Risk prediction and prognosis following cardiac surgery:
The EuroSCORE and new potential prognostic factors

PhD dissertation

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Preface

This PhD thesis is based on studies carried out during my employment as a resident at the Department of Medicine, Regionshospitalet Viborg, Denmark (2005-2007), and at the Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, Skejby, Aarhus, Denmark (2007-2008), and as a PhD student at the Department of Clinical Epidemiology, Aarhus University Hospital, Denmark (2008-2011).

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The present PhD thesis is based in the following papers

Study I

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Study II

Mikkelsen MM, Andersen NH, Christensen TD, Hansen TK, Eiskjaer H, Mogensen CE, Hjortdal VE, Johnsen SP. Microalbuminuria and short-term prognosis in patients undergoing cardiac surgery. Interact CardioVasc Thorac Surg 2009;9:484-90. Epub 2009 Jun 23.

Study III

Mikkelsen MM, Andersen NH, Christensen TD, Hansen TK, Eiskjaer H, Gjedsted J, Johnsen SP, Hjortdal VE. Microalbuminuria is associated with high adverse event rate following cardiac surgery. Eur J Cardiothorac Surg 2011 Jun;39(6):932-8). Epub 2010 Nov 19.

Study IV

Mikkelsen MM, Hansen TK, Gjedsted J, Andersen NH, Christensen TD, Hjortdal VE, Johnsen SP. Insulin resistance, adiponectin and adverse outcomes following elective cardiac surgery: a prospective follow-up study. J Cardiothor Surg 2010 14;5:129.

List of abbreviations

ACE	Angiotensine converting enzyme
AMP	Adenosine monophosphate
AT-II	Angiotensine II
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CABG	Coronary artery bypass grafting
CI	Confidence interval
CV	Coefficients of variation
E/O	Estimated to observed mortality ratio
EuroSCORE	European system for cardiac operative risk evaluation
GLUT	Glucose transporter
HOMA	Homeostasis model assessment
HR	Hazard ratio
ICU	Intensive care unit
ICD	International classification of diseases
IL	Interleukin
MCP	Monocyte chemo-attractant protein
OR	Odds ratio
PCI	Percutaneous coronary intervention
TNFα	Tumor necrosis factor alfa
UACR	Urine albumin creatinine ratio

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1. Introduction

According to the World Health Organization, the estimated proportion of deaths among the European populations related to circulatory diseases is approximately 50% [1]. Ischemic heart disease alone is responsible for about 24%, which makes it the leading cause of death [1]. Various surgical and medical treatment strategies are available for a broad variety of cardiovascular diseases, including both ischemic heart disease and heart valve diseases.

Worldwide, the first records of heart surgery date back to the period of the ancient Greeks [2]. However, with the exception of isolated cases and procedures related to congenital heart defects, open heart surgery was not widely available internationally until the late 1960s and in Denmark from the mid 1970s [3]. More recently, approximately 4,500 surgical cardiac procedures are performed annually in Denmark.

From a modern perspective, the results from the first series of Danish procedures performed in highly selected patients are devastating relative to more recent outcomes [3]. Notable developments in surgical techniques and the improved quality of pre-, peri- and postoperative patient care have since improved patient outcomes significantly. At present, elective cardiac procedures are recognized as relatively safe. Yet, continuous monitoring and quality surveillance are necessary to ensure that the related medical care is maintained at the highest possible level at all times and to facilitate further improvements.

1.1. Risk assessment and quality surveillance

Accurate preoperative assessment of an individual patient's risk of adverse outcomes following surgery is essential when planning cardiac surgery, ultimately to ensure that the selected choices are made on an informed basis. However, risk assessment is also essential when monitoring the quality of care across different populations and centers. Thus, assessments of the quality of surgery and patient care using crude mortality data in cardiac surgery are highly misleading, since patient comorbidities and the type of surgery performed can account for major differences in outcome. Consequently, there has been much interest in the development and testing of clinically applicable risk prediction tools to overcome the existing issues. When developing and applying risk prediction tools the outcome measures of interest, the exposures and the covariates should be considered.

The outcome measure

The outcome measure used for comparison should be well defined and data readily available. Mortality is the most obvious clinical outcome measure following cardiac surgery. However,

reporting mortality is not necessarily a simple task, although it appears in itself to be an easily recognizable dichotomous clinical outcome measure. Worldwide, many institutions lack access to reliable information on patient mortality following hospital discharge, and even if data are available, any resultant comparisons are compromised if the follow-up periods defining mortality are dissimilar. Patients not fit for discharge, and perhaps transferred to other departments or hospitals, may also influence in-hospital mortality data, especially if it causes incomplete follow-up. Therefore, using a standardized follow-up period (e.g., 30 days) is often preferred whenever appropriate acquisition of follow-up data is possible.

As the current short-term mortality for the majority of elective cardiac surgical procedures is relatively low (1−3%), alternative outcomes measures have gained increasing attention (**Table 1**) [4,5]. Moreover, it has been suggested that outcomes beyond the early postoperative phase should also be addressed [4].

Table 1. Outcome measures of interest

- Mortality
- Myocardial infarction
- Stroke
- Renal failure
- Sternal wound infection
- Septicemia
- Other severe infections
- Arrhythmias
- Length of intensive care unit and hospital
- Surgical re-exploration
- Quality of life
- Resource utilization and costs

Exposure and covariate assessment

Not only outcome measures, but also exposures (i.e., type of surgery) and covariates (e.g., severity of underlying diseases, comorbidities) must be available and well-defined for appropriate clinical assessment and comparison. Of note, multivariable risk prediction models constitute possible tools for accounting for differences between otherwise not comparable data.

1.1.1. Multivariable risk prediction models

For further comparison of results, multivariable risk models are necessary to support rational decision making on several other aspects of cardiac surgery and health care (see **Table 2**). Urzua et al. previously assessed the quality of subjective preoperative risk assessments of patients undergoing cardiac surgery recorded by an anesthesiologist, and concluded that, in the absence of a universally valid objective preoperative risk score (as in the late 1970s), subjective risk estimation based on available clinical data provided a good prediction of risk [6]. The subjective preoperative risk assessment performed by experienced physicians remains important today, but the

information used to assess risk should be founded in reliable studies that address preoperative risk in contemporary cohorts. Large-scale population-based studies remain important for providing knowledge on risk prediction, taking into account age, sex, indication for surgery, type of surgery, and comorbidities.

Table 2. Aims for multivariable risk prediction models

- Quality of surgery at an institution
- Administrative purposes
- Performance of the individual surgeon
- Comparison between institutions
- Comparison between countries
- Surgical decision making
- For preoperative patient education and consent

Many different multivariable risk models have been developed in various cardiac surgical settings and patient populations. Some early risk models that were used (e.g., Acute Physiology and Chronic Health Evaluation (Apache) II, Simplified Acute Physiology Score (SAPS) I, Mortality Prediction Model (MPM) II), were developed based on data from nonsurgical intensive care unit (ICU) patients, and were partially adopted to cardiac surgery [7,8]. At a glance, the history of risk assessment models in cardiac surgery prior to the introduction of the European System for Cardiac Operative Risk Evaluation (EuroSCORE) is summarized below and displayed in **Table 3**. The key risk scores mentioned were selected from a Medline query on "Cardiac Surgical Procedures"[All Fields] AND ("Risk Assessment"[MeSH Terms] OR ("Risk"[All Fields] AND "Assessment"[All Fields]) OR "Risk Assessment"[All Fields]), "Thoracic Surgery" [MeSH] OR “Cardiac Surgical Procedures"[MeSH] AND "Risk Assessment"[MeSH] OR “Mortality”[MeSH], and partly from relevant article references.

Table 3. Risk prediction models in cardiac surgery (1980-2001)

Risk score	Authors	Country	Year	Outcome	Type of surgery	Risk variables	Performance
Montreal Heart Institute risk assessment classification	Paiement B et al. [9]	Canada	1980	Early mortality	Bypass and Valve	6	Not specifically stated
Study in Coronary Artery Surgery	Kennedy JW et al. [10]	US	1981	Operative mortality	Bypass	6	Not specifically stated
Bayesian method	Edwards FH et al. [11]	US	1988	Mortality	Bypass	20	E/O 0.95
Parsonnet I	Parsonnet V et al. [12]	US	1989	30-day mortality	Bypass	16	O and E correlation 0.85
Cardiac Surgery Reporting System	Hannan EL et al. [13]	US	1990	In-hospital mortality	All	15	21 of 28 centers had O within the E 95 % range
Veterans Administration	Hammermeister KE et al. [14]	US	1990	Mortality and morbidity	All	11	Not specifically stated
Nothern New England I	O'Conner GT et al. [15]	US	1992	In-hospital mortality	Bypass	8	E/O 0.91; AUC 0.76; HL 0.69
Cleveland Clinic Score I	Higgins TL et al. [16]	US	1992	In-hospital mortality and morbidity	Bypass	13	AUC 0.83; HL 0.69
Tuman Score	Tuman KJ et al. [17]	US	1992	Mortality and morbidity	Bypass and Valve	10	Not specifically stated
Veterans Affairs Risk Model	Grover FL et al. [18]	US	1993	30-day mortality	Bypass	10	Not specifically stated
STS risk model 1994	Edwards FH et al. [19]	US	1994	Operative mortality	Bypass	33	E/O 0.95
French Score	Roques F et al. [20]	France	1995	In-hospital mortality	All	8	AUC 0.75
Ontario Province Risk Score	Tu JV et al. [21]	Canada	1995	In-hospital mortality and length of stay	All	6	AUC 0.75
Magovern Score	Magovern JA et al. [22]	US	1996	In-hospital mortality and morbidity	Bypass	20	O and E correlation 0.97 AUC 0.86
UK Society Risk Score	Society of Cardiothoracic Surgeons in Great Britain & Ireland [23]	UK	1996	30-day and in-hospital mortality	Bypass	20	Report not available
Pons Score	Pons JMW et al. [24]	Spain	1997	30-day and in-hospital mortality	All	14	Not specifically stated
Cleveland Clinic Score II	Higgins TL et al. [25]	US	1997	In-hospital mortality / ICU care	Bypass	13	AUC 0.78; HL >0.05
Parsonnet II	Parsonnet V et al. [26]	US	1996	30-day mortality		41	E/O 1.33; AUC 0.78; HL 0.60
Toronto	Ivanov J et al. [27]	Canada	1999	Operative mortality	Bypass	9	E/O 0.91; AUC 0.78; HL 0.60
EuroSCORE additive model	Nashef SAM et al. [28]	Europe	1999	30-day and in-hospital mortality	All	17	AUC 0.76; HL 0.68
Bernstein-Parsonnet	Bernstein AD et al. [29]	US	2000	30-day and in-hospital mortality	Bypass and Valve	15	E/O 1.00; AUC 0.79
QMMI Score	Fortescue EB et al. [30]	US	2001	Mortality and morbidity	Bypass	11	E/O 0.91; AUC 0.74; HL 0.58

Abbreviations: E = estimated mortality; O = observed mortality; E/O = mortality ratio; ROC = receiver operating characteristics; HL = Hosmer–Lemeshow test

The first generation of risk stratification models introduced in the 1980s only included a few, but important preoperative prognostic factors, such as poor left ventricular function with an ejection fraction below 30%, unstable angina, recent myocardial infarction, advanced age (>65 years) and emergency surgery. These relatively simple risk models classified patients into either normal risk (no risk factors), increased risk (1 risk factor), or high risk (≥ 2 risk factors) [9]. Later, more advanced models, such as the Parsonnet Score [12], the Cleveland Clinic Scores [16,25], the Ontario Province Risk Score [21], and the first Society of Thoracic Surgeons' risk score [19] were introduced. As seen in **Table 3**, there are numerous differences among the many multivariate risk prediction models, including the length of follow-up (primarily in-hospital or 30-day), the outcome (mortality, morbidity, and length of stay), the restrictions to varying surgical procedures, and the number of included variables (6−41 variables).

The construction of a joined European risk prediction model, termed EuroSCORE, was commenced in 1995. The objective of this construction was to establish an accurate 30-day mortality prediction model [31]. The original EuroSCORE dataset included 19,030 adult patients undergoing on-pump cardiac surgery during a 3-month period in 1995. Moreover, 128 European cardiac centers across 8 countries participated in the data collection. Ultimately, 97 prognostic factors had been selected as possible candidates for the prediction model [31].

In 1999, the EuroSCORE study group published results on an additive EuroSCORE model, which allocated incremental risk points according to 17 selected pre- and perioperative risk factors (**Table 4**) [28]. The added risk scores sum up to 1 score (ranging from 0 to 25) that reflects the operative 30-day mortality risk, including death occurring in relation to the primary hospital admission for surgery. The construction of the model was performed on a developmental dataset consisting of 13,302 patients without missing data. In the validation dataset containing another 1,479 patients, which was also from the full EuroSCORE dataset, the area under the receiver operating characteristic curve (AUC) showed moderate to good accuracy (AUC 0.79) and a Hosmer–Lemeshow calibration test showed an acceptable model fit. In 2003, the β-coefficients derived from the logistic regression analysis of the model were made available [32,33]. This allowed for a more precise prediction of risk than the additive model, particularly in the high-risk patients. Michel et al. compared the additive and logistic models in a high-risk patient population, and concluded that the additive EuroSCORE remained a simple and reliable bedside gold standard for risk prediction, whereas the logistic model was a better risk predictor, but it required complex calculations that were not easily accessible at the time. Since its introduction in 1999, the EuroSCORE has been the most commonly used risk assessment model in Europe.

Table 4. EuroSCORE risk factors

Patient related	%	Cardiac related	%	Operation related	%
Age (mean)	62.5*	Unstable angina	8.0	Emergency surgery	4.9
Sex (female)	27.8	LVEF 30-50 %	25.6	Other than isolated CABG	36.4
Chronic pulmonary disease	3.9	LVEF <30 %	5.8	Surgery on thoracic aorta	2.4
Extracardiac arteriopathy	11.3	Recent myocardial infarction	9.7	Postinfarct septal rupture	0.2
Neurological dysfunction	1.4	Pulmonary hypertension	2.0		
Previous cardiac surgery	7.3				
Serum Creatinine >200	1.8				
Active endocarditis	1.1				
Critical preoperative state	4.1				

Abbreviations: LVEF = left ventricular ejection fraction; CABG = coronary artery bypass grafting
*mean age; range 17–94; only 10% of patients were more than 75 years in age

The members of the EuroSCORE study group were also the first investigators to validate the EuroSCORE in individual countries. The EuroSCORE study database was split into country-specific datasets, and it was determined that the AUCs ranged from 0.74 in Spain to 0.87 in Finland, and that the calibration tests showed acceptable model fit [34]. However, these validation results were largely expected, as the prediction model was developed based on at least partly the same patients that comprised the country-specific validation datasets.

During the following years, the EuroSCORE was subjected to extensive validation, and a number of studies compared the EuroSCORE with both existing and new risk prediction models in other populations and in the context of other outcome measures. A Medline query on EuroSCORE [All Fields] AND ("risk assessment"[MeSH Terms] OR ("risk"[All Fields] AND "assessment"[All Fields]) OR "risk assessment"[All Fields]) in combination with relevant article references, were used for retrieval of studies. An overview of the identified studies is presented in **Appendix 1**. A major portion of the studies were hampered by methodological shortcomings, as they validated the EuroSCORE based on in-hospital mortality, and would therefore tend to underestimate mortality compared with the EuroSCORE. Studies addressing 30-day mortality, including discrimination (receiver operating characteristics) and calibration (Hosmer–Lemeshow test) analyses are presented in **Table 5**.

The presented studies with data obtained in the 1990s and up to 2005 showed moderate to good discrimination and acceptable model fit in terms of calibration analysis using the additive EuroSCORE [35-41]. On the contrary, it appears that the studies including more contemporary cohorts

(from 2005) had poorer model fit and tended to overestimate mortality when using the logistic EuroSCORE [40,42,43]. This notion is supported by estimated-to-observed (E/O) mortality ratios from studies listed in **Appendix 1**. Thus, the performance of the EuroSCORE was soon questioned [44]. In fact, Sergeant et al. pointed out in a 2001 study that the EuroSCORE should be used for inter-institutional benchmarking with great caution, since it overestimated mortality in low-risk patients and conversely underestimated risk in high-risk patient [45]. This notion was supported in a review by Gogbashian in 2004 [46]. Overestimation of mortality in low-risk patients was also present in the original EuroSCORE study [28]. Today, mounting evidence point to a general overestimation of mortality across all ranges of predicted risk [42,47-50]. In particular, the β-coefficients of increasing age and performance of valve surgery have attracted attention, as they are apparently not well-calibrated for contemporary cohorts [51-58].

The EuroSCORE has also been validated for use with other surgical procedures and/or outcome measures. In the original EuroSCORE database, all included patients underwent cardiopulmonary bypass, but several studies assessed the EuroSCORE in off-pump coronary artery bypass patients, and generally the model fit well but also tended to overestimate mortality [50,59-64].

Kasimir et al. found that long-term (up to 1 year) mortality prediction following cardiac surgery was also possible using the EuroSCORE [65]. Other authors have reported the same conclusion [56,63,66-69]. However, these studies however mainly estimated associations between different levels of EuroSCORE and long-term mortality, and failed to assess the predictive value and utility of the EuroSCORE in long-term risk prediction.

The EuroSCORE may also be used to predict the costs related to cardiac surgery and the associated postoperative quality of life changes [70-75]. Several studies have assessed other important outcomes in cardiac surgery, such as renal failure, stroke, myocardial infarction, sternal wound infection and length of stay [67,69,73,76,77] (**Appendix 1**).

Table 5. EuroSCORE validation studies

Year	Author & Country	Size & Period	Type	Risk models and/or aims	Results
2010	Chhor V et al. France [51]	n=469 2005-2007	AV	EuroSCORE and CARE Score in the prediction of perioperative mortality among octogenarians (n=134) and non-octogenarians (n=335) with aortic valve stenosis undergoing AV replacement	Octogenarians Add EuroSCORE AUC 0.58; HL 0.52; E/O n/a Log EuroSCORE AUC 0.59; HL 0.09; E/O n/a Non-octogenarians Add EuroSCORE AUC 0.82; HL n/a; E/O n/a Log EuroSCORE AUC 0.81; HL n/a; E/O n/a
2009	Osswald BR et al. Germany [78]	n=1,545 1994-2006	AV	EuroSCORE and mortality in surgical aortic valve replacement. Overall and varying risk group performance	Overall Add EuroSCORE AUC 0.68; HL 0.61; E/O 6.1/2.2=2.8 Add EuroSCORE <3 (n=183): E/O 1.5/0.0 = n/a Add EuroSCORE ≥3 (n=529): E/O 4.1/1.0 = 4.1 Add EuroSCORE ≥6 (n=833): E/O 8.3/3.5 = 2.4 Overall Log EuroSCORE AUC 0.67; HL <0.01; E/O 9.3/2.2=4.2 Log EuroSCORE <3 (n=239): E/O 1.3/0.0 = n/a Log EuroSCORE ≥3 (n=493): E/O 3.8/1.8 = 2.1 Log EuroSCORE ≥6 (n=813): E/O 14.8/3.1 = 4.8 The AUC was reduced and the E/O was larger in the recent years (2002-2006 compared to 1994-1997 and 1998-2001).
2008	D'Errigo P et al. Italy [40]	n=30,610 2002-2004	C	Italian CABG Outcome Project model and EuroSCORE performance on mortality	Add EuroSCORE AUC 0.77; HL 0.23; E/0 2.5/2.5 = 1.0 Log EuroSCORE AUC 0.78; HL <0.01; E/0 6.4/2.5 = 2.6
2007	Feiler E et al. Hungary [39]	n=1,839 2003-2005	n/a	EuroSCORE on mortality Abstract in English	Add EuroSCORE AUC 0.69; HL 0.47; E/0 4.1/3.3 = 1.2 Log EuroSCORE AUC 0.71; HL 0.13; E/0 4.5/3.3 = 1.4
2006	Suojaranta RT et al. Finland [41]	n=162 2001-2003	A	EuroSCORE validation in octogenarians, also using varying age categorization	Mortality AUC 0.77; HL 0.38; E/O n/a Age was a risk factor and appeared well-calibrated in the EuroSCORE
2005	Yap CH et al. Australia [43]	n=2,106 2002-2005	A+C	Validate an approximated EuroSCORE (some definitions of risk factors did not correspond fully to the EuroSCORE) in the entire cohort and CABG only	Add EuroSCORE AUC 0.81; HL <0.01; E/O overall 5.8/3.9 = 1.5; and E/O CABG 4.9/2.6 = 1.9 Log EuroSCORE AUC 0.82; HL <0.01; E/O overall 9.9/3.9 = 2.5; and E/O CABG 7.7/2.6 = 3.0
2004	Syed AU et al. Saudi Arabia [38]	n=194 2002-2004	A	EuroSCORE and Parsonnet retrospectively assessed in Saudi Arabia	EuroSCORE AUC 0.77; HL 0.22; E/O n/a Parsonnet AUC 0.67; HL 0.72; E/O n/a
2004	Zingone B et al. Italy [35]	n=2,426 1999-2004	A	Performance of EuroSCORE on mortality in Italy	Add EuroSCORE AUC 0.79; HL 0.15; E/O 5.6/5.9 = 0.95 Log EuroSCORE AUC 0.80; HL <0.01 E/O 6.9/5.9 = 1.17
2004	Nilsson J et al. Sweden [37]	n=4,497 1996-2001	B	Additive EuroSCORE and STS algorithm validation on mortality in Sweden	EuroSCORE AUC 0.84; HL 0.81; E/O 1.9/1.9 = 1.0 STS algorithm AUC 0.71; HL 0.83; E/O 1.9/1.9 = 1.0
2000	Pitkanen O et al. Finland [36]	n=4,592 1992-1996 n=821 1998-2000	A	To construct a new local risk prediction model on data from 1992-1996 and validate it against the additive EuroSCORE on data from 1998-2000	Mortality (1998-2000): Local model AUC 0.84; HL >0.05; E/O n/a EuroSCORE AUC 0.77; HL >0.05; E/O 3.6/1.1 = 3.3
2000	Roques F et al. EuroSCORE study group [34]	n=14,781 1995	C+V+T	The EuroSCORE study database split into country-specific datasets	AUCs: Germany 0.81; UK 0.79; Spain 0.74; Finland 0.87; France 0.82; Italy 0.82; All HL tests >0.05; E/O n/a
1999	Nashef SA et al. EuroSCORE study group [28]	n=13,302 1995 n=1,479 1995	C+V+T	Developmental dataset had n=13,302. Validation dataset had n=1,479 patients. Applied to three risk groups: EuroSCORE 1-2, 3-5, ≥6	Developmental dataset: AUC 0.79, HL 0.40 Validation dataset AUC 0.76, HL 0.68 Widespread use of the EuroSCORE is recommended.

Abbreviations: A = all; AV = aortic valve replacement; B = on- and off-pump bypass; C = on-pump coronary bypass; T = thoracic aortic surgery; Add = additive; Log = logistic; E = estimated mortality; O = observed mortality; E/O = mortality ratio; AUC = area under curve; HL = Hosmer–Lemeshow test; n/a = not available

1.1.2. Necessity for revision of risk prediction models

The EuroSCORE remains the most attractive and employed risk prediction model in Europe. However, temporal changes in the constellation of baseline comorbidities, improvements in surgical techniques, and the quality of pre-, peri- and postoperative patient care may cause even well-established risk prediction models to be outdated, and thus continuous revision of the models is necessary. In 1992, Tremblay et al. compared patient prognostic factors for in-hospital mortality (as defined by Paiement [9]) in 2 populations that had undergone cardiac surgery at the same institution in either 1980 or 1990, and found that the prevalence of the identified factors was higher in the 1990 patients [79]. Yet, the authors determined that the operative mortality remained the same, indicating that the more adverse baseline prognostic profile of the patient population had been compensated by the improved quality of surgery and care. Similar changes in the comorbidities, age distribution, and procedural types and techniques have been reported within the life-span of the existing EuroSCORE [80].

Improved quality of surgery and patient care would intuitively lead to a gradual temporal decrease in the predictive ability of the EuroSCORE. However, such a development may be difficult to capture, as changes in comorbidities, patient age, and the quality of patient care tend to outbalance each other. As mentioned in the text above, the performance and utility of the EuroSCORE in contemporary surgical cohorts have been extensively discussed in recent years [4,81-84]. A revision of the EuroSCORE is apparently desirable, as indicated by several studies reporting substantial differences in the E/O 30-day mortality ratios [47,50,52,85,86]. Yet, from a methodological perspective, many validation studies have not been performed optimally (**Table 5 and Appendix 1**). More accurate E/O ratios have also been reported in other studies based on data from 2003 to 2007 [39,58,77].

In an attempt to improve the predictive ability of the EuroSCORE, it may be useful to contemplate new markers of risk not considered in the original EuroSCORE study.

1.1.3. New risk markers

In 1988, Reaven defined a cluster of risk factors associated with the development of both diabetes and atherosclerotic artery disease [87]. The cluster was named “Syndrome X” (and later the more common “Metabolic Syndrome”), and was comprised of insulin resistance, glucose intolerance, hyperinsulinemia, increased very low-density lipoproteins, decreased high-density lipoproteins, and hypertension. Since 1988, the constellation and clinical cut-off levels of risk factors included in the original metabolic syndrome have been modified by different international health organizations, with some of the risk factors being dropped and new ones added (**Appendix 2**).

Although the true value of the metabolic syndrome as an individual disease entity has been doubted and remains difficult to assess and compare across different institutional definitions, the metabolic syndrome diagnosis has become accepted worldwide, and is an important clinical term for patients with several cardio-metabolic risk factors simultaneously present [88,89]. In a study on cardiac surgery, Echahidi et al. analyzed data from 5,304 consecutive patients that had undergone coronary artery bypass surgery and reported that the metabolic syndrome, as defined by the National Cholesterol Education Program – Adult Treatment Panel III criteria, was a powerful risk factor for mortality (adjusted relative risk 2.04 [95% confidence intervals (95% CI) 1.73–5.52]) [90].

Insulin resistance and microalbuminuria are components of the metabolic syndrome, as defined by the World Health Organization. In cardiology, both of these markers have attracted much attention as early detectable indicators of increased cardiovascular risk. Other associated markers of risk have also emerged, and they have been proposed to be associated with the metabolic syndrome. Within recent years, blood levels of high-sensitive C-reactive protein and adiponectin in clinically healthy individuals have gained considerable attention, and are apparently associated with an increased risk of adverse cardiovascular and metabolic outcomes [91,92].

Biological markers of disease may constitute the only diagnostic path to disguise subclinical diseases. When thinking beyond the risk of future diabetes and cardiovascular disease in the traditional non-surgical and otherwise healthy or non-critically ill patient populations, each risk factor in the metabolic syndrome (i.e., microalbuminuria, insulin resistance, adiponectin) may contain important information on the risk and prognosis in cohorts subjected to other exposures. Of note, the preoperative presence of microalbuminuria, insulin resistance and levels of adiponectin were not among the 97 potential prognostic factors assessed in the EuroSCORE study [31], but these factors could potentially provide important additional knowledge on unmeasured risk, which could potentially lead to changes in pre-, peri-, and postoperative treatment policies.

The following sections include a wider introduction to microalbuminuria, insulin resistance, and adiponectin.

1.2.1. Introduction to microalbuminuria

Albumin is a protein synthesized in the liver and is abundantly present in blood circulation in the body. This protein exerts a broad variety of important functions as a carrier-protein, in osmotic pressure control, and as an important buffer in acid-base homeostasis.

In normal conditions, the primary glomerular filtration of albumin is minimal and corresponds to approximately 1% of the plasma albumin. Thereafter, albumin undergoes a 99% tubular reabsorption, and the final urinary filtrate contains only 1% of the filtered albumin. As the reabsorption mechanism is nearly saturated, a 1% increase in glomerular permeability results in a 10-fold increase in the final urinary filtrate [93].

A diagnosis of elevated levels of urinary albumin is technically termed microalbuminuria or overt albuminuria (also called macroalbuminuria) depending on the specific concentration present. The term microalbuminuria was first used by diabetologists in risk classification of diabetic patients according to the risk of developing diabetic nephropathy [94]. Urinary albumin can be assessed in a 24-h urine sample or in a spot-urine (preferentially, a morning spot-urine) sample. In the spot-urine analysis, both the albumin concentration and the urinary albumin-to-creatinine ratio (UACR) are assessable. In diabetes, microalbuminuria is traditionally defined as an albumin excretion rate of 30–300 mg/day or an UACR between 2.5 and 25 mg/mmol for males and between 3.5 and 35 mg/mmol for females (**Table 6**).

Table 6. Definitions of urinary albumin excretion rates

	24-hour Urine Albumin Excretion (mg/24 hours)	First Morning Void			
		Urinary Albumin Concentration (mg/L)	Urinary Albumin-to-Creatinine Ratio		
			Sex	mg/mmol	mg/g
Normoalbuminuria	<30	<20	Male	<2.5	<20
			Female	<3.5	<30
Microalbuminuria	30-300	20-200	Male	2.5-25	20-200
			Female	3.5-35	30-300
Macroalbuminuria	>300	>200	Male	>25	>200
			Female	>35	>300

Microalbuminuria is a marker of damaged or hyperpermeable glomeruli, and is often present in diabetic and hypertensive patients [94,95]. However, the vascular problem is not confined to the renal microcirculation, but is instead considered a generalized vascular pathology [96].

The systemic endothelium is often injured from both a hypertensive stress and systemic inflammatory processes of either endogenous (e.g., hyperglycemia) or exogenous (e.g., smoking) stimuli. The resulting increased transendothelial leakage of both albumin and lipids translates into an increased atherosclerotic cardiovascular disease risk [97].

As summarized by Gosling et al., increased levels of urinary albumin excretion are associated with a number of pathologic conditions [93]. The UACR is elevated in a variety of acute conditions, such as trauma, surgery, inflammatory processes, infection, and myocardial infarction, but also in different chronic and perhaps subclinical conditions, such as atherosclerosis, hypertension, diabetes, congestive heart failure, chronic obstructive pulmonary disease, and malignancies [93].

The reported prevalence of microalbuminuria varies between 2–36% according to the presence or absence of related diseases and the used cut-off levels. Yudkin et al. reported a prevalence of 9% in non-diabetic patients and 23% in newly diagnosed diabetic patients [98]. In the “Prevention of Renal and Vascular Endstage Disease” trial, a large-scale follow-up study performed in the general population, microalbuminuria was present in 7% of participants, and was associated with both increased non-cardiovascular and cardiovascular death [99]. In the “Heart Outcomes Prevention Evaluation” (HOPE) study, microalbuminuria was present in 15% of non-diabetic participants and in 32% of patients with diabetes [100]. Furthermore, the “Losartan Intervention For Endpoint reduction” (LIFE) study investigators reported a 23% overall prevalence of microalbuminuria, but it was more prevalent among African Americans (35%), Hispanics (37%) and Asians (36%) [101]. In addition, heavy smokers (32%), diabetics (36%) and patients with left ventricular hypertrophy (29%) had microalbuminuria more frequently [101].

1.2.2. Microalbuminuria, cardiovascular disease, and cardiac surgery

Microalbuminuria has attracted much focus as a risk marker in cardiovascular diseases, especially within the last decade. In the 1999 guidelines on cardiovascular disease risk stratification, the World Health Organization and the International Society of Hypertension introduced slightly elevated urinary albumin excretion as an indicator for the detection of target organ damage in patients with hypertension [102]. In the 2003 guideline update by the European Society of Hypertension and the European Society of Cardiology, microalbuminuria, as originally defined (**Table 6**), was recognized as an important independent risk marker [103].

The exact cut-off level for the definition of microalbuminuria with regard to the risk of developing cardiovascular disease is still debated, but a growing amount of evidence has shown that the risk increases at much lower levels of urine albumin excretion [104,105]. Most likely, the risk attenuates gradually with a continuous rise in albumin excretion.

A Medline query on "Cardiac Surgery"[MeSH] AND "Albuminuria"[MeSH] resulted in 14 hits. After assessment of these studies, only 10 of the studies were of apparent relevance to this thesis, and are thus discussed herein. Similar queries were performed in the Web of Science, which resulted in 9 hits, out of which none were of additional interest.

Using radioiodinated albumin, Fleck et al. found increased albumin transcapillary escape rates in 16 patients undergoing on-pump cardiac surgery, which indicates that increased microvascular permeability is a response to cardiac surgery [106]. In 1988, Gosling et al. also found a transient increase in urinary albumin excretion in response to non-cardiac surgery [107]. However, adverse outcomes were not assessed in either of these studies.

Tsang et al. reported an increased perioperative glomerular permeability to albumin and an increased endothelial release of von Willebrand Factor, which along with elevated levels of inflammatory response markers led the authors to conclude that during cardiopulmonary bypass, patients developed an endothelial dysfunction possibly caused by an inflammatory response [108]. However, this previous study included only 23 patients, and therefore was not designed to evaluate any associations between urinary albumin excretion and adverse outcomes. In another study involving 30 patients undergoing coronary artery bypass grafting (CABG), urinary albumin concentrations increased rapidly after surgery and remained elevated during the entire 1–5 day postoperative follow-up period [109]. The authors of this study concluded that monitoring of urinary markers of incipient renal damage could hold information for detection of renal injury in patients undergoing CABG.

Another study by Fauli et al. supported the notion that urinary albumin excretion was augmented during cardiac surgery [110]. Likewise, in a study comparing on- and off-pump bypass procedures, the urinary albumin excretion level increased perioperatively regardless of the use of cardiopulmonary bypass, although the off-pump technique was apparently associated with a lesser increase from the baseline [111]. Later, Harmoinen et al. concluded that the use off-pump cardiac surgery did not eliminate microalbuminuria or markers of an inflammatory response [112]. Collectively, these studies indicated that not only the use of cardiopulmonary bypass, but also the surgical trauma itself, facilitated an acute inflammatory response and increased urinary albumin excretion.

In 2004, Loef et al. published a randomized controlled study, in which 20 patients without concomitant comorbidity received either dexamethasone or placebo preoperatively [113]. The investigators assessed microalbuminuria in patients 12 h prior to surgery, during surgery, and up to 60 h after weaning from the cardiopulmonary bypass, and they subsequently determined that administration of dexamethasone had no impact on the glomerular albumin excretion, which increased during surgery. However, postoperative outcomes were not assessed.

According to Luo et al., preoperative microalbuminuria is a strong independent predictor of acute renal failure following CABG [114]. In this relatively small previous study that included 148 patients, 27 patients (18%) developed acute renal failure postoperatively. However, whereas microalbuminuria was classified according to acknowledged criteria, the employed statistical methods were insufficiently described, and a multivariate analysis including 11 potential confounders was allowed, which seems likely inappropriate.

To our knowledge, only 1 study has previously investigated whether preoperative measurement of microalbuminuria is associated with mortality or a broader range of adverse outcomes following cardiac surgery. Specifically, Yorgancioglu et al. studied 257 consecutive diabetic patients undergoing CABG [115]. Preoperatively, the investigators measured UACR in 24-h urine collections, and found that 89 patients (35%) were microalbuminuric, as their albumin concentration was ≥30 mg/24-h. Furthermore, they found that the baseline differences between the groups with and without microalbuminuria were limited, but diabetes and markers of decreased glomerular function were more frequent in the group with microalbuminuria. Postoperatively, the need for inotropes, the incidence of new onset atrial fibrillation, and ICU stay were statistically increased in the group with microalbuminuria. The 30-day mortality rates were 3.4% and 0.6% in patients with and without microalbuminuria, respectively. Although the observed 30-day mortalities were of potential clinical importance, they were not statistically different between the groups ($p = 0.09$). The same pattern was observed at the 24-month follow-up, where the crude mortality rates in the group with and without microalbuminuria were 7.9% and 3.0%, respectively. Thus, the authors concluded that microalbuminuria had no major effect on the postoperative course following CABG. However, this conclusion did not appear to be entirely supported by their estimates of associations, but it still may be the most reasonable conclusion, as the study was relatively small and no attempt was made to control for confounding.

1.2.3. Is microalbuminuria a modifiable risk factor?

Whether a reduction in the UACR translates into a reduced cardiovascular, renal, or mortality risk is key to the usage of clinical microalbuminuria screening. In recent years, several large-scale

clinical trials have found that treatment targeting the renin-angiotensin system, such as angiotensin-converting enzyme inhibition and angiotensin II receptor antagonists, can reduce urinary albumin excretion [116-121]. Furthermore, correlations between a treatment-induced reduction in urinary albumin excretion and reduced risks of renal and cardiovascular adverse outcomes including mortality have been demonstrated previously [116,118,119,122,123]. These observations document a particular important clinical feature of microalbuminuria, since it seems that reduced excretion of urinary albumin is linked with a lower risk of adverse outcomes. Potentially, screening for this biomarker would enable a physician to improve medical treatment, thereby potentially improving the postoperative outcome.

1.3.1. Introduction to insulin resistance

Insulin is a hormone produced in the pancreas that exerts many crucial metabolic effects in glucose and lipid metabolism. Insulin resistance is a condition in which the biological effect of insulin in the target tissue (mainly skeletal muscle, liver and adipose tissue) is lower than normal, and perhaps lower than required to maintain normal blood glucose levels. In skeletal muscle, insulin serves to stimulate glucose uptake through insulin-sensitive glucose transporters (i.e., GLUT-4). The normal hepatic insulin response results in liver cell glucose storage through glycogen synthesis activation and glycogen phosphorylase inactivation. In adipose tissue, insulin resistance also leads to a reduction in the release of free fatty acids into the blood stream and increased glucose storage. When insulin resistance is present, the effect from reduced efficiency in all 3 target tissues tends to raise blood glucose levels. Furthermore, pancreatic insulin production can be normal or reduced, but it is often increased in order to maintain blood glucose levels.

The direct cause of insulin resistance is still debated, but genetics is thought to play an important part. Insulin resistance is strongly associated with type 2 diabetes, which is a highly hereditary disease, as the lifetime risk is 40% if 1 parent has the disease and 70% if both parents are diseased [124].

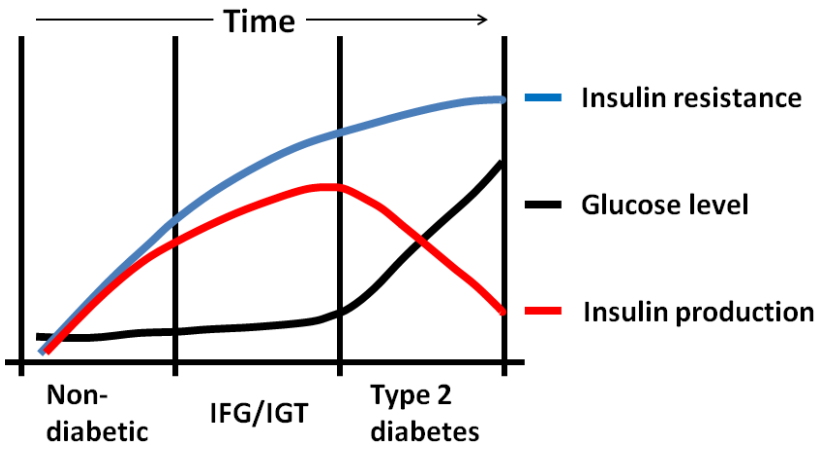
Insulin resistance can be estimated using several different methods, but the hyperinsulinemic euglycemic clamp technique is considered the gold standard [125]. However, this technique is not feasible in daily clinical practice and is primarily used in research settings. The homeostasis model assessment (HOMA), which is based on the level of glucose and insulin in a fasting blood sample, constitutes an appealing alternative technique because it is easily performed and its results correlate well with those from the gold standard [125]. However, insulin resistance is usually not directly tested for in Denmark, although certain groups of patients screened for diabetes, are likely to suffer from insulin resistance, especially if their glucose measurement is within ambiguous limits – called impaired fasting glucose or impaired glucose tolerance (**Table 7**). These conditions are considered to be pre-diabetic states and will often, but not necessarily, develop into type 2 diabetes [126]. The backgrounds responsible for impaired fasting glucose or glucose tolerance may vary, but the most frequent causes are insulin resistance and an impaired glucose mediated insulin response [127]. The suggested progression of insulin resistance is depicted in **Figure 1**.

Table 7. Diabetes: diagnostic values

Diagnose	Fasting venous plasma glucose (mmol/L)	Oral glucose tolerance test (mmol/L)
Normal	< 6.1	< 7.8
Impaired Fasting Glucose	≥ 6.1 & < 7	< 7.8*
Impaired Glucose Tolerance		≥ 7.8 & < 11.1
Type 2 Diabetes Mellitus	≥ 7	≥ 11.1

*if measured to rule out impaired glucose tolerance or type 2 diabetes

Figure 1. Progression of insulin resistance



Abbreviations: IFG = impaired fasting glucose; IGT = impaired glucose tolerance

Data on the prevalence of insulin resistance in the Danish population is sparse. However, it is well established that physical inactivity and calorie overload leading to obesity often precede the development of insulin resistance, the metabolic syndrome, and type 2 diabetes. Therefore, physical inactivity and fat- or carbohydrate-rich diets are some of the major global health threats. In 2007–2008, an estimated 68% of the United States adult population was overweight or obese (body mass index [BMI] ≥ 25) and 34% was obese (BMI ≥ 30) [128]. These numbers reflect the large increase in the prevalence of obesity within the last 2 decades [128]. According to the American Diabetes Association, an estimated 26 million (1 %) American adults have diabetes and another 1 in 3 are in the pre-diabetic state [129]. In Denmark, the prevalence of diagnosed type 2 diabetes is approximately 230,000 patients (4% of the Danish population), and another estimated 150,000 individuals remain undiagnosed [130]. Furthermore, approximately 23,000 new diabetes cases are identified each year in Denmark [130]. Moreover, it has been estimated that 14% of the Danish adult population is obese [131]. Presumably, the prevalence of insulin resistance in the Danish adult population is thus 5–14%. Therefore, there is good reason to believe that a substantial portion of the patients undergoing cardiac surgery in Denmark suffer from undiagnosed insulin resistance or type 2 diabetes.

1.3.2. Insulin resistance, cardiovascular disease, and cardiac surgery

Insulin resistance has been associated with an increased prevalence of cardiovascular disease [132]. In a previous cohort study, patients with high insulin resistance levels (according to HOMA) had a substantially increased risk of cardiovascular disease at 8-year follow-up [133].

Diabetes is an important risk factor for mortality and severe morbidities such as stroke and infections in patients undergoing cardiac surgery [134-136]. The stress response following surgical tissue trauma is known to alter neuroendocrine signalling and can cause incident or aggravated pre-existing insulin resistance associated with the intensity of surgery [137-141]. Furthermore, patients undergoing cardiac surgery experience a major systemic inflammatory response and develop insulin resistance ("diabetes by injury"); in particular, the use of cardiopulmonary bypass appears to increase glycemia and insulin consumption [142,143]. High pre- and perioperative glucose and/or hemoglobin A1c levels are evidently associated with postoperative adverse outcomes following cardiac surgery in patients with or without diabetes [143-147]. In a recent study including both patients with and without diabetes, intraoperative insulin resistance was associated with major complications (a composite of mortality, myocardial infarction, stroke, dialysis, and severe infections) following cardiac surgery [148]. In the same study, the level of preoperative glycosylated hemoglobin A correlated with the intraoperative insulin resistance indices. However, the impact of

preoperative insulin resistance assessment on postoperative adverse outcomes has been less extensively studied in cardiac surgery.

Medline queries on “insulin resistance and cardiac surgery” ([MeSH] and [All Fields]) and “insulin sensitivity and cardiac surgery” ([MeSH] and [All Fields]) resulted in 372 and 105 hits, respectively. Previous cardiac surgery studies have assessed the metabolic syndrome as a preoperative marker of risk [90,142], but apparently no studies have assessed the role of preoperative insulin resistance in short-term outcomes following cardiac surgery. The related studies found in the queries mentioned above are briefly discussed below.

In 1998, Korpilahti et al. reported that CABG patients with progression of atherosclerosis in non-grafted coronary arteries at 5-year follow-up had lower baseline insulin sensitivity [149].

Furthermore, Rapp-Kesek et al. hypothesized that preoperative carbohydrate administration would attenuate insulin resistance, but oppositely found that preoperative HOMA levels were higher in the patients given carbohydrates than in the controls, whereas the postoperative HOMA levels were similar across the groups [140]. Tully et al. found that a preoperative a low glycemic index diet, as opposed to a high glycemic diet, significantly reduced preoperative HOMA levels, but the difference in immediate postoperative HOMA levels did not quite reach statistical significance, perhaps due to a relatively small sample size [150]. In another study, Donatelli et al. showed that preoperative metabolic syndrome and increased HOMA levels were significantly associated with both increased perioperative glucose levels and augmented insulin need [142]. None of these mentioned studies assessed postoperative adverse outcome. However, the study by Donatelli et al. indicated that preoperatively elevated HOMA levels had detrimental impact on the prognosis of patients undergoing cardiac surgery due to perioperative hyperglycemia.

1.3.6. Is insulin resistance a modifiable risk factor?

Several possible pharmacological and non-pharmacological treatment options exist to improve insulin resistance. Lifestyle changes, including regular exercise and diet, can improve insulin resistance and reduces the risk of diabetes and future cardiovascular events [151-153]. Potential preoperative pharmacological strategies include insulin and peroral metformin, but these drugs are not registered for administration to non-diabetic patients.

1.4.1 Introduction to adiponectin

Adiponectin is considered part of the adipokine family together with leptin, resistin, interleukins 6 and 8 (IL-6, IL-8), monocyte chemo-attractant protein (MCP-1), and a growing list of cytokines. Adiponectin is an adipose tissue-produced metabolically active peptide-hormone that circulates at a high concentration, and accounts for approximately 0.01% of total plasma protein [154]. In the blood, it exists in varying molecular weights based on a homotrimer complex that may add up to 18-mers or more [154]. Both low- and high-molecular weight multimers appear to be extremely stable proteins in the circulation, with only limited diurnal variation [155]. Recent data suggest that the high-molecular weight multimers possess the most biologically active properties [156].

In 1999, Arita et al. surprisingly found paradoxically decreased plasma levels of adiponectin in obese individuals [154]. Similar observations have been reported in patients with type 2 diabetes or hyperglycemia, and in both obese and nonobese hyperinsulinemic patients with insulin resistance [157,158]. Oppositely, high levels of circulating adiponectin levels have been found in type 1 diabetic patients, nonobese patients, and in patients suffering from starvation [156,159]. Adiponectin is usually analyzed as a continuous variable grouped into deciles, and no formal agreement exists regarding the specific cut-off levels of adiponectin for patient risk assessment.

Following the identification of adipokines, it was recognized that adipose tissue exerts important endocrine functions other than storage of excess free fatty acids (**Figure 2**). Through secretion of hormones and cytokines, adipose tissue exerts endocrine (i.e., free fatty acid lipolysis), paracrine (i.e., the monocyte chemotactic protein-1 leads to tumor necrosis factor alpha [TNFα] release from macrophages), and autocrine functions involved in the regulation of insulin sensitivity, atherosclerosis, and inflammation. In particular, IL-6 and the monocyte-triggered TNFα release by macrophages appear to cause low-grade local and systemic inflammation, which results in vasoconstriction, endothelial dysfunction, and insulin resistance. On the other hand, adiponectin is involved in glucose and lipid metabolism in insulin-sensitive tissue, and it has been postulated to uphold both anti-inflammatory and anti-atherogenic properties by preventing the effect of TNFα, macrophage recruitment, and foam cell formation [160-163]. However, the exact mechanisms through which adiponectin exerts its actions remain to be fully determined. Likewise, it also remains unclear whether altered adiponectin levels represent cause or effect in dysregulated metabolic states. Nevertheless, in rodents, adiponectin was shown to improve insulin sensitivity by inducing glucose utilization, ultimately resulting in reduced hyperglycemia and hyperinsulinemia [164]. The effects in the skeletal muscles occur partly through activation of 5'-AMP kinases, which also positively influence muscular fatty acid oxidation. In the liver, adiponectin also improves lipid metabolism by

means of reduced influx of free fatty acids, increased oxidation, and reduced triglyceride synthesis, as well as hepatic glucose output.

Figure 2. Proposed effects of adiponectin

Muscle	Liver	Vasculature
↑ Glucose metabolism	↑ Fatty acid oxidation	↓ Inflammation
↑ Insulin sensitivity	↓ Triglyceride synthesis	↓ Endothelial dysfunction
↑ Fatty acid oxidation	↓ Glucose release	↓ Atherosclerosis

1.4.2. Adiponectin, cardiovascular disease, and surgery or critical illness

Contradictory results have led some investigators to conclude that a low adiponectin level is unfavorably associated with future adverse cardiovascular outcomes, whereas others have more cautiously concluded that a bidirectional relationship exists between adiponectin and adverse cardiovascular outcomes, in which the role of underlying comorbidities and metabolic disturbances influence the levels and role of adiponectin.

Case-control and cross-sectional studies on both non-diabetic and type 2 diabetic patients have suggested that adiponectin levels are higher among patients with coronary artery disease than in those patients without the disease [161,165-169]. Similarly, several prospective studies found that a low adiponectin level was associated with a higher cardiovascular risk (coronary artery disease, myocardial infarction, or the need for CABG) [170-175]. However, the data presented in these studies did not reach statistical significance, neither individually nor in a meta-analysis (odds ratio [OR], 0.84 [95% CI, 0.70–1.01]) [174]. Moreover, 2 additional recent prospective follow-up studies similarly suggested that the lowest quartile of adiponectin levels was associated with both an increased risk of coronary artery disease and all-cause death [176,177].

However, other prospective follow-up have reported opposite results, suggesting that high adiponectin levels indicate a higher cardiovascular risk and/or mortality [176,178-183]. In a previous study by Hung et al., the investigators assessed 193 patients with coronary artery disease who underwent elective percutaneous coronary intervention (179 patients) or CABG (14 patients), and found that higher preoperative adiponectin levels were present among type 2 diabetic patients who developed major adverse cardiovascular events (myocardial infarction, percutaneous coronary intervention, CABG, stroke, carotid revascularization or all-cause death) during the mean 15-month follow-up [183]. However, in patients without diabetes, the preoperative adiponectin profile was found to be similar between groups in the same study.

The association between adiponectin and vascular disease appears complex, and it has been suggested that certain individuals may have beneficial physiological elevations in adiponectin levels, whereas others have pathologically driven elevated levels reflecting harmful signals.

Nevertheless, since adiponectin is associated with obesity [154], inflammation [184], insulin resistance [185], endothelial dysfunction [186], incident diabetes, and anti-atherosclerotic properties through modulation of macrophage-to-foam cell transformation [161,163,187], it entails major components of the metabolic syndrome, and thus may also play a central role in the metabolic syndrome and its consequences [185].

The recognition that adipose tissue is not just an innocent bystander in metabolism under normal conditions likely corroborates the important role(s) of the adipose tissue in critically ill patients as well. However, the specific influence of adiponectin in critically ill and surgical patients remains uncertain, although it can be speculated that adiponectin upholds beneficial effects on the inflammatory and insulin resistance responses in patients undergoing cardiac surgery. A Medline query on "Adiponectin"[All Fields] and "Surgery"[MeSH Terms] and "Critical illness"[All Fields] resulted in output the selected studies discussed below.

To date, no studies have assessed adiponectin as a prognostic factor following cardiac surgery. However, it has been found that in critically ill medical patients with and without sepsis, adiponectin levels upon ICU admission were lower than in healthy controls [188,189], and appeared to be independently associated with short-term survival [188]. In another cohort, high adiponectin levels measured within 48 h of the onset of respiratory failure were associated with 28-day mortality of patients, whereas only survivors showed a significant increase in adiponectin levels on day 6 [190]. Thus, it was suggested that adiponectin may actively modulate the response to critical illness through improved insulin sensitivity and anti-inflammatory effects [190,191]. However, data supporting changes in adiponectin during critical illness are sparse and contradictory [191-193]. For instance, in a previous study on 10 adult patients undergoing cardiac surgery, blood glucose and insulin levels increased during surgery (indicating insulin resistance), whereas adiponectin levels remained unchanged [194].

However, post hoc analysis of data obtained from 339 patients admitted to a surgical ICU similarly found lower adiponectin levels in surgical patients than in healthy control individuals, and showed comparable adiponectin levels among short-term survivors and nonsurvivors [191]. Regarding the more long-term association, 2 studies on patients undergoing lower extremity artery bypass surgery suggested that low adiponectin levels were associated with improved graft patency at a

2.5-year follow-up [195], and furthermore, high adiponectin levels were independently associated with increased mortality at a mean follow-up of 3.3 years in another study [177].

In face of the mixed results of the above-mentioned studies, conclusions on the role of adiponectin in critical illness can only be drawn cautiously.

1.4.3. Is adiponectin a modifiable risk marker?

Whether exercise and weight loss improve the levels of adiponectin has been debated. Hulver et al. found no increase in adiponectin levels despite improved insulin sensitivity with exercise [196]. However, a recent study determined that 10 weeks of exercise (3 times a week for 60 min) resulted in improved insulin sensitivity and an increased adiponectin level among 74 otherwise healthy women (age range: 20–66 years) [197].

Recombinant adiponectin (C39S) exists, which enhances whole body insulin sensitivity in murine models, but it is not yet available for humans [198,199].

In humans, treatment with thiazolidinediones has been shown to increase adiponectin levels, which correlated with improved insulin sensitivity [200]. However, thiazolidinediones have unfortunate side effects in other settings and were withdrawn as a treatment option in late 2010. Yet, it appears that pharmacological strategies aimed at augmenting adiponectin levels may hold promising metabolically beneficial effects.

2. Aims

2.1. Study I

To examine the predictive performance of the logistic EuroSCORE model regarding 30-day mortality in a large and contemporary cohort that had undergone on-pump cardiac surgery and was registered in the Western Denmark Heart Registry during the period from January 1999 to March 2010.

2.2. Study II

To examine whether preoperative microalbuminuria was associated with short-term (30 days) adverse outcomes, and whether its inclusion in analysis can improve the short-term preoperative risk-prediction with the EuroSCORE in patients undergoing elective cardiac surgery.

2.3. Study III

To examine whether preoperative microalbuminuria was associated with long-term (31–365 days) adverse outcomes, and whether it would uphold important prognostic information on the preoperative long-term risk-prediction in patients undergoing elective cardiac surgery.

2.4. Study IV

To examine whether preoperative insulin resistance and/or the level of circulating adiponectin were associated with either short-term (30 days) or long-term (31–365 days) adverse outcomes following elective cardiac surgery. Additionally, to assess whether information on insulin resistance and/or adiponectin was useful for preoperative risk-prediction in non-diabetic patients undergoing elective cardiac surgery.

3. Materials and Methods

3.1. Study designs

Study I

Population-based cohort study with 30-day (short-term) follow-up data on mortality.

Studies II–IV

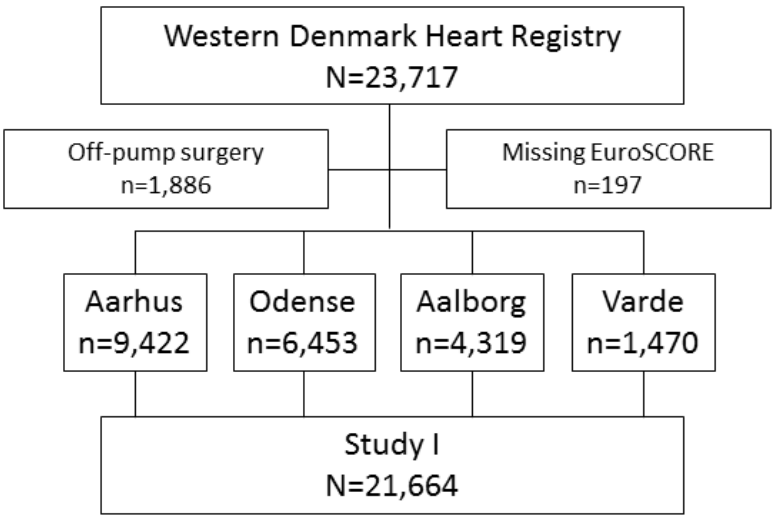
Prospective cohort studies with 30-day and/or 31–365-day (long-term) follow-up data on adverse outcomes.

3.2. Study populations

Study I

This study involves patients that underwent on-pump cardiac surgery performed in Western Denmark during the period from January 1, 1999 to March 31, 2010, and were registered in the Western Denmark Heart Registry. Surgery was performed either at 1 of 3 public surgical cardiac institutions (Aarhus University Hospital, Skejby; Odense University Hospital; Aarhus University Hospital, Aalborg) or at the private Varde Heart Center. Western Denmark covers the Central, North, and South Denmark Regions and has a primarily Caucasian rural-urban population of 3 million inhabitants (approximately 60% of the total Danish population).

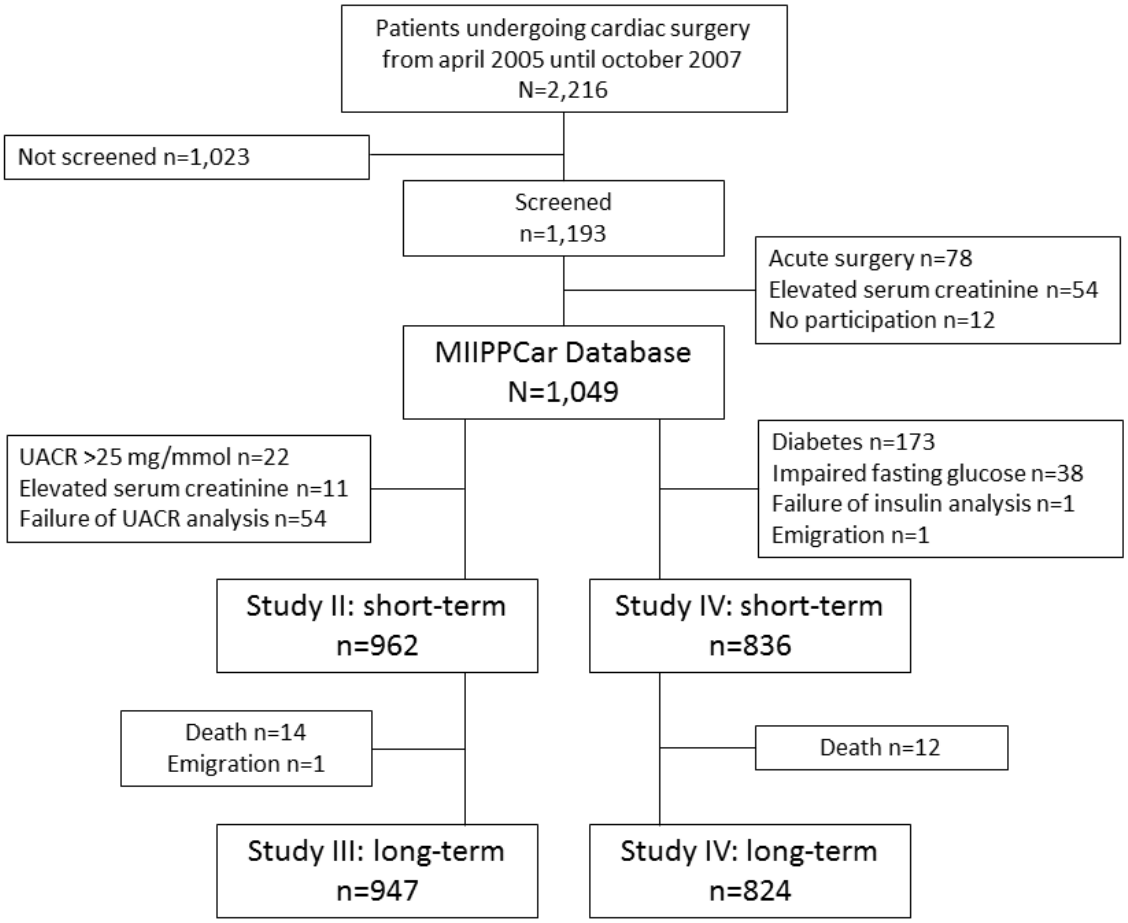
Figure 3. Flowchart for Study I



Studies II–IV

These studies include a sample of patients admitted for elective cardiac surgery in the Department of Cardiothoracic & Vascular Surgery at Aarhus University Hospital, Skejby, Denmark, during the period from April 1, 2005 to October 8, 2007. This institution largely treats individuals from the Central Denmark Region (the former Aarhus, Viborg and Ringkøbing counties), which has a population of approximately 1.2 million inhabitants (approximately 20% of the total Danish population). Only a minor portion of the included patients in these studies had been referred from the North- or South Denmark Regions, which are demographically similar to the Central Denmark Region. Of note, only the Department of Cardiothoracic & Vascular Surgery at Aarhus University Hospital performs cardiac surgery in the Central Denmark Region. Patient screening and recruitment was carried out with the assistance of a project nurse working half-time, why approximately 50% of the candidates for the study were screened consecutively.

Figure 4. Flowchart for Studies II–IV



3.3. Data sources

Data was collected from a preoperative interview and a physical examination of each patient, and from regional as well as national clinical and administrative registries, as listed below. Use of the 10-digit civil registration number, which is unique to each Danish citizen and encodes gender and date of birth, enabled unambiguous record linkage between the different data sources and allowed establishment of the complete preoperative hospitalization and medical prescription histories as well as the postoperative follow-up for each patient.

The Western Denmark Heart Registry

Used for Studies I–IV

The Western Denmark Heart Registry, which was established in 1999, is a regional administrative and clinical register including detailed records on baseline patient characteristics and data regarding all cardiac procedures performed, as well as information on perioperative covariates and outcomes [201]. Since the introduction of this registry, the surgical cardiac centers in Aarhus, Aalborg, and Odense have entered the aforementioned data into the register. Since 2005, Varde Heart Center has also contributed with information on patients who underwent operation. The registry includes data on all of the risk factors included in the EuroSCORE, as well as the total estimated risk. The chief surgeon for each case is responsible for assuring the correct registration of all risk factors. From 1999 to 2006, a risk factor was not registered after EuroSCORE registration initiation was considered as being not present (or reference). However, complete registration of all EuroSCORE risk factors has been mandatory since 2006.

The Danish National Registry of Patients

Used for Studies I–IV

The population-based administrative register called the Danish National Registry of Patients was established in 1977, and holds data on all hospitalizations in somatic Danish hospitals, including the dates of patient admission and discharge, the procedure(s) performed, and up to 20 discharge diagnoses coded by physicians according to the International Classification of Diseases (the 8th revision [ICD-8] until the end of 1993 and the 10th revision [ICD-10] thereafter, as the 9th revision [ICD-9] was not implemented in Denmark). Since 1995, patient discharges from emergency rooms and outpatient clinics have also been registered in this registry.

The MIIPPCar Database

Used for Studies II–IV

Baseline patient characteristics were obtained from a preoperative interview and physical examination. Electronic hospital records and laboratory reports were retrieved for assessment of other baseline and operative covariates, and at the time of discharge were reviewed for registration of in-hospital adverse outcomes (see 2.3. and 2.4.). For each patient, the data was registered in a study-specific case-report-form, which was divided into 1) preoperative data, 2) operative data, 3) discharge data, and 4) data on the 30-day follow-up period if a patient was readmitted to the Department of Cardiothoracic & Vascular Surgery. The prospectively collected data from the case-report-forms were manually entered into a database either by an independent secretary or by a study investigator. Thereafter, conformity between the data in the case-report-form and the database was double-checked by a study investigator. All data acquisition, registration, and entrance into the MIIPPCar database were performed without knowledge of (blinded to) the studied prognostic factors.

The Patient Data Management Database

Used for Studies II–IV

The Patient Data Management Database was introduced at Aarhus University Hospital, Skejby in 2003, and contains extensive information, including data on the time of mechanical ventilation and the use of inotropic drugs at the ICU, that is automatically retrieved from all medico-technical equipment used in the operating theater and at the ICU.

The Laboratory Information Systems

Used for Studies II–IV

The Laboratory Information Systems database was established in 1990 and contains data from the former Aarhus and North Jutland counties. It holds complete information on all patient tests analyzed since 1997. Specifically, data categories include test name, the International Union for Pure and Applied Chemistry code and/or a local analysis code, analyses results, measurement units, codes on commissioned departments, and the dates of test collection and analyses.

The Regional Microbiology Database

Used for Studies II–IV

The Regional Microbiology Database is a microbiological registry maintained by the Department of Clinical Microbiology of Aarhus University Hospital. For instance, the registry keeps data on bacteremic blood cultures from departments affiliated with Aarhus University Hospital, and includes the numbers of positive cultures and bacterial isolates, the names of bacterial species, the departmental place of acquisition, and the date of detection. An independent physician assessed

hospital records on all patients with positive blood cultures to establish whether septicemia or bacteremia only was present.

The Prescription Database

Used for Studies II–IV

The Prescription Database contains data on all redeemed prescriptions at all pharmacies in the Central Denmark Region since 1998. The main variables in this database are the name of the prescribed drug, the anatomical therapeutic chemical (ATC) code, the package identifier (enabling identification of brand, quantity, and formulation of the drug), the date of refill, and codes identifying both the prescribing physician and the dispensing pharmacy. The Danish National Health Service includes a program for refunding the majority of the costs associated with the purchase of most drugs prescribed by physicians. We retrieved a variety of data on the prescriptions (e.g., anti-platelet, -hypertensive, and -diabetic drugs, and lipid lowering drugs), all of which were available by prescription only and had refundable costs.

The Danish Civil Registration System

Used for Studies I–IV

The Danish Civil Registration System has kept current records (electronically updated on a daily basis) of the entire Danish population, including vital status, date of death, residence, and migration, since 1968. For health monitoring and research purposes, information available in this system is automatically transferred to other Danish National Healthcare registries.

The National Register of Causes of Death

Used for Studies II–IV

The National Register of Causes of Death contains information on the dates and causes of death in Denmark since 1973. This registry was used to determine the reported causes and dates of death of the patients included in this study.

3.4. Study approvals

For research purposes, the Danish Data Protection Agency allows linkage between the Danish Healthcare registries, and therefore no specific approval was required for Study I. For Studies II–IV, an ethical approval was obtained from the Regional Ethics Committee. Data acquisition and usage permission were granted by the Danish Data Protection Agency (Reference number 2007-41-1514). Finally, informed consent was obtained from each participating patient.

3.5. Definition of exposures

Studies II–IV

For each participant, both a preoperative fasting blood sample and a morning spot-urine sample were collected were collected and analyzed at the Department of Clinical Biochemistry, Aarhus University Hospital, Skejby, Denmark and/or at the Medical Research Laboratory, Aarhus University Hospital, Aarhus Sygehus, Noerrebrogade, Denmark.

Studies II and III – microalbuminuria

Preoperative microalbuminuria was defined as a UACR between 2.5 and 25 mg/mmol. Using the preoperative urine sample, the urinary albumin level (mg/L) was quantitatively assessed by immunoturbidimetry (COBAS INTEGRA Tina-quant Albumin Gen. 2; La Roche, Basel, Schweiz), and the urinary creatinine level (mmol/L) was estimated by an enzymatic colorimetric test (COBAS INTEGRA Creatinine Jaffé; La Roche). The lower detection limits for urinary albumin and urinary creatinine were 7 mg/L and 0.03 mmol/L, respectively. Since the UACR was calculated by dividing the urinary albumin level by the urinary creatinine level, albumin values below 7 mg/L could not contribute to an exact UACR (mg/mmol). Thus, we defined the UACR to be 0.1 mg/mmol in these patients. For urinary albumin and creatinine analyses, the intra-assay and inter-assay coefficients of variation (CV) were less than 2.5%.

Study IV – insulin resistance and adiponectin

Insulin resistance was calculated using the HOMA. The calculation of HOMA is based on the relationship between fasting glucose and insulin levels.

$$HOMA = (Glucose\ [mmol/L] \times Insulin\ [mU/L])/22.5$$

The fasting blood glucose values (mmol/L) were measured in duplicate immediately after sampling on a glucose analyzer (Beckman Instruments, Palo Alto, CA, USA), and blood insulin values (pmol/L) were measured using a commercial immunological kit (DAKO, Glostrup, Denmark). The constant used for converting insulin from pmol/L to mU/L was 6.945. For insulin, the intra-assay CV was 2.1–3.7%, and the inter-assay CV was 3.4–4.0%.

Serum adiponectin (mg/L) was measured by an in-house time-resolved immunofluorometric assay (R&D Systems, Abingdon, UK). Intra- and inter-assay CV averaged less than 5% and 10%, respectively.

3.6. Definition of outcomes

All-cause mortality was defined as death from any cause within the 30-day follow-up period. We used the E/O mortality ratio to assess the performance of the EuroSCORE risk prediction in biennial periods from 1999 to 2010.

Studies II–IV

The main study outcome was 30-day operative all-cause mortality. Other study outcomes were lengths of ICU stay and total hospital stay (from the day of surgery to ICU and hospital discharge, respectively), incident myocardial infarction or percutaneous coronary intervention, stroke, atrial fibrillation or flutter, renal failure (100% increase in baseline serum creatinine level or the use of dialysis postoperatively), septicemia (positive blood culture and/or clinically suspected sepsis with an infectious background), surgical re-exploration (due to bleeding, ischemia, or repeat operation), and sternal and leg wound infection (at the site of graft harvest) requiring intervention. Events of sternal wound infection were divided into superficial and deep sternal wound infections, according to an independent (blinded to exposure levels) review performed by 2 consulting surgeons with special interest in sternal wound infection management.

For analyses in Study II, we also used a cardiovascular-related composite outcome consisting of all-cause death, myocardial infarction, stroke, and atrial fibrillation. Deep sternal wound infection and septicemia were also considered as a composite outcome. For Studies III and IV, the cardiovascular-related composite outcome was defined as all-cause death, myocardial infarction, and stroke. Postoperative infections were considered alone or in combinations of 3 composite outcomes consisting of 1) deep sternal wound infection and septicemia; 2) deep or superficial sternal wound infection and septicemia; and 3) deep or superficial sternal wound infection, leg wound infection, and septicemia. Only the patient's first episode of each outcome was included in analysis.

3.7. Definition of covariates

Study I

Descriptive baseline characteristics included the EuroSCORE and its 17 individual risk factors. Detailed information on the types of surgery performed was obtained from the Western Denmark Heart Registry and National Danish Registry of Patients.

Studies II–IV

Baseline covariates included age, gender, smoking habits (current, previous, and non-smoker), height, weight, BMI (<25 kg/m^2, 25–30 kg/m^2, and >30 kg/m^2), blood pressure (normal [<140/90

mmHg], grade I [≥140/90 mmHg], grade II [≥160/100 mmHg], and grade III [≥180/110 mmHg]), left ventricular ejection fraction (<30%, 30–50%, >50%), prior ischemic peripheral-, cerebral-, or cardiovascular disease, history of atrial fibrillation or flutter, dyslipidemia, and medically treated type 1 or type 2 diabetes. Furthermore, diabetes was defined as 1) clinical history of diabetes and preoperative anti-diabetic medical treatment obtained from the preoperative patient interview; 2) a hospital discharge diagnosis of type 1 or type 2 diabetes; 3) filling at least one prescription for insulin or an oral anti diabetic drug; and/or 4) an in-hospital preoperative fasting blood sample with elevated glucose levels above 7.0 mmol/L.

The additive and logistic EuroSCORE data were obtained from the Western Denmark Heart Registry. When a mismatch between the additive and logistic EuroSCORE data was present or the EuroSCORE was missing, the score was calculated based on a review of patient records and on data obtained from the Western Denmark Heart Registry. For further comorbidity assessment and possible adjustment, we collected preoperative information on the Charlson Comorbidity Index from the National Danish Registry of Patients and the case-report-form. The Charlson Comorbidity Index includes 19 disease categories. Each disease category has an assigned weight, and this index classifies comorbidity into a score based on the sum of the weights [202]. The index has been adapted for use with hospital discharge registry data in ICD databases for the prediction of both short- and long-term mortality in longitudinal studies [203]. In this thesis, we categorized the sum of index scores into 3 levels of comorbidity: 0 ("low"), 1–2 ("medium"), and >2 ("high") (Studies III and IV).

Data on routine blood measurements taken during the admission period were obtained from the Laboratory Information System, and included serum levels of creatinine (µmol/L), potassium (mmol/L), sodium (mmol/L), albumin (µmol/L), glucose (mmol/L), white blood cell count (10^9/L), hemoglobin (mmol/L), erythrocyte volume fraction (%), and platelet count (10^9/L).

Moreover, the glomerular filtration rate was estimated by the Cockcroft–Gault equation:

$$((140 - \text{age [years]}) \times \text{weight [kg]} \times F) / (\text{plasma creatinine [µmol/L]} \times 0.8136),$$

where F = 1 if the patient is male and F = 0.85 if the patient is female.

We obtained all information on all prescriptions recorded (e.g., angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, beta blockers, calcium channel blockers, diuretics, and lipid-lowering and anti-diabetic drugs) up to 180 days preoperatively and 1 year postoperatively. The information on filled prescriptions was used to construct postoperative time-varying intervals for use of each drug.

For Studies II–IV, the type of surgery for each patient was recorded in the MIIPPCar database, and in ambiguous cases, it was checked using either information on cardiac surgical procedures registered in the National Danish Registry of Patients or information about the procedural description in the patient's record (mainly when validating codes registered for surgical re-exploration). Moreover, we used other peri- and postoperative covariates, including extracorporal circulation, cardiopulmonary bypass time, aortic cross-clamp time, number and type of bypass grafts, use of inotropics at the ICU, and time on mechanical ventilation.

3.8. Statistical analyses

Study I

The prevalence of the individual variables contained in the EuroSCORE model were compared between the Western Denmark Heart Registry and the original EuroSCORE databases using a two-sided equality of proportion test for binomial variables and the independent *t*-test for parametric continuous variables. The ratio between the mean E/O mortality was calculated for each biennial period from 1999 to 2010. Thereafter, the ratios were compared across the 6 biennial periods. The performance of the EuroSCORE risk estimation was assessed based on discrimination and calibration analyses across both biennial periods and the type of surgery performed. Discrimination, which was assessed by the AUC, refers to the ability of the score to distinguish patients who died from those who survived. The AUC is the probability that a patient who died had a higher risk score than a patient who survived; an AUC value of 0.5 indicates random prediction. Calibration refers to the precision of the estimation of a score. Model calibration was assessed using the Hosmer–Lemeshow test. Data were split into 10 groups of equal sizes, and the estimated and observed numbers of death were compared for each group. A significant Hosmer–Lemeshow test result indicates that the observed and estimated values were not comparable.

Studies II–IV

In the risk studies, baseline and procedural characteristics were presented as medians with interquartile ranges or 95% CIs, and categorical data were presented as counts and frequencies. Using Fisher's Exact tests, independent *t*-tests, and the Mann–Whitney or Kruskal–Wallis tests when appropriate, data were compared between groups with and without microalbuminuria, or across the exposure quartile levels for insulin resistance (HOMA) and adiponectin. After logarithmic transformation, we explored correlations between both insulin resistance and adiponectin with baseline and procedural characteristics.

We constructed cumulative risk curves according to the cut-off levels for microalbuminuria, and across quartiles for insulin resistance and adiponectin (the upper quartile versus the 3 lower quartiles).

Data on the lengths of ICU stay and hospital stay were analyzed on a logarithmic scale using linear regression analyses. Thereafter, we transformed the regression estimate and estimated the absolute difference in the median length of stay between groups at different levels of the EuroSCORE. The standard error was calculated using the delta method.

We conducted different regression analyses (logistic regression [OR], Poisson regression [incidence rate ratio], Cox proportional hazard regression [hazard ratio [HR]], competing risk regression [sub-hazard ratio], linear regression, and spline functions regression) to investigate the associations between exposures (individual and composite) and postoperative outcomes in both the short- and long-term follow-up periods. The relative estimates were quite similar across the varying regression models (data not shown). Therefore, the ORs derived from the logistic regression analysis was our preferred estimate of association, except for in Study III, in which we used Cox proportional hazard or competing risk regressions. The crude associations were adjusted for possible confounding covariates using the change-in-estimate method (with a limit of 10%) [204]. However, only a limited number of covariates could be controlled for concomitantly, since failure events were relatively infrequent. In additional spline regressions, we found no specific cut-off levels of any of the exposures that indicated increased risk. For assessment of the potential value of the exposures in risk prediction, we used logistic regression analyses only, and assessed whether discrimination and calibration of the logistic regressions were improved beyond that of the EuroSCORE when including the exposure of interest. For all logistic regression analyses, receiver operating characteristic curves and Hosmer–Lemeshow tests were used to test model accuracy and fit. We assessed the assumption of proportional hazards in the Cox regression model using log(-log(survival)) plots.

For all analyses, a 2-tailed *p*-value less than 0.05 was considered statistically significant. Analyses were performed using the Stata 10 (Study II) or 11.0 (Studies I, III, and IV) package (StataCorp LP, Texas, USA).

4. Results

4.1. Study I

Information on 21,861 patients who had undergone on-pump operations was available. The EuroSCORE was missing in 197 (0.9%) of these patients, leaving 21,664 patients available for analyses. The majority of the individual risk factors contained in the EuroSCORE risk prediction model were more commonly present in the Western Denmark Heart Registry cohort than in the original EuroSCORE study (**Table 8**).

Upon examination of data for the 21,664 patients, we found that the presence of several characteristics changed from 1999 to 2010. For instance, patients undergoing medical treatment for hypercholesterolemia or hypertension increased from 34% to 65% and 32% to 67%, respectively. Likewise, preoperative diabetes was present in 13% of patients in 1999–2000 and in 20% in 2009–2010. Furthermore, 22% (n = 4,721) of the patients in the present study group were more than 75 years in age, whereas this age group represented only 10% in the entire EuroSCORE study population of 19,030 patients. The prevalence of patients above 75 years in age increased gradually from 15% in 1999 and up to 28% in 2009 and 2010 ($p < 0.01$). For isolated CABG patients, the proportion of patients above 75 years in age increased from 13% to 25% during the same period.

Patients from the Western Denmark Heart Registry with a missing EuroSCORE had isolated CABG surgery (113 patients, 57%), isolated aortic valve surgery (19 patients, 10%), or combined CABG and valve surgery (21 patients, 11%), and these patients had predominantly undergone surgery at Varde Heart Center in 2005 (104 patients, 53%). Furthermore, they tended to be 2 years younger on average than the mean patient age ($p = 0.06$), but did not differ with regard to gender (26% female, $p = 0.89$). After the change in the database registration interface that occurred in 2006, less than 0.5% of the patients had missing information on the individual EuroSCORE risk factors. Before 2006, missing values were present in less than 4% of each risk factor, except for left ventricular dysfunction (5%) and serum creatinine above or below 200 µmol/L (36%).

Table 8. EuroSCORE risk factors

EuroSCORE risk factors	Prevalence in the EuroSCORE database	Prevalence in the WDHR cohort	*p*-value for difference
Patient related	**N=19,030**	**N=21,664**	
Age (mean [SD])	62.5 [10.5]	65.5 [11.2]	<0.01
Female	27.8	27.4 (0.3)	0.39
Chronic pulmonary disease	3.9	10.1 (0.2)	<0.01
Extracardiac arteriopathy	11.3	9.0 (0.2)	<0.01
Neurological dysfunction	1.4	7.7 (0.2)	<0.01
Previous cardiac surgery	7.3	5.6 (0.2)	<0.01
Serum creatinine	1.8	3.0 (0.1)	<0.01
Active endocarditis	1.1	1.7 (0.1)	<0.01
Critical preoperative state	4.1	4.9 (0.1)	<0.01
Cardiac related			
Unstable Angina	8.0	13.3 (0.2)	<0.01
LVEF 30-50 %	25.6	27.7 (0.3)	<0.01
LVEF <30 %	5.8	6.4 (0.2)	<0.01
Recent myocardial infarction	9.7	17.3 (0.3)	<0.01
Pulmonary hypertension	2.0	5.5 (0.2)	<0.01
Operation related			
Emergency surgery	4.9	5.6 (0.2)	<0.01
Other than isolated CABG	36.4	41.6 (0.3)	<0.01
Surgery on thoracic aorta	2.4	2.7 (0.1)	0.07
Postinfarct septal rupture	0.2	0.2 (<0.1)	0.29
	The EuroSCORE developmental and validation dataset	**The WHDR cohort**	
Risk model	**N=14,799**	**N=21,664**	
Additive EuroSCORE	4.2 (CI 4.2-4.3)	5.6 (CI 5.6-5.7)	<0.01
Logistic EuroSCORE	4.8 (CI 4.7-4.9)	8.0 (CI 7.9-8.2)	<0.01

Abbreviations: N = number; SD = standard deviation; CI = 95 % confidence interval; WDHR = Western Denmark Heart Registry; LVEF = left ventricular ejection fraction; CABG = coronary artery bypass grafting
Percentage (standard error) or mean [SD]

Annually, approximately 1,900 procedures were performed, except in 1999 when only 1,189 procedures were registered. In summary, the procedural characteristic changed over time. In 1999, isolated on-pump bypass surgery was performed in 77% of the patients, but this surgery only contributed to 40% of the surgeries performed in 2009. Accordingly, procedures other than bypass increased from 23% to 60% during the same period. Furthermore, isolated valve procedures and combined bypass and valve procedures accounted for increases from 12% to 28% and 6% to 13%, respectively.

In **Table 9,** the results on both the overall, the specific procedures, and the biennial periods of EuroSCORE risk prediction are shown, along with the discrimination and calibration test statistics. Briefly, the EuroSCORE overestimated mortality independent of the varying types of surgery performed. Upon accumulating total data, the Hosmer–Lemeshow test showed a poor model fit regarding CABG, combined CABG and valve replacement, and aortic valve replacement (all $p < 0.05$), but an acceptable model fit for mitral valve replacement ($p = 0.20$). The overall study EuroSCORE discrimination was 0.79 (95% CI, 0.77–0.81) (**Table 9**). Discrimination analyses varied from 0.69 (95% CI, 0.65–0.73) for combined CABG and valve replacement up to 0.84 (95% CI, 0.78–0.90) for mitral valve replacement. Across the biennial periods, the E/O ratios appeared to increase for the overall study group and all types of surgery (**Table 9**). When applying weighted regression analyses, these trends of increased overestimation were confirmed (overall group, $p = 0.06$; combined CABG and valve procedures, $p = 0.03$; mitral valve, $p = 0.06$; aortic valve, $p = 0.12$) with the exception of isolated CABG ($p = 0.63$). Moreover, with the exception of isolated aortic or mitral valve replacement, the estimates of the discrimination tests tended to improve over time, whereas most procedure-specific calibration tests showed acceptable model fit over time (**Table 9**). For the overall study group, an approximate 2-fold overestimation of the actual mortality appeared to be independent of the level of estimated risk (**Table 10**). The most noteworthy increases in the E/O ratios throughout the study period were found in low–medium risk patients (0–12%) (**Table 10**).

Table 9. EuroSCORE risk prediction in biennial periods

Total study	Total	1999-2000	2001-2002	2003-2004	2005-2006	2007-2008	2009-2010
Number	**21,664**	3,449	4,387	3,552	3,627	4,196	2,455
Observed %	**3.9**	4.2	3.6	4.4	3.8	3.3	4.2
Estimated %	**7.5**	6.1	6.1	6.6	9.3	8.7	8.8
E/O	**1.92 (1.83-2.08)**	1.45 (1.24-2.69)	1.69 (1.45-2.03)	1.50 (1.29-1.73)	2.45 (2.11-2.91)	2.64 (2.29-3.22)	2.10 (1.76-2.59)
AUC	**0.79 (0.77-0.81)**	0.76 (0.72-0.79)	0.78 (0.74-0.82)	0.81 (0.78-0.85)	0.81 (0.77-0.84)	0.81 (0.78-0.85)	0.81 (0.76-0.85)
HL test	**<0.01**	<0.01	<0.01	<0.01	<0.01	0.03	0.11
Isolated CABG procedures							
Number	**12,427**	2,622	3,097	2,056	1,643	1,992	1,017
Observed %	**2.4**	2.6	1.9	3.0	2.6	2.0	3.3
Estimated %	**5.4**	5.0	4.8	5.1	6.7	5.8	6.4
E/O	**2.25 (2.00-2.45)**	1.92 (1.56-2.50)	2.53 (2.00-3.43)	1.70 (1.38-2.32)	2.58 (1.97-3.72)	2.90 (2.23-4.46)	1.94 (1.45-2.91)
AUC	**0.78 (0.75-0.81)**	0.71 (0.65-0.77)	0.71 (0.64-0.78)	0.84 (0.78-0.89)	0.84 (0.78-0.89)	0.80 (0.72-0.89)	0.84 (0.76-0.91)
HL test	**<0.01**	<0.01	0.22	<0.01	0.17	0.51	0.82
Combined CABG and valve procedures							
Number	**2,735**	233	435	509	574	586	398
Observed %	**7.2**	10.3	9.4	9.2	5.7	4.8	5.8
Estimated %	**10.7**	10.0	10.1	10.0	11.1	11.7	10.5
E/O	**1.49 (1.32-1.73)**	0.97 (0.70-1.56)	1.07 (0.83-1.51)	1.09 (0.85-1.49)	1.95 (1.44-1.92)	2.44 (1.80-3.90)	1.81 (1.30-3.00)
AUC	**0.69 (0.65-0.73)**	0.56 (0.45-0.68)	0.71 (0.64-0.79)	0.65 (0.57-0.73)	0.71 (0.61-0.80)	0.73 (0.63-0.83)	0.82 (0.72-0.92)
HL test	**0.02**	0.24	0.33	0.41	0.02	0.90	0.55
Isolated aortic valve procedures							
Number	**3,396**	294	522	633	699	755	493
Observed %	**3.2**	6.8	4.4	3.5	2.0	1.6	3.4
Estimated %	**8.0**	8.7	7.4	7.4	8.5	8.3	7.7
E/O	**2.50 (2.11-3.08)**	1.28 (0.90-2.23)	1.68 (1.19-2.85)	2.11 (1.51-3.70)	4.25 (2.80-8.50)	5.19 (3.32-11.9)	2.25 (1.51-4.28)
AUC	**0.76 (0.72-0.80)**	0.76 (0.64-0.87)	0.72 (0.62-0.83)	0.81 (0.73-0.89)	0.79 (0.68-0.90)	0.75 (0.63-0.87)	0.74 (0.64-0.84)
HL test	**<0.01**	0.89	0.15	0.20	0.21	0.42	0.33
Isolated mitral valve procedures			**1999-2002**		**2003-2006**		**2007-2010**
Number	**962**		256		387		319
Observed %	**5.2**		7.0		5.7		3.1
Estimated %	**9.8**		9.1		10.6		9.3
E/O	**1.88 (1.48-2.58)**		1.30 (0.89-2.33)		1.86 (1.33-3.12)		3.00 (1.82-7.75)
AUC	**0.84 (0.78-0.90)**		0.87 (0.76-0.98)		0.86 (0.77-0.94)		0.76 (0.58-0.95)
HL test	**0.20**		0.23		0.17		0.94

Abbreviations: AUC = area under curve; HL = Hosmer–Lemeshow test; E/O = estimated to observed mortality ratio

Table 10. E/O ratios in biennial periods and across estimated risk level

				1999-2010 N=21,644	1999-2000 n=3,449	2001-2002 n=4,387	2003-2004 n=3,552	2005-2006 n=3,627	2007-2008 n=4,196	2009-2010 n=2,455	
Risk (%)	**N**	**Estimated (%)**	**Observed (%)**	**1999-2010 E/O**	**E/O**	**E/O**	**E/O**	**E/O**	**E/O**	**E/O**	***p***
0<3	8,802	1.79	0.94 (0.74-1.14)	***1.90*** (1.57-2.42)	**1.18** (0.85-1.96)	**1.54** (1.10-2.60)	**1.74** (1.17-3.41)	**4.6** (2.45-37.1)	**3.49** (2.06-11.3)	**2.08** (1.19-7.97)	0.04
3<6	5,393	4.31	2.26 (1.87-2.66)	***1.91*** (1.62-2.30)	**1.17** (0.86-1.80)	**2.09** (1.48-3.51)	**1.85** (1.31-3.16)	**2.31** (1.57-4.38)	**2.50** (1.70-4.74)	**2.05** (1.33-4.44)	0.07
6<9	2,704	7.36	4.59 (3.80-5.37)	***1.73*** (1.37-1.94)	**1.14** (0.83-1.83)	**1.44** (1.05-2.31)	**1.08** (0.79-1.73)	**2.05** (1.41-3.77)	**2.42** (1.63-4.70)	**2.31** (1.48-5.24)	0.05
9<12	1,382	10.4	4.99 (3.84-6.14)	***1.60*** (1.69-2.71)	**2.09** (1.32-4.99)	**1.50** (1.02-2.78)	**1.47** (0.99-2.89)	**1.89** (1.24-4.05)	**4.28** (2.47-16.2)	**3.08** (1.72-15.0)	0.24
12<15	861	13.3	6.16 (4.55-7.76)	***2.16*** (1.71-2.92)	**3.31** (1.68-143)	**1.34** (0.89-2.69)	**1.62** (1.03-3.79)	**2.49** (1.55-6.36)	**3.54** (2.04-13.3)	**2.21** (1.28-8.16)	0.11
15<25	1,302	19.0	8.83 (7.29-10.4)	***2.15*** (1.83-2.61)	**1.51** (1.06-2.63)	**1.85** (1.32-3.14)	**1.80** (1.25-3.22)	**2.84** (1.96-5.16)	**2.63** (1.88-4.34)	**2.27** (1.54-4.31)	0.05
25<50	867	34.6	17.0 (14.5-19.5)	***2.04*** (1.77-2.39)	**1.39** (1.03-2.15)	**2.20** (1.52-3.96)	**1.39** (1.06-2.00)	**2.38** (1.76-3.67)	**3.05** (2.22-4.86)	**2.03** (1.46-3.29)	0.18
50-100	353	66.2	36.0 (30.9-41.0)	***1.84*** (1.61-2.14)	**2.42** (1.48-6.62)	**1.53** (1.11-2.46)	**1.20** (0.90-1.77)	**2.38** (1.82-3.44)	**1.88** (1.47-2.59)	**1.57** (1.17-2.40)	0.76

Abbreviations: E/O = estimated to observed mortality ratio; N = number; *p* = *p*-value for weighted linear regressions

4.2. Study II

4.2.1. Study cohort and surgical characteristics

The baseline patient characteristics are displayed in **Table 11**. The overall prevalence of microalbuminuria in the cohort was 18.7% (n = 180). On average, patients with microalbuminuria were 3.5 years older than the normoalbuminuric patients, and they had a higher EuroSCORE. Likewise, there were minor differences in the smoking habits, type 2 diabetes prevalence, previous stroke, atrial fibrillation, cardiac ejection fraction, and the preoperative use of medicine between these groups. Furthermore, fewer patients with microalbuminuria had solitary bypass procedures than patients without microalbuminuria (35% vs. 44%, $p = 0.04$). However, microalbuminuria patients had more combined procedures performed (26% vs. 17%, $p < 0.01$). There were no differences between the groups with and without microalbuminuria regarding other procedural characteristics, including the use of extra corporal circulation and aortic cross clamp time.

4.2.2. Associations between microalbuminuria and short-term adverse outcomes

Microalbuminuria was associated with a slightly prolonged length of both ICU stay and total hospital stay. Specifically, a patient with a EuroSCORE equal to 5 had a 0.15-day (95% CI, 0.04–0.26) prolonged ICU stay and a 0.50-day (95% CI, 0.04–0.96) prolonged total hospital stay.

When adjusted for the EuroSCORE, microalbuminuria was not an independent predictor of most individual and combined outcomes (**Table 12**). Still, microalbuminuria remained a strong independent prognostic factor for development of septicemia (OR, 12.1 [95% CI, 3.19–45.9]). Adjustment for other covariates did not change the risk estimates substantially, and analyzing the UACR as a continuous spline function did not reveal any threshold values associated with increased risk. Furthermore, restricting the analyses only to patients undergoing bypass surgery, valve surgery, thoracic aortic surgery, or combined procedures had significant impact on the risk estimates

4.2.3. Microalbuminuria and prediction of short-term adverse outcomes

The EuroSCORE was an independent predictor of mortality (OR, 1.40 [95% CI, 1.21–1.63]) and was significantly associated with stroke (OR, 1.16 [95% CI, 1.05–1.28]), atrial fibrillation (OR, 1.06 [95% CI, 1.01–1.10]), surgical re-exploration (OR, 1.14 [95% CI 1.06–1.23]), renal failure (OR, 1.19 [95% CI, 1.10–1.29]), septicemia (OR, 1.25 [95% CI, 1.07–1.46]). The OR values were virtually unchanged after adding information on microalbuminuria to the EuroSCORE. However, the EuroSCORE + microalbuminuria model appeared to be less strongly associated with septicemia

(OR, 1.15 [95% CI, 0.98–1.36]). The EuroSCORE alone reached high discrimination (AUC, 0.86 [95% CI, 0.79–0.94] with regard to mortality prediction, but otherwise showed poor discrimination. Using the EuroSCORE + microalbuminuria model, the discrimination analysis regarding only septicemia was improved (from 0.73 [95% CI, 0.59–0.88] to 0.85 [95% CI, 0.74–0.96]). The Hosmer-Lemeshow test for calibration revealed good agreement between the observed and expected numbers of deaths, using both the EuroSCORE (p = 0.22, chi^2 = 9.4) and EuroSCORE + microalbuminuria (p = 0.44, chi^2 = 8.0) models. With the exception of surgical re-exploration (p = 0.03, chi^2 = 15.3), the calibration tests of both the combined (p =0.86, chi^2 = 3.3) and individual outcomes (p > 0.51, chi^2 < 6.2) showed good model fits, regardless of adjustment for microalbuminuria.

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Table 11. Baseline patient characteristics

Variables	Total (N=962)	Normoalbuminuria (n=782)	Microalbuminuria (n=180)	*p*
Age (years)	65.6 [18 - 93]	65.0 [18 - 93]	68.5 [33 - 93]	<0.01
Gender (male)	699 (72.7)	573 (73.3)	126 (70.0)	0.40
Smoking habits				0.01
Nonsmoker	341 (35.5)	293 (37.5)	48 (26.7)	
Current smoker	168 (17.5)	138 (17.7)	30 (16.7)	
Previous smoker	453 (47.0)	351 (44.9)	102 (56.7)	
Blood pressure				0.52
Grade I hypertension	286 (29.7)	230 (29.4)	56 (31.1)	
Grade II hypertension	178 (18.5)	142 (18.2)	36 (20.0)	
Grade III hypertension	85 (8.8)	66 (8.4)	19 (10.6)	
Diabetes				
Type 1	17 (1.8)	11 (1.4)	6 (3.3)	0.11
Type 2	127 (13.2)	95 (12.2)	32 (17.8)	0.05
Body Mass Index				0.27
<25	265 (27.6)	207 (26.5)	58 (32.2)	
25-30	401 (41.7)	333 (42.6)	68 (37.8)	
>30	296 (30.8)	242 (31.0)	54 (30.0)	
Previous MI	232 (24.1)	184 (23.5)	48 (26.7)	0.39
Previous AF	145 (15.1)	100 (12.8)	45 (25.0)	<0.01
Previous Stroke	96 (10.0)	69 (8.8)	27 (15.0)	0.02
Previous PAD	50 (5.2)	39 (5.0)	11 (6.1)	0.58
Cardiac ejection fraction				0.02
<30	27 (2.8)	21 (2.7)	6 (3.3)	
30-50	182 (18.9)	135 (17.3)	47 (26.1)	
>50	753 (78.3)	626 (80.1)	127 (70.6)	
EuroSCORE	5.3 [0 - 18]	5.0 [0 - 18]	6.5 [0 - 18]	<0.01
Charlson Comorbidity Index	1.4 [0 - 8]	1.3 [0 - 7]	2.0 [0 - 8]	<0.01
Preoperative medicine				
ACE inhibitors	307 (31.9)	236 (30.2)	71 (39.4)	0.02
ATII antagonists	95 (9.9)	75 (9.6)	20 (11.1)	0.58
Beta blockers	607 (63.1)	491 (62.8)	116 (64.4)	0.73
Calcium channel blockers	258 (26.8)	200 (25.6)	58 (32.2)	0.08
Lipid lowering drugs	643 (66.8)	521 (66.2)	122 (67.8)	0.79
Creatinine (mmol/liter)	85 [22 - 191]	83 [22 - 189]	91 [35 - 191]	<0.01

Abbreviations: ACE = angiotensin converting enzyme; AF = atrial fibrillation; ATII = angiotensin II; MI = myocardial infarction; PAD = peripheral artery disease; eGFR = estimated glomerular filtration rate; N = number; *p* = *p*-value
Medians [interquartile range] or absolute numbers (%)

Table 12. Odds ratios of adverse outcomes according to the presence of microalbuminuria

Outcomes	Number of events		Crude model		Adjusted model*	
	- MA n = 782	+ MA n = 180	OR	95 % CI	OR	95 % CI
All-cause death	9 (1.2)	4 (2.2)	1.95	0.59 - 6.41	1.02	0.29 - 3.64
Myocardial infarction	26 (3.3)	4 (2.2)	0.66	0.22 - 1.92	0.60	0.20 - 1.78
Stroke	29 (3.7)	9 (5.0)	1.37	0.64 - 2.94	1.07	0.48 - 2.37
Atrial fibrillation or flutter	264 (33.8)	65 (36.1)	1.11	0.79 - 1.56	1.02	0.72 - 1.44
Surgical re-exploration	58 (7.4)	21 (11.7)	1.65	0.97 - 2.79	1.35	0.78 - 2.34
Renal failure	49 (6.3)	19 (10.6)	1.77	1.01 - 3.08	1.34	0.75 - 2.40
Sternal wound infection	8 (1.0)	2 (1.1)	1.08	0.22 - 5.16	1.08	0.22 - 5.33
Septicemia	3 (0.4)	10 (5.6)	15.3	4.16 - 56.1	12.1	3.19 - 45.9
Combined outcome I†	296 (37.9)	73 (40.6)	1.12	0.80 - 1.56	1.01	0.71 - 1.42
Combined outcome II‡	102 (13.0)	36 (20.0)	1.67	1.09 - 2.54	1.36	0.88 - 2.10

Abbreviations: MA = microalbuminuria; n = number; OR = odds ratio; CI = confidence interval
Absolute numbers (%)
* Adjusted for the EuroSCORE
† Combined outcome I included deep sternal wound infection and septicemia
‡ Combined outcome II included deep and superficial sternal wound infection, in addition to septicemia

4.3. Study III

During the 30-day follow-up period, 14 patients died and 1 patient emigrated, leaving 947 patients available for complete long-term follow-up in this study (31–365 days). The distribution of patient and preoperative characteristics for Study III was very similar to that of Study II. However, diabetes was significantly more frequent among patients with microalbuminuria available for long-term follow-up than in patients without microalbuminuria (22% vs. 13%), whereas the estimated glomerular filtration rate was lower (72 [95% CI, 68–77] ml/h vs. 84 [95% CI, 82–87] ml/h).

4.3.1. Associations between microalbuminuria and long-term adverse outcomes

The various associations between microalbuminuria and the long-term outcomes in Study III are displayed in **Table 13.** Microalbuminuria was strongly associated with all-cause death (adjusted HR, 2.3 [95% CI, 1.1–4.9]) when the model was adjusted for the logistic EuroSCORE and the Charlson Comorbidity Index. Although microalbuminuria did not appear to be associated with myocardial infarction/percutaneous coronary intervention, it was associated with a higher risk of stroke (adjusted HR 2.9 [95% CI, 1.1–7.8]). Moreover, microalbuminuria was independently associated with the composite adverse outcome consisting of all-cause death, myocardial infarction/percutaneous coronary intervention, and stroke (adjusted HR, 1.7 [95% CI, 1.0–3.0]), which occurred in 60 (6%) patients.

Microalbuminuria appeared to be associated with an increased risk of severe infections. Although the first composite outcome regarding severe infection (deep sternal wound infection or septicemia) did not reach statistical significance (adjusted HR, 2.0 [95% CI, 0.6–6.8]), the point estimate remained unchanged when events of superficial sternal wound infection alone (adjusted HR, 2.3 [95% CI, 1.0 - 5.5]) or in combination with leg wound infection (adjusted HR, 2.4 [95% CI, 1.2–4.9]) were added to the combined infection outcome. No further adjustment of other patient characteristics or postoperative medication use changed the risk estimates substantially.

The adjusted relationship between the continuous UACR and the risk of all-cause death was significant. Each 1 mg/mmol increment in UACR was associated with an increased OR of 1.12 [95% CI, 1.03–1.18]. However, in a continuous spline function, we found no specific UACR cut-off level associated with an increased risk of postoperative all-cause death.

Table 13. Hazard ratios of adverse outcomes according to the presence of microalbuminuria

Outcomes	Number of events		Crude model		Adjusted model*	
	- MA n = 772	+ MA n = 175	HR	95 % CI	HR	95 % CI
All-cause death	17 (2.2)	14 (7.8)	3.7	1.8 - 7.5	2.3	1.1 - 4.9
MI/PCI	19 (2.4)	3 (1.7)	0.7	0.2 - 2.3	0.5	0.2 - 2.0
Stroke	9 (1.2)	6 (3.3)	3.0	1.1 - 8.3	2.9	1.1 - 7.8
All-cause death, MI/PCI or stroke	40 (5.1)	20 (11.1)	2.2	1.3 - 3.8	1.7	1.0 - 3.0
Severe infections 1†	8 (1.02)	6 (3.3)	3.3	1.2 - 9.6	2.0	0.6 - 6.8
Severe infections 2‡	16 (2.1)	12 (6.7)	3.4	1.6 - 7.1	2.3	1.0 - 5.5
Severe infections 3§	21 (2.7)	16 (8.9)	3.4	1.8 - 6.6	2.4	1.2 - 4.9

Abbreviations: MA = microalbuminuria; HR = hazard ratio; n = number; CI = confidence interval; MI = myocardial infarction; PCI = percutaneous coronary intervention

Absolute numbers (%)

*Adjusted for the EuroSCORE and Charlson Comorbidity Index

†Severe infections 1 includes deep sternal wound infection and septicemia

‡Severe infections 2 includes deep and superficial sternal wound infection, in addition to septicemia

§Severe infections 3 includes deep and superficial sternal wound infection, leg wound infection, and septicemia

4.3.3. Risk prediction

Table 14 shows the discrimination analysis for microalbuminuria, EuroSCORE, Charlson Comorbidity Index alone, and for the multivariate models regarding all-cause death.

Considering the other study outcomes, analysis for microalbuminuria alone reached 0.52 [95% CI, 0.45–0.60] for myocardial infarction/percutaneous coronary intervention, 0.61 [95% CI, 0.48–0.74] for stroke, and 0.63 [95% CI, 0.55–0.71] for the third composite severe infection outcome (consisting of septicemia, deep or superficial sternal wound infection, and leg wound infection).

Hosmer–Lemeshow tests for calibration showed good agreement for both the multivariate logistic regression models including i) EuroSCORE + microalbuminuria (p = 0.19, chi^2 = 4.7) and ii) EuroSCORE + microalbuminuria + Charlson Comorbidity Index (p = 0.47, chi^2 = 2.6).

Table 14. Areas under receiver operating characteristic curves regarding all-cause mortality

	All-cause death	
Models	AUC	95 % CI
Microalbuminuria	0.64	0.55 - 0.73
EuroSCORE	0.73	0.65 - 0.81
Charlson Comorbidity Index	0.70	0.63 - 0.78
EuroSCORE and microalbuminuria	0.76	0.68 - 0.83
EuroSCORE, microalbuminuria and Charlson Comorbidity Index	0.78	0.71 - 0.85

Abbreviations: AUC = area under curve; CI = confidence interval

4.4. Study IV

4.4.1. Study cohort and surgical characteristics

From the MIIPPCar database, we included 836 non-diabetic patients for short-term (30 days) and long-term (31–365 days) follow-up analysis. The overall study baseline patient characteristics and their correlations with HOMA and adiponectin are shown in **Table 15**. For insulin resistance, the upper quartile included HOMA levels above 2.6. For adiponectin, the upper quartile included adiponectin values above 11.7 mg/L.

4.4.2. Insulin resistance and postoperative adverse outcomes

There was no difference between the upper quartile and the 3 lower quartiles of HOMA regarding the median length of stay in the ICU (difference, 0.02 days [95% CI, -0.08–0.12]) or total hospital stay (difference, 0.20 days [95% CI, -0.21–0.61]). Furthermore, patients in the upper adiponectin quartile stayed 0.15 (95% CI, 0.04–0.26) days longer in the ICU, and 0.73 (95% CI, 0.27–1.19) days longer in their total hospital stay compared to the lower adiponectin quartiles, upon being adjusted for the logistic EuroSCORE model.

The associations between the HOMA quartiles and the study outcomes at both short- and long-term follow-ups are displayed in **Table 16**. Increased HOMA values (making up the top quartile) were not significantly associated with postoperative mortality when compared to the values making up the lower 3 quartiles (30-day adjusted OR, 1.7 [95% CI, 0.5–5.7] and 31–365-day adjusted OR, 1.7 [95% CI, 0.7–3.3]) (**Figure 7**). For early postoperative infections, the OR was 1.5, but this value did not quite reach statistical significance. In addition, the upper HOMA quartile was not associated with other individual or combined outcomes. Similarly, comparing groups above and below the median HOMA value showed statistically insignificant associations between HOMA and the outcomes. Furthermore, analyzing HOMA as a continuous spline function revealed no specific threshold values in the association with all-cause death.

Table 15. Baseline and preoperative patient characteristics

Clinical features	Total sample N=836	HOMA *r*	HOMA *p*-value	Adiponectin *r*	Adiponectin *p*-value
Male gender	607 (73)	0.14	<0.01	-0.32	<0.01
Age (years)	68 [59-75]	-0.06	0.08	0.15	<0.01
Body Mass Index (kg/(m)^2)	27 [24-30]	0.50	<0.01	-0.38	<0.01
Current smoker	147 (18)	<0.01	0.99	-0.06	0.09
Hypertension	465 (56)	0.05	0.18	-0.02	0.50
Ejection Fraction < 50 %	177 (21)	<0.01	0.87	-0.02	0.48
Myocardial infarction	192 (23)	0.12	<0.01	-0.15	<0.01
Stroke	79 (9)	0.06	0.06	0.03	0.33
EuroSCORE	4.4 [2.2-7.8]	-0.15	<0.01	0.29	<0.01
Charlson Comorbidity Index		0.05	0.18	0.07	0.05
Low	285 (34)				
Medium	432 (52)				
High	119 (14)				
Paraclinics					
Creatinine (mmol/liter)	81 [68-98]	0.03	0.33	<0.01	0.99
UACR (mg/mmol)	0.7 [0.1-1.8]	-0.05	0.13	0.16	<0.01
Microalbuminuria	146 (18)	-0.08	0.02	0.20	<0.01
eGFR (ml/minute)	81 [61-105]	0.23	<0.01	-0.33	<0.01
Glucose (mmol/liter)	5.4 [5.1-5.8]	0.52	<0.01	-0.19	<0.01
Insulin (pmol/liter)	44 [30-71]	0.99	<0.01	-0.42	<0.01
HOMA	1.6 [1.0-2.6]			-0.42	<0.01
Adiponectin (mg/liter)	8.0 [5.6-11.7]	-0.42	<0.01		
Medicine					
RAS inhibitors	297 (36)	0.08	0.02	-0.01	0.62
Beta blockers	521 (62)	0.14	<0.01	-0.22	<0.01
Statins	526 (63)	0.16	<0.01	-0.23	<0.01
Antiplatelets	337 (40)	0.08	0.02	-0.06	0.07
Procedure					
Bypass alone	326 (39)	0.16	<0.01	-0.34	<0.01
Valve alone	258 (31)	-0.12	<0.01	0.22	<0.01
Bypass & Valve	131 (16)	0.01	0.81	0.08	0.02
Others	121 (14)	-0.07	0.03	0.10	<0.01
Procedure related					
ECC (minutes)	91 [68-124]	-0.04	0.19	0.14	<0.01
CCT (minutes)	57 [40-79]	-0.08	0.01	0.20	<0.01

Abbreviations: UACR = urinary albumin creatinine ratio; eGFR = estimated glomerular filtration rate; HOMA = homeostasis model assessment; RAS = renin angiotensin system; ECC = extracorporal circulation; CCT = cross clamp time; N = number; *r* = correlation coefficient. Medians [interquartile range] or absolute numbers (%)

Table 16. Short- and long-term odds ratios considering insulin resistance

	HOMA quartiles		Short-term follow-up			
	I – III	IV	Crude		Adjusted*	
	n = 627	n = 209	OR	95 % CI	OR	95 % CI
Death	8 (1.3)	4 (1.9)	1.5	1.0-9.6	1.7	0.5-5.7
MI/PCI	15 (3.4)	5 (3.4)	1.0	0.5-2.8	1.0	0.4-2.8
Stroke	23 (3.7)	8 (3.8)	1.0	0.5-2.4	1.1	0.5-2.5
Renal failure[†]	39 (6.2)	16 (7.7)	1.2	0.7-2.3	1.4	0.7-2.7
Re-exploration	54 (8.6)	22 (10.5)	1.2	0.7-2.1	1.3	0.8-2.2
Infections	27 (4.3)	13 (6.2)	1.5	0.7-2.9	1.5	0.8-3.0
CVD composite	44 (7.0)	16 (7.7)	1.1	0.6-2.0	1.1	0.6-2.1
	HOMA quartiles		**Long-term follow-up**			
	I – III	IV	Crude		Adjusted[‡]	
	n = 619	n = 205	OR	95 % CI	OR	95 % CI
Death	20 (3.2)	10 (4.9)	1.5	0.7-3.3	1.7	0.7-3.8
MI/PCI	18 (2.9)	4 (2.0)	0.7	0.2-2.0	0.6	0.2-1.8
Stroke	12 (1.9)	1 (0.5)	0.2	0.1-1.9	0.3	0.1-2.0
Infections	20 (3.2)	8 (3.9)	1.2	0.5-2.8	1.2	0.5-2.9
CVD composite	45 (7.3)	14 (6.8)	0.9	0.5-1.7	0.9	0.5-1.7

Abbreviations: CVD = cardiovascular disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; n = number; OR = odds ratio; CI = confidence interval

* Adjusted for the EuroSCORE

[†] Adjusted for the EuroSCORE and estimated glomerular filtration rate

[‡] Adjusted for the EuroSCORE, Charlson Comorbidity Index, and type of surgery

Short-term is defined as 30-day follow-up

Long-term is defined as the follow-up from day 31 until day 365

4.4.3. Adiponectin and postoperative adverse outcomes

As displayed in **Table 17,** adiponectin was not apparently associated with any of the short-term postoperative outcomes, except renal failure (adjusted OR, 1.8 [95% CI, 1.0–3.3]). In contrast, high levels of circulating adiponectin were positively associated with all-cause death that occurred in the 31–365-day window (adjusted OR, 2.9 [95% CI, 1.3–6.4]) in patients in the upper quartile relative to patients in the lower 3 quartiles (**Figure 8**). Furthermore, the increased risk of the combined cardiovascular outcome in the highest adiponectin quartile (adjusted OR, 1.7 [95% CI, 0.9–3.1]) was primarily driven by all-cause mortality, as there were no strong associations between adiponectin and myocardial infarction/percutaneous coronary intervention or stroke. Comparison of groups above and below the median adiponectin level (data not shown) indicated an even higher mortality risk (adjusted OR, 4.4 [95% CI, 1.6–12.1]). Otherwise, using the median cut-off strategy did not reveal substantially different results than those from the primary analyses. When considered as a continuous variable, each 1-mg/L increase in adiponectin was associated with a 1.12-increased [95% CI, 1.08–1.16] adjusted OR for all-cause death. In the spline regression model, we could not determine any specific cut-off level for adiponectin.

Table 17. Short- and long-term odds ratios considering adiponectin

	Adiponectin quartiles		Short-term follow-up			
	I – III	IV	Crude		Adjusted*	
	n = 627	n = 209	OR	95 % CI	OR	95 % CI
Death	10 (1.6)	2 (1.0)	0.6	0.4-5.7	0.4	0.1-2.0
MI/PCI	15 (2.4)	5 (2.4)	1.0	0.4-2.8	1.0	0.3-2.7
Stroke	20 (3.2)	11 (5.3)	1.7	0.8-3.6	1.5	0.7-3.3
Renal failure[†]	33 (5.3)	22 (10.5)	2.1	1.2-3.7	1.4	0.7-2.7
Re-exploration	54 (8.6)	22 (10.5)	1.2	0.7-2.1	0.9	0.6-1.9
Infections	29 (4.6)	11 (5.3)	1.1	0.6-2.3	1.0	0.5-2.1
CVD composite	43 (6.9)	17 (8.1)	1.2	0.7-2.2	1.0	0.6-1.9
	Adiponetin quartiles		**Long-term follow-up**			
	I – III	IV	Crude		Adjusted[‡]	
	n = 617	n = 207	OR	95 % CI	OR	95 % CI
Death	13 (2.1)	17 (8.2)	4.2	2.0-8.7	2.9	1.3-6.4
MI/PCI	18 (2.9)	4 (1.9)	0.7	0.2-2.0	0.7	0.2-2.1
Stroke	8 (1.3)	5 (2.4)	1.9	0.6-5.8	1.4	0.4-4.5
Infections	18 (2.9)	10 (4.8)	1.7	0.8-3.7	1.1	0.5-2.6
CVD composite	36 (5.8)	23 (11.1)	2.0	1.2-3.5	1.7	0.9-3.1

Abbreviations: CVD = cardiovascular disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; OR = odds ratio; n = number

* Adjusted for the EuroSCORE

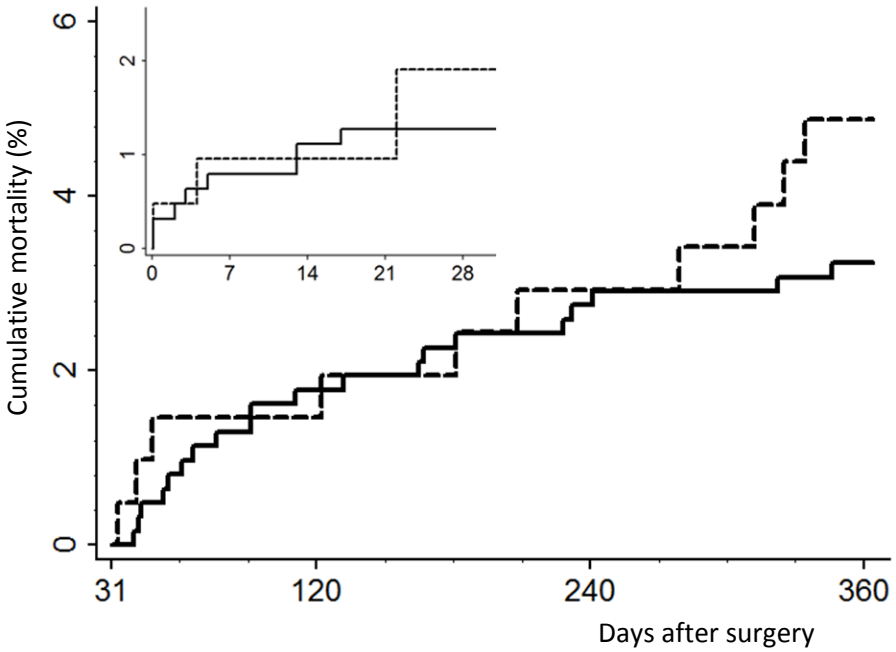
[†] Adjusted for the EuroSCORE and estimated glomerular filtration rate

[‡] Adjusted for the EuroSCORE, Charlson Comorbidity Index, and type of surgery

Short-term is defined as 30-day follow-up

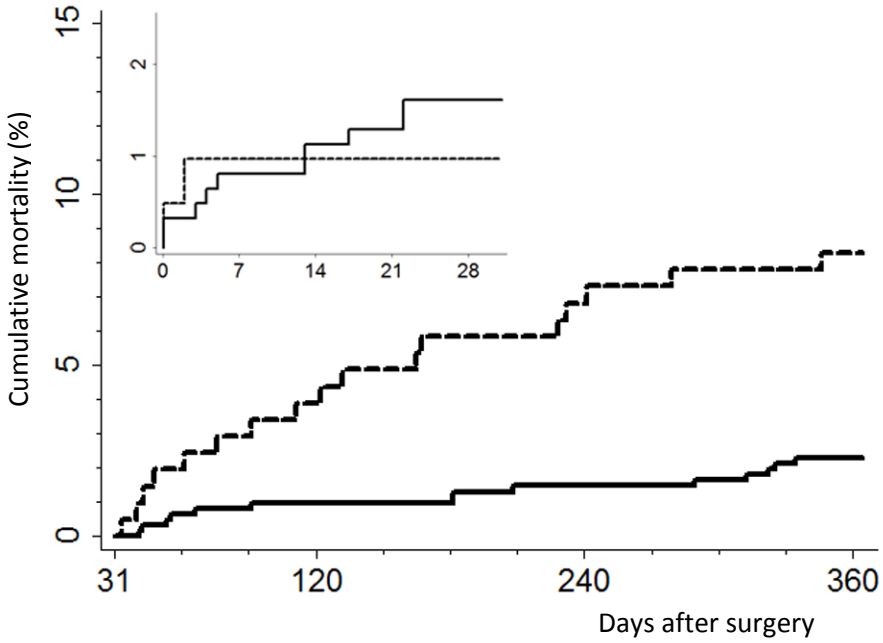
Long-term is defined as the follow-up from day 31 until day 365

Figure 7. Cumulative mortality according to insulin resistance quartiles



Dashed lines = insulin resistance quartile IV; Solid lines = insulin resistance quartiles 1–3
X-axes = days after surgery; Y-axes = cumulative mortality

Figure 8. Cumulative mortality according to adiponectin quartiles



Dashed lines = adiponectin quartile IV; Solid lines = adiponectin quartiles 1–3
X-axes = days after surgery; Y-axes = cumulative mortality

4.4.4. Predictive values of HOMA, adiponectin and the EuroSCORE

The AUC values concerning mortality are shown in **Table 18**. Of note, the AUC was 0.84 [95% CI, 0.75–0.93] for the logistic EuroSCORE regarding short-term mortality and 0.75 [95% CI, 0.67–0.83] for long-term mortality. HOMA did not predict mortality. In contrast, the AUC for adiponectin was 0.75 [95% CI, 0.65–0.85] regarding long-term mortality. Moreover, in a model including both the EuroSCORE and adiponectin factors, the AUC reached 0.78 [95% CI, 0.68–0.88]. In a model with only HOMA and adiponectin, a similar AUC was achieved, and when the EuroSCORE was subsequently added, the AUC increased to 0.81 [95% CI, 0.73–0.89]. Lastly, adding the Charlson Comorbidity Index to the model further increased the AUC to 0.86 [95% CI, 0.81–0.92]. There were no interactions between sex and insulin resistance or adiponectin with regard to the risk of any postoperative outcomes. Hosmer–Lemeshow tests revealed acceptable model fits for the logistic regressions.

Table 18. Areas under receiver operating curves characteristics on all-cause death

	Short-term follow-up		**Long-term follow-up**	
	AUC	**95 % CI**	**AUC**	**95 % CI**
Logistic EuroSCORE	0.84	0.75-0.93	0.75	0.67-0.83
HOMA continuous	0.55	0.36-0.75	0.47	0.34-0.60
HOMA quartiles	0.54	0.40-0.68	0.54	0.46-0.63
ADPN continuous	0.53	0.38-0.68	0.75	0.65-0.85
ADPN quartiles	0.54	0.43-0.65	0.66	0.57-0.76
Logistic EuroSCORE + HOMA continuous	0.84	0.76-0.92	0.77	0.70-0.84
Logistic EuroSCORE + HOMA quartiles	0.77	0.65-0.90	0.76	0.69-0.82
Logistic EuroSCORE + ADPN continuous	0.82	0.68-0.95	0.78	0.68-0.88
Logistic EuroSCORE + ADPN quartiles	0.83	0.70-0.96	0.76	0.68-0.85
HOMA and ADPN continuous			0.77	0.68-0.86
Logistic EuroSCORE + HOMA and ADPN continuous			0.81	0.73-0.89
Logistic EuroSCORE + HOMA and ADPN continuous + Charlson Comorbidity Index			0.86	0.81-0.92

Abbreviations: ADPN = adiponectin; HOMA = homeostasis model assessment; AUC = area under curve; CI = confidence interval

5. Methodological strengths and limitations

In Study I, we aimed to examine the predictive performance of the logistic EuroSCORE model in the context of 30-day mortality in patients who underwent on-pump cardiac surgery in Western Denmark during a period from January 1999 to March 2010. In Studies II–IV, we assessed the associations between 3 individual cardio-metabolic risk markers and adverse outcomes following elective cardiac surgery, and subsequently assessed the value of these markers in predicting risk following cardiac surgery. The reported findings could be prone to systematic errors (bias or confounding) or random error (chance), which should be taken into account when interpreting the results.

5.1. Selection bias

Selection bias arises from 1 or more issues that systematically affect participation in a cohort study, either at the time of patient inclusion or during the follow-up period [205].

5.1.1. Selection bias at inclusion

In Study I, only a few patients were omitted from analysis due to missing data (0.9%). Of note, this group of patients was similar to the overall studied group in terms of age, gender, and the types of surgery performed, which indicates that missing data values likely did not introduce noteworthy selection bias.

For Studies II–IV, a study nurse that worked half time performed both screening and inclusion of patients the day before the scheduled surgery. Consequently, only about 50% of the potential candidates for the study were screened. Preoperative urine and blood samples were collected on the day of surgery (between 6 and 11 a.m.). However, the screening and inclusion of patients in the study were performed prospectively and without knowledge of the prognostic factors to be studied. The selection of patients and the collection of urine and blood samples at different times would most likely cause a non-differential misclassification, if they had any effect at all. Likewise, surgeons and physicians responsible for in-hospital patient treatment had no information on the microalbuminuria, HOMA, or adiponectin level statuses of their patients, nor did they influence patient selection. We excluded 54 patients from analysis due to failures in the UACR analysis, but we found no indications of a skewed distribution of comorbidity in this excluded group compared to the included patients. Furthermore, no substantial changes in medical or surgical treatment policies were introduced during the inclusion period.

5.1.2. Selection bias during follow-up

In Study I, we did not assess emigration (loss to follow-up) before day 30, but this proportion would most likely be negligible and would not introduce bias into our analyses. In Studies III and IV, only 1 patient was lost to follow-up due to emigration in the long-term follow-up study.

When assessing morbidity in the long-term follow-up studies, we used competing risk analyses to control for potential bias introduced by excess mortality in any of the groups studied (Studies III and IV). In the short-term follow-up period, the number of deaths was small, and thus, it will most likely not affect comparability between groups regarding morbidity.

5.2. Information bias

Information bias is systematic error in measuring the exposure or outcome that leads to improper patient categorization (also called misclassification bias) [205]. Such misclassification may be differential or non-differential. A differential misclassification bias is introduced when an interdependent distribution of exposure and outcome status exists. However, in non-differential misclassification bias, the improper measurement results in an independent distribution between exposure and outcome status. In general, a non-differential misclassification of a dichotomous exposure tends to change the estimate of association toward the null hypothesis. In contrast, a differential misclassification can introduce changes in any direction away from the null hypothesis [205].

The studies included in this thesis were all based on prospectively collected data on both the studied prognostic factors and the covariates and outcomes, which minimized the risk of introducing information bias.

Study I

Information on the EuroSCORE was available for the majority of patients included in Study I. However, the EuroSCORE registration process changed during the study period. Before 2006, when the EuroSCORE registration module was electronically opened, an unregistered risk factor was merely considered as reference. This fact may have introduced some misclassification, as information on risk factors may have been missing more often for the emergency patients. Therefore, the EuroSCORE risk prediction may have been underestimated during the early study period for some of the patients, and consequently, the presented E/0 ratios may have been conservative estimates for this period.

The dates of death registered in the Civil Registration System can be assumed to be without error, or at most to contain very limited non-differential misclassification that would not impact the observed 30-day mortality.

Studies II–IV

The UACR and insulin levels have previously been shown to have high 24-h intra-individual variations, whereas adiponectin circulates in more stable concentrations [125,206,207]. Therefore, the one-time measurement of exposure levels could potentially have introduced misclassification in this study. Using preoperative fasting blood samples collected in a relatively narrow time frame would intuitively tend to reduce the risk of any non-differential misclassification. Furthermore, results from one-time measurement of the UACR and HOMA analysis have been shown to correlate well with the results from their corresponding gold standards, namely the 24-h urine sample and the hyperinsulinemic euglycemic clamp method, respectively [125,206].

The Danish National Registry of Patients had acceptable positive predictive values for various conditions (e.g., myocardial infarction, stroke, and atrial fibrillation) [208-211]. However, both septicemia and deep sternal wound infection were more challenging clinical diagnoses that were prone to potential misclassification. For both outcomes, external reviewers (blinded to exposure levels) performed validation of the diagnoses. Moreover, the incidences of septicemia and surgical re-exploration were comparable to the prevalence seen in other studies, and thus indicates that missing information was sparse [212,213]. In any case, the processes leading to generation of missing information and to registering outcome diagnoses would most likely be independent of the exposure levels. Nevertheless, information bias may be present if the exposure level (or related covariates) is associated with the likelihood of having outcome diagnosis (also called measurement bias).

5.3. Confounding

If the presence of a covariate is imbalanced between exposures, and is associated with both the exposure and outcome without being an intermediate step on the causal pathway, it holds potential for confounding the estimate of association [205].

Study I

Due to the design and aim of Study I, it seems unlikely that confounding could have any influential impact the study results or conclusions. However, improvements in surgical techniques and patient care over time could be considered as potential confounders, and this may have impacted the

performance of the EuroSCORE. Calendar time may be considered a proxy variable for these potential confounders. However, these changes should not be regarded as traditional confounders, since the present study aimed to examine the EuroSCORE performance over calendar time.

Studies II–IV

Information obtained from the case-report-form and the population-based registries allowed examination of several potential confounding covariates. In particular, Studies II and III might be subject to confounding since differences in baseline covariates were common in these studies (e.g., patients with microalbuminuria were older, and had different comorbidity profiles and types of procedures performed).

However, in the short-term follow-up periods, the possibility for adjustment of multiple potential confounding factors using regression analyses or stratification was limited, as the outcomes (i.e., mortality and septicemia) were rare. Therefore, we used the summarized information on covariates contained in the EuroSCORE for adjustment of the association between exposure and the outcomes. However, some risk factors included in the EuroSCORE (e.g., recent myocardial infarction, extracardiac arteriopathy, neurological dysfunction, serum creatinine, left ventricular ejection fraction, and critical preoperative state) could be considered intermediate steps between exposure and outcome. Thus, adjusting for the EuroSCORE may have led us to underestimate the true association between the studied exposures and the clinical outcome.

In the long-term follow-up studies (Studies III and IV), the incidences of outcomes were higher, and allowed for adjustment of more than 1 (2 or 3) covariate. Several constellations of covariate adjustment (including the potential confounding effect of varying postoperative medical treatment) were performed. Taking into account the limited number of outcomes in Studies II–IV, the EuroSCORE alone or in combination with the Charlson Comorbidity Index (in combination with the type of surgery for Study IV) appeared to adjust effectively for confounding, since further addition of any individual potential confounder did not change the point estimate substantially. Nevertheless, we cannot entirely rule out residual confounding from unmeasured or misclassified risk factors, or over-adjustment caused by intermediate factors.

5.4. Random error

Random error unsystematically impacts study estimates and thus resists prediction [205]. However, the magnitude of the influence of random error is related to the study sample size. Small studies are susceptible to randomly skewed distributions of covariates, whereas increases in study size tend to balance out random misclassifications of covariates, whereas increases in study size will

balance out random misclassifications of covariates [205]. In other words, random error is associated with the precision of a study, which is reflected by the statistical CIs.

Study I

Study I included a large patient cohort undergoing cardiac surgery. However, in order to assess temporal changes in the performance of the EuroSCORE, the overall study group was divided into minor cohorts. Unfortunately, this process reduced the precision obtained in each group, as illustrated by overlapping CIs for estimated and observed mortality, but it was necessary for the purposes of this study.

Studies II–IV

A power analysis based on data in existing literature was performed prior to inclusion commencement, and it suggested that approximately 1,000 patients would hold a 94% statistical power for identifying a relative risk of ≥2. We assumed a 25% exposure prevalence and a 15% cumulative incidence of a composite outcome. However, both the prevalence of microalbuminuria and the incidence of the adverse outcomes were lower than expected. These findings had a negative influence on our ability to reach statistically significant associations, as demonstrated by the width of the 95% CIs used to report the precision of the estimates throughout the present thesis. Accordingly, the major limitation to Studies II–IV was the precision of our estimates.

6. Discussion

6.1. Study I

Upon comparison of the individual EuroSCORE risk factors between the original EuroSCORE study and the overall Western Denmark Heart Registry population, we found that substantial differences in the prevalence of risk factors were present. Furthermore, when categorized into biennial periods, we documented time trends in the prevalence of the risk factors. These observations are consistent with previous results from registries in other European countries [53,80].

The results from this population-based cohort study suggest that the EuroSCORE overestimated mortality across all levels of estimated risk and types of surgical procedures performed. Moreover, this overestimation appeared to gradually increase over time, i.e. for solitary valve and combined procedures.

The overestimation in mortality (2-fold for the overall population) was greater for valve procedures (up to 5-fold) than for bypass procedures (approximately 2- to 3-fold in recent years). Previous reports by Wendt et al. and Barili et al. documented similar substantially overestimated mortality following aortic valve replacement [85,86], but other studies have found a more moderate overestimation (approximately 2-fold) [52,56]. In a metaanalysis, Parolari et al. reported a 4-fold overestimation of mortality for CABG performed in 1999–2008 [59]. However, this analysis included studies assessing both in-hospital and 30-day mortality, and therefore it tended to augment the EuroSCORE mortality overestimation. Nevertheless, the results from the analysis were in line with those previously reported in a Norwegian study by Engebretsen et al., who found a substantial overestimation of mortality among CABG patients [47]. The present study was comprised of data gathered up to 2010. In contrast, most comparable studies have not included data on patients operated on later than 2007, and have not examined possible changes in risk factors and the performance of the EuroSCORE over time. Therefore, direct comparison across studies faces some limitations, but in general, our up-to-date results are in line with the interpretation of previous studies. In 2004, a meta-analysis by Gogbashian et al. concluded that the additive EuroSCORE model underestimated mortality in high-risk patients [46]. Other studies revealed that the logistic EuroSCORE model improved precision in this group of patients relative to the output of the additive EuroSCORE model [32,214] However, consistent with other studies [35,215], our data suggested that the logistic EuroSCORE overestimated mortality also in high-risk patients.

The Hosmer–Lemeshow test showed poor calibration in the overall dataset and in the data for the surgical subgroups. However, despite overestimation of mortality, varying degrees of acceptable model fit were found in surgical subgroups assessed in biennial periods. In large cohorts, the Hosmer–Lemeshow test becomes sensitive to small and potentially less clinically important deviations from the estimated risk (resulting in *p*-values that indicate poor model fit). On the contrary, smaller sample sizes may show good model fit, but at the same time allow skewed risk prediction with potential substantial clinical importance. Therefore, it is recommended that Hosmer–Lemeshow calibration tests be supported by additional breakdown tables that show the absolute estimates of predicted and observed risk at varying levels of risk.

The overall discriminative accuracy of mortality in this study was comparable to that of the original EuroSCORE study (AUC, 0.79). We found some indications that the discriminative accuracy may have improved over the years (AUC was 0.76 in 1999 and up to 0.81 in 2010). Upon stratification of the patients according to surgery type, this pattern was most pronounced for bypass procedures either isolated (AUC was 0.71 in 1999 and up to 0.84 in 2010) or in combination with aortic valve replacement (AUC was 0.56 in 1999 and up to 0.82 in 2010). In accordance with earlier studies, the EuroSCORE generally reached a somewhat lower discriminative accuracy which remained approximately unchanged over time for isolated aortic valve replacement [42,51,52]. This finding may be explained by the fact that the vast majority (approximately 95%) of patients included in the developmental EuroSCORE dataset underwent CABG, and thus the model would likely tend to perform best in bypass patients.

Despite substantial changes in the constellation of preoperative risk (i.e., age and types of surgery), the progressively increased risk apparently failed to translate into increased 30-day mortality. In fact, the short-term mortality tended to decrease, which suggests that the quality of patient care has likely improved considerably. In recent times, elderly patients (above 80 years in age) and high-risk patients with severe comorbidity or procedural challenges can also face cardiac surgery with an acceptable level of risk. However, applying the estimated probabilities to individual patients should be carried out with caution. In each case, an individual subjective clinical risk assessment and interdisciplinary treatment strategy remain crucial.

Traditional open heart surgery faces challenging competition from less invasive procedures, such as acute and elective percutaneous coronary intervention as well as transapical or percutaneous implantation of stent heart valves. For proper risk stratification, informed patient consent, and quality improvement tools, it is important to have up-to-date knowledge on both predicted and

observed patient risk. From this perspective, the present study emphasizes the need for re-calibration or revision of the EuroSCORE, perhaps with inclusion of new markers of risk.

Comparison of the performance between different risk-prediction models was not possible, since the EuroSCORE was adopted as the primary model registered in the Western Denmark Heart Database. A valid reconstruction of other models than the EuroSCORE (e.g., the Society of Thoracic Surgeons and Parsonnet) based on registry linkage would meet limitations, since not all specific risk-factors could be properly reconstructed. Therefore, for the purpose of this thesis, I focused mainly on the EuroSCORE, which is also predominantly used as the European standard model. However, it should be recognized that the American Society of Thoracic Surgeons Adult Cardiac Surgery Database contains valuable data for risk-prediction. However, limitations exists, as the registration into is voluntary and information on 30-day mortality is not independently accessible through automated registry linkage, and must often be manually collected from readmission records, lab records, or through contact to cardiologist for follow-up information, or when possible through contact to the patient [216].

6.2. Studies II–IV

The 30-day mortality in these studies (approximately 1.5%) was considerably lower than estimated by the EuroSCORE, even if an expected 2-fold overestimation by the EuroSCORE was taken into account. This observation confirms that elective cardiac surgery performed at the Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, Skejby, is of high international standard.

For other outcomes measures, the 30-day postoperative cumulative incidences were in agreement with previous international findings on stroke (4%) [217,218], myocardial infarction or percutaneous coronary intervention (3%) [219], renal failure (7–8%) [220], deep sternal wound infection (1%) [212,221], and septicemia (1%) [221]. However, surgical re-exploration (8–9%) was more frequent in this study compared to that reported in another study [222], which may likely be explained by 3 factors; i) our inclusion of not only re-explorations due to hemorrhage, but also ischemia and redone procedures; ii) more combined procedures performed in the present study; and iii) more complete follow-up after hospital discharge in the present study [222]. Finally, mortality in the 31–365-day follow-up period (approximately 3.2%) was in agreement with that reported by other authors [223].

Microalbuminuria, insulin resistance and adiponectin were not assessed in the EuroSCORE study, since any potential association with adverse outcomes following cardiac surgery had not been examined. Since then, in other settings, they have proven to be associated with an increased risk

of cardiovascular disease, diabetes and mortality. A discussion of our results regarding microalbuminuria, insulin resistance and adiponectin follows below.

6.2.1. Studies II and III - *microalbuminuria*

To our knowledge, this was the first study to examine whether microalbuminuria assessed preoperatively is a clinically useful predictor of adverse outcomes following elective cardiac surgery. One previous study performed in diabetic patients undergoing elective cardiac surgery (CABG only) between 1996 and 1999 assessed whether preoperative measurement of microalbuminuria was associated with adverse outcomes, but the study did not address its value as a tool of risk prediction [115]. In the present study, we included both patients with and without diabetes, which at least partly explains why our population had a lower prevalence of microalbuminuria compared to the level reported in a study by Yorgancioglu et al. (19% vs. 35%) [115]. There were also other discrepancies between the 2 study populations simply due to temporal changes in medical treatment strategies. For instance, the overall frequency of use of antihypertensive drugs, and especially the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists, which are both known to reduce urine albumin excretion, has markedly increased over time. In our study, 42% of patients used renin angiotensin inhibitors, whereas only 24% of patients reported in the Yorgancioglu et al. study used these treatments (data on angiotensin II receptor antagonists not shown) [115].

Like Yorgancioglu et al., we also found a positive crude association between microalbuminuria and risk of 30-day mortality (although the estimate by Yorgancioglu et al. did not quite reach statistical significance) [115]. However, contrary to their study, we adjusted for potential confounding and thereafter found no association. Nevertheless, during the long-term follow-up, our results indicated an approximately 2.5-fold increased adjusted risk of all-cause death, which may be in line with the unadjusted estimate (2.6-fold increase) at a 2-year follow-up reported by Yorgancioglu et al. [115]. Likewise, the length of ICU stay was prolonged among microalbuminuric patients in both studies. However, we did not identify previous studies that examined the possible association between postoperative infections at the sites of incision or graft harvest and microalbuminuria. Yorgancioglu et al. reported only a few in-hospital wound infections in their study, and no infections among patients with microalbuminuria [115].

Several studies have shown that the UACR is increased in relation to a host defense response to acute conditions such as myocardial infarction, stroke, pancreatitis, and sepsis [93]. While microalbuminuria has also been suggested to hold promising predictive value for the severity of disease among ICU patients [224], it has not been previously determined whether microalbuminuria

(as measured before a surgical intervention or presentation of an infectious disease) is associated with and upholds valuable predictive information on the risk of developing severe infection and septicemia, as is suggested by our results. In a recent study, Basu et al. found a higher prevalence of microalbuminuria among patients upon ICU admission, which then persisted longer among non-surgical patients with septicemia during the ICU stay than among patients without septicemia [224]. Furthermore, in line with our results, this previous study also showed that microalbuminuria measured upon admission had moderate discriminative accuracy (AUC, 0.70) in predicting septicemia. According to the Steno hypothesis [97], microalbuminuria reflects systemically increased transendothelial permeability, which when thinking outside the fields of cardiology and nephrology could also potentially render the defense systems vulnerable to the onslaught of intruding microorganisms.

6.2.2. Study IV - *insulin resistance and adiponectin*

Preoperative assessment of insulin resistance in a non-diabetic cohort and its relation to risk and prognosis following cardiac surgery have not been uncovered previously. Only recently, intraoperative insulin resistance was associated with an approximately 2-fold increased risk of major complications following cardiac surgery [148]. On the contrary, in our study, the patients with the highest quartile of insulin resistance did not experience higher adverse event rates for any of the individual or composite outcomes compared with the outcomes of patients in the lower quartiles. In a previous study by Sato et al., the strongest associations were found in patients with overt diabetes, which is at least in part a possible explanation for the apparent differences [148].

Likewise, when it was adjusted for potential confounding, adiponectin was not significantly associated with the short-term patient outcomes. However, an association between adiponectin and long-term mortality may exist, but the strength of the association remains unclear and causality is difficult to infer. Previous studies have suggested that the effect of adiponectin is mediated through improved insulin sensitivity [164]. However, in this study, insulin sensitivity itself did not appear statistically significantly associated with long-term mortality, which indicates that this potential causal pathway for the adiponectin-insulin induced association seems less likely. Other biological roles of adiponectin have been proposed; its apparent impact on subclinical inflammation could constitute an alternative explanation for a causal pathway. However, as described in the Introduction section of this thesis, the biological roles of adiponectin are only to some extent understood, and are far from completely settled. The present study design does not allow us to infer any causality regarding the association between adiponectin and long-term mortality. Despite this, and partly in line with inconsistencies among previous study results, our study adds support to the notion that the role of adiponectin, causal or not, varies among certain constellations of

comorbidity. As in the case of the full biological importance of adiponectin, the reason(s) for the apparent inconsistent direction of associations with adverse outcomes remains unsettled. It was previously speculated that associations between high adiponectin levels and increased risk may be explained by a reduced glomerular filtration rate [225]. However, such associations were not found in our study, as no differences existed in the glomerular filtration rates or serum creatinine levels among patients in the upper and lower adiponectin quartiles, and since adjustment for the glomerular filtration rate did not change the strength of the association.

Not surprisingly, when considering 30-day mortality prediction, the levels of insulin resistance and adiponectin assessed individually did not reach discriminative accuracy beyond the probability of tossing a coin, and therefore apparently play no role in the preoperative risk prediction. Nevertheless, we found some indications that adiponectin alone or in combination with insulin resistance could improve the long-term discriminative accuracy of mortality beyond the EuroSCORE (AUC, 0.75 vs. 0.81).

7. Conclusions

7.1. Study I

The EuroSCORE overestimated 30-day mortality independent of the type of major cardiac surgical procedure performed, as well as across all levels of estimated risk. Most notably, for heart valve procedures alone or in combination with CABG, the E/O mortality ratio increased during the last 11 years of cardiac surgery registered in Western Denmark. Thus, the present EuroSCORE model now requires recalibration for obtaining accurate output. Similarly, future acknowledged risk prediction models should be continuously validated and perhaps recalibrated.

7.2. Study II

Microalbuminuria was not apparently associated with a broad range of early postoperative outcomes, and adding information on microalbuminuria to the EuroSCORE did not improve the performance of the model. However, postoperative septicemia was significantly more frequent, and the lengths of ICU stay and total hospital stay were marginally longer, in patients with microalbuminuria.

7.3. Study III

Microalbuminuria was associated with an increased risk of long-term adverse outcomes in patients undergoing elective cardiac surgery. However, preoperative screening for microalbuminuria provided only modest prognostic information.

7.4. Study IV

High levels of preoperative insulin resistance or adiponectin were not associated with increased 30-day mortality, but a high level of adiponectin implied an increased 31–365-day mortality, and slightly prolonged lengths of ICU stay and total hospital stay. Furthermore, adiponectin level in the 31–365-day follow-up provided only modest prognostic information.

8. Perspectives

8.1. Study I

Our findings are primarily useful for clinicians at cardiac surgical centers, as they should be of value for more accurate assessment and application of the EuroSCORE with regard to preoperative patient selection and information on risk given at preoperative patient consultations. Furthermore, the gap between estimated and observed mortality may suggest that preoperative risk markers not addressed in the EuroSCORE may uphold important predictive information. Our results also emphasize the importance of continuous monitoring of the performance of present and future risk prediction models, both across varying levels of risk and types of surgery. Local assessment of the surgical performance may highlight important local issues that need attention. In Denmark, an annual report monitoring the performance of each surgical institution is published. This report uses the EuroSCORE to obtain an estimate of the predicted (or acceptable) short-term mortality of patients. Likewise, on an institutional or perhaps region-specific level, it is important to recognize strengths and limitations of risk-prediction models both when international comparisons of results are made, but also when new surgical techniques or predictors of outcome are suggested to be obtained for use outside the studied population. Due to the absence of more accurate risk prediction models, the presently accepted EuroSCORE model will likely be used for risk prediction into the near future, since results on the updated EuroSCORE model are not expected to be fully available until 2012.

Furthermore, the results of this study may support assessment of the performance at Danish and international surgical centers, and may potentially help improve conclusions made in the annual Danish report. It appears that linkage of the Western Denmark Heart Registry to other Danish health registries can provide inexpensive and quite complete follow-up information on patients undergoing cardiac surgery in Western Denmark. This linkage possibility is superior to what is available in most other settings (see **Appendix 1**). Consequently, our results likely reflect high clinical reliability compared with studies subjected to less complete availability of follow-up data, and thus the study holds information similarly important to international surgical institutions. Moreover, the presented strengths of the Danish health registry setup will hopefully inspire others in appropriate construction of national databases for quality surveillance. International cardiac surgical databases with standardized entry data and linkage opportunities would likely permit rare exposures, varying constellations of comorbidity, and rare outcomes to be studied with greater statistical precision.

8.2. Studies II–IV

We found no strong indication that the risk markers assessed in the present thesis had any substantial influence (neither association nor predictive value) on short-term mortality or most other adverse outcomes following elective cardiac surgery. Therefore, it appears that information on microalbuminuria, insulin sensitivity, or adiponectin fails to contribute important information applicable for clinical usage related to mortality in the 30-day postoperative period. However, we also considered adverse outcomes in longer postoperative periods (31–365 days), and our results suggest that levels of adiponectin and microalbuminuria should be considered as risk markers that may increase the discrimination in mortality prediction. Since these markers are easily measured, we encourage investigators involved in future large studies to consider adiponectin and microalbuminuria while assessing risk prediction following cardiac surgery. Ultimately, adjusted pre- and postoperative treatment policies targeting e.g. microalbuminuria in order to improve patient risk are of particular future interest, since feasible and well-tolerated medications are available.

Despite some statistical imprecision, we found that microalbuminuria was also associated with an increased risk of severe postoperative infections, including septicemia. Early recognition of septicemia risk is vital, but there are currently no reliable methods available for its assessment. Thus, recognition of microalbuminuria may prove to be a useful clinical tool for identifying patients at risk for developing severe infections in other clinical settings. Although microalbuminuria only had moderate discriminatory value for predicting septicemia according to our results, it seems appealing to regularly examine this factor since the related method is inexpensive, noninvasive, and readily obtainable.

9. English summary

Introduction

In cardiac surgery, the EuroSCORE might now overestimate patient mortality and face a need for recalibration or a reconstruction. In this light, previously unmeasured markers are of interest, as they may uphold additional prognostic information. The aim of Study I in this thesis was to examine the predictive performance of the EuroSCORE in Western Denmark. In Studies II–IV, we sought to examine whether microalbuminuria, insulin resistance, or adiponectin were associated with adverse outcomes following cardiac surgery, and whether these factors would contribute additional prognostic information beyond that of the existing EuroSCORE model.

Materials and Methods

Study I was a population-based cohort study (n = 21,644) based on data prospectively registered in the Western Denmark Heart Registry from 1999 to 2010. The actual 30-day mortality was assessed through linkage of the registry with the Civil Registration System. We assessed the predictive performance of the EuroSCORE using the area under curve (AUC) for discrimination test, the Hosmer–Lemeshow test for calibration, and the estimated-to-observed (E/O) mortality ratio. For Studies II–IV, we prospectively included 1,049 adult patients who had undergone elective cardiac surgery at Aarhus University Hospital, Skejby, Denmark. From preoperative morning spot-urine and fasting blood samples collected on the day of surgery, we assessed the levels of microalbuminuria, insulin resistance and adiponectin. Information on outcomes (i.e., mortality) was obtained from the Danish health registries and assessed in both short-term (30 days) and long-term periods (31–365 days) using multivariate logistic or Cox regression-based analyses (with or without competing risk assessment).

Results

In Study I, the risk profile of patients changed over time. In particular, patients older than 75 years in age accounted for 15% in 1999 and 28% in 2010, and isolated CABG accounted for 77% and 40%, respectively. The overall AUC was 0.79 (95% CI, 0.77–0.81), the Hosmer–Lemeshow test result was $p < 0.01$, and the E/O ratio was 1.9. The overall and procedural-specific E/O ratios increased from 1999 to 2010 (up to 2.6 for the overall group and 5.2 for isolated aortic valve replacement). Across all levels of estimated risk, the EuroSCORE overestimated mortality 2–3 fold.

In Studies II-IV, short-term mortality was not significantly associated with microalbuminuria (adjusted OR, 1.0 [95% CI, 0.3–3.6]), insulin resistance (adjusted OR, 1.7 [95% CI, 0.5–5.7]), or

adiponectin (adjusted OR, 0.4 [95% CI, 0.1–2.0]). In the long-term follow-up, microalbuminuria (adjusted HR, 2.3 [95% CI, 1.1–4.9] and the upper adiponectin quartile (adjusted OR, 2.9 [95% CI, 1.3–6.4]) were independently associated with increased mortality. Microalbuminuria was also associated with both long-term stroke (adjusted HR, 2.3 [95% CI, 1.1–4.9]) and an approximately 2-fold increased risk of varying constellations of severe postoperative infections. The studied prognostic factors provided only modest additional prognostic information beyond the EuroSCORE.

Interpretation

The existing EuroSCORE model can no longer satisfactorily estimate risk in patients undergoing in-pump cardiac surgery. Therefore, it seems necessary to recalibrate or reconstruct the model by inclusion of new potential markers of prognosis. However, based on our findings, it appears that microalbuminuria, insulin resistance, and adiponectin fail to contribute additional prognostic value to predication of 30-day mortality. Whether microalbuminuria and/or adiponectin provide additional information on the long-term outcome following cardiac surgery remains unclear, and thus should be addressed in future studies.

10. Dansk resumé

Introduktion

EuroSCORE er den hyppigst anvendte mortalitets prædiktionsmodel i forbindelse med hjertekirurgi, men synes nu at have behov for en rekalibrering eller rekonstruktion. Set i det lys er tidligere umålte prognostiske markører interessante. Formålet med Studie I var at belyse den prædiktive præcision af EuroSCORE i Vestdanmark. I Studie II–IV ønskede vi at undersøge, hvorvidt mikroalbuminuri, insulin resistens eller adiponektin var associeret med et dårligere resultat efter hjertekirurgi, samt om en eventuel association ville bidrage med prognostisk viden udover EuroSCORE.

Materialer og Metoder

Studie I var et populationsbaseret kohortestudie (n = 21.644) baseret på prospektivt registeret data fra Vestdansk Hjertedatabase fra 1999 til 2000. Data vedrørende den observerede 30-dages dødelighed indhentedes via kobling til danske sundhedsregistre. Vi vurderede den prædiktive præcision af EuroSCORE ved at beregne ”arealet under kurven” (AUC) i en diskriminationstest, Hosmer–Lemeshows kalibreringstest og ratioen mellem estimeret og observeret mortalitet. I Studie II–IV inkluderedes 1.049 voksne patienter, der gennemgik elektiv hjertekirurgi på Aarhus Universitet Hospital, Skejby, Danmark. I en præoperativ urinprøve og faste blodprøve bestemtes niveauerne mikroalbuminuri, insulin resistens og adiponektin. Mikroalbuminuri blev defineret som en urin albumin kreatinin ratio mellem 2,5 og 25 mg/mmol. Data vedrørende endepunkter (primært mortalitet) blev indhentet fra de danske sundhedsregistre. Endepunkterne blev opgjort ved 30 og 365 dage efter hjerteoperationen med anvendelse af multivariate logistiske- og Cox regression modeller (med eller uden competing risk justering).

Resultater

I Studie I steg patienternes risikoprofil med tiden. Antallet af patienter over 75 år var 15% i 1999 og 28% i 2010. Solitær CABG udgjorde 77% af alle operationer i 1999 mod 40% i 2010. For hele populationen var AUC 0,79 (95% CI, 0,77–0,81), Hosmer–Lemeshow $p < 0,01$, og E/O ratio 1,9. Den totale og operationsspecifikke E/O ratio øgedes i perioden fra 1999 til 2010 (op til 2.6 for alle operationer og op til 5.2 for solitær aortaklap operation). EuroSCORE overestimerede mortaliteten 2-3 gange uafhængigt af det prædikterede risikoniveau.

I Studies II-IV var 30-dages mortaliteten ikke statistisk signifikant associeret med hverken mikroalbuminuri (justeret OR, 1,0 [95% CI, 0,3–3,6]), insulin resistens (justeret OR, 1,7 [95% CI,

0,5–5,7]) eller adiponektin (justeret OR, 0,4 [95% CI, 0,1–2,0]). Ved 365-dages opfølgning var mikroalbuminuri (justeret HR, 2.3 [95% CI, 1,1–4,9] og den øvre adiponektinkvartil (justeret OR, 2,9 [95% CI, 1,3–6,4]) selvstændigt associeret med øget mortalitet. Mikroalbuminuri var også forbundet med øget risiko for apopleksi (justeret HR, 2,3 [95% CI, 1,1–4,9]) og en 2-fold øget risiko for alvorlige postoperative infektioner. Som prognostiske faktorer bidrog de undersøgte markører kun beskedent til optimering af EuroSCORE modellen.

Fortolkning

Den eksisterende EuroSCORE model prædikterer ikke tilfredsstillende den operative risiko for død hos hjertekirurgiske patienter. Det er derfor relevant at rekalibrere EuroSCORE og/eller afprøve nye prognostiske markører med henblik på forbedret præoperativ risikovurdering. Baseret på vore resultater er der dog ikke holdepunkt for at niveauerne af mikroalbuminuri, insulin resistens eller adiponectin indeholder vigtig prognostisk information vedrørende 30-dages mortaliteten. Hvorvidt mikroalbuminuri og/eller adiponektin kan bidrage med prognostisk information udover EuroSCORE modellen vedrørende 365-dages mortaliteten skønnes fortsat ikke fuldt afklaret, men fremtidige studier kan bidrage med yderligere viden herom.

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Appendix

Appendix 1: EuroSCORE validation studies

Author & Country	Sample & Inclusion period	Type	Risk-models and/or aims	Outcomes	Follow-up	Results
Sündermann S et al. Germany 2010	n=400 2008-2010	A	EuroSCORE, STS algorithm, and Clinical Frailty Score in elderly (≥74 years) undergoing cardiac surgery. 15% of patients had transapical or transfemoral aortic valve implantation.	Mortality	30 days	Additive EuroSCORE AUC 0.79; HL n/a; E/O n/a STS algorithm AUC 0.76; HL n/a; E/O n/a Frailty score AUC 0.71; HL n/a; E/O n/a
van Straten AH et al. Netherlands 2010	n=5,249 2004-2008	C	Additive and logistic EuroSCORE	n/a	n/a	Additive EuroSCORE AUC 0.80; HL n/a Logistic EuroSCORE AUC 0.81; HL n/a E/O ≈ 2.0
Chhor V et al. France 2010	n=469 2005-2007	A	EuroSCORE and CARE score in the prediction of perioperative mortality among octogenarians (n=134) and non-octogenarians (n=335) with aortic valve stenosis undergoing AVR	Mortality	30 days	Octogenarians Additive EuroSCORE AUC 0.58; HL 0.52; E/O n/a Logistic EuroSCORE AUC 0.59; HL 0.09; E/O n/a Care Score AUC 0.56; HL 0.06; E/O n/a Non-octogenarians Additive EuroSCORE AUC 0.82; HL n/a; E/O n/a Logistic EuroSCORE AUC 0.81; HL n/a; E/O n/a Care Score AUC 0.77; HL n/a; E/O n/a *Predictive performance of all models was poor for octogenarians*
Wang C et al. China 2010	n=1,726 2003-2007	V	EuroSCORE in Chinese heart valve patients. Abstract	Mortality	Hospital	Additive EuroSCORE AUC 0.64; HL 0.20; E/O 3.5/4.5 = 0.8 Logistic EuroSCORE AUC 0.65; HL 0.04; E/O 2.9/4.5 = 0.6 *Revised model needed for valve surgery.*
Ghazy T et al. Germany 2010	n=1,497 2000-2007	AV	EuroSCORE in isolated and elective aortic valve patients. A retrospective study.	Mortality	30 days	EuroSCORE AUC 0.62; HL n/a; E/O 5.3/2.5 = 2.1 EuroSCORE should no longer be used in its present form.
Hirose H et al. Japan 2010	n=1,162 (C) 1991-1998 n=1,318 (D) 2000-2006	C D	EuroSCORE in comparing CABG and OPCAB. Of note, two very different inclusion periods is a major limitation. Also, the follow-up period was not defined.	Mortality Morbidty	n/a “postop”	CABG Mortality AUC 0.92; HLn/a; E/O n/a OPCAB Mortality AUC 0.67; HL n/a; E/O n/a Plot regarding estimated to observed mortality showed good calibration in low-risk patients (≤4-5%). Similar plots for morbidity are shown.
Ranucci M et al. Italy 2010	n=11,150 2001-2007		Assessed risk-models with few variables			Models with a limited number of factors may work better than complex models when applied to a limited number of patients

Sastry P et al. UK 2010	n=925 2000-2004	D	Whether left ventricular end-diastolic dysfunction (LVEDP) improved EuroSCORE. Retrospective study on relatively old data in OPCAB patients.	Mortality	Hospital	EuroSCORE AUC 0.70; HL n/a; E/O n/a EuroSCORE+LVEDP AUC 0.78; HL n/a; E/O n/a *LVEDP as a marker of diastolic dysfunction seems an important variable in predicting patient-specific risk and should be considered for incorporation in future risk models*
Kobayashi KJ et al. US 2009	n=233 2000-2004	CV	EuroSCORE in relative high-risk combined CABG and aortic valve replacement *relatively old data	Mortality	30 days 1 year 2 years 5 years	Additive EuroSCORE AUC 0.76; HL n/a; E/O 8.8/9.4 = 0.9 Logistic EuroSCORE AUC 0.75; HL n/a; E/O 16.1/9.4 = 1.7 EuroSCORE risk groups were associated with long-term mortality
Iyem H et al. Turkey 2009	n=128 2008-2009	A	EuroSCORE. Authors attempted to validate EuroSCORE in high-risk elderly, but mean only age was 72 ±9 years (64-91 years). Abstract	Mortality	Hospital	EuroSCORE AUC n/a; HL n/a; E/O 11.2/6.3 = 1.8 Small cohort, and the observed mortality was within the 95 % CI of that estimated.
van Gameren M et al. Netherlands 2009	n=1,205 2004-2006	A	EuroSCORE, recalibrated EuroSCORE and levels of creatinine or Cockcroft Gault estimated glomerular filtration rate.	Mortality	Hospital	EuroSCORE AUC 0.78; HL n/a; E/O n/a Locally recalibrated EuroSCORE AUC 0.80; HL n/a + binary creatinine AUC 0.80; HL n/a + continous creatinine AUC 0.83; HL n/a + categorized eGFR AUC 0.83; HL n/a + continuos eGFR AUC 0.82; HL n/a
Wendt D et al. Germany 2009	n=652 1999-2007	AV	EuroSCORE,STS algorithm, and Parsonnet in aortic valve replacement.	Mortality	30 days	EuroSCORE AUC n/a; HL n/a; E/O 8.5/2.5 = 3.4 STS algorithm AUC n/a; HL n/a; E/O 4.4/2.5 = 1.8 Parsonnet AUC n/a; HL n/a; E/O 9.9/2.5 = 4.0
Kalavouziotis D et al. Canada 2009	EuroSCORE ≥20 n=237 1995-2005 EuroSCORE <20: n=1,184 1995-2005	AV	EuroSCORE in high-risk aortic valve replacement. A retrospective study.	Mortality	30 days	EuroSCORE <20 AUC n/a; HL n/a; E/O 5.4/3.2 = 1.7 EuroSCORE ≥20 AUC n/a; HL n/a; E/O 38.7/11.4 = 3.4 New model for AVR is needed
Hirose H et al. Japan 2009	n=1,552 1991-2006	C	EuroSCORE in a Japanese single center cohort.	Mortality Morbidity	n/a	Additive EuroSCORE mortality AUC 0.89; HL n/a EuroSCORE correlated with the total incidence of major complications, heart failure, renal failure, stroke, pneumonia and mediastenitis, and parameters of recovery time. Temporal results could however vary, as the inclusion period was 17 years.
Wang DJ et al. China 2009	n=310 2005-2007	C	EuroSCORE retrospectively validated in risk categories. Abstract	Mortality	30 days	Overall EuroSCORE AUC 0.78; HL n/a; E/O 3.6/1.6 = 2.3 Low-risk (quartile 1) E/O 1.4/0.0 = n/a Medium-risk (quartile 2+3) E/O 2.7/1.3 = 2.1 High-risk (quartile 4) E/O 7.4/3.7 = 2.0

Nissinen J et al. Finland 2009	n=3,613 2005-2006	A	Logistic EuroSCORE was recalibrated and adjusted regarding age, estimated GFR and procedure related data.	Mortality	30 days 1 year 14 years	Logistic EuroSCORE AUC 0.84; HL n/a; E/O 5.9/2.5 = 2.4 Performed well in identifying high-risk patients, but significantly overestimated mortality. Adjusted EuroSCORE AUC 0.87; HL 0.76; E/O ≈ 1.0 EuroSCORE risk categories were associated with long-term mortality.
Leontyev S et al. Germany 2009	n=282 1996-2006	AV	EuroSCORE in elderly (>=80 years) aortic valve patients.	Mortality	30 days	EuroSCORE AUC n/a; HL n/a; E/O 16.2/9.2 = 1.8 Imprecise overall mortality prediction mortality among octogenarian AVR patients, but no attempt to assess temporal differences in E/O
Ranucci M et al. Italy 2009	n=11,150 2001-2007 n=1,459 2003-2007	A	Logistic EuroSCORE and a recalibrated logistic EuroSCORE in high-risk patients (EuroSCORE ≥5). Validated in an external dataset (n=1,459).	Mortality	Hospital	Developmental dataset overall (n=11,150) EuroSCORE AUC 0.76; HL <0.01; E/O 6.6/3.8 = 1.7 Developmental high-risk dataset (n=4,279) EuroSCORE AUC 0.70; HL <0.01; E/O 13.2/7.4 = 1.8 Recalibrated EuroSCORE AUC 0.70; HL 0.14; E/O = 1.0 Validation dataset (n=1,459) EuroSCORE AUC 0.70; HL 0.86; E/O 17/6.4 = 2.7 Recalibrated EuroSCORE AUC 0.70; HL 0.89; E/O 9.2/6.4 = 1.4
Barili F et al. Italy 2009	n=339 2001-2008	AV	EuroSCORE in isolated aortic valve patients.	Mortality	30 days	EuroSCORE AUC n/a; HLn/a; E/O 6.2/0.6 = 10.3 EuroSCORE failed in predicting hospital mortality. An AVR dedicated risk prediction model is warranted.
Messaoudi N et al. Belgium 2009	n=1,578 2005-2006	A	EuroSCORE and prolonged ICU stay (≥7 days) in aortic valve surgery. Retrospectively collected data.	ICU stay	2 days 5 days 7 days	ICU ≥2 days: EuroSCORE AUC 0.68 (95 % CI 0.65-0.70); HL n/a ICU ≥5 days: EuroSCORE AUC 0.75 (95 % CI 0.72-0.78); HL n/a ICU ≥7 days: EuroSCORE AUC 0.77 (95 % CI 0.73-0.81); HL n/a
Putman LM et al. Netherlands 2009	n=963 1990-2007	G	EuroSCORE in grown-up congenital heart surgery.	Mortality	30 days	Logsitic EuroSCORE AUC 0.59 (95 % CI 0.45-0.72); HL n/a; E/O 5.4/1.5 = 3.6 EuroSCORE overestimated risk. The results are supported by Jacquet L et al., 2007.
Gummert JF et al. Germany 2009	n=32,806 n=26,501 (B) n=6,305 (AV) 2006-2007	B AV	EuroSCORE performance in Germany regarding bypass and aortic valve surgery Follow-up period was not clearly specified.	Mortality	Hospital	Coronary bypass EuroSCORE AUC 0.77; HL 0.61; E/O 5.2/2.6 = 2.0 AVR EuroSCORE AUC 0.68; HL 0.61; E/O 7.3/3.9 = 2.0 The overestimation was greater in high-risk and in elderly patients.
Parolari A et al. Italy 2009	Single institution: n=3,440 (C) n=1,140 (D) 1999-2007 Metaanalysis: n=19,212 (C) n=5,461 (D) 1999-2008	C O	EuroSCORE in CABG and OPCAB patients assessed in two designs. A single institution with in-hospital mortality and a metaanalysis with either in-hospital or 30-day mortality.	Mortality	Hospital 30 days	Single institution OPCAB AUC 0.77; HL 0.51; E/O 4.1/0.8 = 5.1 Single institution CABG AUC 0.81; HL 0.41; E/O 3.3/0.8 = 4.1 Metaanalysis OPCAB AUC 0.77; HL n/a; E/O n/a Metaanalysis CABG AUC 0.77; HL n/a; E/O n/a

Osswald BR et al. Germany 2009	n=1,545 1994-2006	AV	EuroSCORE and surgical aortic valve replacement.	Mortality	30 days	Additive EuroSCORE AUC 0.68; HL 0.61; E/O 6.1/2.2 = 2.8 Additive EuroSCORE = <3 (n=183): E/O 1.5/0.0 = n/a Additive EuroSCORE = ≥3 (n=529): E/O 4.1/1.0 = 4.1 Additive EuroSCORE = ≥6 (n=833): E/O 8.3/3.5 = 2.4 Logistic EuroSCORE AUC 0.67; HL <0.01; E/O 9.3/2.2 = 4.2 Logistic EuroSCORE = <3 (n=239): E/O 1.3/0.0 = n/a Logistic EuroSCORE = ≥3 (n=493): E/O 3.8/1.8 = 2.1 Logistic EuroSCORE = ≥6 (n=813): E/O 1.3/0.0 = 2.4 The overestimation becomes greater in the recent years.
Engebretsen KV et al. Norway 2009	n=1,336 2003-2006	C	EuroSCORE	Mortality	30 days	Overall EuroSCORE AUC n/a; HL n/a; E/O 3.6/0.8 = 4.5 EuroSCORE = 1-2 (n=325): observed mortality = 0% EuroSCORE = 3-4 (n=386): observed mortality = 0.8% EuroSCORE = 5-6 (n=277): observed mortality = 1.1% EuroSCORE = ≥7 (n=177): observed mortality = 2.3%
Zheng Z et al. China 2009	n=9,248 2004-2005	C	EuroSCORE applied on data from Chinese CABG Registry; a multicenter study	Mortality	Hospital	EuroSCORE AUC 0.72; HL n/a; E/O 5.5/3.3 = 1.7 E/Os varied in different estimated risk categories EuroSCORE did not accurately fit Chinese in-hospital mortality. A new model was warranted.
Campagnucci VP et al. Brazil 2008	n=100 2005-2006	C	EuroSCORE retrospectively validated in a small CABG sample	Mortality	Hospital	EuroSCORE AUC 0.94; HL <0.05 Methods poorly described. Patients were grouped according to EuroSCORE risk 1) 0-2 : E/O 0.4/0.0 2) 3-5 : E/O 1.5/0.0 3) ≥6 : E/O *3.2*/7.9 Remains unanswered how the predicted risk in group three could be lower than according to group categorization.
Kaartama T et al. Finland 2008	n=378 1999-2003	MV	EuroSCORE and mitral valve surgery	Mortality	30 days	In 1-year periods from 1999-2003 the EuroSCORE estimation changed from underestimation to overestimation of mortality in mitral valve replacement
Silva J et al. Spain 2008	n=2,014 2005-2007	A	Assess if the MDRD-4 glomerular filtration estimate can improve the EuroSCORE in on-pump cardiac surgery.	Mortality	30 days	EuroSCORE AUC 0.75; HL n/a; E/O 8.1/7.2 = 1.1 EuroSCORE + MDRD-4 AUC 0.77; HL n/a; E/O n/a MDRD-4 an independent risk predictor and slightly improved the EuroSCORE
Lafuente S et al. Spain 2008	n=498 2004-2006	C	EuroSCORE in CABG patients in a single center in Spain.	Mortality	Hospital	Additive EuroSCORE AUC 0.84; HL n/a; E/O 3.9/5.8 = 0.67 Logistic EuroSCORE AUC 0.83; HL 0.32; E/O 4.2/5.8 = 0.72 In high-risk patients, mortality was underestimated by both models, but mortality estimated using the logistic model came closer to the actual mortality than compared to the additive model.
Ribera A et al. Spain 2008	n=1,605 2001-2003	C	EuroSCORE and the local CATHY risk model.	Mortality	Hospital	EuroSCORE AUC 0.76; HL 0.03; E/0 4.3/4.8 = 0.9 CATHY model AUC 0.74; HL <0.01; E/0 9.5/4.8 = 2.0 Both systems ok when internally recalibrated.

Van Gameren M et al. Netherlands 2008	n=904 (V) n=395 (CV)	V CV	EuroSCORE and New York State valve model in solitary and combined heart valve procedures	Mortality	Hospital	Isolated valve EuroSCORE AUC 0.76; HL <0.01; E/0 6.1/2.8 = 2.2 New York State AUC 0.86; HL 0.63; E/0 3.0/2.8 = 1.1 Combined valve and bypass EuroSCORE AUC 0.72; HL 0.76; E/0 7.8/6.8 = 1.1 New York State AUC 0.74; HL 0.03; E/0 5.9/6.8 = 0.9
D'Errigo P et al. Italy 2008	n=30,610 2002-2004	C	Italian CABG Outcome Project model and EuroSCORE	Mortality	30 days	Additive EuroSCORE AUC 0.77; HL 0.23; E/0 2.5/2.5 = 1.0 Logistic EuroSCORE AUC 0.78; HL <0.01; E/0 6.4/2.5 = 2.6 Italian CABG model AUC 0.80; HL 0.17; E/0 2.5/2.5 = 1.0 Italian CABG model uses fewer variables and performs better. When properly recalibrated, the EuroSCORE fits well.
Grossi EA et al. US 2008	n=731 1996-2006	AV	EuroSCORE in elderly high-risk aortic valve replacement.	Mortality	Hospital	Additive EuroSCORE AUC 0.80; HL n/a; E/0 9.7/7.8 = 1.2 Logistic EuroSCORE AUC 0.80; HL n/a; E/0 17.2/7.8 = 2.2
Grant SW et al. UK 2007	n=14,637 2002-2005	A	EuroSCORE, recalibrated EuroSCORE and a local model.	Mortality	Hospital	EuroSCORE AUC 0.80; HL n/a; E/0 5.8/3.1 = 1.9 Recalibrated EuroSCORE AUC 0.80; HL n/a; E/0 3.1/3.1 = 1.0 Local model AUC 0.82; HL 0.33; E/0 3.1/3.1 = 1.0
Antunes PE et al. Portugal	n=4,567 1992-2001	C	EuroSCORE, Parsonnet, Ontario and a local derived model.	Mortality	Hospital	EuroSCORE AUC 0.74; HL <0.01; E/0 2.3/1.0 = 2.3 Parsonnet AUC 0.66; HL <0.01; E/0 4.4/1.0 = 4.4 Ontario AUC 0.68; HL <0.01; E/0 1.7/1.0 = 1.7 Local model AUC 0.75; HL 0.98; E/0 n/a
Ad N et al. USA 2007	n=2,433 males n=692 females 2001-2004	C	EuroSCORE and STS algorithm stratified on gender in CABG patients. Retrospective.	Mortality	30 days	Males Additive EuroSCORE AUC 0.81; HL n/a; E/0 3.9/1.5 = 2.6 Logistic EuroSCORE AUC 0.81; HL n/a; E/0 4.5/1.5 = 3.0 STS algorithm AUC 0.80; HL n/a; E/0 2.1/1.5 = 1.4 Females Additive EuroSCORE AUC 0.86; HL n/a; E/0 4.3/2.9 = 1.5 Logistic EuroSCORE AUC 0.85; HL n/a; E/0 7.9/2.9 = 2.7 STS algorithm AUC 0.83; HL n/a; E/0 4.1/2.9 = 1.4
Riera M et al. Spain 2007	n=1,053 2002-2006	A	EuroSCORE in all on-pump surgery performed in a single center in Spain. Abstract	Mortality	n/a	Additive EuroSCORE AUC 0.78; HL n/a; E/0 5/2.2 = 2.3 Logistic EuroSCORE AUC 0.79; HL n/a; E/0 4.5/2.2 = 2.0
Mestres CA et al. Spain 2007	n=191 1955-2006	V	EuroSCORE in patients with preoperative active endocarditis. Data collected retrospectively.	Mortality	30 days	Additive EuroSCORE AUC 0.83; HL n/a; E/0 10.4/28.8 = 0.4 Logistic EuroSCORE AUC 0.89; HL n/a; E/0 27.1/28.8 = 0.9
Youn YN et al. Korea 2007	n=757 2002-2006	D	EuroSCORE in OPCAB patients with short- and long-term follow-up. Split into risk categories.	Mortality	Hospital 5 years	Hospital mortality Additive EuroSCORE AUC 0.72; HL 0.03; E/0 4.5/1.3 = 3.5 Logistic EuroSCORE AUC 0.71; HL 0.04; E/0 5.0/1.3 = 3.6 Long-term mortality (mean 32.8 months) Additive EuroSCORE AUC 0.71; HL >0.05 Logistic EuroSCORE AUC 0.71; HL >0.05 Groups according to increasing EuroSCORE risk were associated with long-term mortality using Cox regression

Feiler E et al. Hungary 2007	n=1,839 2003-2005	n/a	Additive and lostistic EuroSCORE Abstract in English	Mortality	30 days	Additive EuroSCORE AUC 0.69; HL 0.47; E/0 4.1/3.3 = 1.2 Logistic EuroSCORE AUC 0.71; HL 0.13; E/0 4.5/3.3 = 1.4
Heikkinen J et al. Finland 2007	n=180	M	EuroSCORE and short- and long-term outcomes in mitral valve surgery Abstract	Mortality	30 days 10 years	Additive EuroSCORE AUC 0.80; HL n/a; E/0 n/a Logistic EuroSCORE AUC 0.80; HL n/a; E/0 n/a EuroSCORE overestimated mortality in high-risk patient (EuroSCORE ≥4) EuroSCORE also associated with long-term outcomes
Paul M et al. Israel 2007	n=809 2004	B CV	EuroSCORE, STS algorithm and National Nosocomial Infection Surveillance risk index in prediction of sternal wound infection	Mortality Infection	30 days 180 days	Sternal wound infection: EuroSCORE AUC 0.73; HL n/a STS algorithm AUC 0.72; HL 0.25 NNIS Index AUC 0.64; HL n/a Mortality: EuroSCORE 30 and 180 days AUC 0.78, 0.77; HL n/a STS algorithm 30 and 180 days AUC 0.82, 0.82; HL n/a NNIS Index 30 and 180 days AUC 0.65, 0.64; HL n/a
Farrokhyar F et al. Canada 2007	n=1,693 (C) n=1,657 (D) 2001-2002	C D	EuroSCORE and STS algorithm In CABG and OPCAB patients	Mortality	Hospital	CABG EuroSCORE AUC 0.81; HL 0.85 ; E/0 n/a CABG STS AUC 0.82; HL 0.92; E/O n/a OPCAB EuroSCORE AUC 0.79; HL 0.34; E/0 n/a OPCAB STS AUC 0.81; HL 0.48; E/0 n/a
Healy DG et al. Ireland 2006	n=66 2000-2001	C	EuroSCORE in patients treated with an intra-aortic balloon pump during CABG surgery	Mortality	30 days	EuroSCORE ≥5 was associated with increased risk of intra-aortic balloon pump use Patients with preoperative intra-aortic balloon pump hade lower mortality than estimated; E/O 12.6/6.3 = 2.0
Klinceva M et al. Czech 2006	n=460 n/a	A	Validate EuroSCORE in patients admitted for cardiac surgery, and being either accepted (n=262) or rejected (n=198) surgical treatment. Abstract.	Mortality	30 days	Accepted for cardiac surgery AUC 0.76; HL n/a; E/O n/a Rejected for cardiac surgery AUC 0.72; HL n/a; E/O n/a EuroSCORE performed well in patients rejected for cardiac surgery
Nishidi T et al. Japan 2006	n=327 1976-2005	T	EuroSCORE for long-term follow-up in thoracic aortic surgery	Mortality	30 days 10 years 20 years 30 years	10-, 20- and 30 years mortality: Additive EuroSCORE AUC 0.73, 0.73, 0.68; HL n/a Logistic EuroSCORE AUC 0.75, 0.74, 0.69; HL n/a 30-day mortality: AUC n/a; HL n/a; E/O n/a It was stated that, the logistic EuroSCORE had better E/O accuracy than the additive EuroSCORE
Soujaranta RT et al. Finland 2006	n=162 2001-2003	A	EuroSCORE validation in octogenarians, and using varying age categorization	Mortality Morbidity	30 days	Mortality AUC 0.77; HL 0.38; E/O n/a Morbidity AUC 0.62; HL 0.51; E/O n/a Age is an important risk factor, and appear acceptable calibrated in the EuroSCORE

Biancari F et al. Finland 2006	n=917 1992-1998	C	EuroSCORE early (30 days) and late (median 11.7 years) outcomes across EuroSCORE quintiles	Mortality	30 days	Short-term AUC 0.86; HL n/a; E/0 n/a In the long-term, both the additive and logistic EuroSCORE quintiles were associated with survival
Bhatti F et al. UK 2006	n=9,995 2002-2004	A	EuroSCORE as an overall predictor and in procedural subgroups, as well as in low- and high-risk (-/+ 5 percent risk)	Mortality	Hospital	Overall EuroSCORE AUC 0.79; HL n/a; E/O = 1.7 CABG AUC 0.77; HL n/a; E/O = 2.0 Valve AUC 0.79; HL n/a; E/O = 2.3 CABG + valve AUC 0.73; HL n/a; E/O = 1.3 Low-risk AUC 0.69; HL n/a; E/O = 1.8 High-risk AUC 0.72; HL n/a; E/O = 1.7
Berman M et al. Israel 2006	n=1,639 2003-2004	A	EuroSCORE and Bernstein-Parsonnet. Stratified into 5 risk groups	Mortality	Hospital	EuroSCORE AUC 0.73; HL n/a; E/O 5.8/4.8 = 1.2 Bernstein-Parsonnet AUC 0.83; HL n/a; E/O n/a Both models had accurate E/Os in the five risk groups
Nilsson J et al. Sweden 2006	n=6,222 1996-2001	A	Comparison between the EuroSCORE and 18 other risk scores	Mortality	30 days 1 year	Additive EuroSCORE 30 days AUC 0.84; AUC CABG 0.85; HL n/a EuroSCORE 365 days AUC 0.77; AUC CABG 0.75; HL n/a Logistic EuroSCORE 30 days AUC 0.84; AUC CABG 0.86; HL n/a EuroSCORE 365 days AUC 0.77; AUC CABG 0.75; HL n/a
Jin R et al. US 2005	n=23,463 1997-2004	A	Additive and logistic EuroSCORE applied in a multicenter database. Data on some EuroSCORE risk factors (unstable angina, endocarditis, ventricular septal rupture) were imputed.	Mortality	n/a	Additive EuroSCORE AUC 0.79; HL <0.01; E/O 5.4/3.6 = 1.5 Logistic EuroSCORE AUC 0.79; HL <0.01; E/O 8.3/3.6 = 2.3
Shanmugam G et al. Scotland 2005	n=6,535 1994-2004	A	EuroSCORE overall and grouped into three risk-categories	Mortality	Hospital	Additive EuroSCORE AUC 0.75; HL 0.64; E/O 4.1/2.95 = 1.1 Logistic EuroSCORE AUC 0.75; HL 0.47; E/O 5.2/2.95 = 1.8 Low and high-risk overestimation by the logistic EuroSCORE
Vázquez Roque F et al. Spain 2005	n=762 1997-2002	C	EuroSCORE, Parsonnet, Cleveland, Ontario, and French Score in CABG procedures	Mortality Morbidity	30 days	EuroSCORE mortality AUC 0.86; HL n/a; morbidity AUC 0.74; HL n/a, E/O n/a Parsonnet mortality AUC 0.82; HL n/a; morbidity AUC 0.72; HL n/a, E/O n/a Cleveland mortality AUC 0.80; HL n/a; morbidity AUC 0.68; HL n/a, E/O n/a Ontario mortality AUC 0.71; HL n/a; morbidity AUC 0.64; HL n/a, E/O n/a French mortality AUC 0.55; HL n/a; morbidity AUC 0.57; HL n/a, E/O n/a
Vanagas G et al. Lithuania 2005	n=1,002 2003-2004	C	EuroSCORE retrospectively assessed in CABG patients	Mortality	n/a “operative”	AUC 0.71; HL n/a; E/O 4.8/5.8 = 0.8

Yap CH et al. Australia 2005	n=2,106 2002-2005	A	Validate approximated EuroSCORE (some definitions of risk factors did not correspond fully to the EuroSCORE) in the entire cohort and CABG only	Mortality	30 days	Additive EuroSCORE AUC 0.81; HL <0.01; E/O overall 5.8/3.9 = 1.5; and E/O CABG 4.9/2.6 = 1.9 Logistic EuroSCORE AUC 0.82; HL <0.01; E/O overall 9.9/3.9 = 2.5; and E/O CABG 7.7/2.6 = 3.0
Toumpoulis IK et al. US 2005	n=1,035 1992-2002	CV V	Additive and logistic EuroSCORE ability to predict short- and long-term mortality *Subgroup of the n=5.051 cohort by Toumpoulis IK et al., 2005 (see below)	Mortality	Hospital 5 years	Hospital mortality AUC n/a; HL n/a; E/O n/a Logistic EuroSCORE risk categories associated with long-term mortality
Toumpoulis IK et al. US 2005	n=3,760 1992-2002	C	EuroSCORE *Same cohort as Toumpoulis IK et al., 2004 (see below). Results refer to in-hospital events. The follow-up definition is inadequately described.	Mortality Morbidity LOS	Hospital 30 days	Mortality: Additive AUC 0.75; HL 0.59; Logistic AUC 0.75; HL <0.05 Renal failure: Additive AUC 0.80; HL 0.51; Logistic AUC 0.80; HL 0.10 Respiratory failure: Additive AUC 0.68; HL n/a; Logistic AUC 0.68; HL n/a Stroke: Additive AUC 0.59; HL n/a; Logistic AUC 0.59; HL n/a Sepsis/endocarditis: Additive AUC 0.72; HL n/a; Logistic AUC 0.72; HL n/a LOS ≥12 days: Additive AUC 0.71; HL <0.05; Logistic AUC 0.71; HL <0.05
Toumpoulis IK et al. US 2005	n=1,105 n/a	CV V	Additive and logistic EuroSCORE in prediction of mortality, morbidity and LOS Abstract *Unclear whether or not the cohort is a subgroup of the n=5.051 cohort by Toumpoulis IK et al., 2005	Mortality Morbidity LOS	Hospital	For both additive and logistic EuroSCORE: Mortality AUC 0.72; HL >0.05; E/O n/a Renal failure AUC 0.78; HL >0.05 Stroke AUC 0.74; HL >0.05 Gastrointestinal complications AUC 0.73; HL >0.05 Respiratory failure AUC 0.71; HL >0.05 (Logistic EuroSCORE HL <0.05) LOS AUC 0.71; HL <0.05
Toumpoulis IK et al. US 2005	n=5,051 1992-2002	A	Additive and logistic EuroSCORE in prediction of mortality, morbidity, and LOS ≥12 days	Mortality Morbidity LOS	Hospital 90 days	Logistic EuroSCORE: Early mortality AUC 0.77; HL <0.05; E/O n/a 90 days mortality AUC 0.73; HL <0.05; E/O n/a Renal failure AUC 0.80; HL <0.05 Sepsis AUC 0.74; HL 0.08 Respiratory failure AUC 0.71; HL <0.05 LOS AUC 0.71; HL <0.05 Additive EuroSCORE had similar AUCs and was more accurately calibrated
Collart F et al. France 2005	n=215 1993-2003	V	Validate EuroSCORE in octogenarians undergoing valve surgery	Mortality	Hospital	Logistic EuroSCORE overestimated risk in both Low-risk E/0 = 8.7/7.4 = 1.2 Medium-risk E/0 = 14.9/6.9 = 2.2 High-risk E/0 = 34.1/12.9 = 2.6

Di Bella I et al. Italy 2005	n=794 2002-2004	B	EuroSCORE in an Italian single center cohort Abstract in English	Mortality	Hospital	EuroSCORE overestimated mortality in low-risk patients and underestimated mortality high-risk patients
De Maria R et al. Italy 2005	n=1,230 2000-2002	A	Assess ability of the EuroSCORE in prediction of short- and long-term outcomes	Mortality ICU stay LOS	30 days 20 months	30-day mortality AUC n/a; HL n/a; E/O 4.5/2.8 = 1.6 EuroSCORE was associated with long-term mortality, ICU stay and LOS
Chen CC et al. Taiwan 2004	n=801 1999-2004	B	Validate EuroSCORE in a Taiwanese aged less than 80 years	Mortality	Hospital	Additve EuroSCORE AUC 0.75; HL n/a; E/O 5.0/10.6 = 0.5 Additive EuroSCORE underestimated mortality 2-fold from 2000-2004 Logistic EuroSCORE AUC 0.74; HL n/a; E/O 8.0/10.6 = 0.8 Logistic EuroSCORE showed temporal increasing accurate E/O from 2000-2004
Syed AU et al. Saudi Arabia 2004	n=194 2002-2004	A	EuroSCORE and Parsonnet retrospectively assessed in Saudi Arabia	Mortality Morbidity	30 days	Mortality EuroSCORE AUC 0.77; HL 0.22; E/O n/a Parsonnet AUC 0.67; HL 0.72; E/O n/a Morbidity EuroSCORE AUC 0.63; HL n/a; E/O n/a Parsonnet AUC 0.66; HL n/a ; E/O n/a
Fukuda M et al. Japan 2004	n=154 2002-2003	n/a	EuroSCORE grouped in risk categories in Japan Abstract in English	Mortality Morbidity	n/a	EuroSCORE was associated with mortality and morbidity Mortality AUC n/a; HL n/a; E/O 5.6/7.1 = 0.8
Zingone B et al. Italy 2004	n=2,426 1999-2004	A	Logistic and additive EuroSCORE in Italy	Mortality	30 days	Additive EuroSCORE AUC 0.79; HL 0.15; E/O 5.6/5.9 = 0.95 Logistic EuroSCORE AUC 0.80; HL <0.01 E/O 6.9/5.9 = 1.17
Nilsson J et al. Sweden 2004	n=3,413 1999-2002	A	Assess if EuroSCORE predicts different components of resource utilization	Costs ICU stay		Additive EuroSCORE was associated with ICU stay (≥2 days) and ICU costs.
Karthik S et al. UK 2004	n=1,769 1997-2002	B+CV V	Additive and logistic EuroSCORE in bypass and valve surgery	Mortality	Hospital	Overall additive EuroSCORE AUC 0.73; HL n/a; E/O 6.7/1.9 = 0.8 Overall logistic EuroSCORE AUC 0.73; HL n/a; E/O 9.4/1.9 = 1.1 Logistic EuroSCORE was more accurate than additive EuroSCORE in high-risk patients with EuroSCORE ≥5.
Kasimir MT et al. Austria 2004	n=258 1998-2001	B V	Assess if EuroSCORE predicts long-term mortality in combined bypass and valve surgery Abstract	Mortality	2 years	EuroSCORE was associated with long-term mortality in combined bypass and valve surgery AUC n/a; HL n/a; E/O n/a
Barmettler H et al. Switzerland 2004	n=367 1994-2000	T	Validate EuroSCORE and a modified model with aortic dissection and preoperative malperfusion in patients undergoing thoracic aorta surgery	Mortality	Hospital	Original models Additive EuroSCORE: AUC 0.68; HL n/a; E/O n/a Logistic EuroSCORE: AUC 0.72; HL n/a; E/O n/a Modified models with aortic dissection and malperfusion Additive EuroSCORE: AUC 0.91; HL n/a; E/O n/a Logistic EuroSCORE: AUC 0.86; HL n/a; E/O n/a

Gogbashian A et al. UK 2004	n=15,999 1994-2002	A	Metaanalysis in 6 peer-reviewed additive EuroSCORE validation studies	Mortality	Hospital or 30 days	The additive EuroSCORE overestimates mortality in low-risk patients and underestimates mortality in high-risk patients
Pierri MD et al. Italy 2004	n=3,111 n/a	B	EuroSCORE, STS algorithm and Northern New England score Abstract in English	Mortality	n/a	EuroSCORE AUC 0.77; HL n/a; E/O 4.2/2.2 = 1.9 STS algorithm AUC 0.82; HL n/a; E/O 1.9/2.2 = 0.9 Northern New England AUC 0.78; HL n/a; E/O 1.9/2.2 = 0.9
Nilsson J et al. Sweden 2004	n=4,497 1996-2001	B	Additive EuroSCORE and STS algorithm on mortality	Mortality	30 days	EuroSCORE AUC 0.84; HL 0.81; E/O 1.9/1.9 = 1.0 STS algorithm AUC 0.71; HL 0.83; E/O 1.9/1.9 = 1.0
Ugolini C et al. Italy 2004	n=6,457 2000-2001	C	Charlson Comorbidity Index (as adapted by Romana et al. J Clin Epi 1993) obtained from administrative databases with EuroSCORE in CABG risk-prediction	Mortality	Hospital	2000 Charlson AUC 0.68; HL <0.05 Charlson + administrative data AUC 0.76; HL >0.05 EuroSCORE AUC 0.78; HL >0.05 2001 Charlson AUC 0.70; HL <0.05 Charlson + administrative data AUC 0.80; HL >0.05 EuroSCORE AUC 0.77; HL >0.05
Goodwin AT et al. UK 2003	n=65 1996-2001	A	EuroSCORE and Parsonnet in emergency redo cardiac surgery	Mortality	Hospital	Additive EuroSCORE E/O 11/43 = 0.3 Logistic EuroSCORE E/O 31/43 = 0.7 Parsonnet E/O 26/43 = 0.6
Toumpoulis IK et al. US 2003	n=3,760 1992-2002	B	EuroSCORE in prediction of short- and long-term mortality and across risk categories	Mortality Morbidity LOS	Hospital 30 days 10 years	Long-term mortality AUC 0.72; HL n/a *poorly specified short-term follow-up with lower observed hospital mortality than 30-day mortality EuroSCORE risk categories were associated long-term mortality, short- long-term morbidity, and LOS
Vanagas G et al. Lithuania 2003	n=444 2002	A	EuroSCORE, Parsonnet, Ontario and QMMI score	Mortality	Hospital	EuroSCORE AUC 0.79; HL n/a; E/O 7.8/5.6 = 1.4 Parsonnet AUC 0.90; HL n/a; E/O 14.9/5.6 = 2.7 Ontario AUC 0.79; HL n/a; E/O 3.6/5.6 = 0.6 QMMI score AUC 0.87; HL n/a; E/O 10.4/5.6 = 1.9 All scores: HL n/a; Pearson correlation coefficient <0.05
Huijskes RV et al. Netherland 2003	n=7,282 1997-2001	C+CV V	Validate additive EuroSCORE and the local Amphiascore	Mortality	Hospital	EuroSCORE AUC 0.84; HL n/a; E/O n/a *Mortality was overestimated in high-risk patients Amphiascore AUC 0.84; HL n/a;
Al-Ruzzeh A et al. UK 2003	n=2,223 1996-2000	D	EuroSCORE, Parsonnet, ACC/AHA and UK CABG Bayes score in a multicenter comparison on OPCAB surgery	Mortality	Hospital	EuroSCORE AUC 0.75; HL <0.01; E/0 2.6/1.4 = 1.9 *EuroSCORE poor fit for OPCAB Parsonnet AUC 0.74; HL <0.01; E/0 5.4/1.3 = 4.2 ACC/AHA AUC 0.75; HL 0.71; E/0 1.3/1.3 = 1.0 UK CABG Bayes AUC 0.81; HL 0.30; E/0 1.9/1.3 = 1.5

Alvarez M et al. Spain 2003	n=175 1999-2001	B+CV V	EuroSCORE in low-risk patients (EuroSCORE ≤2)	Mortality	Hospital	AUC n/a; HL n/a; E/0 = 1.3/0.8 = 1.6
Karabulut H et al. Turkey 2003	n=1,123 1999-2001	A	EuroSCORE in a Turkish cohort	Mortality	30 days	Overall AUC 0.82; HL n/a; E/0 3.7/1.2 = 3.1 CABG only AUC 0.83; HL n/a; E/O 3.2/1.1 = 2.9
Asimakopoulos G et al. UK 2003	n=2,223 1996-2000	C	EuroSCORE, Parsonnet, ACC/AHA and UK CABG Bayes score comparison	Mortality	Hospital	EuroSCORE AUC 0.76; HL <0.01; E/O = 0.9 Parsonnet AUC 0.73; HL <0.01; E/O = 1.7 ACC/AHA AUC 0.76; HL <0.01; E/O = 0.4 UK CABG Bayes AUC 0.77; HL <0.01; E/O = 0.9
Bridgewater B et al. UK 2003	n=8,572 1999-2002	B	Additive EuroSCORE grouped into low- and high-risk	Mortality	Hospital	Overall; AUC 0.75; HL n/a; E/O 3.0/1.7 = 1.8 Low-risk: AUC 0.72; HL n/a; E/O 2.3/1.0 = 2.3 High-risk: AUC 0.62; HL n/a; E/O 7.4/5.3 = 1.4
Michel P et al. France 2003	n=14,799 1995 EuroSCORE database	C+CV V T	Assessment of the additive and logistic EuroSCORE using the EuroSCORE database	Mortality	30 days	Additive EuroSCORE AUC 0.78; HL n/a; E/O 4.2/4.7 = 0.9 Logistic EuroSCORE AUC 0.78; HL n/a; E/O 4.8/4.7 = 1.0 The additive EuroSCORE model remains a simple "gold standard" for risk assessment in European cardiac surgery, usable at the bedside without complex calculations or information technology. The logistic model is a better risk predictor especially in high-risk patients and may be of interest to institutions engaged in the study and development of risk stratification
Gurler S et al. Germany 2003	n=751 1998	A	EuroSCORE grouped into low, medium and high-risk cate categories	Mortality	30 days	AUC n/a, HL n/a; E/O n/a EuroSCORE risk groups were associated with increased mortality
Mortasawi A et al. Germany 2003	n=8,769 1996-2002	A	EuroSCORE with and without age as a risk factor	Mortality	30 days	The 30 day mortality and the incidence of postoperative complications increased significantly with increasing age. The EuroSCORE without age estimated mortality more accurate as estimated from E/O ratios. AUC n/a; HL n/a
Calafiore AM et al. Italy 2003	n=510 CABG n=510 OPCAB 1994-2001	C D	Validate EuroSCORE in high- risk patients (EuroSCORE ≥6)	Mortality	30 days	CABG AUC n/a, HL n/a; E/O 7.8/5.9 = 1.3 OPCAB AUC n/a, HL n/a; E/O 7.8/3.1 = 2.5 Estimated mortality higher than observed in both OPCAB and CABG
Benites R et al. Lithuania 2002	n=1,698 1997-2001	B	Validate the EuroSCORE retrospectively Abstract available in English	Mortality	Hospital	AUC n/a, HL n/a; E/O n/a/4.7 = n/a Non-survivors had higher EuroSCORE than survivors
Nashef SA et al. UK 2002	n=401,684 1998-1999 n=188,913 1995	B+CV V	Validate EuroSCORE on mortality in two North American cohorts from the STS database	Mortality	Hospital or 30 days	1995 Overall AUC 0.77; HL n/a; E/O 4.2/4.2 = 1.0 CABG AUC 0.78; HL n/a 1998-99 Overall AUC 0.77; HL n/a; E/O 4.0/4.0 = 1.0 CABG AUC 0.75; HL n/a

Kawachi Y et al. Japan 2002	n=260; 1994-96 n=259; 1996-98 n=284; 1998-2000	A	Validate EuroSCORE on mortality in three Japanese cohorts and according to risk categories	Mortality	30 days	Overall AUC 0.82; HL n/a; E/O n/a/4.5 = n/a 1994-96 AUC 0.83; HL n/a; E/O 5.3/6.5 = 0.8 1996-98 AUC 0.83; HL n/a; E/O 5.1/3.9 = 1.3 1998-2000 AUC 0.81; HL n/a; E/O 5.4/3.2 = 1.7 Observed mortality was lower than predicted mortality in 5 estimated risk categories. Quality of surgical care has improved gradually over the years
von Domburg RT et al. Netherlands 2002	n=832 1995-1996	C	EuroSCORE and Parsonnet	Mortality	Hospital 5 years	EuroSCORE and Parsonnet overestimated hospital risk in low-risk patients (EuroSCORE ≤8) and underestimated risk in high-risk patients. AUC n/a; HL n/a; E/O n/a
Kurki TS et al. Finland 2002	n=1,132 1999-2000	C	Validate EuroSCORE, CABDEAL, and Cleveland model	Mortality Morbidity	Hospital	EuroSCORE AUC 0.83 for mortality, and 0.69 for morbidity CABDEAL AUC0.71 for mortality, and 0.77 for morbidity Cleveland AUC 0.86 for mortality, and 0.69 for morbidity HL n/a
Pintor PP et al. Italy 2002	n=418 1993-1994	C	Validation of EuroSCORE, Parsonnet, Cleveland, French	Mortality	30 days	EuroSCORE AUC 0.81; HL n/a; E/O 2.3/1.7 = 1.4 Parsonnet AUC 0.60, HL n/a; E/O 1.1/1.7 = 0.6 Cleveland AUC 0.86; HL n/a; E/O 1.5/1.7 = 0.9 French Score AUC 0.82; HL n/a; E/O 1.8/1.7 = 1.1
Riha M et al. Austria 2002	n=126 1998-2001	D	EuroSCORE Retrospective	Mortality Morbidity	n/a “operative”	AUC n/a; HL n/a High EuroSCORE was associated with adverse OPCAB outcomes
Sergeant P et al. Belgium 2001	n=2,051 1997-2000	C	EuroSCORE in a single center cohort	Mortality	Hospital	AUC 0.83; HL n/a Overestimates in low risk, and underestimates in high risk patients. Should only be used for inter-institutional benchmarking with great caution.
Kawachi Y et al. Japan 2001	n=803 1994-2000	T	EuroSCORE and Parsonnet on mortality in cardiac and thoracic aorta surgery	Mortality	30 days	EuroSCORE AUC 0.82; HL n/a Parsonnet AUC 0.72; HL n/a
Pitkanen O et al. Finland 2000	n=4,592 1992-1996 n=821 1998-2000	A	To construct a new local risk prediction model and validate it against the EuroSCORE	Mortality Morbidity ICU stay	30 days	Mortality Local model AUC 0.84 EuroSCORE AUC 0.77 Morbidity Local model AUC 0.74 EuroSCORE AUC 0.74 ICU ≥2 days Local model AUC 0.81 EuroSCORE AUC 0.79 HL tests > 0.05 except on morbidity in the 1992-96 data.

Geissler HJ et al. Germany 2000	n=504 1998-1999	C+CV V T	Comparison of EuroSCORE, Parsonnet, Cleveland, French, Pons and Ontario risk scores	Mortality Morbidity	30 days	EuroSCORE AUC 0.79 for mortality, and 0.64 for morbidity Parsonnet AUC 0.76 for mortality, and 0.64 for morbidity Cleveland AUC 0.73 for mortality, and 0.69 for morbidity French Score AUC 0.72 for mortality, and 0.64 for morbidity Pons Score AUC 0.75 for mortality, and 0.68 for morbidity Ontario AUC 0.70 for mortality, and 0.62 for morbidity No information on HL calibration test was available The EuroSCORE, Parsonnet and Pons Score overestimated mortality
Stoica SC et al. UK 2000	n=3,118 1999-2000	A	EuroSCORE in a single center cohort	Mortality	Hospital	AUC 0.86 (0.81-0.90); HL 0.97
Roques F et al. EuroSCORE study group 2000		C+CV V T	The EuroSCORE study database was split country-specific datasets	Mortality	30 days	AUC: Germany 0.81; UK 0.79; Spain 0.74; Finland 0.87; France 0.82; Italy 0.82 All HL tests >0.05
Nashef SA et al. EuroSCORE study group 1999	n=13,302 (D) 1995 n=1,479 (V) 1995	C+CV V T	Developmental dataset had n=13,302. Validation dataset had n=1,479 patients. Applied to three risk groups: EuroSCORE 1-2, 3-5, >=6.	Mortality	30 days	Developmental dataset: AUC 0.79, HL 0.40 Validation dataset AUC 0.76, HL 0.68 Widespread use of the EuroSCORE is recommended.
Roques F et al. EuroSCORE study group 1999	n=19,030 1995	C+CV V T	Describe risk factors in the EuroSCORE database, n=19,030, 1995			

Abbreviations: A = all surgical procedures; B = on- and off-pump bypass; C = on-pump coronary bypass; D = off-pump coronary bypass; V = valve surgery ; AV = aortic valve replacement; MV = mitral valve replacement; CV= combined bypass and valve procedure; T = thoracic aortic surgery; G = grown-up congenital cardiac surgery; E = estimated mortality; O = observed mortality; E/O = mortality ratio; AUC = area under curve; HL = Hosmer-Lemeshow test; n/a = not available

Appendix 2: Definitions of the metabolic syndrome.

CLINICAL MEASURE	REAVEN 1998	WHO 1999	EGIR 1999	NCEPATP III 2001	AHA 2004	IDF 2006
Waist circumference	-	-	≥94 cm in men, ≥80 cm in women	≥102 cm in men, ≥88 cm in women	≥102 cm in men, ≥88 cm in women	Yes
BMI kg/m^2	-	>30 kg/m^2	-	-	-	>30 kg/m^2
Triglycerides mmol/L	-	≥1.7 mmol/L	≥2.0 mmol/L	≥1.7 mmol/L	≥1.7 mmol/L	≥1.7 mmol/L or treatment for hypertriglyceridemia
HDL-C	Increased LDL-C Decreased HDL-C	<0.9 mmol/L in men <1.0 mmol/L in women	<1.0 mmol/L or treatment for dyslipidemia	<1.0 mmol/L in men <1.3 mmol/L in women	<1.0 mmol/L in men <1.3 mmol/L in women	<1.0 mmol/L in men <1.3 mmol/L in women
Blood Pressure	Yes	≥140/90 mm Hg	≥140/90 mm Hg or antihypertensive treatment	≥130/85 mm Hg	≥130/85 mm Hg or antihypertensive treatment	≥130/85 mm Hg or antihypertensive treatment
Glucose	IGT	IGT, IFG, or T2DM	IFG ≥6.1 mmol/L	IFG ≥6.1 mmol/L	IFG ≥5.6 mmol/L or treatment for hyperglycemia	IFG ≥5.6 mmol/L or treatment for hyperglycemia or previously T2DM
Insulin Resistance	Yes Hyperinsulinemia	Yes	Yes	-	-	-
Microalbuminuria	-	Yes	-	-	-	-

Abbrevitations: HDL-C = high density lipoprotein - cholesterol; LDL-C = Low density lipoprotein - cholesterol; IGT = impaired glucose tolerance; IFG = impaired fasting glucose; T2DM = type 2 diabetes mellitus; WHO = World Health Organization; EGIR = European Group for the study of Insulin Resistance; NCEP-ATPIII = Third National Cholesterol Education Program Adult Treatment Panel; AHA = American Heart Association; IDF = International Diabetes Federation

Study I

Title

The EuroSCORE in Western Denmark. A population-based study.

Authors

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Abstract

Background: The predictive performance of the EuroSCORE has been questioned, as the constellation of risk factors has changed over time and quality of surgery has improved. Several existing validation studies have been hampered by methodological shortcomings. The present study aimed to examine the predictive ability of the EuroSCORE.

Methods: Prospectively registered patient and procedural characteristics were obtained from the Western Denmark Heart Registry on 21,664 patients, who had undergone on-pump cardiac surgery in 1999 to 2010. Complete follow-up regarding 30-day mortality was available through data linkage with the Danish Civil Registration System. The predictive ability of the logistic EuroSCORE was assessed using the area under curve (AUC) for discrimination test, the Hosmer–Lemeshow (HL) calibration test, and the ratio between the mean estimated and observed mortality (E/O).

Results: The prevalence of most individual EuroSCORE variables increased over time (in especially, patients became older and had more valve or combined procedures performed). The overall AUC was 0.79 (CI 95% 0.77–0.81), HL $p < 0.01$, and E/O 1.9. For CABG, AUC was 0.78 (CI 95% 0.75–0.81), HL $p < 0.01$, and E/O 2.3. For combined CABG and valve replacement, AUC was 0.69 (CI 95% 0.65–0.73), HL $p = 0.02$, and E/O 1.5. For aortic valve replacement, AUC was 0.76 (CI 95% 0.72–0.80), HL $p < 0.01$, and E/O 2.5. Furthermore, the overall and procedural specific E/O ratios tended to increase from 1999 to 2010. The EuroSCORE overestimated mortality across all levels of estimated risk, and in low and medium risk patients this overestimation increased most notably with time.

Conclusions: The EuroSCORE appear to uphold moderate to good discrimination and poor calibration. Despite substantial changes in risk factors during the study period, the EuroSCORE consistently overestimated 30-day mortality independent of the preoperative risk level and surgical procedure performed, indicating improved quality of surgery and patient care. A recalibration of the EuroSCORE is warranted.

1. Introduction

The EuroSCORE remains the most widely used preoperative risk prediction model in European cardiac surgery. However, during recent years a need for a revised preoperative risk prediction model has emerged [1, 2], as reports showing declining performance of the EuroSCORE risk-prediction are mounting [3-9]. Since the primary data collection in 1995 and the introduction of the EuroSCORE in 1999, surgical techniques and non-surgical patient care have improved and the constellation of comorbidity, patient age, as well as the type of surgery performed have changed [9]. Mortality now appears to be highly overestimated [4, 5, 9, 10]. However, many previous validation studies have been hampered by methodological shortcomings, such as small sample sizes, non-population based cohorts, and incomplete follow-up limited to the postoperative in-hospital period [5, 9, 11-14].

Exact knowledge of the accuracy of the presently used version of the EuroSCORE remains important mainly to facilitate proper preoperative patient information and outcome quality measures used for comparison between countries, institutions and surgeons. In Denmark, detailed pre- and perioperative data have been registered in the Western Denmark Heart Registry (WDHR) since 1999. The registry now contains valuable data on more than 23,000 cardiac surgical procedures performed at four regional surgical institutions [15]. Record linkage between the Danish health care registries offers an opportunity for complete patient follow-up also after patient discharge.

We hypothesized, that the logistic EuroSCORE overestimated patient risk both overall and independent of the different type of cardiac surgery performed, and secondly that the ratio between the estimated and observed 30-day postoperative mortality gradually increased in a period from 1999 to 2010. The present study aimed to assess the overall and the procedure-specific predictive ability of the logistic EuroSCORE regarding 30-day mortality in a large Danish cohort, including the possible temporal changes.

2. Materials and Methods

2.1. Design

We conducted a population-based prospective cohort study in Western Denmark, which has a primarily Caucasian mixed rural-urban population of approximately 3 million inhabitants. The Danish National Health Services provides a free universal tax-supported health care to the entire population. Since 1968 all Danish residents have been assigned a unique 10-digit civil registration number that allows unambiguous record linkage on individual level data between the Danish health databases. Prospectively registered patient and procedural characteristics were obtained from the WDHR and the Danish National Registry of Patients. Information on mortality was obtained from the Danish Civil Registration System. The Danish Data Protection Agency permits linkage between the databases used in the present study. No individual patient consent was required.

2.2. Patient population

All adult patients undergoing on-pump cardiac surgery from January 1, 1999 to March 31, 2010 at 1 in 4 regional cardiac centers (Aarhus University Hospital, Skejby; Odense University Hospital; Aarhus University Hospital, Aalborg; Varde Heart Centre) were included. Inclusion criteria were therefore in accordance to those reported in the original EuroSCORE study [16].

2.3. Outcome

The predictive ability of the EuroSCORE and estimated-to-observed mortality ratio (E/O) was assessed regarding the 30-day postoperative mortality.

2.3. Covariates

The additive and logistic EuroSCORE as well as the individual EuroSCORE risk factors were obtained from the WDHR. The 17 individual EuroSCORE risk factors have been described

elsewhere [17]. As also depicted in **Table 1**, the risk factors were grouped into patient-related, cardiac-related and surgery-related variables.

For the purpose of the clinical interpretation of the results, in addition to the overall study group 4 procedural groups were constructed according to the type of surgery performed: 1) isolated coronary artery bypass grafting (CABG), 2) combined CABG and valve surgery, 3) isolated aortic valve surgery, and 4) isolated mitral valve surgery. Other constellations of procedures, e.g. replacement or repair of tricuspidal and pulmonary heart valves, surgery on the thoracic aorta, and composite aortic grafts were not examined as individual subgroups.

Other baseline patient characteristics included smoking habits, body mass index, blood pressure, diabetes, dyslipidemia, prior ischemic peripheral-, cerebral-, or cardiovascular disease, history of arrhythmias, as well as previous cardiac surgery. Information on the preoperative use of ACE inhibitors, AT-II antagonists, beta blockers, calcium channel blockers, anti-diabetic, lipid lowering and anti-platelet drugs were also available.

If data regarding date of surgery as registered in the WDHR was incomplete or did not internally correspond to data regarding induction of anaesthesia or admission to the intensive care unit, the dates of operation were ascertained through linkage to the Danish National Registry of Patients. Likewise, inadequate registration of procedure codes was ascertained through registry linkage to the Danish National Registry of Patients.

2.4. Registries and databases

The WDHR, which was established in 1999, is a regional administrative and clinical register including detailed records on baseline patient characteristics and data regarding all cardiac procedures performed, as well as perioperative covariates and outcomes [15]. Since the introduction of this registry, the surgical cardiac centers in Aarhus, Odense, and Aalborg have entered the aforementioned data into the register. Since 2005, Varde Heart Center has also contributed with information on patients who underwent operation. The registry includes data on all

of the risk factor included in the EuroSCORE, as well as the total estimated risk. In each case, the chief surgeon is responsible for assuring the correct registration of all risk factors. The database platform was set up for preoperative registration of risk factors. In emergency cases however, postoperative data registration is allowed. From 1999 to 2006, a risk factor not registered after EuroSCORE registration initiation was considered as being not present (or reference). However, after a change in the database interface, complete registration of all EuroSCORE risk factors has been mandatory since 2006.

The Danish National Registry of Patients is a population-based administrative register established in 1977. It holds data on all hospitalizations in somatic Danish hospitals, including the dates of patient admission and discharge, the procedure(s) performed, and up to 20 discharge diagnoses coded by physicians according to the International Classification of Diseases (the 8th revision [ICD-8] until the end of 1993 and 10th revision [ICD-10] thereafter, as the 9th revision [ICD-9] was not implemented in Denmark). Since 1995, patient discharges from emergency rooms and outpatient clinics have also been registered in this registry.

The Danish Civil Registration System has kept current records (electronically updated on a daily basis) of the entire Danish population, including vital status, date of death, residence, and migration, since 1968.

2.5. Statistical analyses

The prevalence of the individual variables of the EuroSCORE model were compared between the WDHR and the original EuroSCORE databases using a two-sided equality of proportion test for binomial variables and the independent *t*-test for comparison of means for parametric continuous variables. In order to assess changes over time, the dataset was split into six biennial periods. The performance of the EuroSCORE risk estimation was assessed from discrimination and calibration analyses as well as use of the estimated-to-observed (E/O) mortality ratios across both biennial periods, the type of surgery performed, and across varying levels of estimated preoperative risk.

Discrimination refers to the ability of the score to distinguish patients who died from those who survived. Discrimination was assessed by the area under the receiver operative characteristic curve (AUC). The AUC is the probability that a patient who died had a higher risk score than a patient who survived. An AUC value of 0.5 indicates random prediction. Calibration refers to the accuracy of a score's estimation. Model calibration was assessed using the Hosmer–Lemeshow (HL) test. Data were split into 10 groups of equal sizes, on the basis of the estimated probability of death. In each group, the estimated and observed number of deaths were then compared. A significant HL test indicates that the observed and estimated values were not satisfactory similar. Weighted linear regression analyses were applied to the E/O ratios across the biennial periods in order to estimate statistical significance in the temporal changes.

For all analyses, a two-tailed *p*-value less than 0.05 were considered statistically significant. Analyses were performed using the Stata® 11.0 package (StataCorp LP, Texas, US).

4. Results

Information on 21,861 patients who had undergone on-pump operations was available. The EuroSCORE was missing in 197 (0.9%) of these patients, leaving 21,664 patients available for analyses. Aarhus University Hospital, Skejby, contributed with 9,422 (44%) patients, Odense University Hospital with 6,453 (30%), Aarhus University Hospital, Aalborg, with 4,319 (20%), and Varde Heart Center contributed with 1,470 (7%) patients. The majority of the individual risk factors contained in the EuroSCORE risk prediction model were more prevalent in the WDHR cohort than in the original EuroSCORE study (**Table 1**).

Upon examination of data for the 21,664 patients, we found that the presence of several characteristics changed from 1999 to 2010. Patients undergoing medical treatment for hypercholesterolemia or hypertension increased from 34% to 65% and 32% to 67%, respectively. Likewise, preoperative diabetes was present in 13% of patients in 1999–2000 and in 20% in 2009–2010. Furthermore, twenty-two percent (n = 4,721) of the patients in the present study group were more than 75 years in age, whereas this age group represented only 10% in the original EuroSCORE study population of 19,030 patients.

Patients from the WDHR with missing EuroSCORE had isolated CABG (113 patients, 57%), isolated aortic valve surgery (19 patients, 10%), or combined CABG and valve surgery (21 patients, 11%) and had predominantly undergone surgery at Varde Heart Center in 2005 (104 patients, 53%). Furthermore, they tended to be 2 years younger on average ($p = 0.06$), but did not differ with regard to gender (26% female, $p = 0.89$). After the change in the database registration interface that occurred in 2006, less than 0.5% of the patients had missing information on the individual EuroSCORE risk factors. Before 2006, missing values were present in less than 4% of each risk factor, except for left ventricular dysfunction (5%) and serum creatinine above or below 200 µmol/L (36%).

The type of surgery changed over time. In 1999, isolated CABG was performed in 77% of the patients, but this surgery only contributed with 40% of the procedures performed in 2009 and 2010. Accordingly, procedures other than bypass increased from 23% to 60% during the same period. Furthermore, isolated valve procedures and combined bypass and valve procedures accounted for increases from 12% to 28% and 6% to 13%, respectively.

In **Table 2,** the results on both the overall, specific procedures, and biennial periods of EuroSCORE risk prediction are shown, along with the discriminative and calibrations test statistics. Briefly, the EuroSCORE overestimated mortality independent of the surgery performed. The calibration test showed poor model fit regarding CABG, combined CABG and valve replacement, aortic valve replacement, and other procedures (all $p < 0.05$), but an acceptable model fit for mitral valve replacement ($p = 0.20$). The overall study EuroSCORE discrimination was 0.79 (CI 95% 0.77–0.81). Discrimination analyses varied from 0.69 (95% CI 0.65–0.73) for combined CABG and valve replacement and up to 0.84 (95% CI 0.78–0.90) regarding mitral valve replacement. Across the biennial periods, the E/O ratios appeared to increase for the overall study group and all types of surgery. When applying weighted regression analyses, these trends of increased overestimation were confirmed (overall group, $p = 0.06$; combined CABG and valve procedures, $p = 0.03$; mitral valve, $p = 0.06$; aortic valve, $p = 0.12$) with the exception of isolated CABG ($p = 0.63$). Moreover, with the exception of isolated aortic or mitral valve replacement, the estimates of the discrimination tests tended to improve over time, whereas most procedure specific calibration tests showed acceptable model fit over time (**Table 2**). For the overall study group, an approximate 2-fold overestimation of actual mortality appeared to be independent of the level of estimated risk (**Table 3**). However, regarding the estimated risk levels, the most noteworthy biennial increases in E/O was found in patients with low-medium risk (0-12%) (**Table 3**).

4. Discussion

The results from this population-based cohort study suggest that the EuroSCORE overestimated mortality across all levels of estimated risk and independent of the type of surgery performed.

Upon comparison of the individual EuroSCORE risk factors between the original EuroSCORE study and the overall Western Denmark Heart Registry population, we found substantial differences in the risk profiles. These observations are consistent with previous results from registries in other European countries [5, 9].

The overestimation in mortality (2-fold for the overall population) was greater for valve procedures (up to 5-fold) than for CABG procedures (approximately 2- to 3-fold in recent years). Previous reports by Wendt et al. and Barili et al. documented similar substantially overestimated mortality following aortic valve replacement [18, 19], whereas other studies have found a more moderate overestimation (approximately 2-fold) [20, 21]. In a metaanalysis, Parolari et al. reported a 4-fold overestimation of mortality for CABG performed in 1999–2008 [22]. However, this analysis included studies assessing both in-hospital and 30-day mortality, which may have augmented the EuroSCORE mortality overestimation. Nevertheless, the results from our study were in line with those previously reported in a Norwegian study by Engebretsen et al., who found a substantial overestimation of mortality among CABG patients [3]. The present study was comprised of data gathered up to 2010. In contrast, most comparable studies have not included data on patients operated on later than 2007, and have not examined possible changes in risk factors and the performance of the EuroSCORE over time. Therefore, direct comparison across studies faces some limitations, but in general, our up-to-date results are in line with the interpretation of previous studies. In 2004, a meta-analysis by Gogbashian et al. concluded that the additive EuroSCORE model underestimated mortality in high-risk patients [4]. Other studies revealed that the logistic EuroSCORE model improved precision in this group of patients relative to the output of the additive

EuroSCORE model [23, 24]. However, consistent with other studies, our data suggested that the logistic EuroSCORE overestimated mortality also in operated high-risk patients [11, 25].

The HL test showed poor calibration in the overall dataset and in the data for the surgical subgroups. However, despite overestimation of mortality, varying degrees of acceptable model fit were found in surgical subgroups assessed in biennial periods. This seemingly paradox may be explained by small subgroup sizes, as the HL test then might show good model fit, but at the same time allow skewed risk prediction with potential substantial clinical importance.

The overall discriminative accuracy of mortality in this study was comparable to that of the original EuroSCORE study (AUC, 0.79) [17]. We found some indications that the discriminative accuracy may have improved over the years (AUC was 0.76 in 1999 and up to 0.81 in 2010). Upon stratification of the patients according to surgery type, this pattern was most pronounced for bypass procedures either isolated (AUC was 0.71 in 1999 and up to 0.84 in 2010) or in combination with aortic valve replacement (AUC was 0.56 in 1999 and up to 0.82 in 2010). In accordance with earlier studies, the EuroSCORE generally reached a somewhat lower discriminative accuracy which remained approximately unchanged over time for isolated aortic valve replacement [7, 20, 26]. This finding may be explained by the fact that the vast majority (approximately 95%) of patients included in the developmental EuroSCORE dataset underwent CABG, and thus the model would likely tend to perform best in bypass patients.

Despite substantial changes in the constellation of preoperative risk (i.e., age and types of surgery), the progressively increased risk apparently failed to translate into increased 30-day mortality. In fact, the short-term mortality tended to decrease, which suggests that the quality of patient care has likely improved considerably. In recent times, elderly patients (above 80 years in age) and high-risk patients with severe comorbidity or procedural challenges can also face cardiac surgery with an acceptable level of risk. However, applying the estimated probabilities to individual

patients should be carried out with caution. In each case, an individual subjective clinical risk assessment and interdisciplinary treatment strategy remain crucial.

Traditional open heart surgery faces challenging competition from less invasive procedures. Therefore, for proper risk stratification, quality assessment, and quality improvement tools, it is important to have up-to-date knowledge on both predicted and observed risk. From this perspective, the present study emphasizes the need for recalibration or revision of the EuroSCORE, perhaps with inclusion of new markers of risk or procedure-specific models.

Strengths and limitations

We studied a well-defined population-based cohort undergoing on-pump cardiac surgery in Western Denmark. The WDHR is a valuable registry for longitudinal clinical research, and data on valve and CABG registration show a high degree of correspondence to data registered in the Danish National Registry of Patients (97% and 98% respectively) [15].

The dates of death registered in the Civil Registration System are assumed to be without error, or at most, to contain very limited non-differential misclassification that would not impact the observed 30-day mortality.

Only 0.9% of the EuroSCORE was missing, and when considering gender, age and type of surgery, it appeared that these patients were mainly low risk patients who would most likely not score significantly different than the full study group. For most individual EuroSCORE risk factors, we had only very few missing values, and thus, the study had high data completeness.

We recognize that a relatively large prevalence of missing values regarding serum creatinine does not support this notion. The vast majority of missing creatinine values was present before 2006, when complete data registration for each risk factor was not mandatory. However, among the missing creatinine values, it seems likely that the fraction of creatinine levels below 200 µmol/L, would be greater than that registered, as high creatinine levels tend to enhance the surgeons care

for correct and complete data registration. If so, misclassification of risk factors due to incomplete data registration would most likely have led to conservative E/O estimates in the early years, and consequently, any temporal changes in E/O ratios may have been outbalanced.

The EuroSCORE study group has recently commenced the immense task of establishing a new European risk prediction algorithm. We look forward to those results, but until then, knowledge on the performance of the existing EuroSCORE in contemporary data remains important internationally.

We conclude that in Western Denmark, the EuroSCORE risk prediction model overestimates 30-day mortality notably and independent of the type of major cardiac surgical procedure performed as well as across all levels of estimated risk. Furthermore, for heart valve procedures alone or in combination with CABG, the estimated/observed mortality ratio increased significantly during the last 11 year of cardiac surgery registered in Western Denmark. The present EuroSCORE can no longer resist recalibration and future acknowledged risk prediction models should be continuously validated and recalibrated when needed.

5. Acknowledgements

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Table 1. EuroSCORE risk factors

EuroSCORE risk factors	Prevalence in the EuroSCORE database	Prevalence in the WDHR cohort	*p*-value for difference
Patient related	**N=19,030**	**N=21,664**	
Age (mean [SD])	62.5 [10.5]	65.5 [11.2]	<0.01
Female	27.8	27.4 (0.3)	0.39
Chronic pulmonary disease	3.9	10.1 (0.2)	<0.01
Extracardiac arteriopathy	11.3	9.0 (0.2)	<0.01
Neurological dysfunction	1.4	7.7 (0.2)	<0.01
Previous cardiac surgery	7.3	5.6 (0.2)	<0.01
Serum creatinine	1.8	3.0 (0.1)	<0.01
Active endocarditis	1.1	1.7 (0.1)	<0.01
Critical preoperative state	4.1	4.9 (0.1)	<0.01
Cardiac related			
Unstable Angina	8.0	13.3 (0.2)	<0.01
LVEF 30-50 %	25.6	27.7 (0.3)	<0.01
LVEF <30 %	5.8	6.4 (0.2)	<0.01
Recent myocardial infarction	9.7	17.3 (0.3)	<0.01
Pulmonary hypertension	2.0	5.5 (0.2)	<0.01
Operation related			
Emergency surgery	4.9	5.6 (0.2)	<0.01
Other than isolated CABG	36.4	41.6 (0.3)	<0.01
Surgery on thoracic aorta	2.4	2.7 (0.1)	0.07
Postinfarct septal rupture	0.2	0.2 (<0.1)	0.29
	The EuroSCORE developmental and validation dataset	**The WHDR cohort**	
Risk model	**N=14,799**	**N=21,664**	
Additive EuroSCORE	4.2 (CI 4.2-4.3)	5.6 (CI 5.6-5.7)	<0.01
Logistic EuroSCORE	4.8 (CI 4.7-4.9)	8.0 (CI 7.9-8.2)	<0.01

Abbreviations: N = number; SD = standard deviation; CI = 95 % confidence interval; WDHR = Western Denmark Heart Registry; LVEF = left ventricular ejection fraction; CABG = coronary artery bypass grafting
Legends: percentage (standard error)

Table 2. EuroSCORE risk prediction in biennial periods

Total study		**1999-2000**	**2001-2002**	**2003-2004**	**2005-2006**	**2007-2008**	**2009-2010**
Number	**21,664**	3,449	4,387	3,552	3,627	4,196	2,455
Observed	**3.9**	4.2	3.6	4.4	3.8	3.3	4.2
Estimated	**7.5**	6.1	6.1	6.6	9.3	8.7	8.8
E/O	**1.92 (1.83-2.08)**	1.45 (1.24-2.69)	1.69 (1.45-2.03)	1.50 (1.29-1.73)	2.45 (2.11-2.91)	2.64 (2.29-3.22)	2.10 (1.76-2.59)
AUC	**0.79 (0.77-0.81)**	0.76 (0.72-0.79)	0.78 (0.74-0.82)	0.81 (0.78-0.85)	0.81 (0.77-0.84)	0.81 (0.78-0.85)	0.81 (0.76-0.85)
HL test	**<0.01**	<0.01	<0.01	<0.01	<0.01	0.03	0.11
Isolated CABG procedures							
Number	**12,427**	2,622	3,097	2,056	1,643	1,992	1,017
Observed	**2.4**	2.6	1.9	3.0	2.6	2.0	3.3
Estimated	**5.4**	5.0	4.8	5.1	6.7	5.8	6.4
E/O	**2.25 (2.00-2.45)**	1.92 (1.56-2.50)	2.53 (2.00-3.43)	1.70 (1.38-2.32)	2.58 (1.97-3.72)	2.90 (2.23-4.46)	1.94 (1.45-2.91)
AUC	**0.78 (0.75-0.81)**	0.71 (0.65-0.77)	0.71 (0.64-0.78)	0.84 (0.78-0.89)	0.84 (0.78-0.89)	0.80 (0.72-0.89)	0.84 (0.76-0.91)
HL test	**<0.01**	<0.01	0.22	<0.01	0.17	0.51	0.82
Combined CABG and valve procedures							
Number	**2,735**	233	435	509	574	586	398
Observed	**7.2**	10.3	9.4	9.2	5.7	4.8	5.8
Estimated	**10.7**	10.0	10.1	10.0	11.1	11.7	10.5
E/O	**1.49 (1.32-1.73)**	0.97 (0.70-1.56)	1.07 (0.83-1.51)	1.09 (0.85-1.49)	1.95 (1.44-1.92)	2.44 (1.80-3.90)	1.81 (1.30-3.00)
AUC	**0.69 (0.65-0.73)**	0.56 (0.45-0.68)	0.71 (0.64-0.79)	0.65 (0.57-0.73)	0.71 (0.61-0.80)	0.73 (0.63-0.83)	0.82 (0.72-0.92)
HL test	**0.02**	0.24	0.33	0.41	0.02	0.90	0.55
Isolated aortic valve procedures							
Number	**3,396**	294	522	633	699	755	493
Observed	**3.2**	6.8	4.4	3.5	2.0	1.6	3.4
Estimated	**8.0**	8.7	7.4	7.4	8.5	8.3	7.7
E/O	**2.50 (2.11-3.08)**	1.28 (0.90-2.23)	1.68 (1.19-2.85)	2.11 (1.51-3.70)	4.25 (2.80-8.50)	5.19 (3.32-11.9)	2.25 (1.51-4.28)
AUC	**0.76 (0.72-0.80)**	0.76 (0.64-0.87)	0.72 (0.62-0.83)	0.81 (0.73-0.89)	0.79 (0.68-0.90)	0.75 (0.63-0.87)	0.74 (0.64-0.84)
HL test	**<0.01**	0.89	0.15	0.20	0.21	0.42	0.33
Isolated mitral valve procedures			**1999-2002**		**2003-2006**		**2007-2010**
Number	**962**		256		387		319
Observed	**5.2**		7.0		5.7		3.1
Estimated	**9.8**		9.1		10.6		9.3
E/O	**1.88 (1.48-2.58)**		1.30 (0.89-2.33)		1.86 (1.33-3.12)		3.00 (1.82-7.75)
AUC	**0.84 (0.78-0.90)**		0.87 (0.76-0.98)		0.86 (0.77-0.94)		0.76 (0.58-0.95)
HL test	**0.20**		0.23		0.17		0.94

Abbreviations: AUC = area under curve; HL = Hosmer–Lemeshow test; E/O = estimated to observed mortality ratio

Table 3. E/O ratios in biennial periods and across estimated risk level

				1999-2010 N=21,644	1999-2000 n=3,449	2001-2002 n=4,387	2003-2004 n=3,552	2005-2006 n=3,627	2007-2008 n=4,196	2009-2010 n=2,455	
Risk (%)	**N**	**Estimated (%)**	**Observed (%)**	**1999-2010 E/O**	**E/O**	**E/O**	**E/O**	**E/O**	**E/O**	**E/O**	***p***
0<3	8,802	1.79	0.94 (0.74-1.14)	***1.90*** (1.57-2.42)	**1.18** (0.85-1.96)	**1.54** (1.10-2.60)	**1.74** (1.17-3.41)	**4.6** (2.45-37.1)	**3.49** (2.06-11.3)	**2.08** (1.19-7.97)	0.04
3<6	5,393	4.31	2.26 (1.87-2.66)	***1.91*** (1.62-2.30)	**1.17** (0.86-1.80)	**2.09** (1.48-3.51)	**1.85** (1.31-3.16)	**2.31** (1.57-4.38)	**2.50** (1.70-4.74)	**2.05** (1.33-4.44)	0.07
6<9	2,704	7.36	4.59 (3.80-5.37)	***1.73*** (1.37-1.94)	**1.14** (0.83-1.83)	**1.44** (1.05-2.31)	**1.08** (0.79-1.73)	**2.05** (1.41-3.77)	**2.42** (1.63-4.70)	**2.31** (1.48-5.24)	0.05
9<12	1,382	10.4	4.99 (3.84-6.14)	***1.60*** (1.69-2.71)	**2.09** (1.32-4.99)	**1.50** (1.02-2.78)	**1.47** (0.99-2.89)	**1.89** (1.24-4.05)	**4.28** (2.47-16.2)	**3.08** (1.72-15.0)	0.24
12<15	861	13.3	6.16 (4.55-7.76)	***2.16*** (1.71-2.92)	**3.31** (1.68-143)	**1.34** (0.89-2.69)	**1.62** (1.03-3.79)	**2.49** (1.55-6.36)	**3.54** (2.04-13.3)	**2.21** (1.28-8.16)	0.11
15<25	1,302	19.0	8.83 (7.29-10.4)	***2.15*** (1.83-2.61)	**1.51** (1.06-2.63)	**1.85** (1.32-3.14)	**1.80** (1.25-3.22)	**2.84** (1.96-5.16)	**2.63** (1.88-4.34)	**2.27** (1.54-4.31)	0.05
25<50	867	34.6	17.0 (14.5-19.5)	***2.04*** (1.77-2.39)	**1.39** (1.03-2.15)	**2.20** (1.52-3.96)	**1.39** (1.06-2.00)	**2.38** (1.76-3.67)	**3.05** (2.22-4.86)	**2.03** (1.46-3.29)	0.18
50-100	353	66.2	36.0 (30.9-41.0)	***1.84*** (1.61-2.14)	**2.42** (1.48-6.62)	**1.53** (1.11-2.46)	**1.20** (0.90-1.77)	**2.38** (1.82-3.44)	**1.88** (1.47-2.59)	**1.57** (1.17-2.40)	0.76

Abbreviations: E/O = estimated to observed mortality ratio; N = number; *p* = *p*-value for weighted linear regressions

Study II

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Negative results - Cardiac general

Microalbuminuria and short-term prognosis in patients undergoing cardiac surgery☆

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Abstract

Objective: To examine if preoperative microalbuminuria (MA) is associated with in increased risk of adverse outcomes in patients undergoing elective cardiothoracic surgery, and if adding information on MA could improve the accuracy of the additive EuroSCORE. **Methods:** In a follow-up study we included 962 patients undergoing elective cardiothoracic surgery from 1 April 2005 to 30 September 2007 at our department. MA (urine albumin/creatinine ratio between 2.5–25 mg/mmol) was assessed in a morning spot-urine sample. We used population-based medical registries for 30-day follow-up and compared the length of stay and adverse outcomes including (i) all-cause death, myocardial infarction, stroke, or atrial fibrillation, (ii) surgical reintervention, renal insufficiency, sternal wound infection, or septicaemia among patients with and without MA. **Results:** MA was found in 180 (18.7%) patients. The risk of both combined outcomes (adjusted odds ratios (ORs): 1.00 (95% confidence interval (CI): 0.77–1.30) and 1.18 (95% CI: 0.79–1.75), respectively) and most individual outcomes did not differ between the micro- and normoalbuminuric patients. The patients with MA and an additive EuroSCORE of 5 had a significantly prolonged median length of intensive care unit (ICU) stay (0.15 days [95% CI: 0.04–0.26]) and total hospital stay (0.5 days [95% CI: 0.04–0.96]). Patients with MA had a higher risk of postoperative septicaemia (OR: 12.1 [95% CI: 3.2–45.9]). Area under receiver operating characteristics curves of the EuroSCORE with regard to 30-day mortality was 0.86 both with and without MA. **Conclusions:** Preoperative MA in patients undergoing elective cardiothoracic surgery was not associated with most early adverse outcomes. However, risk of septicaemia was higher and patients with MA also had a marginally longer length of ICU and hospital stay. Information on preoperative MA did not improve the accuracy of the additive EuroSCORE.

Keywords: Adult; Cardiothoracic surgery; Comorbidity; Kidney; Outcomes

1. Introduction

Microalbuminuria (MA) is a well-known cardiovascular marker of risk in both diabetic and non-diabetic patients [1–3]. Increased urinary albumin excretion is a marker of endothelial dysfunction and severity of vascular disease [4], and for primary prevention of cardiovascular adverse events the early detection of MA is important [5]. The association between preoperative MA and postoperative outcomes in patients undergoing cardiothoracic surgery has only been sparsely examined and is as yet not clarified. In a relatively small prospectively studied population of 257 diabetic patients undergoing coronary artery bypass surgery, MA with a 30-mg/day cut-off was associated with a longer intensive care unit (ICU) stay but not significantly with a higher mortality [6]. Echahidi and colleagues retrospectively analyzed data from 5304 consecutive patients that had undergone coronary artery bypass surgery and reported that MA was not associated with operative mortality [7]. However, MA is closely related to the metabolic syndrome, a clustering of several cardiovascular risk factors, which was found to be a powerful risk factor of adverse outcome in patients undergoing coronary bypass surgery [7, 8]. Predictive models, such as the EuroSCORE are widely used in routine clinical practice for risk-prediction of patients undergoing cardiothoracic surgery [9]. These models are of major importance both for clinical decision making and for analysis and comparison of patient outcomes (e.g. between different types of interventions or

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across institutions). New markers of disease or adverse outcomes are constantly proposed and some of these markers may improve the accuracy of the established risk scoring systems. No existing studies have to our knowledge evaluated the effect of adding information on MA to the models. The aim of this study was to evaluate whether preoperative MA was associated with adverse outcomes at 30-day follow-up and whether MA could improve preoperative risk-prediction with EuroSCORE in patients undergoing elective cardiothoracic surgery.

2. Materials and methods

2.1. Design and setting

We conducted a prospective follow-up study in a region of Western Denmark with a mixed rural-urban population of ~1.2 million. From 1 April 2005 to 30 September 2007 we included patients undergoing elective cardiothoracic surgery at the Department of Cardiothoracic and Vascular Surgery at Aarhus University Hospital, Skejby, Denmark. All patients gave informed consent prior to inclusion. The study protocol was approved by the Regional Ethics Committee and the Danish Data Protection Agency.

2.2. Study population

Inclusion criteria were (i) age older than 18 years, (ii) elective cardiothoracic surgery (surgery performed more than two days after planning of the procedure) – including CABG or OPCAB surgery, valve surgery, thoracic aortic surgery, pulmonary thromboendarterectomy, grown up congenital heart disease procedures, or combined procedures. Exclusion criteria were (i) severe renal disease defined as a serum creatinine above 200 mmol/l or (ii) macroalbuminuria defined as a urine albumin creatinine excretion ratio (UACR) above 25 mg/mmol and (iii) previous heart or renal transplant surgery.

During the study period a total of 2216 patients underwent cardiothoracic surgery at the department. Patient screening and recruitment was done with assistance of a project nurse working half-time. Approximately 50% ($n=1193$) of the potential candidates for the study could therefore be screened consecutively. Seventy-eight were excluded because of acute surgery, 54 had known renal disease with serum creatinine >200 mmol/l. Out of the remaining, 1061 patients were randomly invited to participate. Only 12 patients did not accept participation and 1049 patients were included. Thereafter, a preoperative in-hospital baseline serum creatinine analyses revealed another 11 patients with increased levels above our exclusion criteria (Fig. 1). The UACR assessment resulted in exclusion of 22 patients with macroalbuminuria, and another 54 patients were excluded due to failure of UACR analyses, leaving 962 patients available for follow-up (Fig. 1).

2.3. Laboratory analyses

A preoperative fasting blood sample and a morning spot urine sample were collected and analyzed at the Department of Clinical Biochemistry, Aarhus University Hospital, Skejby, Denmark.

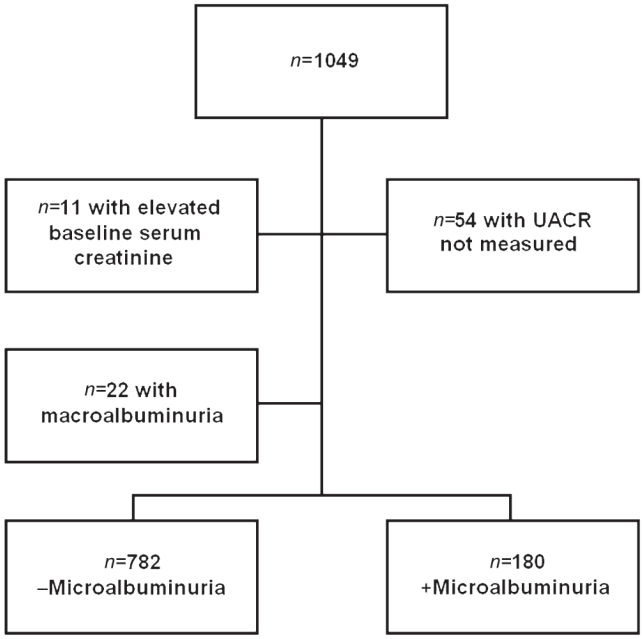

Fig. 1. Flowchart. UACR, urine albumin creatinine ratio

We defined MA as a UACR from 2.5 to 25 mg/mmol. Using a preoperative urine sample, the urinary albumin (mg/l) was assessed quantitatively by immunoturbidimetry and the urinary creatinine (mmol/l) was estimated by an enzymatic colorimetric test. The sensitivity level for urinary albumin was 7 mg/l. Since the UACR was constructed by dividing urinary albumin with urinary creatinine, albumin values below 7 mg/l could not contribute to an exact UACR (mg/mmol). We defined the UACR to be 0.1 mg/mmol in these patients.

2.4. Study outcomes

The study outcomes were a composite of (i) all-cause mortality, myocardial infarction, stroke, and atrial fibrillation or flutter, and (ii) surgical reintervention, deep sternal wound infection, septicaemia (defined as a positive bacteriaemic blood sample and/or clinical sepsis), and renal insufficiency (defined as more than a 100% increase of s-creatinine from baseline and/or use of dialysis). We also examined the individual elements of the composite outcomes as well as the length of stay in the ICU, and the total length of hospital stay.

Since 1968, all Danish residents have been assigned a unique civil registration number that allows unambiguous record linkage between the Danish health databases. The following Danish health databases were used for follow-up: the Danish Registry of Patients, the Prescription Database of Central Denmark Region, the Western Denmark Heart Registry and the National Register of Causes of Death.

The Danish National Registry of Patients was established in 1977 and holds data on all hospitalizations from somatic Danish hospitals, including dates of admission and discharge, procedure(s) performed, and up to 20 discharge diagnoses coded by physicians according to the International Classification of Diseases [8th revision (ICD-8) until the end of 1993, end 10th revision (ICD-10) thereafter]. Dis-

charge diagnoses are determined exclusively by the physician who discharges the patient and cannot be altered later for any other purposes. The Prescription Database contains data on all redeemed prescriptions at all pharmacies in the region since 1998. The main variables are the name of the drug, ATC code, package identifier, date of refill and codes identifying the prescribing physician. The Western Denmark Heart Registry, established in 1999, is a regional clinical register including detailed patient baseline characteristics, data for all cardiothoracic procedures performed, and per- and postoperative outcomes. The National Register of Causes of Death is a complete registry of dates and all causes of death in Denmark since 1973.

2.5. Covariates

Baseline characteristics and in-hospital preoperative data were collected from a preoperative interview, patient medical records, the Prescription Database, and the National Patient Register. For each patient a case-report-form was used.

Baseline data included age, gender, smoking habits, body mass index, blood pressure, prior ischaemic peripheral-, cerebro-, or cardiovascular disease, history of arrhythmias, diabetes and dyslipidaemia, cardiac ejection fraction, EuroSCORE, Charlson Comorbidity Index, serum levels of creatinine, electrolytes, albumin, glucose, white and red blood cell counts, thrombocytes and the UACR. We obtained information on use of medication up to 180 days preoperatively (e.g. ACE inhibitors, AT-II antagonists, beta blockers, calcium channel blockers, diuretics, lipid lowering drugs and antidiabetics).

The EuroSCORE was obtained from linkage to the Western Denmark Heart Registry. Missing values of the EuroSCORE were computed from information in the case-report-form and the medical records.

The Charlson Comorbidity Index was constructed by combining data from the case-report-form with data from the National Registry of Patients. The Charlson Comorbidity Index is a method of classifying comorbidity and in longitudinal studies predicts both short- and long-term mortality [10].

The pre- and postoperative covariates included type of operation, cardiopulmonary bypass time, aortic cross-clamp time, number and type of grafts, use of inotropics and antibiotics, and mechanical ventilation.

2.6. Statistical analyses

Baseline characteristics and pre- and postoperative variables were compared between groups with and without MA using Fisher's Exact test, independent *t*-tests and the Mann–Whitney test. The associations between MA and the composite and individual outcomes were then adjusted for both the additive EuroSCORE and other baseline potential confounding factors using multivariate logistic regression analyses.

Data on the length of ICU and hospital stay were analyzed on a logarithmic scale using linear regression analyses. Thereafter, we transformed the regression estimate and estimated the absolute difference in median length of stay between groups at different levels of the EuroSCORE. The standard error was calculated using the delta method. Kaplan–Meier survival curves were also constructed.

Discrimination and calibration analyses were done in order to examine whether MA in combination with EuroSCORE would predict risk more accurately than EuroSCORE alone. The association between the EuroSCORE and the combined as well as the single outcomes was estimated using logistic regression. Receiver operating characteristic curves were constructed to perform discrimination analyses. Calibration of the predicted risk was performed by Hosmer–Lemeshow goodness of fit analyses. The analyses were repeated using the logistic EuroSCORE. We also examined the association between the level of UACR and risk of various outcomes with spline regression in order to identify any non-linear patterns. Finally, separate subgroup analyses were done for the 877 patients undergoing only bypass surgery, valve surgery, thoracic aortic surgery, or combined procedures.

A two-tailed *P*-value <0.05 was considered statistically significant. Analyses were performed using the Stata® 10.0 package (StataCorp LP, Texas, US).

3. Results

3.1. Study cohort and surgical characteristics

Baseline patient and preoperative characteristics according to presence of MA are displayed in Table 1. The overall prevalence of MA in the cohort was 18.7% ($n=180$). The EuroSCORE was available for all included patients and the median EuroSCORE of the study cohort was 5.3 (range: 0–18).

On average patients with MA were 3.5 years older and had a higher EuroSCORE than the normoalbuminuric patients. Likewise, there were minor differences in smoking habits, type II diabetes, previous stroke, atrial fibrillation, ejection fraction, and use of antihypertensive medication.

Patients with MA had less solitary bypass procedures and more combined procedures performed, but there were no differences between groups with regard to use of extra corporal circulation and aortic cross-clamp time. The number of grafted coronary vessels in patients undergoing on- or off-pump coronary artery bypass surgery was slightly lower in the MA group.

3.2. The association between MA and postoperative adverse outcomes

In both the crude analyses and when adjusted for EuroSCORE length of ICU stay and total hospital stay were significantly prolonged in patients with MA (Fig. 2 and Fig. 3). A patient with an additive EuroSCORE equal to 5 had a 0.15 days (95% confidence interval (CI): 0.04–0.26) prolonged ICU stay and a 0.50 days (95% CI: 0.04–0.96) prolonged total hospital stay. Adjustment for additional covariates did not change these findings.

The crude and adjusted associations between MA and study outcomes are displayed in Table 2. Overall, the first predefined combined adverse outcome occurred in 369 (38%) patients, whereas the second combined outcome occurred in 140 (14.6%) patients.

Table 1
Baseline and peroperative patient characteristics

Variables	Total ($n=962$)	Normoalbuminuria ($n=782$)	Microalbuminuria ($n=180$)	*P*-value
Age (years)	65.6 [18–93]	65.0 [18–93]	68.5 [33–93]	<0.01
Gender (male)	699 (72.7)	573 (73.3)	126 (70.0)	0.40
Smoking habits				0.01
Non-smoker	341 (35.5)	293 (37.5)	48 (26.7)	
Current smoker	168 (17.5)	138 (17.7)	30 (16.7)	
Previous smoker	453 (47.0)	351 (44.9)	102 (56.7)	
Blood pressure				0.52
Grade I hypertension	286 (29.7)	230 (29.4)	56 (31.1)	
Grade II hypertension	178 (18.5)	142 (18.2)	36 (20.0)	
Grade III hypertension	85 (8.8)	66 (8.4)	19 (10.6)	
Diabetes				
Type I	17 (1.8)	11 (1.4)	6 (3.3)	0.11
Type II	127 (13.2)	95 (12.2)	32 (17.8)	0.05
Body mass index				0.27
<25	265 (27.6)	207 (26.5)	58 (32.2)	
25–30	401 (41.7)	333 (42.6)	68 (37.8)	
>30	296 (30.8)	242 (31.0)	54 (30.0)	
Previous MI	232 (24.1)	184 (23.5)	48 (26.7)	0.39
Previous AF	145 (15.1)	100 (12.8)	45 (25.0)	<0.01
Previous stroke	96 (10.0)	69 (8.8)	27 (15.0)	0.02
Previous PAD	50 (5.2)	39 (5.0)	11 (6.1)	0.58
Cardiac ejection fraction				0.02
<30	27 (2.8)	21 (2.7)	6 (3.3)	
30–50	182 (18.9)	135 (17.3)	47 (26.1)	
>50	753 (78.3)	626 (80.1)	127 (70.6)	
EuroSCORE	5.3 [0–18]	5.0 [0–18]	6.5 [0–18]	<0.01
Charlson comorbidity index	1.4 [0–8]	1.3 [0–7]	2.0 [0–8]	<0.01
Preoperative medicine				
ACE inhibitors	307 (31.9)	236 (30.2)	71 (39.4)	0.02
ATII antagonists	95 (9.9)	75 (9.6)	20 (11.1)	0.58
Beta blockers	607 (63.1)	491 (62.8)	116 (64.4)	0.73
Calcium channel blockers	258 (26.8)	200 (25.6)	58 (32.2)	0.08
Lipid lowering drugs	643 (66.8)	521 (66.2)	122 (67.8)	0.79
s-Creatinine	85 [22–191]	83 [22–189]	91 [35–191]	<0.01
Bypass surgery alone	404 (42.0)	341 (43.6)	63 (35.0)	0.04
Grafted vessels	2.5 [1–5]	2.6 [1–5]	2.3 [1–4]	0.01
Valve surgery alone	280 (29.1)	229 (29.3)	51 (28.3)	0.86
Composite aortic surgery	14 (1.5)	13 (1.7)	1 (0.56)	0.49
Aortic surgery	13 (1.4)	11 (1.4)	2 (1.1)	1.00
PTEA surgery	22 (2.3)	16 (2.1)	6 (3.3)	0.28
GUCH surgery	33 (3.4)	28 (3.6)	5 (2.8)	0.82
Other surgery	16 (1.7)	11 (1.4)	5 (2.8)	0.20
Combined procedures	180 88.7	133 17.0	47 26.1	0.01
ECC	853 (88.7)	694 (88.8)	159 (88.3)	0.90
ECC time (min)	103 [24–474]	102 [24–427]	108 [24–474]	0.25
Cross-clamp time (min)	62 [0–226]	62 [0–226]	65 [0–177]	0.31
Postoperative outcomes				
Outcomes[a]				
ICU stay (days)	1.0 [0–26]	1.0 [0–23]	1.0 [1–26]	<0.01
Ward stay (days)	4.0 [0–30]	4.0 [0–30]	4.0 [0–30]	0.68
Total hospital stay (days)	6.0 [0–30]	6.0 [0–30]	6.0 [2–30]	<0.01
Inotropics	131 (13.6)	88 (11.3)	43 (23.9)	<0.01
Mech. ventilation (h)	4.7 [0–544]	4.7 [0–505]	5.3 [1–544]	0.02

[a]Data are presented as means [range] or absolute numbers (%).
ACE, angiotensine converting enzyme; AF, atrial fibrillation or flutter; ATII, angiotensine II; ECC, extra corporal circulation; GUCH, grown-up congenital heart; MI, myocardial infarction; PAD, peripheral artery disease; PTEA, pulmonary artery thromboendarterectomy; ICU, intensive care unit; Mech., mechanical.

MA was not an independent predictor of most individual outcomes when adjusted for EuroSCORE. Still, MA remained a strong independent predictor of developing septicaemia (odds ratio (OR): 12.1 [3.19–45.9]). In the crude analysis MA was significantly associated with the second combined outcome (reintervention, sternal wound infection, septicaemia, and renal insufficiency) but not the first combined outcome (all-cause mortality, myocardial infarction, stroke, and atrial fibrillation or flutter). However, when adjusted for EuroSCORE this association did not remain significant. Further adjustment for other covariates did not change the risk estimates substantially.

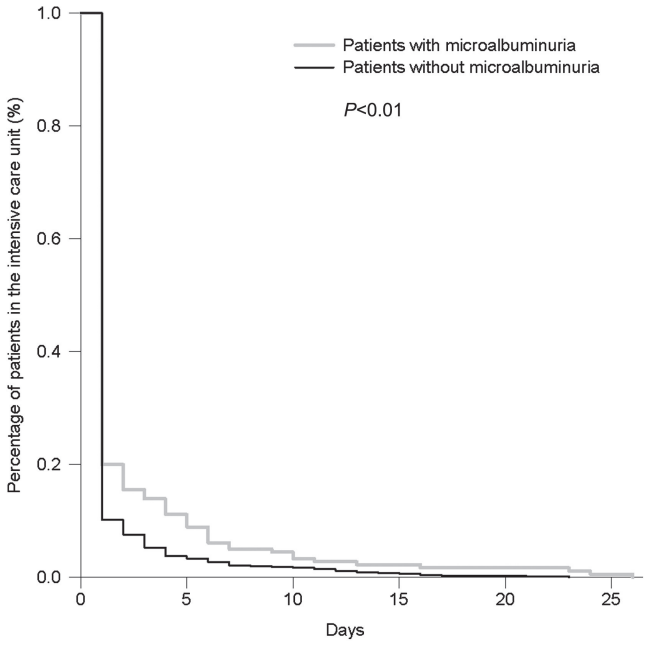

Fig. 2. Kaplan–Meier curves of the intensive care unit stay.

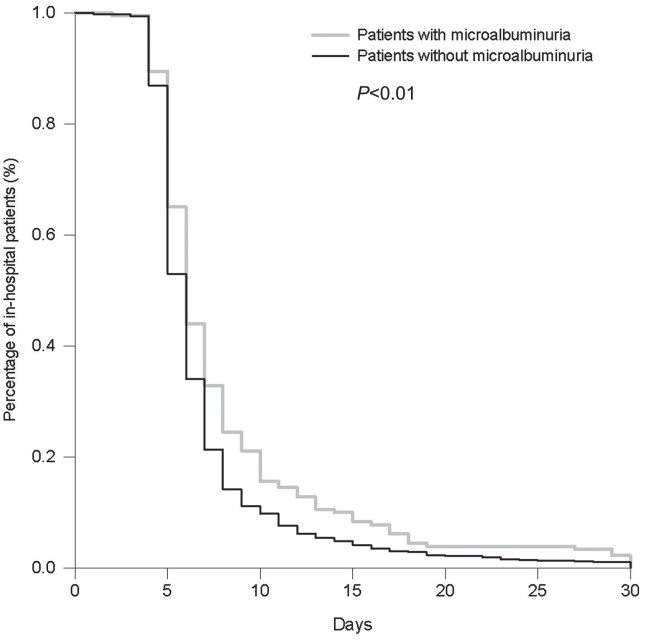

Fig. 3. Kaplan–Meier curves of the total hospital stay.

Analyzing the UACR as a continuous spline function did not reveal any threshold values in the association with postoperative outcomes. Furthermore, neither repeated analyses using the logistic EuroSCORE nor restricting all the analyses only to patients undergoing bypass surgery, valve surgery, thoracic aortic surgery, or combined procedures had significant impact on the risk estimates.

3.3. MA and the accuracy of the EuroSCORE

Table 3 shows the associations between the additive EuroSCORE and the postoperative outcomes. The ORs represent the increase in risk for each increment of 1 in the additive EuroSCORE. The EuroSCORE was an independent predictor of operative mortality (OR: 1.4 [1.20–1.63]) and was significantly associated with most other postoperative outcomes. Adding MA to the model had no impact on any of the relative risk estimates. The MA adjusted EuroSCORE was not statistical significantly associated with myocardial infarction, sternal wound infection, or septicaemia. The Hosmer–Lemeshow test for calibration showed good agreement for both the EuroSCORE (P-value = 0.22, $\chi^2 = 9.4$) and the EuroSCORE + MA (P-value = 0.44, $\chi^2 = 8.0$) model between the observed and expected number of deaths within 30 days after surgery. Except from 'surgical reintervention' (P-value = 0.03, $\chi^2 = 15.3$) the calibration tests of both the combined (P-value = 0.86, $\chi^2 = 3.3$) and the individual outcomes (P-values > 0.51, $\chi^2 < 6.2$) also showed statistical acceptable agreements, which were not substantially changed when information about MA wad added to the EuroSCORE (P-values > 0.32, $\chi^2 < 9.3$). The results of the discriminative statistics displayed in Table 4 show the areas under curves, which were not changed when the receiver operating characteristics of the EuroSCORE alone and the EuroSCORE + MA were compared.

4. Discussion

MA was found in almost one out of five patients in this prospective cohort of elective patients undergoing cardiothoracic surgery. Patients with MA had marginally longer ICU and total hospital stays and a higher risk of postoperative septicaemia. However, MA was not independently associated with other postoperative outcomes, including mortality, and adding information on MA did not improve the accuracy of the additive EuroSCORE.

The prevalence of MA depends on the underlying source population. Our study included patients with an a priori high cardiovascular risk-profile. The prevalence of MA was low when compared to the study by Yorgancioglu et al. [6], who found an overall prevalence of 34.6%. However, in contrast to their study, we included primarily non-diabetic patients.

The longer ICU stay in the group with MA corresponds well to earlier findings regarding MA and length of ICU stay [6]. The absolute differences in ICU and total hospital stay were small and may only be of little clinical relevance. However, the prolonged stay may represent complicated admissions in the group with MA. A longer ICU stay could potentially also through more intense care reduce the incidence of adverse outcomes in the patients with MA and thereby weaken the risk associated with MA.

MA is considered a marker of endothelial disease severity. Gosling and colleagues found a transient increase in albumin excretion rate in patients admitted with acute myocardial infarction [11]. The pathophysiologic cause of this increased leakage of albumin is not fully understood, but an acute inflammatory response is thought to participate in a worsening of endothelial dysfunction. In other settings it has been reported that the level of MA is related to adverse outcome after surgery or in acute diseases [11–15]. The surgical stress may accentuate this preoperative condition, primarily attributed to a systemic and renal

Table 2
Crude and adjusted odds ratios for postoperative outcomes according to preoperative microalbuminuria

Outcomes	Number of events		Crude model		Adjusted model[a]	
	−MA $n=782$	+MA $n=180$	OR	95% CI	OR	95% CI
All-cause death	9 (1.2)	4 (2.2)	1.95	0.59–6.41	1.02	0.29–3.64
Myocardial infarction	26 (3.3)	4 (2.2)	0.66	0.22–1.92	0.60	0.20–1.78
Stroke	29 (3.7)	9 (5.0)	1.37	0.64–2.94	1.07	0.48–2.37
Atrial fibrillation or flutter	264 (33.8)	65 (36.1)	1.11	0.79–1.56	1.02	0.72–1.44
Reintervention	58 (7.4)	21 (11.7)	1.65	0.97–2.79	1.35	0.78–2.34
Renal insufficiency	49 (6.3)	19 (10.6)	1.77	1.01–3.08	1.34	0.75–2.40
Sternal wound infection	8 (1.0)	2 (1.1)	1.08	0.22–5.16	1.08	0.22–5.33
Septicaemia	3 (0.4)	10 (5.6)	15.3	4.16–56.1	12.1	3.19–45.9
Combined outcome (i)	296 (37.9)	73 (40.6)	1.12	0.80–1.56	1.01	0.71–1.42
Combined outcome (ii)	102 (13.0)	36 (20.0)	1.67	1.09–2.54	1.36	0.88–2.10

[a]Adjusted for the additive EuroSCORE.
Combined outcome (i) includes all-cause mortality, myocardial infarction, stroke, and atrial fibrillation or flutter.
Combined outcome (ii) includes surgical reintervention, deep sternal wound infection, septicaemia, and renal insufficiency.
CI, confidence interval; MA, microalbuminuria; OR, odds ratio.

Table 3
Crude and adjusted odds ratios of postoperative outcomes according to the additive EuroSCORE

Outcomes	Crude model		Adjusted model[a]	
	OR	95% CI	OR	95% CI
All-cause death	1.40	1.21–1.63	1.40	1.20–1.63
Myocardial infarction	1.05	0.93–1.18	1.06	0.94–1.20
Stroke	1.16	1.05–1.28	1.15	1.04–1.28
Atrial fibrillation or flutter	1.06	1.01–1.10	1.05	1.01–1.10
Reintervention	1.14	1.06–1.23	1.13	1.05–1.22
Renal insufficiency	1.19	1.10–1.29	1.18	1.09–1.28
Sternal wound infection	1.00	0.81–1.24	1.00	0.81–1.24
Septicaemia	1.25	1.07–1.46	1.15	0.98–1.36
Combined outcome (i)	1.07	1.02–1.12	1.07	1.02–1.12
Combined outcome (ii)	1.15	1.08–1.22	1.14	1.07–1.21

[a]Adjusted for microalbuminuria.
Combined outcome (i) includes all-cause mortality, myocardial infarction, stroke, and atrial fibrillation or flutter.
Combined outcome (ii) includes surgical reintervention, deep sternal wound infection, septicaemia, and renal insufficiency.
CI, confidence interval; OR, odds ratio.

Table 4
Areas under receiver operating characteristic curves (AUC) for EuroSCORE and EuroSCORE + MA

Outcomes	EuroSCORE		EuroSCORE + MA	
	AUC	95% CI	AUC	95% CI
All-cause death	0.86	0.79–0.94	0.86	0.79–0.94
Myocardial infarction	0.53	0.42–0.64	0.53	0.43–0.63
Stroke	0.66	0.57–0.74	0.66	0.57–0.74
Atrial fibrillation or flutter	0.55	0.51–0.59	0.55	0.51–0.59
Reintervention	0.62	0.56–0.68	0.62	0.55–0.68
Renal insufficiency	0.67	0.60–0.74	0.67	0.61–0.74
Sternal wound infection	0.51	0.31–0.70	0.53	0.36–0.70
Septicaemia	0.73	0.59–0.88	0.85	0.74–0.96
Combined outcome (i)	0.56	0.53–0.60	0.56	0.53–0.60
Combined outcome (ii)	0.63	0.57–0.68	0.63	0.58–0.68

Combined outcome (i) includes all-cause mortality, myocardial infarction, stroke, and atrial fibrillation or flutter.
Combined outcome (ii) includes surgical reintervention, deep sternal wound infection, septicaemia, and renal insufficiency.
AUC, area under curve; MA, microalbuminuria; CI, confidence interval.

increase in vascular permeability, as part of an early induced inflammatory process. We found a 12-fold increase in the risk of developing septicaemia postoperatively in patients with MA. This has not been reported before in patients undergoing cardiothoracic surgery. However, the result needs to be interpreted with caution, since the number of septicaemic events was small and the diagnosis problematic as it is dependent on either a positive bacteriaemic blood sample or clinical sepsis in a patient population that has a systemic inflammatory response due to the surgery performed and extra corporal circulation.

Our study has both strengths and limitations: we studied a well-defined cohort that was representative of the patient population undergoing cardiothoracic surgery at our department. We had a complete follow-up on all included patients, since our design relied on national health registries with complete coverage. Recruitment of patients to be invited to participate in the study was random and the level of UACR was not known at the time of invitation. The usability of hospital discharge and other disease registries as data sources is dependent on the validity of the registered data and it is well known that the validity of routine hospital discharge diagnoses may vary. However, the predictive values have previously been reported to be high (~80–99%) for several of the outcomes in our study including myocardial infarction, stroke and atrial fibrillation [16–19]. Any misclassification would in any case most likely be independent of the presence of MA and would bias the findings toward the null hypothesis.

We calculated the UACR from a morning spot-urine sample, which is considered a well-validated sampling approach with regard to UACR [20]. This is an inexpensive and feasible approach. The one-time measurement of UACR introduces limitation to the study because of intra-individual variation in the urinary albumin excretion with time. This variation is mainly because of the state of hydration and physical activity, and three consecutive samples over three days would be optimal. However, such a setup does not seem feasible [21]. A preoperative morning spot-urine tends to minimize the effect of exercise and the UACR adjusts

for part of both the individual and physical albumin excretion variation by correcting for urinary creatinine concentration, and by including a large number of patients the risk of bias due to variation in albumin excretion was reduced. However, we cannot rule out some extent of bias because of hydration and different muscle masses between individuals.

MA assessed in a morning spot-urine did not substantially contribute with more knowledge about adverse 30-day postoperative outcomes in elective cardiothoracic surgery than did the EuroSCORE itself. The EuroSCORE is a sensitive predictor of 30-day postoperative mortality, but it has been shown to overestimate mortality in low-risk patients and to underestimate mortality in high-risk patients [22]. Therefore, also the EuroSCORE should be continually used and refined in risk prediction of patients undergoing cardiothoracic surgery. The present results do not seem to advocate for the general assessment of preoperative UACR as a supplement to EuroSCORE in elective cardiac surgery. Whether MA independently predicts long-term postoperative outcome in this patient group remains to be assessed.

We conclude that preoperative presence of MA in patients undergoing elective cardiothoracic surgery was not associated with a broad range of early postoperative outcomes, and that adding information on MA will not improve the accuracy of the additive EuroSCORE. However, postoperative septicaemia was significantly more frequent and the length of ICU and total hospital stay was longer in patients with MA than patients without MA.

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Study III

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Microalbuminuria is associated with high adverse event rate following cardiac surgery☆

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Abstract

Objective: To examine if preoperative microalbuminuria is associated with an increased risk of long-term adverse outcomes following elective cardiac surgery and if it provides additional prognostic information beyond the European System for Cardiac Operative Risk Evaluation (EuroSCORE). **Methods:** In a prospective follow-up study, we included 1049 patients undergoing elective cardiac surgery from 1 April 2005 to 30 September 2007. Microalbuminuria (urine albumin/creatinine ratio between 2.5 and 25 mg $mmol^{-1}$) was assessed preoperatively in a morning spot-urine sample. We used population-based medical registries for follow-up from day 31 until day 365 postoperatively, and compared all-cause death, myocardial infarction, cerebral stroke and a composite outcome of severe infections including septicaemia, deep or superficial sternal wound infection, or leg wound infection among patients with or without microalbuminuria using Cox proportional hazard and competing risk regressions. **Results:** Microalbuminuria was found in 175 (18.5%) out of 947 patients available for follow-up. The adjusted risks of all-cause death (adjusted hazard ratio 2.3 (95% confidence interval 1.1—4.9)), stroke (adjusted hazard ratio 2.9 (95% confidence interval 1.1—7.8)) and severe infection composite outcome (adjusted hazard ratio 2.4 (95% confidence interval 1.2—4.9)) were doubled to tripled in patients with preoperative microalbuminuria. The risk of myocardial infarction was not increased. Adding information on microalbuminuria improved the predictive accuracy of the EuroSCORE regarding mortality (areas under receiver operating characteristic curves were: for the EuroSCORE 0.73 (95% confidence interval 0.65—0.81) and for EuroSCORE + microalbuminuria 0.76 (95% confidence interval 0.68—0.83). **Conclusions:** Preoperative microalbuminuria is associated with an increased risk of long-term adverse outcomes in patients undergoing elective cardiac surgery, and it appears to provide prognostic information on mortality.

Keywords: Cardiothoracic surgery; Comorbidity; Kidney; Outcomes

1. Introduction

Microalbuminuria (MA) reflects the glomerular component of a systemic capillary dysfunction and is a sensitive marker of cardiovascular risk and mortality in both diabetic and non-diabetic patients [1—3]. Increased urinary albumin excretion is often present in patients with established atherosclerotic disease, as also in patients with early asymptomatic vascular disease as well as in patients with hypertension or heart failure [4—7]. Information on MA was found to improve existing risk prediction in patients with acute myocardial infarction [4], and it is also closely related to metabolic syndrome, a clustering of several cardiovascular risk factors, found to be a powerful risk factor for adverse outcomes in patients undergoing coronary bypass surgery [5,6].

In cardiac surgery, we face a need to revise existing risk prediction models and address a wider spectrum of adverse outcomes in longer postoperative time-spans [7]. In this context, preoperative MA has attracted only very modest attention. However, in a recently published article, we assessed the prevalence of MA and its association with short-term adverse outcomes after elective cardiac surgery [8]. We

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found no significant association between MA and early all-cause death, but a significantly increased risk of septicaemia and a longer intensive care unit and total hospital stay in patients with MA [8]. When considering the long-term adverse outcomes following cardiac surgery, it still remains unknown whether patients with preoperative MA independently fare a worse prognosis than patients without MA.

Accordingly, the aims of the present study were to evaluate whether preoperative MA was associated with adverse postoperative outcomes beyond the early postoperative period in patients undergoing elective cardiac surgery and, if so, whether assessment of MA upholds predictive information alone and in a combined model beyond currently acknowledged risk assessments.

2. Materials and methods

2.1. Design and setting

We conducted a prospective follow-up study in the Central Denmark Region, which has a mixed rural–urban population of approximately 1.2 million. From 1 April 2005 to 30 September 2007, we included patients undergoing elective cardiac surgery at the Department of Cardiothoracic and Vascular Surgery at Aarhus University Hospital, Skejby, Denmark. All patients gave informed consent prior to inclusion. The study protocol was approved by the Regional Ethics Committee and the Danish Data Protection Agency (Reference no. 2007-41-1514).

2.2. Study population

Inclusion criteria were (1) age greater than 18 years and (2) elective cardiac surgery (surgery performed more than 2 days after planning of the procedure) — including on- and off-pump coronary artery bypass grafting, valve surgery, thoracic aortic surgery, pulmonary thromboendarterectomy, adult congenital heart disease procedures or combined procedures. Exclusion criteria were (1) severe renal disease defined as a serum creatinine value above 200 μmol l^{-1} or (2) macroalbuminuria defined as a urine albumin/creatinine excretion ratio (UACR) above 25 mg $mmol^{-1}$ and (3) previous heart or renal transplant surgery.

During the study period, a total of 2216 patients underwent cardiac surgery at the department. Patient screening and recruitment were done by a project nurse working half-time. Approximately 50% ($n = 1193$) of the potential candidates for the study were, therefore, screened consecutively. Seventy-eight were excluded because of acute surgery, and 54 had known renal disease with serum creatinine above 200 μmol l^{-1}. The remaining 1061 patients were invited to participate. Only 12 patients did not accept participation and 1049 patients were included.

2.3. Laboratory analyses

A preoperative fasting blood sample and a morning spot-urine sample were collected and analysed at the Department of Clinical Biochemistry, Aarhus University Hospital, Skejby, Denmark.

MA was defined as an UACR between 2.5 and 25 mg $mmol^{-1}$. Using a preoperative urine sample, urinary albumin (mg l^{-1}) was assessed quantitatively by immunoturbidimetry and urinary creatinine (mmol l^{-1}) was estimated by an enzymatic colorimetric test. The sensitivity level for urinary albumin was 7 mg l^{-1}. Because UACR was constructed by dividing urinary albumin with urinary creatinine, albumin values below 7 mg l^{-1} could not contribute to an exact UACR (mg $mmol^{-1}$). We defined UACR to be 0.1 mg $mmol^{-1}$ in these patients.

2.4. Study outcomes

The association between MA and all-cause death, myocardial infarction or percutaneous coronary intervention (PCI), and stroke was examined, respectively, and as a composite outcome. We also compared three composite outcomes regarding severe infections consisting of (1) deep sternal wound infection and septicaemia (defined as a positive bacteriaemic blood sample and/or clinical sepsis), (2) deep sternal or superficial sternal wound infection and septicaemia and (3) deep sternal or superficial sternal wound infection, septicaemia or leg wound infection (at the site of extracted bypass graft).

Since 1968, all Danish residents have been assigned a unique civil registration number that allows unambiguous record linkage between the Danish health databases. We used the Danish Registry of Patients, the Western Denmark Heart Registry and the National Register of Causes of Death for assessing outcomes.

The Danish National Registry of Patients was established in 1977, and holds data on all hospitalisations from somatic Danish hospitals, including dates of admission and discharge, procedures performed and up to 20 discharge diagnoses coded by physicians according to the International Classification of Diseases (8th revision (ICD-8) until the end of 1993, end 10th revision (ICD-10) thereafter). Since 1995, discharges from emergency rooms and outpatient clinics have also been included in this registry. The Western Denmark Heart Registry, established in 1999, is a regional clinical register including detailed patient baseline characteristics, data for all cardiac procedures performed and per- and postoperative outcomes. The National Register of Causes of Death is a complete registry of dates and all causes of death in Denmark since 1973.

2.5. Covariates

Baseline characteristics and in-hospital peroperative data were collected from a preoperative interview, patient medical records, the Western Denmark Heart Registry, the Prescription Database and the Danish National Registry of Patients. For each patient, a case-report-form was used.

Baseline data included age, gender, smoking habits, body mass index, blood pressure, prior ischaemic peripheral-, cerebral- or cardiovascular disease, history of arrhythmias, diabetes and dyslipidaemia, cardiac ejection fraction, European System for Cardiac Operative Risk Evaluation (EuroSCORE), Charlson Comorbidity Index, glomerular filtration rate as estimated by the Cockcroft–Gault formula,

serum levels of creatinine, electrolytes, albumin, glucose, white and red blood cell counts, platelets and the UACR. The EuroSCORE was obtained by linkage to the Western Denmark Heart Registry.

The Charlson Comorbidity Index classifies co-morbidity and, in longitudinal studies, it predicts both short- and long-term mortality [9]. The index was constructed by combining data from the case-report form with data from the National Registry of Patients, and for analyses, we categorised the index score into three levels of co-morbidity: 0 ('low'), 1—2 ('medium') and >2 ('high').

Data from the Western Denmark Heart Registry on the peroperative covariates included type of operation, cardiopulmonary bypass time, aortic cross-clamp time and number and type of grafts.

From a regional prescription database, we obtained data on the use of medication up to 180 days preoperatively and 365 days postoperatively. The database contains data on all redeemed prescriptions at all pharmacies in the region since 1998. The main variables are the unique civil registration number, name and drug code, package identifier (enabling identification of brand, quantity and formulation of the drug) and dates of refill.

2.6. Statistical analyses

Baseline characteristics and per- and postoperative variables were compared between groups with and without MA using Fisher's exact test, independent *t*-tests and the Mann—Whitney test. Continuous variables are presented as medians with interquartile range (IQR) and categorical data as counts and frequencies. Cumulative risk curves of all-cause death and the combined outcomes were constructed. The associations between MA and the outcomes (individual and composite) were examined using multivariate competing risk regressions or Cox regression analyses (for all-cause death and the composite of all-cause death, stroke and myocardial infarction/PCI) with adjustment for possible baseline confounding factors and postoperative use of prescribed cardiovascular drugs. The latter were included as time-dependent covariates.

In the competing risk regression models, all-cause death was considered as the potential competing failure event impeding the non-fatal outcomes of interest. All multivariate models were also analysed using logistic regression, which did not substantially change the risk estimates, but allowed for discrimination analyses of the multivariate models and construction of receiver operating characteristic curves. Calibration analyses were performed using the Hosmer—Lemeshow tests. Furthermore, the association between the continuous level of UACR and risk of various outcomes was also estimated using spline regression to identify any non-linear patterns. Finally, analyses were done in separate subgroups of patients undergoing only coronary bypass surgery, cardiac valve surgery alone or a combination of bypass- and valve surgery.

A two-tailed *p*-value less than 0.05 was considered statistically significant. Analyses were performed using the Stata® 11.0 package (Stata Corp LP, TX, USA).

3. Results

3.1. Study cohort and surgical characteristics

Baseline and peroperative patient characteristics according to presence of MA are displayed in Tables 1 and 2, respectively. A preoperative in-hospital baseline serum creatinine analysis revealed 11 patients with levels above our exclusion criteria. The UACR assessment resulted in the exclusion of 22 patients with macroalbuminuria, and another 54 patients were excluded due to failure of the UACR analyses. Fourteen patients died within 30 days of surgery, and during follow-up one patient emigrated, leaving 947 patients available for complete long-term follow-up (Fig. 1). The overall prevalence of MA in the cohort was 18.5% (n = 175). The logistic EuroSCORE was available for all included patients and the median logistic EuroSCORE of the study cohort was 4 (IQR 2—8).

Patients with MA had a slightly higher level of co-morbidity at baseline. They had a higher median EuroSCORE, and the median age was 3 years greater than the normoalbuminuric patients. Likewise, there were minor differences in smoking habits, diabetes, previous stroke, atrial fibrillation, cardiac ejection fraction, serum creatinine and the glomerular filtration rate. Use of angiotensin-converting enzyme inhibitors and calcium-channel blockers tended to be more frequent in microalbuminuric patients, whereas the use of beta blockers, angiotensin-II receptor blockers or lipid-lowering agents was similar between groups.

Patients with MA had less solitary bypass procedures and more combined procedures performed, but there were no differences between groups with regard to use of extra-corporeal circulation and aortic cross-clamp time. The number of grafted coronary vessels in patients undergoing on- or off-pump coronary artery bypass surgery was slightly lower in the MA group.

3.2. Associations between MA and postoperative adverse outcomes

The crude and adjusted associations between MA and study outcomes are displayed in Table 3. The cumulative incidence of all-cause mortality and the composite infection outcome during the follow-up period are shown in Figs. 2 and 3, respectively.

MA was strongly associated with all-cause death (adjusted hazard ratio (HR) 2.3 (95% confidence interval (CI) 1.1—4.9)), when adjusted for the logistic EuroSCORE and the modified Charlson Comorbidity Index.

MA did not appear to be associated with myocardial infarction/PCI; however, it was associated with a higher risk of cerebral stroke (adjusted HR 2.9 (95% CI 1.1—7.8). Moreover, MA was independently associated with the composite adverse outcome consisting of all-cause death, myocardial infarction/PCI and stroke (adjusted HR 1.7 (95% CI 1.0—3.0)), which occurred in 60 (6%) patients.

The first combined outcome regarding severe infection consisted of deep sternal wound infection or septicaemia, and occurred in only 14 (1.5%) patients. MA appeared to be associated with an increased risk of this infection outcome (adjusted HR 2.0 (95% CI 0.6—6.8)). Although this association was not statistically significant, the estimate remained

Table 1. Baseline patient characteristics.

Variables	Total (N = 947)	Normoalbuminuria (n = 772)	Microalbuminuria (n = 175)	p
Age (years)	68 [59–75]	67 [59–74]	70 [64–77]	<0.01
Gender (male)	687 (73)	566 (73)	121 (69)	0.26
Smoking habits				0.01
Nonsmoker	334 (35)	287 (37)	47 (27)	
Previous smoker	448 (47)	348 (45)	100 (57)	
Current smoker	165 (17)	137 (18)	28 (16)	
Blood pressure				0.44
Grade I hypertension	285 (30)	230 (30)	55 (31)	
Grade II hypertension	174 (18)	138 (18)	36 (21)	
Grade III hypertension	82 (9)	64 (8)	18 (10)	
Diabetes	142 (15)	104 (13)	38 (22)	0.01
Body mass index				0.21
<25	260 (27)	203 (26)	57 (33)	
25–30	394 (42)	329 (43)	65 (37)	
>30	293 (31)	240 (31)	53 (30)	
Previous MI	227 (24)	181 (23)	46 (26)	0.43
Previous AF	144 (15)	99 (13)	45 (26)	<0.01
Previous stroke	93 (10)	66 (9)	27 (15)	0.01
Previous PAD	50 (5)	39 (5)	11 (6)	0.51
Cardiac ejection fraction				0.01
<30	26 (3)	21 (3)	5 (3)	
30–50	180 (19)	133 (17)	47 (27)	
>50	741 (78)	618 (80)	123 (70)	
EuroSCORE	4 [2–8]	4 [2–7]	6 [3–12]	<0.01
Charlson Index				<0.01
0	276 (29)	247 (32)	29 (17)	
1–2	488 (52)	401 (52)	87 (50)	
≥3	183 (19)	124 (16)	59 (34)	
Preoperative medicine				
ACE inhibitors	300 (32)	233 (30)	67 (38)	0.04
ATII antagonists	94 (10)	74 (10)	20 (11)	0.46
Beta blockers	598 (63)	485 (63)	113 (65)	0.67
Calcium-channel blockers	257 (27)	199 (26)	58 (33)	0.05
Lipid-lowering drugs	634 (67)	515 (67)	119 (68)	0.74
Antithrombotics	403 (43)	321 (42)	82 (47)	0.20
S-creatinine (μmol l^{-1})	81 [68–98]	80 [68–96]	87 [71–105]	<0.01
eGFR (ml h^{-1})	84 [82–87]	84 [82–87]	72 [68–77]	<0.01

Data are presented as medians [interquartile range] or absolute numbers (%). ACE: angiotensin-converting enzyme; AF: atrial fibrillation or flutter; ATII: angiotensin-II inhibitors; MI: myocardial infarction; PAD: peripheral artery disease; and eGFR: estimated glomerular filtration rate.

robust, even when events of superficial sternal wound infection requiring surgical intervention alone (adjusted HR 2.3 (95% CI 1.0–5.5)) or in combination with leg wound infection requiring surgical intervention (adjusted HR 2.4 (95% CI 1.2–4.9)) were added to the combined infection outcome.

Any further adjustment for other patient characteristics or postoperative medication use did not change the risk estimates substantially.

The adjusted relationship between continuous UACR and the risk of all-cause death was significant. Each 1 mg $mmol^{-1}$ increment in UACR was associated with and increased odds ratio of 1.12 (95% CI 1.03–1.18). In a continuous spline function, we found no specific UACR cut-off level associated with an increased risk of postoperative all-cause death.

3.3. Subgroups

Considering all-cause death, the descriptive analyses were then restricted to the subgroups of patients undergoing (1) bypass surgery alone (n = 403) where none out of nine dead patients had MA, (2) valve surgery alone (n = 272) where 8 out of 10 dead patients had MA and (3) combined bypass and valve procedures (n = 153) where 2 out of 5 dead patients had MA.

Table 2. Peroperative patient characteristics.

Variables	Total (N = 947)	Normoalbuminuria (n = 772)	Microalbuminuria (n = 175)	p
Bypass surgery alone	403 (43)	341 (44)	62 (35)	0.04
Grafted vessels	3 [2–3]	3 [2–3]	2 [2–3]	0.01
Valve surgery alone	272 (29)	224 (29)	48 (27)	0.68
Bypass and valve surgery	153 (16)	114 (15)	39 (22)	0.02
Other procedures	119 (13)	93 (12)	26 (15)	0.31
ECC	840 (89)	686 (89)	154 (88)	0.75
ECC time (min)	90 [68–121]	88 [67–121]	97 [71–116]	0.15
Cross-clamp time (min)	57 [40–79]	56 [40–78]	63 [43–85]	0.10

Data are presented as medians [interquartile range] or absolute numbers (%). ECC: extracorporeal circulation; and min: minutes.

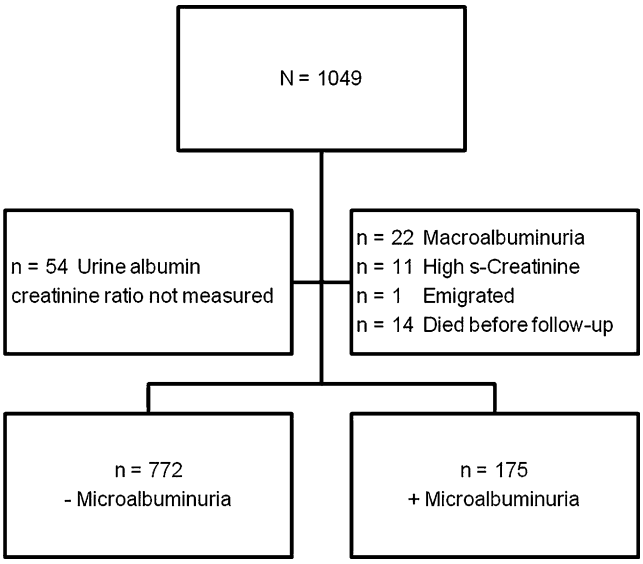

Fig. 1. Flowchart.

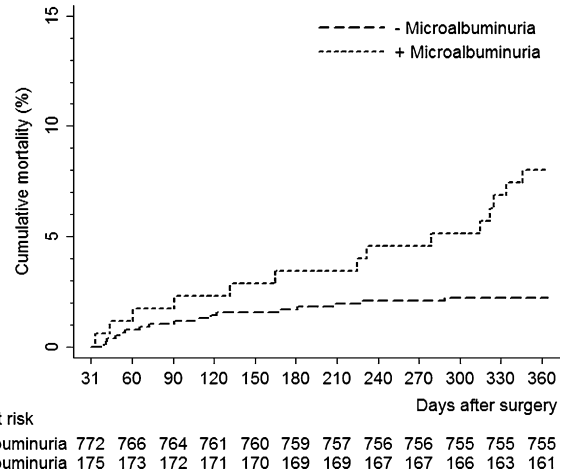

Fig. 2. Cumulative all-cause mortality. Figure shows the cumulative all-cause mortality and the corresponding number of patients at risk.

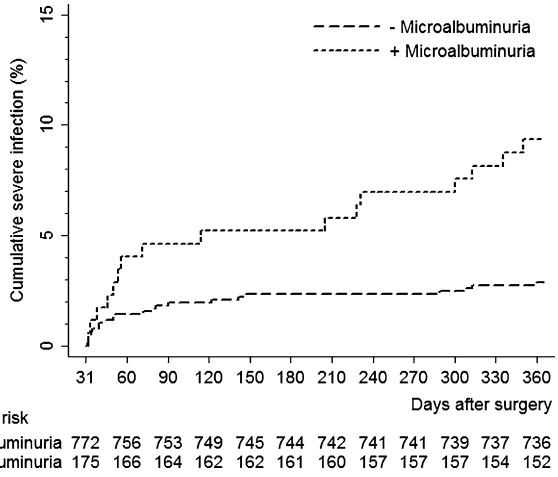

Fig. 3. Cumulative severe infections. Figure shows the cumulative incidence of severe infections and the corresponding number of patients at risk.

3.4. Risk prediction

Table 4 shows the area under the receiver operating characteristic curves (AUCs) for MA, EuroSCORE, Charlson Comorbidity Index alone and for the multivariate logistic models regarding all-cause death. The logistic EuroSCORE predicted all-cause death (AUC 0.73 (95% CI 0.65–0.81)) more accurately than did MA (AUC 0.64 (95% CI 0.55–0.73)) and Charlson Comorbidity Index (AUC 0.70 (95% CI 0.63–0.78)). In a model including both EuroSCORE and MA, AUC reached 0.76 (95% CI 0.68–0.83), and, thereafter, adding information on Charlson Comorbidity Index again slightly increased AUC up to 0.78 (95% CI 0.71–0.85).

Considering other study outcomes, the AUCs for MA alone was 0.52 (95% CI 0.45–0.60) for myocardial infarction/PCI, 0.61 (95% CI 0.48–0.74) for stroke and 0.63 (95% CI 0.55–0.71) for the third composite severe infection outcome.

Hosmer–Lemeshow tests for calibration showed good agreement for both the multivariate logistic regression models including (1) EuroSCORE + MA (p-value = 0.19, chi^2 = 4.7) and (2) EuroSCORE + MA + Charlson Comorbidity Index (p-value = 0.47, chi^2 = 2.6).

3.5. Causes of death

Sixteen patients had cardiovascular deaths, five had infections-related deaths and the remaining 10 had other causes (including five patients with 'Unknown cause of

Table 3. Crude and adjusted hazard ratios for postoperative outcomes according to preoperative microalbuminuria.

Outcomes	Number of events		Crude model		Adjusted model*	
	−MA (n = 772)	+MA (n = 175)	HR	95% CI	HR	95% CI
All-cause death	17 (2.2)	14 (7.8)	3.7	1.8–7.5	2.3	1.1–4.9
MI/PCI	19 (2.4)	3 (1.7)	0.7	0.2–2.3	0.5	0.2–2.0
Stroke	9 (1.2)	6 (3.3)	3.0	1.1–8.3	2.9	1.1–7.8
All-cause death, MI/PCI or stroke	40 (5.1)	20 (11.1)	2.2	1.3–3.8	1.7	1.0–3.0
Severe infections 1†	8 (1.02)	6 (3.3)	3.3	1.2–9.6	2.0	0.6–6.8
Severe infections 2‡	16 (2.1)	12 (6.7)	3.4	1.6–7.1	2.3	1.0–5.5
Severe infections 3§	21 (2.7)	16 (8.9)	3.4	1.8–6.6	2.4	1.2–4.9

CI: confidence interval; HR: hazard ratio; MA: microalbuminuria; MI: myocardial infarction; and PCI: percutaneous coronary intervention.

* Adjusted for the logistic EuroSCORE and the modified Charlson Comorbidity Index.

† Severe infections 1 includes deep sternal wound infection and septicaemia.

‡ Severe infections 2 includes deep and superficial sternal wound infection, and septicaemia.

§ Severe infections 3 includes deep and superficial sternal wound infection, leg wound infection, and septicaemia.

Table 4. Areas under receiver operating characteristic curves regarding all-cause mortality.

Models	All-cause death	
	AUC	95% CI
Microalbuminuria	0.64	0.55–0.73
EuroSCORE	0.73	0.65–0.81
Charlson Comorbidity Index	0.70	0.63–0.78
EuroSCORE and microalbuminuria	0.76	0.68–0.83
EuroSCORE, microalbuminuria and Charlson Comorbidity Index	0.78	0.71–0.85

AUC: area under curve; and CI: confidence interval.

mortality' (ICD-10: R99.9)). A Fisher's exact test showed equal distribution of MA across the three categories of causes of death.

4. Discussion

In the present study, the presence of MA was found to be independently associated with increased all-cause mortality, stroke and a composite outcome consisting of all-cause death, myocardial infarction/PCI and stroke in a prospective cohort of patients undergoing elective cardiac surgery. Furthermore, we found a significant association between MA and severe postoperative infections. Preoperative assessment of MA predicted all-cause death, and appears to provide only modest, however potentially important, additional prognostic information compared with EuroSCORE alone.

The prevalence of MA (18.5%) in our study was lower than reported in a population of 257 diabetic patients undergoing coronary artery bypass grafting [10]. At a mean follow-up of 31 (±16) months, Yorgancioglu and colleagues observed only 12 deaths and found no significant difference between diabetics with and without MA regarding fatal events [10].

MA was not associated with an increased risk of postoperative myocardial infarction/PCI in our study. On the contrary, the adjusted estimate (HR 0.5) even suggested a negative association, but CI was very wide, and based on existing knowledge and the relative few events reported in this study, we believe the estimate is more likely to be a chance finding rather than reflecting a biological protective mechanism of MA.

When analyses were restricted to subgroups, the patients undergoing bypass surgery alone had very low mortality, whereas the descriptive statistics showed higher mortality among patients with MA undergoing valve surgery alone. This indicates that especially patients with MA undergoing valve procedure may be at higher risk. The subgroups were small and regression analyses were impossible.

The EuroSCORE is regarded as the most accurate predictor of postoperative mortality, but was constructed to predict 30-day mortality only and, furthermore, it overestimates risk in low-risk patients and underestimates mortality in high-risk patients [7]. Evidence is sparse and conflicting as to how accurately the EuroSCORE predicts longer time-span mortality in patients undergoing cardiac surgery [7,11,12]. Models designed to predict long-term adverse outcomes after cardiac surgery are not available, but seem desirable [7]. In this study, MA was strongly associated with adverse outcomes, but MA alone did not distinguish survivors from non-survivors accurately (see Table 4). The present results do not indicate that routine assessment of preoperative MA should be recommended in elective cardiac surgery. However, we cannot rule out that information on MA may provide new knowledge that can lead to the identification of a subgroup of patients that may benefit from for example, changes in postoperative medical treatment. Although the predictive accuracy of MA was limited in the present study, we still suggest, owing to our results, that MA should be considered as a potential risk marker in a larger study addressing a revision of multivariate risk prediction models in patients undergoing cardiac surgery.

Our study has both strengths and limitations: we studied a well-defined cohort that was representative of the patient population undergoing cardiac surgery at our department. We had a practically complete follow-up on all included patients, as our design relied on national health registries with complete coverage. Recruitment of participants was prospective and independent of the presence of MA. We found no indication supporting a skewed distribution of the 54 patients who were excluded due to failure of UACR analysis or among the patients who died within day 30, postoperatively. In addition, UACR was not known by the physicians treating the patients and the risk of information bias was therefore minimal. Through the case-report form and the national health registries, we were able to compute the Charlson Comorbidity Index and, thereby, effectively adjust for the influence of baseline co-morbidity on the association between MA and the postoperative outcomes. When considering registry data validity, the predictive values have previously been reported to be high (approximately 80–99%) for several of the outcomes in our study, including myocardial infarction and stroke [13–15]. Any misclassification would, in any case, most likely be independent of the presence of MA and would bias the findings toward the null hypothesis. The one-time measurement of UACR may introduce a limitation into the study because of intra-individual variation in urinary albumin excretion with time. Three consecutive samples over 3 days are considered more optimal, but the use of one morning spot-urine sample for UACR assessment is, however, considered a well-validated, inexpensive and feasible approach [16,17].

In conclusion, the preoperative presence of MA was associated with an increased risk of long-term adverse outcomes in patients undergoing elective cardiac surgery. Preoperative screening for MA, however, provided only modest prognostic information, and future studies are warranted to further clarify the role of MA in long-term risk assessment in cardiac surgery.

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Study IV

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RESEARCH ARTICLE Open Access

Insulin resistance, adiponectin and adverse outcomes following elective cardiac surgery: a prospective follow-up study

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Abstract

Background: Insulin resistance and adiponectin are markers of cardio-metabolic disease and associated with adverse cardiovascular outcomes. The present study examined whether preoperative insulin resistance or adiponectin were associated with short- and long-term adverse outcomes in non-diabetic patients undergoing elective cardiac surgery.

Methods: In a prospective study, we assessed insulin resistance and adiponectin levels from preoperative fasting blood samples in 836 patients undergoing cardiac surgery. Population-based medical registries were used for postoperative follow-up. Outcomes included all-cause death, myocardial infarction or percutaneous coronary intervention, stroke, re-exploration, renal failure, and infections. The ability of insulin resistance and adiponectin to predict clinical adverse outcomes was examined using receiver operating characteristics.

Results: Neither insulin resistance nor adiponectin were statistically significantly associated with 30-day mortality, but adiponectin was associated with an increased 31-365-day mortality (adjusted odds ratio 2.9 [95% confidence interval 1.3-6.4]) comparing the upper quartile with the three lower quartiles. Insulin resistance was a poor predictor of adverse outcomes. In contrast, the predictive accuracy of adiponectin (area under curve 0.75 [95% confidence interval 0.65-0.85]) was similar to that of the EuroSCORE (area under curve 0.75 [95% confidence interval 0.67-0.83]) and a model including adiponectin and the EuroSCORE had an area under curve of 0.78 [95% confidence interval 0.68-0.88] concerning 31-365-day mortality.

Conclusions: Elevated adiponectin levels, but not insulin resistance, were associated with increased mortality and appear to be a strong predictor of long-term mortality. Additional studies are warranted to further clarify the possible clinical role of adiponectin assessment in cardiac surgery.

Trial Registration: The Danish Data Protection Agency; reference no. 2007-41-1514.

Background

Insulin resistance and circulating levels of adiponectin are associated with an increased risk of cardiovascular disease, the metabolic syndrome and a subclinical inflammatory response in the vascular endothelium [1,2].

Insulin resistance is a measure of the biological efficiency of the endogenously produced insulin and is present when a higher than normal level of insulin is required in order to maintain normoglycemia. Its prevalence in the apparently healthy population is rising [3]. However, it also declines during critical illness and as a response to surgery [1]. In a recently published study in patients undergoing cardiac surgery, intraoperative insulin resistance was associated with an increased risk of short-term adverse outcomes [4]. Moreover, hyperglycemia during cardiopulmonary bypass and preoperative metabolic syndrome, in which insulin resistance plays a

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key role, were powerful risk factors of mortality and morbidity in patients undergoing cardiac surgery [5,6].

Adiponectin, a hormone derived from the adipose tissue, is considered an insulin sensitizer and it upholds both anti-atherogenic and anti-inflammatory effects [2,7,8]. In non-healthy individuals, high levels of adiponectin have been associated with an increased cardiovascular disease risk in patients presenting with chest pain, increased mortality in patients with chronic heart failure, and predictive of survival after peripheral artery bypass surgery [9-11].

This strongly indicates that patients with insulin resistance or elevated adiponectin levels may have certain subclinical features, such as chronic low-grade inflammation, that can increase the risk related to cardiac surgery. Further insights in the relation between metabolic risk-markers in cardiac surgery could potentially open new avenues for improving pre-, per-, and postoperative care, but could also prove useful for preoperative risk assessment.

Indeed, improvement of risk prediction in cardiac surgery has been requested, as the EuroSCORE overestimates mortality in low-risk patients [12]. We therefore face a need to address new adverse outcome markers, including preoperative insulin resistance and adiponectin which have attracted practically no attention concerning preoperative risk prediction in cardiac surgery.

Accordingly, the aim of this study was to examine whether preoperative insulin resistance or the level of circulating adiponectin were associated with either short-term adverse outcomes within 30 days or long-term adverse outcomes (31-365 days). Secondly, we aimed to assess if information on these factors may potentially be useful for risk prediction in non-diabetic patients undergoing elective cardiac surgery.

Methods

Design and Setting

We conducted a single-center prospective follow-up study in the Central Denmark Region, which has a mixed rural-urban population of approximately 1.2 million. From 1 April 2005 to 30 September 2007 we included patients undergoing elective cardiac surgery at the Department of Cardiothoracic and Vascular Surgery at Aarhus University Hospital, Skejby, Denmark. The study complied to the Helsinki declaration and all patients gave informed consent prior to inclusion. The study protocol was approved by the Regional Ethics Committee and the Danish Data Protection Agency (Reference no. 2007-41-1514).

Study population

Inclusion criteria were i) age older than 18 years, ii) elective cardiac surgery (surgery performed more than two days after planning of the procedure) - including on- and off-pump coronary artery bypass grafting, valve surgery, thoracic aortic surgery, pulmonary thrombendarterectomy, grown up congenital heart disease procedures. Exclusion criteria were i) Type I and Type II diabetes mellitus, ii) fasting blood glucose value above or equal to 7.0, or iii) previous heart transplant surgery. During the study period a total of 2,216 patients underwent cardiac surgery at the department. Patient screening and recruitment was done by a project nurse working half-time. Approximately 50% (n = 1193) of the potential candidates for the study were therefore screened consecutively. We included 876 patients with no prior history of diabetes. A preoperative in-hospital baseline fasting blood sample identified 38 patients with increased blood glucose levels above the diabetic exclusion criteria. One patient was excluded due to failure of insulin analysis, and one patient emigrated, leaving 836 patients available for 30-day (short-term) and 31-365 days (long-term) follow-up.

Laboratory analyses

For each participant a preoperative fasting blood sample was collected (between 6 a.m. and 11 a.m.) and analyzed at the Department of Clinical Biochemistry, Aarhus University Hospital, Skejby, Denmark, and at the Medical Research Laboratory, Aarhus University Hospital, Aarhus Sygehus, Noerrebrogade, Denmark.

The fasting blood glucose values (mmol/liter) were measured in duplicate immediately after sampling on a glucose analyzer (Beckman Instruments, Palo Alto, CA), and blood insulin values (pmol/liter) were measured using a commercial immunological kit (DAKO, Glostrup, Denmark). For insulin, the intraassay coefficient of variation (CV) was 2.1-3.7%, and the interassay CV was 3.4-4.0%. We calculated the insulin resistance using the homeostasis model assessment (HOMA), where the calculation of HOMA is based on the relationship between fasting glucose and insulin levels.

$$\mathrm{HOMA} = (\mathrm{Glucose[mmol\,/\,liter]} \times \mathrm{Insulin[mU\,/\,liter]}) \,/\, 22.5.$$

The used constant converting insulin from pmol/liter to mU/liter was 6.945. Serum adiponectin (mg/liter) was measured by an in-house time-resolved immunofluorometric assay (R&D Systems, Abingdon, United Kingdom). Intra- and interassay CV averaged less than 5 and 10%, respectively.

Study outcomes

The study outcomes were a composite of i) all-cause mortality, myocardial infarction or percutaneous coronary intervention (PCI), and stroke, and ii) deep and

superficial sternal wound infection, leg wound infection (at the site of bypass graft harvest) and septicemia (defined as a positive blood culture and/or clinical sepsis). We also examined the individual elements of the composite outcomes, the risk of renal failure (defined as more than a 100% increase of serum creatinine from baseline and/or use of dialysis), risk of surgical re-exploration, as well as the length of stay in the intensive care unit and the total length of hospital stay.

Since 1968 all Danish residents have been assigned a unique civil registration number that allows unambiguous record linkage between the Danish health databases. We used the Danish Registry of Patients and the Western Denmark Heart Registry for assessing outcomes. The Danish National Registry of Patients was established in 1977 and holds data on all hospitalizations from somatic Danish hospitals, including dates of admission and discharge, procedure(s) performed, and up to 20 discharge diagnoses coded by physicians according to the International Classification of Diseases [8^{th} revision (ICD-8) until the end of 1993, end 10^{th} revision (ICD-10) thereafter]. Since 1995 discharges from emergency rooms and outpatient clinics have also been registered in this registry. The Western Denmark Heart Registry, established in 1999, is a regional clinical register including detailed patient baseline characteristics, data for all cardiac procedures performed, and per- and postoperative outcomes.

Covariates

Baseline characteristics and in-hospital peroperative data were collected from a preoperative interview, patient medical records, the Western Denmark Heart Registry, the Prescription Database of Central Denmark Region, and the Danish National Registry of Patients. For each patient a case-report-form was used.

Baseline data included age, sex, smoking habits, body mass index, hypertension (defined as systolic pressure 140 mmHg or greater and/or diastolic pressure 90 mmHg or greater), prior ischemic peripheral, cerebro-, or cardiovascular disease, history of arrhythmias, diabetes and dyslipidemia, cardiac ejection fraction, EuroSCORE, Charlson Comorbidity Index, glomerular filtration rate as estimated by the Cockcroft Gault formula (eGFR), serum levels of creatinine, electrolytes, albumin, fructosamine, white and red blood cell counts, platelets and the urine albumin creatinine ratio.

The Charlson Comorbidity Index classifies comorbidity and in longitudinal studies it predicts both early and late mortality [13]. The index was constructed by combining data from the case-report-form with data from the National Registry of Patients, and for analyses, we categorized the index score into three levels of comorbidity: 0 ("low"), 1-2 ("medium"), and >2 ("high").

Data from the Western Denmark Heart Registry on the peroperative covariates included type of operation, cardiopulmonary bypass time and aortic cross-clamp time.

From a regional prescription database, we obtained data regarding the use of medication up to 180 days preoperatively and 1 year postoperatively. The database contains data on all redeemed prescriptions at all pharmacies in the region since 1998. The main variables are the unique civil registration number, name and drug code, package identifier (enabling identification of brand, quantity and formulation of the drug), and dates of refill.

Statistical analyses

Baseline and procedural characteristics are presented as medians with interquartile ranges or 95% confidence intervals (95% CI) and categorical data as counts and frequencies. HOMA and adiponectin were logarithmically transformed prior to correlation with baseline and procedural characteristics. Both baseline and procedural variables were also compared across quartiles of adiponectin and HOMA using the Chi^2 or Kruskal-Wallis test (data not shown). Based on the quartiles of HOMA and adiponectin respectively, we divided patients into two groups. The reference groups consisted of patients with levels in the three lower quartiles (the adiponectin quartiles with the observed lowest risk) and they were compared with the upper quartiles of HOMA and adiponectin respectively.

Data on the length of intensive care unit and hospital stay were analyzed on a logarithmic scale using linear regression analyses. Thereafter, we transformed the regression estimate and estimated the absolute difference in median length of stay between groups at different levels of the EuroSCORE. The standard error was calculated using the delta method. For both short- and long-term follow-up we constructed cumulative mortality curves.

The associations between HOMA and adiponectin groups with both short- and long-term outcomes (individuals and composites) were examined using multivariate logistic regression analyses, and the associations with long-term outcomes were also examined using multivariate Cox proportional hazard analyses (for all-cause death and the composite of all-cause death, stroke and myocardial infarction/PCI) or competing risk regressions (for stroke, myocardial infarction/PCI, and infections). In the competing risk regression models, all-cause death was considered as the potential competing failure event impeding the non-fatal outcomes of interest. Using the change-in-estimate method, we examined if adjustment for possible baseline confounding factors and postoperative time-dependent use of prescribed cardiovascular

drugs had impact on the risk-estimates. As there was no substantial difference between estimates from the logistic regressions and Cox or competing risk regressions, results are presented as odds ratios derived from the logistic regressions. Discrimination analyses and construction of receiver operating characteristic curves of both the uni- and multivariate models were performed to assess the predictive values of HOMA and adiponectin alone and in combination with the EuroSCORE. Hosmer-Lemeshow test was used for calibration analyses. Furthermore, we also included HOMA and adiponectin as continuous variables in an additional spline regression analysis in order to identify any non-linear patterns. A two-tailed *p*-value less than 0.05 was considered statistically significant. Analyses were performed using the Stata® 11.0 package (StataCorp LP, Texas, US).

Results

Study cohort and surgical characteristics

The overall study baseline patient characteristics and correlations with HOMA and adiponectin are shown in Table 1. For insulin resistance the upper quartile was HOMA index levels above 2.6, and for adiponectin the upper quartile was adiponectin values above 11.7 mg/liter. HOMA correlated positively with male gender, body mass index, former myocardial infarction, eGFR, glucose and insulin as well as the use of beta blockers, statins and antiplatelets. HOMA was inversely correlated with adiponectin, the EuroSCORE, microalbuminuria, type of procedure performed and cross-clamp time, but showed no correlation with age (Table 1). Adiponectin correlated positively with age, logistic EuroSCORE, urine albumin creatinine ratio, level of fructosamine, time on extra corporal circulation as well as aortic cross clamp time, and inversely with male gender, body mass index, former myocardial infarction, eGFR, and the levels of glucose, insulin and HOMA as well as the use of beta blockers and statins (Table 1). Moreover, patients with high HOMA levels had more solitary coronary bypass and less valve procedures performed, whereas increasing adiponectin levels were correlated with more valve procedures and less bypass procedures being performed (Table 1).

Length of stay

There was no difference between the upper quartile and the three lower quartiles of HOMA regarding median length of stay in the intensive care unit (difference: 0.02

Table 1 Baseline and peroperative characteristics.

	Total sample	HOMA		Adiponectin	
Clinical features	**N = 836**	***r***	***p*-value**	***r***	***p*-value**
Male gender	607 (73)	0.14	<0.01	-0.32	<0.01
Age (years)	68 [59-75]	-0.06	0.08	0.15	<0.01
BMI (kg/(m)^2)	27 [24-30]	0.50	<0.01	-0.38	<0.01
Current smoker	147 (18)	<0.01	0.99	-0.06	0.09
Hypertension	465 (56)	0.05	0.18	-0.02	0.50
EF <50%	177 (21)	<0.01	0.87	-0.02	0.48
MI	192 (23)	0.12	<0.01	-0.15	<0.01
Stroke	79 (9)	0.06	0.06	0.03	0.33
EuroSCORE	4.4 [2.2-7.8]	-0.15	<0.01	0.29	<0.01
Charlson Index		0.05	0.18	0.07	0.05
Low	285 (34)				
Medium	432 (52)				
High	119 (14)				
Paraclinic					
Creatinine (mmol/liter)	81 [68-98]	0.03	0.33	<0.01	0.99
UACR (mg/mmol)	0.7 [0.1-1.8]	-0.05	0.13	0.16	<0.01
Microalbuminuria	146 (18)	-0.08	0.02	0.20	<0.01
eGFR (ml/minute)	81 [61-105]	0.23	<0.01	-0.33	<0.01
Glucose (mmol/liter)	5.4 [5.1-5.8]	0.52	<0.01	-0.19	<0.01
Fructosamine (μmol/liter)	230 [213-246]	0.02	0.61	0.21	<0.01
Insulin (pmol/liter)	44 [30-71]	0.99	<0.01	-0.42	<0.01
HOMA	1.6 [1.0-2.6]			-0.42	<0.01
Adiponectin (mg/liter)	8.0 [5.6-11.7]	-0.42	<0.01		
Medicine					
RAS inhibitors*	297 (36)	0.08	0.02	-0.01	0.62
Beta blockers	521 (62)	0.14	<0.01	-0.22	<0.01
Statins	526 (63)	0.16	<0.01	-0.23	<0.01
Antiplatelets	337 (40)	0.08	0.02	-0.06	0.07
Procedure					
Bypass alone	326 (39)	0.16	<0.01	-0.34	<0.01
Valve alone	258 (31)	-0.12	<0.01	0.22	<0.01
Bypass & Valve	131 (16)	0.01	0.81	0.08	0.02
Others	121 (14)	-0.07	0.03	0.10	<0.01
Procedure related					
ECC (minutes)	91 [68-124]	-0.04	0.19	0.14	<0.01
CCT (minutes)	57 [40-79]	-0.08	0.01	0.20	<0.01

Data are presented as medians [interquartile range] or absolute numbers (%)

r is the correlation coefficient

* Includes angiotensin-converting enzyme inhibitors and angiotensin-II receptor antagonists

AF - Atrial fibrillation or flutter; BMI - Body mass index; CCT - Cross clamp time; ECC - Extra corporal circulation; eGFR - Estimated glomerular filtration rate; EF - Ejection fraction; HOMA - Homeostasis model assessment; Kg - Kilogram; M - Meter; MI - Myocardial infarction; UACR - Urinary albumin creatinine ratio; RAS - Renin angiotensin system

Table 2 Short- and long-term odds ratios considering insulin resistance.

	HOMA quartiles		Short-term follow-up			
	I - III	IV	Crude		Adjusted*	
	n = 627	n = 209	OR	95% CI	OR	95% CI
Death	8 (1.3)	4 (1.9)	1.5	1.0-9.6	1.7	0.5-5.7
MI/PCI	15 (3.4)	5 (3.4)	1.0	0.5-2.8	1.0	0.4-2.8
Stroke	23 (3.7)	8 (3.8)	1.0	0.5-2.4	1.1	0.5-2.5
Renal failure[†]	39 (6.2)	16 (7.7)	1.2	0.7-2.3	1.4	0.7-2.7
Re-exploration	54 (8.6)	22 (10.5)	1.2	0.7-2.1	1.3	0.8-2.2
Infections	27 (4.3)	13 (6.2)	1.5	0.7-2.9	1.5	0.8-3.0
CVD composite	44 (7.0)	16 (7.7)	1.1	0.6-2.0	1.1	0.6-2.1
	HOMA quartiles		**Long-term follow-up**			
	I - III	IV	Crude		Adjusted[‡]	
	n = 619	n = 205	OR	95% CI	OR	95% CI
Death	20 (3.2)	10 (4.9)	1.5	0.7-3.3	1.7	0.7-3.8
MI/PCI	18 (2.9)	4 (2.0)	0.7	0.2-2.0	0.6	0.2-1.8
Stroke	12 (1.9)	1 (0.5)	0.2	0.1-1.9	0.3	0.1-2.0
Infections	20 (3.2)	8 (3.9)	1.2	0.5-2.8	1.2	0.5-2.9
CVD composite	45 (7.3)	14 (6.8)	0.9	0.5-1.7	0.9	0.5-1.7

* Adjusted for the logistic EuroSCORE

[†] Adjusted for the logistic EuroSCORE and estimated glomerular filtration rate

[‡] Adjusted for the logistic EuroSCORE, Charlson Comorbidity Index and type of surgery

Short-term is defined as 30-day follow-up

Long-term is defined as follow-up from day 31 until 365

CI - Confidence interval; CVD - Cardiovascular disease; HOMA - Homeostasis model assessment; MI - Myocardial infarction; OR; - Odds ratio; PCI - Percutaneous coronary intervention

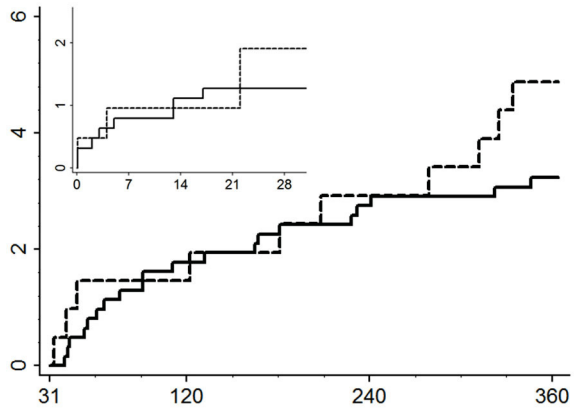

Figure 1 Cumulative mortality considering HOMA quartiles. Large graph shows the cumulative mortality from day 31 until 365 (Log rank $p > 0.05$). Small graph shows the cumulative mortality from day 0 until 30 (Log rank $p > 0.05$). x-axes - Days after surgery; y-axes - Cumulative mortality (%); Dashed lines - Insulin resistance quartile 4; Solid lines - Insulin resistance quartiles 1-3; HOMA - Homeostasis model assessment.

days [95% CI -0.08-0.12]) or total hospital stay (difference: 0.20 days [95% CI -0.21-0.61]). Patients in the upper adiponectin quartile stayed 0.15 (95% CI 0.04-0.26) days longer in the intensive care unit, and had a 0.73 (95% CI 0.27-1.19) days prolonged total hospital stay as compared to the lower adiponectin quartiles and adjusted for the logistic EuroSCORE.

Insulin resistance and postoperative adverse outcomes

The associations between HOMA quartiles and study outcomes at both short- and long-term follow-up are displayed in Table 2. Increased HOMA values were not statistically significantly associated with postoperative mortality when compared to the lower three quartiles (30-day adjusted OR 1.7 [95% CI 0.5-5.7] and 31-365-days adjusted OR 1.7 [95% CI 0.7-3.3]) (Figure 1). For early postoperative infections, the odds ratio was 1.5, but did not reach statistical significance. Moreover, the upper HOMA quartile was also not associated with other individual or combined outcomes. Similarly, comparing groups above and below the median HOMA value showed statistically insignificant associations between HOMA and outcomes. Furthermore, analyzing HOMA as a continuous spline function revealed no specific threshold values in the association with all-cause death.

Adiponectin and postoperative adverse outcomes

As displayed in Table 3 adiponectin was not associated with any of the short-term postoperative outcomes, except from renal failure (adjusted OR 1.8 [95% CI 1.0-3.3]. In contrast, high levels of circulating adiponectin were positively associated with all-cause death in the 31-365 days time window (adjusted OR of 2.9 [95% CI 1.3-6.4]) for patients in the upper quartile compared with patients in the lower three quartiles (Figure 2). The increased risk of the combined cardiovascular outcome in the highest adiponectin quartile (adjusted OR 1.7 [95% CI 0.9-3.1]) was primarily driven by all-cause mortality, as there were no strong associations between adiponectin and myocardial infarction/PCI or stroke. Comparing groups above and below the median adiponectin (data not shown) indicated an even higher mortality risk (adjusted OR 4.4 [95% CI 1.6-12.1]). Otherwise, the median cut-off showed no substantially different trends. Considered as a continuous variable, each 1 mg/liter increase in adiponectin was associated with a 1.12 [95% CI 1.08-1.16] increased adjusted OR for all-cause death. In the spline regression model we could not determine any specific cut-off level for adiponectin.

Table 3 Short- and long-term odds ratios considering adiponectin.

	Adiponectin quartiles		Short-term follow-up			
	I - III	IV	Crude		Adjusted*	
	n = 627	n = 209	OR	95% CI	OR	95% CI
Death	10 (1.6)	2 (1.0)	0.6	0.4-5.7	0.4	0.1-2.0
MI/PCI	15 (2.4)	5 (2.4)	1.0	0.4-2.8	1.0	0.3-2.7
Stroke	20 (3.2)	11 (5.3)	1.7	0.8-3.6	1.5	0.7-3.3
Renal failure	33 (5.3)	22 (10.5)	2.1	1.2-3.7	1.4	0.7-2.7
Re-exploration	54 (8.6)	22 (10.5)	1.2	0.7-2.1	0.9	0.6-1.9
Infections	29 (4.6)	11 (5.3)	1.1	0.6-2.3	1.0	0.5-2.1
CVD composite	43 (6.9)	17 (8.1)	1.2	0.7-2.2	1.0	0.6-1.9
	Adiponectin quartiles		**Long-term follow-up**			
	I - III	IV	Crude		Adjusted‡	
	n = 617	n = 207	OR	95% CI	OR	95% CI
Death	13 (2.1)	17 (8.2)	4.2	2.0-8.7	2.9	1.3-6.4
MI/PCI	18 (2.9)	4 (1.9)	0.7	0.2-2.0	0.7	0.2-2.1
Stroke	8 (1.3)	5 (2.4)	1.9	0.6-5.8	1.4	0.4-4.5
Infections	18 (2.9)	10 (4.8)	1.7	0.8-3.7	1.1	0.5-2.6
CVD composite	36 (5.8)	23 (11.1)	2.0	1.2-3.5	1.7	0.9-3.1

* Adjusted for the logistic EuroSCORE

† Adjusted for the logistic EuroSCORE and estimated glomerular filtration rate

‡ Adjusted for the logistic EuroSCORE, Charlson Comorbidity Index and type of surgery

Short-term is defined as 30-day follow-up

Long-term is defined as follow-up from day 31 until 365

CI - Confidence interval; CVD - Cardiovascular disease; MI - Myocardial infarction; OR - Odds ratio; PCI - Percutaneous coronary intervention

Predictive values of HOMA, adiponectin and the EuroSCORE

The areas under the receiver operating characteristic curves (AUC) concerning mortality are shown in Table 4. The AUC was 0.84 [95% CI 0.75-0.93] for the logistic EuroSCORE regarding short-term all-cause death and 0.75 [95% CI 0.67-0.83] for long-term all-cause death. HOMA did not predict mortality. In contrast, the AUC for adiponectin was 0.75 [95% CI 0.65-0.85] regarding long-term mortality and in a model including both the EuroSCORE and adiponectin the AUC reached 0.78 [95% CI 0.68-0.88]. In a model with only HOMA and adiponectin a similar AUC was achieved, and when the EuroSCORE was then added, the AUC increased up to 0.81 [95% CI 0.73-0.89]. Lastly, adding the Charlson Comorbidity Index to the model further increased the AUC to 0.86 [95% CI 0.81-0.92]. There were no interactions between sex and insulin resistance or adiponectin with regard to the risk of any postoperative outcomes. Hosmer-Lemeshow tests showed acceptable model fit of the logistic regressions.

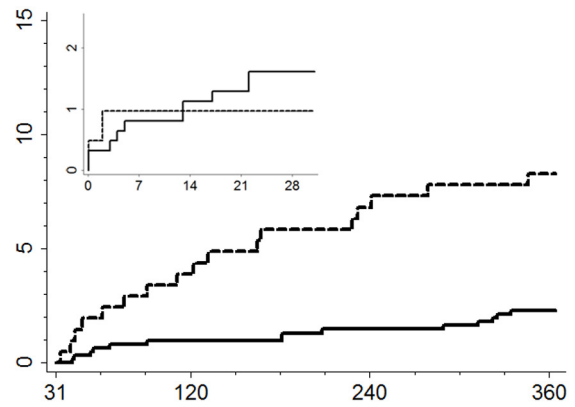

Figure 2 Cumulative mortality considering adiponectin quartiles. Large graph shows the cumulative mortality from day 31 until 365 (Log rank $p < 0.05$). Small graph shows the cumulative mortality from day 0 until 30 (Log rank $p > 0.05$). x-axes: Days after surgery. y-axes: Cumulative mortality (%). Dashed lines: Adiponectin quartile 4. Solid lines: Adiponectin quartiles 1-3.

Discussion

In the present study, high levels of adiponectin were associated with an increased 31-365-day mortality following elective cardiac surgery. In addition, adiponectin had a predictive value corresponding to that of the EuroSCORE, whereas insulin resistance alone did not contribute with any important prognostic information on mortality.

The association between preoperative insulin resistance and short-term mortality (1.7-fold increased risk) did not reach statistical significance, but seems clinically interesting since high HOMA indices may help identify a subgroup of non-diabetic patients at higher risk - and with a possible pre- and intraoperative medical intervention available (i.e. insulin sensitizers and insulin). A recent study showed an approximately 2-fold increased risk of mortality and major adverse outcomes in patients with intraoperatively decreased insulin sensitivity [4]. A low-grade inflammation associated with insulin resistance might be accentuated during surgery, and in particular patients undergoing cardiac surgery experience aggravated inflammation and insulin resistance - which participates in a worsening of endothelial dysfunction, glycemic control, and increase risk of postoperative adverse outcomes [14-16]. Moreover, per- and postoperative aggravated insulin resistance and hyperglycemia are apparently important factors in studies documenting the effect of postoperative tight glycemic control with insulin therapy on morbidity and mortality [17,18]. However, not all studies support the notion that tight intraoperative glycemic control with insulin therapy reduces adverse outcomes following cardiac surgery [19]. The present result showed poor predictive values of preoperatively measured insulin resistance alone and therefore does not support the use of routine preoperative assessment of insulin resistance in cardiac surgery.

Table 4 Areas under receiver operating curves characteristics on all-cause death.

	Short-term follow-up		Long-term follow-up	
	AUC	95% CI	AUC	95% CI
Logistic EuroSCORE	0.84	0.75-0.93	0.75	0.67-0.83
HOMA continuous	0.55	0.36-0.75	0.47	0.34-0.60
HOMA quartiles	0.54	0.40-0.68	0.54	0.46-0.63
ADPN continuous	0.53	0.38-0.68	0.75	0.65-0.85
ADPN quartiles	0.54	0.43-0.65	0.66	0.57-0.76
Logistic EuroSCORE + HOMA continuous	0.84	0.76-0.92	0.77	0.70-0.84
Logistic EuroSCORE + HOMA quartiles	0.77	0.65-0.90	0.76	0.69-0.82
Logistic EuroSCORE + ADPN continuous	0.82	0.68-0.95	0.78	0.68-0.88
Logistic EuroSCORE + ADPN quartiles	0.83	0.70-0.96	0.76	0.68-0.85
HOMA and ADPN continuous			0.77	0.68-0.86
Logistic EuroSCORE + HOMA and ADPN continuous			0.81	0.73-0.89
Logistic EuroSCORE + HOMA and ADPN continuous + CCI			0.86	0.81-0.92

Short-term is defined as 30-day follow-up

Long-term is defined as follow-up from day 31 until 365

ADPN - Adiponectin; AUC - Area under curve; CI - Confidence interval; CCI - Charlson Comorbidity Index; HOMA - Homeostasis model assessment

The association between adiponectin and all-cause death found in our study is in accordance with the results reported by Kistorp et al, who found a high adiponectin level to predict mortality in patients with congestive heart failure [10]. Moreover, the "AtheroGene study", including 1890 patients with coronary artery disease, found a positive correlation between adiponectin levels and the risk of a new cardiovascular event (HR 1.17 for each increase in adiponectin quartile) [20]. In addition, another study on adiponectin in patients with coronary artery disease indicated that high adiponectin levels was associated with an increased risk of cardiovascular death, but when controlled for potential confounding the association did not remain statistically significant [21]. However, in 2006 results from a metaanalysis indicated that low adiponectin levels were associated with a higher risk of cardiovascular disease [22]. A bidirectional association between adiponectin and cardiovascular disease influenced by the constellation of existing comorbidity appears plausible, but the role of adiponectin as a risk factor or independent prognostic marker in different constellations of comorbidities remains contracdictious and sparsely understood [21,23,24].

Preoperative assessment of adiponectin was not associated with short-term risk. However, high adiponectin levels in the present population identified patients with increased cardiovascular risk on the long term, corresponding to what was achieved by the multifactorial risk stratification contained in the EuroSCORE.

The EuroSCORE is a sensitive predictor of 30-day postoperative mortality, but it has been shown to overestimate mortality in low-risk patients and to underestimate mortality in high-risk patients [12]. Therefore, it is important to improve risk prediction both with and beyond the EuroSCORE (and other alternative risk assessment tools) by investigating the predictive ability of new potential markers of risk. In the present study, neither the HOMA index nor adiponectin levels assessed in a preoperative fasting blood sample contributed with better risk prediction regarding the adverse 30-day postoperative outcomes than the EuroSCORE itself. Nevertheless, our results suggest that preoperative assessment of especially adiponectin levels may contribute with additional risk stratification and especially help identify patients with increased long-term risk. However, since elective cardiac surgery in general is considered to be safe with a low mortality, a larger number of patients and morbid events may however be required to demonstrate improved accuracy of the logistic EuroSCORE from assessment of either insulin resistance or adiponectin.

Limitations and strengths

The study design does not allow us to infer causality between the insulin resistance, adiponectin and postoperative outcomes. Even so, we studied a well-defined cohort that was representative of the patient population undergoing cardiac surgery at our department. We had a practically complete follow-up on all included patients, since our design relied on population-based registries with complete coverage. Recruitment of participants was prospective and independent of exposure levels. Besides that, the levels of insulin resistance and adiponectin were not known to the surgeons and physicians treating the patients and therefore the risk of information bias was minimal. When considering registry data validity,

the predictive value have previously been reported to be high (approximately 80-99%) for several of the outcomes in our study including myocardial infarction and stroke [25,26]. Any misclassification would in any case most likely be independent of the level of insulin resistance and adiponectin and would bias the findings toward the null hypothesis. Although insulin is excreted in a pulsatile fashion, and the average of three independent samples would be a more precise estimate of the true plasma insulin value, the use of only one sample is acceptable and yields similar results compared to three samples in large datasets [27].

Conclusions

In conclusion, high levels of preoperative insulin resistance or adiponectin are not associated with increased 30-day mortality, but a high level of adiponectin implies an increased 31-365-day mortality, and slightly prolonged length of intensive care unit and total hospital stay. Owing to our results on prognostic values, we suggest additional studies to further clarify the potentially important role of preoperative insulin resistance and in particular adiponectin in preoperative risk assessment in cardiac surgery.

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Authors' contributions

MMM: principal investigator. All authors: study design. MMM, TKH, TDC, VH, SPJ: data aquisition. MMM and SPJ: data analyses. MMM: article writing. MMM, TKH, JG, NHA, TDC, VH, SPJ: critical reviews of article drafts and approval of the final version to be published.

Competing interests

The authors declare that they have no competing interests.

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