Table 1AS: Studies that report adequate data on bleeding rates and blood product transfusion in severe or massive bleeding episodes in cardiac surgery (according to the universal definition), that were analyzed in the review regarding massive bleeding in cardiac surgery. The first 17 studies in the table are research articles. The last five studies are interesting case reports that report adequate data.

	Study	Type of study	Type of surgery	Aim of the study	Transfusion criteria	Groups	Group dividing characteristic	No pf pts in groups	Results - Significant variables for outcome
1	Bischof, 2015[1]	Prospective, observational	All cardiac surgery	Investigate whether Sonoclot can identify bleeders	• RBC if Hct <25% in pts with good EF • RBC if Hct <30% in pts with EF < 30% or emergency operation • As per institution protocol for the rest blood products and concentrates	1. Non bleeders 2. Bleeders	Drain output >800 ml/4h	1. 250 2. 50	Sonoclot test after heparin reversal can identify bleeders (cutoff points: ACT: 273 s, CR: 7.8, PF: 1.8)
2	Greilich, 2015[2]	Prospective, non-blinded, interventional feasibility study	Complex cardiac surgery	Reduction in blood products transfusion by adhering to pre-defined protocol	• Hemostatic protocol (PLT, FFP, cryoprecipitate) • RBC: Hct >21% on CPB, >24% post CPB, • Hct up to 30% if: rapid blood loss, additional hemodilution, inadequacy of oxygen delivery, low SvO_2	1. Excessive bleeding (EB) 2. No-excessive bleeding (No-EB)	Hemostasis score ≥3 (Bleeding Rate post protamine: >600 mL/h, Intermittent packing required)	1. EB: 27 2. No-EB: 16	Bleeding management protocol (blood products plus factor concentrates) based on Hemostasis score could identify and treat 78% of patients with excessive bleeding, 22% had bleeding refractory to protocol
3	Doussau, 2014[3]	Prospective, observational	All cardiac surgery (including transplantations)	Effectiveness of certain plasma doses in reducing mortality in excessively bleeding patients	ANSM guidelines (2012-2014, 2015) For RBC: Hb 7 =10 g/dL depending on co-morbidities For FFP (15 ml/kg): • microvascular bleeding despite adequate reversal of heparin and adequate platelet number (>50 x 10^9/L) and function • Laboratory evidence of clotting factors deficiency (≤40%, or INR >1.8 or aPTT >ratio >1.8 with normal TT) • RBC: FFP at 1:1 for aortic aneurysm rupture	1. Receiving FFP 2. Not receiving FFP	Transfusion of FFP	1. 562 2. 405	• FFP doses up to 30 ml/kg could not reduce mortality in excessive bleeding patients • EuroSCORE, INR, aPTT and RBC transfusion were found to be independent predictors of death
	Tanaka, 2014[4]	Prospective, interventional	Valve or complex surgery	Estimate the relative efficacy of Fibrinogen or PLT 5supplementation in severely bleeding patients	• If bleeding score: 2-3 -> randomization to intervention • Additional treatment: if bleeding >200 ml/h -> transfusion • If PLT <100 x 10^9/L -> 1 apheresis unit of PLT • If INR >1.6 -> FFP • If Fib <200 mg/dL -> 10 units or Cryoprecipitate	1. Randomization to Fibrinogen concentrate 2. Randomization to PLT	Fibrinogen 4 g or 1 apheresis unit of PLT	1. 10 2. 10	Administration of 4 g of Fibrinogen concentrate achieves plasma levels of >2 g/L and mitigates bleeding
5	Kremke, 2013[5]	Retrospective, observational	CABG ± aortic valve surgery	To examine the correlation of antiplatelet therapy before CABG with postoperative bleeding, transfusion and adverse cardiovascular events	• Allogeneic transfusions were based on routine laboratory measurements of aPTT, ACT, and INR, fibrinogen, Hb and Hct. • Use of blood products was based on hemodynamic and physiological data, the rate of blood loss and the comorbidities. • Hb target level tended to be higher with increasing patient age.	1. Patients on APT 2. Patients without APT	APT with 5 days prior to surgery	1. 1132 2. 1132	Preoperative APT is associated with increased bleeding and greater transfusion requirements after CABG. Clopidogrel exposure is associated with greater reoperation rates and is an independent risk factor for severe postoperative bleeding
6	Andersen, 2012[6]	Retrospective, observational	Aortic surgery with or without DHCA	To investigate efficacy of low dose rFVIIa in stopping bleeding	• Hct <24% for RBC • INR >1.3 for FFP • PLT <100 x 10^9/L for PLT • Fibrinogen <2 g/L for Cryoprecipitate • rFVIIa (10-20 μg/kg) in bleeding did not stop with the above treatment	1. Received rFVIIa 2. Did not receive rFVIIa	Administration of low dose rFVIIa to stop bleeding	1. 44 2. 44	The use of low dose rFVIIa in propensity-matched patient groups, improved postoperative hemostasis with no apparent increase in adverse events.
7	Chapman, 2011[7]	Retrospective, observational	All cardiac surgery	Safety of rFVIIa when used in massive bleeding	rFVIIa for: • persistent, massive, and life-threatening hemorrhage in non-hemophiliac patients in a non-futile setting, with an arterial pH >7.2. • Additional doses within 15-20 min if unresponsive	1. rFVIIa 2. No rFVIIa	Administration of rFVIIa	1. 236 2. 213	rFVIIa does not increase mortality of likelihood of thrombo-embolic events and renal failure
8	Williams, 2011[8]	Retrospective, observational	Aortic surgery with DHCA	To produce predictive model for massive transfusion	ASA guidelines, *Anesthesiology. 2006;105:198-208*	1. MT (massive transfusion 2. No-MT (no-massive transfusion)	Transfusion of ≥ 5 units RBC within 48h	1. MT: 49 2. No-MT: 119	Age, weight, Preoperative Hb, CPB time, emergency status and re-sternotomy are independent predictors for massive transfusion
9	Girdauskas, 2010[9]	Prospective, controlled	Aortic surgery with DHCA	Effect of ROTEM transfusion requirements	ROTEM based or: • INR >1.5 or aPTT >60s for FFP • PLT <100 x 10^9/L for PLT • Fibrinogen <1.2 g/L for fibrinogen • a2-Antiplasmin <80% for TXA	1. ROTEM 2. Control	Use of ROTEM	1. 27 2. 29	ROTEM use resulted in 44% decrease in allogenic transfusions and massive transfusions (from 35% to 19%)
10	Willis, 2010[10]	Prospective, observational	All cardiac surgery	Effectiveness of different doses of rFVIIa in controlling bleeding	• Per institution protocol	1. <40 μg/kg 2. 41-60 μg/kg 3. 61-80 μg/kg 4. 81-10 μg/kg 5. >100 μg/kg	Requiring rFVIIa to control bleeding	1. 4 2. 107 3. 104 4. 368 5. 183	There were no significant differences in the rate of thromboembolic adverse events, response to bleeding or 28-day mortality
11	Christensen, 2009[11]	Retrospective, observational	All cardiac surgery	Evaluate the added cost of excessive postoperative bleeding	• Per institution protocol	1. Severely bleeding 2. Not bleeding severely	Bleeding >200/h or ≥2 ml/kg/h for 2 hours during the first 6 hours	1. 76 2. 1112	Excessive postoperative bleeding imposes significant financial costs and correlated with increased morbidity and mortality
12	Masud, 2009[12]	Retrospective, observational	All cardiac surgery	Effectiveness of different doses of rFVIIa in reducing transfusions	• rFVIIa was given when lack of response to conventional • treatment with RBC, FFP, PLT and Cryoprecipitate	Received rFVIIa for transfusion reduction	Received rFVIIa for transfusion reduction	93	The RBC transfusion reducing effect was not different among doses of >30 μg/kg
13	Wasowicz, 2009[13]	Retrospective, observational	All cardiac surgery	Evaluate the utility of TEG in guiding therapy with rFVIIa	• At least 4 units of RBC transfused or blood loss >2,000 mL or precluding sternal closure in the OR • No surgical source of bleeding after >2 h of re-exploration • Use of antifibrinolytics • Received >4 FFP + 5 PLT • INR, aPTT <x1.5 of normal • Hct >24%	1. Responders 2. Non-responders	Requiring rFVIIa for uncontrolled bleeding	1. 28 2. 10	Patients with ≥2 abnormalities in kaolin-activated TEG were less likely to respond to rFVIIa than those with <2 abnormalities.
14	Karkouti, 2008[14]	Retrospective, observational	All cardiac surgery	Estimate effectiveness and safety of rFVIIa use in massive bleeding	• First dose was given when > 8 RBC (5-12), >8 FFP (5-12), 10 (10-15) PLT, >0 (0-10) Cryoprecipitate were transfused • Per Canadian national guidelines for use of rFVIIa	1. Received rFVIIa 2. Did no receive rFVIIa	Rescue use of rFVIIa for bleeding	1. 503 2.Cohort > 120000 pts	Median elapsed time from CPB to first dose of rFVIIa: 280 min Responders to rFVIIa - 380 patients (78%) received ≤ 5 RBCs within 24 hours post-treatment
15	Trowbridge, 2008[15]	Prospective, observational	All cardiac surgery	To describe demographic and operative parameters of patients with uncontrolled hemorrhage that necessitated use of rFVIIa	• For RBC: • Hct <22% for patients < 65 years old, • Hct <24% for patients >65 years old • For FFP: TEG guidance • For Cryo: TEG guidance + fibrinogen < 1 g/L • For PLT: if <100 x 10^9/L	1. Not massive bleeding 2. Massive bleeding	Need for use of rFVIIa	1. 187 2. 17	Pts with uncontrolled hemorrhage had more multiple procedures and/or aortic surgery, more auto-transfusion, longer bypass times, more DHCA and more transfusions.
16	Karkouti, 2006[16]	Prospective, observational	All cardiac surgery	Production of a prediction score for massive bleeding and transfusion	• Full blood count, aPTT, PT, INR • RBC: Hct >18-20% on CPB, > 24-27% post CPB • FFP: INR >1.5 • PLT: PLT <50-80 x 10^9/L or continued microvascular bleeding • rFVIIa	1. Training set 2. Validation set	Production (in 60% of the pts) and validation (in 40% of the pts) of the score	1. 6651 2. 4016	Age, BSA, preoperative Hb and PLT, shock, complex procedure, redo operation, non-elective, CPB time, circulatory arrest time, nadir Hct on CPB and high blood lose surgeon can predict massive bleeding and transfusion
17	Chen, 2004[17]	Prospective, observational	CABG surgery	Evaluation of a protocol in reducing transfusions in patients with recent intake of clopidogrel	• Hb <6 g/dL in CPB or <8 g/dL post CPB for RBC • INR >1.5 for FFP • Aggregometry ADP response <50% or PFA 100 • CT >128 s for PLT	3. Receiving Clopidogrel 4. Not receiving Clopidogrel	Clopidogrel with 5 days from surgery	1. 45 2. 45	Strict transfusion algorithm can reduce the transfusion requirement for all blood components.
	Study	**Type of study**	**Type of surgery**	**Aim of the study**	**Transfusion criteria**	**Groups**	**Group dividing characteristic**	**No pf pts in groups**	**Results - Significant variables for outcome**
1	Stein, 2014[18]	Case report	Aortic dissection	Massive bleeding treatment	• INR, Factor V and XIII levels, ROTEM, TT, aPTT, anti IIa - dabigatran	Massive transfusion	One patient on preoperative dabigatran	1	Clearance of Dabigatran with RRT resulted in effective bleeding control
2	Warkentin, 2012[19]	Case report	Aortic valve surgery	Massive bleeding treatment	• INR, TT, aPTT, anti IIa - dabigatran	Massive transfusion	One patient on preoperative dabigatran	1	Bleeding from dabigatran ingestion could not be stopped – fatal outcome
3	Barua, 2011[20]	Retrospective, observational case report series	All cardiac surgery	Effectiveness of rFVIIa administration in controlling bleeding	• Per institution protocol	Uncontrolled bleeding	Requiring rFVIIa to control bleeding	10	rFVIIa effectively controlled bleeding without adverse complications
4	Bishop, 2006[21]	Series of case reports	Complex cardiac surgery	Review of rFVIIa use	• Non-red cell support according to Coag screen—first cycle of 5U platelets, 5U FFP, and 5U cryoprecipitate • Repeat coagulation screen • If abnormal or persistent excessive blood loss—hematology consultation • Second cycle of 5U platelets, 5U FFP, 5U cryoprecipitate • Persistent excessive bleeding	Uncontrolled bleeding	Received rFVIIa	12	rFVIIa is a safe and dramatically effective for coagulopathic postoperative hemorrhage in cardiac surgery. The exact timing of administration, is yet to be determined
5	van de Garde, 2006[22]	Series of case reports	Aortic surgery ± valve ± CABG	Uncontrollable bleeding treatment	• Per institution protocol	Uncontrollable bleeding	Received rFVIIa	7	Low dose rFVIIa was effective in achieving hemostasis in severely bleeding cardiac surgical patients.

RBC: Red Blood Cells, Hct: Hematocrit, EF: Ejection Fraction, ACT: Activated Clotting Time, CR, PF, PLT: Platelets, FFP: Fresh Frozen Plasma, CPB: Cardio-Pulmonary Bypass, SvO2: Mixed venous oxygen saturtion, ANSM: Agence Nationale de Sécurité du Médicament, FRACNE, Hb: Hemoglobin, INR: International Normalized Ratio, aPTT: activated Partial Thromboplastin Time, TT: Thrombin Time, EuroSCORE: European System for Cardiac Operative Risk Evaluation, Fib: Fibrinogen, APT: Antiplatelet therapy, CABG: coronary artery bypass grafting, rFVIIa: Recombinant activated factor VII, DHCA: Deep hypothermic circulatory arrest, ASA: American Society of Anesthesiologists, MT: Massive transfusion, ROTEM: Rotational ThromboElastoMetry, TEG: ThromboElastoGraphy, Cryo: Cryoprecipitate, BSA: Body Surface Area, ADP: Adenosine DiPhosphate, CT: Clotting Time, anti-IIa: factors counteracting activated clotting factor II, RRT: Renal Replacement Therapy, U: Unit(s).

Table 1BS: Characteristics of the severe, massive or excessive bleeding and transfusion groups in the studies listed on Table 1AS (studies that report adequate data on bleeding rates and blood product transfusion in severe or massive bleeding episodes in cardiac surgery).

Study	No patients	Total blood loss (median or mean)	Blood loss rate (ml/h. mean ± SD)	RBC (median)	FFP (median)	RBC:FFP	PLT (median)	Total blood product units	Re-explo-ration	Death	Fibrino-gen	Cryoprecipitate (units)	DDAVP	PCC	rFVIIa	FXIII
Bischof, 2015[1]	250 50	1.0 ± 0.4 L/12 hours 2.4 ± 1.1 L/12 hours	NA	Mean: 1.8 ± 4.8 Mean: 5.6 ± 5.0	1.0 ± 1.9 3.1 ± 3.4	Approx.: 1.8:1 Approx.: 1.8:1	0.3 ± 0.9 1.2 ± 1.5	NA	1 (0.4%) 10 (20%)	2 (1%) 4 (8%)	0.4 ± 1.0 g 3.4 ± 7.4 g	NA	NA	547 ± 836 IU 1,800 ± 1,271 IU	NA	NA
Greilich, 2015[2]	(respond-ers-non-respond-ers) 27 (21 – 6)	(responders-non-responders) 2,337-5,351 in 24h	1,420 ± 957 ml/h	(responders-non-responders) 4 - 14	(responders-non-responders) 4 - 8	(responders-non-responders) 1:1 up to 1.75:1 (approx)	(responders-non-responders) 1 - 3.5 apheresis units	-	1 (17%)	1 (17%)	-	(responders-non-responders) 10 - 20	(respond-ers-non-re-sponders) 10 - 3 pts (dose: 24 μg)	NA	5 no-responders (83%), dose 25-60 μg/kg/dose	NA
Doussau, 2014[3]	965 (562 - 405)	Cell saver salvaged blood > 1000 ml: 18.4%	NA	Percentage of pts transfused with RBC: 100%	Percentage of pts transfused with FFP: 58.11%	NA	Percentage of pts transfused with PLT: 48.5%	NA	215 (22.2%)	109 (11.3%)	NA	NA	NA	NA	NA	NA
Tanaka, 2014[4]	20	Fib: 925 (500-1693)/12h PLT: 1315 (653-2965)/12h	NA	Fib: Ap-prox. 2500, (0-7000) ml PLT: Approx. 3100, (0-4500) ml (PLT)	Fib: 0, (0-2400) ml PLT: 700, (0-2250) ml	NA	Fib: 0, (0-6) apheresis units PLT: 2, (1-6) apheresis units	Total donor exposures: Fib: 0, (0-13.3) PLT: 16.5 (1.0-39.8)	Fib: 1/10 PLT: 2/10	Fib: 0% PLT: 0%	NA	Fib: 0, (0-1600) ml PLT: 400, (0-1200) ml	NA	NA	NA	NA
Kremke, 2013[5]	59 239	989 ml in ICU 1112 ml in ICU	NA	420 ± 1224 ml (CLOP) 507 ± 913 ml (DUAL)	417 ± 780 ml (CLOP) 453 ± 884 ml (DUAL)	1.18:1 (approx.) 0.98:1 (approx.)	306 ± 609 ml (CLOP) 367 ± 496 ml (DUAL)	NA	10.2 (CLOP) 8.2 (DUAL)	15 (1.3%)	NA	NA	NA	NA	NA	NA
Andersen, 2012[6]	44	Total intra-op-erative: 750 ml (500–1200)	Total post-operative: 570 ml/12h (range: 398–846)	Intra-operative: 1050 ml (range: 700–1750)	Intra-operative: 2000 ml (range: 1000-2313)	0.5:1	Intra-operative: 600 ml (range: 598–800)	NA	0	1 (2.3%)	NA	100 ml (range: 0–100)	NA	NA	Median: 32 μg/kg (range: 16-43 μg/kg)	NA
Chapman, 2011[7]	235	NA	NA	4.7	4	1.17:1	9.2 single units	NA	26 (11%)	18 (7.7%)	NA	NA	NA	NA	Mean: 6.5 ± 3.8	NA
Williams, 2011[8]	49	1050 ± 864 / 12h + 715 ml from cell saver	1050 ± 864 / 12h	6	11	0.54:1	5 apheresis units	22 (18 - 31)	21 (43%)	2 (4%)	NA	NA	NA	NA	5 (10%)	NA
Girdauskas, 2010[9]	ROTEM: 27 Control: 29	890/24h (range 600–1250) 950/24h (range 650–1400)	600/12h (range 380–950) 680/12h (range 450–1000)	6.0 (range 2.0–13.0) 9.0 (range 4.0–14.0)	3.0 (range 0–12.0) 8.0 (range 4.0–18.0)	2:1 1.1:1	apheresis units 1.0 (range 0–4.0) 2.0 (range 1.0–3.0)	9.0 (range 2.0–30.0) 16.0 (range 9.0-23.0)	5 (19%) 7 (24%)	4 (15%) 5 (17%)	2.0 g (range 2.0–3.0) 2.0 g (range 2.0–3.0)	-	-	0 IU (range 0–2000) 3000 IU (range 2000–3000)	1 (4%) 2 (7%)	-
Willis, 2010[10]	42 107 104 368 183	NA	NA	6 (3–10) + 2 (1–4) 5 (2–10) + 2 (1–3) 6 (4–9) + 2 (1–5) 6 (3–9) + 2 (1–5) 7 (4–10) + 2 (1–6)	8 (6–12) + 0 (0–4) 6 (4–10) + 2 (0–4) 6 (4–10) + 2 (0–5) 6 (4–10) + 2 (0–4) 7 (4–10) + 2 (0–5)	Approx: 0.75:1 Approx: 0.83:1 Approx: 1:1 Approx: 1:1 Approx: 1:1	4 (2–8) + 0 (0–1) 2 (2–5) + 0 (0–2) 3 (2–5) + 1 (0–2) 3 (2–5) + 1 (0–2) 3 (2–6) + 1 (0–3)	NA	NA	7 (17%) 15 (14%) 17 (16%) 67 (18%) 36 (20%)	NA	1 (0–10) + 0 (0–5) 5 (0–10) + 0 (0–1) 5 (0–8) + 0 (0–2) 8 (0–10) + 0 (0–5) 8 (0–10) + 0 (0–6)	NA	NA	1.< 40 μg/kg 2.41-60 g/kg 3.61-80 g/kg 4.81-10 g/kg 5.> 100 g/kg	NA
Christensen, 2009[11]	76 1112	Bleeding: 1,669 (± 1170) ml/6h Not bleeding: 472 (± 873) ml/6h	NA	Bleeding: 4.5 (±3.8) Not bleeding: 0.9 (±1.9)	Bleeding: 4.1 (±5.2) Not bleeding: 0.3 (±1.6)	1.1:1	Bleeding: n = 19 (25.0%) Not bleeding: n = 19 (1.7%)	NA	Bleeding: 45 (59.2%) Not bleeding: 38 (3.4%)	Bleeding: 17 (22.4%) Not bleeding: 61 (5.5%)	NA	NA	NA	NA	NA	NA
Masud, 2009[12]	93	NA	NA	Before:7.6 ± 6.8 After: 3.5 ± 4.7	Before: 6.9 ± 7.3 After: 1.7 ± 3.39	Approx: 1.1:1 Approx: 2:1	Before: 6.04 ± 12 After: 1.07 ± 1.9	NA	11 (11.8%)	21 (22.6%	NA	Before: 16.1 ± 19.9 After: 8.1 ± 24.6	NA	NA	56.2 ± 26.5	NA
Wasowicz, 2009[13]	28 10	Before rFVIIa: Res: 433 (260-545) NRes: 1,063 (505-1275) After rFVIIa: Res: 248 (0-618) /12h NRes: 470 (100-1000) /12h	NA	Before rFVIIa: Res: 5.5 (3.5- 7) NRes: 7 (4-10) After rFVIIa: Res: 2 (1-3) NRes: 2 (1-5)	Before rFVIIa: Res: 6.5 (4-9) NRes: 8 (6-10) After rFVIIa: Res: 0 (0-0) NRes: 2 (1-4)	Before rFVIIa: Res: 0.84:1 NRes: 0.87:1 After rFVIIa: Res: 2:0 NRes: 1:1	Before rFVIIa: Res: 10 (5-10) NRes: 10 (10-15) After rFVIIa: Res: 0 (0- 0) NRes: 5 (0-10)	NA	Before rFVIIa: 36% vs 20% After rFVIIa: 0% vs 33%	NA	NA	NA	NA	NA	NA	NA
Karkouti, 2008[14]	503	NA	NA	13 (8-20)	12 (8-20)	1.1:1	20 (10-25)	55 (40-84)	259 (53%)	159 (32%)	NA	10 (0-20)	NA	NA	Median: 62 μg/kg (range 40-89 μg/kg)	NA
Trowbridge, 2008[15]	17	Cell saver salvaged blood: 3046 ± 2104	NA	5.4 ± 3.5	8.6 ± 5.5	0.62:1	6.5 ± 8.7 single units	NA	NA	NA	NA	11.4 ± 9.4	NA	NA	17 (100%)	100%
Karkouti, 2006[16]	476	NA	NA	Percentage of pts transfused with ≥ 5 RBC: 8.7%, ≥ 7 RBC: 4.4%	NA	NA	NA	NA	187 (39%)	59 (12%)	NA	NA	NA	NA	NA	NA
Chen, 2004[17]	45	1329 ± 154 /24h	NA	4.3 ± 0.6	1.0 ± 0.6	4.3:1	9.0 ± 1.7 single units	NA	4 (10)	1 (2.2%)	NA	NA	NA	NA	NA	NA
Study	**No patients**	**Total blood loss (median or mean)**	**Blood loss rate (ml/h. mean ± SD)**	**RBC (median)**	**FFP (median)**	**RBC:FFP**	**PLT (median)**	**Total blood product units**	**Re-explo-ration**	**Death**	**Fibrino-gen**	**Cryoprecipitate (units)**	**DDAVP**	**PCC**	**rFVIIa**	**FXIII**
Stein, 2014[18]	1	> 3750 ml	Very high	55	36	1.52:1	20 single units	111	X 2	1	68 g	NA	40 μg	17,000 IU	Mean: 7 mg	7,500 IU + FVIII/vWf: 2000 IU
Warkentin, 2012[19]	1	> 7000 ml	> 1500 ml/h x 3h	26	22	1.18:1	5 apheresis units	73	No	No	NA	50	No	No	Mean: 21.6	No
Barua, 2011[20]	10	NA	1758.5 ± 163.9/6h mL -> 405.6 ± 50.5 mL/6h	NA	NA	NA	NA	19.6 ± 1.5 U -> 4.4 ± 0.6 U	8/10 (80%), then 2/8 (25%), then rFVIIa	NA	NA	NA	NA	NA	65 μg/kg	NA
Bishop, 2006[21]	12	Mean: 743 mL (range, 245–1,550)	NA	Before rFVIIa: 7.7 (0–18) After rFVIIa: 0.08 (0–1)	Before rFVIIa: 18.7 (10–40) After rFVIIa: 0.15 (0–2)	Before: 0.41:1 After: 0.53:1	Before rFVIIa: 22.5 (10–40) After rFVIIa: 0	NA	No re-exploration rFVIIa stopped bleeding in the OR	0/12 (0%)	NA	Before: 19.5 (8–32) After: 0	NA	NA	100 μg/kg	NA
van de Garde, 2006[22]	7	Median: 850 (550-1700) plus 3400 (960-6000) ml form cell saver	NA	3 (1-10) before treatment + 0 (0-2) post treatment	4 (2-10) before treatment + 0 (0-0) post treatment	0.75:1 before treatment	2 (1-2) before treatment + 0 (0-0) post treatment	In total: 14 (13-31)	No re-exploration rFVIIa stopped bleeding in the OR	1/7 (14%)	NA	NA	NA	NA	40 (26-111) μg/kg	NA

Approx: Approximately, RBC: Red Blood Cells, FFP: Fresh Frozen Plasma, PLT: Platelets, DDAVP: Desmopressin acetate, PCC: Prothrombin Complex Concentrate, rFVIIa: recombinant Factor VII, FXIII: clotting Factor XIII, pts: patients.

Table 2S: Prediction models for perioperative bleeding of any magnitude in cardiac surgery, found in the literature.

Variable	**Any RBC Transfusion model[23] (Odds ratio)**		**BRiSc[24]**	**(points)**	**TRACK[25]**	**(points)**	**TRUST[26]**	**(points)**	**LITMATHE-CABG[27]**	**(points)**	**TRS-CABG[28]**	**(points)**
Age	Age per 10 year Age per 10 year^2	1.29 1.03	<75 years ≥75 years	0 1	>67 years	6	>65 years	1	>70 years	1	>74 years	2
Gender	Female	1.76	-	-	Female	4	Female	1	Female	1	Female	2
Weight, height, BMI	Height per 10 cm Weight per 10 kg	0.96 0.85	BMI ≥25 BMI <25	0 1	Weight <60 kg (female) Weight <85 kg (male)	2 2	Weight <77 kg	1	-	-	BMI ≤24	2
Preoperative Hb	Preoperative Hb in g/L if CPB Preoperative Hb in g/L if no CPB	0.71 0.60	-	-	Hct - points per each value (%) <40% (max 13 points)	1-13	Hb <13.5 g/L	1	Hb <11 g/L	3	Low RBC mass <1500 ml per nomogram	2
Previous cardiac surgery	Previous cardiac surgery	1.74	-	-	-	-	Previous cardiac surgery	1	Previous cardiac surgery	2	Previous cardiac surgery	1
Type of operation	Operation type by sex: Female and CABG only Female and valve only Female and other only Female and CABG + valve Female and CABG + other Female and valve + other Female and CABG + valve + other Male and CABG only Male and valve only Male and other only Male and CABG + valve Male and CABG + other Male and valve + other Male and CABG + valve + other Major aortic procedure	 1 0.85 0.59 1.66 1.05 0.83 1.16 1 1.05 1.14 2.38 1.70 1.22 2.16 2.02	CABG or single valve All other surgery types No Aortic valve disease AV Stenosis, regurgitation, or both	0 1 0 1	Complex surgery	7	Non-isolated surgery	1	-	-	-	-
Status of operation	-	-	Elective Urgent or emergency	0 1	-	-	Non-elective surgery	1	Emergency operation Urgent operation	4 2	Emergency operation Urgent operation	4 3
Serum Creatinine	(Serum creatinine in μmoles per litre)/100 (Serum creatinine in μmoles per litre)/100)^2	2.12 0.89	-	-	-	-	Serum creatinine > 1.36 mg/dL	1	Serum creatinine > 1.6 mg/dL	1	Serum creatinine >1.8 mg/dL	1
LV EF%	Good (> 50%) Moderate (30 - 49%) Poor (< 30%)	1 1.09 1.40	-	-	-	-	-	-	Left ventricle EF <0.35	3	Left ventricle EF <0.3	2
Shock state	Cardiogenic shock IABP used preoperatively	2.38 1.82	-	-	-	-	-	-	Cardiogenic shock	3	Cardiogenic shock	3
Previous stroke	Previous neurological accident	1.28	-	-	-	-						
Diabetes mellitus	Diabetic on medication	1.13	-	-	-	-	-	-	Diabetes (insulin dependent)	1	Diabetes (insulin dependent)	1
Previous MI	MI at ≤ 30 days before operation	1.37	-	-	-	-	-	-	-	-	-	-
Use of CPB	CPB used at any point	2.33	-	-	-	-	-	-	-	-	-	-
Peripheral vascular disease	-	-	-	-	-	-	-	-	-	-	Peripheral vascular disease	1
Preoperative albumin	-	-	-	-	-	-	-	-	-	-	<4 g/dL	1
Least-Maximum score				0-5		20-32		0-8		0-19		0-22
Predictions	**Logistic calculation**		**Score: 0, 3% probability (2-4%)** **Score: 1-2, 8% probability (7-10%)** **Score: ≥3, 21% probability (18-24%)**		**Score: 2, 25-35% approx, Low zone** **Score: 4, 33-41% approx, Low zone** **Score: 6, 37-47% approx, Medium zone** **Score: 8, 47-55% approx, Medium zone** **Score: 10, 50-57% approx, Medium zone** **Score: 12, 55-63% approx, Medium zone** **Score: 14, 58-65% approx, Medium zone** **Score: 16, 67-73% approx, High zone** **Score: 18, 72-77% approx, High zone** **Score: 20, 77-80% approx, High zone**		**Score: 0, 0-19%, Baseline risk** **Score: 1, 20-39%, Low risk** **Score: 2, 40-59%, Intermediate risk** **Score: 3, 60-79%, High risk** **Score: 4-8, 80-100%, Very high risk**		**NA**		**Score: 0-1, 26% approx., Low risk** **Score: 2-6, 67% approx., intermediate risk** **Score: >7, 96% approx., High risk**	

BMI: Body Mass Index, Hb: Hemoglobin, Hct: Hematocrit, RBC: Red Blood Cells, CABG: Coronary Artery Bypass Grafting, EF: Ejection Fraction, IABP: Intra-Aortic Balloon Pump, MI: Myocardial Infarction, CPB: CardioPulmonary Bypass.

Table 3S: Prediction models for severe or massive perioperative bleeding in cardiac surgery, found in the literature.

Variable	**Karkouti et al[16]**	**points**	**LVBT[23]**	**0dds ratio**	**Williams et al[8]**	**Odds ratio**	**Bedside Risk Score (BRS) – BRiSc[24]**	**points**
Age	70-80 years	0.5	Age per 10 yr	1.22	-	-	60-69 years	3
	>80 years	1					70-79 years	6
							80-89 years	9
							90-99 years	12
Somatometric data	BSA: 1.5-1.9 m^2	0.5	Weight per 10 kg	0.86	-	-	BSA: <1.5 m^2	12
	BSA <1.5 m^2	1					BSA: 1.5-1.59 m^2	11
							BSA: 1.6-1.69 m^2	10
							BSA: 1.7-1.79 m^2	9
							BSA: 1.80-1.89 m^2	8
							BSA: 1.90-1.99 m^2	7
							BSA: 2.00-2.09 m^2	6
							BSA: 2.10-2.19 m^2	5
							BSA: 2.20-2.29 m^2	4
							BSA: 2.30-2.39 m^2	3
							BSA: 2.40-2.49 m^2	2
							BSA: 2.50-2.59 m^2	1
							BSA: >2.60 m^2	0
Preoperative shock	Preoperative shock state	1	IABP used preoperatively	1.94	-	-	IABP or inotropes	4
Preoperative platelet count	PLT 100-150 x 10^9/L	0.5			-	-	ADPi (ADP inhobitors) without GPIIb/IIIa	6
	PLT <100 x 10^9/L	2					ADPi + GPIIb/IIIa	10
Preoperative Hb	Hb 11-13 g/dL	0.5	Preoperative Hb in g/dL	0.71	Preoperative hemoglobin	0.543	-	-
	Hb <11 g/dL	1			(per 1-g/dL increment)			
Type of surgery	complex procedure	0.5	Major aortic procedure	2.61	-	-	-	-
			CABG only	1				
			Valve only	1.17				
			Other only	1.66				
			CABG + valve	2.73				
			CABG + other	2.07				
			Valve + other	1.52				
			CABG + valve + other	2.43				
Status of operation	Non-elective surgery	0.5	Urgency × MI:		Emergency	4.02	Emergency (no resuscitation)	6
			No MI + not urgent	1			Emergency – salvage (with resuscitation)	13
			MI + urgent	1.84				
			MI + not urgent	1.90				
			No MI + urgent	1.69				
Surgeon	High blood loss surgeon	0.5			-	-		
Previous cardiac surgery	Re-do surgery	1	Previous cardiac surgery	2.25	-	-	Previous cardiovascular interventions	5
DHCA duration	Circulatory arrest: 0-30 min	0.5			-	-		
	Circulatory arrest: > 30 min	2						
Duration of CPB	Duration: 120-180 min	1	CPB used at any point	3.37	Duration of CPB (per	1.15		
	Duration: > 180 min	2.5			10-min increase)			
Lowest Hct in CPB	Hct: 18-22%	0.5	-	-	-	-		
	Hct: <18%	1						
Gender	-	-	Female	1.12	-	-	White race	0
							Non-white race	2
							Male gender	5
							Female gender	0
Renal function	-	-	Chronic dialysis	0.29	-	-	Serum Creatinine: < 1 mg/dL	0
			(Serum creatinine in	1.97			Serum Creatinine: 1-1.9	4
			Mmoles/L)/100				Serum Creatinine:2.0-2.9	8
							Serum Creatinine:3.0-3.9	12
							Serum Creatinine:4.0-4.9	16
							Serum Creatinine:≥ 5.0	20
							No Dialysis	0
							On dialysis	11
Previous neurological accident	-	-	Previous stroke	1.13	-	-		
Diabetes mellitus	-	-	Diabetic on medication	1.22	-	-	No Diabetes Mellitus	2
							Diabetes Mellitus	0
LV ejection fraction	-	-	EF category:		-	-		
			Good (> 50%)	1				
			Moderate (30 - 49%)	1.18				
			Poor (< 30%)	1.05				
Preoperative MI	-	-	MI within 30 days from	See: status	-	-	Diseased vessels < 3	0
			operation + urgent status	of opera-tion			Diseased vessels ≥ 3	2
Total score		0-14						
Predictions	**Score <2.5, Low risk (5%)**		**Logistic**		**Logistic**		**Risk for re-operation**	
	Score: 2.5-4.5, Intermediate risk (27%)						**BRS: 0-12 -> 1.25% approx.**	**BRS: 22 -> 2.25% approx.**
	Score >4.5: High risk (58%)						**BRS: 13-14 -> 1.6% approx.**	**BRS: 23 -> 2.4% approx.**
							BRS: 15 -> 1.7% approx.	**BRS: 24 -> 2.65% approx.**
							BRS: 16-17 -> 1.8% approx.	**BRS: 25-26 -> 2.8% approx.**
							BRS: 18 -> 1.9% approx.	**BRS: 27 -> 3% approx.**
							BRS: 19 -> 1.95% approx.	**BRS: 28-30 -> 3.6% approx.**
							BRS: 20 -> 2% approx.	**BRS: 31-84 -> 4.9% approx.**
							BRS: 21 -> 2.1% approx.	

BSA: Body Surface Area, IABP: Intra-Aortic Balloon Pump, PLT: Platelets, ADP: Adenosine Di-Phosphate, GPIIb-IIIa: Glyco-Protein IIb-IIIa, Hb: Hemoglobin, CABG: Coronary Artery Bypass Grafting, MI: Myocardial Infarction, CPB: Cardio Pulmonary Bypass, Hct: Hematocrit, LV: Left Ventricle. EF: Ejection Fraction.

Table 4S: Factors that affect mortality after massive transfusion in cardiac surgery, published in the literature.

Variable	Studies							
	Dyke et al[29]	HR / OR, [95% confidence interval], (p)	Doussau et al[3]	HR, [95% confidence interval], (p)	Karkouti et al[30]	OR, [95% confidence interval], (p)	Karkouti et al[14]	OR, [95% confidence interval], (p)
Severity of bleeding	UDPB class	2.18, [1.55-3.07], (<0.1 x 10^{-2})	-	-	> 5 units RBC / 24h	8.1, [3.9-17.0], (<0.1 x 10^{-3})	-	-
EuroSCORE	-	-	3.6-5.9 vs. ≤3.6 5.9-9.5 vs. ≤3.6 9.5-18.3 vs. ≤3.6 >18.3 vs. ≤3.6	0.9, [0.3-3.5], (<10^{-3}) 0.8, [0.2-2.5], (<10^{-3}) 1.8, [0.5-6.3], (<10^{-3}) 2.5, [0.9-6.7], (<10^{-3})	-	-	-	-
Preoperative INR	-	-	INR ≥ 1.2 vs. < 1.2	1.7, [1.2-2.5], (10^{-2})	INR > 1.2	1.9, [1.2-3.0], (<0.4 x 10^{-2})	-	-
aPTT ratio	-	-	aPTT ratio > 1.2 vs. ≤ 1.2	1.6, [1.2-2.2], (10^{-2})	-	-	-	-
RBC transfusion	-	-	5-6 units (vs. ≤4) ≥7 units (vs. ≤4)	2.2, [1.3-3.7], (<10^{-3}) 2.9, [1.6-5.2], (<10^{-3})	-	-	> 10 units RBC before treatment > 10 RBC with 24h of treatment 6-10 RBC with 24h of treatment	2.4, [1.4–4.0] 8.9, [3.6–22.0] 2.6, [1.3–5.1]
Age	-	-	-	-	≥ 70 years	1.6, [1.1-2.4], (<0.2 x 10^{-1})	> 50 years	2.6, [1.3–5.4]
Urgent status	-	-	-	-	Urgent surgery	2.0, [1.3-3.1], (<0.2 x 10^{-2})	-	-
Previous cardiac surgery	-	-	-	-	Yes	2.1, [1.3-3.4], (<0.2 x 10^{-2})	-	-
Duration of CPB	-	-	-	-	Duration of CPB in minutes	1.007, [1.004-1.011], (<0.1 x 10^{-3})	In min	1.003, [1.001–1.006]
DHCA	-	-	-	-	Circulatory arrest: Yes	2.4, [1.3-4.3], (<0.5 x 10^{-2})	-	-
Weaning for CPB	-	-	-	-	Inotropes or IABP	3.0, [1.7-5.6], (<0.2 x 10^{-3})	-	-
Re-exploration	-	-	-	-	Yes	3.5, [1.7-7.4], 0.6 x 10^{-3})	-	-
Peri-operative shock	-	-	-	-	Low-output syndrome (CI < 2.2 L/kg/min, ± medications or IABP for > 30 min)	10.1, [6.5-15.7], (0.1 x 10^{-5})	Requiring hemodynamic support Unstable before rFVIIa	2.7, [1.5–4.9] 2.2, [1.3–3.6]
Neurologic status	-	-	-	-	Stroke	13.2, [5.3-33.2], 0.1 x 10^{-3})	-	-
Renal function	-	-	-	-	RRT	13.8, [8.1-23.3], (0.1 x 10^{-3})	creatinine > 100 μmol/L in women or > 110 μmol/L in men; or on dialysis	1.7, [1.1–2.8]
Pulmonary complications	-	-	-	-	Pneumonia, ARDS, re-intubation	2.5, [1.3-4.6], (<0.4 x 10^{-2})	-	-
pH before intervention	-	-	-	-	-	-	pH < 7.2 7.2 ≤ pH < 7.3 7.3 ≤ pH < 7.4	7.9, [2.7–23.3] 3.1, [1.5–6.3] 2.0, [1.1–3.6]

HR: Hazard Ratio, OR: Odds Ratio, UDPB: Universal Definition of Perioperative Bleeding, 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, IABP: Intra-Aortic Balloon Pump, CI: Cardiac Index, rFVIIa: Recombinant activated Factor VII, RRT: Renal Replacement Therapy, ARDS: Adult Respiratory Distress Syndrome.

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