Applying CIRS-BRAT Framework in a Regulatory Setting: Updated Benefit-Risk Assessment for Fibrinogen Concentrate in the Setting of Complex Cardiac Surgery

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DISCLOSURE

This assessment was funded by CSL Behring through a contract with RTI Health Solutions (RTI HS). AG is a salaried employee of RTI HS, an independent nonprofit research organization that does work for government agencies and pharmaceutical companies. AB is a salaried employee of CSL Behring. SC is a former employee of CSL Behring and contributed to the abstract but was not available to review the poster content.

BACKGROUND

- Fibrinogen concentrate (human) (FCH) has been successfully used in perioperative bleeding in complex cardiac surgery (CCS), as reported in several single-center, single-arm and randomized trials; however, a global, multicenter randomized clinical trial (REPLACE BI3023-3002)[1] did not show efficacy superiority over placebo, while the safety endpoints were favorable to FCH.
- As part of the 2015 periodic safety update report (PSUR) submitted to the European Medicines Agency (EMA), the sponsor conducted a benefit-risk assessment (BRA) using the Centre for Innovation in Regulatory Science (CIRS) Benefit-Risk Action Team (BRAT) (CIRS-BRAT) framework to evaluate the evidence for the use of FCH in cardiac surgery.[2]
- The EMA agreed that the benefit-risk profile was favorable at that time and requested an update of the BRA for the 2018 PSUR.

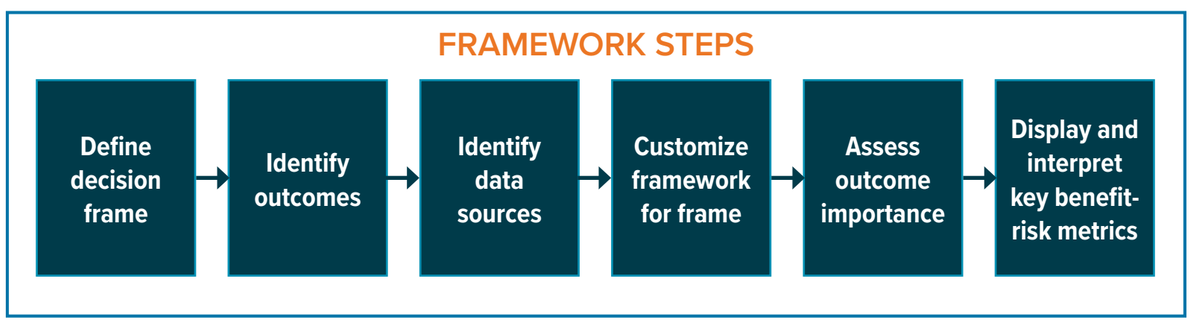
OBJECTIVE

To update the benefit-risk profile of FCH in the clinical setting of CCS, taking into account all published evidence and completed clinical trials as of April 2018.

METHODS

- The CIRS-BRAT framework was followed to update the benefit-risk profile of FCH in the clinical setting of CCS.
- An updated systematic literature review was conducted to identify new randomized and observational studies published since the original BRA.
- Forest plots were generated to display rate differences for each benefit and risk outcome where rate difference was defined as the difference in the proportion of patients with outcome in the FCH group compared with the proportion of patients in the placebo or standard of care group by:
  - Each benefit and risk outcome
  - Each study
  - Crude pooled analyses of placebo-controlled clinical trials

Figure 1. CIRS-BRAT Framework Steps



RESULTS

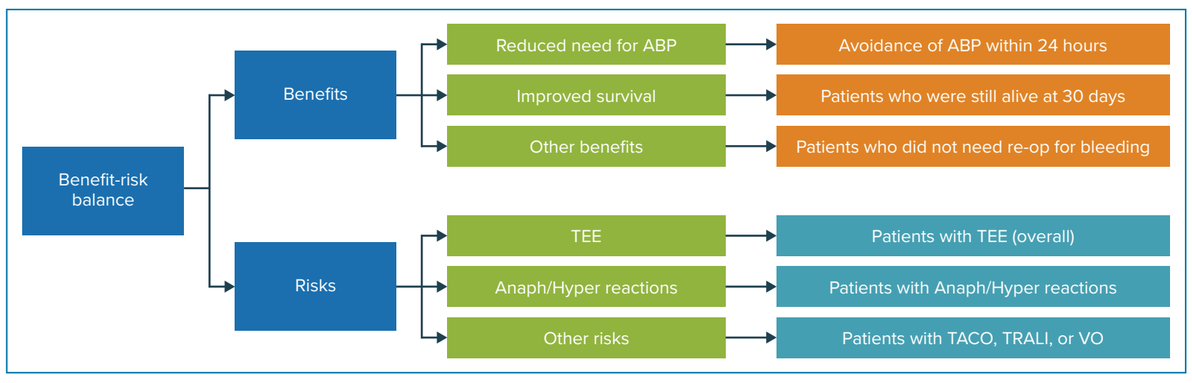
- The original BRA included 6 studies, and the updated literature search identified 1 new randomized clinical trial[3] and 1 new observational study[4] that met criteria included in the decision frame (Table 1).

Table 1. Decision Frame

Objective	To describe and compare the benefits and risks of FCH Human used during CCS
Indication	Fibrinogen concentrate as a hemostatic therapy within the management of bleeding in the setting of CCS
Drug	FCH
Formulation and dosage(s)	Dosing as reported in clinical studies or clinical use
Comparative treatment alternative	Placebo OR standard of care (e.g., allogeneic blood products)
Population	Patients (all ages) undergoing CCS
Populations not studied	Patients excluded from clinical trials (e.g., pregnant women, emergency surgery, surgery for infection, recent thrombosis, re-operation of same anatomic site, coagulation disorder, use of anticoagulants, sensitivity to study drug(s))
Time horizon for outcomes	Hemostatic efficacy: up to 24 hours after surgery Blood loss: at 24 hours after surgery Mortality: 30 days after dosing of FCH Re-operation: until hospital discharge Other safety: up to 45 days after surgery
Stakeholder perspective	Reference point: CSL Behring

- Benefits and risks included in the original and updated BRA assessment are displayed in the value tree shown in Figure 2. There was only one single event in one study with "other risks," so it was excluded from the visual displays.
- Results from each study by outcome are shown in Figures 3-7. Evaluated benefits (Figures 3-5) favored FCH in most studies, and the point estimates were similar in the FCH and comparator groups for the risk outcomes (Figures 6-7).
- The crude pooled analysis of rate differences for the 4 randomized clinical trials is shown in Figure 8.

Figure 2. Value Tree



ABP = allogeneic blood products; Anaph/Hyper reactions = anaphylactic and hypersensitivity reactions; TACO = transfusion associated circulatory overload; TEE = thromboembolic events; TRALI = transfusion-related lung injury; VO = volume overload.

Figure 3. Avoidance of ABP Transfusion Within 24 Hours

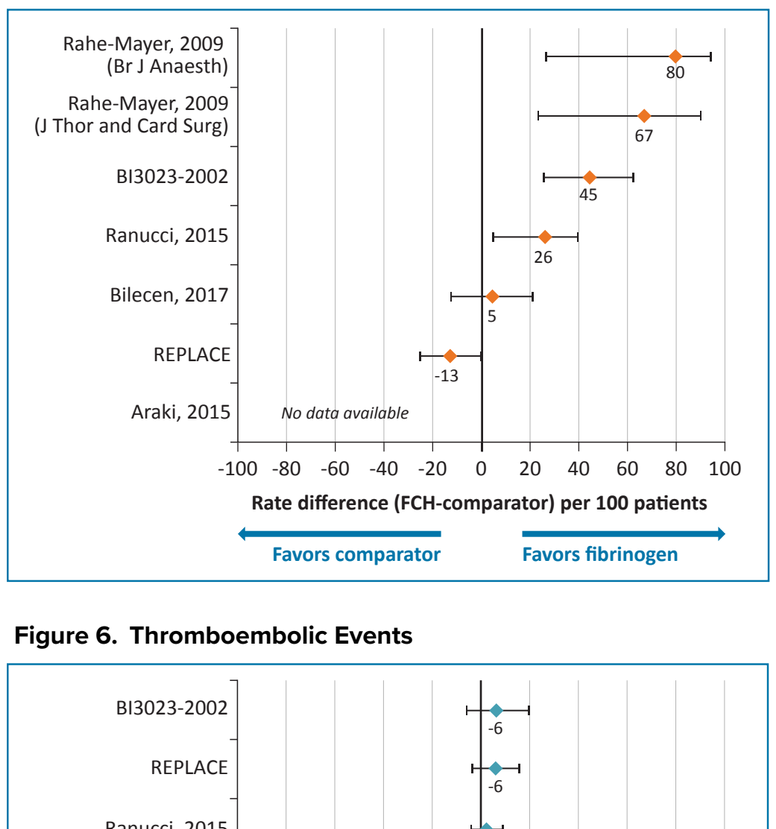


Figure 4. Survival at 30 Days

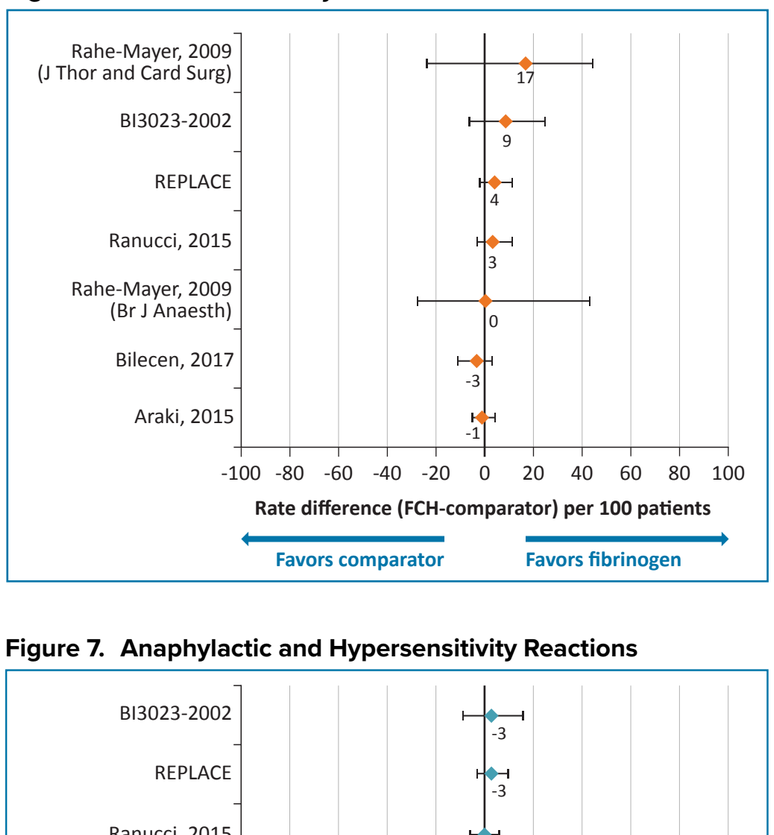


Figure 5. Avoidance of Re-operation Due to Bleeding

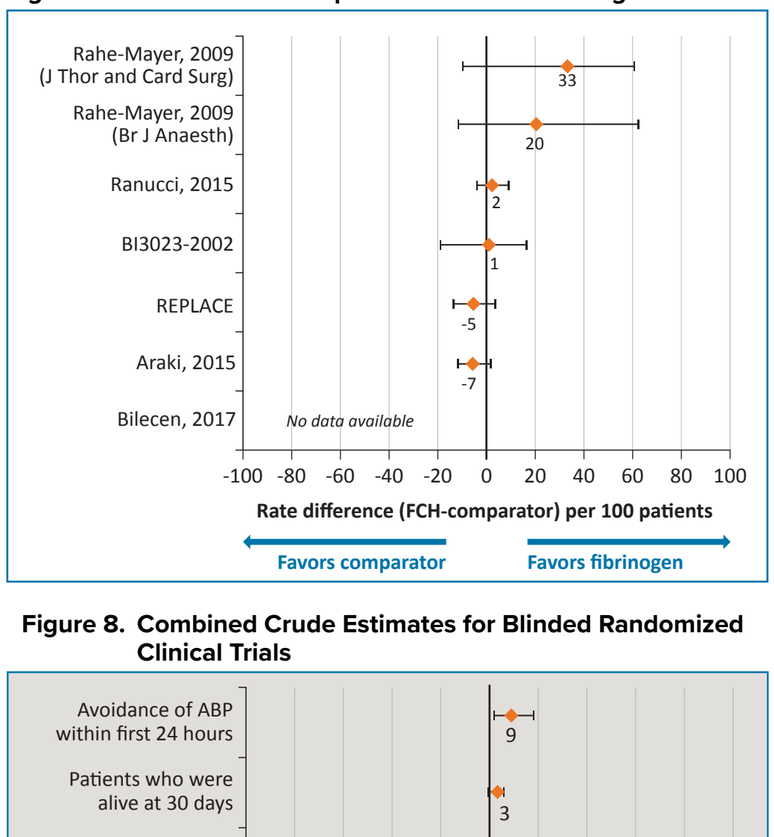


Figure 6. Thromboembolic Events

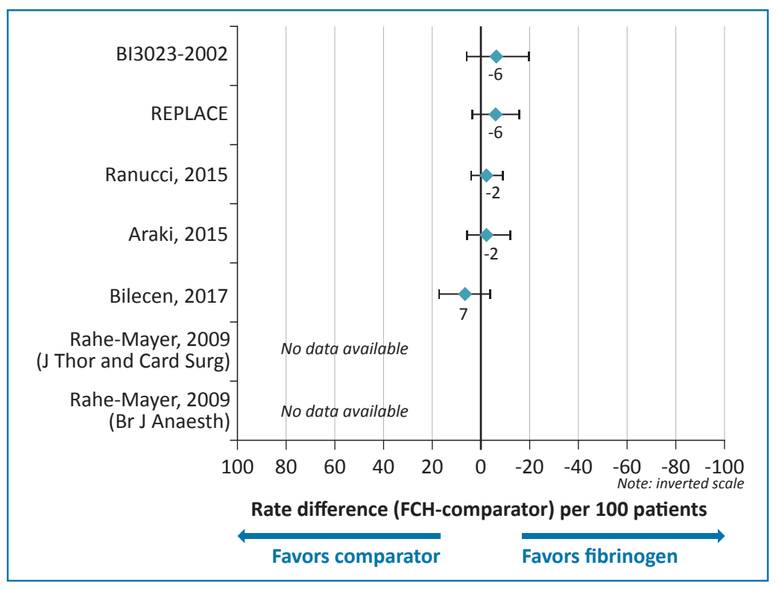


Figure 7. Anaphylactic and Hypersensitivity Reactions

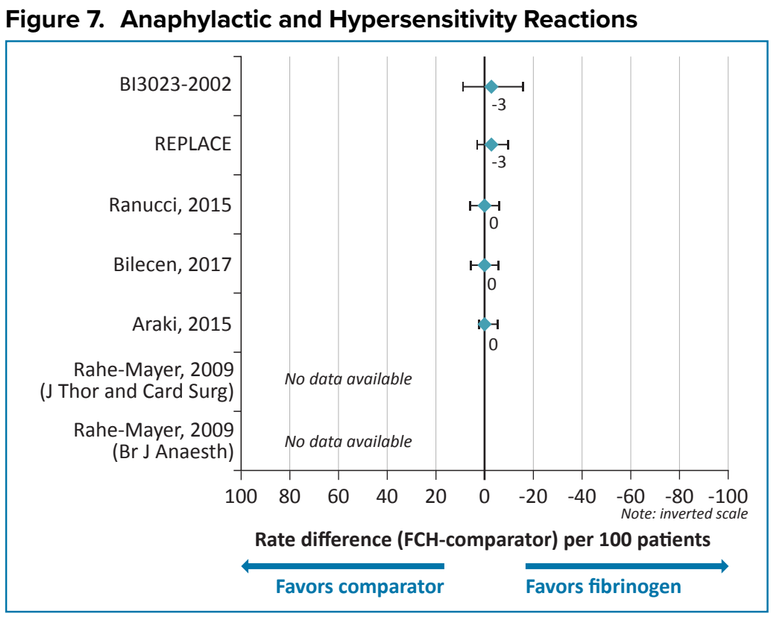
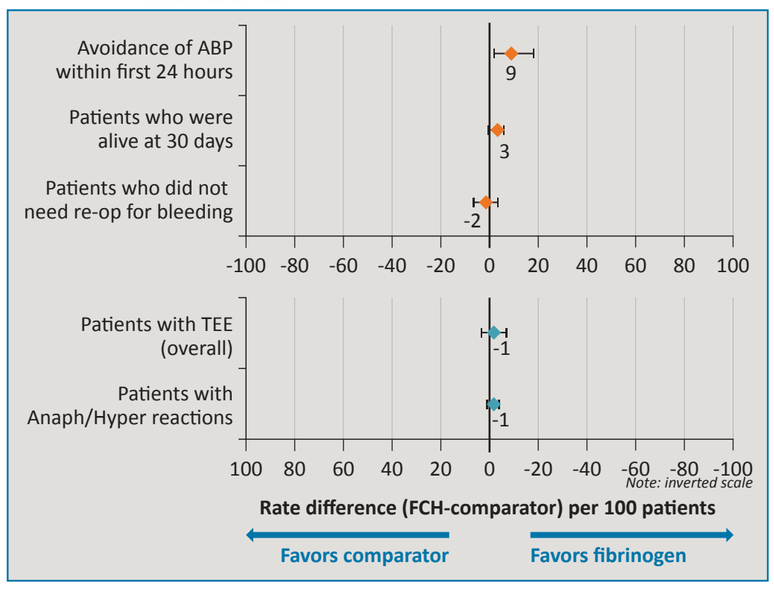


Figure 8. Combined Crude Estimates for Blinded Randomized Clinical Trials



CONCLUSIONS

- Effective hemostasis is critical in patients undergoing CCS, and although transfusion safety has significantly improved, ABP transfusions are not devoid of risk. Therefore, reducing the number of patients needing ABP or the amount of ABP transfused is an important and commonly accepted clinical goal.
- This updated structured BRA shows a consistent trend for numerical reduction in ABP transfusions, as well as a numerical improvement in 30-day survival for patients treated with FCH compared with patients not treated with FCH.
- In addition, in most studies, none of the clinically meaningful risks assessed were found to be greater for patients treated with FCH; therefore, the benefit-risk profile of FCH in the setting of CCS is considered to be favorable.

REFERENCES

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