Factor Concentrates

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Factor Concentrates & Cardiac Surgery

The Problem

Cardiac Surgery:
- CPB \(\rightarrow\) bleeding \(\rightarrow\) morbidity/death
- Treat bleeding with transfusions
- Transfusions \(\rightarrow\) morbidity/death

The Proposal

Factor Concentrates:
- Reduce bleeding & transfusions

Factor Concentrates

Advantages
- Avoid many transfusion-related complications
- Small volume
- No blood bank
- Easy, fast administration

Disadvantages
- Thromboembolic events
- Other risks?
- Off-label indication (USA)
- Insufficient data (indications, dose, timing, etc)
Overview

Open-heart surgery literature (last 6 years)

- Laboratory investigations
- Clinical studies
Factor Concentrates & ex-vivo Tests

- **PLATELET ACTIVATION**
  - FVa, FVIIIa, FXa, FXIa, thrombin

- **THROMBIN BURST**
  - TF-FVIIa, FXa, FIXa, thrombin

- **X-LINKED FIBRIN CLOT**
  - Fibrinogen, Fibrin, FXIIIa, FXIa, TAFI, Lysis

Tests:

- **Platelet aggregation tests**
  - Platelets

- **Thrombin generation curve**
  - Platelets

- **Viscoelastic tests**
  - Platelets

Additives:

- rFVIIa, 3F-PCC, 4F-PCC, FEIBA
- FC, FXIII
Surgery
TF-FVIIa
FXa
FIXa
thrombin

PLATELET ACTIVATION

FVα, FVIIIα
FXa

THROMBIN BURST

Fibrinogen
Fibrin
FXIIIa
TAFI
Lysis

Platelet aggregation & count during open-heart surgery

Platelet count
- Degree of hemodilution
- Duration of CPB

Platelet function
- Degree of hypothermia

Platelet function tests
- TEG / ROTEM insensitive platelet function tests
- Multiplate aggregation – useful?

(Ninivaggi 2014, Romlin 2014)
Thrombin generation curve
Ex-vivo test, platelet poor plasma

<table>
<thead>
<tr>
<th>Comment</th>
<th>Agent</th>
<th>Lag time</th>
<th>Peak</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lag time=primary effect</td>
<td>CPB</td>
<td>Prolonged</td>
<td>Smaller</td>
<td>Slower</td>
</tr>
<tr>
<td>No thrombin generation</td>
<td>Fibrinogen</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Aids thrombin generation</td>
<td>Platelets</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>No FII, FIX, FX</td>
<td>rFVIIa</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>FII supplementation</td>
<td>rFVIIa + FII</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Has FII, FIX, FX but no FVII</td>
<td>3F-PCC</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Has FII, FIX, FX &amp; FVII</td>
<td>4F-PCC</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Has FII, FIX, FX &amp; FVIIa</td>
<td>FEIBA</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

(Guzzetta 2014, Percy 2015, Guzzetta 2016, Andreasen 2016)
Surgery

TF-FVIIa
FXa
FIXa
thrombin

PLATELET ACTIVATION

FVIIIa
FXa
FXIa

THROMBIN BURST

Fibrinogen
Fibrin
FXIIia
TAFI
Lysis

X-LINKED FIBRIN CLOT

Stable fibrin clot FC, FXIII

<table>
<thead>
<tr>
<th>ROTEM</th>
<th>CT (s)</th>
<th>CFT (s)</th>
<th>MCF (mm)</th>
<th>FIBTEM (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-CPB</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

(Hakimi 2014)
Surgery

TF-FVIIla
FXa
FIXa
thrombin

PLATELET
ACTIVATION

FVa, FVIIIa
FXa,
FXIa

THROMBIN
BURST

Fibrinogen
Fibrin
FXIIIa
TAFI
Lysis

X-LINKED
FIBRIN
CLOT

Stable fibrin clot FC, FXIII

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<th>ROTEM</th>
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<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

(a)

(rotem)

CT Cloting time
CFT Clot formation time
alpha Alpha-angle
A10 Amplitude 10 min after CT
MCF Maximum clot firmness
LI30 Lysis index 30 min after CT
ML Maximum lysis

B

Δ CFT (s)

Baseline  Low dose  Medium dose  High dose

(Hakimi 2014)
Factor Concentrates & Cardiac Surgery

- Product description
- Indications for use
- Mechanisms of action
- Use in cardiac surgery
  - Efficacy as Rescue Strategy
  - Efficacy as Transfusion Reduction Strategy
- Safety
- Dose
- Summary of data
Factor Concentrates

- Activated Factor VII (rFVIIa)
- Fibrinogen Concentrate (FC)
- Prothrombin Complex Concentrates (PCC)
  - 3F-PCC
  - 4F-PCC
  - FEIBA
ComposiLon
• Synthetic product from hamster kidney cells

IndicaLons for use
• Hemophilia A and B patients with inhibitors against FVIII and FIX
• Congenital FVII deficiency

Mechanism of action
• Tissue Factor dependent: TF-aFVIIa complex ➔ thrombin burst
• Tissue Factor independent: Platelets-aFVIIa ➔ FXa ➔ thrombin burst

Cardiac surgery
• Off-label
• Guidelines (pediatric & adult): Rescue only

Recombinant Activated Factor Seven (rFVIIa)
**Pediatric Registries: Efficacy as Rescue strategy**

**Reduced bleeding & transfusions:**
- NZ/Aus off-label (388 children) 52% OHS (McQuilten 2012)
- SeveNBleeP off-label (137 children) 4% OHS. (Blatny, 2014)

**Adult Registries: Efficacy as Rescue strategy**

**Reduced bleeding & transfusions:**
- Canada; 4yr off-label (1378 total), 72% OHS (Karkouti 2014)
- NZ/Aus 10yr off-label (3446 total), 45% OHS (Zatta 2015)

**Poor response:**
- Non-surgical bleeding (Zatta, 2015)
- pH<7.1 – poor response (80% mortality) (Zatta, 2015)

**Special Rescue Indications (small n)**
- ECMO (child & adult)
- Lung transplant (adult)
- VAD (adult)

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**Pediatric cardiac surgery (n=202)**
94% responded to aFVIIa

- <1 yr: (p<0.001) RBC, FFP, platelet, cryo
- >1 yr: (p<0.001) RBC, platelet, cryo

12% mortality at 28 days

**Poor outcome (all patients)**
Low pH, non-surgical bleeding

**Product** | **Before rFVIIa** | **Up to 24 hr after rFVIIa** | **P value**
---|---|---|---
Red blood cells | 7 [4-11] | 2 [1-5] | < 0.0001
Platelets | 10 [10-15] | 5 [0-10] | < 0.0001
Plasma | 8 [5-11] | 2 [0-4] | < 0.0001

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**Cardiac Surgery**

Response  | Mortality
--- | ---
0 | 0
10 | 10
20 | 20
30 | 30
40 | 40
50 | 50
60 | 60
70 | 70
80 | 80
90 | 90
100 | 100
Safety of Rescue strategy:

Registries:
- Adverse events related to bleeding severity
  - Thrombotic (17%), Non-thrombotic (37%), Mortality (34%)
- Adverse events (adult/child) unrelated to rFVIIa dose
- Adult OHS: thrombosis 12%, majority arterial
- Pediatric OHS: thrombosis 5%, majority arterial. Higher rate if ECMO

Single Center retrospective studies:
- **rFVIIa v. FEIBA** (Rao 2014)
  - No difference in safety outcomes
  - Adverse events unrelated to rFVIIa dose
- **rFVIIa v. matched control** (Alfirevic 2014)
  - FVIIa > control for: mortality - OR 2.82; renal morbidity - OR 2.07
  - Adverse events unrelated to rFVIIa dose  (FVIIa=144; control=359)

**Conclusion** (Karkouti):
- Rescue rFVIIa reasonable. Survival – responders (80%) v. non-responders (38%)
Efficacy as Transfusion Reduction strategy

Very little evidence.

- **Pediatric cardiac surgery** (Winch 2013)
  - Retrospective (n=9), age <16 months, 90 mcg/kg FVIIa
  - 3 patients received FVIIa as 1st line therapy – no blood products used

Doses used for Rescue

- **Adult**: Median dose 47-91 mcg/kg
- **Pediatric**: Median dose 90-120 mcg/kg
- Younger children received higher doses
  
  (McQuilten 2012)
Summary

• Rescue:
  - Good response if cardiac surgery
  - Expect thrombosis, mainly arterial
  - May require higher dose for infants

• 1st line Rx:
  - Minimal data to support this use
Fibrinogen Concentrate (FC)

**Composition**
- From pooled human plasma – powder
- Pasteurized – viral inactivation, less immunogenic risk
- Dose response: adult=child; Half-life: adult (77hr), child less

**Indications for use**
- Bleeding from congenital fibrinogen deficiency

**Mechanism of action**
- Critical for clot formation, amplification, and strength
- Substrate for thrombin, plasmin, FXIIIa. Binds with platelets

**Cardiac surgery**
- Off-label (USA)
- Guidelines (pediatric & adult): Nil
Fibrinogen Concentrate

Efficacy as Rescue strategy for cardiac surgery

Fibrinogen is key substrate for clot formation & the 1st coagulation factor to fall to critical levels during hemodilution & blood loss

Pediatric studies:
- Post-CPB fibrinogen predict blood loss
  - Plasma <150 mg/dL (Faraoni 2014)
  - ROTEM: EXTEM A10, FIBTEM A10 (Nakayama 2015)

Adult studies:
- Preoperative fibrinogen <300 mg/dL predict transfusion after CABG. (Karlsson 2008)
- Fibrinogen <220 mg/dL on arrival ICU predicts bleeding (Kindo 2014)

Conclusion
- Hemodilution & bleeding quickly reduce fibrinogen to levels that compromise clot formation & strength. FC is standard Rescue Rx in Europe (no cryo)
Efficacy as Transfusion Reduction strategy for cardiac surgery

Pediatric studies:

- **FC** (60 mg/kg) v. **Cryoprecipitate** (10 mL/kg) (Galas 2014)
  - RCT, enrolled if post-CPB bleeding & fibrinogen <100 mg/dL
  - N=63. Median age: 3.5 months

  FC equivalent to Cryo – similar fibrinogen level, blood loss, transfusions

- **Comment** (Faraoni 2015)
  43% patients received additional cryoprecipitate
  – perhaps trigger to treat (100 mg/dL) was too low

![Graph showing fibrinogen concentration over time](image)
Fibrinogen Concentrate

Efficacy as Transfusion Reduction strategy for cardiac surgery

Adult studies:

• **FC v. saline:** Blinded RCT (Rahe-Meyer 2012)
  
  FC = 1\textsuperscript{st} line Rx, dose targeted to FIBTEM 22mm

<table>
<thead>
<tr>
<th></th>
<th>FC</th>
<th>Placebo</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Median units transfused</td>
<td>2</td>
<td>13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients transfused</td>
<td>45%</td>
<td>100%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrinogen at end of surgery</td>
<td>260</td>
<td>189</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

  *Perhaps useful to keep fibrinogen levels >200 mg/dL*

• **FC v. saline:** Blinded RCT (Ranucci 2015)
  
  FC = 1\textsuperscript{st} line Rx
  2\textsuperscript{nd} line Rx: - FC group given 4F-PPC
  - Control group given saline

  *Factor concentrates reduced transfusions*
Efficacy as Transfusion Reduction strategy for cardiac surgery

Adult studies:

• **FC v. Platelets:**

  - Open-label RCT, FC = 1\textsuperscript{st} line Rx. (Tanaka 2014)
  - FC 4g (50mg/kg) v. 1 unit apheresis platelets

<table>
<thead>
<tr>
<th></th>
<th>FC group</th>
<th>Platelet group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>209</td>
<td>165</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>101</td>
<td>133</td>
<td></td>
</tr>
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</table>

**Fibrinogen concentrate:**
- Less platelet transfusions
- Less donor exposure
- Similar blood loss

<table>
<thead>
<tr>
<th></th>
<th>FC group</th>
<th>Platelet group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRBC</td>
<td>9/10</td>
<td>9/10</td>
<td>1.0</td>
</tr>
<tr>
<td>Platelets</td>
<td>4/10</td>
<td>10/10</td>
<td>0.01</td>
</tr>
<tr>
<td>FFP</td>
<td>3/10</td>
<td>5/10</td>
<td>0.65</td>
</tr>
<tr>
<td>Cryo</td>
<td>3/10</td>
<td>4/10</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Safety

Postmarketing pharmacovigilance (27 years) (Solomon 2015):
• Hypersensitivity reactions: 1 per 32,600 doses
• Thromboembolic events: 1 per 23,300 doses
• No viral transmission proven

Fibrinogen Concentrate v. Control (Fassl 2015)
• Propensity matched (n=190 per group)
• No association with mortality, thromboembolic or cardiac events within 1yr.

Dose
• Pediatric = Adult
• Dose range: 25 – 100 mg/kg
• Dose (g) = desired increase in fibrinogen level (g/L) x plasma volume (L)
• Alternative dosing targets are FIBTEM MCF (ROTEM) or FF (TEG)
Summary

Rescue Rx:

- Standard in Europe – cryo not available

1st Line Rx:

- Efficacy equivalent to cryo.
- Efficacy > placebo.
- Efficacy > platelets.
- Efficacy FC + PCCs > blood product algorithm.

Efficacy: may depend on:

- Timing (early post-CPB perhaps better).
- Target level (>200 mg/dL perhaps better).

Safety: Encouraging profile.

Guidelines: European vary. (No USA guidelines).
Prothrombin Complex Concentrates (PCCs)

Composition
- Lyophilized, from human plasma – Vit K-dependent factors (Tanaka 2014)
- Viral inactivation
- Small volume
- Each PCC different
  - Composition
  - Function

<table>
<thead>
<tr>
<th>PCC</th>
<th>FII</th>
<th>FVII</th>
<th>FIX</th>
<th>FX</th>
<th>PS</th>
<th>PC</th>
<th>Heparin</th>
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</thead>
<tbody>
<tr>
<td>3F (Bebulin)</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>4F (Kcentra)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4Fa (FEIBA)</td>
<td>+</td>
<td>FVIIa</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Indications for use (USA)
- 4F-PCC: Urgent reversal of vitamin K antagonist therapy
- FEIBA: Factor VIII bypassing therapy in hemophilia patients with inhibitors
- (Europe: Rx & prophylaxis of bleeding from acquired factor deficiencies)

Mechanism of action
- PCCs increase thrombin generation potential
- Promote prothrombinase (FXa-FVa) complex, → thrombin burst →:
  - Activate platelets
  - Cleave fibrinogen into fibrin to form a stable clot
  - Positive feedback to FXa
  - Activates FXIII & TAFI to stabilize fibrin clot
**PCCs for reversal of Vitamin K antagonists**

**4F-PCCs** (Kinard 2014)

- 4F-PCC is superior to FFP for INR correction
- Non-inferior to FFP for hemostatic efficacy and safety
- Small volume, prompt action – requirements for emergency surgery
- Low risk of thromboembolic complications (<1%)
- Also need Vit K iv to sustain hemostatic levels of vitamin K-dependent factors
- 3F-PCCs lack FVII & are inferior to 4F-PCCs

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>INR 4.5–10 with no bleeding</td>
<td>INR &gt;5–8 with no bleeding</td>
<td>Hold VKA dose(s)</td>
</tr>
<tr>
<td>INR &gt;10 with no bleeding</td>
<td>INR &gt;8 with no bleeding</td>
<td>Give oral vitamin K</td>
</tr>
<tr>
<td>Any major bleeding</td>
<td>Any bleeding irrespective of INR</td>
<td>4F-PCC‡ and intravenous vitamin K§</td>
</tr>
<tr>
<td>INR &gt;5.0 but &lt;9.0†</td>
<td>Surgery that can be delayed 6–12 h</td>
<td>Intravenous vitamin K</td>
</tr>
<tr>
<td></td>
<td>Urgent surgery that cannot be delayed</td>
<td>4F-PCC‡ and intravenous vitamin K§</td>
</tr>
</tbody>
</table>
Drugs (NOACs)

• **Direct thrombin inhibitors:** Dabigatran etexilate (Pradaxa)

• **Direct FXa inhibitors:** Rivaroxaban (Xarelto), apixaban (Eliquis)

**Reversal**

• Specific reversal agents/antidotes are currently lacking

• If bleeding & urgent surgery, standard therapy should include:
  
  - 4F-PCC: 25 to 50 U/kg, or
  - FEIBA: 30/50 U/kg

  (Faraoni 2015)
Efficacy as Rescue strategy for cardiac surgery

Pediatric
- Zero

Adult
- **FEIBA v. rFVIIa: retrospective**, *(FEIBA:rFVIIA n=107:61)* (Rao 2014)
  - Platelet transfusions: rFVIIa (3.1 units) > FEIBA (1.7 units) *(p<0.001)*
  - Other blood product requirements were similar

- **3F-PCC v. rFVIIa: retrospective matched**, *(3F-PCC:rFVIIA n=50:100)* (Tanaka 2013)
  - PCC group bled less, received fewer transfusions & costs were less

<table>
<thead>
<tr>
<th></th>
<th>Incidence of transfusion (%)</th>
<th>Total units</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3F-PCC</td>
<td>rFVIIa</td>
</tr>
<tr>
<td>RBCs</td>
<td>94</td>
<td>99</td>
</tr>
<tr>
<td>Platelets</td>
<td>88 *</td>
<td>100</td>
</tr>
<tr>
<td>FFP</td>
<td>78 *</td>
<td>100</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>94</td>
<td>100</td>
</tr>
</tbody>
</table>

- **3F-PCC** (Bruce 2008); **FEIBA** (Song 2014). Efficacy in small retrospective series
Efficacy as Transfusion Reduction strategy for cardiac surgery

**Pediatric**

- **4F-PCC v. Matched control** (n=14/11): prospective (Giorni 2013)
  Infants. 4F-PCC (Kcentra) 30 min post-CPB
  4F-PCC: ICU – bled less, fewer received RBCs. Similar total donor exposure

**Adult**

- **4F-PPC + FC**: retrospective (n=3865) (Gorlinger 2011)
  Transfusion algorithm (guided by POC tests):
  - 1st line Rx: Fibrinogen concentrate, 4F-PCC
  - 2nd line Rx: FFP, Platelets
  - 3rd line Rx: rFVIIa, FXIII
  4F-PCC+FC: less transfusion, less thrombosis

![Graph showing transfusion reduction](image)
Prothrombin Complex Concentrates (PCCs)

Efficacy as Transfusion Reduction strategy for cardiac surgery

Adult

• 4F-PPC v. FFP: retrospective (Ortmann 2015)
  Pulmonary endarterectomy surgery. PCC=55, FFP=45, Both=8
  PCC group bled less but no difference in transfusions & patient outcomes (adjusted)

Conclusion:
“PCC may be an alternative to FFP”

• Editorial (Welsby 2015)
  PCCs may present an alternative to FFP in some patients with bleeding after complex cardiac surgery
  Require prospective studies
Prothrombin Complex Concentrates (PCCs)

**Dosing**

**3F-PCCs & 4F-PCCs**
- Prothrombin (FII) levels fall >50% after CPB
- Critical FII level is 25-30%
- 1 unit of PCC/kg increases factor levels by 1%
- Reported doses range 20–40 units/kg PCC

**FEIBA**
- Reported doses range 19-25 units/kg
- Stanford practice: 10 units/kg increments x3 (max)
Prothrombin Complex Concentrates (PCCs)

**Safety**

*Concern* (Grottke 2015)

- PCCs increase thrombin potential for 3-4 days
- FII excess ➔ prothrombotic state
- Safety data from Vit K antagonist reversal studies – hemostatic profile during cardiac surgery is different

**Recommendations for use** (Grottke 2015)

- Restore fibrinogen levels first
- Monitor thrombin generation via EXTEM CT (ROTEM) or R time (TEG) (However, relatively insensitive test)
- Start with low PCC doses
- Monitor closely, particularly if patient has risk factors for thrombosis

<table>
<thead>
<tr>
<th>Protein</th>
<th>Half-life (h)</th>
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<tbody>
<tr>
<td>FII</td>
<td>42-72</td>
</tr>
<tr>
<td>FVII</td>
<td>4-6</td>
</tr>
<tr>
<td>FIX</td>
<td>21-30</td>
</tr>
<tr>
<td>FX</td>
<td>27-48</td>
</tr>
<tr>
<td>Proten C</td>
<td>3</td>
</tr>
<tr>
<td>Protein S</td>
<td>60</td>
</tr>
</tbody>
</table>
Prothrombin Complex Concentrates (PCCs)

Summary

Rescue:

• Better efficacy, similar safety v. rFVIIa
• Expect thrombosis

1st Line Rx:

• Reduced donor exposure
• Efficacy best if algorithm uses FC + PCC
• Safety: unclear – caution advised
Drugs, pH >7.2, Temp >35°C, Antifibrinolytics

Hemostasis Management

Rescue

#1

FC

Cryo or Whole blood

#2

Platelets

FEIBA

#3

More products

FVIIa

(Gorlinger 2013)
Summary

Factor concentrates
  • Can reduce bleeding
  • Can reduce transfusion requirements

Use Rx algorithm + POC tests

Safety profile uncertain

Administration – decide benefit / risk

RCTs required
Factor Concentrates: references


51. Lancé MD, Ninivaggi M, Schols SEM, Feijge MAH, Oehrl SK, Kuiper GJAJ, Nikiforou M, Marcus MAE, Hamulyak K, van Pampus ECM, ten Cate H, Heemskerk JWM.


70. Ranucci M, Baryshnikova E, Crapelli GB, Rahe-Meyer N, Menicanti L, Frigiola A; Surgical Clinical Outcome REsearch (SCORE) Group. Randomized, double-blinded,


90. Yan W, Xuan C, Ma G, Zhang L, Dong N, Wang Z, Xu R. Combination use of platelets and recombinant activated factor VII for increased hemostasis during