QUEST
Quality Utilization Efficacy Safety Transfusion

Canadian Blood Services
BLOOD
PLASMA
STEM CELLS
ORGANS
& TISSUES

Plasma, PCC, Cryoprecipitate & Fibrinogen concentrate

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Disclosures

F. Masaisa

- No relevant financial conflicts of interest

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- No relevant financial conflicts of interest
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Scope

- Interpretation of basic laboratory test values – INR, aPTT, fibrinogen
- Evidence for plasma, PCC, cryoprecipitate and fibrinogen concentrate use
- Practical advice to think through real world challenges

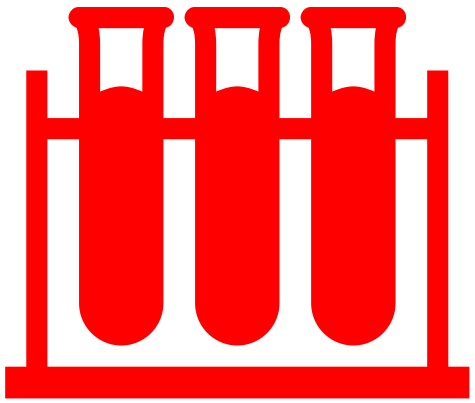
PT/INR and aPTT

Laboratory “coagulation” tests do not…

1. Rule-out bleeding disorder
2. Inform us about bleeding risk

- INR validated for warfarin (VKA) monitoring
- aPTT can detect FVIII <30% & UFH monitoring

- INR ↑ most commonly from liver disease which is a hypercoagulable state
- aPTT ↑ most common reasons ↓FXII, Lupus anticoagulant, which are both non-bleeding states



Send laboratory testing in select patients

- Procedures are moderate to high-risk for bleeding or >10% chance of transfusion
- Family history of bleeding
- Personal history of a bleeding tendency as determined by
  - Screening with a Bleeding assessment tool (BAT)
- Medication monitoring (Warfarin, heparin)

Plasma and PCC

What are the indications for plasma use?

Moderate to severe bleeding

To prevent peri-procedural bleeding in patients with acquired factor deficiency*

Massive Transfusion before INR results are available

Warfarin reversal ONLY if PCC unavailable

Factor replacement if factor concentrate unavailable

Plasmapheresis for Thrombotic thrombocytopenic purpura (TTP)

**** Procedures with high risk of bleeding if*** *INR ≥ 1.8 (no liver disease) or >2.5 in those with liver disease*

Transfusion. 2010;50(6):1227-1239
J Vasc interv Radiol 2019; 30:1155-1167

Plasma is not indicated in...

Non-bleeding patients + elevated INR and no planned procedures

Warfarin reversal when PCCs available

Mild bleeding

Factor replacement when factor concentrates are available

Most plasma transfused is unnecessary

Study	Country	Number of infusions	Patient type	Percent unnecessary
Khandelwal et al Vox Sang 2022	Canada	11490	All patients	71% under-dosed 35% inappropriate indication
ORBCON audit 2015	Canada	329	All patients	52%
Shih et al Vox Sang 2015	Canada	111	ICU	45%
Tinmouth et al Transfusion 2013	Canada	559	All patients	29%
Stanworth et al. Crit Care 2011	UK	366	ICU	43%*
Stanworth et al Transfusion 2011	UK	3648	All patients (included kids)	58%*
Palo et al. Transfusion 2006	Finland	11590	All patients	66%*

*estimated from tables and texts

Plasma can be harmful

- TACO and TRALI are the leading causes of transfusion associated mortality
- Plasma has the highest risk of TACO and TRALI compared to other blood products[1]
  - TRALI risk is 7x higher compared to RBCs
  - TACO risk is higher with each plasma dose
- Plasma use also associated with:
  - higher risk of ventilator-associated pneumonia in critically ill patients[2]
  - higher risk of bleeding in pre-operative patients undergoing non-CV surgery and INR $\geq$ 1.5[3]

1. Transfusion. 2009;49(3):440-52.
2. Crit Care Med. 2008;36(4):1114-8.
3. Lancet Haematol. 2016;3(3):e139-48.

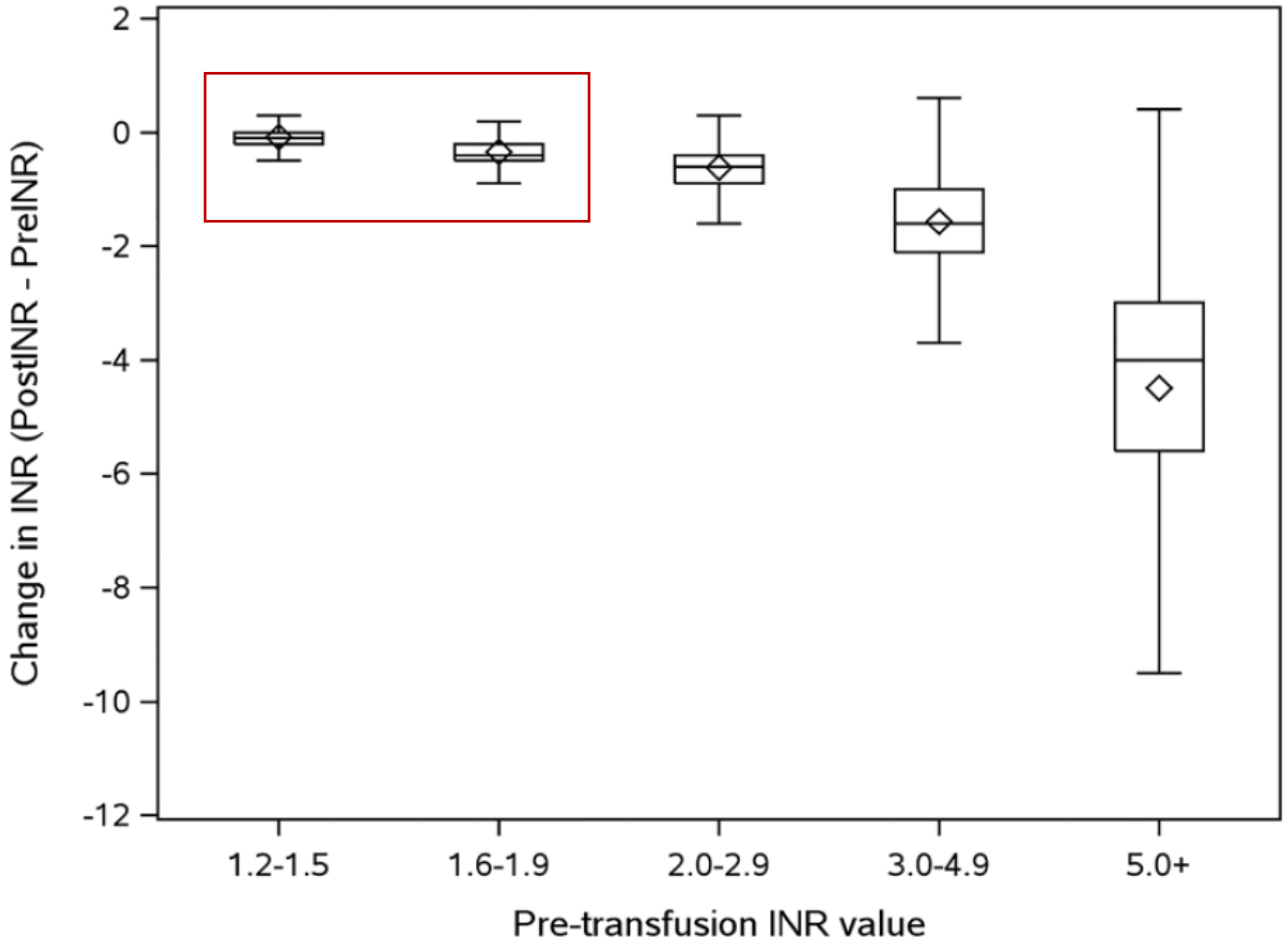
Plasma dose

- Plasma standard dose is 15 mL/kg
  - Increase factor levels by 15-20%
  - For a 70 kg individual it is ~ 1000 mL = 4 units of 250 mL each
  - Dose based on ex vivo laboratory testing showing factor level increase NOT based on clinical outcomes
- Ideally, factor levels >30% required to reverse coagulopathy
  - 1 in 5 patients with low factors have an increase to >30% [1]
  - Strongest effect if INR is >2, minimal change if INR is <1.7[3]
- No decrease in bleeding risk with prophylactic plasma use for elevated INR has been established[4]

1. Transfusion. 2010;50(6):1227-39
2. Br J Haematol. 2004;125(1): 69-73
3. Am J Clin Pathol. 2006;126(1):133-9
4. Transfus Apher Sci. 2012;46(3):293-8

High INR Procedure/Bleed

4 units of FFP



N=6779 patients

Warner MA, et al. A & A 2018

CSTM SCMT
Canadian Society for Transfusion Medicine
Société canadienne de médecine transfusionnelle

Choosing Wisely Canada™

Don’t transfuse plasma to correct mildly elevated INRs (<1.8) or PTT before a procedure

British Society for Haematology
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The impact of commonly used doses of plasma to correct clotting results, or to reduce the bleeding risk, is very limited particularly when the INR is between 1.5–1.9 (Recommendation: 2C)

Chronic liver disease and coagulopathy

- Re-balanced coagulation seen
  - 50 patients with acute liver injury, mean INR 3.4
  - Endogenous thrombin potential preserved due to decreased protein C
  - Clot lysis had not occurred by 3 hours in 74% of the liver patient samples
  - These patients are in a **pro-thrombotic** state, hence caution when giving FP
- Vascular dilation with nutritional deficiencies leads to more friable tissues
- Thrombocytopenia: better than the number
- Fibrinolysis: hyperfibrinolysis in severe liver disease

Lisman , J Thromb Haemost 2012; 20: 1312-9.

Liver biopsy and “coagulation testing”

- Ewe K. Dig Dis Sci 1981;26:388-93.
  - 200 patients undergoing liver biopsy observed
  - No correlation of liver bleeding time and laboratory test results
  - Even patients with INR>3 and PLT<50 did not bleed more than patients with ‘better’ test results
- Piccinino F et al J of Hepatology 1986; 2: 165-73.
  - Very large series of 68,276 percutaneous biopsies found that major bleeding occurred in only 42 patients = 1 in 1626 patients!

Random distribution

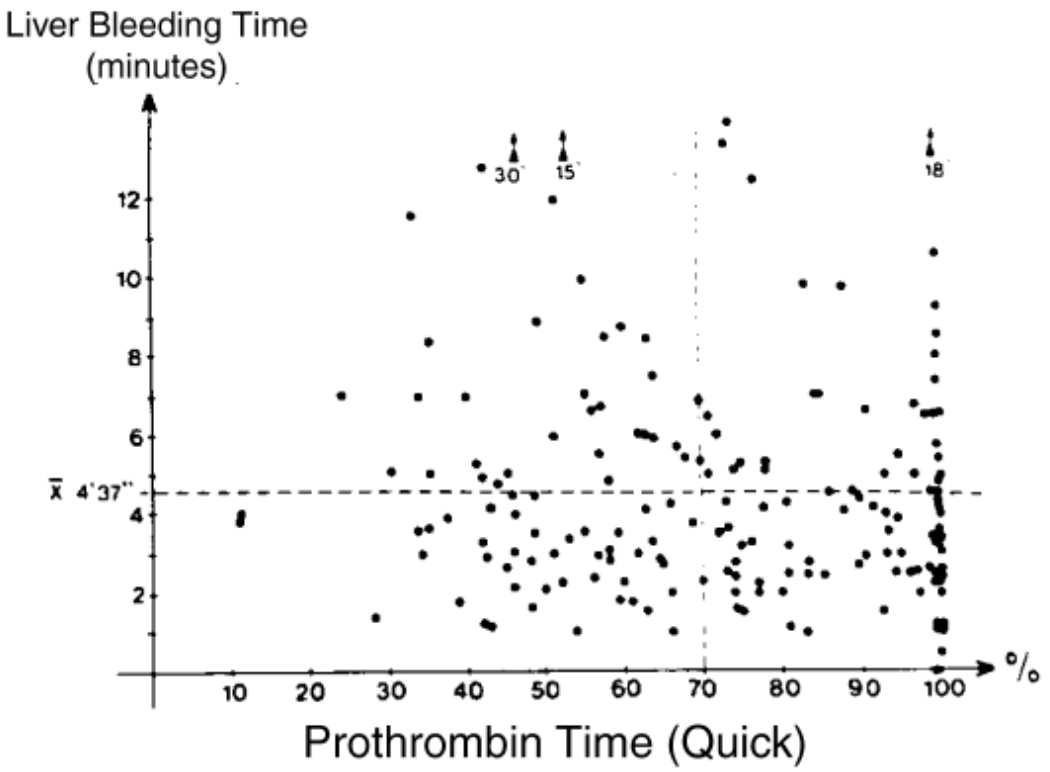


Figure 1-5. Lack of relationship between the liver bleeding time and the preprocedure PT. The time that the liver was directly observed to bleed after biopsy is plotted as a function of the percentage of activity of the PT. Use with permission from Ewe et al.[70]

Ewe K. Dig Dis Sci 1981;26:388-93.

Paracentesis and coagulopathy

- Grabau CM, et al. Hepatology. 2004;40:484-8.
  - 1100 paracenteses
  - All performed without ultrasound guidance
  - No transfusion of platelets or plasma
  - Lowest platelet count was 19 (IQR 42-56)
  - Highest INR was 8.7 (IQR 1.4-2.2)
  - There was no significant bleeding in any patient

Grabau CM, et al. Hepatology. 2004;40:484-8.

Guidelines

British Society for Haematology
Listening • Learning • Leading

- We endorse the liver society recommendations that prophylactic transfusion of FFP and cryoprecipitate is not given in low bleeding risk procedures, such as paracentesis (1C).
- There is no good evidence to support a role for prophylactic FFP to reduce the risk of bleeding from percutaneous liver biopsy. An alternative procedure with a lower bleeding risk, (e.g. transjugular liver biopsy), should be considered instead (2C).

British Journal of Haematology, 2018, **181**, 54–67

CAIR endorsed SIR Guidelines 2019

STANDARDS OF PRACTICE

Society of Interventional Radiology Consensus Guidelines for the Periprocedural Management of Thrombotic and Bleeding Risk in Patients Undergoing Percutaneous Image-Guided Interventions—Part II: Recommendations

Endorsed by the Canadian Association for Interventional Radiology and the Cardiovascular and Interventional Radiological Society of Europe

Indravadan J. Patel, MD, Shiraz Rahim, MD, Jon C. Davidson, MD, Sue E. Hanks, MD, Alda L. Tam, MD, T. Gregory Walker, MD, Luke R. Wilkins, MD, Ravi Sarode, MD, and Ido Weinberg, MD

Procedure related risk

Bleeding risk	Low (<1%)	Moderate to Severe
Vascular procedures	Central line removal Dialysis access IVC filter placement PICC placement Transjugular liver biopsy Subcutaneous port placement Tunneled drainage catheter Venography Venous catheter	Ablation Arterial interventions (sheath >7 Fr) Catheter directed thrombolysis Chemoembolization Complex venous interventions CNS and Spine procedures incl epidural Radioembolization Tunneled venous catheter Urinary tract interventions Uterine fibroid embolization
Non-vascular procedures	Arthrocentesis + joint injection Catheter exchange Dental extraction (up to 2) Endoscopy without biopsy Lumbar puncture Pacemaker insertion Paracentesis Peripheral nerve block Superficial aspiration, drainage, skin biopsy Thoracentesis Thyroid biopsy	Ablation Biliary interventions Bone marrow biopsy Complex dental procedures Deep abscess drainage Solid organ biopsy Endoscopy with biopsy Gastrostomy/gastrojejunostomy placement Lymph node biopsy Percutaneous enteric tube (new tract) Spinal procedures

Laboratory testing targets

Parameter	Individuals WITHOUT chronic liver disease		Individuals WITH liver disease	
	Low Risk	**High Risk**	**Low Risk**	**High Risk**
INR	Not routinely recommended If on Warfarin, ensure within therapeutic range	< 1.8	N/A	<2.5
PTT (s)	Not recommended	Not recommended	Not recommended	Not recommended
Platelet count ($x10^9$/L)	If checked, transfuse if <20	Transfuse if <50, <70 for neuraxial anesthesia	>20 >30 for liver biopsy	>30
Fibrinogen (g/L)	Not recommended	Not recommended	>1	>1

Prothrombin Complex Concentrate (PCC)

Case

- 83-year-old male found with a GCS of 12 at the bottom of the stairs by his wife
- Large scalp laceration with substantial blood loss
- Patient on warfarin for atrial fibrillation
- You send a STAT INR – result not back yet
- Patient in CT – large subdural that needs evacuation
- You have paged neurosurgery
- How do you reverse his warfarin STAT?

Emergency reversal of warfarin

- Short-term plan
  - Prothrombin complex concentrates 1000-3000 IU depending on the INR
    - Lasts 6 hours
    - Contains factors II, VII, IX, and X (Pr C/S, heparin)
    - Only contraindication: HIT (only time you use plasma)
- Long-term plan
  - Intravenous vitamin K
    - Intravenous is faster than oral
    - Starts working in 6 hours (prevents rebound)

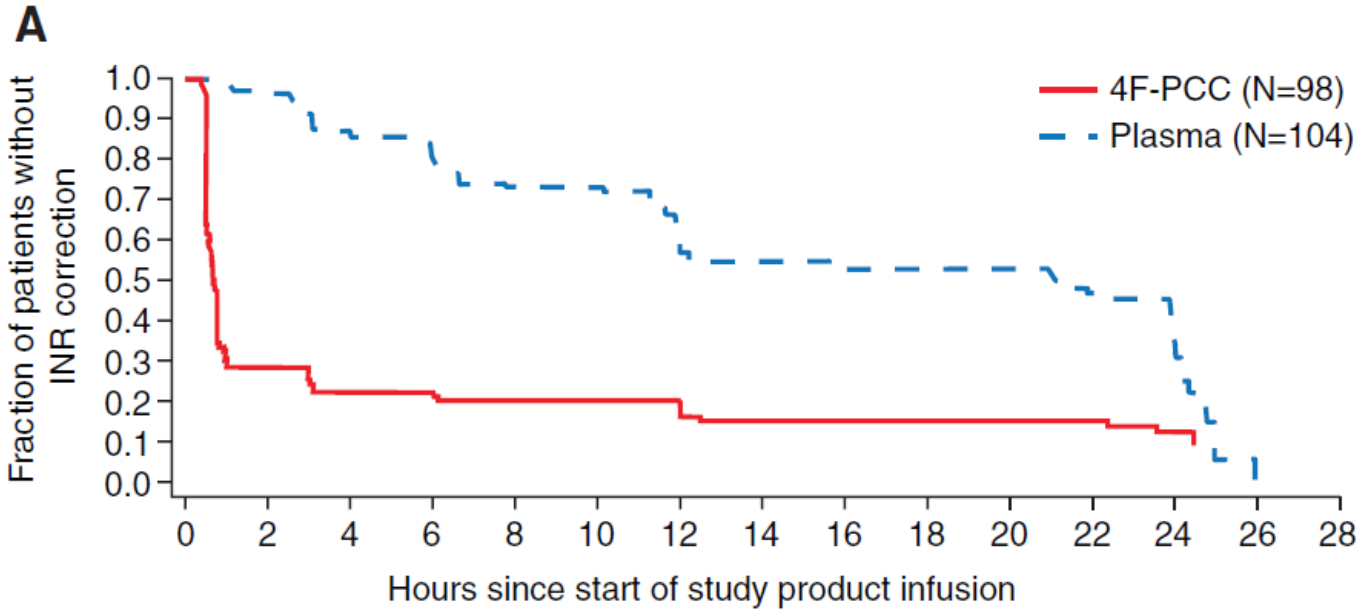
When should you consider reversal with PCC?

- Limb or life-threatening bleeding
  - Intracranial hemorrhage
  - Pericardial bleed
- Emergency surgical procedure within the next 6 hours
  - Not just because operating room time in available in 1 hour
  - Traumatic rupture of a spleen, perforated viscous, ruptured aneurysm

Why use PCCs vs. Plasma?

PCC	Plasma
Pooled, virally inactivated Prion reduction process	Not virally inactivated
Lyophilized Needs to be reconstituted	Needs ABO group (10min) Needs to be thawed (30min)
Volume 40-80mL Infused at 40 mL/5 min	Volume 15mL/kg (~1000mL) Infused over hours
Less risk of transfusion rxns	Risk of transfusion rxns: TRALI, TACO, anaphylaxis
Only lasts 6-8 hours	

PCC vs. Plasma



Use of PCC showed:

- Faster onset of action
- Lower mortality
- Lower risk of CHF
- No difference in thrombosis rates

Circulation. 2013;128:1234-1243; originally published online August 9, 2013;

http://dx.doi.org/10.1160/TH16-04-0266
Thromb Haemost 2016; 116: 879–890

National Advisory Committee on Blood and Blood Products

Dosage: less than the manufacturer's recommended dose

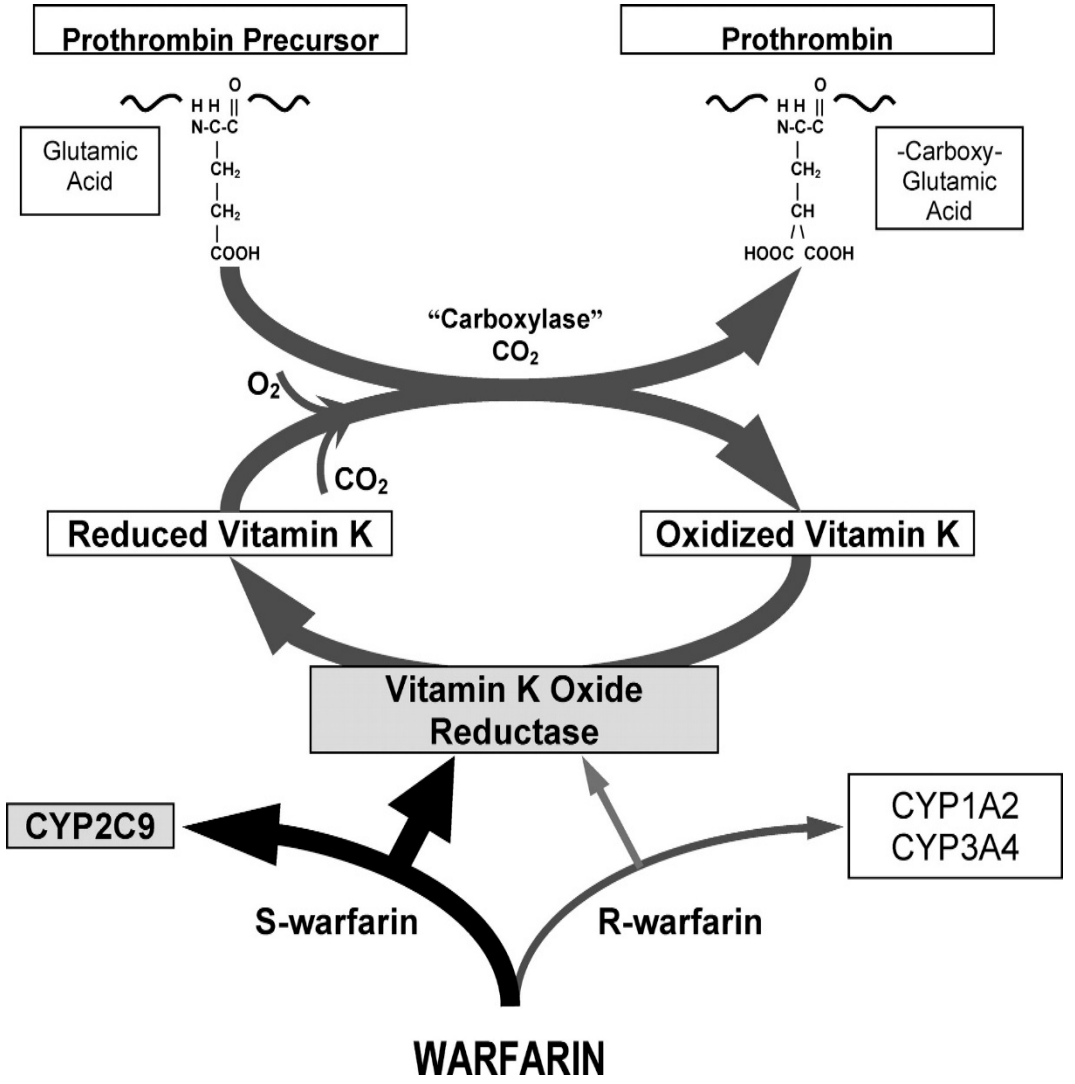
Adult patients:
INR <3 -1000; INR 3-5 – 2000; INR >5 – 3000 IU
Can't wait for the INR – 2000 IU

Maximum total dose: 3000 IU Factor IX activity (adult patients)
Note: listed dose is 50 IU/kg = 3,750 IU for 75 kg patient

Administration: 1000 IU/5 mins; effect is instantaneous!

What about Vitamin K?

- Vitamin K works fast
  - The factors are already synthesized & just need a final conversion step
- Intravenous Vitamin K is safe
  - Historically contained castor oil which lead to increased anaphylaxis
  - Now anaphylaxis risk is 0.04-11/10,000 doses
- DO NOT use subcutaneously or intramuscularly in an emergency setting
- Intravenous formulation can also be given orally



Fiore et al. J Thromb Thrombolysis 2001; 11:175-83

3 situations where vitamin K should suffice

1. Asymptomatic high INRs
   - INR>8-10

   2 mg PO
2. Non-emergency surgery
   - Delay 6 hours

   10 mg IV
3. Non-critical bleeding
   - Epistaxis, dental bleeding etc.

   1 mg IV

1. Tran et al. Med J Austral 2013; 198: 198-9.
2. Holbrook et al. Chest 2012; 141: e152S-184S.
3. Keeling et al. Br J Haematol 2011; 154:311-24
4. Denas et al. J Thromb Thrombolysis 2009;27:340-7

Fibrinogen Replacement

Case

- 38 year old G3P2 immediately post delivery develops vaginal bleeding
- The bleeding fails to respond to escalating doses of prostaglandins and 2g of tranexamic acid
- 4 ***uncrossmatched*** RBCs requested due to transient BP drop
- Bakri balloon inserted into uterus and en route to OR for hysterectomy
- BP better at 90, HR 98 after 4 RBCs and bleeding continues – you have ordered 4 more RBCs
- Fibrinogen level and coagulation studies pending
- Should you administer 4 grams of fibrinogen or 10 units of cryoprecipitate even though no fibrinogen level available?

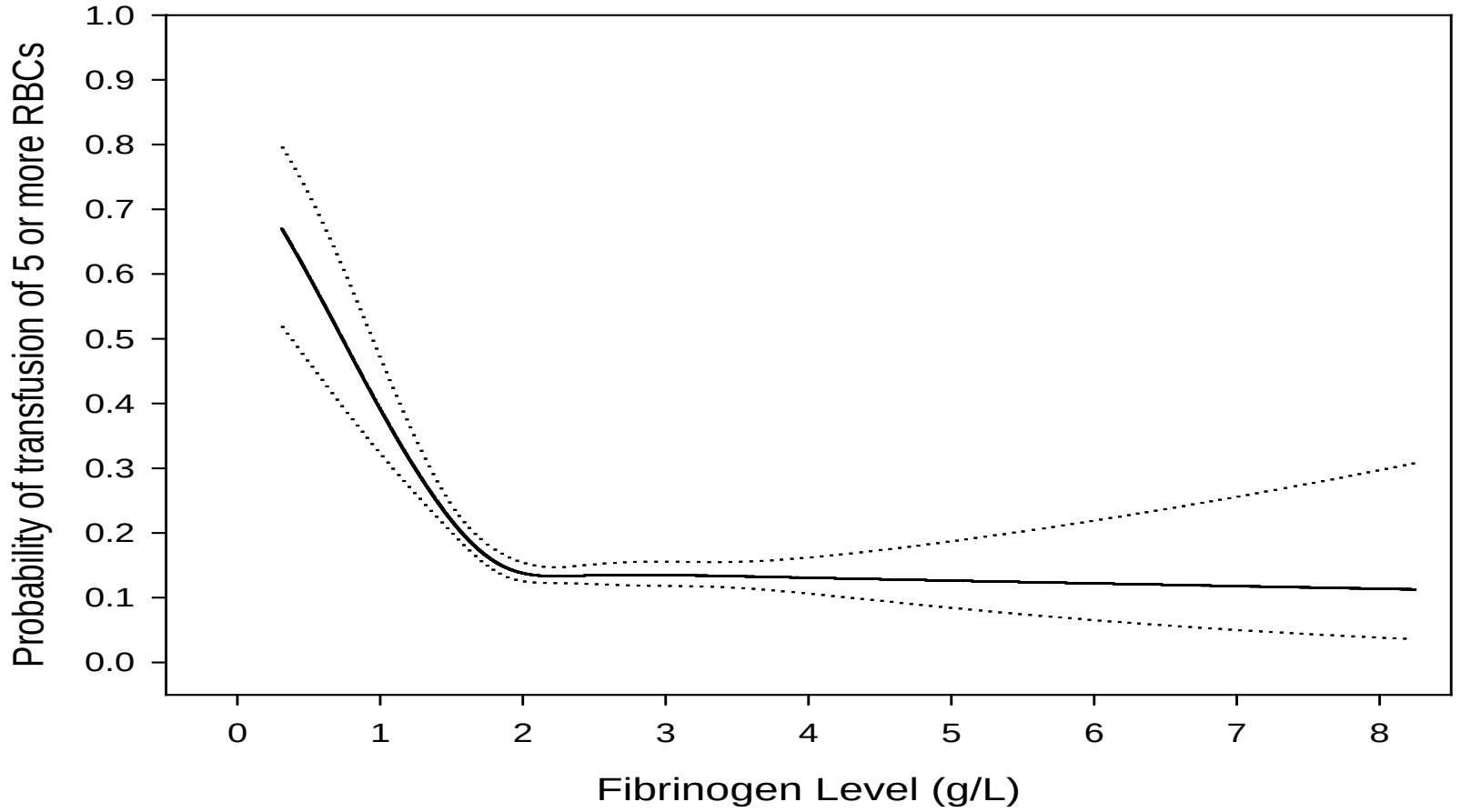
Cryoprecipitate and Fibrinogen Concentrates

- Dosage - 4 g fibrinogen (50 mg/kg in kids) or 1 unit cryoprecipitate per 10 kg to a max of 10 units (paediatrics)
- The two products are hemostatically equivalent
- ***Measure fibrinogen frequently*** during active bleeding
  - **Call the coagulation lab and ask for it to be added to the INR if you forget**
  - **Transfuse if fibrinogen <1.5 - 2.0 g/L**
- Extreme hemorrhages…don't wait for results…just give it

Indications for fibrinogen replacement

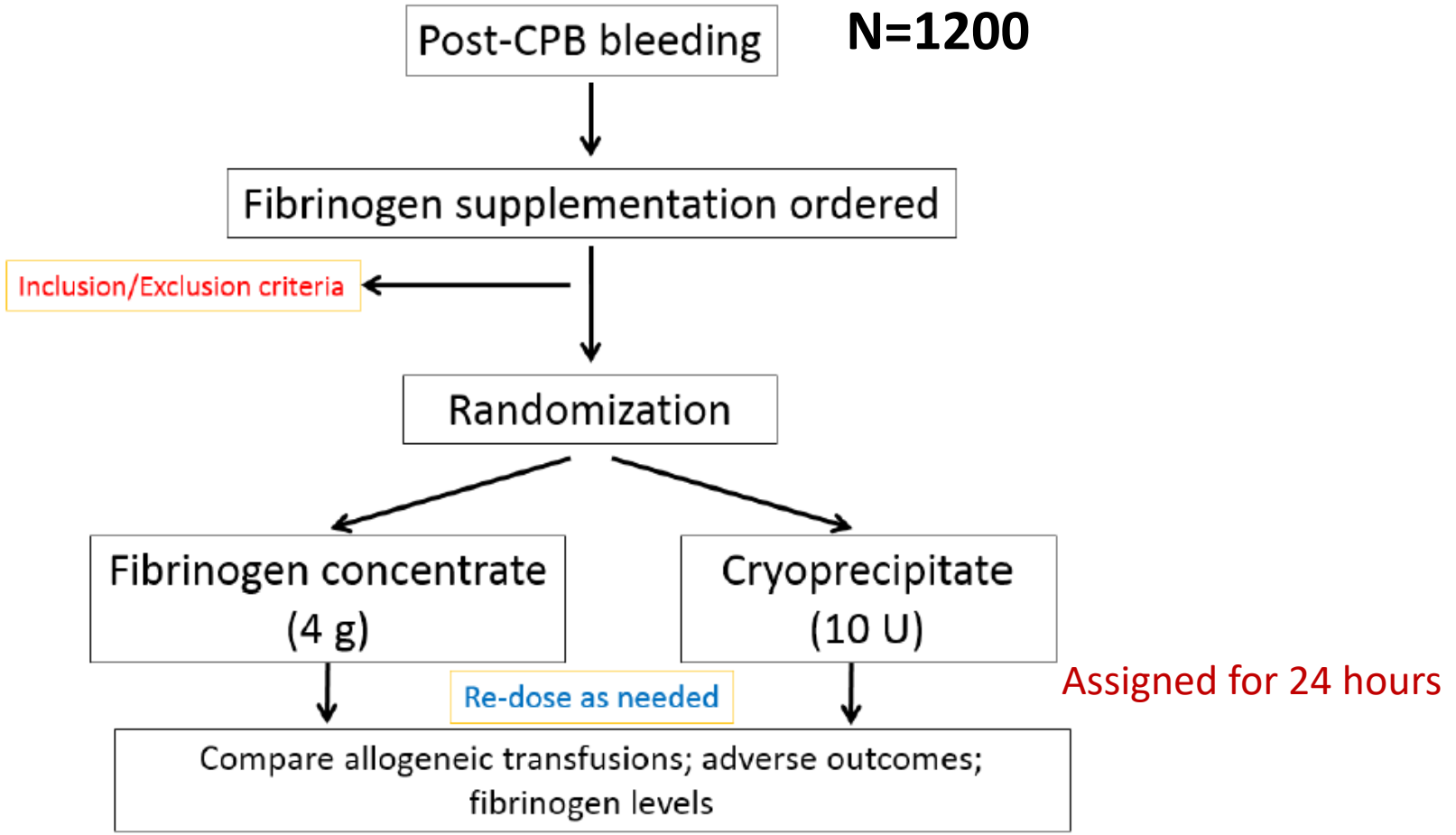
- Major massive hemorrhage from surgery or trauma when fibrinogen <1.5 g/L
  - European trauma guidelines and European Anesth Guidelines Crit Care 2016 Apr 12;20:100 (<1.5 - 2.0 g/L)
  - British Committee for Standards in Haematology – Haematology management of massive hemorrhage 2015 (<1.5 g/L)

Fibrinogen <2 g/L coming off pump increases risk of excessive blood loss (5 units or more) post cardiac surgery



Karkouti et al. Anesth Analg. 2013 May 17

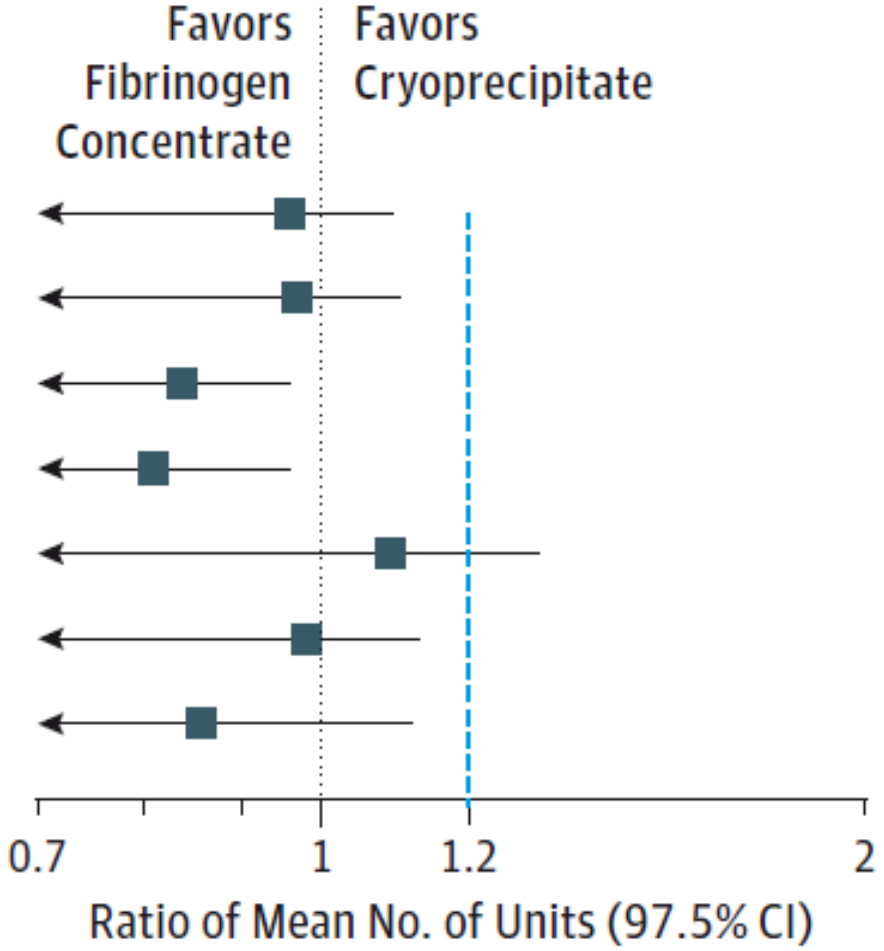
Design



Callum, Karkouti - JAMA. 2019;322(20):1966-1976.

Figure 2. Ratio of Mean Number of Allogeneic Blood Components Transfused in the 24 Hours After Cardiopulmonary Bypass for the Primary Analysis Set, Per-Protocol Analysis Set, and A Priori–Defined Subgroups

Group/Subgroup	Ratio (97.5% CI)
Primary analysis set	0.96 (-∞ to 1.09)
Per-protocol analysis set	0.97 (-∞ to 1.10)
Excluding patients in critical state	0.84 (-∞ to 0.96)
Elective surgery	0.81 (-∞ to 0.96)
Nonelective surgery	1.09 (0 to 1.31)
Complex surgery	0.98 (-∞ to 1.13)
Noncomplex surgery	0.86 (-∞ to 1.12)



Case

- 14-year-old with ALL undergoing induction chemotherapy
- Blood work shows progressive decline in fibrinogen levels due to DIC
- This morning PLT count 14, fibrinogen level 0.8 g/L
- No active bleeding, no oral bleeding
- Scattered petechiae
- No planned procedures
- Should you fix the fibrinogen level?

What do the guidelines recommend if the patient is bleeding in DIC?

Role of plasma, fresh frozen plasma (FFP), coagulation factors, and platelets

Recommendations:

1 The transfusion of platelets is recommended in DIC patients with active bleeding and a platelet count of $<50 \times 10^9$ L^{-1} or in those with a high risk of bleeding and a platelet count of $<20 \times 10^9$ L^{-1} (low quality).

2 The administration of FFP may be useful in patients with active bleeding with either prolonged PT/APTT (>1.5 times normal) or decreased fibrinogen (<1.5 g dL^{-1}). It should be considered in DIC patients requiring an invasive procedure with similar laboratory abnormalities (low quality).

3 The administration of fibrinogen concentrate or cryoprecipitate may be recommended in actively bleeding patients with persisting severe hypofibrinogenemia (<1.5 g L^{-1}) despite FFP replacement (low quality).

Wada et al for ISTH. J Thromb Haemost. 2013 Feb 4.

Acute Promyelocytic leukemia (APL)

- This is the exception: Management of newly diagnosed APL
- Maintain platelet count >30-50 (>100 with CNS bleeding)
- Maintain fibrinogen >1.0-1.5 g/L (with cryoprecipitate)

Stein et al. Best Practice and Research Clinical Hematology 2009; 22: 153-63.
Choundhry et al. Am J Hematol. 2012 Jun;87(6):596-603. doi: 10.1002/ajh.23158. Epub 2012 May 2.

Summary – Plasma

- Different patient populations have different INR thresholds for plasma transfusion before procedures → You must know why the INR is high
- In liver disease, plasma for INRs 1.3 to 1.8 is unlikely to change the INR and also does not reduce bleeding risk before procedures
  - Don’t transfuse plasma if INR<1.8 in a patient with liver disease without hemorrhage
  - Don’t transfuse plasma if INR elevated before low risk procedures (PLT>20)
  - Limit to high risk procedures (PLT>30, INR<2.5, FIB>1.0 only)
  - Use lower risk techniques when possible (transjugular liver biopsy)

Summary - PCCs

Emergency reversal

- Vitamin K 10 mg IV
- PCC:
  - INR<3 – 1000
  - INR 3-5 – 2000
  - INR>5 – 3000
  - INR unknown – 2000
  - Each 1000 over 5 min

Non-emergency

- Vitamin K only!
- INR > 8 to 10: 2 mg po
- Urgent surgery: 10 mg IV
- Non-critical bleeding: 1 mg iv

Summary - Fibrinogen

- Fibrinogen replacement:
  - Transfuse fibrinogen or cryo for bleeding patients <1.5-2.0 g/L
  - Acute promyelocytic leukemia patients if fibrinogen<1.5 g/L in acute phase even without bleeding (no other non-bleeding patients)