values in parentheses are percentages.

### 5.1.1 Overall results

Table 6 summarizes the clinical and operative data for the patients. The overall survival rates at 30 days, 1 year, 3 years and 5 years were 83.8%, 76.0%, 72.4% and 66.8%, respectively (S.E.< 0.048). Univariate analysis showed that left ventricular ejection fraction ( $p = 0.002$ ), critical preoperative status ( $p = 0.002$ ), congestive heart failure ( $p = 0.03$ ), preoperative use of intraaortic balloon pump ( $p < 0.0001$ ), preoperative use of inotropes ( $p < 0.0001$ ), preoperative tracheal intubation ( $p = 0.001$ ), preoperative resuscitation ( $p = 0.005$ ), preoperative creatinine level ( $p = 0.043$ ) and preoperative cardiac index (data in only 142 patients:  $p = 0.001$ ) were predictors of 30-day mortality. Logistic regression evaluating the 141 patients with complete data (due to missing cardiac index data in 19 patients) showed that preoperative cardiac index ( $p = 0.001$ , O.R. 0.200, 95%C.I. 0.076-0.528), preoperative inotropic support ( $p = 0.011$ , O.R. 4.552, 95%C.I. 1.407-14.727) and preoperative resuscitation ( $p = 0.047$ , O.R. 3.937, 95%C.I. 1.016-15.258) were independent predictors of 30-day postoperative mortality (Hosmer-Lemeshow:  $p = 0.328$ ). The area under the ROC curve for cardiac index was 0.728 (95%C.I. 0.622-0.835) and its best cut-off value was 2.2 L/min/m<sup>2</sup> (at logistic regression:  $p = 0.014$ , O.R. 3.919, 95%C.I. 1.319-11.643).

Univariate analysis showed that left ventricular ejection fraction ( $p = 0.022$ ), critical preoperative status ( $p = 0.021$ ), preoperative use of intraaortic balloon pump ( $p < 0.0001$ ), preoperative use of inotropes ( $p = 0.001$ ), preoperative tracheal intubation ( $p = 0.005$ ), preoperative resuscitation ( $p = 0.025$ ), preoperative creatinine level ( $p = 0.046$ ) and preoperative cardiac index (data in only 141 patients:  $p = 0.035$ ) were predictors of 30-day mortality. The Cox regression model showed that cardiac index ( $p = 0.011$ , R.R. 0.484, 95% C.I. 0.277-0.845), left ventricular ejection fraction ( $p = 0.032$ ), preoperative use of intraaortic balloon pump ( $p = 0.003$ , R.R. 3.222, 95% C.I. 1.499-6.929), preoperative tracheal intubation ( $p = 0.009$ , R.R. 3.443, 95% C.I. 1.365-8.683) and preoperative level of creatinine ( $p = 0.002$ , R.R. 1.004, 95% C.I. 1.002-1.007) were independent predictors of late death.

### **5.1.2 Comparison of operative techniques**

Table 7 summarizes the main outcome end-points in the study groups. BHCAB was associated with a somewhat lower risk of adverse outcome, but the difference failed to achieve statistical significance. The only significant difference was the lower amount of red blood cell units transfused in the BHCAB group. The CCAB group had better mid-term survival rates (at 5-year, 74.3% vs. 59.0%,  $p = 0.42$ , Tab. 2), but this difference failed to achieve statistical significance (log-rank:  $p = 0.42$ ), even when adjusted for the logistic EuroSCORE ( $p = 0.42$ ).

When only emergency operations were taken into account, CCAB was associated with a higher risk of 30-day mortality (32.0% vs. 16.3%,  $p = 0.13$ ), stroke (12.0% vs. 2.3%,  $p = 0.10$ ) and severe complications (60.0% vs. 48.8%,  $p = 0.37$ ), this likely being because of the increased operative risk (logistic EuroSCORE: CCAB 39.5% vs. OPCAB/BHCAB 33.3%,  $p = 0.16$ ). The five-year survival rate after emergency operation was 71.1%, which was somewhat better in the BHCAB group (74.7% vs. 64.0%,  $p = 0.23$ ).

When the results of surgeons with a prevalent BHCAB approach were compared with those of surgeons with a prevalent CCAB approach (logistic EuroSCORE 29.1% vs. 30.4%,  $p = 0.71$ ), the 30-day mortality rate (16.7% vs. 27.9%,  $p = 0.15$ ) and stroke rate (2.8% vs. 4.7%,  $p = 0.60$ ) were somewhat better in the former group. Patients operated on by BHCAB surgeons also had a slightly better 5-year survival rate (65.3% vs. 57.4%,  $p = 0.35$ ), when adjusted for logistic EuroSCORE:  $p = 0.19$ ). Such a difference in intermediate survival was also

observed among patients who underwent emergency operation (5-year overall survival: BHCAB 70.3% vs. CCAB 53.3%,  $p = 0.19$ ).

**Table 7. Immediate and intermediate outcome after isolated off-pump/beating heart coronary artery bypass surgery (OPCAB/BHCAB) and conventional coronary artery bypass surgery (CCAB) in patients with an additive EuroSCORE  $\geq 10$ .**

Outcome variable	CCAB 61 patients	BHCAB 99 patients	<i>p</i> -value
30-day mortality	11 (18.0)	16 (16.2)	0.73
In-hospital mortality	10 (16.4)	14 (14.1)	0.70
Stroke	3 (4.9)	2 (2.0)	0.37
Cardiac low-output syndrome <sup>1</sup>	23 (37.7)	36 (36.4)	0.87
Need for inotropes >12 hours	41 (67.2)	52 (52.5)	0.07
Intra-aortic balloon pump	11 (18.0)	16 (16.2)	0.83
Acute renal failure requiring <i>De novo</i> dialysis	3 (4.9)	5 (5.1)	1.00
Resternotomy for bleeding	7 (11.5)	7 (7.1)	0.39
Red blood cells units	5.4 $\pm$ 5.3	3.4 $\pm$ 3.7	0.004
Sepsis	5 (8.2)	6 (6.1)	0.75
Atrial fibrillation	34 (55.7)	58 (58.6)	0.74
Pneumonia	19 (31.1)	35 (35.4)	0.61
Combined adverse end-point <sup>2</sup>	31 (50.8)	43 (43.4)	0.42
Length of stay in the ICU (days)	5.0 $\pm$ 4.7	4.9 $\pm$ 4.7	0.47
Length of stay in the ICU >4 days	23 (37.7)	35 (35.4)	0.76
Overall survival			0.49
1-year	77.0%	75.4%	
3-year	74.3%	68.9%	
5-year	74.3%	59.0%	

<sup>1</sup>: Postoperatively cardiac index <2.0 L/min/m<sup>2</sup> at least twice; <sup>2</sup>: 30-day mortality, stroke, length of stay in ICU  $\geq 5$  days and/or acute renal failure requiring *De novo* dialysis; ICU: Intensive care unit. Survival estimates are according to the Kaplan-Meier analysis. Values in parentheses are percentages.

## 5.2 Coronary artery bypass grafting outcome in survivors of out-of-hospital cardiac arrest

### 5.2.1 Preoperative care and patient characteristics

Clinical characteristics and operative data are summarized in Table 8. No significant differences were observed between the OHCA and control groups in terms of baseline variables, but the OHCA group had significantly higher values

for EuroSCORE and modified EuroSCORE, mainly because of these patients' critical preoperative status related to the OHCA event, as defined by these two risk scoring methods. A propensity score was estimated and had an area under the ROC curve of 0.757 (95% CI 0.662-0.853).

Before resuscitation, 44 patients had ventricular fibrillation (91.7%), one had asystole (2.1%), one had pulseless electrical activity (2.1%), and there was no clear information as to the type of arrhythmia causing the resuscitation in two patients. All these patients were found to have suffered myocardial infarction-related cardiac arrest. Accordingly, myocardial enzymes were found to be elevated in all OHCA patients, but they were not taken into account in this analysis due to the heterogeneity of types and method of measurement of these enzymes.

Hypothermia treatment after successful resuscitation was employed in 14 OHCA patients (29.2%) because of neurological derangement related with cardiac arrest. Hypothermia was carried out at about 32.0-33.0°C for 24 hours. Four of these patients displayed a neurological deficit even after hypothermia treatment. A neurological status could not be assessed in eight patients who were intubated at arrival to the operating room due to their unstable cardiopulmonary conditions. In all of the latter patients, however, attempts to relieve sedation preoperatively revealed severe neuropsychological derangements.

Among OHCA patients, at coronary angiography 41 (85.4%) had three-vessel disease, six (12.5%) had two-vessel disease and one (2.1%) had one-vessel disease. Three OHCA patients (6.3%) underwent surgical revascularization within 30 days after percutaneous coronary intervention. The mean delay from OHCA to CABG was 10.3±13.0 days (median 7.0 days, interquartile range 7.5) and only two patients (4.2%) were operated on an elective basis. The immediate postoperative outcome is summarized in Table 8. Despite not being statistically significant, the 30-day postoperative mortality was higher among OHCA patients than controls (6.3% vs. 0%,  $p = 0.24$ , propensity score adjusted analysis:  $p = 1.00$ ). As expected on the basis of the preoperative status, neuropsychological derangements were more frequently observed among OHCA patients (27.1% vs. 8.3%,  $p < 0.0001$ ; propensity score adjusted analysis:  $p = 0.14$ ). Postoperative stroke occurred in one patient in each study group.

An electrophysiological study was performed in four OHCA patients and failed to reveal any sustained ventricular tachycardia. A cardioverter defibrillator was implanted in two other patients in whom an electrophysiological study was

not otherwise performed. These two patients were alive 3.8 and 4.4 years after CABG, respectively.

**Table 8. Clinical and operative data on patients with out-of-hospital cardiac arrest and matched controls with recent myocardial infarction <3 months who underwent isolated coronary artery bypass surgery.**

Patient characteristic	OHCA (48 patients)	Controls (48 patients)	<i>p</i> -value
Age (years)	65.2±1.2	65.2±1.2	0.97
Female gender	6 (12.5)	6 (12.5)	1.00
Dyslipidemia	16 (33.3)	18 (37.5)	0.67
Pulmonary disease	6 (12.5)	4 (8.3)	0.74
Hypertension	25 (52.1)	16 (33.3)	0.06
Serum creatinine (mmol/l)	89±5	83±3	0.78
Atrial fibrillation	9 (18.8)	7 (14.6)	0.79
Transient ischemic attack	1 (2.1)	4 (8.3)	0.35
Stroke	3 (6.3)	0 (0)	0.24
Neurological dysfunction	4 (8.3)	1 (2.1)	0.36
Extracardiac arteriopathy	4 (8.3)	3 (6.3)	1.00
Previous vascular/endovascular surgery	2 (4.2)	2 (4.2)	1.00
Previous cardiac surgery	1 (2.1)	0 (0)	1.00
Previous percutaneous transluminal angioplasty	4 (8.3)	1 (2.1)	0.36
Left main stenosis>50%	20 (41.7)	15 (31.3)	0.29
LVEF>50%	26 (54.2)	30 (62.5)	0.70
30-50%	18 (37.5)	15 (31.3)	
<30%	4 (8.3)	3 (6.3)	
Critical preoperative status	32 (66.7)	2 (4.2)	<0.0001
Preoperative inotropic support	7 (14.6)	4 (8.3)	0.52
Tracheal intubation at OR arrival	8 (16.7)	2 (4.2)	0.09
Nitrates infusion at OR arrival	16 (33.3)	18 (37.5)	0.67
Systolic pulmonary a. pressure>60 mmHg	2 (4.2)	1 (2.1)	1.00
Cardiac index (L/min/m <sup>2</sup> )	2.7±0.6	2.6±0.7	0.47
Emergency operation	6 (12.5)	5 (10.4)	0.86
Off-pump surgery	20 (41.7)	23 (47.9)	0.54
Diseased ascending aorta	5 (10.4)	5 (10.4)	1.00
At least one mammary a. graft	46 (95.8)	46 (95.8)	1.00
No. distal anastomoses	3.7±0.1	3.8±0.1	0.84
Logistic EuroSCORE (%)	14.3±2.3	7.8±1.6	0.003
Logistic modified EuroSCORE (%)	5.5±1.1	1.1±0.4	<0.0001

Continuous variables are reported as mean±standard deviation; LVEF: left ventricular ejection fraction; OR: operating room; Variables definition criteria are according to EuroSCORE. Values in parentheses are percentages.

**Table 9. Immediate and late outcome in patients with out-of-hospital cardiac arrest and matched controls with recent myocardial infarction <3 months who underwent isolated coronary artery bypass surgery.**

Variable	Out-of-hospital cardiac arrest (48 patients)	Controls (48 patients)	Unadjusted <i>p</i> -value	Propensity score adjusted <i>p</i> -value
30-day mortality	3 (6.3)	0 (0)	0.24	1.00
In-hospital mortality	2 (4.2)	0 (0)	0.50	1.00
Stroke	1 (2.1)	1 (2.1)	1.00	0.53
Neuropsychological derangement	13 (27.1)	4 (8.3)	0.03	0.14
Cardiac low-output syndrome <sup>1</sup>	5 (10.4)	6 (12.5)	1.00	0.96
Need for inotropes>12 hours	10 (20.8)	13 (27.1)	0.47	0.29
Intra-aortic balloon pump	3 (6.3)	1 (2.1)	0.62	0.21
<i>De novo</i> dialysis	0 (0)	1 (2.1)	0.32	1.00
Resternotomy for bleeding	2 (4.2)	2 (4.2)	1.00	0.69
Red blood cell units transfused	2.3±0.4	2.2±0.4	0.06	0.22
Sepsis	2 (4.2)	1 (2.1)	1.00	0.81
Atrial fibrillation	21 (43.8)	20 (41.7)	0.84	0.90
Pneumonia	7 (14.6)	5 (10.4)	0.76	0.96
Length of stay in the ICU (days)	2.2±0.3	3.0±0.6	0.59	0.25

<sup>1</sup>: Postoperatively cardiac index<2.0 L/min/m<sup>2</sup> at least twice; ICU: Intensive care unit. Values in parentheses are percentages.

### 5.2.2 Follow-up

The mean length of follow-up was 4.9±0.4 years for OHCA patients and 4.6±0.4 years for control patients. Despite a slightly higher early mortality among the OHCA patients, at 5-year the overall survival rate was similar in the study group, having been 80.7% in OHCA patients and 84.5% in control patients (10 patients vs. 10 patients, respectively, log-rank test: *p* = 0.98, Fig. 2). A propensity score-adjusted analysis confirmed that no difference in survival existed between the study groups (*p* = 0.87, HR 1.09, 95% CI 0.39-3.05). At 5-year, survival freedom from fatal cardiac event was 86.1% in OHCA patients and 86.5% in control patients (6 patients vs. 8 patients, respectively, log-rank test: *p* = 0.61; propensity score adjusted analysis: *p* = 0.90, HR 0.93, 95% CI 0.28-3.08).

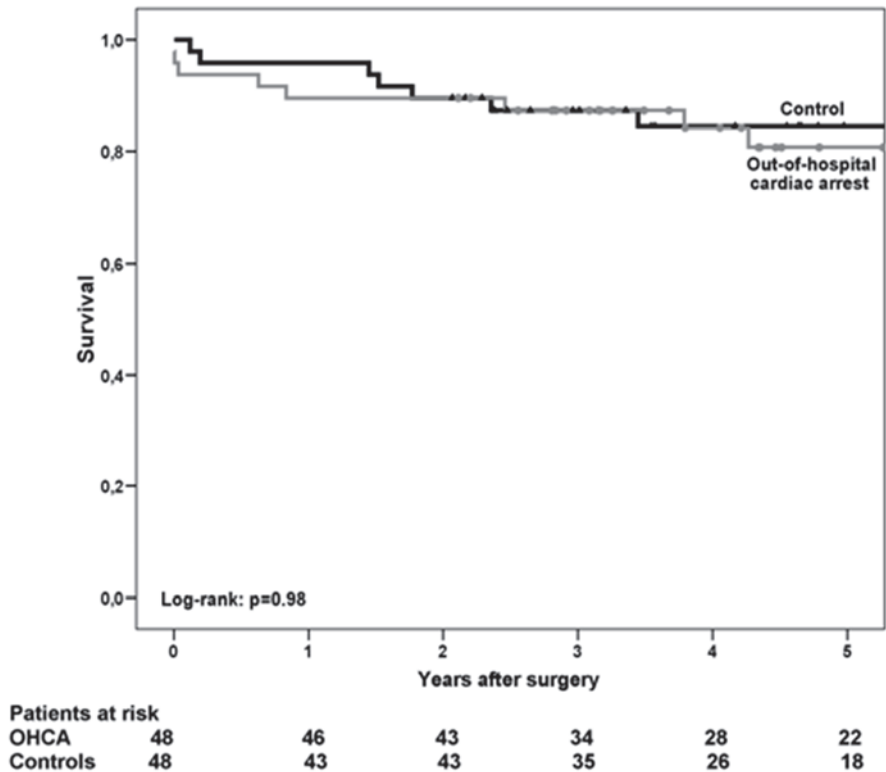


Fig. 2. Kaplan-Meier's estimate of overall survival after coronary artery bypass surgery in patients with out-of-hospital cardiac arrest and in control patients who suffered myocardial infarction without ventricular arrhythmia within 3 months prior to surgery.

### 5.3 Impact of chronic kidney disease on outcome of coronary artery bypass grafting

The clinical and operative data of patients included in Study III are summarized in Table 10 and the immediate postoperative complications are summarized in Table 11. The overall survival rates at 30 days, 5 years and 10 years were 97.6%, 89.4% and 74.3%, respectively (S.E.< 0.03). Patients with Stage 1-2 CKD had overall survival rates at 30 days, 5 years and 10 years of 98.5%, 91.1% and 74.7%, and for patients with Stage 3 CKD were 92.6%, 80.8%, and 65.8%, respectively ( $p = 0.002$ ). Patients with Stage 4-5 CKD had 30-day and 5-year

survival rates of 66.7% and 66.7%. Because of the small number of patients with Stage 4-5 CKD, further analysis with this study group was not feasible.

Freedom from fatal cardiac event and/or fatal stroke at 30 days, 5 years and 10 years in CKD Stage 1-2 patients was 98.7%, 95.0% and 90.0%, respectively and in CKD Stage 3 patients 93.7%, 82.4% and 72.8%, respectively ( $p < 0.0001$ ). Stage 3 CKD class was an independent predictor of late cardiovascular mortality ( $p = 0.028$ , RR 1.91, 95% CI 1.07-3.39) when adjusted for age and additive EuroSCORE.

**Table 10. Clinical and operative data of 88 patients with stage 3 CKD who survived after isolated coronary artery bypass surgery.**

Variable	No. (%)
Age (years)	70.5±7.4
Female gender	44 (50)
Pulmonary disease	5 (5.7)
Diabetes	27 (30.7)
Type 1 Diabetes mellitus	6 (6.8)
Type 2 Diabetes mellitus	21 (23.9)
Hypertension	56 (63.6)
Atrial fibrillation	15 (17.0)
Stroke	13 (14.8)
Transient ischemic attack	3 (3.4)
Neurological dysfunction	4 (4.5)
Myocardial infarction<3 months	37 (42.0)
Extracardiac arteriopathy	16 (18.2)
Previous peripheral endovascular/vascular procedure	9 (10.2)
Previous cardiac surgery	0 (0)
Previous percutaneous coronary intervention	7 (8.0)
Acute renal failure	0 (0)
Preoperative creatinine (mg/dl)	1.3±0.3
Baseline eGFR ml/min/1.73 m <sup>2</sup>	50.7±7.4
Left ventricular ejection fraction>50%	64 (72.7)
30-50%	19 (21.6)
<30%	5 (5.7)
Unstable angina pectoris	22 (25)
Critical preoperative status	7 (8)
Systolic pulmonary a. pressure>60 mmHg	2 (2.3)
Emergency operation	1 (1.1)
Off-pump coronary artery bypass surgery	14 (15.9)
Single mammary artery graft	78 (88.6)
Bilateral mammary artery grafts	4 (4.5)
Radial artery graft	14 (15.9)
No. proximal anastomoses	1.9±0.8
No. distal anastomoses	4.0±1.1
Additive EuroSCORE	5.8±3.3
Logistic EuroSCORE (%)	7.7±8.2

Continuous variables are reported as mean±standard deviation; eGFR: estimated glomerular filtration rate; \*: Definition criteria for preoperative variables are according to EuroSCORE.

**Table 11. Immediate postoperative complications among 88 survivors with stage 3 CKD after isolated coronary artery bypass surgery.**

Postoperative complication	No. (%)
Dialysis	3 (3.4)
Transient ischemic attack	1 (1.1)
Stroke	6 (6.8)
Atrial fibrillation	37 (42)
Pneumonia	4 (4.5)
Ventilation support >24h	10 (11.4)
Reoperation due to infection	1 (1.1)
Reoperation due to bleeding	5 (5.7)
Low cardiac output syndrome	9 (10.2)
Postoperative intraaortic balloon pump	2 (2.3)
Length of stay in intensive care unit (days)	2.9±5.2
Intensive care unit stay>2 days	32 (36.4)

### **5.3.1 Outcome in patients with Stage 3 CKD**

Seven out of 95 patients with Stage 3 CKD died during the 30-day postoperative period and have been excluded from further analysis because the main aim of the present study was to evaluate the long-term progression of kidney failure as well as late mortality and cardiovascular morbidity.

Tables 9 and 10 summarize the clinical variables and immediate postoperative complications in these 88 operative survivors. The mean duration of follow-up in these patients was 6.7±3.1 years (median: 6.6 years, range: 0.12-11.9 years). The overall 5- and 10-year survival rates of these operative survivors with preoperative Stage 3 CKD were 87.2% and 71.0%, respectively. Freedom rates from fatal cardiac events and fatal ischaemic stroke at 5 and 10 years were 87.9% and 77.7%, respectively.

Freedom rates from any cardiovascular events at 5 and 10 years were 61.2% and 44.4%, respectively. Freedom rates from dialysis at 30 days, 5 years and 10 years were 97.7%, 95.3% and 82.7%, respectively. During the follow-up period, 7 patients required dialysis. Two of them required dialysis immediately within 30 days after surgery. Two of them discontinued dialysis after successful kidney transplantation.

At the 30-day, 5-year and 10-year follow-ups, a nephrologists' consultation was done in 5.7%, 22.2% and 26.9% of patients.

### **5.3.2 Change in estimated glomerular filtration rate**

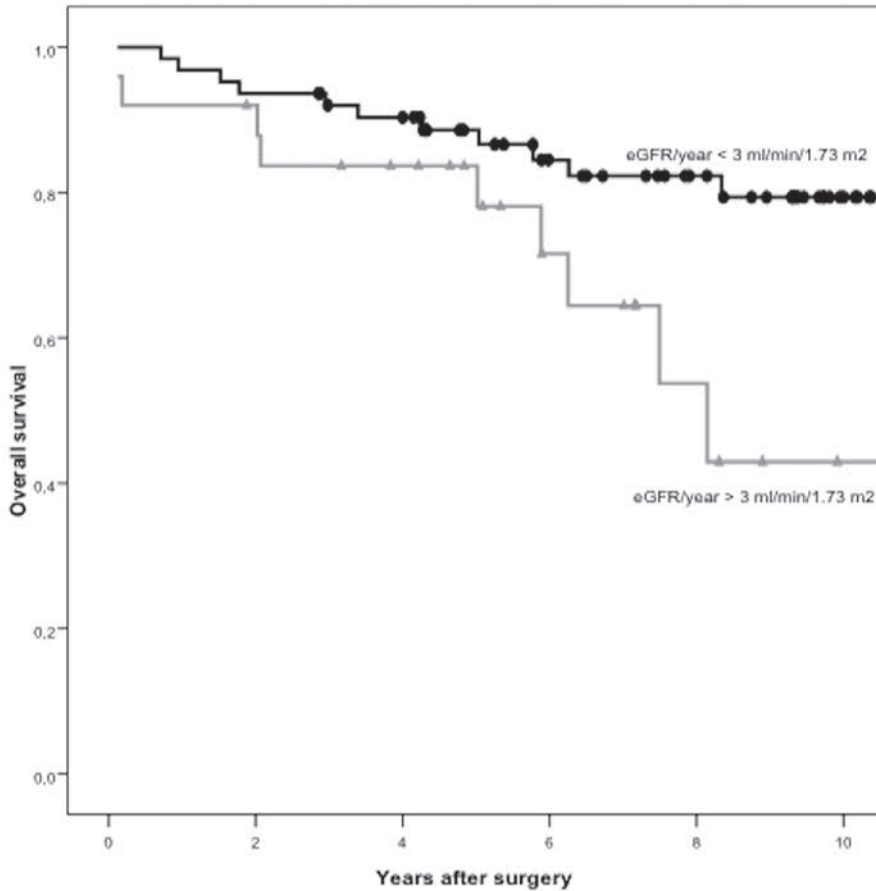
The mean duration of follow-up for measurement of serum creatinine was  $6.6 \pm 3.2$  years (median: 6.6 years, range: 0.12-11.9 years), which was similar to the overall length of follow-up.

The mean change of eGFR/year was  $-3.8 \pm 26.8$  ml/min/1.73 m<sup>2</sup>. Eight patients (9.1%) had an improvement of eGFR/year  $> 5$  ml/min/1.73 m<sup>2</sup>, 31 patients (35.2%) an improvement of eGFR/year  $> 1$  ml/min/1.73 m<sup>2</sup>, 19 patients (21.6%) had a stable eGFR/year (change/year -1 to + 1 ml/min/1.73 m<sup>2</sup>), 38 patients (43.2%) had a decline of eGFR/year  $> 1$  ml/min/1.73 m<sup>2</sup>, 25 patients (28.4%) a decline of eGFR/year  $> 3$  ml/min/1.73 m<sup>2</sup>, and 10 patients (11.4%) a decline of eGFR/year  $> 5$  ml/min/1.73 m<sup>2</sup>.

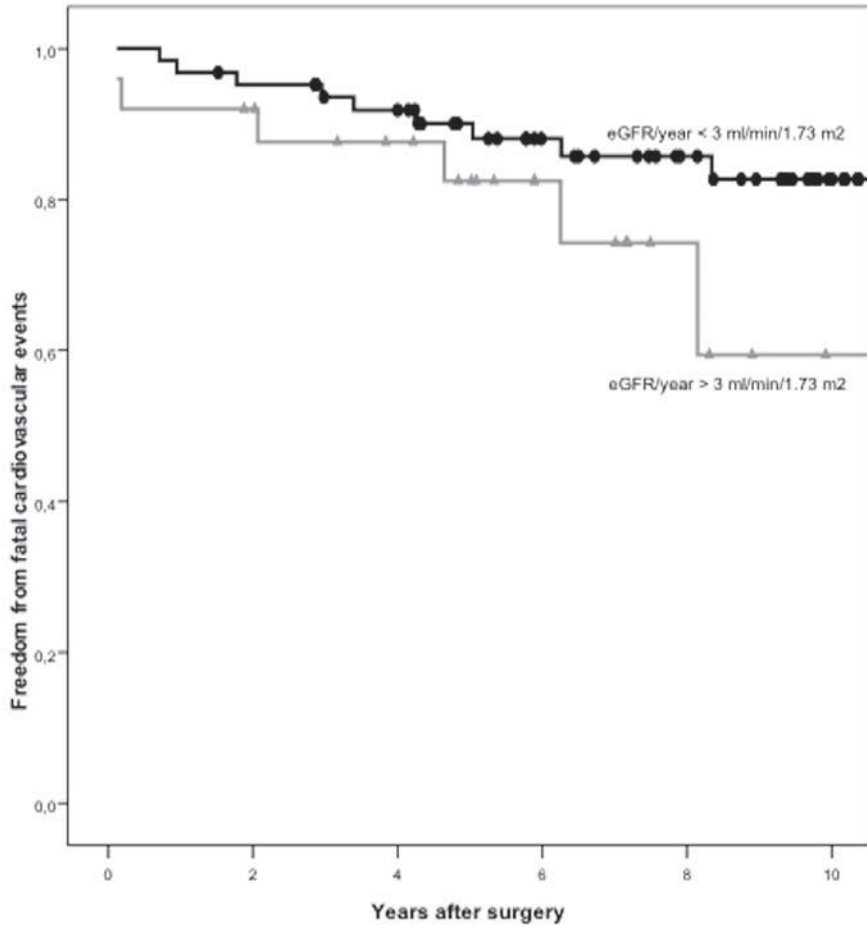
Preoperative left ventricular ejection fraction  $\leq 50\%$ , previous vascular/endovascular peripheral surgery and preoperative systolic pulmonary pressure  $> 60$  mmHg were independent predictors for change of eGFR/year (Table 12). The results did not change when the length of follow-up for creatinine measurements was included in the linear regression analysis model.

Multivariate analysis showed that change in eGFR/year was an independent predictor of all-cause mortality ( $p < 0.0001$ , RR 0.969, 95% CI 0.953-0.985), cardiovascular mortality ( $p = 0.005$ , RR 0.977, 95% CI 0.961-0.993) (Table 11). It also tended to predict cardiovascular mortality, as well ( $p = 0.063$ , RR 0.989, 95% CI 0.978-1.001).

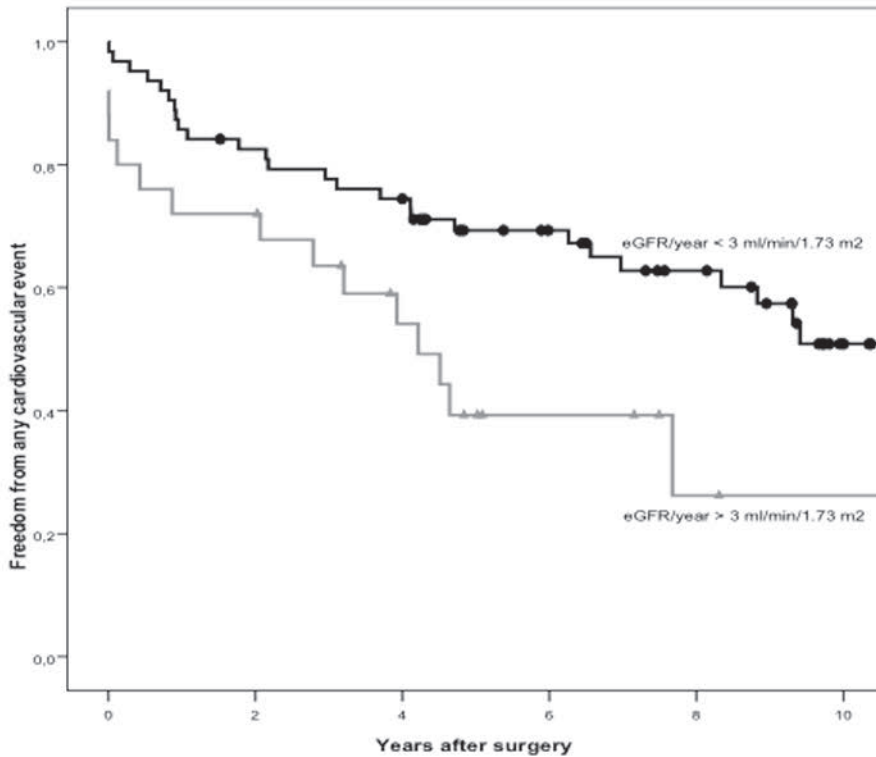
Patients with a decline of eGFR/year  $> 3$  ml/min/1.73 m<sup>2</sup> had a significantly poorer overall survival (at 10 years: 42.9% vs. 79.3%,  $p = 0.022$ , Fig. 3), a significantly lower freedom from any cardiovascular event (at 10 years: 22.6% vs. 50.8%,  $p = 0.012$ , Fig. 4) and a somewhat lower freedom from fatal cardiovascular events (at 10 years: 59.4% vs. 82.7%,  $p = 0.127$ , Fig. 5).



**Fig. 3. Overall survival ( $p = 0.028$ , RR 2.712, 95% C.I. 1.112-6.610) among 88 patients with preoperative Stage 3 CKD who survived after isolated coronary artery bypass surgery according to a decline of estimated glomerular filtration rates (eGFR) per year of either more or less than 3 ml/min/1.73 m<sup>2</sup>. Relative risks are adjusted for age and additive EuroSCORE.**



**Fig. 4. Freedom from fatal cardiovascular events ( $p = 0.22$ , RR 1.939, 95% C.I. 0.679-5-535) among 88 patients with preoperative Stage 3 CKD who survived after isolated coronary artery bypass surgery according to a decline of estimated glomerular filtration rates (eGFR) per year of either more or less than 3 ml/min/1.73 m<sup>2</sup>. Relative risks are adjusted for age and additive EuroSCORE.**



**Fig. 5. Freedom from any major cardiovascular event ( $p = 0.047$ , RR 1.948, 95% C.I. 1.010-3.758) among 88 patients with preoperative Stage 3 CKD who survived after isolated coronary artery bypass surgery according to a decline of estimated glomerular filtration rates (eGFR) per year of either more or less than 3 ml/min/1.73 m<sup>2</sup>. Relative risks are adjusted for age and additive EuroSCORE.**

**Table 12. Independent predictors of late outcome among 88 patients with stage 3 CKD who survived isolated coronary artery bypass surgery.**

Variable	Decline in eGFR/year> 3 ml/min/1.73 m <sup>2</sup>		All-cause mortality		Cardiovascular mortality		Cardiovascular events	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
Age	0.963	-	0.854	-	-	-	0.902	-
Female gender	0.181	-	0.509	-	0.578	-	0.316	-
Pulmonary disease	0.969	-	0.379	-	0.829	-	0.667	-
Diabetes	0.935	-	0.046	0.01	0.395	-	0.370	-
Hypertension	0.259	-	0.053	-	0.269	-	0.527	-
Atrial fibrillation	0.245	-	0.988	-	0.620	-	0.057	-
Stroke	0.541	-	0.656	-	0.880	-	0.195	0.010
Neurological dysfunction	0.642	-	<0.0001	<0.0001	0.007	-	0.009	0.026
Myocardial infarction<3 months	0.091	-	0.927	-	0.255	-	0.003	0.003
Extracardiac arteriopathy	0.128	-	0.005	-	0.004	0.015	<0.0001	<0.0001
Previous peripheral endovascular/vascular procedure	0.027	0.007	0.057	-	0.108	-	0.021	-
Previous percutaneous coronary intervention	0.603	-	0.196	-	0.259	-	0.876	-
Creatinine	0.365	-	0.921	-	0.749	-	0.029	-
Baseline eGFR	0.634	-	0.360	-	0.255	-	0.018	0.013
Change in eGFR/year	-	-	0.001	<0.0001	0.001	0.005	<0.0001	-
Left ventricular ejection fraction≤50%	0.018	0.022	0.580	-	0.173	-	0.332	-
Unstable angina pectoris	0.561	-	0.685	-	0.810	-	0.214	-

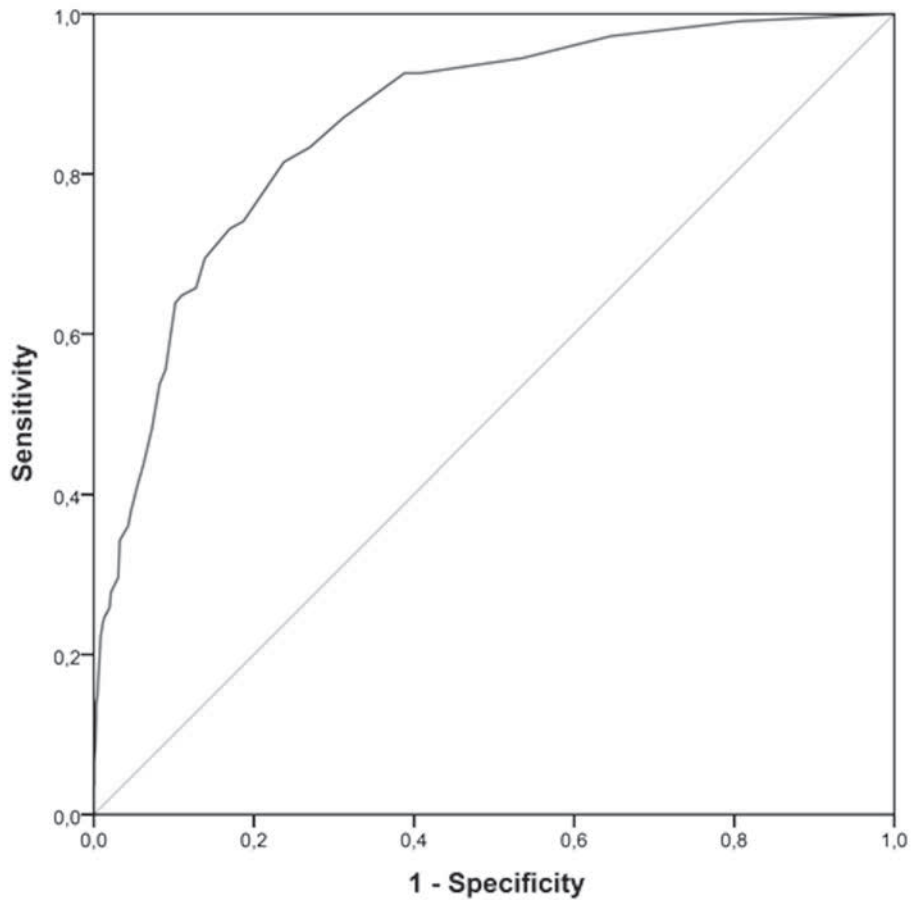
Variable	Decline in eGFR/year> 3 ml/min/1.73 m <sup>2</sup>		All-cause mortality		Cardiovascular mortality		Cardiovascular events	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
	Critical preoperative status	0.156	-	0.216	-	0.005	0.003	0.031
Syst. pulmonary a. pressure>60 mmHg	<0.0001	<0.0001	0.268	-	0.143	-	0.901	-
Emergency operation	0.935	-	0.614	-	0.663	-	0.446	-
Off-pump coronary artery bypass surgery	0.430	-	0.463	-	0.237	-	0.060	-
No. distal anastomoses	0.103	-	0.768	-	0.626	-	0.815	-
Need for postoperative dialysis	0.005	-	0.334	-	0.210	-	<0.0001	0.004
Postop. low cardiac output syndrome	0.331	-	0.216	-	0.083	-	0.020	0.021
Additive EuroSCORE	0.143	-	0.387	-	0.046	-	0.009	-

#### **5.4 Results for the evaluation of the postoperative complication grading method**

Patient characteristics from the overall study population and in each E-CABG grade are summarized in Table 13. Table 14 summarizes the proportion of patients included in each E-CABG complication grade and the prevalence of postoperative adverse events in this series. The in-hospital mortality was 2.4%. The median additive score for each grade indicated that within increasing grades of complications, the number of complications also increased markedly (grade 1, 4.0; grade 2, 10.0; grade 3, 21.0).

This grading method was predictive of the length of stay in the intensive care unit (grade 0: 1.2±0.6 days; grade 1: 1.6±1.1 days; grade 2: 2.9±2.1 days; grade 3: 4.9±5.2 days; Kruskal-Wallis test:  $p < 0.0001$ ). The E-CABG complication additive score also correlated significantly with the length of stay in the intensive care unit (Spearman's test: rho, 0.514;  $p < 0.0001$ ).

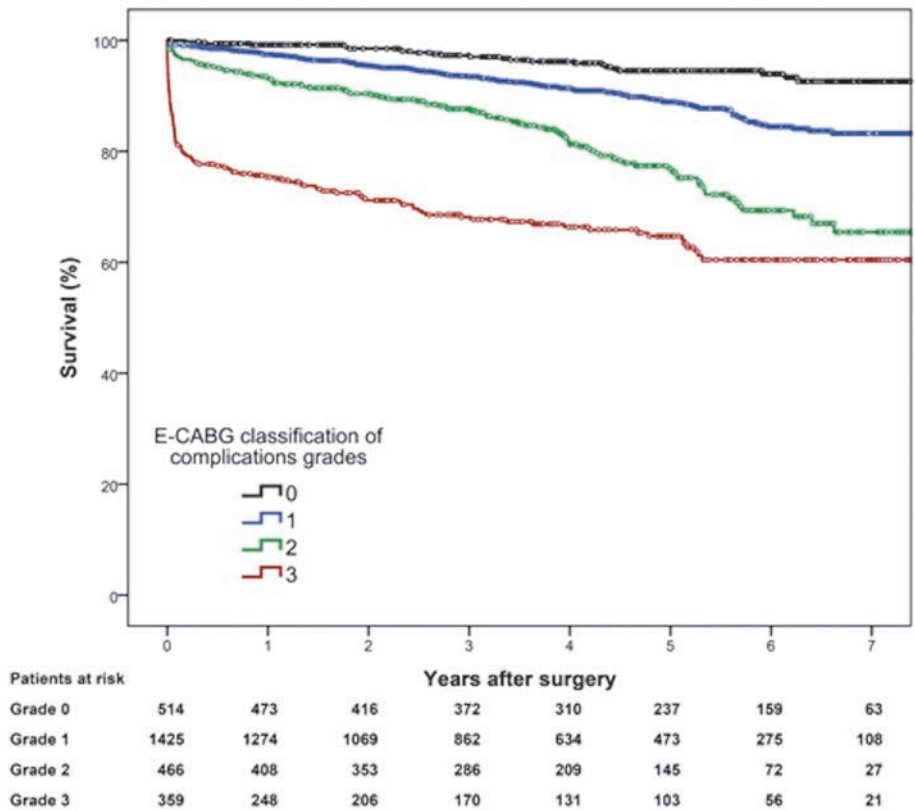
The E-CABG complication grades were predictive of 30-day (grade 0: 0%; grade 1: 0.4%; grade 2: 1.7%; grade 3: 14.5%;  $p < 0.0001$ ) and 90-day mortality (grade 0: 2%; grade 1: 1.1%; grade 2: 3.7%; grade 3: 21.5%,  $p < 0.0001$ ). Similarly, increasing quintiles of the E-CABG complication score were associated with increased 30-day mortality (0%, 0.3%, 1.1%, 3.1%, 12.6%;  $p < 0.0001$ ) and 90-day mortality (0.2%, 0.6%, 1.3%, 3.9%, 15.0%;  $p < 0.0001$ ).



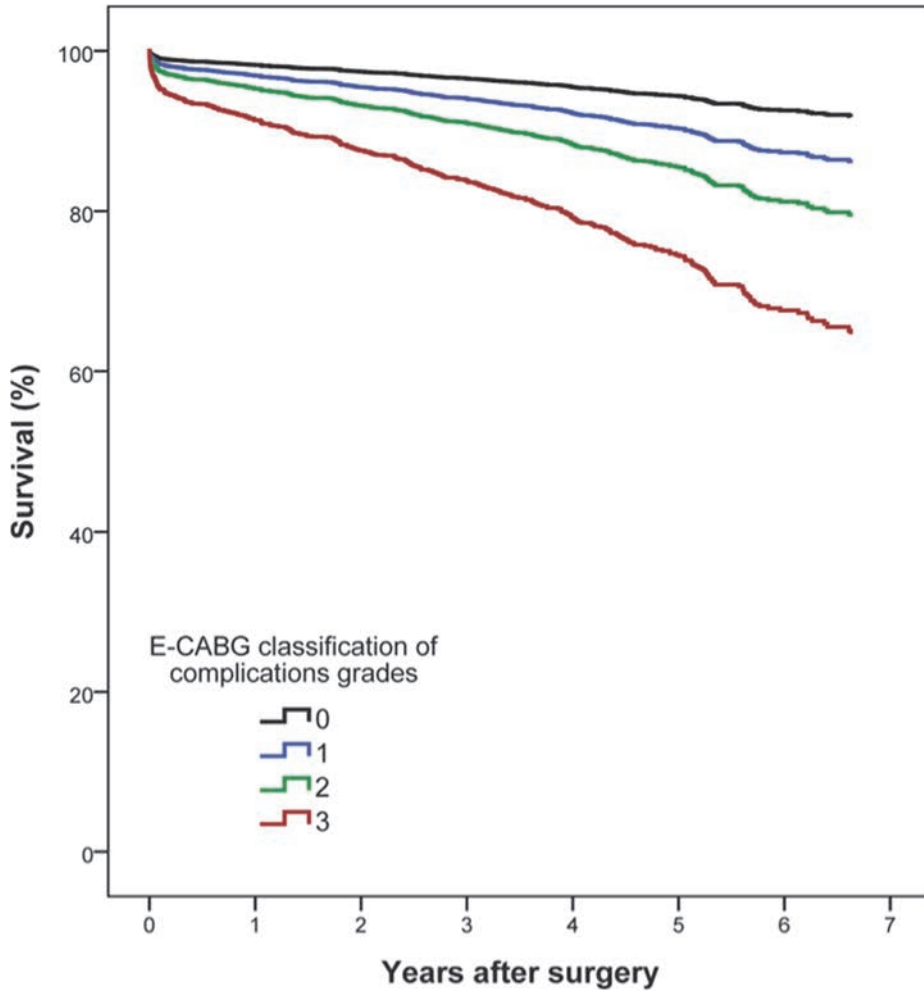
**Fig. 6. Receiver operating characteristics curve of the E-CABG complication classification score in predicting 30-day all-cause mortality.**

A receiver operating characteristics (ROC) analysis confirmed that the E-CABG complication score was predictive of 30-day all-cause mortality (area under the ROC curve 0.876, 95% CI 0.844-0.908) and 90-day all-cause mortality (area under the ROC curve 0.863, 95% CI 0.829-0.897; Fig. 6). Because the grading method is the result of a breakdown of this additive score, an ROC analysis was also performed for the E-CABG complication grades and demonstrated that these were predictive of 30-day all-cause mortality (area under the ROC curve 0.866, 95% CI 0.829-0.903) and 90-day all-cause mortality (area under the ROC curve 0.850, 95% CI 0.812-0.887).

The E-CABG complication grades were predictors of increased mortality in Kaplan-Meier (at 5 years - grade 0: 5.5%; grade 1: 11.1%; grade 2: 23.1%; grade 3: 35.3%; log-rank:  $p < 0.0001$ ) (Fig. 7) and Cox regression adjusted analysis (2 651 patients included in the multivariate model;  $p < 0.0001$ ; grade 1: HR 1.757, 95% CI 1.111-2.778; grade 2: HR 2.704, 95% CI 1.664-4.394; grade 3: HR 5.081, 95% CI % 3.148-8.201) (Table 14, Fig. 8).



**Fig. 7. Kaplan-Meier estimates of all-cause mortality according to different E-CABG complications classification grades (log-rank:  $p < 0.0001$ ).**



**Fig. 8. Adjusted Cox proportional hazards estimates of all-cause mortality according to different E-CABG complications classification grades ( $p < 0.0001$ ; grade 1: HR 1.757, 95% CI 1.111-2.778; grade 2: HR 2.704, 95% CI 1.664-4.394; grade 3:HR 5.081, 95% CI 3.148-8.201).**

**Table 13. Baseline and operative characteristics and in-hospital deaths of the study population and subgroups according to the E-CABG grading.**

Patient characteristic	Overall series n=2764	Grade 0 n= 514	Grade 1 n= 1425	Grade 2 n=466	Grade 3 n= 359	p-value
Age (years)	67.0±9.1	63.3±8.4	67.1±8.9	69.6±9.4	68.1±8.7	<0.001
Female gender	582 (21.1)	60 (11.7)	289 (20.3)	151 (32.4)	82 (22.8)	<0.001
Pulmonary disease	274 (9.9)	48 (9.3)	126 (8.8)	52 (11.2)	48 (13.4)	0.05
Diabetes	788 (28.5)	120 (23.3)	381 (26.7)	176 (37.8)	111 (30.9)	<0.001
Hypertension	1547 (56.0)	269 (52.3)	794 (55.7)	280 (60.1)	204 (56.8)	0.11
Stroke	95 (3.4)	10 (1.9)	46 (3.2)	20 (4.3)	19 (3.4)	0.04
Neurologic dysfunction	50 (1.8)	1(0.2)	32 (2.2)	8 (1.7)	9 (2.5)	0.02
Extracardiac arteriopathy	265 (9.6)	33 (6.4)	117 (8.2)	59 (12.7)	56 (15.6)	<0.001
eGFR (mL/min/1.73 m <sup>2</sup> )	86.1±25.2	92.3±20.8	87.0±23.1	81.2±29.4	79.9±30.2	<0.001
Dialysis	22 (0.8)	1 (0.2)	8 (0.6)	3 (0.6)	10 (2.8)	<0.001
Atrial fibrillation	282 (10.2)	7 (1.4)	159 (11.2)	64 (13.7)	52 (14.5)	<0.001
Recent myocardial infarction	1319 (47.7)	144 (28.0)	652 (45.8)	307 (65.9)	216 (60.2)	<0.001
Previous PCI	201 (7.3)	34 (6.6)	94 (6.6)	41 (8.8)	32 (8.9)	0.23
Previous cardiac surgery	46 (1.7)	6 (1.2)	17 (1.2)	11 (2.4)	12 (3.3)	0.02
Unstable angina requiring nitrate at OR arrival	364 (13.2)	13 (2.5)	141 (9.9)	110 (23.6)	100 (27.9)	<0.0001
Left ventricular ejection fraction						<0.001
30-50%	612 (22.1)	81 (16.2)	284 (20.8)	131 (29.2)	116 (33.7)	
<30%	87 (3.1)	4 (0.4)	39 (2.9)	28 (6.3)	16 (4.7)	
Critical preoperative status	217 (7.9)	12 (2.3)	81 (5.7)	62 (13.3)	62 (17.3)	<0.001
Operative data						
Type of operation						<0.001
Elective	1260 (45.6)	340 (66.1)	688 (48.3)	115 (24.7)	117 (32.6)	
Urgent	1306 (47.3)	173 (33.7)	677 (47.5)	289 (62.0)	167 (46.5)	

Patient characteristic	Overall series n=2764	Grade 0 n= 514	Grade 1 n= 1425	Grade 2 n= 466	Grade 3 n= 359	p-value
Emergency	197 (7.1)	1 (0.2)	60 (4.2)	62 (13.3)	75 (20.9)	
Mammary artery graft	2642 (95.6)	508 (98.8)	1385 (97.2)	432 (92.7)	317 (88.3)	<0.001
Potent antiplatelets within 5 days	512 (18.5)	37 (7.2)	242 (17.0)	139 (29.8)	94 (26.2)	<0.001
Off-pump coronary surgery	1510 (54.6)	311 (60.5)	789 (55.4)	230 (49.4)	180 (50.1)	0.01
Number of distal anastomoses	4.0±1.1	4.0±1.1	3.9±1.1	4.0±1.1	3.8±1.0	0.07
In-hospital death	67 (2.4)	0 (0.0)	6 (0.4)	8 (1.7)	53 (14.8)	<0.001

Continuous variables are reported as mean and standard deviation. Categorical variables are reported as absolute numbers and percentages; eGFR: estimated glomerular filtration rate; PCI: percutaneous coronary intervention; OR: operating room. Definition criteria are according to EuroSCORE II.

**Table 14. E-CABG classification of postoperative complications or interventions for their treatment and their prevalence. Adjusted risk estimates for postoperative early and late mortality are reported.**

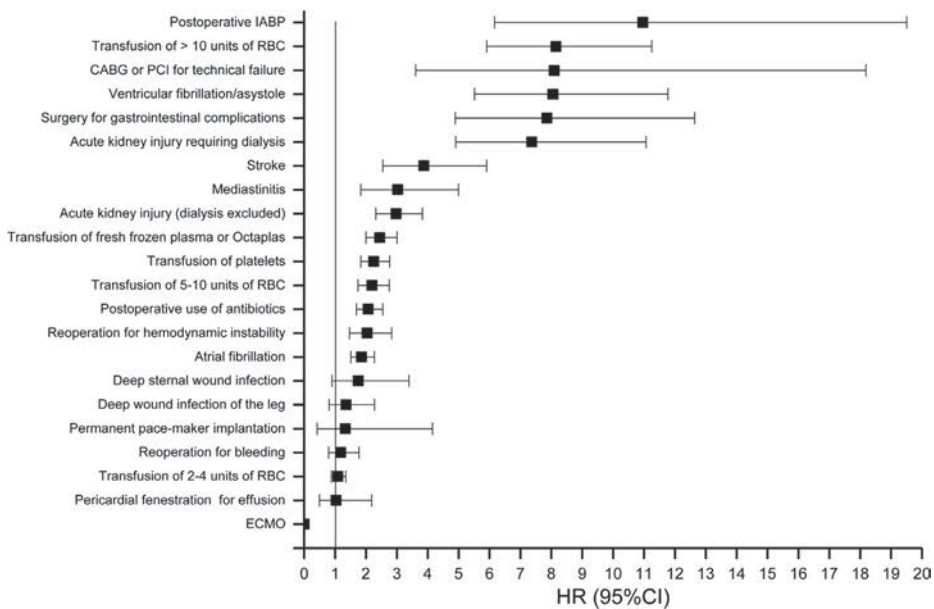
Grades	Postoperative complications or interventions for their treatment	Additive score	No. (%)	Adjusted analysis for mortality HR (95%CI)	Multiple propensity score adjusted analysis for mortality	Reference category
Grade 0	None of the below mentioned complications/interventions	0	514 (18.6)	Reference category	Reference category	
Grade 1	Postoperative use of antibiotics	2	1425 (51.6)	1.76 (1.11-2.78)	1.69 (1.06-2.68)	
	Atrial fibrillation	2	937 (33.9)			
	Transfusion of platelets	2	1186 (42.9)			
	Transfusion of fresh frozen plasma or Octoplas	3	826 (29.9)			
	Transfusion of 2-4 units of RBC	3	738 (26.7)			
	Deep wound infection of the leg	3	939 (34.0)			
	Permanent pace-maker implantation	3	78 (2.8)			
Grade 2			18 (0.7)	2.70 (1.66-4.39)	2.71 (1.65-4.43)	
			466 (16.9)			

Grades	Postoperative complications or interventions for their treatment	Additive score	No. (%)	Adjusted analysis for mortality HR (95%CI)	Multiple propensity score adjusted analysis for mortality	
Grade 3	Pericardial fenestration for effusion	4	47 (1.7)			
	Acute kidney injury (dialysis excluded)	4	258 (89.3)*			
	Transfusion of 5-10 units of RBC	5	443 (16.0)			
	Reoperation for bleeding	5	163 (5.9)			
	Deep sternal wound infection	5	40 (1.4)			
	Postoperative IABP	5	16 (0.6)			
				359 (13.0)	5.08 (3.15-8.20)	4.57 (2.81-7.43)
	Transfusion of > 10 units of RBC	7	68 (2.5)			
	Acute kidney injury requiring dialysis	7	42 (1.5)*			
	Mediastinitis	7	43 (1.6)			
	Stroke	7	58 (21)			
	CABG or PCI for technical failure	7	14 (0.5)			
	Reoperation for hemodynamic instability	8	168 (6.1)			
	Ventricular fibrillation/asystole	8	49 (1.8)			
	Surgery for gastrointestinal complications	9	32 (1.2)			
	Postoperative ECMO	9	0		-	

Definition criteria are according to the E-CABG criteria [12]; HR: hazard ratio; CI: confidence interval; RBC: red blood cell; IABP: intra-aortic balloon pump; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; ECMO: extracorporeal membrane oxygenation; \* patients on preoperative dialysis excluded from this analysis.

When patients who died within 30 days were excluded from the analysis, this grading method was still associated with the late mortality (2 562 patients included in the multivariate model;  $p < 0.0001$ ; grade 1: HR 1.760, 95% CI 1.1356-2.283; grade 2: HR 2.936, 95% CI 1.798-4.794; grade 3: HR 3.209, 95% CI 1.929-5.338).

Figure 9 summarizes the unadjusted risk estimates of any early and late mortality for each postoperative adverse event. This analysis confirmed that the adverse events included among grade 3 complications were associated with a formidable risk of death. A postoperative use of intra-aortic balloon pump was associated with a very high mortality, likely because extracorporeal membrane oxygenation was not in use in this series. Multivariate analysis of the prognostic impact of these adverse events was not performed due to the risk of overfitting.



**Fig. 9. Unadjusted estimates of all-cause mortality according to different postoperative adverse events included in the E-CABG complication classification. IABP, intra-aortic balloon pump; RBC, red blood cell; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention; HR, hazard ratio; CI, confidence interval**

## **5.5 Results of emergency coronary artery bypass graft surgery**

### **5.5.1 Immediate Outcome**

Sixty patients (absolute rate: 10.1%, pooled rate/random effects: 8.7%) died during the in-hospital stay after emergency CABG. The other major postoperative complications observed in these patients are summarized in Table 15. Reoperation for excessive bleeding was performed in 7.9%, whilst 70.6% of patients required red blood cell transfusion. In the overall series, the mean number of transfused units of red blood cells was  $3.6 \pm 4.4$  (mean  $5.0 \pm 4.5$  among those who received them). Reoperation for hemodynamic instability associated or not to excessive bleeding was performed in 3.4% of patients. Extracorporeal membrane oxygenation was used in 6 patients and 3 of them (50.0%) survived the immediate postoperative period. Intensive care unit ( $3.8 \pm 4.3$  days) and hospital stay ( $10.4 \pm 8.4$  days) were rather long in this series.

Patients who underwent salvage operation, i.e. those requiring external cardiac massage en route to the operating room or before induction of anesthesia, had an in-hospital mortality rate of 26% and a 3-year survival of 53.8%. Only 12 patients underwent surgery with an altered neurological status (preoperative verified or suspected stroke) and their in-hospital mortality rate was 41.7% whereas their 1-year mortality was 58.3%.

Univariate analysis showed a number of variables associated with in-hospital mortality (Table 16). Logistic regression showed that escalating emergency classes ( $p < 0.0001$ ), recent myocardial infarction ( $p = 0.019$ ), left ventricular ejection fraction  $\leq 30\%$  ( $p = 0.034$ ), on-pump surgery according to the intention-to-treat principle ( $p = 0.012$ ), and participating centers ( $p < 0.0001$ ) were independent predictors of in-hospital mortality (all 596 patients with complete data included in this regression model) (Table 16, Hosmer-Lemeshow's test:  $p = 0.335$ ). The area under the receiver operating characteristic curve of this regression model was 0.849 (95% confidence interval 0.800-0.899). These findings did not change after adjusting for EuroSCORE II ( $p = 0.0643$ ).

**Table 15. Immediate outcome after emergency coronary artery bypass surgery**

Outcome end point	n (%)
In-hospital mortality	60 (10.1)
30-day mortality	63 (10.6)
Stroke	17 (2.9)
<i>De novo</i> dialysis	29 (4.9)
Reoperation for bleeding	47 (7.9)
Inotropic support >12 hours	365 (61.2)
Reoperation for hemodynamic instability	10 (3.4)
Postoperative IABP	148 (24.8)
Postoperative ECMO	6 (1.0)
Atrial fibrillation	276 (46.3)
Gastrointestinal complications	15 (2.5)
Deep sternal wound infection	12 (2.0)
Mediastinitis	3 (0.5)
RBC transfusion	421 (70.6)
RBC transfused units	3.6±4.4
FFP/Octaplas transfused units	2.0±3.4
Platelets transfused units	3.8±7.0
ICU length of stay (days)	3.8±4.3
Hospital length of stay (days)	10.4±8.4

IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; RBC red blood cell; FFP, fresh frozen plasma; ICU, intensive care unit.

**Table 16. Baseline characteristics and operative data of patients who underwent emergency coronary artery bypass grafting. In-hospital mortality rates in patients with and without risk factors are shown. Results of univariate and multivariate analysis for in-hospital mortality are given.**

Patient characteristics	Mean or No. (%)	Risk factor absent No. (%)	Risk factor present No. (%)	Univariate analysis p-value	Multivariate analysis OR, 95%CI
Age	68.1±9.4	-	-	0.483	
Octogenarians	55 (9.2)	51 (10.4)	4 (7.4)	0.470	
Female gender	138 (23.2)	41 (9.0)	19 (13.8)	0.107	
Emergency classes				<0.0001	
1 - Stable hemodynamics	351 (58.9)	-	16 (4.6)		Reference cat.
2 - Stable hemodynamics with inotropes	74 (12.4)	-	10 (13.5)		2.25, 2.99-13.96
3 - Unstable hemodynamics despite inotropes	148 (24.8)	-	28 (18.9)		6.46, 2.99-13.96
4 - Salvage operation	23 (3.9)	-	6 (26.1)		12.49, 3.57-43.74
Creatinine clearance (ml/min)	70±30	-	-	0.351	
Dialysis	14 (2.3)	60 (10.3)	0	0.205	
Diabetes	204 (34.2)	44 (11.2)	16 (7.8)	0.193	
Extracardiac arteriopathy	112 (18.8)	49 (10.1)	11 (8.8)	0.924	
Pulmonary disease	81 (13.6)	54 (10.5)	6 (7.4)	0.392	
Poor mobility	5 (0.8)	60 (10.2)	0	0.452	
Prior stroke	37 (6.2)	57 (10.2)	3 (8.1)	0.683	
Altered neurological status	12 (2.0)	55 (9.4)	5 (41.7)	<0.0001	
Acute stroke, responsive	1 (0.2)	-	0		
Coma/unresponsive (stroke not assessed)	10 (1.7)	-	4 (40.0)		
Coma/unresponsive (stroke assessed)	1 (0.2)	-	1 (100)		
Prior cardiac surgery	13 (2.2)	57 (9.8)	3 (23.1)	0.134	
Prior PCI	124 (20.8)	45 (9.5)	15 (12.1)	0.399	
Heart failure	153 (25.7)	26 (5.9)	34 (22.2)	<0.0001	

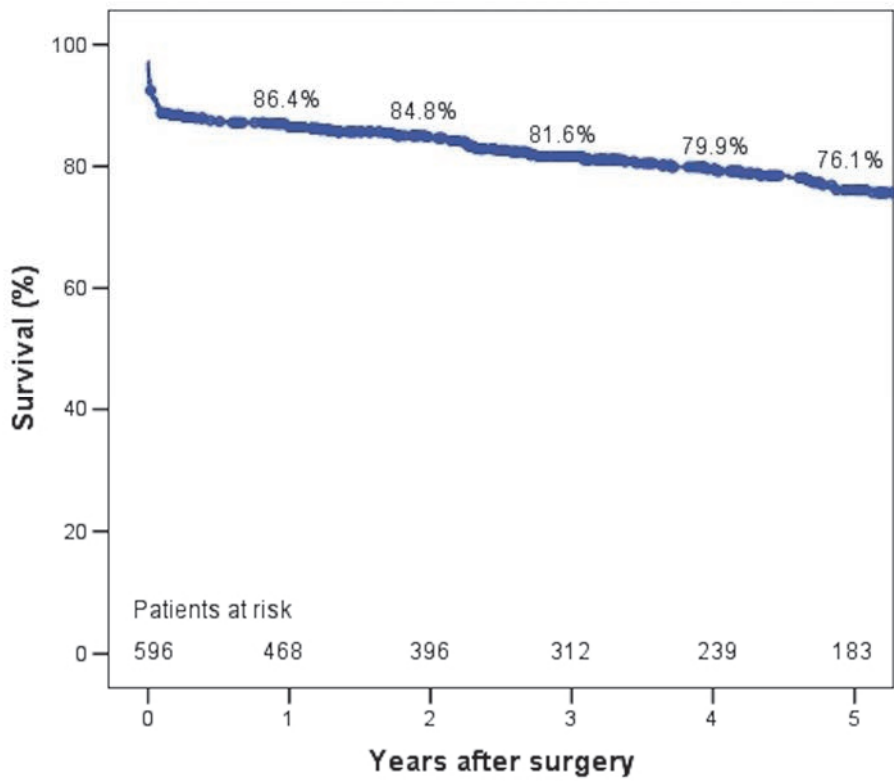
Patient characteristics	Mean or No. (%)	Risk factor absent No. (%)	Risk factor present No. (%)	Univariate analysis p-value	Multivariate analysis OR, 95%CI
No. diseased vessels	2.7±0.5	-	-	0.237	
Left ventricular ejection fraction >50%	243 (40.8)	-	17 (7.0)	<0.0001	
31-50%	231 (38.8)	-	15 (6.5)		
21-30%	101 (16.9)	-	22 (21.8)		
<21%	21 (3.5)	-	6 (28.6)		
Left ventricular ejection fraction ≤ 30%	122 (20.5)	32 (6.8)	28 (23.0)	<0.0001	2.05, 1.05-3.96
Systolic pulmonary pressure <31 mmHg	246 (41.3)	-	13 (5.3)	0.003	
31-55 mmHg	319 (53.5)	-	41 (12.9)		
>55 mmHg	31 (5.2)	-	6 (19.4)		
Recent myocardial infarction (<3 months)	372 (62.4)	6 (2.7)	54 (14.5)	<0.0001	3.17, 1.20-8.32
STEMI	193 (32.4)	29 (7.2)	31 (16.1)	0.001	
Left main stenosis	270 (45.3)	36 (11.0)	24 (8.9)	0.384	
Critical preoperative state	248 (41.6)	18 (5.2)	42 (16.9)	<0.0001	
Preop. ventricular arrhythmia	58 (9.7)	47 (8.7)	13 (22.4)	0.001	
Preop. IABP	148 (24.8)	35 (7.8)	25 (16.9)	0.001	
Direct transferal from cathlab	90 (15.1)	44 (8.7)	16 (17.8)	0.008	
Failure of primary PCI	50 (8.4)	49 (9.0)	11 (22.0)	0.003	
PCI-related complication	41 (6.9)	54 (9.7)	6 (14.6)	0.314	
Ischemia despite successful PCI	21 (3.5)	59 (10.3)	1 (4.8)	0.411	
Revascularization technique				<0.0001	
Off-pump surgery (intention-to-treat)	152 (25.5)	-	14 (9.2)	<0.0001	0.38, 0.18-0.81
Conversion to on-pump beating heart	6 (1.0)	-	3 (50.0)		
On-pump surgery	389 (65.3)	-	30 (7.7)		

Patient characteristics	Mean or No. (%)	Risk factor absent No. (%)	Risk factor present No. (%)	Univariate analysis p-value	Multivariate analysis OR, 95%CI
On-pump beating heart surgery	55 (9.2)	-	16 (29.1)		
Non-use of mammary artery graft	102 (17.1)	31 (6.3)	29 (28.4)	<0.0001	
No. of distal anastomoses	3.1±1.0	-	-	0.052	
EuroSCORE II (%)	16.3±13.8	-	-	<0.0001	
Institutions				<0.0001	
Verona	106 (17.8)	-	3 (2.8)		Reference cat.
Varese	220 (36.9)	-	13 (5.9)		3.14, 0.82-12.2
Catania	78 (13.1)	-	6 (7.7)		8.26, 1.78-38.64
Oulu	192 (32.2)	-	38 (19.8)		24.14, 6.11-95.35

Variables are defined according to EuroSCORE II criteria; continuous variables are reported as the mean and standard deviation; nominal and ordinal variables are reported as absolute numbers and percentages; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; IABP: intra-aortic balloon pump; OR: odds ratio; CI: confidence interval.

### **5.5.2 Late Survival**

The mean follow-up of these patients was  $3.5 \pm 2.6$  years. Survival rates at 1, 3, and 5 years were 86.4%, 81.6%, and 76.1%, respectively (Fig. 10). Significant differences between institutions were observed in terms of late survival (Table 18) and persisted after excluding in-hospital deaths (log-rank test:  $p = 0.001$ ). Such differences were similar to the in-hospital mortality rates. Univariate analysis showed a number of other covariates being associated with immediate and late mortality (Table 17). Advanced age, class of emergency, decreased creatinine clearance, altered neurological status, left ventricular ejection fraction  $\leq 30\%$ , and participating centers were independent predictors of late mortality. Among these risk factors, class of emergency had an evident impact on the late outcome (Fig. 11). The use of a mammary artery graft tended to improve late survival, but the difference did not reach statistical significance ( $p = 0.079$ ), even when operative deaths were excluded from the analysis ( $p = 0.526$ ).



**Fig. 10. Kaplan-Meier estimate of survival after emergency coronary artery bypass surgery.**

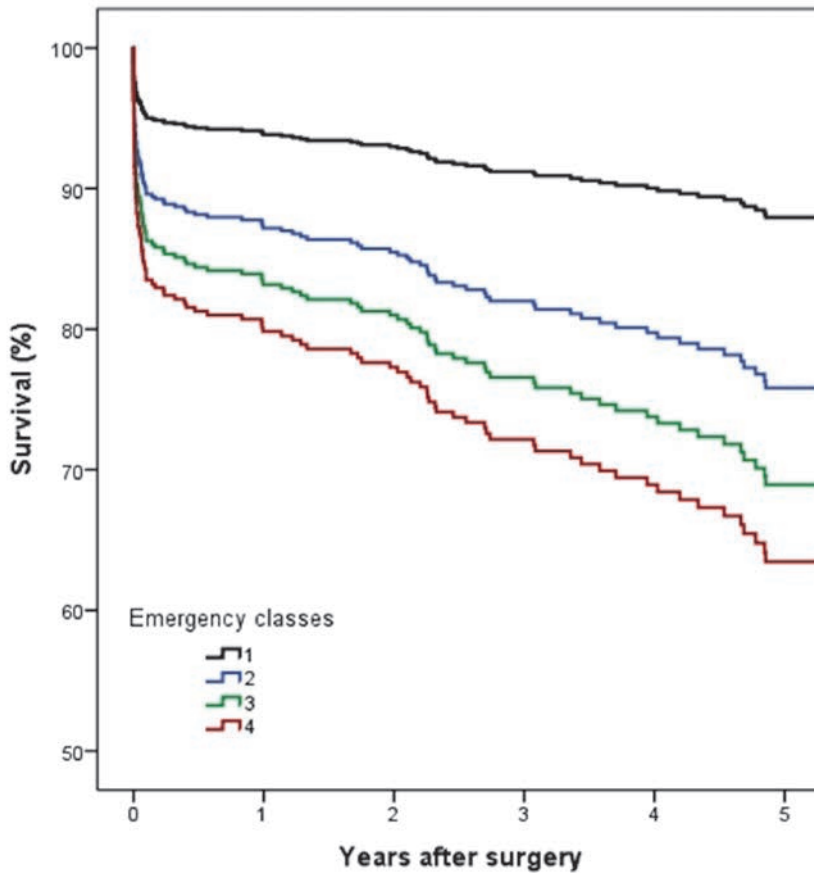


Fig. 11. Cox proportional hazards adjusted estimates of survival according to different emergency classes.

### 5.5.3 Inter-Institutional Differences

Patient populations of participating centers differed significantly in most baseline characteristics (Table 18). Even when the proportion of salvage CABG was rather small and similar in the participating centers, the proportion of patients with class 1 emergency CABG varied markedly between centers. Recent myocardial infarction was observed in about 90% of patients in the Oulu cohort, whereas this proportion was much lower in the other centers. Similarly, the proportion of PCI-related complication was about 15% among the Oulu cohort and below 5% in the

other centers. Intra-aortic balloon pump was inserted preoperatively in half of the Verona patients, whereas this figure was as low as 8% among the patients from Oulu. In line with this supportive approach, Verona was the most active in using extracorporeal membrane oxygenation and 3 out of 5 patients (60%) treated with this strategy, survived the operation. One of these 3 patients died 5 months after surgery, another died 2.2 years later, and the third was alive 3.3 years after surgery.

Data on preoperative antithrombotic strategies was not available. Significant differences between participating centers were observed, however, in terms of the proportion of red blood cell transfusions (Verona: 35.8%, Varese: 65.9%, Catania: 83.3%, Oulu: 92.7%,  $p < 0.0001$ ).

Off-pump surgery was mostly performed in Oulu and Catania in emergency CABG class 1 and 2 patients. This approach was associated with a better operative survival in these centers as observed on multivariate analysis. On the other hand, this strategy was only used in Verona if cardiopulmonary bypass was contraindicated, thus in less than 3% of the population (Table 18). Similarly, cross-clamp time significantly varied among the different centers (Table 18).

**Table 17. Impact of baseline and operative variables on late survival of patients who underwent emergency coronary artery bypass grafting. Results of univariate and multivariate analysis for in-hospital mortality are given.**

Patient characteristics	Univariate analysis	Multivariate analysis
	<i>p</i> -value	HR, 95%CI
Age (per year)	0.003	1.02, 1.00-1.05
Octogenarians	0.579	
Female gender	0.642	
Emergency classes	<0.0001	
1 - Stable hemodynamics		Reference cat.
2 - Stable hemodynamics with inotropes		2.16, 1.34-3.47
3 - Unstable hemodynamics despite inotropes		2.90, 1.84-4.56
4 - Salvage operation		3.54, 1.65-7.60
Creatinine clearance (ml/min)	0.038	0.99, 0.98-1.00
Dialysis	0.953	
Diabetes	0.909	
Extracardiac arteriopathy	0.224	
Pulmonary disease	0.091	
Poor mobility	0.016	
Prior stroke	0.914	
Altered neurological status	<0.0001	2.51, 1.14-5.53

Patient characteristics	Univariate analysis	Multivariate analysis
	p-value	HR, 95%CI
Prior cardiac surgery	0.292	
Prior PCI	0.990	
Heart failure	<0.0001	
No. diseased vessels	0.167	
Left ventricular ejection fraction ≤ 30%	<0.0001	1.85, 1.25-2.73
Systolic pulmonary pressure classes	<0.0001	
Recent myocardial infarction (<3 months)	<0.0001	
STEMI	0.003	
Left main stenosis	0.887	
Critical preoperative state	<0.0001	
Preop. ventricular arrhythmia	<0.0001	
Preop. IABP	0.017	
Direct transferal from cathlab	0.021	
Failure of primary PCI	<0.0001	
PCI-related complication	0.759	
Ischemia despite successful PCI	0.715	
Off-pump surgery (intention-to-treat)	0.051	
Non-use of mammary artery graft	<0.0001	
No. of distal anastomoses	0.011	
EuroSCORE II (%)	<0.0001	
Institution	<0.0001	
Verona		Reference cat.
Varese		2.18, 0.89-5.31
Catania		3.07, 1.14-8.26
Oulu		8.14, 3.30-20.10

PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; IABP: intra-aortic balloon pump; HR: hazard ratio; CI: confidence interval.

**Table 18. Baseline and operative variables as well as main outcome end-points according to the participating centers.**

Patient characteristics	Catania	Oulu	Varese	Verona	p-value
	78 pts	192 pts	220 pts	106 pts	
Incidence (patients/year)	11.1	25.6	20.0	30.3	-
Age	69.8±7.3	68.1±9.6	67.8±9.9	68.1±9.2	0.441
Female gender	24 (30.8)	44 (22.9)	49 (22.3)	21 (19.8)	0.346
Emergency classes					<0.0001
1 - Stable hemodynamics	32 (41.0)	118 (61.5)	151 (68.6)	50 (47.2)	
2 - Stable hemodynamics with inotropes	27 (34.6)	42 (21.9)	3 (1.4)	2 (1.9)	
3 - Unstable hemodynamics despite inotropes	17 (21.8)	29 (15.1)	56 (25.5)	46 (43.4)	
4 - Salvage operation	2 (2.6)	3 (1.6)	10 (4.5)	8 (7.5)	
Creatinine clearance (ml/min)	60±27	83±35	67±25	63±25	<0.0001
Dialysis	1 (1.3)	1 (0.5)	6 (2.7)	6 (5.7)	0.039
Diabetes	46 (59.0)	60 (31.3)	44 (20.0)	54 (50.9)	<0.0001
Extracardiac arteriopathy	22 (28.2)	33 (17.2)	32 (14.5)	25 (23.6)	0.029
Pulmonary disease	8 (10.3)	30 (15.6)	19 (8.6)	24 (22.6)	0.004
Poor mobility	0	5 (2.6)	0	0	0.014
Prior stroke	1 (1.3)	8 (4.2)	17 (7.7)	11 (1.4)	0.034
Altered neurological status	0	10 (5.2)	0	2 (1.9)	0.001
Prior cardiac surgery	2 (2.6)	6 (3.1)	3 (1.4)	2 (1.9)	0.662
Prior PCI	13 (16.7)	44 (22.9)	31 (14.1)	36 (34.0)	<0.0001
Heart failure	10 (12.8)	67 (34.9)	67 (30.5)	9 (8.5)	<0.0001
No. diseased vessels	2.8±0.5	2.8±0.5	2.8±0.5	2.6±0.5	<0.0001
Left ventricular ejection fraction ≤ 30%	9 (11.5)	46 (24.0)	50 (22.7)	17 (16.0)	0.065
Systolic pulmonary pressure					<0.0001
<31 mmHg	49 (62.8)	47 (24.5)	106 (48.2)	44 (41.5)	
31-55 mmHg	29 (37.2)	132 (68.8)	113 (51.4)	45 (42.5)	
>55 mmHg	0	13 (6.8)	1 (0.5)	17 (16.0)	
Recent myocardial infarction (<3 months)	27 (34.6)	172 (89.6)	124 (56.4)	49 (46.2)	<0.0001
STEMI	26 (33.3)	75 (39.1)	68 (30.9)	24 (22.6)	0.033
Left main stenosis	78 (100)	62 (32.3)	90 (40.9)	40 (37.7)	<0.0001
Critical preoperative state	23 (29.5)	95 (49.5)	73 (33.2)	57 (53.8)	<0.0001
Preop. ventricular arrhythmia	1 (1.3)	32 (16.7)	15 (6.8)	10 (9.4)	<0.0001
Preop. IABP	17 (21.8)	16 (8.3)	61 (27.7)	54 (50.9)	<0.0001
Direct transferral from cathlab	0	52 (27.1)	14 (6.4)	24 (22.6)	<0.0001
Failure of primary PCI	2 (2.6)	32 (16.7)	3 (1.4)	13 (12.3)	<0.0001
PCI-related complication	0	28 (14.6)	10 (4.5)	3 (2.8)	<0.0001
Ischemia despite successful PCI	2 (2.6)	3 (1.6)	2 (0.9)	14 (13.2)	<0.0001
Off-pump surgery (intention-to-treat)	18 (23.1)	108 (56.3)	23 (10.5)	3 (2.8)	<0.0001

Patient characteristics	Catania 78 pts	Oulu 192 pts	Varese 220 pts	Verona 106 pts	p-value
Use of mammary artery graft	65 (83.3)	126 (65.6)	199 (90.5)	104 (98.1)	<0.0001
No. of distal anastomoses	3.2±1.1	3.6±1.1	2.8±0.8	2.7±0.5	<0.0001
Aortic cross-clamping time	99±38	89±23	55±24	48±18	<0.0001
EuroSCORE II (%)	14.4±9.7	16.9±13.0	14.3±13.1	20.8±17.7	0.001
Outcome					
In-hospital mortality	6 (7.7)	38 (19.8)	13 (5.9)	3 (2.8)	<0.0001
Observed/expected in-hospital mortality ratio	0.53	1.17	0.41	0.13	-
Stroke	0	7 (3.6)	5 (2.3)	5 (4.7)	0.229
Reoperation for bleeding	5 (6.4)	19 (9.9)	12 (5.5)	11 (10.4)	0.262
RBC transfusion	60 (83.3)	178 (92.7)	145 (65.9)	38 (35.8)	<0.0001
ECMO	0	0	1 (0.5)	5 (4.7)	<0.0001
ICU stay (days)	2.9±4.3	4.7±4.4	3.9±4.6	2.7±3.1	<0.0001
3-year survival	81.2%	67.2%	89.8%	90.6%	<0.0001

PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; IABP: intra-aortic balloon pump; ECMO: extracorporeal membrane oxygenation; RBC: red blood cell.



## 6 Discussion

### 6.1 Impact of critical preoperative status on the outcome of coronary artery bypass surgery

#### 6.1.1 Outcome of coronary artery bypass surgery in very high risk patients

The results of study I showed that very high-risk patients as defined by an additive EuroSCORE  $\geq 10$  have a rather poor immediate survival, but the mid-term survival rates can be considered satisfactory. These patients represent, however, a small proportion (5.5%) of the population undergoing CABG, but also the ones whose prognosis is most susceptible to improvements by optimizing perioperative care.

The present findings confirmed previous observations on a certain trend for better results when high-risk patients undergo OPCAB or BHCAB (Hannan *et al.* 2007) These data failed to show a statistically and clinically significant difference, however, in most of the outcome end-points. This may be related to the small size of this series as well as a certain imbalance in the size of study groups, as most patients during the last years have been operated on using the OPCAB/BHCAB technique. Furthermore, a learning curve in the management of such high-risk patients with OPCAB/BHCAB certainly existed and affected the overall results. The retrospective nature and small size of this study are major limitations of this analysis. The baseline characteristics of the study groups were similar, however, and prevented us performing propensity score analysis. This suggests that the study groups were comparable and comparative analysis was likely reliable.

We did not observe any statistically significant benefit when the OPCAB/BHCAB surgeon's results were compared to the results of the CCAB surgeons. This trend was also observed in our previous studies (Biancari *et al.* 2007, Biancari *et al.* 2008). Importantly, the latter seems to have a favourable effect on immediate as well as intermediate results. This might not mean that OPCAB surgeons are more experienced or skilled than CCAB, but rather that OPCAB surgeons have the opportunity to develop their individual methods of heart manipulation/stabilization, improving the exposure of target vessels and possibly also the anastomosis technique even in difficult situations. Indeed, these

aspects are of fundamental importance for a complete and technically perfect revascularization and can only be achieved when surgeons are motivated and dedicated to OPCAB. In fact, the well demonstrated protective effects of OPCAB on the myocardium (Chowdhury *et al.* 2008) as well as on extra-cardiac tissues (Pojar *et al.* 2008) are likely to be lost when revascularization is incomplete, the quality of anastomoses is suboptimal and the intraoperative manoeuvres of cardiac manipulation/stabilization are improper. These aspects can hardly be quantified, and probably represent a major bias in any comparative analysis of OPCAB versus CCAB. Because of these limitations, along with possibly heterogenous intraoperative hemodynamic and anesthesiologic management, any prospective, randomized study, particularly in high risk patients, would hardly be feasible, or its analysis reliable.

In conclusion, the results of this study suggest that OPCAB/BHCAB can be safely performed in very high-risk patients. The benefits of this technique seems to be more evident and durable when performed by surgeons with a prevalent OPCAB approach.

### **6.1.2 Out-of-hospital cardiac arrest survivors**

The results of study II confirm that the 5-year survival after CABG in survivors of OHCA can be about 80% or more as previously observed in three previous studies on this topic (Every *et al.* 1992, Kelly *et al.* 1990, Mangi *et al.* 2002). Contrary to the study by Mangi and colleagues (Mangi *et al.* 2002), the good results observed herein have been achieved in this series despite cardioverter defibrillators being implanted very selectively. In fact, in the study by Mangi and colleagues (Mangi *et al.* 2002) an electrophysiological study was performed in 88% of patients and a cardioverter defibrillator was implanted in 32% of patients. Furthermore, the mean delay between an OHCA event and CABG was about 29 days in the study by Mangi *et al.* (Mangi *et al.* 2002), whereas it was 10 days in the present study with 12.5% of patients requiring an emergency operation. In the study by Every and colleagues (Every *et al.* 1992) CABG was associated with an operative mortality of 2.3%, but again the mean delay from the OHCA and surgery was rather long, 43 days, which may suggest a bias in referring these patients to cardiac surgeons. Interestingly, only 40% of their patients were operated on during their hospital stay after resuscitation (Every *et al.* 1992). This may indicate a different treatment policy along with different patients' conditions, which in turn may also explain our higher operative mortality as compared to

previous studies (Every *et al.* 1992, Mangi *et al.* 2002). The early mortality observed herein can be considered acceptable in view of the high operative risk of OHCA patients. Interestingly, the observed in-hospital mortality was similar to the one predicted by the modified EuroSCORE risk scoring method (Biancari *et al.* 2010, Nissinen *et al.* 2009).

CABG has been recognized as an effective treatment in reducing the risk of ventricular tachycardia (Autschbach *et al.* 1994, Every *et al.* 1992). Every and colleagues (Every *et al.* 1992) reported on a series of 85 patients in 1992 who underwent CABG after OHCA and compared them with a series of OHCA patients treated medically. These patients did not undergo either percutaneous coronary intervention or implantation of a cardioverter defibrillator. Acute myocardial infarction was detected in 17% of CABG patients and in 32% of medically treated patients. During a mean follow-up of 4.9 years, 13% of CABG-treated and 42% of medically-treated patients had a second cardiac arrest. Twenty-six percent of CABG patients and 62% of medically-treated patients died or had a second, nonfatal cardiac arrest. These findings are of clinical importance as none of their patients underwent percutaneous coronary intervention or received a cardioverter defibrillator, therefore the investigators had the opportunity to evaluate the real impact of CABG-only treatment on the outcome of OHCA patients. Kelly and colleagues (Kelly *et al.* 1990) reported that 80% of patients had inducible ventricular arrhythmias prior to CABG and 45% after CABG. Despite the high rate of postoperative inducible arrhythmias, they reported a 5-year survival of 88%, a freedom from fatal cardiac events of 98% and an arrhythmia-free survival of 88%.

This study was not planned to address the question whether CABG achieves better results than percutaneous coronary intervention. We believe that such a comparative analysis is not feasible in either a randomized study or in a propensity adjusted analysis as percutaneous coronary intervention is usually performed in these patients as a first treatment strategy in the urgent/emergency setting. In fact, it is likely that cardiologists more frequently face such critically ill patients than do cardiac surgeons, possibly with severe neurological complications after resuscitation, and are thus more prone to perform percutaneous coronary interventions as a compassionate and much less invasive alternative treatment to surgical revascularization. This may provide an explanation for the reported high immediate mortality rates after percutaneous coronary intervention (Dumas *et al.* 2010, Lettieri *et al.* 2009, Maynard *et al.* 2009). In any case, such good early and intermediate results observed after CABG

suggest a confident approach toward surgical revascularization in this study's critically ill patient population.

The retrospective nature is the main limitation of this study. In Finland, however, the invasive treatment of coronary artery disease is centralized and the patients' follow-up data can be reliably retrieved from our University hospital as well as from the central hospitals from which they were referred. We do not have data as to whether the patients died of recurrent malignant arrhythmia, but survival data from our national registry provided reliable data as to the generic cause of late death. The mean follow-up of this small series was about five years and we do not know whether it is long enough to detect any major differences in the outcome of these patients. The present study includes patients who suffered acute myocardial infarction-related OHCA and needed prompt coronary revascularization. This has likely eliminated a potential selection bias otherwise possible in previous studies reporting patients treated a mean of 30 to 43 days after OHCA and not all of them suffering myocardial infarction (Every *et al.* 1992, Kelly *et al.* 1990).

In conclusion, the present results suggest that isolated and complete surgical revascularization of the myocardium in patients with acute myocardial infarction-related OHCA can be associated with a good 5-year prognosis. Such good early and intermediate results observed after CABG suggest a confident approach toward surgical revascularization in this critically ill patient population.

### **6.1.3 Outcome of emergency coronary artery bypass grafting**

Study V confirmed the results of a number of series which demonstrated that emergency CABG can be performed with an operative mortality less than 10% (Kerendi *et al.* 2005, Rastan *et al.* 2006, Thielmann *et al.* 2006). In fact, despite large variability in the results from these four participating centers, the pooled rate of in-hospital mortality was 8.7%. Importantly, in these high-risk patients, 5-year survival approached 80% (including operative deaths) as has also been reported in previous studies (Darwazah *et al.* 2009b, Locker *et al.* 2003, Sezai *et al.* 2012) and justifies any attempt for surgical revascularization in emergency situations, even in the presence of severe comorbidities. The main finding of this analysis, however, is the large heterogeneity in the patients' baseline characteristics, perioperative treatment approach and outcome. The definition of acute coronary syndrome as an indication for emergency surgery may, to some extent, account for the reported discrepancy in terms of hospital outcome. All the

centers participating in this study adopted the EuroSCORE's definition criteria for emergency operation, i.e. an operation performed before the beginning of the next working day after the decision to operate. None of these centers used the severity of coronary artery disease as the sole indication for emergency surgery. The threshold for emergency surgery may have varied, however, as the prevalence of preoperative myocardial infarction differed significantly between institutions. In order to avoid any possible divergence in the definition of the need for emergency surgery, we further stratified the emergency status into four categories, which provides a more detailed description of the increasing need for prompt myocardial revascularization in these patients.

Significant inter-institutional differences in outcome after CABG have been previously reported (Seccareccia *et al.* 2006). Such differences can be partly ascribed to analysis biases (Biondi-Zoccai *et al.* 2006) and/or to other than patient-specific risk factors. Centers with outlying results exist (Seccareccia *et al.* 2006), however, and such differences may be most evident in the emergency setting. In this context, the referral pathway of patients with acute coronary syndrome assumes a major importance as any delay in its appropriate treatment may endanger the vitality of the myocardium (Luca *et al.* 2004, Toleva *et al.* 2014). In the present study, the long distances to the primary care center and any delay to the tertiary referral center characterized the pathway for most patients residing in Northern Finland. Indeed, non-trivial access to medical centers is often due to the very long distances and adverse meteorological conditions affecting Northern Scandinavia. Among the operative deaths occurring in the Finnish center, the mean distance between the patients' place of residence and the Oulu University Hospital was 143 km and most of these patients were treated first at a secondary referral center. These factors, along with other patients' characteristics, may explain the higher prevalence of acute heart failure, increased pulmonary artery pressure and myocardial infarction among Finnish patients. Furthermore, an excessive prevalence of PCI-related complications were observed among Oulu patients and this contributed to a non-significant, but still clinically relevant increased risk of mortality which is in line with previous reports (Darwazah *et al.* 2009a, Haan *et al.* 2006, Loubeyre *et al.* 1999, Roy *et al.* 2009, Seshadri *et al.* 2002). These factors, along with possible suboptimal secondary prevention, may partly explain the increased late mortality among Finnish survivors after operative care.

Differences between institutions have also been observed in the perioperative approach to these critically ill patients. The Verona University Hospital achieved

excellent early and late results and their myocardial supportive approach, either using a prophylactic intra-aortic balloon pump or postoperative extracorporeal membrane oxygenation, was significantly more aggressive than the other centers. Although the controversy on the value of intra-aortic balloon pump in the treatment of acute coronary syndrome is still unsolved, there are many findings suggesting its potential benefits in very high-risk patients (Perera *et al.* 2013). Its benefits seem to become more evident over the long-term, as was detected in this analysis. Indeed, it has been previously reported in a single-center study that preoperative IABP significantly improved hospital outcome in high-risk CABG, with benefits extending up to 4 years after surgery (Santarpino *et al.* 2009). Another multicenter European study demonstrated a significantly lower 30-day mortality, perioperative AMI, low cardiac output syndrome, shorter hospitalization and better myocardial segmental and overall contractility in high-risk surgery patients undergoing perioperative IABP, compared to those who did not receive prophylactic counterpulsation (though the prevalence of emergent/salvage CABG only accounted for less than 10% of the overall population) (Lorusso *et al.* 2010). The present study showed that, the more frequently an intra-aortic balloon pump was used preoperatively in emergent CABG, the lower the early and late mortality (Table 17). Although this finding did not reach statistical significance.

In this study, off-pump coronary surgery was associated with a significantly lower mortality when adjusted for participating centers. This finding confirms those of previous studies demonstrating the benefits of avoiding cardiopulmonary bypass in the emergency setting (Darwazah *et al.* 2009b, Kerendi *et al.* 2005, Rastan *et al.* 2006). Off-pump surgery only achieved better results in the two centers, however, which had most actively adopted this technique (Oulu and Catania). This suggests that off-pump surgery may be safely employed in emergent scenarios in centers with surgeons skilled with this technique, provided the patient's hemodynamic stability allows an avoidance of cardiopulmonary bypass. We speculate that in acute coronary syndrome, beating heart surgery may provide better myocardial protection than a prolonged aortic cross-clamping in the absence of prophylactic counterpulsation. The other method to treat these patients, i.e. prophylactic counterpulsation, short aortic cross-clamping time and adequate myocardial protection, may be safe and effective in preserving endangered myocardium vitality.

This study also provided insight regarding whether emergency CABG would or would not be warranted in certain subsets of high-risk patients. The present

analysis did not address the incidence, operative risk and outcome of patients to whom surgery was not offered. In many cases, however, such as patients undergoing salvage CABG or those who had a preoperatively unclear neurological status, the operation was performed on a compassionate basis. The present data showed that patients who require external cardiac massage en route to the operating theatre or prior to induction of anaesthesia had an in-hospital mortality rate of 26%, whereas their 3-year survival was 53.8%. Therefore, even dramatically poor hemodynamic conditions can not be considered a contraindication to CABG. On the other hand, the benefit of emergency CABG in patients with altered neurological status before surgery is less clear. Only 12 patients underwent surgery with an altered neurological status (preoperative verified or suspected stroke) and their in-hospital mortality rate was 41.7% whereas their 1-year mortality was 58.3%. We do not have data on their quality of life after surgery, however, and this prevents conclusive results on the real benefits of compassionate surgery in these critically ill patients.

In conclusion, the immediate and mid-term survival of patients undergoing emergency CABG is satisfactory despite a significant operative risk. The results of coronary surgery markedly differed between the participating institutions, however, varying according to differences in the referral pathways, the baseline characteristics of the patients as well as perioperative treatment strategies. An evaluation of these factors is crucial for the implementation of treatment in centers with suboptimal results.

## **6.2 Progression of moderate chronic kidney function after coronary artery bypass surgery**

Study III confirmed the impact of moderate degrees of renal failure on the late outcome of patients undergoing CABG as previously observed in another study series (Kangasniemi *et al.* 2008). In that study, eGFR was demonstrated to be an independent predictor of all-cause mortality, cardiovascular mortality and any fatal and non-fatal cardiovascular event. These observations support the results reported by Holzmann and colleagues who have evaluated the impact of preoperative renal insufficiency on long-term survival and on the incidence of myocardial infarction in patients who undergo CABG (Holzmann *et al.* 2007). Similar results have been also reported previously by other authors (Domburg *et al.* 2008, Wal *et al.* 2005). Thus, there is strong evidence showing that mild or

moderate renal insufficiency has a major impact on long-term survival of patients with coronary artery disease.

Jones and colleagues have compared how referral to a nephrologist affects the decline in kidney function and mortality in patients with CKD stage 3-5 (Jones *et al.* 2006). Their results show, that GFR decline slowed significantly after the referral and this was also associated with significantly better survival rates. They reported that more than half of the patients with a progressive GFR decline rate ( $\geq 1$  ml/min/1.73m<sup>2</sup>/year) before referral improved to a non-progressive GFR decline ( $< 1$  ml/min/1.73m<sup>2</sup>/year) after the referral. The risk of death was lower among those patients whose GFR decline rate slowed, when compared to those whose decline rate of GFR was unchanged or progressed after referral.

Taskapan and colleagues reported that patients that are referred to a nephrologist at early stage of CKD have a greater improvement in glomerular filtration rate than patients referred at stage 3 or 4 (Taskapan *et al.* 2008). Their results suggest that a more efficient affect on the progression of CKD can be achieved at an early stage of development of the condition. These results point out that referral is particularly desirable in situations in which a progressive slope of GFR is noticed or when eGFR is less than 60 ml/min/1.73m<sup>2</sup>.

Hypertension is considered to be a contributing factor in the progression of CKD, and is associated with poorer outcomes (Methven & MacGrefor 2009). Yoshida and colleagues reported in their study that, in the early stages of CKD smoking, proteinuria, hypertension and low serum high-density lipoprotein were strongly related to an acceleration in the progression of early-stage CKD to end stage renal disease (Yoshida *et al.* 2008).

In addition to lowering systemic blood pressure, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-2 receptor blockers (ARBs) offer renal protection. They slow the decline of kidney function and reduce proteinuria regardless of blood pressure (Jafar *et al.* 2001). Among patients suffering from type 1 diabetes mellitus with nephropathy and non-diabetic CKD and a significant proteinuria ( $> 1$ g/day), ACEI treatment has been shown to slow progression of the CKD (Ruggenti *et al.* 1999, The GISEN group 1997, Wright *et al.* 2002). In diabetic patients, especially patients with type 2 diabetes, a more aggressive intervention policy to slow the progression of CKD is necessary as it has been demonstrated that the progression of diabetic nephropathy can be delayed in this way (Parving *et al.* 2001). ACEIs and ARBs are indicated in diabetic patients with microalbuminuria even when they are not hypertensive (Methven & MacGrefor 2009). ACEIs, beta-blockers and long-acting dihydropyridine calcium

antagonist provide equal renal protection as blood pressure lowering medications in diabetic patients (Parving *et al.* 2001).

The treatment of high levels of LDL and triglycerides with statins in CKD patients have been demonstrated to be safe and as efficient as in normal population. Although statins have not been shown to have an effect on all-cause mortality, they have been demonstrated to reduce the risk of cardiovascular mortality and non-fatal cardiovascular events, as well as a decline in eGFR (Huskey *et al.* 2009, Strippoli *et al.* 2008).

As all patients were residents of Oulu at the time of surgery and during the study period, we believe that all patients have been treated at our institution, which is a referral centre for many specialities such as cardio-thoracic and vascular surgery, internal medicine, cardiology, nephrology and neurology. According to our results, many of these patients were referred to a nephrologist. Thus, at this stage we cannot measure the impact of any specific intervention on CKD, but rather observe the effect of this condition on the outcome of patients who underwent CABG.

The main limitation of the present study is its reliance on retrospective data. The retrospective nature of this study as well as the length of follow-up also prevented further analysis on the effects of drugs used during the study period and other variables that might affect renal function.. Our laboratory database contains all data from the the primary health care units in the city, however, where patients will likely have been referred to for control or for treatment of any minor morbid condition.

In conclusion, this study showed that an eGFR < 60 ml/min/1.73m<sup>2</sup> is a determinant of all-cause mortality, cardiovascular mortality and cardiovascular events after CABG. In our study, 28.4% of patients with stage 3 CKD had a significant decline in eGFR. We believe that these patients would benefit from early referral to a nephrologist.

### **6.3 Grading of postoperative complications**

The present analysis showed that the E-CABG complication classification performed well when used either as a four-grade classification system or as an additive score. In fact, both the E-CABG complication grades and score were predictive of increased early and late mortality as well as of the length of stay in the intensive care unit in patients undergoing isolated CABG. As seen in Figure 9, the adverse events included among grade 3 complications were particularly well

associated with a remarkably increased risk of death. Mortality in patients with a postoperative use of an intra-aortic balloon pump was very high due to the severely depressed hemodynamic conditions of these patients. Extracorporeal membrane oxygenation was not used in this series, but we may assume that patients requiring it may have a similarly increased risk of death as well.

A multivariate analysis to adjust the postoperative complications for baseline and operative characteristics was not performed as this model would have been too complex and might have led to overfitting. Risk estimates of several postoperative complications appeared to be so great in univariate analysis, however, that it is not plausible that this was caused by bias alone. Previous studies have also reported a significant mortality associated with postoperative complications such as increased RBC transfusion (Murphy *et al.* 2007, Vivacqua *et al.* 2011), acute kidney injury (Han *et al.* 2015, Hansen *et al.* 2015), mediastinitis (Risnes *et al.* 2010), gastrointestinal complications (Filsoufi *et al.* 2007, Mangi *et al.* 2005), use of IABP (Arafa *et al.* 1998, Saura *et al.* 2015) and atrial fibrillation (Phan *et al.* 2015). Welsby *et al.* investigated patients undergoing cardiac surgery with cardiopulmonary bypass and found that, after adjusting for preoperative and intraoperative risk factors, the occurrence of non-cardiac complications only and cardiac complications with other organ involvement significantly increased mortality as well as the length of stay in the hospital and intensive care unit when compared with cardiac complications only (Welsby *et al.* 2002).

In addition to the potential independent effect of complications on patient survival, there seemed to be an interaction between postoperative adverse events. The median additive score for each grade showed that the number of complications increased significantly within increasing grades of complications, as indicated by an increased additive score. This was particularly high in Grade 3.

Study V demonstrated that a number of complications in the lower grades of the classification are not likely to affect patient survival (Fig. 9), even though contradictory results have also been reported (Filsoufi *et al.* 2009). Even complications that are considered as less severe may cause discomfort to the patient, however, as well as increasing the costs of their treatment. Moreover, the additive effect of multiple, even minor, adverse events may cause even the lower complication grades to achieve clinical significance, as seen in the adjusted analyses of the effect of different complication grades on patient survival (Table 14).

An important finding emerging from this analysis was that the risk of death is not limited to the in-hospital stay: patients may die shortly after discharge. In patients classified as Grade 3, the 30-day mortality was 14.5% and the 3-month mortality 21.5%. Such a high mortality is not acceptable, considering the potentially preventable nature of a number of postoperative complications.

In support of the results from study V, some previous studies have emphasized that in-hospital mortality may not be the most adequate variable to measure the quality of care in patients undergoing CABG (Ghali *et al.* 1998, Silber *et al.* 1995). Silber *et al.* compared 57 American hospitals and observed that the reported complication rates did not correlate with the rates of in-hospital mortality (Silber *et al.* 1995). Instead, several hospital characteristics generally associated with a higher quality of treatment were associated with rather low mortality rates, but higher complication rates (Silber *et al.* 1995). In addition, Ghali *et al.* concluded that complications after CABG are common and may provide more information as to hospital quality than does in-hospital mortality rates (Ghali *et al.* 1998).

The retrospective nature of this study is an important limitation of this analysis. Some of the complications can be treated in central hospitals so the number of these complications that occur over an extended period of time after the surgery can actually be larger than represented in our results. Even though there is some retrospectively collected data, the data on important outcome endpoints were retrieved from prospective electronic registries, which can be considered reliable. Furthermore, data on patient's death are retrieved from a national registry, which collects data on the entire Finnish population.



## 7 Conclusions

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

1. The long-term survival of very high-risk patients is satisfactory and OPCAB/BHCAB can be performed safely in these patients.
2. The isolated and complete revascularization of the myocardium in patients with acute myocardial infarction related OHCA can be associated with a good 5-year prognosis. Good early and intermediate results observed after CABG suggest a confident approach towards surgical revascularization in this critically ill patient population.
3. An eGFR value lower than 60 ml/min/1.73m<sup>2</sup> is a determinant of all-cause mortality, cardiovascular mortality and cardiovascular events after CABG. Patients with declining kidney function would benefit from early intervention of this condition.
4. The E-CABG complication classification system seems to be a promising tool for stratification of the severity and prognostic impact of postoperative complications in patients undergoing isolated coronary artery bypass surgery.
5. Despite the increased operative risk of patients undergoing an emergency CABG, the immediate and mid-term outcome is satisfactory. The results of coronary surgery markedly differed between the participating institutions, according to differences in the referral pathways, the baseline characteristics of patients and perioperative treatment strategies. The evaluation of these factors is crucial for the implementation of treatment in centers with suboptimal results.



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## Original publications

- I Mosorin MA, Heikkinen J, Pokela M, Anttila V, Mosorin M, Lahtinen J, Juvonen T & Biancari F (2011) Immediate and 5-year outcome after coronary artery bypass surgery in very high-risk patients (additive EuroSCORE  $\geq 10$ ). (2011) *J Cardiovasc Surg (Torino)* 52:271–276
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Original publications are not included in the electronic version of the dissertation.



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