Transfusion Updates
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BLOOD
PLASMA
STEM CELLS
ORGANS
& TISSUES

QUEST

Quality Utilization Efficacy Safety Transfusion

Disclosures and Acknowledgements

- Affiliations:
  - Canadian Blood Services
  - QUEST Research group at University of Toronto

- Content shared in collaboration with Dr. Yulia Lin
- START study content from Ms. Amie Kron

Transfusion Medicine Update: Studies Included

- The REALITY Trial: Ducrocq et al. JAMA 2021:325:552-560
- The START Study: Kron A et al. Transfusion 2021;61:410-422

- The FARES Phase II Pilot: JAMA Network Open. 2021;4(4):e213936.

- Electronic audit of plasma use in Ontario (unpublished)

- CONCOR-1 Update (unpublished)

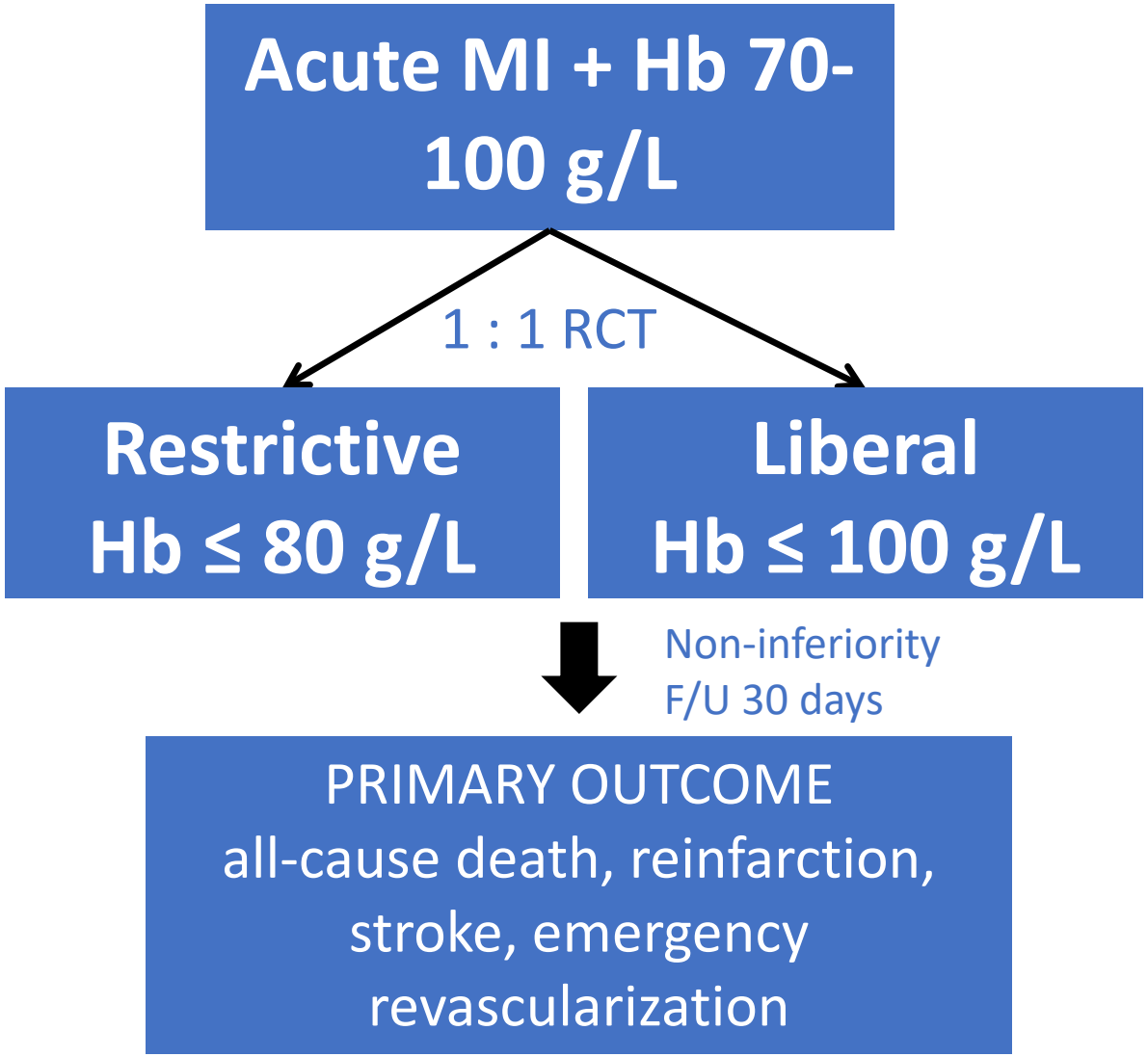
JAMA | Original Investigation

Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Major Cardiovascular Events Among Patients With Acute Myocardial Infarction and Anemia
The REALITY Randomized Clinical Trial

Gregory Ducrocq, MD, PhD; Jose R. Gonzalez-Juanatey, MD; Etienne Puymirat, MD; Gilles Lemesle, MD, PhD; Marine Cachanado, MSc; Isabelle Durand-Zaleski, MD, PhD; Joan Albert Arnaiz, MD, PhD; Manuel Martinez-Sellés, MD, PhD; Johanne Silvain, MD, PhD; Albert Ariza-Solé, MD; Emile Ferrari, MD; Gonzalo Calvo, MD, PhD; Nicolas Danchin, MD; Cristina Avendaño-Solá MD; Jerome Frenkiel, MD; Alexandra Rousseau, PhD; Eric Vicaut, MD, PhD; Tabassome Simon, MD, PhD; Philippe Gabriel Steg, MD; for the REALITY Investigators

Ducrocq et al. REALITY Trial; JAMA 2021:325:552-560

The REALITY TRIAL



35 Centers across Spain and France

Important Exclusions:

- Cardiogenic shock
- PCI or CABG complicated by MI
- Transfusion in the previous 30 days
- Any known hematologic disease
- Massive bleeding

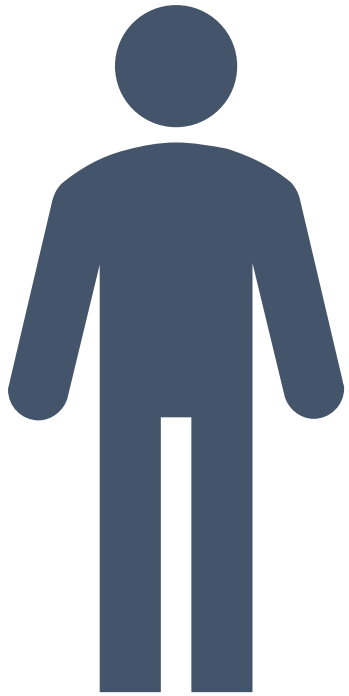
Ducrocq et al. REALITY Trial; JAMA 2021:325:552-560

RBC REALITY TRIAL: Baseline Characteristics

N=666 enrolled, 342 in restrictive and 324 in liberal arm

~ 70% NSTEMI, 30% STEMI

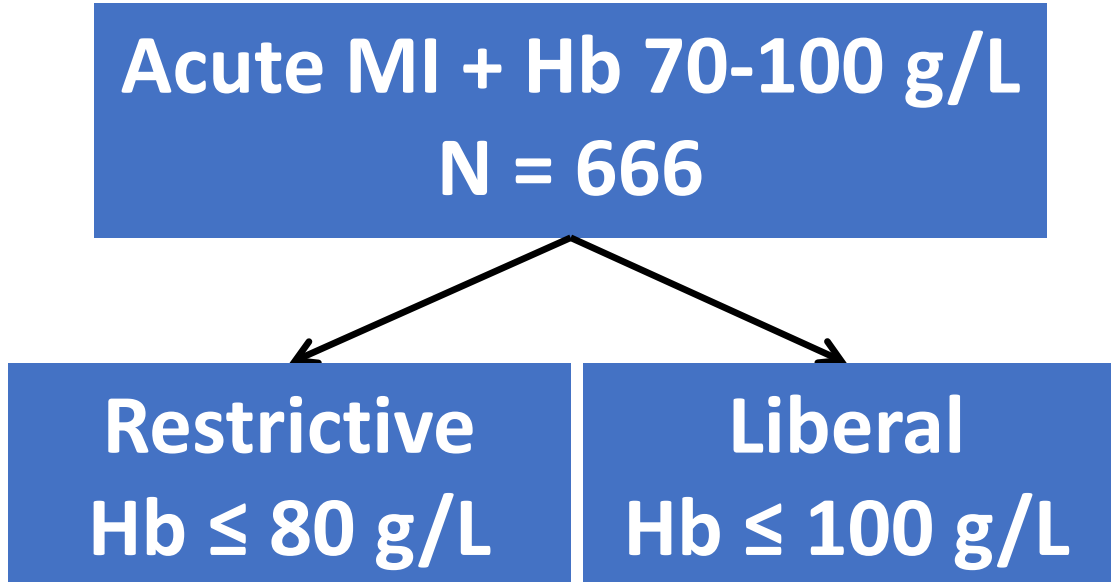
- Median age 78yrs (restrictive), 76 yrs (liberal)
- Sex - 57% men
- Race - 83 to 89% self-reported Caucasian
- Comorbidities:
  - Majority had hypertension and dyslipidemia
  - 50% had diabetes
  - 1/3 had prior ACS or PCI before index event



77 y.o. M, previous smoker, hx of DLP, HTN, chronic anemia now NSTEMI

RBC REALITY TRIAL

RR 0.79
(97.5% CI 0.00 - 1.19)

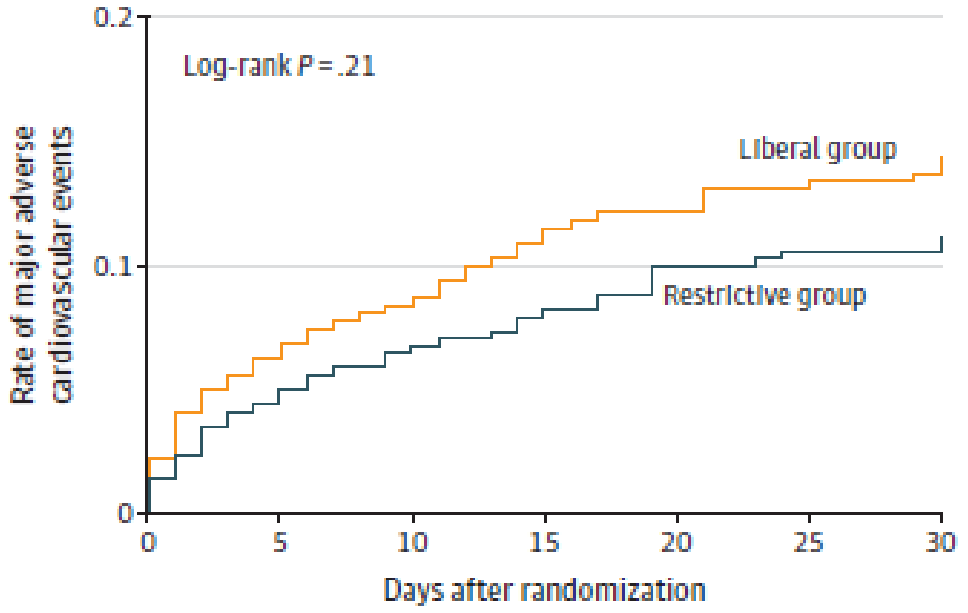


N	342	324
Major CV events at 30d	11%	14%
Death	5.6%	7.7%
Recurrent MI	2.1%	3.1%
Emergency revasc	1.5%	1.9%
Number of units	342	758
RBC transfusion	35.7%	99.7%

Courtesy of Dr. Yulia Lin

Ducrocq et al. REALITY Trial; JAMA 2021:325:552-560

Figure 2. Rate of Major Adverse Cardiovascular Events in a Study of the Effect of a Restrictive vs Liberal Blood Transfusion Strategy Among Patients With Acute Myocardial Infarction and Anemia



No. of patients at risk

Liberal group	324	301	293	285	281	278	275
Restrictive group	342	326	319	314	307	305	305

Results shown are of analyses including the as-randomized population. All patients were followed up to the first event or 30 days. Major adverse cardiovascular events are a composite of all-cause death, stroke, recurrent myocardial infarction, or emergency revascularization prompted by ischemia.

Table 4. Adverse Events Among the As-Randomized Population in a Study of the Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Patients With Acute Myocardial Infarction and Anemia

Adverse event	No. (%)	
	Restrictive (n = 342)	Liberal (n = 324)
At least 1 adverse event	40 (11.7)	36 (11.1)
Acute kidney injury[a]	33 (9.7)	23 (7.1)
Acute heart failure[b]	11 (3.2)	12 (3.7)
Severe allergic reaction[a]	3 (0.9)	0
Acute lung injury/ARDS[a]	1 (0.3)	7 (2.2)
Multiorgan system dysfunction[a]	1 (0.3)	3 (0.9)
Infection[a,c]	0	5 (1.5)

Abbreviation: ARDS, acute respiratory distress syndrome.

[a] According to investigator judgment.

[b] Adjudicated according to the following criteria: new or worsening symptoms due to congestive heart failure, objective evidence of new congestive heart failure (physical examination, laboratory, imaging or hemodynamic evidence), and initiation or intensification of chronic heart failure treatment.

[c] Documented bacterial infection/bacteremia acquired at any time after the first transfusion.

Ducrocq et al. REALITY Trial; JAMA 2021:325:552-560

START Study

Screening by Technologists and Auditing to Reduce Transfusion

Kron A, Collins A, Cserti-Gazdewich C et al. Transfusion 2021;61:410-422

- Prospective audit of RBC transfusions at 15 hospitals
- Apply **multifaceted interventions** to improve the appropriate use of RBCs at **15 hospitals** with a **baseline appropriateness rating less than 90%**

Pre-intervention 5 months	Intervention 3 months	Post-intervention 10 months
Audit 10 RBCs/month	Adopt RBC guidelines	Audit 10 RBCs/month
	Education	Order screening by MLTs
	Order screening by MLTs	

OUTCOME
Proportion of appropriate RBCs
Proportion of 1u RBCs
Monthly RBCs per 100 AIPD

START Study

- Identified 23 hospitals with <90% appropriate RBC use
- Hospital characteristics:
  - Use ≥ 2000 u RBC / yr
  - ≥ 4u RBC transfused per 100 acute inpatient days
  - 11 community sites, 5 academic in 3 provinces
- Inclusion of 15 hospitals:
  - All RBC orders
  - Inpatients
  - Age ≥ 18 years
- Exclusions:
  - Out-patients
  - Sickle cell anemia
  - Thalassemia
  - Patients < 18 years of age

Pre-intervention 5 months	15 hospitals
Intervention 3 months	13 hospitals
Post-intervention 10 months	13 hospitals

START Study. Transfusion 2021;61:410-422

START Study – Adjudication Criteria

TABLE 1 Criteria used to adjudicate single and multi-unit red blood cell transfusion orders

Hb pre (g/L)	Hb post (g/L)	Symptomatic?[a]	Bleeding?[b]	Details	Appropriate?	Category
≤70	-	No	No	No known cardiac disease	Yes	A1
>70					No	I1
≤80	-	No	No	Known cardiac disease	Yes	A2
>80					No	I2
≤90	-	Yes	No	All patients	Yes	A3
>90					No	I3
≤70	≤90	-	Yes	No known cardiac disease	Yes[c]	A4
>70	>90				No[d]	I4
≤80	≤100	-	Yes	Known cardiac disease	Yes[c]	A5
>80	>100				No[d]	I5
≤100	≤100	-	Yes	Marked ongoing blood loss (>4 units over 24 hours)	Yes[c]	A6
>100	>100				No[d]	I6

	Pre-intervention (n = 650)	Post-intervention 1 (n = 650)	Post-intervention 2 (n = 650)	Aggregate post-intervention (N = 1300)
Sex (%)				
Male	319 (49.1)	306 (47.1)	311 (47.9)	617 (47.5)
Female	331 (50.9)	344 (52.9)	339 (52.2)	683 (52.5)
Age (%)				
18-35	37 (5.7)	38 (5.9)	34 (5.2)	72 (5.5)
36-65	189 (29.1)	205 (31.5)	192 (29.5)	397 (30.5)
66-80	248 (38.2)	226 (34.8)	245 (37.7)	471 (36.2)
>80	176 (27.1)	181 (27.9)	179 (27.5)	360 (27.7)
Admitting diagnosis (%)				
Gastrointestinal	164 (25.2)	147 (22.6)	136 (20.9)	283 (21.8)
Cardiac	70 (10.8)	66 (10.2)	73 (11.2)	139 (10.7)
Orthopedic	73 (11.2)	72 (11.1)	62 (9.5)	134 (10.3)
Renal/urologic	69 (10.6)	48 (7.4)	50 (7.7)	98 (7.5)
Oncologic	54 (8.3)	50 (7.7)	59 (9.1)	109 (8.4)
Hematologic	44 (6.8)	59 (9.1)	54 (8.3)	113 (8.7)
Respiratory	40 (6.2)	45 (6.9)	45 (6.9)	90 (6.9)
Ob/Gyn	26 (4.0)	20 (3.1)	28 (4.3)	48 (3.7)
Trauma	11 (1.7)	10 (1.5)	11 (1.7)	21 (1.6)
Cerebrovascular	12 (1.9)	8 (1.2)	9 (1.4)	17 (1.3)
Not known	5 (0.8)	17 (2.6)	5 (0.8)	22 (1.7)
Other	82 (12.6)	108 (16.6)	118 (18.2)	226 (17.4)
Comorbidities (%)				
Cardiac	284 (43.7)	294 (45.2)	266 (40.9)	560 (43.1)
Renal/urologic	147 (22.6)	156 (24.0)	166 (25.5)	322 (24.8)
Respiratory	113 (17.4)	114 (17.5)	116 (17.9)	230 (17.7)
Cerebrovascular	58 (8.9)	51 (7.9)	65 (10.0)	116 (8.9)
None of the above	246 (37.9)	239 (36.8)	264 (40.6)	503 (38.7)

START Study

- 1,950 pts audited
- 2,877 RBCs transfused

OUTCOME

Proportion of appropriate RBCs	73.5% --> 84.6%
Proportion of 1u RBCs	37.4% --> 61.1%
Monthly RBCs per 100 AIPD	5.2 --> 4.5%

START Study

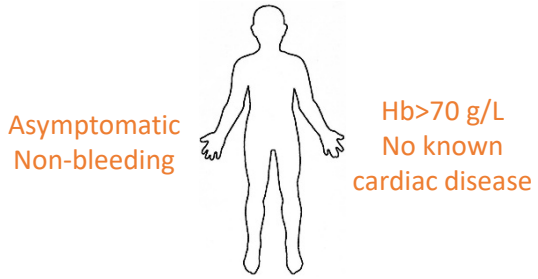
Screening by Technologists and Auditing to Reduce Transfusion

1,950 patients audited, 2,877 total RBC units transfused, 26.5% RBC units transfused were adjudicated as inappropriate pre-intervention

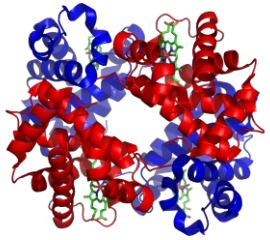
Proportions of appropriateness increased significantly from pre- to post-intervention (73.5% to 85%)

Significant decrease in number of RBCs transfused (average decrease of 458 units per month)

Emergency physicians fell into the lowest proportion of appropriateness (16.9%)

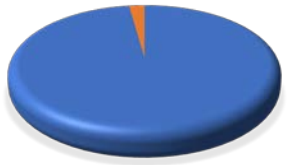


Clinical inpatient scenarios with lowest percentage of appropriate transfusions



Median pre-transfusion Hb decreased from 72 g/L to 69 g/L (p<0.0001) post-intervention

Proportion of single-unit RBC transfusions significantly increased from 46.2% to 68.2%



194 under-transfusion events (Hb <60 g/L) – 2.2% not explained by lab error or clear medical/religious reason

Intervention had no impact on length of stay, need for ICU support, or in-hospital mortality

Courtesy of Ms. Amie Kron (Kron et al., 2021)

FARES Trial

JAMA Network | Open™

Original Investigation | Surgery

Comparison of 4-Factor Prothrombin Complex Concentrate With Frozen Plasma for Management of Hemorrhage During and After Cardiac Surgery

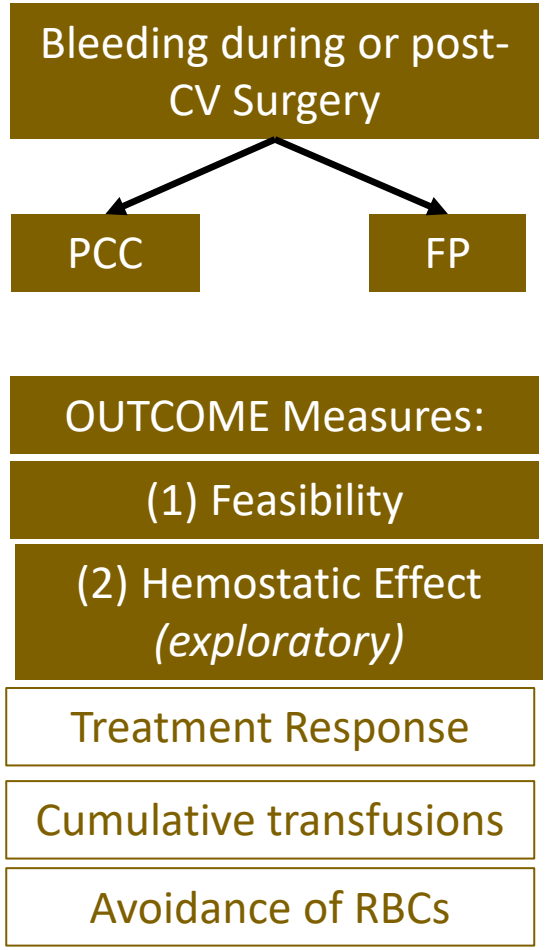
A Randomized Pilot Trial

Keyvan Karkouti, MD; Justyna Bartoszko, MD; Deep Grewal, MD; Cielo Bingley, RN; Chantal Armali, BSc; Jo Carroll, BHA; Hans-Peter Hucke, PhD; Amie Kron, MSc; Stuart A. McCluskey, MD; Vivek Rao, MD; Jeannie Callum, MD

Karkouti K et al. JAMA Network Open. 2021;4(4):e213936. doi:10.1001/jamanetworkopen.2021.3936

FARES Trial: Phase 2 Pilot RCT

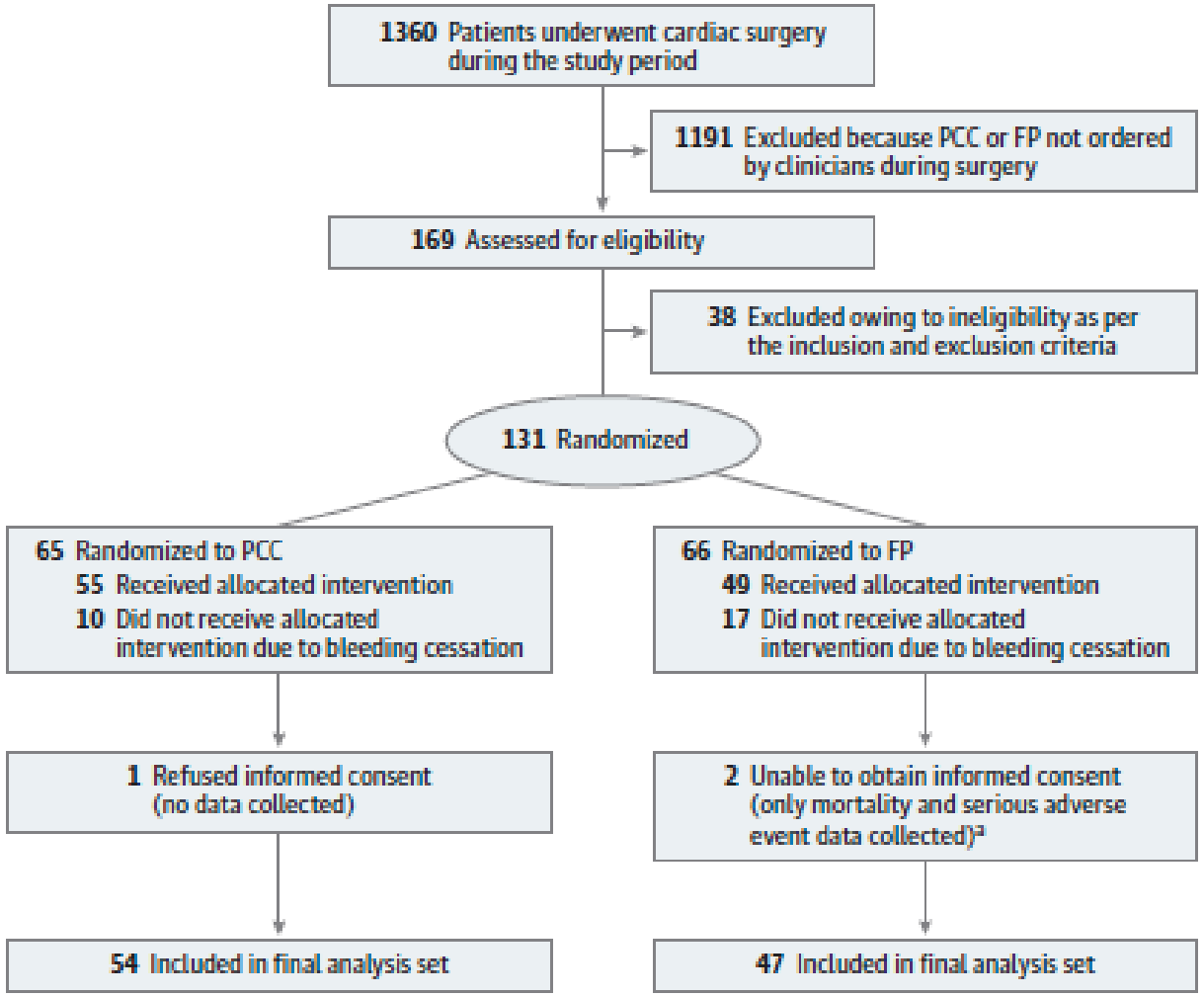
- FP used in 15% of patients undergoing CV surgery
- Can PCC be used in bleeding patients during and post-CV Surgery?
- Target N = 120 (to obtain 100 treated patients)
- 2 Sites



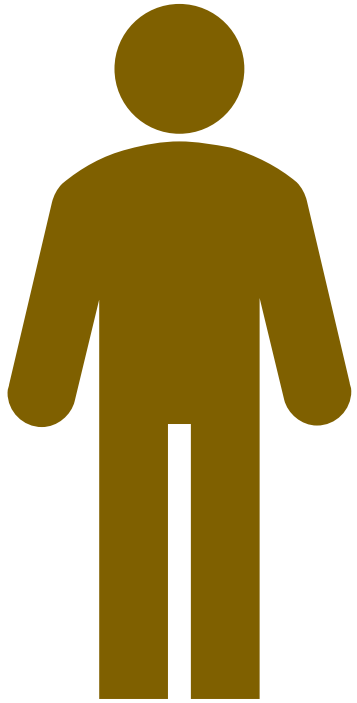
Exclusions:
Pre-op FP or PCC
Severe allergic reaction
HIT
Pregnancy
Refusal of blood products
Heart transplant or VAD or TAA repair
On Warfarin with INR >1.5 or DOAC <48h

FARES Trial: Phase 2 Pilot RCT

Figure. Enrollment, Randomization, and Treatment of Study Population

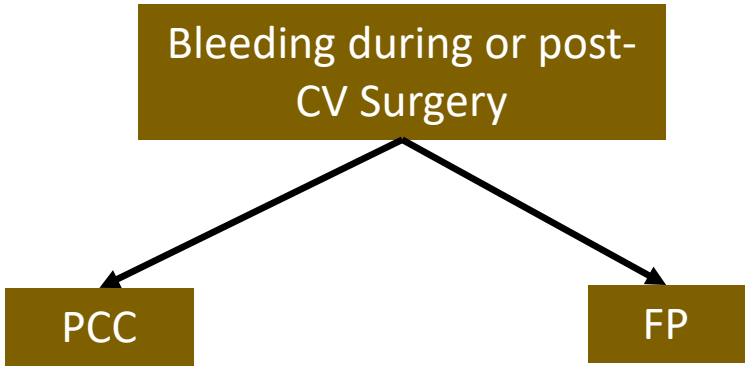


Average Participant



66 y.o. M, Caucasian
history of HTN, DLP
No history of MI
NYHA Class II, EF >50%
Undergoing Aortic valve procedure
With CP bypass duration of 170 min

FARES Trial: Phase 2 Pilot RCT



N=54	N=47
Male 74.1%	70.2%

- Primary outcome: Larger trial feasible
- Exploratory outcomes:
  - PCC group required less hemostatic therapy at 24h
  - PCC group had less bleeding at 24h
  - PCC group had lower overall transfusions within 24 h (6u vs. 14 u)
  - No difference in adverse events at 28d

FARES-2 RCT is currently underway

Table 2. Details of Intervention, Laboratory Values, Bleeding Severity, and Hemostatic Therapies (continued)

Variable	PCC group (n = 54)	FP group (n = 47)	*P* value
Bleeding severity and hemostatic therapies			
Postintervention hemostatic therapy from 60 min to 4 h, No. (%)[e]			
No	43 (79.6)	32 (68.1)	.25[a]
Yes	11 (20.4)	15 (31.9)	
Postintervention hemostatic therapy from 60 min to 24 h, No. (%)[e]			
No	41 (75.9)	31 (66.0)	.28[a]
Yes	13 (24.1)	16 (34.0)	
Bleeding categories according to modified UDPB classification[f]			
Moderate (class 2), No. (%)	42 (79.2)	29 (61.7)	.08[a]
Severe or massive (classes 3 and 4), No. (%)	11 (20.8)	18 (38.3)	
Chest tube drainage, mL			
12 h			<.001[b]
No.	53		
Median (IQR)	310 (250-455)	500 (310-750)	
24 h			<.001[b]
No.	53		
Median (IQR)	450 (370-630)	700 (470-950)	

Electronic Audit of Plasma Use in Ontario

Manuscript in review

Why Audit Plasma use in Ontario?

- Inappropriate plasma use is a universal problem
  - 2007 Ontario audit showed 45% of plasma use was inappropriate[1]
  - ICUs in Australia and New Zealand had 26% of plasma transfusion in non-bleeding patients with INR <1.5[2]
- Plasma has higher risk of both TACO and TRALI compared to other blood products[3]
  - TRALI risk is 7x higher with plasma, compared to RBCs
  - TACO risk is higher with plasma
- Plasma use 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[4]

1. Transfusion. 2013;53(10):2222-9.
2. Intensive Care Med. 2010;36(7):1138-46.
3. Transfusion. 2009;49(3):440-52.
4. Lancet Haematol. 2016;3(3):e139-48.

What are the indications for plasma use?

Moderate to severe bleeding

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

Warfarin reversal ONLY if PCC is contraindicated

Factor replacement if factor concentrate unavailable*

Plasmapheresis for TTP or in patients with bleeding*

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

** SDP may be indicated here*

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

Plasma is not indicated in...

Non-bleeding patients with elevated INR with no planned procedures

Warfarin reversal if PCCs can be used

Mild bleeding

Facor replacement when factor concentrates are available

Plasma dose

- Plasma standard dose is 15 mL/kg
  - For a 70 kg individual it is 4 units
  - Decided based on laboratory testing showing increase in factor levels rather than clinical outcomes
- Ideally, factor levels >30% required for reversing 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]
- Decrease in bleeding risk with prophylactic plasma use for elevated INR has not 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

Electronic Plasma Audit in Ontario

- AIM: Determine appropriateness of plasma use for in-patients at 5 academic centres across Ontario
- Include:
  - All in-patients at selected centres between Jan 1, 2017 to Dec 31, 2017
  - 18 years of age or older
  - Received ≥1 plasma units
- Exclude:
  - Outpatients
  - Age <18 years (Paediatric patients)
  - Out-patients
  - Plasma exchange

Definitions of inappropriate plasma use

Indication	Dose
• INR <1.5 pre-plasma transfusion, within 24h, with no to moderate bleeding • INR ≥1.5 within 24h pre-plasma transfusion, with no or mild bleeding and no invasive procedure performed within 1 calendar day • no INR pre- or post-plasma transfusion and no INR within 12h post-plasma transfusion	• Non-therapeutic dose of ≤ 2 units • 1u = 250mL

Electronic Audit of Plasma Use in Ontario

- >175,000 hospital admissions occurred in 2017 at the 5 sites
- In 2630 (1.5%) hospital admissions met inclusion criteria
- 11 490 plasma units transfused
- Age 61.6 ±16.7 years
- Sex 63% male
- ICU admission in 86% of patients
- Severe bleeding was seen in 71% of admissions
- Top reason for admission was cardiovascular disease in 41.1%
  - Then trauma 18.7%

Electronic Audit of Plasma Use in Ontario

Inappropriate dose or indication
77%

Under-dosing
71%

Mean dose 2.5 ± 1.9 u

Inappropriate indication
35% (25 to 40%)

62% INR<1.5 + no/mild bleed or no procedure

Pre-transfusion INR <1.8 in 53 to 86%

CONCOR-1

Hospitalized patients with acute COVID-19

Age 16yrs and over

On supplemental oxygen

Convalescent Plasma

Standard of Care

OUTCOME – Intubation or Death at 30 days

STOPPED AFTER INTERIM ANALYSIS FOR FUTILITY

Summary: Updates in Transfusion Medicine

- In patients with acute MI, RBC transfusion threshold of 80g/L is non-inferior to 100g/L for cardiovascular morbidity and mortality
- Adoption of standard RBC transfusion guidelines, education, and active screening by TM MLTs can reduce inappropriate RBC use
- PCC may be a safe and effective alternative in patients bleeding during or after cardiovascular surgery
- In Ontario, up to 77% of plasma use may be inappropriate either due to under-dosing or given for prolonged INR without bleeding/procedure
- Convalescent plasma did not decrease intubation or death in hospitalized patients with COVID-19 illness on supplemental oxygen