

Prothrombin Complex Concentrates (Octaplex®): A Safety Review of The Management of Massive Transfusion Following Cardiac Surgery

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Introduction

Excessive postoperative bleeding requiring multiple transfusions remains a relatively frequent occurrence in Cardiac Surgery. Prophylactic platelet and frozen plasma transfusions are often used to minimize the risk of postoperative bleeding, despite evidence suggesting that this practice is unwarranted.

Some experimental animal models of cardiopulmonary bypass induced coagulopathy have demonstrated superior hemostasis with the use of concentrated **Prothrombin Complex Concentrates (PCC)** over frozen plasma transfusion and activated recombinant Factor VII.

Increasingly, PCCs have been used to treat refractory bleeding in cardiac surgery patients despite a paucity of well-designed comparison trials to conventional transfusion practices in Canada.



Figure 1. (1)(2)(3)(4) Beriplex® and Octaplex® vs Fresh Frozen Plasma. Beriplex® and Octaplex® are Human Prothrombin Complex Concentrates that are approved for reversal of anticoagulation from Coumadin® (Warfarin) of other Vitamin K antagonists. The use of PCC for the treatment of bleeding in the absence of Coumadin anticoagulation is not currently approved by Health Canada and is considered 'off label' usage. Fresh Frozen Plasma is currently the standard to treat life-threatening bleeding in the other cases where patients have deficiencies of coagulation proteins.

Methods

Study Design

- Single center retrospective safety audit of all heart surgery patients at the University of Ottawa Heart Institute from December 2008 until January 2011
- All patients who received PCCs after heart surgery were identified and charts were reviewed
- Identified patients who received PCCs for treatment of refractory bleeding and not for Coumadin reversal
- The primary objective was to determine the incidence of thrombotic events in cardiac surgery patients treated with PCCs
- Transfusions were also quantified as PCCs are felt to be superior in treating post CPB induced coagulopathy, thus reducing exposure to blood components

Study population

- 72 patients met the inclusion criteria for complete review

Results

Characteristics	Parameter values
Number of patients	n = 72
Male (n, %)	54 (75%)
Age (years), mean ± SD	62.3 ± 13.7
BSA (square meters), mean ± SD	1.91 ± 0.21
Preoperative Hb/Hct, mean ± SD	125.5 ± 46.0
Platelet count, mean ± SD	180 ± 80
Initial INR, mean ± SD	1.3 ± 0.3
Types of Surgeries Performed (n, %)	
Complex	35 (48.6%)
LVAD and OHT [†]	14 (19.4%)
Valve	10 (13.9%)
Aorta	9 (12.5%)
CABG*	4 (5.6%)
Mortality Rate	17 (23.6%)
CPB time, (minutes), median [25th/75th percentile]	207 [154/242.25]
Cross clamp time (minutes), median [25th/75th percentile]	97.5 [69/126.5]
ESL (mL), mean ± SD	3041.6 ± 2249.2
24h chest tube drainage in CSICU, (mL), mean ± SD	853 ± 796
RBC transfused (units), mean ± SD	6.8 ± 4.1
FFP transfused (units), mean ± SD	7.6 ± 4.3
Platelets transfused (units), mean ± SD	9.1 ± 5.3
Cryoprecipitate transfused (units), mean ± SD	14.6 ± 12.0
Patients Co-administrated Factor VIIa	46 (63.9%)
Factor VIIa administered (mg), mean ± SD	4.1 ± 2.1
Octaplex (units), mean ± SD	61.9 ± 31.0

Table 1. Patient demographics, baseline characteristics and outcomes

*CABG = Coronary Artery Bypass Graft surgery; † LVAD = Left Ventricular Assist Device; OHT = Orthotopic Heart Transplantation; ‡ Complex = Redo sternotomy, CABG and valve, multiple valve, aortic root surgery; Other Abbreviations: BSA = Body Surface Area; CPB = Cardiac Pulmonary Bypass; CSICU = Cardiac Surgery Intensive Care Unit; ESL = Estimated blood loss; FFP = Fresh Frozen Plasma; RBC = Red Blood Cells

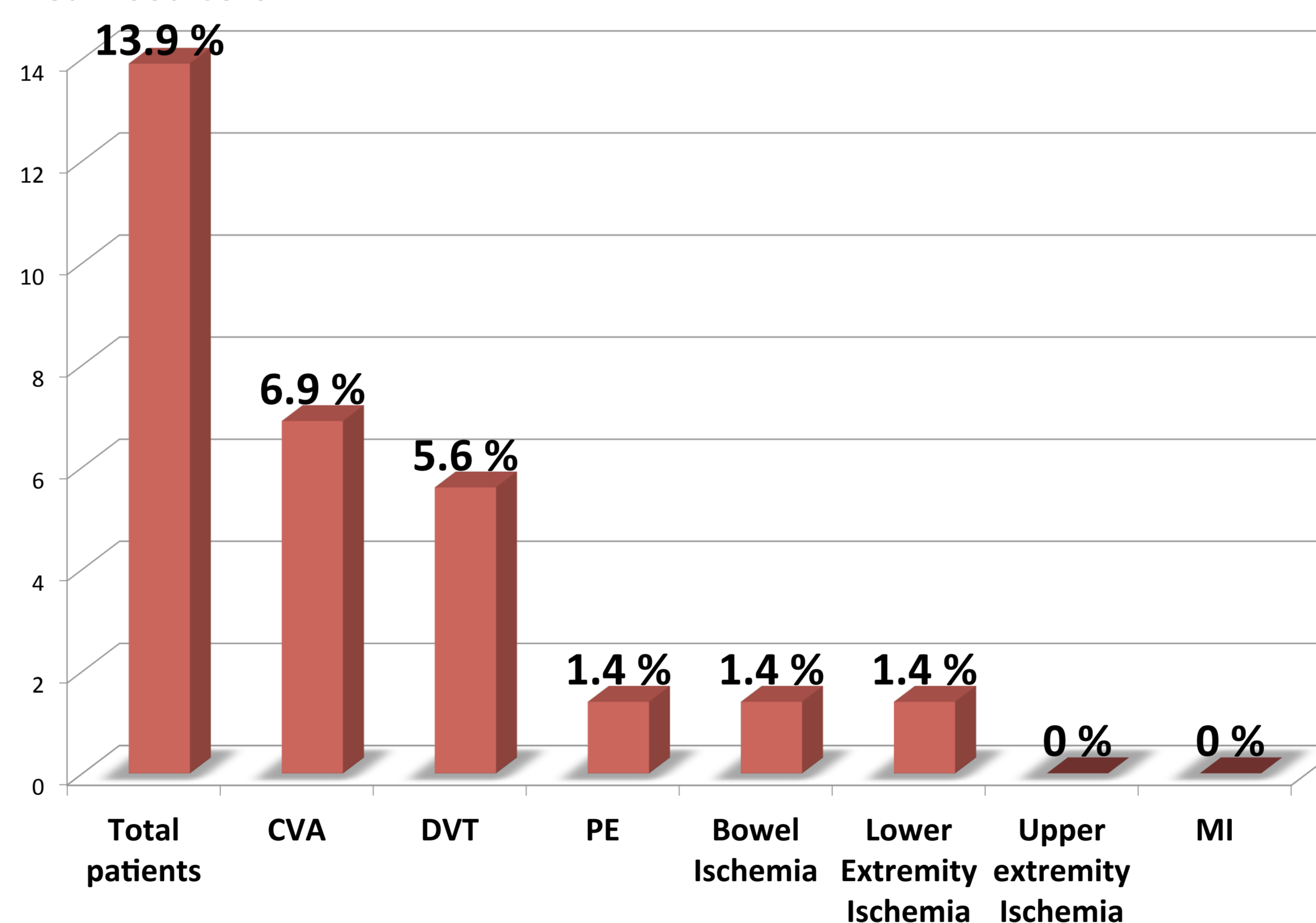


Figure 2. Thrombotic complication encountered by patients. 10 patients on the 72 patients receiving Octaplex during surgery reported to have encountered a complication. From those 10 patients, 12 thrombotic complications were distributed as following among those patients: 5 CVA (6.9%), 4 DVT (5.6%), 1 PE (1.4%), 1 Bowel Ischemia (1.4%) and 1 Lower Extremity Ischemia (1.4%). Abbreviations: CVA = Cerebrovascular accident; DVT = Deep vein thrombosis; MI = Myocardial Infarction; PE = Pulmonary Embolism

Discussion

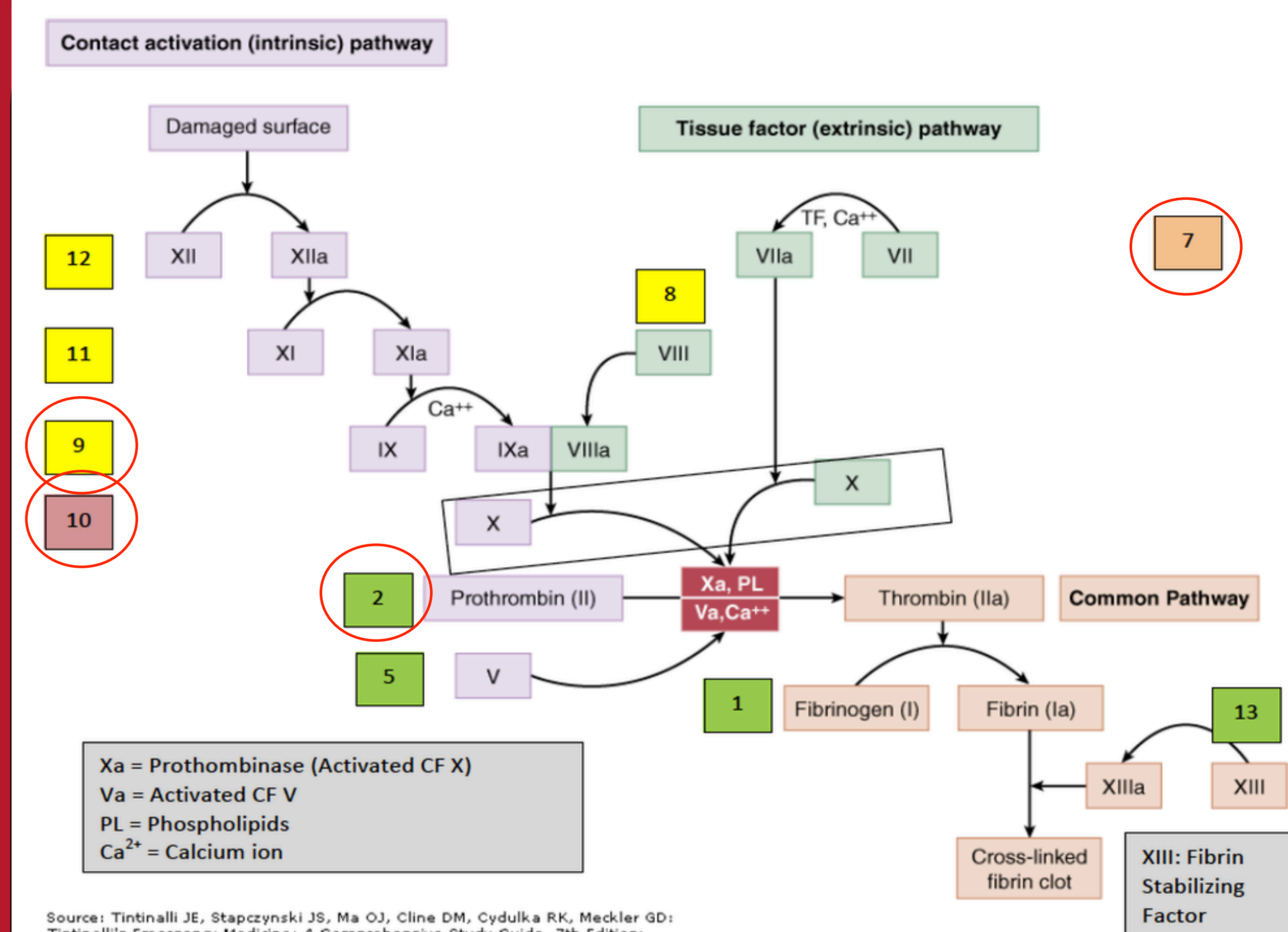


Figure 3. (5) The Coagulation Cascade in a normal bleeding state
1) Octaplex in the coagulation cascade:

Octaplex is a four factor Prothrombin complex concentrate (PCC) containing blood clotting factors II, VII, IX and X, as well as protein C and S. By providing those key elements in high concentrations and low volumes, PCCs create an ideal environment for the 'thrombin burst' that accelerates the creation of a stable fibrin clot to stop the bleeding.

2) Thrombotic complications associated with Octaplex:

On the 72 patients of this study, 10 patients (13.9%) encountered a thrombotic complication during or after their surgery. This is significantly higher than other published retrospective audits in cardiac surgery patients(6,7). Of note, most early studies looked at 3 factor PCC and not the 4 factor PCCs currently available in Canada. Moreover, 4 reported incidents of CVA (Cerebrovascular accident) were most likely due to surgical factors rather than thrombotic events and 1 DVT was secondary to an indwelling catheter and less likely due to the use of PCCs. This would reduce the incidence to 6.9% which is still much higher than previously reported. This may be in part to the high rate of co-administration of Factor VIIa in our patients (63.9%) or to the severity of illness of patients who received PCCs as a salvage therapy when all other had failed. Further retrospective cohort or matched control studies are required to determine if PCC administration or other potential confounders are responsible for the high incidence of thrombotic complications reported in this review.

Conclusion

Thrombotic events occurred in 10 of 72 patients (13.9%) receiving PCCs for the management of refractory bleeding after cardiac surgery. Further studies are required to determine if the co-administration of Factor VIIa or other confounders are responsible for the abnormally high rate of thrombotic events observed.

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