Validation of Bleeding Classifications in Coronary Surgery

Short title: Bleeding classifications

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Abstract

Background: Perioperative bleeding is a determinant of poor outcome in patients undergoing coronary artery bypass grafting (CABG), but there is a lack of adequate stratification of its severity.

Methods: The ability of the E-CABG, UDPB, PLATO, CURRENT-OASIS 7, ESSENCE and STEEPLE bleeding classifications to predict early mortality, stroke, acute kidney injury (AKI) stage 3 and deep sternal wound infection/mediastinitis, was investigated in 3730 patients from the prospective, multicentre E-CABG registry.

Results: Increasing grades of the E-CABG, UDPB, PLATO and CURRENT-OASIS 7 classifications were associated with increasing risks of early mortality, had similar receiver-operating characteristic area under the curves (AUC) (>0.7) and were predictive also when adjusted for EuroSCORE II. The E-CABG and UDPB classifications had satisfactory AUCs (>0.6) in predicting stroke, AKI stage 3 and deep sternal wound infection/mediastinitis even when adjusted for EuroSCORE II. The PLATO and CURRENT-OASIS 7 classifications had similar predictive ability for stroke and AKI stage 3 as confirmed by multivariate analysis adjusted for EuroSCORE II, but showed inferior ability in predicting severe wound infection compared to the E-CABG and UDPB classifications. The STEEPLE and ESSENCE classifications had a poor ability of predicting all these adverse events. Decision curve analysis showed a benefit of the E-CABG bleeding classification over the other classifications in predicting all adverse events.

Conclusions: The E-CABG, UDPB, PLATO and CURRENT-OASIS 7 bleeding classifications have a satisfactory ability in predicting adverse events after CABG. Decision curve analysis showed that the E-CABG bleeding classification had the best predictive performance.

Clinical Trial Registration: NCT02319083 (https://clinicaltrials.gov/ct2/show/NCT02319083)

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Perioperative bleeding has a negative impact on the early and late outcome of patients undergoing cardiac surgery.[1-3] This issue is of particular importance in patients undergoing coronary artery bypass grafting (CABG) since they are often under treatment with potent antithrombotics. The importance of an accurate stratification of the severity of periprocedural bleeding has been recognized in the assessment of the efficacy and safety of antiplatelet and anticoagulant drugs in patients undergoing percutaneous coronary intervention.[4] Because of this, several bleeding classifications have been developed and are currently in use in interventional cardiology.[5-17] Bleeding during cardiac surgery is far more severe, yet only two specific bleeding classifications for patients undergoing cardiac surgery have been proposed.[18,19] In this study, we sought to evaluate the performance of a number of currently available bleeding classifications in predicting major adverse outcomes after CABG.

Methods

The E-CABG is an on-going European multicentre, prospective registry collecting data on patients undergoing CABG operated in 16 European centres of cardiac surgery in six European countries (England, Finland, France, Germany, Italy, Sweden). For the present analysis, the data were collected from January to December 2015. The E-CABG registry is registered in Clinicaltrials.gov (Identifier: NCT02319083) and its detailed protocol and definition criteria have been previously published.[19]

Data on baseline characteristics of patients were collected prospectively. The operative risk was estimated according to the EuroSCORE II.[20] Periprocedural bleeding classifications were chosen for this analysis based on their ability to stratify the severity of hemorrhage and the use of blood products in at least three grades of increasing severity. Therefore, other binary bleeding classifications were not considered for this analysis. Patients' severity of bleeding was therefore stratified according to the E-CABG,[19] UDPB,[18] PLATO,[12] CURRENT-OASIS 7,[8] STEEPLE[14] and

ESSENCE [9] bleeding classifications. A detailed description of these bleeding classifications is given in the Supplementary material.

In view of an expected impact of excessive bleeding and use of blood products on the risk of early adverse events, four major outcomes were chosen for the evaluation of the perioperative bleeding classifications. The primary outcome of this study was in-hospital or 30-day mortality. The secondary outcomes were postoperative stroke, acute kidney injury (AKI) stage 3 and deep sternal wound infection/mediastinitis. Postoperative stroke was defined as any focal or global neurological syndrome occurring during the in-hospital stay caused by ischemia and/or hemorrhage not resolving within 24 h.[17] AKI was stratified according to the Kidney Disease: Improving Global Outcomes (KDIGO) definition criteria.[21] Accordingly, AKI stage 3 was defined as an increase in serum creatinine of ≥ 3.0 times the baseline creatinine or an increase in serum creatinine ≥ 4.0 mg/dl or initiation of renal replacement therapy. Deep sternal wound infections or mediastinitis were graded according to the Centers for Disease Control and Prevention definitions of surgical site infections.[22]

Statistical analysis was performed using the SPSS statistical software (version 23.0 IBM Corporation; Armonk, New York, USA) and the freely available software easyROC (ver. 1.3, http://www.biosoft.hacettepe.edu.tr/easyROC/, accessed on September 28, 2016). No attempt to replace missing values was made. Continuous variables were reported as the mean and standard deviation. Nominal variables were reported as counts and percentages. The discriminatory ability of the bleeding classifications was evaluated by c-statistics. The area under the curve (AUC) of the receiver operating characteristic (ROC) of each bleeding classification in predicting adverse outcome was estimated along with its 95% confidence interval (95%CI). Differences between the AUCs of these bleeding classifications were evaluated by the DeLong test.[23] Calibration of the risk scores was assessed by the Hosmer-Lemeshow's (HL) test.[24] A decision curve analysis[25] was performed in order to estimate the clinical usefulness of each bleeding score. The decision curve analysis estimates the net benefit of a model by the difference between the number of true-positive and false-positive results, weighted by the odds of the selected threshold probability of risk. The net benefit of a model compared with the reference net benefit or with another model can be interpreted as the net increase in the proportion of cases identified. For any given threshold probability cutpoint, the risk model with the greatest net benefit would be the preferred model. The risk estimates of adverse events were adjusted for baseline characteristics by including the EuroSCORE II[22] as a covariate in the logistic regression models. All tests were two-sided with the alpha level set at 0.05 for statistical significance.

Results

Data were obtained from a series of 3730 consecutive patients who underwent isolated CABG and with complete data on bleeding-related parameters. Baseline characteristics of these patients are summarized in Table 1. In this study, 67 (1.8%) patients died during the in-hospital stay or within the first 30 postoperative days. AKI stage 3 was observed in 2.5% of patients, stroke in 1.4% and deep sternal wound infection/mediastinitis in 2.6% of patients.

Increasing grades of the E-CABG, UDPB, PLATO, CURRENT-OASIS 7, STEEPLE and ESSENCE classifications were associated with increasing risk of early death (Tab. 2). However, only the E-CABG, UDPB, PLATO and CURRENT-OASIS 7 classifications showed an AUC larger than 0.7 (Tab. 2, Fig. 1). Furthermore, EuroSCORE II adjusted logistic regression confirmed the predictive ability of the latter classifications and showed that the STEEPLE and ESSENCE classifications were not predictive of early mortality (Tab. 2). The DeLong test confirmed that the AUC of the STEEPLE and ESSENCE classifications were significantly smaller than of the other bleeding classifications (Tab. 3). Despite the AUCs of the PLATO and CURRENT-OASIS 7 being smaller than those of the E-CABG and UDPB classifications, these differences were not statistically significant in the DeLong test.

C-statistics confirmed that the E-CABG and UDPB classifications had satisfactory AUC (in all cases larger than 0.6) for prediction of stroke, AKI stage 3 and deep sternal wound infection/mediastinitis. These findings were confirmed in multivariate analysis adjusted for EuroSCORE II (Tab. 2). The AUCs of the PLATO and CURRENT-OASIS 7 were satisfactory for prediction of stroke and AKI stage 3, their AUCs were similar to the E-CABG and UDPB classifications' AUCs (Tab. 3) and their prognostic impact was confirmed in multivariate analysis adjusted for EuroSCORE II (Tab. 2). However, the PLATO and CURRENT-OASIS 7 had an inferior ability of predicting severe wound infection compared to the E-CABG and UDPB classifications. The STEEPLE and ESSENCE classifications had a poor ability of predicting these secondary outcomes.

The decision curve analysis showed a net benefit for the E-CABG bleeding classification over the other classifications in terms of prediction of early mortality, stroke, AKI stage 3 and deep sternal wound infection/mediastinitis (Fig. 2). This benefit was particularly evident in predicting early mortality and AKI stage 3.

Discussion

The value of periprocedural bleeding classifications lies in the ability to provide prognostic information and risk discrimination among patients undergoing cardiac surgery or interventional cardiology procedures. In this study, the risk of poor outcome significantly increased along with the severity of bleeding as stratified by the E-CABG, UDPB, PLATO and CURRENT-OASIS 7 bleeding classifications. However, decision curve analysis showed that the E-CABG bleeding classification had the best predictive performance. On the contrary, the STEEPLE and ESSENCE classifications showed a poor predictive ability likely because their criteria are poorly applicable to surgical patients. In fact, retroperitoneal, intracranial, subconjunctival or intraocular hemorrhages are alarming events, but rarely observed after coronary surgery. Furthermore, the cut-off value specified for hemoglobin drop and blood transfusion in these classifications do not provide a good discrimination among these patients. Indeed, bleeding causing a decrease in hemoglobin of ≥3 g/dl as well as the need for transfusion of 1 or 2 units of red blood cells, as used in these classifications, is not equal to excessive bleeding in cardiac surgery patients. Despite being developed for patients undergoing percutaneous coronary interventions, the PLATO and CURRENT-OASIS classifications had a satisfactory ability in stratifying perioperative bleeding also in patients undergoing CABG. Both these bleeding classifications consider a hemoglobin drop ≥5 g/dL and the need for transfusion ≥4 units of red blood cells. These criteria seem to accurately identify those patients with significant bleeding and an excessive risk of adverse events as shown also in previous studies.[26] A limitation of these classifications could be the definition of hypotension and hypovolemic shock, since there is no evidence that they are caused directly by bleeding. The E-CABG and UDPB showed a good predictive ability and this is likely due to the fact that these methods were specifically developed for CABG patients and effectively consider multiple degrees of hemorrhage and use of blood products, therefore identifying a broad range of significant bleeding. Contrary to other bleeding classifications developed for patients undergoing interventional cardiology, the E-CABG and UDPB classification do not consider a perioperative decrease in hemoglobin or hematocrit, but are rather based on interventions to reduce on going bleeding and correct perioperative anemia. The UDPB demonstrated a somewhat better discriminative ability than the E-CABG, but its use in clinical and research fields is limited by its complexity and the need of data on six different blood or procoagulant products. Furthermore, chest drain output probably does not accurately define the degree of perioperative blood loss since significant bleeding may occur after removal of drainage tubess. On the contrary, the E-CABG bleeding classification is based on the amount of red blood cells, platelets and fresh frozen plasma transfusions as well as the need of reoperation for excessive bleeding, which simplifies its use. Indeed, the E-CABG bleeding classification may be accurate in stratifying the severity of bleeding also in patients undergoing invasive cardiology procedures and its simplicity may allow its use also in retrospective studies. However, this needs further validation studies.

Most of the bleeding classifications currently in use are not applicable to cardiac surgery patients or do not allow a proper stratification of these patients. For this reason, the ACUITY/HORIZONS-AMI,[5] GRACE,[18] CURE[7], TIMI for CABG patients,[15] BARC for CABG patients, [27] Amlani et al.,[19] ISAR-REACT 3[11] and REPLACE 2[13] classifications were excluded from this analysis, since they provide only a single definition for major bleeding. Although Kappetein et al.[27] applied the BARC classification to patient undergoing cardiac surgery, showing a good accuracy in predicting adverse events, we excluded also this VARC-2/BARC classification since it uses the same criteria as the PLATO classification. The GUSTO[10] classification was excluded as well from this study, since it uses arbitrarily defined outcomes that are not standardized.

The results of this study can be affected by a number of limitations which must be acknowledged. First, the E-CABG registry does not collect data on intraocular, gastrointestinal, urinary or airway bleeding. Despite being of clinical significance, it is likely that these parameters do not affect the early outcome of patients undergoing CABG unless resulting in significant anemia and the need for blood transfusion. Second, data on intracranial bleeding was collected retrospectively. Third, some of these bleeding classifications consider as a major bleeding the one resulting in the death of patient. However, it is rather difficult to disentangle the direct impact of perioperative bleeding on the early mortality after CABG. Therefore, in this study, in-hospital/30-day mortality was not considered in any case as directly related to excessive bleeding unless clearly caused by massive bleeding. Finally, in the studied cohort, there was no central transfusion protocol used in all centers.

Conflicts of interest: None

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Legend to figures

Figure 1. Receiver operating characteristics curves of different bleeding classification systems for prediction of adverse events after coronary artery bypass grafting.

Figure 2. Decision curves for the predicted early death according to different perioperative bleeding classifications.

Table 1. Baseline characteristics and operative data of the study population.

Clinical variables	*No. (%) / Mean*±SD
Age, years	67.2 ± 9.3
Females	625 (16.8%)
Hemoglobin, g/dL	136.1 ± 16.4
eGFR mL/min/1.73m^2	81.0 ± 25.7
Dialysis	46 (1.2%)
Diabetes on medical treatment	1188 (31.8%)
Extracardiac arteriopathy	780 (20.9%)
Stroke	52 (1.4%)
Chronic lung disease	345 (9.2%)
Atrial fibrillation	283 (7.6%)
LVEF classes	
31-50%	888 (23.8%)
21-30%	159 (4.3%)
<21%	21 (0.6%)
Prior cardiac surgery	32 (0.9%)
Prior PCI	823 (22.1%)
Left main stenosis	1358 (36.4%)
Syntax score	28.1 ± 10.9
Recent myocardial infarction	1136 (30.5%)
Urgency	
Urgent	1478 (39.6%)
Emergency	150 (4.0%)
Salvage	8 (0.2%)
Critical preoperative state	131 (3.5%)
Antithrombotic treatment	
Aspirin	3330 (89.3%)
Warfarin/coumadin/phenprocoumon	85 (2.3%)
Clopidogrel	705 (18.9%)
Ticagrelor	509 (13.6%)
Prasugrel	43 (1.2%)
Unfractioned heparin	314 (8.4%)
Fondaparinux	153 (4.1%)
Off-pump surgery	776 (20.8%)
Bilateral internal mammary a. graft	1405 (37.7%)
Radial graft	50 (1.3%)
EuroSCORE II	2.5 ± 3.7

Continuous values are reported as the mean and standard deviation (SD); nominal variabes are reported and counts and percentages (in parentheses); GFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; LVEF, left ventricle ejection fraction; PCI, percutaneous coronary

Table 2. Predictive performance of current bleeding classifications in predicting major adverse events in patients undergoing coronary surgery.

Classifications / Outcomes	*Severity of perioperative bleeding*					*AUC of the ROC curve (95%CI)*	*Hosmer-Lemeshow's test p-value*	*EuroSCORE II adjusted analysis p-value*
E-CABG	0	1	2	3				
Early mortality	0.6 %	1.6%	13.3%	33.3%		0.793 (0.731-0.854)	0.037	<0.0001
Stroke	1.1%	1.7%	3.3%	8.3%		0.597 (0.517-0.676)	0.606	0.042
AKI stage 3	1.6%	2.6%	9.7%	39.1%		0.665 (0.592-0.738)	0.025	<0.0001
Deep sternal wound infection/mediastinitis	1.7%	3.3%	7.6%	20.8%		0.637 (0.583-0.693)	0.553	<0.0001
UDPB	0	1	2	3	4			
Early mortality	0.5%	1.1%	1.4%	9.7%	21.4%	0.795 (0.736-0.855)	0.005	<0.0001
Stroke	0.8%	1.9%	1.7%	3.0%	4.8%	0.633 (0.554-0.713)	0.361	0.022
AKI stage 3	1.5%	1.3%	3.0%	6.8%	25.0%	0.668 (0.594-0.742)	0.032	<0.0001
Deep sternal wound infection/mediastinitis	1.5%	2.6%	2.7%	8.0%	11.9%	0.657 (0.600-0.713)	0.065	<0.0001
PLATO	No significant bleeding	Major bleeding	Life-threatening bleeding					
Early mortality	0.4%	0.7%	4.0%			0.721 (0.670-0.772)	0.086	<0.0001
Stroke	0.9%	0.9%	2.3%			0.614 (0.535-0.693)	0.172	0.009
AKI stage 3	2.0%	1.4%	4.5%			0.623 (0.554-0.692)	0.002	<0.0001
Deep sternal wound infection/mediastinitis	2.4%	2.1%	3.3%			0.547 (0.491-0.603)	0.180	0.261
CURRENT-OASIS 7	No significant bleeding	Major bleeding	Severe bleeding					
Early mortality	0.5%	1.0%	4.0%			0.725 (0.676-0.775)	0.499	<0.0001
Stroke	0.9%	1.0%	2.3%			0.617 (0.540-0.695)	0.936	0.008
AKI stage 3	1.4%	2.3%	4.5%			0.646 (0.577-0.715)	0.839	<0.0001
Deep sternal wound infection/mediastinitis	1.8%	3.8%	3.3%			0.577 (0.526-0.629)	0.097	0.030
STEEPLE	No significant bleeding	Minor bleeding	Major bleeding					
Early mortality	0.5%	0.3%	2.1%			0.562 (0.540-0.584)	0.181	0.120
Stroke	0.5%	0.8%	1.5%			0.539 (0.491-0.587)	0.514	0.357
AKI stage 3	2.5%	1.6%	2.7%			0.518 (0.465-0.571)	0.323	0.755
Deep sternal wound infection/mediastinitis	1.5%	2.2%	2.7%			0.521 (0.489-0.553)	0.866	0.624
ESSENCE	No significant bleeding	Minor bleeding	Major bleeding					
Early mortality	0.4%	1.0%	2.1%			0.570 (0.545-0.595)	0.908	0.094
Stroke	0.7%	1.9%	1.5%			0.535 (0.482-0.587)	0.389	0.344
AKI stage 3	2.0%	1.9%	2.7%			0.522 (0.468-0.576)	0.812	0.873
Deep sternal wound infection/mediastinitis	1.9%	4.9%	2.7%			0.510 (0.474-0.547)	0.095	0.277

AUC: area under the curve; ROC: receiver operating characteristic

Table 3. Comparative analysis between the receiver operating characteristics curves of the bleeding classifications.

30-day mortality

	E-CABG	UDPB	CURRENT-OASIS 7	PLATO	ESSENCE	STEEPLE
E-CABG	-	0.952	0.097	0.079	**<0.0001**	**<0.0001**
UDPB	0.952	-	0.077	0.063	**<0.0001**	**<0.0001**
CURRENT-OASIS 7	0.097	0.077	-	0.905	**<0.0001**	**<0.0001**
PLATO	0.079	0.063	0.905	-	**<0.0001**	**<0.0001**
ESSENCE	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	-	0.662
STEEPLE	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	0.662	-

Stroke

	E-CABG	UDPB	CURRENT-OASIS 7	PLATO	ESSENCE	STEEPLE
E-CABG	-	0.521	0.708	0.757	0.206	0.228
UDPB	0.521	-	0.783	0.737	**0.042**	**0.047**
CURRENT-OASIS 7	0.708	0.783	-	0.950	0.083	0.092
PLATO	0.757	0.737	0.950	-	0.101	0.111
ESSENCE	0.206	**0.042**	0.083	0.101	-	0.905
STEEPLE	0.228	**0.047**	0.092	0.111	0.905	-

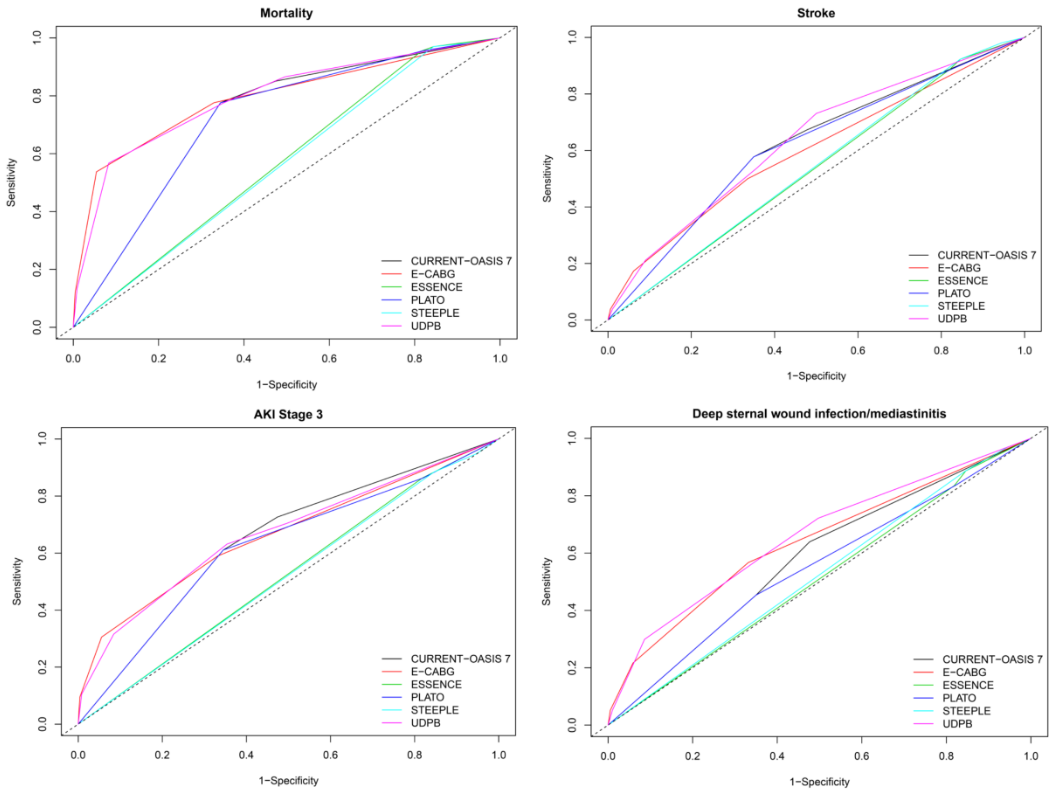
AKI stage 3

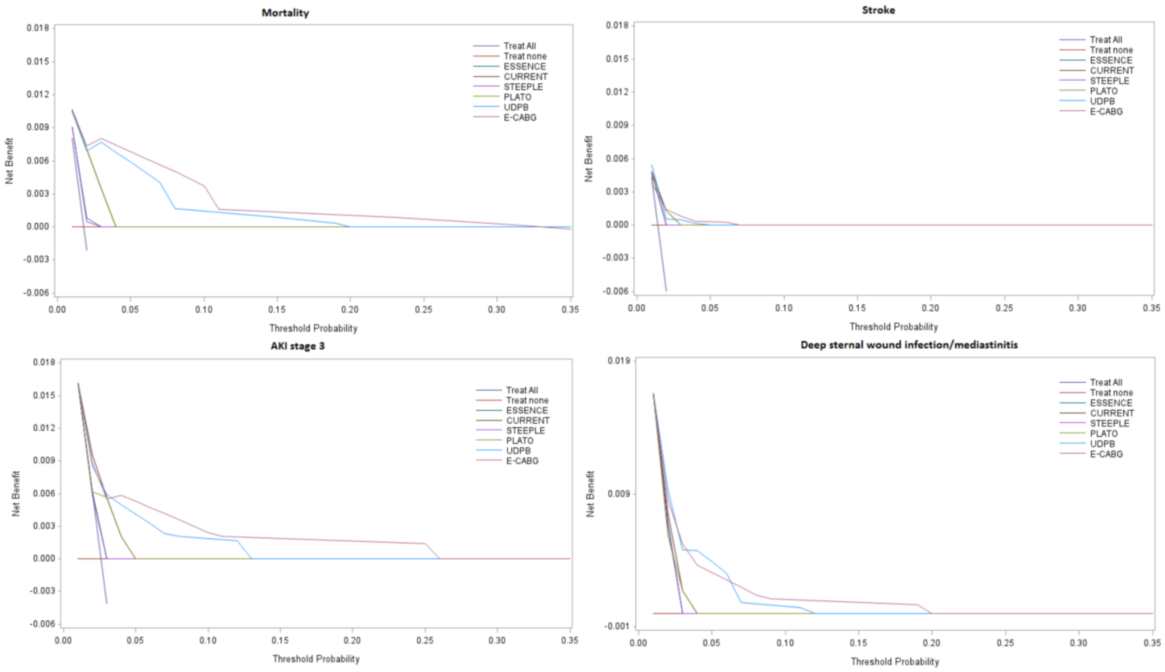
	E-CABG	UDPB	CURRENT-OASIS 7	PLATO	ESSENCE	STEEPLE
E-CABG	-	0.953	0.703	0.412	**0.002**	**0.001**
UDPB	0.953	-	0.660	0.381	**0.002**	**0.001**
CURRENT-OASIS 7	0.703	0.660	-	0.650	**0.006**	**0.004**
PLATO	0.412	0.381	0.650	-	**0.025**	**0.018**
ESSENCE	**0.002**	**0.002**	**0.006**	**0.025**	-	0.912
STEEPLE	**0.001**	**0.001**	**0.004**	**0.018**	0.912	-

Deep sternal wound infection or mediastinitis

	E-CABG	UDPB	CURRENT-OASIS 7	PLATO	ESSENCE	STEEPLE
E-CABG	-	0.641	0.116	**0.023**	**0.0002**	**0.0003**
UDPB	0.641	-	**0.042**	**0.007**	**<0.0001**	**<0.0001**
CURRENT-OASIS 7	0.116	**0.042**	-	0.4339	**0.0376**	**0.068**
PLATO	**0.023**	**0.007**	0.434	-	0.2826	0.430
ESSENCE	**0.0002**	**<0.0001**	**0.038**	0.283	-	0.666
STEEPLE	**0.0003**	**<0.0001**	**0.068**	0.430	0.666	-

Numbers are p-values estimated by the DeLong's test. Statistically significant p-values are reported in bold.


Mortality
Stroke
AKI Stage 3
Deep sternal wound infection/mediastinitis
Sensitivity
1−Specificity
0.0
0.2
0.4
0.6
0.8
1.0
CURRENT−OASIS 7
E−CABG
ESSENCE
PLATO
STEEPLE
UDPB



Mortality
Net Benefit
Threshold Probability
Stroke
Net Benefit
Threshold Probability
AKI stage 3
Net Benefit
Threshold Probability
Deep sternal wound infection/mediastinitis
Net Benefit
Threshold Probability
Treat All
Treat none
ESSENCE
CURRENT
STEEPLE
PLATO
UDPB
E-CABG