# Clinical significance and determinants of the universal definition of perioperative bleeding classification in patients undergoing coronary artery bypass surgery

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**Objectives:** We evaluated the clinical significance and identified the predictors of the universal definition of perioperative bleeding (UDPB) classes in patients undergoing isolated coronary artery bypass grafting (CABG).

**Methods:** Data on antithrombotic medication, perioperative bleeding, blood transfusion, and adverse events were available for 2764 patients who had undergone isolated CABG.

**Results:** The Papworth risk score correlated significantly with the UDPB classes (rate of UDPB class 3-4 and Papworth risk score of 0, 12.1%; 1, 23.9%; 2, 37.5%; and 3, 45.0%; $P < .0001$). Ordinal regression showed that increased age, female sex, low body mass index, low estimated glomerular filtration rate, low hemoglobin, dialysis, urgent or emergency operation, critical status, on-pump surgery, potent antiplatelet drug pause of <5 days, and warfarin pause of <2 days were independent predictors of high UDPB classes. These risk factors also predicted UDPB classes 3-4 in logistic regression analysis. Increasing UDPB classes were associated with an increased risk of in-hospital mortality ($P = .002$), stroke ($P = .023$), low cardiac output ($P < .0001$), prolonged use of inotropes ($P < .0001$), renal replacement therapy ($P < .0001$), length of stay in the intensive care unit ($P < .0001$), and late mortality ($P < .0001$) as assessed by multilevel propensity score-adjusted analysis. Similar findings were observed in the propensity score-adjusted analysis for the most severe grades of perioperative bleeding (ie, UDPB class 3-4).

**Conclusions:** High UDPB classes were associated with significantly poorer immediate and late outcomes. The UDPB classification seems to be a valuable research tool to estimate the severity of bleeding and its prognostic impact affect after coronary surgery. (J Thorac Cardiovasc Surg 2014;148:1640-6)

Supplemental material is available online.

Significant perioperative bleeding[1,2] and the related need of blood transfusion[2,3] are known to make patients susceptible to adverse outcomes. However, the magnitude at which bleeding and the transfusion of blood products become clinically significant is unknown. Dyke and colleagues[1] recently proposed a classification for the severity of perioperative bleeding in patients undergoing adult cardiac surgery, the universal definition of perioperative bleeding (UDPB) (Table E1). This classification is based on a logical, but still arbitrary, weighting of the amount of postoperative blood loss, the need for blood products, and the need for pharmacologic measures to treat significant perioperative bleeding. The clinical significance of this classification has been evaluated to date only by its proposers. The aim of the present study was to validate the UDPB classification and identify the risk factors predicting high UDPB classes in patients undergoing isolated coronary artery bypass grafting (CABG).

## METHODS

### Patient Population and Data Collection

The present study included 2764 consecutive patients who had undergone isolated CABG from June 2006 to December 2013 at the Oulu University Hospital (Oulu, Finland). The study included elective, urgent, and emergency operations performed in either an off-pump or on-pump setting.

Complete pre-, intra-, and postoperative data were available for all patients from an institutional electronic cardiac surgery database containing the baseline and operative data and data on immediate postoperative adverse events. Data on the preoperative use of warfarin, clopidogrel, prasugrel, and ticagrelor and the perioperative use of

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**Abbreviations and Acronyms**

CABG = coronary artery bypass grafting
CI = confidence interval
HR = hazard ratio
ICU = intensive care unit
OR = odds ratio
RBC = red blood cell
UDPB = universal definition of perceived bleeding

prothrombin complex concentrate and recombinant factor VIIa were collected retrospectively. 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 that collected data on any transfusion of blood products. Data on the amount of postoperative blood loss were retrieved from a prospective electronic registry of our intensive care unit (ICU). The patient characteristics are summarized in Tables E2 and E3.

The glomerular filtration rate was estimated using the Modification of Diet in Renal Disease formula.[4] The clinical variables were defined according to the EuroSCORE II definition criteria.[5] The bleeding risk was estimated according to the Papworth bleeding risk score.[6] The UDPB classification[1] was used to stratify the severity of perioperative bleeding (Table E1). Data on patient death were retrieved from the Central Statistical Office of Finland (Tilastokeskus), which collects the certificates of death for all inhabitants of Finland. The data for the present study were provided up to December 31, 2013. We have assumed that no data on immediate and late death were missing for the present study population.

## Perioperative Antithrombotic Treatment, Blood Transfusion, and Resternotomy for Excessive Bleeding

The main strategy for patients referred for elective surgery was that warfarin was discontinued 2 days before surgery and no heparins were given preoperatively. Enoxaparin was used preoperatively, instead of warfarin, only in selected patients with acute coronary syndromes or a mechanical heart valve. Potent antiplatelet drugs (clopidogrel, prasugrel, and ticagrelor) were discontinued for ≥5 days when feasible (ie, when the patient's condition allowed us to postpone surgery for a few days). Aspirin was discontinued for 7 days during the first part of the study period until 2012; subsequently, it was continued until surgery.

Heparin (3.0 mg/kg) was administered intravenously after sternotomy to maintain an activated coagulation time of >450 seconds, and it was neutralized at the end of the procedure by protamine sulfate (3.0 mg/kg). Additional protamine was given in the case of bleeding during closure of the chest or within the first hour after surgery according to the activated coagulation time. Aprotinin was not used in any of these patients. Tranexamic acid was administered intraoperatively at the discretion of the anesthesiologist. Packed leukoreduced RBCs were transfused on the day of operation if the hemoglobin was <90 g/L. Later, leukoreduced RBCs were transfused if the hemoglobin was <80 g/L. Octaplas and platelets were transfused according to the amount of intra- and postoperative bleeding, international normalized ratios, and the platelet count. Recombinant factor VII was used only in cases of unrelenting massive bleeding. Resternotomy was performed in the case of excessive bleeding according to criteria previously described.[7]

All blood lost during the operation was collected into a cell saver reservoir and washed. Salvaged RBCs were transfused during or at completion of the operation. Mediastinal blood/fluid was collected after surgery in a sterile collection chamber connected to 15-cm $H_2O$ wall suction by an underwater seal and then discarded.

Enoxaparin (40-80 mg once daily) was started the evening of surgery for those patients without excessive bleeding (<1000 mL). Aspirin 100 mg was restarted on the first postoperative day. Warfarin was started on the first postoperative day in patients receiving chronic oral anticoagulation unless significant bleeding had occurred or started de novo in the case of persistent atrial fibrillation. Clopidogrel and ticagrelor were used postoperatively only in the case of allergy to aspirin or recent percutaneous coronary intervention.

Platelet function was not tested preoperatively in these patients. The activated coagulation time was measured before heparin administration, intraoperatively, and 20 to 30 minutes after protamine administration. The activated coagulation time was measured later in the case of excessive bleeding. Additional doses of protamine were given in the case of significant bleeding and a prolonged activated coagulation time compared with the preoperative level. Thromboelastography was performed postoperatively in the case of excessive bleeding during the last 2 years of the study period.

## Operative Techniques

Intermittent antegrade and retrograde cold blood cardioplegia was used during on-pump CABG. Epiaortic ultrasonography was performed according to surgeon preference. The ascending aorta was left untouched in the case of a grade III diseased aorta.[8] Proximal anastomoses were sutured to the ascending aorta during side clamping or crossclamping, when considered safe. The Octopus stabilizer (Medtronic, Minneapolis, MN) and intracoronary shunts were routinely used in patients who underwent off-pump CABG.

## Outcome Endpoints

The UDPB classes were the outcome endpoints of interest in the analysis to identify the predictors of severe bleeding. UDPB was then dichotomized (UDPB class 0-2 vs 3-4), because the preliminary analysis showed that UDPB classes 3 and 4 were associated with markedly poorer outcomes.

The other outcome endpoints of interest were in-hospital and late mortality, length of stay in the ICU, low cardiac output syndrome (postoperative cardiac index < 2.0 L/min/$m^2$, measured at least twice), a prolonged use of inotropes (>12 hours), intra-aortic balloon pump, stroke, renal replacement therapy, atrial fibrillation, postoperative blood loss after 12 hours, resternotomy for excessive bleeding, number of RBC units, Octaplas units, and platelet units transfused, and the use of prothrombin complex concentrate and recombinant factor VIIa.

Stroke was defined as a new, neurologic deficit after surgery lasting >24 hours and accompanied by new structural changes on computed tomography or magnetic resonance imaging. Renal replacement therapy was defined as postoperative renal failure requiring temporary or prolonged dialysis. The RBC, Octaplas, and platelet units and prothrombin complex concentrate and recombinant factor VIIa were counted from the operation day to a maximum of 1 month postoperatively. Cryoprecipitate was not used in the study population.

## Ethical Considerations

The institutional review board of the Oulu University Hospital approved the study protocol.

## Statistical Analysis

Statistical analysis was performed using SPSS, version 22.0, statistical software (IBM Corp, Armonk, NY). No attempt to replace missing values was made. The Fisher exact test, chi-square test, Mann-Whitney *U* test, and Kruskal-Wallis test were used for univariable analysis. Correlations between continuous and ordinal variables were estimated using the

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