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Abstract

Objective: We aimed to validate the E-CABG classification of postoperative complications in patients undergoing coronary artery bypass grafting (CABG).

Design: Retrospective, observational study.

Setting: University hospital.

Participants: 2764 patients with severe coronary artery disease. Complete baseline, operative and postoperative data were available for who underwent isolated CABG.

Interventions: Isolated CABG.

Measurements and Main Results: The E-CABG complication classification was employed to stratify the severity and prognostic impact of postoperative adverse events. Primary outcome end-points were 30-day, 90-day and long-term all-cause mortality. Secondary outcome end-point was the length of intensive care unit stay. Both the E-CABG complication grades and additive score were predictive of 30-day (area under the ROC curve 0.866, 95%CI 0.829-0.903 and 0.876, 95%CI 0.844-0.908, respectively) and 90-day (area under the ROC curve 0.850, 95%CI 0.812-0.887 and 0.863, 95%CI 0.829-0.897, respectively) all-cause mortality. The complication grades were independent predictors of increased mortality at actuarial (Log-rank: p<0.0001) and adjusted analysis (p<0.0001, grade 1: HR 1.757, 95%CI 1.111-2.778, grade 2: 2.704, 95%CI 1.664-4.394; grade 3: 5.081, 95CI% 3.148-8.201). When patients who died within 30 days were excluded from the analysis, this grading method was still associated with late mortality (p<0.0001). The grading method (p<0.0001) and the additive score (rho, 0.514; p<0.0001) were predictive of the length intensive care unit stay.

Conclusions: The E-CABG postoperative complication classification seems to be a promising tool for stratifying the severity and prognostic impact of postoperative complications in patients undergoing cardiac surgery.

Abstract word count: 235 words

Key words: Coronary artery bypass; cardiac surgery; complication; classification.

INTRODUCTION

Adult cardiac surgery is associated with significant postoperative mortality and morbidity. Moreover, a number of postoperative complications are rather frequent and may compromise the recovery of patients undergoing cardiac surgery.[1,2] Such complications also increase the burden of resource use[1,2] and may affect late survival.[3-7] Few grading methods for complications after major surgery have been developed to assess the quality of surgical treatment.[8,9] However, these grading systems are not applicable to patients undergoing cardiac surgery and therefore a specific grading method for these patients is needed. The E-CABG (European multicenter study on coronary artery bypass grafting) investigators recently proposed a classification of postoperative complications as a part of their study protocol.[10] The present study was planned to assess the ability of the E-CABG complication classification in predicting early and long-term mortality as well as length of intensive care unit stay of patients undergoing isolated coronary artery bypass grafting (CABG).

METHODS

Patient population and data collection

The present study included 2764 consecutive patients who underwent isolated CABG from June 2006 to December 2013 at the Oulu University Hospital, Finland. The study included elective, urgent and emergency operations carried out with either off-pump or on-pump technique. Patients' characteristics and operative data are summarized in Table 1. Definition criteria of baseline characteristics are according to the EuroSCORE criteria.[11]

Complete pre- intra- and postoperative data were available in all these patients as obtained from institutional electronic cardiac surgery database collecting baseline and operative data as well as data on immediate postoperative adverse events. These data were collected by two research nurses and three colleagues. The senior author (FB) has checked all the data along the years. In 2014 and 2015, this database was again checked by two researchers (EMK and MAM). Twenty-eight patients without data on serum levels of creatinine were still included in this analysis as in most of the cases they died immediately after surgery and their postoperative creatinine level was not checked. The amount of transfused blood products such as red blood cells (RBCs), platelets and solvent/detergent-treated plasma (Octaplas; Octapharma AG, Lachen, Switzerland) was retrieved from a prospective electronic hospital registry collecting data on any transfusion of blood products. These blood products were administered intraoperatively and throughout the in-hospital stay. Data on the amount of postoperative blood losses were retrieved from a prospective electronic registry of our intensive care unit. Glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease (MDRD) formula.[12] Clinical variables were defined according to the EuroSCORE II definition criteria.[12]

Data on patients' death were retrieved from Statistics Finland (Tilastokeskus) which collects the certificates of death of all inhabitants of Finland. The data for this study were provided up to December 31st, 2013. We assume that there are no missing data on immediate and late death of this study population.

Operative Techniques

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

E-CABG postoperative complication classification method

E-CABG is a European multicenter study currently recruiting patients undergoing isolated CABG. The study protocol of this study with detailed definition criteria of baseline, operative and postoperative variables has been published previously.[10] The E-CABG investigators proposed a classification method to stratify the adverse outcome events occurring in these patients.

Twenty-four investigators selected and stratified the severity burden of 25 complications or interventions for their treatment with potentially negative prognostic impact on the course of patients undergoing adult cardiac surgery. Each investigator assigned a score of 0-10 in regards of the expected negative impact on outcome of each of these adverse events/interventions. A score of 10 was supposed to measure the worst postoperative complication, i.e. patient's death. The medians of scores for each complication/intervention were used to stratify the prognostic importance of these adverse events and to develop a four-grade classification of postoperative complications (Tab. 2). In case of multiple adverse events occurring in a particular patient, the event with the highest score defines the grade to which the patient belongs to. The median scores are used as an additive score as well.

Outcome endpoints

The main outcome measures of this study were all-cause 30-day, 90-day and long-term mortality. The secondary outcome end-point was the length of intensive care unit stay. We did not consider the length of in-hospital stay as an outcome measure as the timing of discharge of these patients reflects the availability of beds at rehabilitation clinics.

Ethical considerations

This study was approved by the Institutional Review Board of the Oulu University Hospital and it was not financially supported.

Statistical analysis

Statistical analysis was performed with the SPSS v. 22.0 statistical software (IBM Corporation, 1 New Orchard Road Armonk, New York 10504-1722, United States). No attempt to replace missing values was made. Fisher exact test, Chi-square test, Mann-Whitney and Kruskal-Wallis tests were used for univariate analysis. Correlation between continuous and ordinal variables was estimated by the Spearman's test. Survival analysis at 90 days was performed including only patients with a potential follow-up longer than 3 months. C-statistics were calculated to assess the predictive ability of the E-CABG complication classification either as additive score or grades. Kaplan-Meier method was used to estimate late survival. Cox proportional hazards analysis was performed to adjust the E-CABG complication grades for baseline and operative variables potentially associated with poor late survival. These variables were age, eGFR, gender, diabetes, hypertension, prior stroke, neurological dysfunction, extracardiac arteriopathy, previous percutaneous coronary intervention, previous cardiac surgery, recent myocardial infarction, pulmonary disease, left ventricular ejection fraction classes, dialysis, elective/urgent/emergency operation, unstable angina requiring nitrates at operating room arrival, critical preoperative status, systolic pulmonary pressure, off-pump surgery, number of distal anastomoses and any mammary artery graft. Because of imbalance in baseline and operative characteristics of patients in different E-CABG classification grades, probabilities (propensity scores) estimated by multinomial regression analysis were employed to adjust the risk of early and late mortality in these patients with different E-CABG grades (multiple propensity score adjusted analysis). Propensity scores were calculated by a regression model entering all baseline and operative variables listed above. All tests were two-sided with the alpha level set at 0.05 for statistical significance.

RESULTS

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

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

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

Receiver operating characteristics (ROC) analysis confirmed that the E-CABG complication score was predictive of 30-day (area under the ROC curve 0.876, 95%CI 0.844-0.908) and 90-day (area under the ROC curve 0.863, 95%CI 0.829-0.897, Fig. 1) all-cause mortality. Since the grading method is the result of a breakdown of this additive score, ROC analysis was performed also for the E-CABG complication grades and showed that these were predictive of 30-day (area under the ROC curve 0.866, 95%CI 0.829-0.903) and 90-day (area under the ROC curve 0.850, 95%CI 0.812-0.887) all-cause mortality.

The E-CABG complication grades were independent predictors of increased mortality at Kaplan-Meier (at 5 years: grade 0, 5.5%; grade 1, 11.1%; grade 2, 23.1%; grade 3, 35.3%, Log-rank: p<0.0001) (Fig. 2) and Cox regression adjusted analysis (2651 patients included in the multivariate model; p<0.0001, grade 1: HR 1.757, 95%CI 1.111-2.778, grade 2: 2.704, 95%CI 1.664-4.394; grade 3: 5.081, 95CI% 3.148-8.201) (Tab. 2, Fig. 3).

When patients who died within 30 days were excluded from the analysis, this grading method was still associated with late mortality (2562 patients included in the multivariate model; p<0.0001, grade 1: HR 1.760, 95%CI 1.1356-2.283, grade 2: 2.936, 95%CI 1.798-4.794; grade 3: 3.209, 95CI% 1.929-5.338).

Figure 4 summarizes the unadjusted risk estimates of any early and late mortality for each postoperative adverse event. This analysis confirmed that the adverse events included among grade 3 complications were associated with a formidable risk of death. Postoperative use of intra-aortic balloon pump was associated with a very high mortality, likely because extracorporeal membrane oxygenation was not in use in this series. Multivariate analysis of the prognostic impact of these adverse events was not performed because of the risk of overfitting.

DISCUSSION

The present analysis showed that the E-CABG complication classification performed well when used either as a four-grade classification system or as additive score. In fact, both the E-CABG complication grades and score were predictive of increased early and late mortality as well as of the length of stay in the intensive care unit in patients undergoing isolated CABG. As seen in Figure 4, particularly the adverse events included among grade 3 complications were associated with a remarkably increased risk of death. Mortality in patients with postoperative use of intra-aortic balloon pump was very high, possibly due to their severely depressed hemodynamic conditions of these patients. Indeed, our institutional policy is to use intra-aortic balloon pump only after CABG is accomplished and patient has low cardiac output despite optimal inotropic support. Extracorporeal membrane oxygenation was not used in this series.

We did not perform a multivariate analysis to adjust the postoperative complications for baseline and operative characteristics because this model would have been too complex and might have led to overfitting. However, risk estimates of several postoperative complications appeared such large in univariate analysis that it is not plausible that this was caused solely by bias. Also previous studies have reported significant mortality associated with postoperative complications such as increased RBC transfusion,[13,14] acute kidney injury,[4,6] mediastinitis,[7] gastrointestinal complications,[15,16] use of IABP[17,18] and atrial fibrillation.[3] Welsby et al. investigated patients undergoing cardiac surgery with cardiopulmonary bypass and found that, after adjusting for preoperative and intraoperative risk factors, the occurrence of non-cardiac complications only and cardiac complications with other organ involvement significantly increased mortality as well as the length of stay in the hospital and intensive care unit when compared with cardiac complications only.[19]

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

The present study showed that a number of complications in lower grades of the classification are not likely to affect patients' survival (Fig. 4) even though also opposite results have been reported.[5] However, even complications that are considered less severe may cause discomfort to the patient and increase the costs for their treatment. Moreover, the synergistic effect of multiple, even minor, adverse events may also make the lower complication grades of clinically significance as seen in the adjusted analyses (Tab. 2).

An important finding emerging from this analysis was that the risk of death is not limited to the in-hospital stay: indeed, patients are discharged and die shortly after surgery. In patients classified as Grade 3, 30-day mortality was 14.5% and 90-day mortality 21.5%. Such a high mortality is not acceptable and therefore, considering the potentially preventable nature of a number of these postoperative complications, preventive methods should be employed to improve the outcome of these patients. Future studies investigating the predictors of Grade 3 complications may identify patients at high risk and indicate different treatment strategies.

Supporting the results of the present study, previous studies emphasized that in-hospital mortality may not be the most adequate variable to measure the quality of care in patients undergoing CABG.[20,21] Silber et al. compared 57 American hospitals and observed that reported complication rates did not correlate with rates of in-hospital mortality.[20] Instead, several hospital characteristics generally associated with a higher quality of treatment were associated with rather low mortality rates, but higher complication rates.[20]

Also Ghali et al. concluded that complications after CABG are common and may provide more informations about hospital quality than in-hospital mortality rates.[21]

A number of limitations which may affect the results of this study should be acknowledged. The retrospective nature of this study is an important limitation of this analysis. However, even if there are some retrospectively collected data, data on important outcome end-points were retrieved from prospective electronic registries which can be considered reliable. Furthermore, data on patient's death are retrieved form a national registry which collects data on all Finnish population. This study assessed the prognostic impact of the E-CABG complication classification in patients undergoing isolated CABG at a single institution and including patients who underwent either off-pump or on-pump surgery. Therefore, this classification method should be validated in patients operated in other institutions, particularly in those undergoing cardiac procedures other than isolated CABG.

CONCLUSIONS

The E-CABG complication classification seems to be a promising tool for stratification of the severity and prognostic effect of postoperative complications in patients undergoing isolated CABG. This classification method may be of benefit in clinical research in this field.

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Legend to figures

Figure 1. Receiver operating characteristics curve of E-CABG complication classification score in predicting 30-day all-cause mortality.
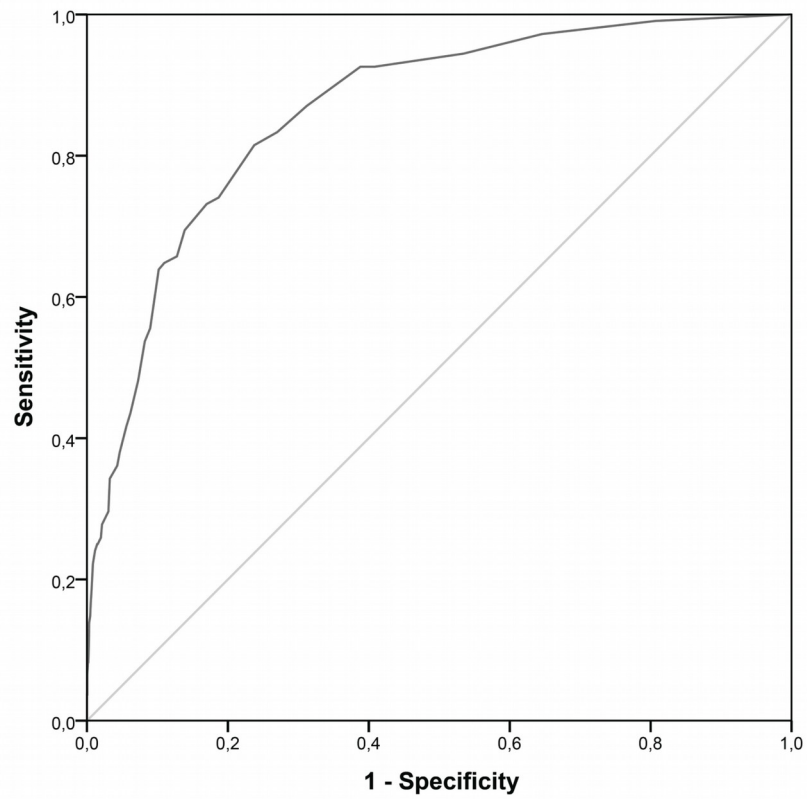
Figure 2. Kaplan-Meier estimates of all-cause mortality according to different E-CABG complication classification grades (log-rank: p<0.0001).
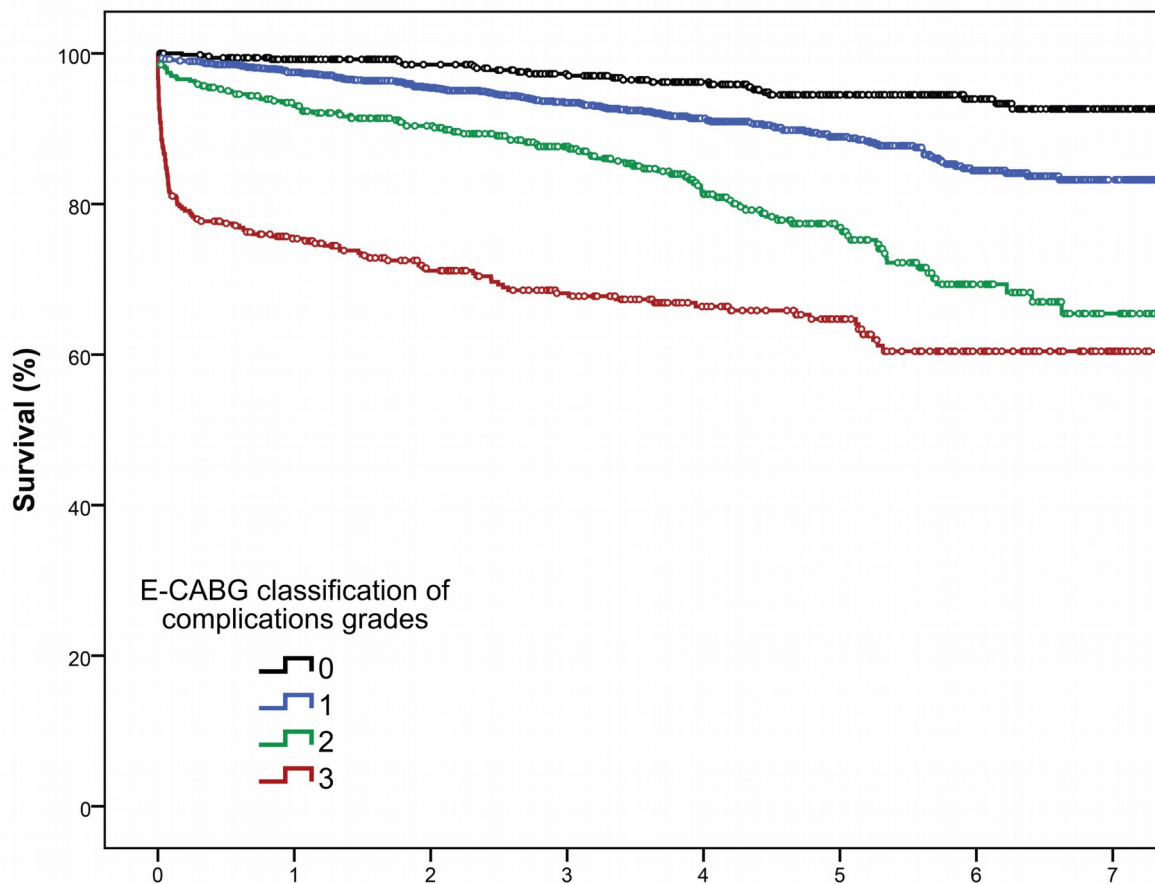
Patients at risk								
	0	1	2	3	4	5	6	7
Grade 0	514	473	416	372	310	237	159	63
Grade 1	1425	1274	1069	862	634	473	275	108
Grade 2	466	408	353	286	209	145	72	27
Grade 3	359	248	206	170	131	103	56	21

Figure 3. Adjusted Cox proportional hazards estimates of all-cause mortality according to different E-CABG complication classification grades (p<0.0001, grade 1: HR 1.757, 95%CI 1.111-2.778, grade 2: 2.704, 95%CI 1.664-4.394; grade 3: 5.081, 95CI% 3.148-8.201).
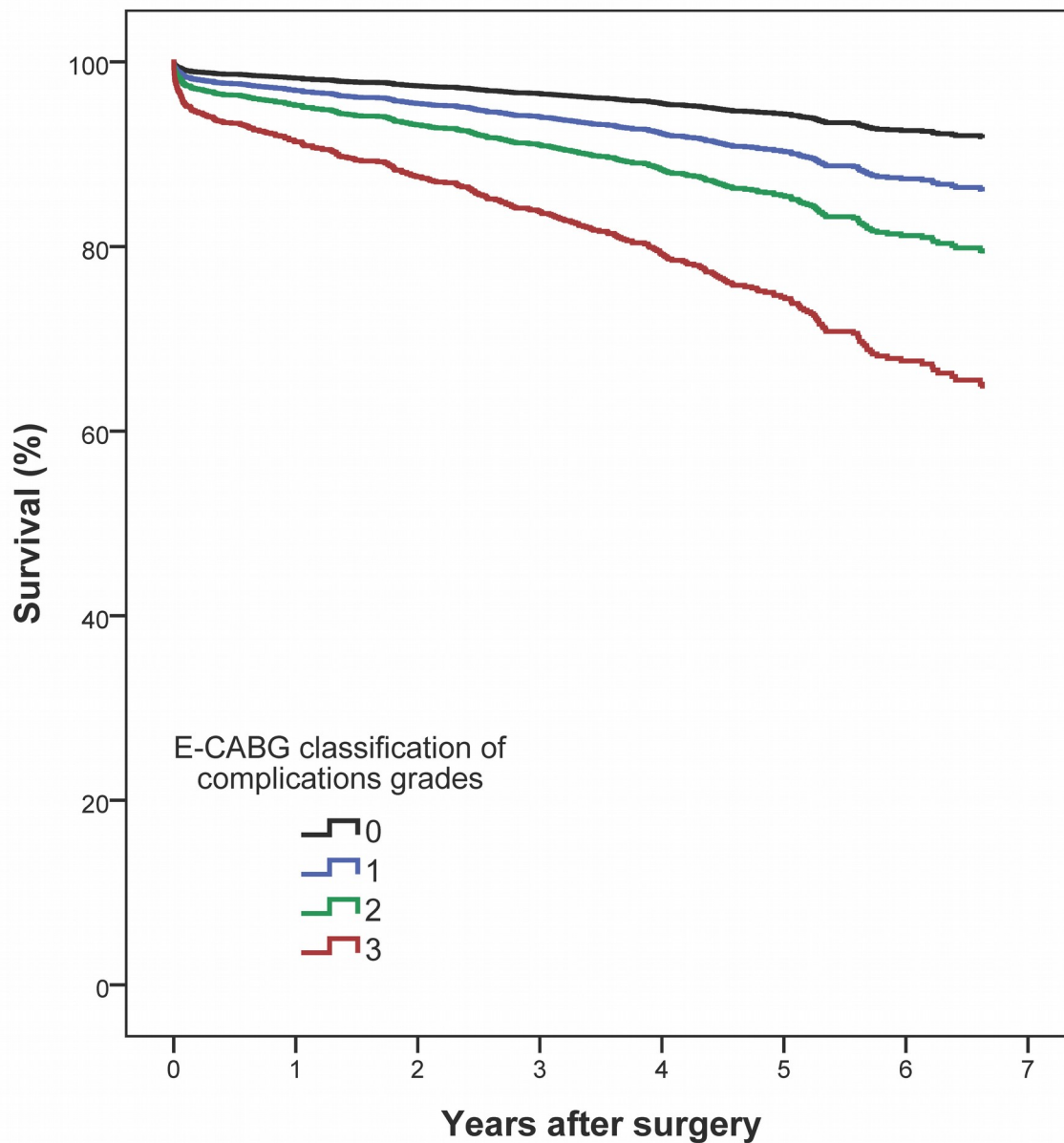
Figure 4. Unadjusted estimates of all-cause mortality according to different postoperative adverse events included in the E-CABG complication classification. IABP: intra-aortic balloon pump; RBC: red blood cell; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; ECMO: extracorporeal membrane oxygenation; HR: hazard ratio; CI: confidence interval.
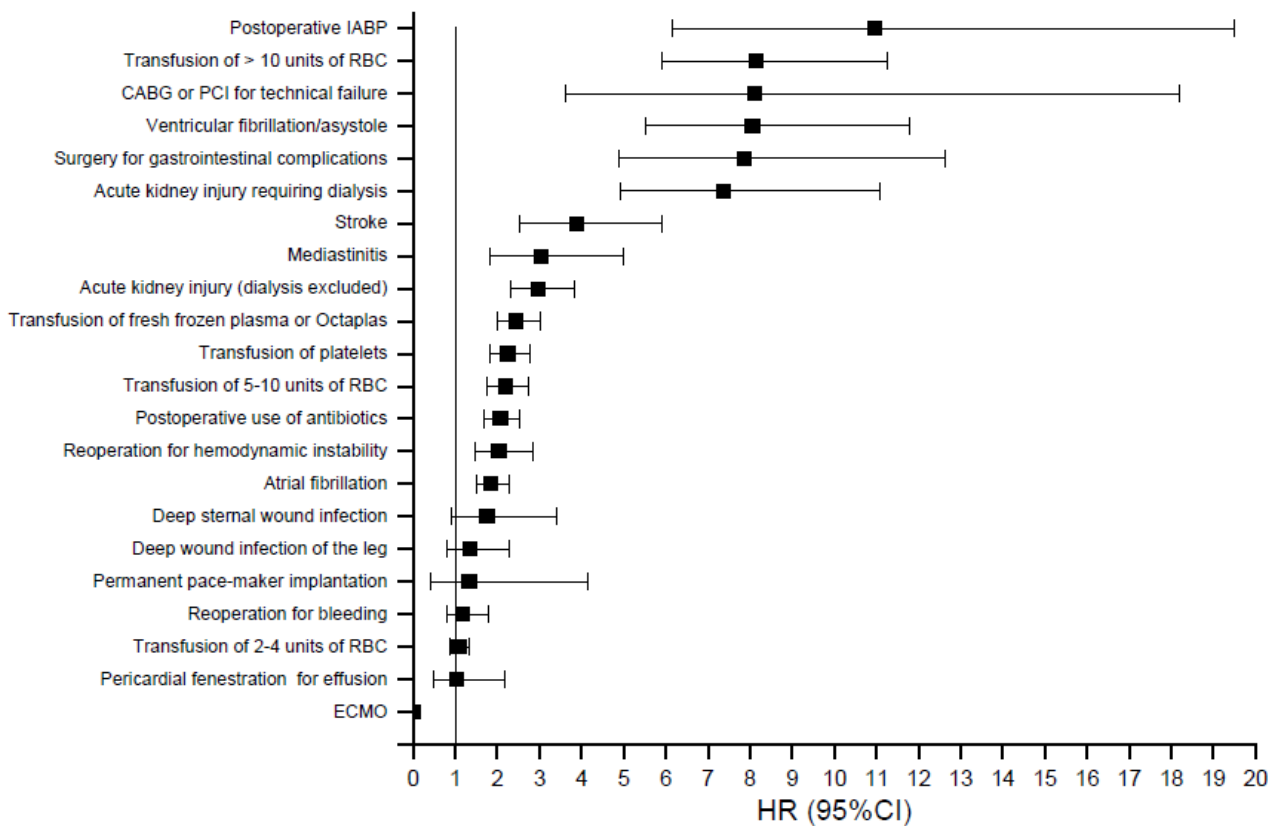
Table 1. Baseline and operative characteristics and in-hospital deaths of the study population and subgroups according to the E-CABG grading.

	Overall series n=2764	Grade 0 n= 514	Grade 1 n= 1425	Grade 2 n= 466	Grade 3 n= 359	P-value
Age (years)	67.0±9.1	63.3±8.4	67.1±8.9	69.6±9.4	68.1±8.7	<0.001
Female	582 (21.1)	60 (11.7)	289 (20.3)	151 (32.4)	82 (22.8)	<0.001
Pulmonary disease	274 (9.9)	48 (9.3)	126 (8.8)	52 (11.2)	48 (13.4)	0.05
Diabetes	788 (28.5)	120 (23.3)	381 (26.7)	176 (37.8)	111 (30.9)	<0.001
Hypertension	1547 (56.0)	269 (52.3)	794 (55.7)	280 (60.1)	204 (56.8)	0.11
Stroke	95 (3.4)	10 (1.9)	46 (3.2)	20 (4.3)	19 (3.4)	0.04
Neurologic dysfunction	50 (1.8)	1(0.2)	32 (2.2)	8 (1.7)	9 (2.5)	0.02
Extracardiac arteriopathy	265 (9.6)	33 (6.4)	117 (8.2)	59 (12.7)	56 (15.6)	<0.001
eGFR (mL/min/1.73 m^2)	86.1±25.2	92.3±20.8	87.0±23.1	81.2±29.4	79.9±30.2	<0.001
Dialysis	22 (0.8)	1 (0.2)	8 (0.6)	3 (0.6)	10 (2.8)	<0.001
Atrial fibrillation	282 (10.2)	7 (1.4)	159 (11.2)	64 (13.7)	52 (14.5)	<0.001
Recent myocardial infarction	1319 (47.7)	144 (28.0)	652 (45.8)	307 (65.9)	216 (60.2)	<0.001
Previous PCI	201 (7.3)	34 (6.6)	94 (6.6)	41 (8.8)	32 (8.9)	0.23
Previous cardiac surgery	46 (1.7)	6 (1.2)	17 (1.2)	11 (2.4)	12 (3.3)	0.02
Left ventricular ejection fraction						<0.001
30-50%	612 (22.1)	81 (16.2)	284 (20.8)	131 (29.2)	116 (33.7)	
<30%	87 (3.1)	4 (0.4)	39 (2.9)	28 (6.3)	16 (4.7)	
Critical preoperative status	217 (7.9)	12 (2.3)	81 (5.7)	62 (13.3)	62 (17.3)	<0.001
Operative data						
Type of operation						<0.001
Elective	1260 (45.6)	340 (66.1)	688 (48.3)	115 (24.7)	117 (32.6)	
Urgent	1306 (47.3)	173 (33.7)	677 (47.5)	289 (62.0)	167 (46.5)	
Emergency	197 (7.1)	1 (0.2)	60 (4.2)	62 (13.3)	75 (20.9)	
Mammary artery graft	2642 (95.6)	508 (98.8)	1385 (97.2)	432 (92.7)	317 (88.3)	<0.001
Potent antiplatelets within 5 days	512 (18.5)	37 (7.2)	242 (17.0)	139 (29.8)	94 (26.2)	<0.001
Off-pump coronary surgery	1510 (54.6)	311 (60.5)	789 (55.4)	230 (49.4)	180 (50.1)	0.01
Number of distal anastomoses	4.0±1.1	4.0±1.1	3.9±1.1	4.0±1.1	3.8±1.0	0.07
In-hospital death	67 (2.4)	0 (0.0)	6 (0.4)	8 (1.7)	53 (14.8)	<0.001

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

Table 2. E-CABG classification of postoperative complications or interventions for their treatment and their prevalence. Adjusted risk estimates for postoperative early and late mortality are reported.

Grades	Postoperative complications or interventions for their treatment	Additive score	No. (%)	Adjusted analysis for mortality HR (95%CI)	Multiple propensity score adjusted analysis for mortality
Grade 0					
	None of the below mentioned complications/interventions	0	514 (18.6)	Reference category	Reference category
Grade 1			1425 (51.6)	1.76 (1.11-2.78)	1.69 (1.06-2.68)
	Postoperative use of antibiotics	2	937 (33.9)		
	Atrial fibrillation	2	1186 (42.9)		
	Transfusion of platelets	2	826 (29.9)		
	Transfusion of fresh frozen plasma or Octaplas	3	738 (26.7)		
	Transfusion of 2-4 units of RBC	3	939 (34.0)		
	Deep wound infection of the leg	3	78 (2.8)		
	Permanent pace-maker implantation	3	18 (0.7)		
Grade 2			466 (16.9)	2.70 (1.66-4.39)	2.71 (1.65-4.43)
	Pericardial fenestration for effusion	4	47 (1.7)		
	Acute kidney injury (dialysis excluded)	4	258 (89.3)*		
	Transfusion of 5-10 units of RBC	5	443 (16.0)		
	Reoperation for bleeding	5	163 (5.9)		
	Deep sternal wound infection	5	40 (1.4)		
	Postoperative IABP	5	16 (0.6)		
Grade 3			359 (13.0)	5.08 (3.15-8.20)	4.57 (2.81-7.43)
	Transfusion of > 10 units of RBC	7	68 (2.5)		
	Acute kidney injury requiring dialysis	7	42 (1.5)*		
	Mediastinitis	7	43 (1.6)		
	Stroke	7	58 (21)		
	CABG or PCI for technical failure	7	14 (0.5)		

Reoperation for hemodynamic instability	8	168 (6.1)	
Ventricular fibrillation/asystole	8	49 (1.8)	
Surgery for gastrointestinal complications	9	32 (1.2)	
Postoperative ECMO	9	0	-

Definition criteria are according to the E-CABG criteria [10]; HR: hazard ratio; CI: confidence interval; RBC: red blood cell; IABP: intra-aortic balloon pump; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; ECMO: extracorporeal membrane oxygenation; * patients on preoperative dialysis excluded from this analysis.