Use of Factor Replacement Agents in Cardiac Surgery

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Use of Factor Replacement Agents in Cardiac Surgery

- Scope of Problem
- Treatment Options
- Evidence To Date
- Thoughts
- Summary
Use of Factor Replacement Agents in Cardiac Surgery

Problem

despite decades of cardiac surgery
30–80 % of cases receive blood products
3–5 % of cases pts receive > 10 PRBC’s
up to 10 % of cases require re-exploration!
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Patients at Risk for Transfusion

- Increased Age
- Low pre-op Hg
- Pre-op anti Plts
- Re-do Sx/ Complex Sx
- Emergency Sx
- Pump time > 120 min
- Co-morbidities (renal/hepatic/hematopoetic)
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Source of Bleeding

Surgical
(factor VI)
Non Surgical
(anesthesia)
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Solution
just transfuse!
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Standard Treatment
replacement/transfusion of blood products
RBC; FFP; Pts; Cryoppt

Not without consequence:
morbidity
mortality
cost
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Increased mortality, morbidity, and cost associated with red blood cell transfusion after cardiac surgery
Barnaby C. Reeves and Gavin J. Murphy

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Purpose of review
Literature since 2006 was reviewed to identify the harms and costs of red blood cell (RBC) transfusion.

Recent findings
Several studies, in people having various cardiac surgery operations, found strong associations of RBC transfusion with mortality and postoperative morbidity. The effect on mortality was strongest close to the time of operation but extended to 5 years. Morbidity outcomes included serious wound and systemic infections, renal failure, prolonged ventilation, low cardiac index, myocardial infarction, and stroke. RBC transfusion was also strongly associated with increased cardiac intensive care unit and ward postoperative stay, and hence, increased cost of admission; available studies did not consider all resources used and the associated costs.

Summary
The harms of RBC transfusion have potentially serious and long-term consequences for patients and are costly for health services. This evidence should shift clinicians’ equipoise towards more restrictive transfusion practice. The immediate aim should be to avoid transfusing a small number of RBC units for general malaise attributed to anaemia, a practice that appears to occur in about 50% of transfused patients. Randomized trials comparing restrictive and liberal transfusion triggers are urgently needed to directly compare the benefits and harms from RBC transfusion.
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Mortality of Transfusion
hazard ratio 1.41/ unit transfused

Morbidity of Transfusion
- dialysis: OR 2.06/ unit
- intubation: OR 1.79/ unit
- neurologic: OR 1.37/ unit
- infection: OR 1.76/ unit
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Alternatives to Transfusion

Factor rVIIa
Fibrinogen
PCC (prothrombin complex concentrate)
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CAB
Asc/CA
Major Vascular (TAAA)
LVAD
Transplant
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What is Factor rVIIa

- It is a vitamin K-dependent glycoprotein consisting of 406 amino acid residues (MW 50 K Dalton).
- It is structurally similar to human plasma-derived Factor VIIa.
- It is intended for promoting hemostasis by activating the extrinsic pathway of the coagulation cascade.
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How Does Factor VII Work?

Initiation
Amplification
Propagation
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Initiation (starting factor activation)
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Amplification (forming thrombin)
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Propagation (thrombin burst and fibrin clot)
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Factor VIIa Dosing

Low dose (1.0 mg = 10–20 μg/kg)

Intermediate dose (2.0 mg = 30–50 μg/kg)

High dose (4.0 mg or more = 70–90 μg/kg)
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Factor VII

Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia (Review)

Simpson E, Lin Y, Stanworth S, Birchall J, Doroee C, Hyde C
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Factor rVII vs Re-Exploration

- Diprose P: 1/10, 0/10; OR (random) = 16.51, 95% CI: 3.32 [0.12, 91.60]
- von Heymann C: 6/26, 7/24; OR (random) = 27.56, 95% CI: 0.73 [0.21, 2.59]
- Gelsonino S: 3/40, 35/40; OR (random) = 26.33, 95% CI: 0.01 [0.00, 0.05]
- Gill R: 13/104, 17/68; OR (random) = 29.60, 95% CI: 0.43 [0.19, 0.95]

Total events: 23 (Treatment), 59 (Control)
Test for heterogeneity: Chi² = 22.96, df = 3 (P < 0.0001), I² = 66.9%
Test for overall effect: Z = 1.31 (P = 0.19)
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Factor rVII vs MI
Use of Factor Replacement Agents in Cardiac Surgery

Factor rVII vs Emboli
Use of Factor Replacement Agents in Cardiac Surgery

Factor rVII vs AKI

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>OR (fixed) 95% CI</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karkouti</td>
<td>15/51</td>
<td>6/51</td>
<td>3.13 [1.10, 8.87]</td>
<td></td>
</tr>
<tr>
<td>Tritapepe</td>
<td>1/23</td>
<td>2/23</td>
<td>0.48 [0.04, 5.66]</td>
<td></td>
</tr>
<tr>
<td>Gelsomino</td>
<td>1/40</td>
<td>2/40</td>
<td>0.49 [0.04, 5.60]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>1.86 [0.81, 4.31]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 17 (Treatment), 10 (Control)
Test for heterogeneity: \( \chi^2 = 3.27, \text{df} = 2 (P = 0.20), I^2 = 38.8\% 
Test for overall effect: \( Z = 1.46 (P = 0.15) \)
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Factor rVII vs Stroke
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Factor rVII vs Death

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diprose</td>
<td>0/10</td>
<td>1/10</td>
<td>0.30 [0.01, 8.33]</td>
</tr>
<tr>
<td>Karkouk</td>
<td>7/51</td>
<td>7/51</td>
<td>1.00 [0.32, 3.09]</td>
</tr>
<tr>
<td>von Heymann</td>
<td>10/26</td>
<td>8/24</td>
<td>1.25 [0.39, 3.99]</td>
</tr>
<tr>
<td>Tritapepe</td>
<td>3/23</td>
<td>3/23</td>
<td>1.00 [0.18, 5.56]</td>
</tr>
<tr>
<td>Gelsomino</td>
<td>2/40</td>
<td>3/40</td>
<td>0.65 [0.10, 4.11]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>150</td>
<td>148</td>
<td>0.96 [0.50, 1.86]</td>
</tr>
</tbody>
</table>

Total events: 22 (Treatment), 22 (Control)
Test for heterogeneity: $\chi^2 = 0.85$, df = 4 ($P = 0.93$), $I^2 = 0$
Test for overall effect: $Z = 0.12$ ($P = 0.90$)
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Factor rVII Summary
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Factor rVII Summary

Prophylactic use: NO
Rescue use: wk
yes
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Fibrinogen
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FFP

1 Unit (200 ml)

- 200U factors
- 2 mg fibrinogen / ml
- 400 mg fibrinogen

Recover 40 %

- 160 mg fibrinogen
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Cryopptpe

1 Unit Cryo (15 ml)
- 15 mg/ml
- 200–250 mg fibrinogen

1 Dose = 10 Units (150 ml)
- 2000–2500 mg fibrinogen

Recover 75%
- 1500 mg fibrinogen
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Fibrinogen Concentrate

Supplied as 1gm powder
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Fibrinogen
Use of Factor Replacement Agents in Cardiac Surgery

Fibrinogen vs Bleeding
Use of Factor Replacement Agents in Cardiac Surgery

Fibrinogen vs RBC Transfusion

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean (Fibrinogen)</th>
<th>SD (Fibrinogen)</th>
<th>Total (Fibrinogen)</th>
<th>Mean (Control)</th>
<th>SD (Control)</th>
<th>Total (Control)</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Cui Y (2010)</td>
<td>0.00</td>
<td>1.10</td>
<td>20</td>
<td>1.50</td>
<td>1.70</td>
<td>20</td>
<td>12.2%</td>
<td>-1.50 (-2.39 to -0.61)</td>
</tr>
<tr>
<td>Fenger-Eriksen C (2009)</td>
<td>0.00</td>
<td>1.50</td>
<td>11</td>
<td>1.50</td>
<td>1.50</td>
<td>10</td>
<td>7.4%</td>
<td>-1.50 (-2.78 to -0.22)</td>
</tr>
<tr>
<td>Jeppsson A (2016)</td>
<td>0.63 (1.17)</td>
<td>26</td>
<td>3.11</td>
<td>26</td>
<td>7.5%</td>
<td>10</td>
<td>9.3%</td>
<td>-0.70 (-1.98 to 0.58)</td>
</tr>
<tr>
<td>Karlsson M (2009)</td>
<td>2.00</td>
<td>0.50</td>
<td>10</td>
<td>1.70</td>
<td>10</td>
<td>10</td>
<td>9.3%</td>
<td>0.00 (-1.10 to 1.10)</td>
</tr>
<tr>
<td>Najafi A (2014)</td>
<td>0.80 (1.01)</td>
<td>15</td>
<td>1.20</td>
<td>15</td>
<td>13.8%</td>
<td>15</td>
<td>13.8%</td>
<td>-0.26 (-1.05 to 0.53)</td>
</tr>
<tr>
<td>Rahe-Meyer N (2013)</td>
<td>0.20</td>
<td>2.20</td>
<td>2</td>
<td>2.20</td>
<td>11.0%</td>
<td>42</td>
<td>11.0%</td>
<td>-2.00 (-2.97 to -1.03)</td>
</tr>
<tr>
<td>Ranucci M (2015)</td>
<td>0.00 (0.70)</td>
<td>58</td>
<td>1.50</td>
<td>58</td>
<td>22.0%</td>
<td>58</td>
<td>22.0%</td>
<td>-1.00 (-1.43 to -0.57)</td>
</tr>
<tr>
<td>Sabate A (2016)</td>
<td>2.00 (4.4)</td>
<td>40</td>
<td>4</td>
<td>4.40</td>
<td>3.9%</td>
<td>41</td>
<td>3.9%</td>
<td>-1.00 (-2.92 to 0.92)</td>
</tr>
<tr>
<td>Sadeghi M (2014)</td>
<td>1.50 (1.8)</td>
<td>30</td>
<td>2</td>
<td>1.50</td>
<td>13.0%</td>
<td>30</td>
<td>13.0%</td>
<td>-0.50 (-1.34 to 0.34)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>248</td>
<td>252</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.93 (-1.33 to -0.52)</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.15; chi-square = 13.80, df = 8 (p = 0.09); I² = 42%
Test for overall effect: z = 4.47 (p < 0.00001)
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Fibrinogen vs Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fibrinogen</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Fenger-Eriksen C (2009)</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Galas FR (2014)</td>
<td>0</td>
<td>30</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Jeppsson A (2016)</td>
<td>0</td>
<td>26</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Karlsson M (2009)</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Rahe-Meyer N (2013)</td>
<td>1</td>
<td>38</td>
<td>4</td>
<td>0.28 (0.03-2.36)</td>
</tr>
<tr>
<td>Rahe-Meyer N (2015)</td>
<td>1</td>
<td>74</td>
<td>5</td>
<td>0.18 (0.02-1.53)</td>
</tr>
<tr>
<td>Ranucci M (2015)</td>
<td>1</td>
<td>58</td>
<td>3</td>
<td>0.33 (0.04-3.11)</td>
</tr>
<tr>
<td>Sabate A (2016)</td>
<td>1</td>
<td>51</td>
<td>3</td>
<td>0.31 (0.03-2.91)</td>
</tr>
<tr>
<td>Tanaka KA (2014)</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Wikkelso AJ (2015)</td>
<td>0</td>
<td>124</td>
<td>0</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

Total (95% CI) 432 430 100.0% 0.26 (0.09, 0.78)

Total events 4 15

Heterogeneity: chi-square = 0.18, df = 3 (P = 0.98); I² = 0%

Test for overall effect: z = 2.41 (P = 0.02)
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Fibrinogen Summary

FC probably useful (but studies not insufficient power)
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Prothrombin Complex Concentrate (PCC)
vit K dependant factors
high concentration (25X)

3 factor
II IX X

4 Factor
II VII IX X
# Use of Factor Replacement Agents in Cardiac Surgery

**Factor**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>fibrinogen</td>
</tr>
<tr>
<td>II</td>
<td>prothrombin</td>
</tr>
<tr>
<td>III</td>
<td>tissue factor</td>
</tr>
<tr>
<td>IV</td>
<td>Ca++</td>
</tr>
<tr>
<td>V</td>
<td>proaccelerin</td>
</tr>
<tr>
<td>VI</td>
<td>proline</td>
</tr>
<tr>
<td>VII</td>
<td>proconvertin</td>
</tr>
<tr>
<td>VIII</td>
<td>antihemophilic factor A</td>
</tr>
<tr>
<td>IX</td>
<td>antihemophilic factor B</td>
</tr>
<tr>
<td>X</td>
<td>Stuart-Prower</td>
</tr>
<tr>
<td>XI</td>
<td>thromboplastin</td>
</tr>
<tr>
<td>XII</td>
<td>Hageman factor</td>
</tr>
<tr>
<td>XIII</td>
<td>fibrin stabilizing factor</td>
</tr>
</tbody>
</table>
Use of Factor Replacement Agents in Cardiac Surgery

PCC

Fixed dose FEIBA
500U INR < 5
1000U INR > 5

Variable Dose (K centra)
25 U/kg INR < 4
35 U/kg INR 4–6
50U/kg INR >6
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PCC 1st line therapy vs FFP

225 propensity score matched CAB pts

reduced blood loss
reduced RBC transfusion
increased risk of AKI
mortality same
Use of Factor Replacement Agents in Cardiac Surgery

Pulm Endarterectomy

351

transfusion rate

30%

PCC vs FFP

reduced blood loss

Same; transfusion rate; mortality; LOS
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PCC vs rVIIa
CAB pts 270
retrospective chart review

reduced bleeding;
transfusion;
dialysis

similar mortality
Use of Factor Replacement Agents in Cardiac Surgery

Effects of Intraoperative Four-Factor Prothrombin Complex Concentrate Use on Blood Utilization During Orthotopic Cardiac Transplantation (SCA2017)

Results:
73 consecutive LVAD/OHT patients during this time period. Of these patients, 32 received 4F-PCC and 41 did not. A median of 2500 (2000-3000) units of 4F-PCC was given per patient. There were no differences in age, gender, BMI, pre-operative lab findings (creatinine, INR, HCT), duration of cardio-pulmonary bypass, or number of prior sternotomies. Median (IQR) units of RBC transfused were 2 (1-2.5) and 5 (3-7) in groups 1 and 2, respectively (p<0.001). Notably, median units of plasma transfused were 1.3 (0-2) and 6 (4-8) in groups 1 and 2, respectively (p<0.001). Furthermore, controlling for pre-op hematocrit, pre-op INR and CPB duration, multivariate regression analysis showed that patients receiving 4F-PCC required fewer RBC and plasma units (p<0.001). No difference was seen in post-operative ICU length of stay or post-operative length of hospital stay. No thrombotic complications occurred in either group.

Visal H. Patel, MD, MD, MS, Boston, MA, United States
Use of Factor Replacement Agents in Cardiac Surgery

Effects of Intraoperative Four-Factor Prothrombin Complex Concentrate Use on Blood Utilization During Orthotopic Cardiac Transplantation

Conclusions:
The use of 4F-PCC post-bypass for patients undergoing OHT with pre-existing LVAD decreases both RBC and plasma transfusions. Use of 4F-PCC was not associated with shorter lengths of ICU stay or overall hospital stay, and was not associated with thrombotic complications.

Visal H. Patel, MD, MD, MS, Boston, MA, United States
Use of Prothrombin Complex Concentrates (PCCs) in Patients Undergoing Heart Transplant Surgery: Clinical Experience at a University Hospital

The Journal of Heart and Lung Transplantation, Vol 35, No 4S, April 2016

S.L. Rao, 1 Y.P. Salamanca, 1 W.E. Pae.2 1Department of Anesthesiology & Perioperative Medicine, Penn State Hershey Medical Center, Hershey, PA; 2Department of Surgery, Penn State Hershey Medical Center, Hershey, PA.

Results: Among the 39 patients that underwent OHTS in this time period, the average 24-hr postoperative blood loss (mediastinal drainage) in the 21 patients who received PCC was 1068 ml, compared to 1047 ml, in 18 patients who did not receive PCC. PCCs were used as a rescue treatment after conventional therapy using FFP, Cryoprecipitate and Platelets failed to secure adequate hemostasis. The decision to use PCCs was made intraoperatively by the operative team following the reversal of heparin with protamine.

Conclusion: Patients who received PCCs were perhaps at higher risk of bleeding & may not be comparable to those who did not receive PCCs. Patients who received PCCs after failure of conventional therapy, had similar outcomes to those treated conventionally. Perhaps PCCs should be used earlier in the course of therapy.
Use of Factor Replacement Agents in Cardiac Surgery

What Does All This Mean?

Bleeding still a problem
Factor replacement useful in rescue setting
rVIIa highest risk
Use of Factor Replacement Agents in Cardiac Surgery

What Does All This Mean?

Surgical technique still important

Need to conduct randomized prophylactic not rescue use study of PCC based on “pre-protamine” coag tests
Use of Factor Replacement Agents in Cardiac Surgery

CLINICAL PRACTICE GUIDELINES


Linda Sheeh-Lessmon, MD, Robert A. Baker, PhD, CCP, Victor A. Ferraris, MD, PhD, Philip E. Goodrich, MD, David Fitzgerald, MPH, CCP, Philip Roman, MD, MPH, and John W. Hammong, MD

Despite more than a half century of "safe" cardiopulmonary bypass (CPB), the evidence base surrounding the conduct of anticoagulant therapy for CPB has not been organized into a useful guideline. For this and other reasons, there is enormous practice variability relating to the use and dosing of heparin, monitoring heparin anticoagulation, reversal of anticoagulation, and the use of alternative anticoagulant agents. To address this and other gaps, The Society of Thoracic Surgeons, The Society of Cardiovascular Anesthesiologists, and The American Society of Extracorporeal Technology developed an Evidence-Based Clinical Practice Guideline for Anticoagulation During Cardiopulmonary Bypass. This guideline was authored by a multidisciplinary panel of experts gathered to summarize the evidence and create practice recommendations for various aspects of CPB. To date, anticoagulation practices in CPB have not been standardized in accordance with the evidence base. This clinical practice guideline was written to address the lack of existing guidelines and to establish best practices in anticoagulation during CPB.

Critical Care Clinics

Bleeding in Cardiac Surgery: Its Prevention and Treatment—an Evidence-Based Review

Richard Whitlock, MD, MSc, Mark A. Crowther, MD, MSc, FRCP⁎,*
Heng J. Ng, MBBS, MMed, MRCP

Department of Medicine, McMaster University, St. Joseph's Hospital, Hamilton, Ontario, Canada

Expert and unexpected bleeding occur frequently in patients undergoing cardiac surgery; cardiac surgery patients use 10% to 25% of the blood products transfused annually in the United States [1-3]. Although unexpected bleeding after this surgery is common, reducing this bleeding in a desirable clinical goal, because such bleeding is associated with adverse outcomes [4-11]. Unlike other settings, however, overly aggressive treatment of bleeding is also likely to be associated with adverse outcomes because induction of a hemorrhagic state might be associated with early death [12,13]. A variety of definitions of excessive bleeding in the postoperative cardiac surgery patient have been proposed (Table 1). Using these definitions, excessive bleeding occurs in about 5% of cases [14-17]. Patients with significant bleeding often require reparative; ratio of reoperation for bleeding vary between 3% and 14% a surgically correctable source of bleeding is found in 50 to 67% of patients [10,18,19]. Bleeding and surgical re-exploration are both independent predictors of an adverse outcome [4-11].

Bleeding after cardiac surgery can be broadly divided into two groups: surgical (unrecognized bleeding vessel, anastomosis, or other suture line) or non-surgical bleeding (caused by coagulopathy). Factors influencing both surgical