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).