REVIEW ARTICLE

Massive bleeding in cardiac surgery. Definitions, predictors and challenges

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Abstract
Background: Severe or massive bleeding in cardiac surgery is an uncommon but important clinical scenario. Its existing definitions are diverse. Its characteristics constantly change during an active hemorrhage and, thus is difficult to define appropriately.
Methods: In this narrative, non-systematic review, we performed a literature search to retrieve data that could contribute to answering clinical questions on the definition and grading of severe hemorrhage and massive transfusion, identifying factors that predict and affect bleeding and transfusion-related mortality and describing the risks of re-exploration and the economic impact of severe bleeding in cardiac surgery.
Results: Massive perioperative bleeding is currently described by indices of its rate and extent and the magnitude of the consequent blood products transfusion. It has a significant impact on mortality, service logistics, and hospital financing. Proper and early identification of a massive bleeding is possible. Among other factors, patient's co-morbidities, bleeding severity and transfusion volume seem to predict the associated mortality. Consequent to severe bleeding, re-exploration, is also a potentially hazardous adverse event that also affects morbidity and mortality.
Conclusions: Severe perioperative hemorrhage in cardiac surgery carries significant morbidity and mortality. Currently, prediction and identification of massive bleeding is a feasible but incomplete clinical task despite the availability of effective treatment regimens. A still missing, compact definition of massive perioperative bleeding in cardiac surgery that incorporates all phases of treatment could augment clinical preparedness, allow for the development of accurate prediction tools and permit the application of well-validated protocols of management. Hippokratia 2016, 20(3): 179-186.

Key words: Massive bleeding, severe bleeding, massive transfusion, cardiac surgery, adult

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Introduction

Severe or massive hemorrhage in cardiac surgery is an infrequent but clinically significant event. Estimations vary considerably (2-10 %) depending on the definition of massive hemorrhage but are nevertheless associated with high mortality[1-5].

Failed or delayed treatment of a massive bleeding can result in irreversible end-organ damage (e.g., renal failure), cardiovascular events (e.g., stroke, myocardial injury) or death, accompanied by significantly increased costs[6,7]. Massive transfusion protocols are effective in reducing large volume [≥five units of red blood cells (RBC)] transfusion rate (from 15.9 % to 8.5 %) as well as massive (>10 units of RBC) transfusion incidence and re-exploration rate (4.6 % to 2.6 % and 5.6 % to 3.4 % respectively)[8-12]. But they are usually anchored on various definitions of massive bleeding and thus are quite often incomparable regarding triggers, timing, and extent of intervention.

Conforming with the need for appropriate identification of a potentially lethal massive bleeding episode[13], we performed a review of the literature in order to contribute to the following objectives: How do we currently define massive bleeding and transfusion in cardiac surgery? Can we predict massive bleeding? Does massive bleeding affect mortality? Can we make any predictions about it? Is re-exploration risky? Is there an economic impact of such a bleeding event?

Methods

We aimed at describing the existing definitions of massive bleeding and massive transfusion in cardiac surgery and comment on their diversity. So, we searched PubMed for articles defining massive bleeding, massive transfusion, and massive transfusion protocols in adult cardiac surgery, focusing on the last ten years (2006-2016). We used the following search words: massive or severe bleeding, massive or severe hemorrhage, massive transfusion, cardiac surgery. We then expanded this search to guidelines on bleeding in cardiac surgery and retracted additional literature to support our statements in the text. Duplicate and irrelevant articles were excluded from further analysis (Figure 1).

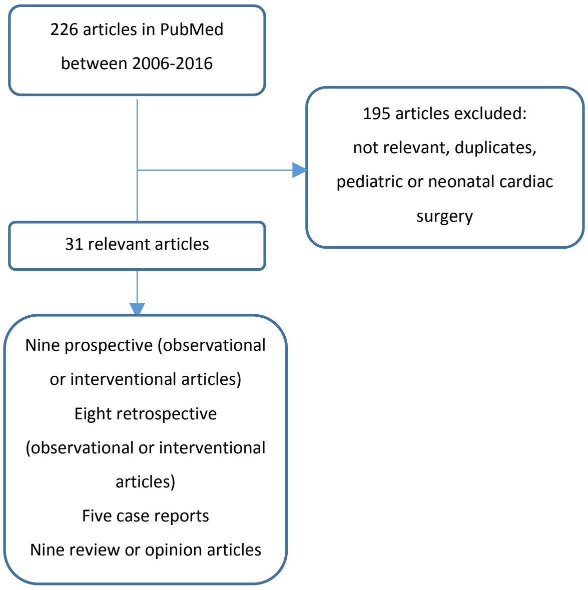

Figure 1: Flow chart of the recovered and analyzed studies in PubMed regarding articles defining massive bleeding, massive transfusion, and massive transfusion protocols in adult cardiac surgery, focusing on literature of the last ten years (2006-2016).

We proceeded in discussing the various predictors of massive bleeding and transfusion and collected data on the existing prediction models. Then we tried to retrieve data on the bleeding associated mortality, the impact of massive bleeding and re-exploration on patient mortality rates and describe its implications on hospital finances. Retrieved studies that do not refer in detail to the rates of blood volumes lost perioperatively or amounts and ratios of blood products transfused to confirm fitting to any massive bleeding definition, were not used in the reporting of definitions of massive bleeding and transfusion that we were seeking.

The descriptive nature of the answers in search and the lack of homogeneity of the collected data precluded a structured systematic review and meaningful statistical analysis of the retrieved data. Thus, a narrative but comprehensive review of the declared topics is presented.

Results

From the 226 articles retrieved, only a few deal with the definition of massive transfusion in cardiac surgery and most studies use arbitrarily chosen custom definitions (Figure 1, supplementary Table 1AS, supplementary Table 1BS)[3,7,10,14-25]. Twenty-two articles provide sufficient data on bleeding rates and transfusion of blood products in cases of severe or massive bleeding[3,7,10,14-32]. Among them, five case reports on massive bleeding were judged useful for their reporting data[28-32]. Six other studies although not providing adequate data for comparison, offer useful details on outcomes of severely or massively bleeding patient groups (supplementary Table 1AS, supplementary Table 1BS)[1,33-37]. We also retrieved three recent guideline articles from the major Anesthesiologist and Cardiothoracic Surgeon Societies[38-40] and we commented on their contribution.

What is massive bleeding?

As clinicians recognize that measurement of actual blood loss in the setting of a massive bleeding episode is unreliable[41], many of the given definitions of massive bleeding are based on the resultant transfusion of blood products[42].

According to the Hemostasis Score[10,42], intraoperative massive hemorrhage is present when operating field blood loss exceeds 600 ml/h necessitating, among other measures, the intermittent application of packing and when the chest drains poor out >300 mL/h or 150 ml/h of blood for two hours postoperatively (67 % positive predictive value)[10]. The PLASMACARD study defined excessive bleeding as abnormal diffuse or microvascular bleeding that cannot be controlled by compression and electrocoagulation, necessitates ≥two or three units of RBC transfusion or ≥400 or 600 mL of cell salvage blood depending on patient's weight (less or more than 60 kg, respectively) and a postoperative drain output of ≥1.5 mL/kg/h for at least three hours or a need for surgical re-exploration for hemostasis during the first 48 hours[15].

The universal definition of perioperative bleeding in cardiac surgery (UDPB)[2] attempted a more holistic approach. It uses five classes of bleeding (0: insignificant, 1: mild, 2: moderate, 3: severe, 4: massive) and considers a bleeding as severe when sternal closure is delayed (left open or packed for hemostatic issues), or five to ten units of RBC or fresh frozen plasma (FFP) have been transfused to the patient after chest closure, or the chest drains exceed 1,000 ml/12h or surgical re-exploration has already been applied. Massive bleeding occurs when more than ten units of RBC or FFP have been transfused, or drains exceed 2,000 ml/12h or when the administration of recombinant activated factor VII (rFVIIa) was judged compulsory to stop bleeding. Perioperative RBC transfusions for compensation for the extracorporeal circulation hemodilution were not included in the definition[2].

The BART study and the BRiSc (Papworth Bleeding Risk Score) use only postoperative indices for massive or excessive bleeding (BART: chest drainage of >1.5 L within any eight-hour-period postoperatively - approximating a mean rate of 200 ml/h, the evolution of cardiac tamponade, re-exploration for or death from bleeding; BRiSc: mean blood loss exceeding 2 ml/kg/h between arrival in ICU and the earliest of the following events: the elapse of three hours; the start of transfusion of any one of FFP, PLT or cryoprecipitate; return to theatre or death)[37]. Of note, intraoperative bleeding and the consequent transfusion of blood products were considered "standard surgical practice" and were not taken into ac-

Table 1: Factors contributing to the bleeding prediction models, found in the literature.

Variable	Any RBC Transfusion model[33]	BRiSc[1]	TRACK[46]	TRUST[47]	TRS-CABG[49]
Age	+	+	+	+	+
Gender	+	-	+	+	+
Weight, height, BMI	+	+	+	+	+
Preoperative Hb	+	-	+	+	+
Previous cardiac surgery	+	-	-	+	+
Type of operation	+	+	+	+	-
Status of operation	-	+	-	+	+
Serum Creatinine	+	-	-	+	+
LV EF%	+	-	-	-	+
Shock state	+	-	-	-	+
Previous stroke	+	-	-		
Diabetes mellitus	+	-	-	-	+
Previous MI	+	-	-	-	-
Use of CPB	+	-	-	-	-
Peripheral vascular disease	-	-	-	-	+
Preoperative albumin	-	-	-	-	+

RBC: Red Blood Cells, BRiSc: Papworth Bleeding Risk Score, TRUST: Transfusion Risk Understanding Scoring Tool, BMI: Body Mass Index, Hb: Hemoglobin, LV EF: Left Ventricle Ejection Fraction, MI: Myocardial Infarction, CPB: Cardio Pulmonary Bypass.

count in this study[1]. Karkouti et al consider the administration of more than five units of RBC within 24 hours as the cutoff point for identifying massive bleeding and confirmed this transfusion to correspond to one blood volume substitution (considering a normal preoperative Hb concentration of 16 g/dL, a blood volume of 70 ml/kg and a trigger of 8 g/dL of Hb to transfuse RBC)[43]. Some studies identify massive bleeding in the transfusion of four or more RBC during hospitalization[33] while others as a chest tube drainage of more than 1,000 ml either at discharge from ICU or until removal of drains[26].

What is massive transfusion?

Despite the fact that huge amounts of blood products can be transfused in complex cardiac surgery [for instance 29.4 RBC units, 27.7 FFP units and 39 platelet (PLT) units in patients undergoing heart transplant or implantation of heart/lung support devices][44], current definitions of massive transfusions are far less impressive. In a transfusion cohort of 104 cardiothoracic surgery patients who received massive transfusions per three different definitions (5/4h, 6/6h, 10/24h, meaning the administration of equal or more than five, six or ten units of RBC within any four-, six- or 24-hour-period) found that those in the 5/4h definition had significantly better survival rates compared to those who met 6/6h and 10/24h definitions (88.4 % vs 71.1 % respectively)[45]. The BART study used the 10/24h criterion as an indication for massive transfusion[37].

The most recent European Society of Anesthesiologists (ESA) guidelines on severe perioperative bleeding, the Society of Thoracic Surgeons (STS) blood conservation clinical practice guidelines and the American Society of Anesthesiologists (ASA) practice guidelines for perioperative blood management recommend the incorporation of indices that reflect oxygen availability in the mixed venous blood (mixed venous oxygen saturation) and the cerebral tissue (near infrared spectrometry) into the decision making for RBC transfusion but detail neither cutoff values nor appropriate combinations of them with other indices[38-40].

Predictors of massive bleeding and transfusion

There are quite many transfusion prediction scores available in the literature. Most of them have been produced in the last decade, have been validated accordingly and possibly predict even massive transfusion events (Table 1, supplementary Table 2S)[1,33,46-49].

Age, female gender, somatometric data [weight, height or Body Mass Index (BMI)], and renal function (mainly as serum creatinine levels), left ventricle ejection fraction, a preoperative shock state [defined either clinically or with the use of intra-aortic balloon pump (IABP)], logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation), preoperative hemoglobin, cardiopulmonary bypass time, emergency status of the operation, recent cardiac catheterization, other comorbidities [recent myocardial infarction (MI), congestive heart failure, non-smoker, New York Heart Association (NYHA) classification], coagulation defect [elevated international normalized ratio (INR), elevated bleeding time], preoperative heparin, preoperative antiplatelet drugs, lowest temperature during cardio pulmonary bypass (CPB), protamine insufficiency or excess, the use of antifibrinolytic drugs, large volumes of intraoperative salvaged cells transfused, multiple coronary anastomoses, special types of surgery (namely heart transplant or the implantation of mechanical circulatory support devic-

Table 2: Factors contributing to the massive perioperative bleeding prediction models, found in the literature.

Variable	Karkouti et al[25]	LVBT[33]	Williams et al[19]	BRS[55]
Age	+	+	-	+
Somatometric data	+	+	-	+
Preoperative shock	+	+	-	+
Preoperative platelet count	+		-	+
Preoperative Hb	+	+	+	-
Type of surgery	+	+	-	-
Status of operation	+	+	+	+
Surgeon	+		-	-
Previous cardiac surgery	+	+	-	+
DHCA duration	+	-	-	-
Duration of CPB	+	+	+	
Lowest Hct in CPB	+	-	-	-
Gender	-	+	-	+
Renal function	-	+	-	+
Previous neurological accident	-	+	-	-
Diabetes mellitus	-	+	-	+
LV ejection fraction	-	+	-	-
Preoperative MI	-	+	-	+

LVBT: Large Volume Blood Transfusion score, BRS: Bedside Risk Score, Hb: Hemoglobin, DHCA: Deep Hypothermic Circulatory Arrest, CPB: Cardio Pulmonary Bypass, LV: Left Ventricle, MI: Myocardial Index.

es), prior cardiac surgery with significant blood loss and the lactate levels when admitted to the intensive care unit (ICU) postoperatively, have all previously been associated with an increased risk of postoperative bleeding in general or for severe postoperative bleeding[2,25,26,2250-53]. In one study, recent intake of clopidogrel or dual antiplatelet therapy led to increased incidence of re-exploration (10.2 and 8.2 vs 3.9 %, p <0.005) and increased the probability of transfusion (54.2 % and 57.5 % vs 29.8 %, p <0.0001)[26].

In a few but important studies, BRiSc seems to perform poorly in severe bleeding[1,54,55]. while the Transfusion Risk Score (TRS) presented adequate discrimination ability [Area Under the Curve (AUC): 0.7827 at the validation][49]. The Transfusion Risk Understanding Scoring Tool (TRUST) score presented excellent calibration (Hosmer-Lemeshow χ^2 2.192, p =0.70 at external validation) whereas the LITMATHE and the TRS achieved low discrimination indices (Hosmer-Lemeshow χ^2 12.6, p =0.049 and 21.8, p <0.001, respectively)[46].

A few scores have been produced specifically for prediction of severe or massive perioperative bleeding (Table 2, supplementary Table 3S). The Karkouti et al score has negative predictive value for low risk of transfusion at 95 % and a positive predictive value for the high-risk group over 60 %[25]. The large volume blood transfusion score (LVBT) was developed and tested on a multicenter study population (n =27,353)[33]. It presented excellent calibration and discrimination (AUC: 0.8 at validation) and performed better that the other three, all transfusion category models (TRUST: AUC: 0.71, TRACK: AUC: 0.71, BRiSc: AUC: 0.69)[33], but it should be noted that multiple parameters can distort prediction models calibration[33].

Viscoelastic methods like the Sonoclot® test (Sienco Inc., Arvada, CO, USA), performed after heparin reversal can effectively identify bleeders (those with >800 ml/4h drain output) in cardiac surgery[12,14], whereas thromboelastometry guidance decreases the total number of blood products transfused as well as the total number of patients suffering massive transfusion[20,34].

Given that surgeon's skills (some surgeons perform better than others in the average blood loss during a certain operation), contribute statistically significantly to perioperative bleeding, it seems that the entire setting, within which any procedure is carried out, affects considerably either clinical or investigational outcomes[26,55]. Research has discovered significant correlation of genes rs1799809 (related to protein C activity), rs27646 (related to glycoprotein Ia) and rs1062535 (which codes for the alpha chain of the platelet collagen receptor integrin α2β1), rs630014 (in the ABO gene), and rs6048 (which codes for the coagulation factor IX pre-protein) with excessive postoperative bleeding (defined either as drain output >2 ml/kg/h or according to the universal definition)[56].

Independent predictors of mortality in massive bleeding and transfusion

Perioperative transfusion (irrespective of its magnitude or kind of blood products transfused) was found to be a significant contributor to short and long-term (one to five years) postoperative mortality with a sharp effect during the first six months (risk ratio of 2.4, 95 % confidence interval: 2.0 to 2.8; p <0.001)[57,58]. In another study, each RBC unit increased the probability of death by 77 % and the risk of infection by 23 %[5,59]. The TRACS study found that the transfusion of more than six units of RBC

Table 3: Factors contributing to the prediction models for mortality from massive perioperative bleeding, found in the literature.

Variable	Studies			
	Dyke et al[2]	Doussau et al[15]	Karkouti et al[43]	Karkouti et al[3]
Severity of bleeding	+	-	+	-
EuroSCORE	-	+	-	-
Preoperative INR	-	+	+	-
aPTT ratio	-	+	-	-
RBC transfusion	-	+	-	+
Age	-	-	+	+
Urgent status	-	-	+	-
Previous cardiac surgery	-	-	+	-
Duration of CPB	-	-	+	+
DHCA	-	-	+	-
Weaning for CPB	-	-	+	-
Re-exploration	-	-	+	-
Peri-operative shock	-	-	+	+
Neurologic status	-	-	+	-
Renal function	-	-	+	+
Pulmonary complications	-	-	+	-
pH before intervention	-	-	-	+

EuroSCORE: European System for Cardiac Operative Risk Evaluation, INR: International Normalized Ratio, aPTT: activated Partial Thromboplastin Time, RBC: Red Blood Cells, CPB: Cardio Pulmonary Bypass, DHCA: Deep Hypothermic Circulatory Arrest.

had a hazard ratio (HR) of 9.7 for mortality despite comparable mortality rates in the groups with restricted vs liberal transfusion policies[60]. The coexistence of massive bleeding (exceeding 900 ml/12h or undergoing surgical revision for bleeding), RBC transfusions (of any amount) and preoperative anemia (hematocrit <36 %) correlates with significantly higher mortality (7.5 % adjusted, 24.2 % unadjusted) than any other combination of these three variables and constitute the "deadly triad" in cardiac surgery that is associated with increased thromboembolic events, postoperative infections, and re-exploration[61].

There are only a few studies dealing with the prediction of mortality after a massive bleeding in cardiac surgery (Table 3, supplementary Table 4S). EuroSCORE, severity of transfusion and hemostatic indices [PLT, INR, activated Partial Thromboplastin Time (aPTT) ratio] seem to predict perioperative mortality after a massive bleeding (supplementary Table 4S)[2,25,43], but INR prolongation carries decreased specificity in identifying patients with low factor VII activity and aPTT also has low positive predictive value for clotting factor deficiencies perioperatively[62].

The risks of re-exploration

Multiple studies have proven that re-exploration for bleeding carries an increased risk of morbidity and mortality, irrespective of the magnitude of accompanying transfusion[63-66]. A very recent one describes a mean re-exploration rate of 6 % for elective [4.5 % for coronary artery bypass grafting (CABG), 5.5 % for single valve surgery, 9.6 % for combined surgery and 7.9 % for the rest of their cardiac surgery cohort] and 15 % for emergency surgery[67]. Re-exploration is significantly associated with increased mortality (7.6 % vs 2.4 % for those without re-exploration, unadjusted rate) and more perioperative stroke, renal dysfunction, prolonged mechanical ventilation and increased need for mechanical circulatory support[63,67]. Unfortunately, almost one-third to one-half of all re-explorations fail to discover the source of bleeding[65,67]. Low BMI, high EuroSCORE, low preoperative fibrinogen plasma concentration, long extracorporeal circulation time, combined heart valve and coronary artery bypass operations, and dual antiplatelet therapy within five days are considered independent risk factors for re-exploration[65,67].

The Bedside Risk Score accurately predicts the need for re-exploration due to hemorrhage[55]. It reveals decreasing mortality from re-operation for bleeding over time but predicts increasing rates for severe bleeding due to the new oral anticoagulants administration[55].

The economic impact of severe bleeding.

Perioperative bleeding seems to be quite costly, independent of the costs of agents used to treat it[68]. In complex cardiac surgery the cost of care for transfused patients (receiving at least one unit of RBC, FFP, PLT or cryoprecipitate) is 133.2 % greater compared with those not transfused ($50,344 vs $21,590, for RBC, FFP, PLT as well as fibrin sealants, tranexamic acid, protamine, rFVIIa and cell saver use)[68,69]. One study attempted to evaluate the economic impact of severe postoperative bleeding[7]. It found that patients that bled severely (1,669 ± 1,170 ml) required almost double the cost of treatment compared with those without severe bleeding (€15,404 ± €8,986 vs €8,027 ± €7,557). When adjusting for potential confounding factors, the incremental costs of excessive postoperative hemorrhage was determined at €6,251 (95 % confidence interval, €4,594-7,909)[7]. These costs compare to those reported in an older study in CABG patients that required re-exploration for bleeding (or bled >800 ml/4h postoperatively)[69].

Discussion

The current concept of early coagulation support during bleeding by adopting structured, monitored and targeted coagulation factor administration has been proven effective in treating perioperative bleeding in cardiac surgery[70,71]. Cases that do not respond to treatment eventually end up in massive bleeding (up to 8.3 % in complex cardiac surgery, or from one in 50 up to one in 10 patients)[24].

Unquestionably, severe or massive bleeding imposes additive morbidity and mortality burden in cardiac surgery patients (an eight-fold increase of death probability), just next to low cardiac output syndrome, perioperative stroke, and acute and chronic renal failure[18,43].

Massive bleeding and massive transfusion are not identical entities and should not be used interchangeably. The deleterious effects of massive bleeding (acute anemia, hypovolemia, hypotension, end-organ ischemia, compensatory stress reaction) are different in origin and effect from those arising from massive transfusion (immunological reaction, blood storage lesion, dilution effect)[42]. Additionally, very high bleeding rates (>150 ml/min) sometimes last only for a few minutes and then cease due to prompt surgical intervention, so the rate of bleeding cannot be used as the sole indicator for a massive transfusion.

The universal definition of perioperative bleeding seems to be quite inclusive for most cases of severe bleeding[2]. The Hemostasis Score more effectively describes an intraoperative bleeding episode, albeit with increased complexity in estimating the true blood loss in the operating field. To the contrary, some of the proposed extended time frame observations (such as 2,000 ml/12 hours which equals approximately to 170 ml/h)[2] might delay the identification of a true massive bleeding[24,37,43]. So, it seems imperative to further improve the definition of massive bleeding in a more comprehensive way.

Some prediction models (like the TRS and TRUST or LVBT for massive bleeding) perform quite satisfactory and perhaps could be implemented in identifying patients with a potentially severe bleeding. But most available data indicate that we currently cannot effectively predict which patient is going to bleed significantly. This is probably due to the dual nature of postoperative bleeding that cannot be adequately depicted in the proposed predictors: an initial systemic hypo-coagulation phase, secondary to excessive consumption and/or dilution of both clotting factors and platelet-mediated hemostasis and a subsequent phase of a more persistent, regional fibrinolytic bleeding in the mediastinum[72].

The point of care testing with elastometric and other analog techniques seem to contribute significantly to the perioperative management of severe bleeding. In cardiac surgery, thromboelastometry and thromboelastography, as well as other point-of-care methods of coagulation monitoring, have proven quite effective in predicting excessive hemorrhage, reducing perioperative bleeding, transfused blood products and associated morbidity, but their effect on mortality is still debatable[11,14,73-75].

The main limitation of this review is its narrative nature. A structured, systematic review and a consequent meaningful meta-analysis was hindered by the heterogeneity of the studies regarding massive bleeding definition and lack of adequate available data on perioperative transfusions.

Conclusions

Massive bleeding in cardiac surgery is a dynamic clinical entity that requires a more accurate definition due to its temporally fluctuating nature and etiology. It contributes to significant perioperative mortality, impacts blood banks and pharmacy logistics and heightens hospital expenses. Given that multiple and sometimes interrelated factors are responsible for its appearance and clinical course, a definition of massive perioperative bleeding in cardiac surgery that incorporates all leading aspects and phases of the event could allow for adequate clinical preparedness and hopefully augment management efficacy.

Conflict of interest

No author has any conflict of interest with the material presented in this review.

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In the electronic version of the paper supplementary material is provided that contains detailed data on the studies reviewed. Supplementary Table 1AS and Table 1BS summarize the twenty-two articles that provide sufficient data on bleeding rates and transfusion in cases of severe or massive bleeding in cardiac surgery. Supplementary Table 2S and Table 3S summarize the prediction models for perioperative bleeding in cardiac surgery while Supplementary Table 4S summarizes the few studies dealing with the prediction of mortality after massive bleeding in cardiac surgery. Also a separate reference list is provided regarding the papers included in the supplementary Tables as some studies presented in these Tables are not detailed in the Review and the original reference list.

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