Prediction of Severe Bleeding after Coronary Surgery: the WILL-BLEED Risk Score

Short title: Severe bleeding in coronary surgery

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Abstract

Background: Severe perioperative bleeding after coronary artery bypass grafting (CABG) is associated with poor outcome.

Methods: An additive score for prediction of severe bleeding was derived (n=2494) and validated (n=1250) in patients from the E-CABG registry. Severe bleeding was defined as E-CABG bleeding grades 2-3 (transfusion of >4 units of red blood cells or reoperation for bleeding).

Results: The overall incidence of severe bleeding was 6.4%. Preoperative anemia (3 points), female gender (2 points), eGFR <45 mL/min/1.73 m² (3 points), potent antiplatelet drugs discontinued less than 5 days (2 points), critical preoperative state (5 points), acute coronary syndrome (2 points), use of low molecular weight heparin/fondaparinux/unfractionated heparin (1 point) were independent predictors of severe bleeding. The WILL-BLEED score was associated with increasing rates of severe bleeding in both the derivation and validation cohorts (scores 0-3: 2.9% vs 3.4%; scores 4-6: 6.8% vs 7.5%; scores >6: 24.6% vs 24.2%, both p<0.0001). The WILL-BLEED score had a better discriminatory ability (AUC 0.725) for prediction of severe bleeding compared to the ACTION (AUC 0.671), CRUSADE (AUC 0.642), Papworth (AUC 0.605), TRUST (AUC 0.660) and TRACK (AUC 0.640) bleeding scores. The net reclassification index and integrated discrimination improvement using the WILL-BLEED score as opposed to the other bleeding scores were significant (p<0.0001). The decision curve analysis demonstrated a net benefit with the WILL-BLEED score compared to the other bleeding scores.

Conclusions: The WILL-BLEED risk score is a simple risk stratification method which allows the identification of patients at high risk of severe bleeding after CABG.

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

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Introduction

Severe perioperative bleeding is associated with poor outcome in patients undergoing cardiovascular procedures.¹⁻³ Identification of patients at increased risk of perioperative bleeding is important to adopt measures to reduce perioperative blood loss as well as the exposure to blood products. A bleeding risk score would be of particular importance in patients undergoing coronary artery bypass grafting (CABG) as they are frequently treated with potent antithrombotics and are in need of effective measures to reduce excessive perioperative bleeding. Furthermore, a valid risk score would be helpful to address the risk of severe bleeding in case of medicolegal litigations. A number of scoring methods are available for bleeding risk prediction during percutaneous coronary interventions⁵⁻⁸ and adult cardiac surgery.⁹⁻¹¹ However, these scores are not specific for patients undergoing CABG and, importantly, do not take into account preoperative antithrombotic regimens. The aim of this study was to develop a scoring method to stratify the risk of severe bleeding in patients undergoing CABG according to their baseline risk factors and antithrombotic treatment.

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). Twelve of these centres are university hospitals, two centres are central hospitals and two centres are private hospitals with agreements with the regional health authorities. This study was approved by the Institutional Review Board of the participating centers, and it was not financially supported. Informed consent was collected in Institutions where it was required by the internal Institutional Review Board, otherwise it was waived.

For the present analysis, the data were collected from January 1 to December 31, 2015. The E-CABG study is registered in Clinicaltrials.gov (Identifier: NCT02319083) and its detailed protocol

and definition criteria have been previously published.¹² Of importance for this study, preoperative anemia was defined as hemoglobin level <120 g/L in women and <130 g/L in men. Estimated glomerular filtration rate was dichotomized according to a cut-off of 45 mL/min/1.73m², i.e. chronic kidney disease classes 1-3A vs. 3B-5, after univariate and multivariate analyses showed that this cutoff value had the largest impact on the severity of perioperative bleeding. Clopidogrel and ticagrelor were considered as potent antiplatelet drugs and potential triggers of excessive bleeding when discontinued less than five days. Although a pause of five days has been shown to be necessary for clopidogrel, a shorter pause is probably enough for ticagrelor.¹³ However, this issue is still controversial and for the sake of simplicity we used a pause of at least five days as a safe wash-out period for both these drugs. The use of low molecular weight heparin, fondaparinux and/or unfractionated heparin was considered as a single covariate and without taking into consideration their period of pause because of their pharmacologic characteristics and the fact that, when used, they are infrequently discontinued before surgery. Critical preoperative state was defined as any of the following conditions: ventricular tachycardia or ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before anesthetic room, preoperative inotropes or intra-aortic balloon pump, preoperative acute renal failure (anuria or oliguria <10 ml/hr). Acute coronary syndrome was defined as any unstable angina, non-ST elevation or ST-elevation myocardial infarction requiring myocardial revascularization during the index hospitalization.

Data on baseline, intraoperative and postoperative variables were prospectively collected in an Access datasheet by researchers who were trained for data collection into this registry. Data were checked by researchers from each participating center before submitting dataset to the principal investigator for merging. External auditing of the data was not possible because of linguistic and geographical barriers. The principal investigator evaluated the databases for consistency by asking for missing and random data.

Outcomes

The primary outcome of this analysis was severe bleeding as defined by the E-CABG bleeding grades 2-3, i.e. transfusion of more than four units of red blood cells and/or re sternotomy for excessive bleeding.¹⁰ Secondary outcome measure of this study was in-hospital/30-day mortality.

Statistical analysis

Statistical analysis was performed using an SPSS statistical software (version 23.0, IBM Corporation; Armonk, New York, USA), SAS statistical software (version 9.4, SAS Institute Inc., Cary, NC, USA) and EasyROC online software (<http://www.biosoft.hacettepe.edu.tr/easyROC/>, accessed on October 12th, 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 Fisher's exact test, Chi-square test, Mann-Whitney test, Spearman test and Kruskal-Wallis tests were used for univariate analysis. Logistic regression with the backward stepwise entry method was employed to identify independent predictors of E-CABG grades 2-3 of perioperative bleeding. Only baseline covariates with $p < 0.2$ in univariate analysis were included in this regression model. The discriminatory ability of the regression model was assessed using the receiver operating characteristic (ROC) curve analysis. An additive risk score, the WILL-BLEED score, was developed by assigning a weighted integer to each independent risk factor on the basis of the coefficients of the final regression model using the Schneeweiss' method.¹⁴ A score for each patient was calculated by adding these weighted integers. Youden's test was used to identify the best cutoff of the WILL-BLEED score.¹⁵ The discriminatory ability of the WILL-BLEED score and of other bleeding risk scores (CRUSADE,⁷ ACTION,⁸ Papworth,⁹ TRUST¹⁰ and TRACK¹¹ bleeding risk scores, Suppl. Tab. 1) was evaluated by c-statistics. The DeLong test was used to determine if the difference between the area under the ROC curves (AUC)

of these bleeding risk scores was statistically significant.¹⁶ Calibration of the risk scores was assessed by the Hosmer-Lemeshow's (HL) test.¹⁷

The improvement of discrimination of the WILL-BLEED score as compared to the other scores was estimated by calculating the net reclassification index (NRI) and integrated discrimination improvement (IDI).¹⁸ For the NRI, the risk categories were stratified into three groups of E-CABG bleeding grades 2-3, i.e. <5%, 5-11%, >11%. A decision curve analysis¹⁹ 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. Furthermore, the performance of the WILL-BLEED score was assessed by using it as an ordinal covariate and calculating the rates of severe bleeding for each category. Chi-squared automatic interaction detection (CHAID) analysis was performed to evaluate the interaction between the WILL-BLEED score and the impact of severity of perioperative bleeding on early postoperative mortality. The WILL-BLEED score was stratified in three categories of increasing severity (from 0 to 3, from 4 to 6 and higher than 6) and was forced as a first variable in to the CHAID regression model. All tests were two-sided with the alpha level set at 0.05 for statistical significance.

Results

Study population

Data was obtained from a series of 3788 consecutive patients who underwent isolated CABG. Patients treated with prasugrel (n=43) and cangrelor (n=1) were excluded from this analysis because no data on the timing of discontinuation of these drugs were collected. The final study population

included 3744 patients and their rate of severe bleeding as defined by the E-CABG bleeding grades 2-3 was 6.4% (n=240). This population was divided after electronic random sampling into a derivation cohort (n=2494, 66.6%) and a validation cohort (n=1250, 33.4%). In the overall series, Baseline characteristics of patients of the derivation cohort were similar to those of the validation cohort (Tab. 1).

Derivation and validation of the bleeding risk score

Table 2 summarizes the baseline covariates associated with E-CABG bleeding grades 2-3 in univariate analysis of the derivation cohort. Logistic regression including baseline covariates with $p < 0.2$ in univariate analysis (HL test: $p = 0.100$, AUC of the ROC curve: 0.738, 95%CI 0.692-0.784) identified baseline anemia, female gender, eGFR < 45 mL/min/1.73 m², potent antiplatelet drugs (clopidogrel and ticagrelor) discontinued less than five days, critical preoperative state, acute coronary syndrome as well as use of low molecular weight heparin, fondaparinux and/or unfractionated heparin as independent predictors of E-CABG bleeding grade 2-3 (Tab. 3). These variables were used to estimate the WILL-BLEED risk score by adding the weighted integers as listed in Table 3.

Severe bleeding defined as E-CABG bleeding grades 2-3 in both the derivation and validation cohorts was stratified according to the WILL-BLEED risk score (Fig. 1). The rate of severe bleeding increased across increasing scores in both the derivation and validation cohorts ($p < 0.0001$). Youden's test showed that the best cutoff of this score was 5 (sensitivity 63.9%, specificity 74.7%).

The WILL-BLEED score maintained its ability to predict severe bleeding according to the E-CABG bleeding classification ($p < 0.0001$, OR 1.393, 95%CI 1.323-1.467) even when adjusted for participating centers.

The WILL-BLEED score correlated well with the observed bleeding, with increasing scores across

increasing E-CABG grades of bleeding (Kruskal-Wallis test: $p<0.0001$; Spearman test: ρ : 0.304, $p<0.0001$) (Fig. 2).

Discrimination, calibration, reclassification and decision curve analysis of the WILL-BLEED score compared to other bleeding risk scores

In a series of 3621 patients with complete data to estimate all the following bleeding risk scores, ROC analysis showed an adequate discriminatory ability of the WILL-BLEED score (AUC 0.725, 95%CI 0.686-0.763, HL test: $p=0.033$) for prediction of E-CABG bleeding grades 2-3. The discriminatory ability for prediction of E-CABG bleeding grades 2-3 was lower for the ACTION (AUC 0.671, 95%CI 0.631-0.710, HL test: $p=0.469$, DeLong test: $p=0.06$), CRUSADE (AUC 0.642, 95%CI 0.602-0.681, HL test: $p=0.016$, DeLong test: $p=0.004$), Papworth (AUC 0.605, 95%CI 0.568-0.643, HL test: $p=0.028$, DeLong test: $p=0.0001$), TRUST (AUC 0.660, 95%CI 0.621-0.698, HL test: $p=0.279$, DeLong test: $p=0.02$) and TRACK (AUC 0.640, 95%CI 0.600-0.681, HL test: $p=0.102$, DeLong test: $p=0.004$) bleeding scores as compared with the WILL-BLEED score. HL test for the WILL-BLEED score showed that this score underestimated the risk of severe bleeding in low risk patients. The HL test showed that the WILL-BLEED score had a $p=0.408$ when patients with a score 0 to 1 were aggregated, and a $p=0.679$ when patients with a score 0 were excluded from the analysis.

The NRI improvement using the WILL-BLEED score as opposed to the other bleeding scores was statistically significant ($p<0.0001$) with a correct reclassification of events ranging from 19% to 25% and a significant IDI ranging from 2.8% to 6.3% ($p<0.0001$) (Tab. 4 and Suppl. Tab. 2).

The decision curve analysis demonstrated a net benefit with the WILL-BLEED score compared to the other bleeding risk scores in predicting E-CABG grades 2-3 bleeding (Fig. 3).

The WILL-BLEED score and early mortality

The WILL-BLEED score was predictive of early mortality (AUC: 0.782, 95% CI 0.732-0.832) and correlated with the EuroSCORE II (ρ : 0.531, $p < 0.0001$). Youden's test showed that the best cutoff of the WILL-BLEED score in predicting early mortality was 4 (sensitivity 78.5%, specificity 66.8%).

CHAID analysis showed that the occurrence of E-CABG bleeding grades 2-3 was associated with significantly increased early mortality across increasing risk categories of the WILL-BLEED score (Fig. 4).

Discussion

This study showed that the WILL-BLEED score, based on a few baseline characteristics and antithrombotic treatment, allows an accurate stratification of the risk of perioperative bleeding across increasing grades of the E-CABG classification. Furthermore, this study showed that the WILL-BLEED score was predictive of early mortality and the risk of early death was increased by the occurrence of severe bleeding.

Severe bleeding is a common problem in patients undergoing cardiac surgery as it is associated with decreased oxygen delivery and need for blood transfusions, resulting in increased morbidity and mortality. This issue is of particular importance in patients undergoing CABG, since urgent or emergency revascularization is often indicated in patients with acute coronary syndrome. In these patients, P2Y₁₂ platelet receptor inhibitors, i.e., clopidogrel, prasugrel and ticagrelor, along with other antiplatelet and anticoagulant drugs are the cornerstone of treatment of acute coronary syndrome, albeit at the expense of a significantly increased risk of bleeding.²⁰ Because of this, identification of patients at increased risk of bleeding after CABG may be of importance for optimization of antithrombotic therapy with the least risk of bleeding,²⁰ when feasible. Indeed, this study confirmed that preoperative use of potent antiplatelet drugs and of parenteral anticoagulants were independent predictors of severe bleeding. On the other hand, modification of the

antithrombotic regimen according to any risk stratification remains problematic because the most powerful baseline risk factors for ischemic complications are usually the same as for bleeding risk.²⁰ Importantly, most of the risk factors underlying an increased risk of bleeding are not modifiable. However, a number of bleeding-prevention and blood-saving strategies can be adopted in patients at high risk for hemorrhage. Vasques et al.²¹ summarized these strategies in three points: 1) preoperative optimization of hemoglobin²²; 2) preoperative optimization of coagulation status by point-of-care coagulation testing²³ and withdrawal of antithrombotics when feasible¹³; 3) minimization of intra- and postoperative blood loss by meticulous surgical technique,²⁴ blood cell salvage and reinfusion,²⁵ point-of-care coagulation tests,²³ and administration of procoagulantss.^{26,27} These strategies have been shown to safely prevent significant blood loss and exposure to blood products in Jehovah's witnesses undergoing cardiac surgery,²¹ but are not used on daily basis.²² In this regard, identification of patients at high risk of bleeding by the WILL-BLEED score may lead to optimization of patient blood management in these patients with a possible benefit for their early and late outcome. In fact, patients who experience severe postoperative bleeding defined as E-CABG bleeding grades 2-3 have been shown to be at high risk of early and late mortality.²⁸

The WILL-BLEED score shares a number of risk factors for bleeding common to other bleeding risk scores derived from patients undergoing percutaneous coronary intervention and general cardiac surgery (Suppl. Tab. 1). Preoperative anemia defined by different thresholds of baseline hemoglobin^{8,29} and hematocrit^{7,10,11} is one of the most important components of the ACTION, CRUSADE, TRACK and TRUST risk scores. Although this finding is intuitive, since anemic patients require more frequently blood transfusions to maintain adequate levels of oxygen delivery, it is also possible that a decreased number of circulating erythrocytes may impair coagulation. In fact, there is a growing body of evidence showing that erythrocytes have an active role in hemostasis by enhancing platelet aggregation and degranulation and serve as a procoagulant surface

for the reactions of the coagulation cascade.³⁰ These findings suggest that optimization of preoperative hemoglobin could be one of the most important interventions in the patient blood management process.

Renal failure is a well-recognized risk factor for perioperative bleeding,³¹ and is a common component of current bleeding risk scores.^{6,7,8,10,29} Among the risk scores herein validated, the ACTION, CRUSADE and TRUST score shared this risk factor. The impact of chronic kidney disease on bleeding is partly due to the prolonged half-life of certain antithrombotics in patients with renal failure.³² However, renal failure by itself has a profound impact on the coagulation pathway, which may induce either pronounced bleeding or thrombosis. Regarding the uremia-related risk of bleeding, it seems to be secondary to insufficient platelet function, reduced interaction between platelets and vessel wall as well as anemia-related coagulopathy.³² Although chronic kidney disease is a non-modifiable risk factor in patients undergoing cardiac surgery, knowledge of their increased risk of bleeding may guide strategies to improve the coagulation status of uremic patients by avoiding or reducing the dose of certain antithrombotics and adopt more strict measures to avoid blood loss perioperatively. It is worth noting that in the present study we stratified the severity of renal failure according to eGFR values, which may be more accurate than simply evaluating baseline creatinine levels of these patients.

Female gender is associated with a higher risk of bleeding after cardiovascular intervention as shown in several trials,³³ and is a constant component of most of risk bleeding scores.^{5-8,10,11} Among the risk scores herein validated, the ACTION, CRUSADE, TRACK and TRUST scores included female gender as a risk factor for increased bleeding. The higher risk of bleeding among women was confirmed also in this study. Although women's vessel anatomy, body mass index and hemoglobin levels may result in possible unfavorable differences during cardiovascular interventions, the increased risk of bleeding among females may be related to peculiar differences in the coagulation process between genders. In fact, even when adjusted for important baseline risk

factors, women undergoing percutaneous coronary intervention have been shown to have a higher risk of both ischemic and bleeding events.³³ In the present study, we were not able to confirm the prognostic importance of advanced age and decreased body mass index/weight on the risk of severe perioperative bleeding as observed in previous studies.^{9,10,11,29} These variables were investigated as continuous as well as dichotomous covariates according to previously proposed cutoff values, but analyses failed to confirm their impact on severe bleeding as observed also in the CRUSADE study.⁷ On the other hand, advanced age and low body mass index were associated with increasing postoperative bleeding across increasing severity grades of the E-CABG bleeding classification (both variables, Kruskal-Wallis test: $p < 0.0001$). However, severe bleeding is the one which showed being of most prognostic significance in patients undergoing CABG.²⁸

Comparative analysis of the AUCs of the WILL-BLEED score with the other bleeding risk scores showed that the former score had a significantly better discriminatory ability than the CRUSADE, Papworth, TRUST and TRACK bleeding risk scores. Such a difference tended to be statistically significant also for the ACTION score ($p = 0.07$). NRI, IDI and decision curve analysis confirmed that the WILL-BLEED score had a better performance in predicting severe bleeding. It is worth noting that the calibration for this score was not optimal. In fact, the HL test showed that the WILL-BLEED score underestimated the risk of severe bleeding in low risk patients. This could be due to unexpected excessive bleeding in low risk patients related to a non-meticulous surgical technique. The HL test showed that the WILL-BLEED score had a $p = 0.408$ when patients with a score 0 to 1 were aggregated, and a $p = 0.679$ when patients with a score 0 were excluded from the analysis.

The use of a tool for stratification of the risk of postoperative bleeding such as the WILL-BLEED score has a number of research and clinical implications. This scoring method allows a preoperative estimation of the risk of bleeding which is of value for comparative analysis of the benefits and harms of using antithrombotics and procoagulants in patients with either stable angina or acute coronary syndrome. Estimation of the risk of bleeding may be useful also in comparative analyses

of the efficacy of point-of-care bleeding management and blood conservation strategies.

Furthermore, it may provide a valid measure for the evaluation of individual surgeon and interinstitutional variability of perioperative bleeding and requirement of blood products. Regarding the clinical implications of this scoring method, Figure 5 shows an algorithm which summarizes the risk factors for severe bleeding, their increasing impact on perioperative bleeding and the measures to be adopted in order to reduce blood loss and the need of blood transfusion. Most of the components of this risk score are not modifiable and a direct action is feasible only on preoperative anemia and antithrombotic treatment. However, even when feasible, preoperative optimization of hemoglobin and discontinuation of antithrombotics should be carefully considered according to the specific clinical conditions in view of their potential harms. However, recognizing the clinical importance of excessive perioperative bleeding, the WILL-BLEED score easily provides an estimation of the risk of severe bleeding and may guide surgeons and anesthesiologists to adopt adequate measures to prevent bleeding at least in high risk patients. The central role of surgeon in preventing intra- and postoperative bleeding cannot be overemphasized.²⁴ A pooled analysis showed that diffuse bleeding (diffuse ooze, no surgical cause identified) was found at re-exploration in only 21% of cases.³⁵ This finding confirms the “surgical nature” of most of severe hemorrhages and confirms the importance of a meticulous surgical technique as one of the most important measure to prevent blood loss. Importantly, the “surgical nature” of bleeding after CABG and a possible inter-individual variability among surgeons may explain the suboptimal goodness-of-fit of the WILL-BLEED score, which was due to an underestimation of the bleeding risk in low risk patients. Indeed, CABG in low risk patients is often performed by less experienced surgeons. This may expose these patients to longer operation time, which increases the period of intraoperative bleeding and the risk of cardiopulmonary bypass-related coagulopathy and suboptimal surgical hemostasis. In general, the prognostic impact of a non-meticulous surgical technique is not

quantifiable and may be responsible for the excessive bleeding still sporadically occurring in low risk patients.

Another key issue in preventing bleeding in patients undergoing cardiac surgery is the adoption of point-of-care coagulation testing and an integrated transfusion algorithm, which has been shown to effectively guide clinicians in reducing blood loss and transfusion.³⁶ These measures could be of benefit particularly in patients with high WILL-BLEED score.

Several limitations of the present study should be considered. This is a multicenter study involving 16 centers of cardiac surgery with possible differences in terms of referral pathways, operative risk, antithrombotic treatments and patient blood management strategies. However, analysis adjusted for the participating centers showed that the WILL-BLEED score maintained its ability to predict severe bleeding. Furthermore, this registry does not collect data on individual surgeons and this represents another limitation of this study, particularly in view of the recognized surgeon's impact on the risk of excessive bleeding.²⁴ On the other hand, the multicenter nature of this registry and the large number of surgeons who operated these patients would prevent a reliable analysis of this issue.

In conclusion, The WILL-BLEED risk score seems to be a simple tool to identify patients at high risk of severe bleeding after isolated CABG. The present findings as well as those of previous studies suggest that stratification of the risk of bleeding in patients undergoing cardiovascular intervention is feasible. This could be a valid means for prevention of excessive blood loss and exposure to blood products in patients undergoing cardiovascular procedures.

Conflicts of interest: None

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Figure 1. Rates of severe bleeding defined as E-CABG bleeding grades 2-3 in the derivation and validation cohorts according to the WILL-BLEED risk score.

Figure 2. Boxplots of the WILL-BLEED score across increasing E-CABG bleeding grades (Kruskal-Wallis' test: $p < 0.0001$).

Figure 3. Decision curves for the predicted probabilities of E-CABG grade 2-3 bleeding estimated by the WILL-BLEED, ACTION, CRUSADE, TRACK, TRUST and Papworth bleeding scores.

Figure 4. Chi-squared automatic interaction detection analysis showing the impact of severity of bleeding (E-CABG bleeding grades 0-1 vs 2-3) on 30-day mortality in different WILL-BLEED score classes.

Figure 5. Algorithm of risk estimation and prevention of severe bleeding in coronary surgery.

Extra table

1. What is known on this topic

- Severe perioperative bleeding is associated with poor outcome after cardiac surgery
 - The use of potent antithrombotics may add a significant risk of bleeding in patients undergoing coronary surgery
 - There are no specific risk scoring methods to stratify the risk of bleeding after coronary surgery
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2. What this paper adds

- The WILL-BLEED score is a rather accurate method to predict severe bleeding after coronary surgery
 - The WILL-BLEED is made up of seven easily retrievable clinical variables which make easy its use at bed-side
 - The WILL-BLEED may be useful to improve patient-blood management in patients at high risk of perioperative bleeding
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Table 1. Baseline characteristics and operative data of the derivation and validation cohorts.

<i>Covariates</i>	<i>Derivation</i> (<i>n</i> =2494)	<i>Validation</i> (<i>n</i> =1250)	<i>P-value</i>
Age, years	67.3 ± 9.4	67.4 ± 9.2	0.710
Females	409 (16.4)	219 (17.5)	0.404
BMI >25 kg/m ²	718 (29.0)	360 (29.0)	1.000
Hemoglobin, g/dL	136.2 ± 16.5	135.9 ± 16.4	0.354
Anemia	564 (22.6)	294 (23.5)	0.536
Platelets, g/dL	227.1 ± 67.7	226.5 ± 68.0	0.577
TT-INR	1.1 ± 0.2	1.1 ± 0.2	0.433
eGFR mL/min/1.73m ²	81.2 ± 25.8	80.1 ± 25.8	0.046
Hypertension	1959 (78.5)	1017 (81.4)	0.048
Diabetes on medical treatment	762 (30.6)	438 (35.1)	0.006
Extracardiac arteriopathy	502 (20.1)	276 (22.1)	0.172
Stroke	93 (3.7)	52 (4.2)	0.530
Chronic lung disease	232 (9.3)	115 (9.2)	0.952
Atrial fibrillation	192 (7.7)	99 (8.0)	0.796
LVEF classes			
31-50%	591 (23.7)	299 (24.0)	0.742
21-30%	106 (4.3)	56 (4.5)	0.724
<21%	17 (0.7)	5 (0.4)	0.937
Prior cardiac surgery	22 (0.9)	9 (0.7)	0.704
Prior PCI	531 (21.3)	269 (21.5)	0.866
Number of prior PCIs	1.5 ± 0.9	1.4 ± 0.8	0.519
Left main stenosis	933 (37.4)	436 (35.0)	0.150
Syntax score	28.1 ± 11.1	28.5 ± 10.4	0.118
No. of diseased vessels	2.7 ± 0.6	2.7 ± 0.6	0.747
Acute coronary syndrome	1174 (47.0)	602 (48.2)	0.532
Recent myocardial infarction	750 (30.1)	386 (30.9)	0.624
Urgent or emergency surgery	1099 (44.1)	547 (43.8)	0.862
Critical preoperative state	96 (3.8)	42 (3.4)	0.520
Antithrombotic treatment			
Potent antiplatelet pause <5 days	342 (13.7)	174 (13.9)	0.880
Warfarin/coumadin/phenprocoumon	51 (2.0)	36 (2.9)	0.134
Glycoprotein 2b/3a inhibitors	23 (0.9)	22 (1.8)	0.037
LMWH/fondaparinux/unfract. heparin	1048 (42.0)	548 (43.8)	0.293
Off-pump surgery	509 (20.4)	262 (21.0)	0.700
No. of distal anastomoses	2.7 ± 1.1	2.7 ± 0.9	0.483
EuroSCORE II	2.6 ± 4.0	2.6 ± 3.7	0.525

TT-INR, thromboplastin time – international normalized ratio; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; BMI, Body mass index; LMWH, low molecular weight heparin; LVEF, left ventricle ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Table 2. Baseline characteristics and operative data in patients of the derivation cohort who experienced or not severe bleeding defined as E-CABG bleeding grades 2-3.

<i>Covariates</i>	<i>E-CABG bleeding grades 0-1 (n=2336)</i>	<i>E-CABG bleeding grades 2-3 (n=156)</i>	<i>Univariate analysis P-value</i>
Age, years	67.2 ± 9.4	68.1 ± 9.4	0.200
Females	364 (15.6)	45 (28.5)	<0.0001
BMI >25 kg/m ²	27.5 ± 4.2	27.3 ± 4.6	0.396
Hemoglobin, g/dL	137 ± 16	126 ± 21	<0.0001
Anemia	489 (20.9)	75 (47.8)	<0.0001
Platelets, g/dL	227 ± 65	227 ± 97	0.264
TT-INR	1.1 ± 0.2	1.1 ± 0.2	0.001
eGFR, mL/min/1.73m ²	82 ± 25	72 ± 31	<0.0001
Number of prior PCIs	1.5 ± 0.8	1.7 ± 1.3	0.376
Extracardiac arteriopathy	464 (19.9)	38 (24.1)	0.204
Stroke	88 (3.8)	5 (3.2)	1.000
Diabetes on medical treatment	709 (30.4)	53 (33.5)	0.401
Hypertension	1836 (78.6)	123 (77.8)	0.825
Chronic lung disease	210 (9.0)	22 (13.9)	0.039
Atrial fibrillation	171 (7.3)	21 (13.3)	0.007
LVEF classes			<0.0001
31-50%	542 (23.2)	49 (31.0)	
21-30%	93 (4.0)	13 (8.2)	
<21%	12 (0.5)	5 (3.2)	
Prior cardiac surgery	19 (0.8)	3 (1.9)	0.159
Prior PCI	497 (21.3)	34 (21.5)	0.942
Left main stenosis	867 (37.1)	66 (41.8)	0.242
Syntax score	28.0 ± 11.1	29.6 ± 10.6	0.057
No. of diseased vessels	2.7 ± 0.6	2.7 ± 0.5	0.357
Acute coronary syndrome	1063 (45.5)	110 (69.6)	<0.0001
Recent myocardial infarction	671 (28.7)	79 (50.0)	<0.0001
Urgent or Emergency	995 (42.6)	104 (65.8)	<0.0001
Critical preoperative state	67 (2.9)	29 (18.4)	<0.0001
Antithrombotic treatment			
Warfarin/coumadin/phenprocoumon	46 (2.0)	5 (3.2)	0.253
Glycoprotein 2b/3a inhibitors	2 (0.9)	1 (0.6)	1.000
LMWH/fondaparinux/UFH	960 (41.1)	88 (55.7)	<0.0001
Potent antiplatelet pause < 5 days	304 (13.0)	38 (24.1)	<0.0001
Off pump surgery	418 (20.6)	28 (17.7)	0.386
No. of distal anastomoses	2.7 ± 1.0	2.7 ± 0.9	0.508
EuroSCORE II	2.4 ± 3.3	6.0 ± 8.6	<0.0001

TT-INR, thromboplastin time - international normalized ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; LMWH, low molecular weight heparin; UFH, unfractionated heparin; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention;

Table 3. Independent predictors of E-CABG bleeding grades 2-3 in the derivation cohort and their weighted integer scores.

<i>Covariate</i>	<i>Beta</i>	<i>p-value</i>	<i>OR</i>	<i>95%CI</i>	<i>Score</i>
LMWH/ fondaparinux/UFH	0.376	0.035	1.456	1.027-2.064	1
Potent antiplatelet drugs pause <5 days	0.514	0.016	1.671	1.100-2.539	2
Females	0.521	0.009	1.683	1.140-2.485	2
Acute coronary syndrome	0.483	0.013	1.621	1.106-2.374	2
Anemia	0.924	<0.0001	2.520	1.768-3.591	3
eGFR <45 mL/min/1.73m ²	0.928	<0.0001	2.530	1.587-4.033	3
Critical preoperative state	1.565	<0.0001	4.782	2.846-8.034	5
Constant	-3.916	<0.0001			

OR: odds ratio; CI: confidence interval; LMWH, low molecular weight heparin; UFH, unfractionated heparin; eGFR, estimated glomerular filtration rate.

Table 4. Net reclassification index and integrated discrimination improvement between the WILL-BLEED score other bleeding risk scores in predicting E-CABG bleeding grades 2-3.

Bleeding scores	NRI			IDI			
	NRI	95%CI	p-value	Correctly reclassified	IDI	95%CI	p-value
ACTION	0.518	0.388-0.649	<0.0001	23%	0.028	0.017-0.039	<0.0001
CRUSADE	0.493	0.362-0.625	<0.0001	21%	0.046	0.035-0.058	<0.0001
TRACK	0.491	0.358-0.622	<0.0001	19%	0.049	0.037-0.061	<0.0001
TRUST	0.567	0.437-0.697	<0.0001	25%	0.046	0.034-0.057	<0.0001
Papworth	0.762	0.632-0.891	<0.0001	25%	0.063	0.049-0.077	<0.0001

NRI, net reclassification index; IDI, integrated discrimination improvement; CI: confidence interval.

Supplemental material

Prediction of Severe Bleeding after Coronary Surgery: the WILL-BLEED Risk Score

Supplemental Table 1. Bleeding risk scores evaluated in this analysis.

WILL-BLEED bleeding score	
<i>Variable</i>	<i>Score</i>
LMWH/ fondaparinux/unfractionated heparin	1
Potent antiplatelet drugs pause <5 days	2
Females	2
Acute coronary syndrome	2
Anemia	3
eGFR <45 mL/min/1.73m ²	3
Critical preoperative state	5

ACTION bleeding score									
<i>Age (years)</i>	<i>Score</i>	<i>Baseline creatinine (mg/dl)</i>	<i>Score</i>	<i>Systolic blood pressure on admission (mmHg)</i>	<i>Score</i>	<i>Baseline Hb (g/dl)</i>	<i>Score</i>	<i>Heart rate on admission (bts/min)</i>	<i>Score</i>
≤40	0	<0.8	0	≤90	4	<5	17	≤40	0
41-50	1	0.8-1.59	1	91-100	3	5-7.9	15	41-60	2
51-60	2	1.6-1.99	2	101-120	2	8-9.9	13	61-70	3
61-70	3	2.0-2.99	4	121-140	1	10-10.9	12	71-80	5
71-80	4	3.0-3.99	6	141-170	0	11-13.9	9	81-100	6
81-90	5	4.0-4.99	8	171-200	1	14-15.9	6	101-110	8
≥91	6	5.0-5.99	10	≥201	2	≥16	2	111-120	9
		≥6	11					121-130	11
		Dialysis	11					131-150	12
								≥151	14
<i>Weight (kg)</i>	<i>Score</i>	<i>Gender</i>	<i>Score</i>	<i>Home warfarin use</i>	<i>Score</i>	<i>Diabetes mellitus</i>	<i>Score</i>		
≤50	5	Female	4	No	0	No	0		
51-70	4	Male	0	Yes	2	Yes	3		
71-100	3								
101-120	2								
121-140	1								
≥141	0								
<i>Heart failure ± shock on admission</i>	<i>Score</i>	<i>ECG changes</i>		<i>Score</i>	<i>Previously peripheral artery disease</i>		<i>Score</i>		
None	0	No ST-segment changes		0	No		0		
Heart failure only	3	ST-segment depression or transient elevation		3	Yes		3		
Heart failure with shock	15	ST-segment elevation		7					

CRUSADE bleeding score							
<i>Baseline hematocrit</i>	<i>Score</i>	<i>Systolic blood pressure</i>	<i>Score</i>	<i>Creatinine clearance</i>	<i>Score</i>	<i>Heart rate</i>	<i>Score</i>
<31	9	91-100	8	>15-30	35	71-80	1
31-33.9	7	101-120	5	>30-60	28	81-90	3
34-36.9	3	121-180	1	>60-90	17	91-100	6
37-39.9	2	181-200	3	>90-120	7	101-110	8
		≥201	5	>120	0	111-120	10
						≥121	11
<i>Diabetes mellitus</i>	<i>Score</i>	<i>Prior vascular disease</i>	<i>Score</i>	<i>Heart failure</i>	<i>Score</i>	<i>Female</i>	<i>Score</i>
No	0	No	0	No	0	No	0
Yes	6	Yes	6	Yes	7	Yes	8

Papworth bleeding score		
<i>Risk factor</i>	<i>Score=0</i>	<i>Score=1</i>
Surgery priority	Elective	Urgent or emergency
Surgery Type	CABG or single valve	All other surgery types
Aortic valve disease	None	Stenosis, regurgitation, both
BMI	BMI greater/equal to 25	BMI less than 25
Age	Younger than 75	75 years or older

TRACK bleeding score	
<i>Factor</i>	<i>Score</i>
Age >67 years	6
Weight <60kg (F), 85kg (M)	2
Female	4
Complex surgery	7
Hematocrit	1 point per each value (%) below 40%

TRUST bleeding score	
<i>Variable</i>	<i>Score</i>
Hemoglobin level <135g/L	1
Weight <77 kg	1
Female sex	1
Age >65 years	1
Non elective surgery	1
Serum creatinine level >120 µmol/L	1
Previous cardiac surgery	1
Non-isolated surgery	1

Supplemental Table 2. Reclassification using the WILL-BLEED score compared to other bleeding risk scores in predicting E-CABG bleeding grades 2-3.

Bleeding scores and risk categories	Low risk	Intermediate risk	High risk	Total
ACTION bleeding score				
Low risk (<5%)	51 (73.1)	14 (20.3)	4 (5.8)	69
Intermediate risk (5-11%)	22 (23.9)	38 (41.3)	32 (34.8)	92
High Risk (>11%)	2 (3.1)	12 (18.5)	51 (78.5)	65
Total	75	64	87	226
CRUSADE bleeding score				
Low risk (<5%)	45 (60.8)	24 (32.4)	5 (6.8)	74
Intermediate risk (5-11%)	29 (30.5)	32 (33.7)	34 (35.8)	95
High Risk (>11%)	1 (1.8)	8 (14.0)	48 (84.2)	57
Total	75	64	87	226
TRACK bleeding score				
Low risk (<5%)	25 (46.3)	21 (38.9)	8 (14.8)	54
Intermediate risk (5-11%)	49 (41.5)	34 (28.8)	35 (29.7)	118
High Risk (>11%)	1 (1.9)	9 (16.7)	44 (81.5)	54
Total	75	64	87	226
TRUST bleeding score				
Low risk (<5%)	31 (75.6)	10 (24.4)	0	41
Intermediate risk (5-11%)	38 (40.0)	34 (35.8)	23 (24.2)	95
High Risk (>11%)	6 (6.7)	20 (22.2)	64 (71.1)	90
Total	75	64	87	226
Papworth bleeding score				
Low risk (<5%)	50 (59.5)	19 (22.6)	15 (17.9)	84
Intermediate risk (5-11%)	24 (17.7)	45 (33.1)	67 (49.3)	136
High Risk (>11%)	1(16.7)	0	5 (83.3)	6
Total	75	64	87	226

Values are counts and percentages (in parentheses).