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## 322.DISORDERS OF COAGULATION OR FIBRINOLYSIS: CLINICAL AND EPIDEMIOLOGICAL

# Randomized, Active-Control Phase 3 Study of Four-Factor Prothrombin Complex Concentrate Versus Frozen Plasma in Bleeding Adult Cardiac Surgery Patients

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**Background and Significance:** Patients following cardiac surgery often develop coagulopathic bleeding and associated poor outcomes. The development of coagulopathy is multifactorial, including anticoagulation, hemorrhage, hemodilution and consumptive losses after tissue injury and during cardiopulmonary bypass (CPB). Reduced thrombin generation due to coagulation factor deficiency is an important contributor to post-CPB bleeding. Prothrombin complex concentrate (PCC; off-label) and frozen plasma (FP) are administered for coagulation factor replacement during surgery. The LEX-211 (FARES-II) study will determine if four-factor PCC (4F-PCC, Octaplex, Octapharma) is clinically non-inferior to FP regarding hemostatic effectiveness in cardiac surgery patients requiring coagulation factor replacement.

**Study Design and Methods:** LEX-211 (FARES-II; NCT05523297) is a multicenter, randomized, active-control, prospective, Phase 3 trial that is being conducted at 13 hospitals in Canada and the United States. The study is being conducted in accordance with the Declaration of Helsinki. The study includes patients ≥18 years old undergoing cardiac surgery with CPB who require coagulation factor replacement due to bleeding and known (e.g., as indicated by international normalized ratio) or suspected coagulation factor deficiency. Exclusion criteria include heart transplant, insertion/removal of ventricular assist devices, high probability of death within 24 hours, severe right heart failure, heparin contraindications, thromboembolic events within the prior 3 months, and IgA deficiency. Patients will be randomized to 4F-PCC or FP when the blood bank receives the first order for coagulation factor replacement (Figure 1). For 4F-PCC dosing, patients weighing ≤60 kg will receive 1,500 international units (IU), and those >60 kg will receive 2000 IU. For FP, patients weighing ≤60 kg will receive 3 U and patients weighing >60 kg will receive 4 U. Patients are treated according to their assigned group until a maximum of 2 doses of 4F-PCC/FP have been administered during the treatment period (24 hours after initiation). If additional treatment is required, patients in both groups receive FP. The primary endpoint is the hemostatic response to 4F-PCC vs. FP, rated 'effective' if no further hemostatic intervention (systemic hemostatic agents, i.e., platelets, cryoprecipitate, other coagulation factor products, or a second dose of study drug, or surgical re-opening for bleeding) is required within 60 minutes to 24 hours after initiation of the first dose. Secondary and safety endpoints, with their timings, are described in Table 1. An unblinded interim analysis (100 evaluable patients/group) will test sample size assumptions and enable re-estimation if necessary. Depending upon the interim results, and accounting for dropouts (20% anticipated), the total sample size will range between 513-1,250 patients. The non-inferiority of the primary endpoint of 'haemostatic response' will be tested for 4F-PCC vs. FP using a Farrington-Manning score test with a non-inferiority margin of 0.10 at a one-sided significance level alpha of 2.5%. If non-inferiority is demonstrated, the superiority of 4F-PCC with regard to the primary endpoint will be investigated.

LEX-211 (FARES-II) is in progress, with the first study site initiated in Q4 2022. Currently, >150 patients have been included in the study. Completion is expected in Q4 2024. The results of this study will inform clinical practice for bleeding cardiac surgery patients requiring coagulation factor replacement, potentially reducing allogeneic blood product usage and improving patient outcomes.

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**OffLabel Disclosure:** Octaplex is a four-factor freeze-dried human prothrombin complex concentrate (4F-PCC) that is administered intravenously. The Octaplex clinical development program has established the efficacy and safety of Octaplex for treatment of congenital coagulation factor deficiencies and vitamin K antagonist reversal (currently labelled indications). This study explores the use of Octaplex in cardiac surgery.

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Figure 1.
Study flow

* OR personnel will remain blinded to treatment until treatment decision. Patients will be blinded to treatment allocation

† A second dose of 4F-PCC or plasma can be given if the patient continues to have at least a grade 2 bleeding and INR ≥1.5 after the first dose. For subsequent doses, the patient will receive plasma

** Plasma in 1 U increment as per the ordering physician

4F-PCC, 4-factor prothrombin complex concentrate; BW, body weight; IU, international units; OR, operating room; U, units

**Table 1. Study endpoints**

| Endpoint | Variable to be compared between groups | Timing |
|---|---|---|
| **Primary endpoint** | Hemostatic treatment response, defined as 'effective' if no additional hemostatic intervention is required, e.g., administration of systemic hemostatic agents or surgical intervention | 60 min – 24 h after initiation of the first dose of IMP |
| **Secondary endpoints: efficacy parameters** | Global hemostatic response, based on requirement for additional hemostatic intervention (as above) and hemoglobin levels | 60 min – 24 h after initiation of the first dose of IMP |
| | Total chest tube drainage | 12 and 24 h after chest closure |
| | Incidence of severe to massive bleeding using a modification of the UDPB in cardiac surgery | First 24 h after the start of surgery, after the end of CPB, and after IMP initiation |
| | Mean number of total allogeneic blood components administered | First 24 h after the end of CPB |
| | Mean number of total non-IMP allogeneic blood components administered | First 24 h after the end of CPB, and the first 24 h and 7 days after IMP initiation |
| | Mean number and incidence of transfusion of individual allogeneic blood components and incidence of administration of non-IMP coagulation factor products | First 24 h and 7 days after the start of surgery, after the end of CPB, and after IMP initiation |
| | Incidence of ICH, GI hemorrhage, and surgical re-exploration | First 24 h after the start of surgery, after the end of CPB, and after IMP initiation |
| | Change in INR | Within 30 min before to within 60 min after IMP initiation |
| | Changes in coagulation parameters | Within 75 min before to within 75 min after IMP initiation |
| | Time elapsed from initiation of first IMP dose to leaving the operating room | (To be measured) |
| **Secondary endpoints: safety parameters** | • Incidence of serious treatment-emergent adverse events<br>• Duration of mechanical ventilation<br>• Duration of ICU stay<br>• Duration of hospitalization<br>• Incidence of death<br>• Number of days alive and out of hospital | From the beginning of surgery up to postoperative Day 30 |

CPB, cardiopulmonary bypass; HFC, human fibrinogen concentrate; FVIII, factor VIII; GI, gastrointestinal; ICH, intracerebral hemorrhage; ICU, intensive care unit; IMP, investigational medicinal product; VWF, von Willebrand factor; UDPB, universal definition of perioperative bleeding

**Figure 1**