Something Old, Something New… Whole Blood in Canada

Dr. Johnathan Mack, MD
November 2023

Canadian Blood Services
BLOOD
PLASMA
STEM CELLS
ORGANS
& TISSUES

DISCLOSURES

- Medical officer with CBS

Overview

- Brief overview of the history of whole blood
- Review LrWB product characteristics
- Discuss potential benefits and risks
- Describe some of the clinical evidence

Context

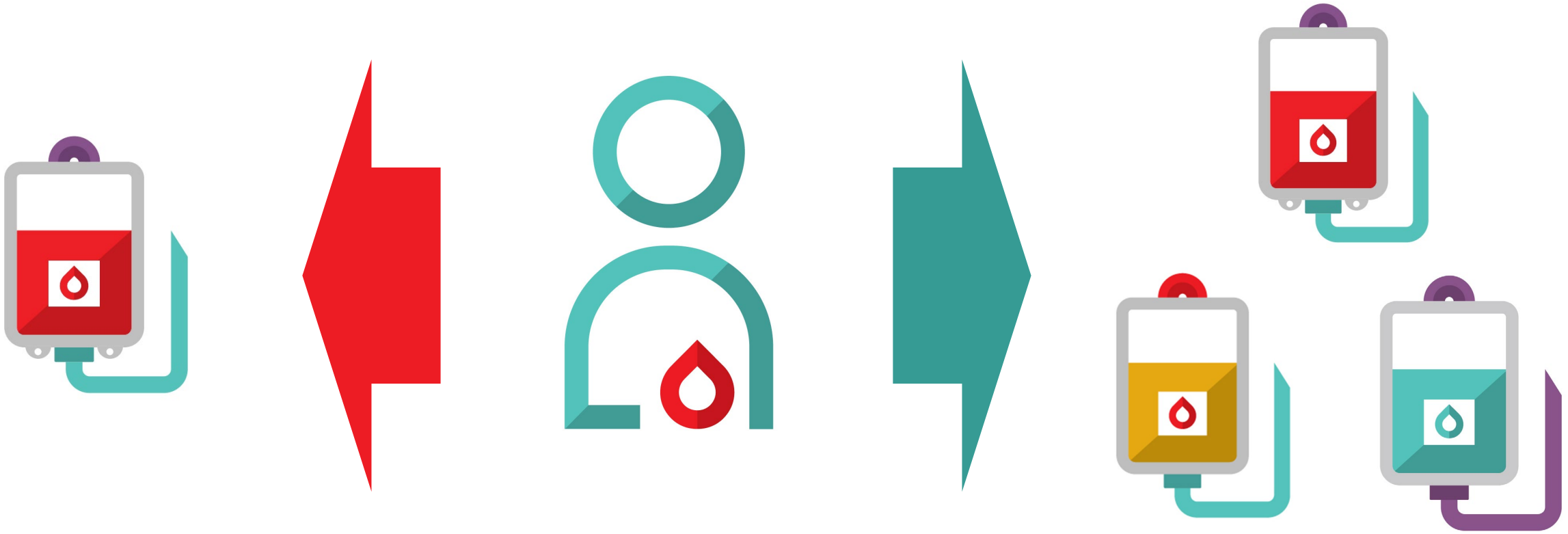
In October 2022, Canadian Blood Services received Health Canada approval for a new product: **Whole Blood, Leukocytes reduced**

The product is currently exclusively for military use.

Expansion to non-military use will be guided by NAC recommendations.

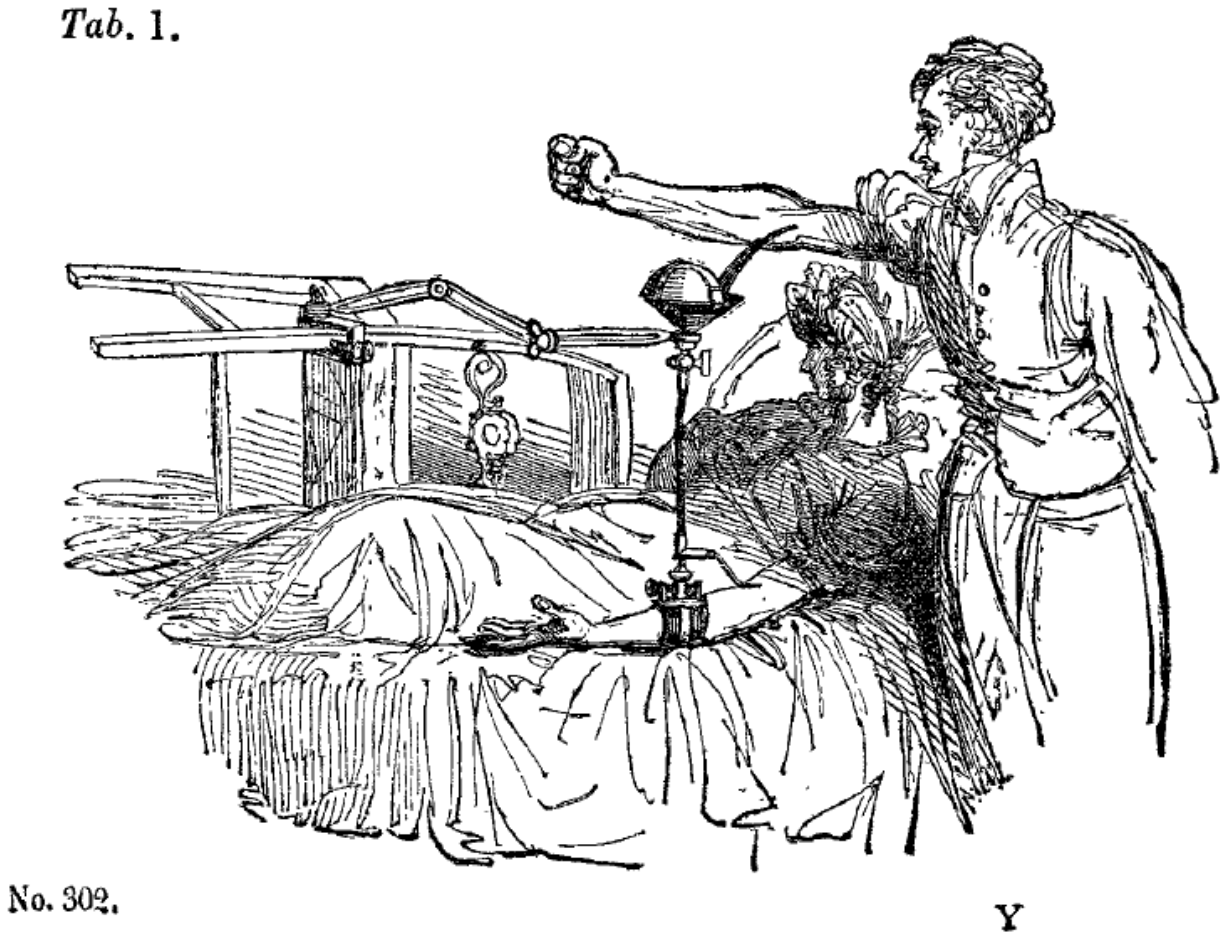
What is Whole Blood?

Whole Blood and ”Conventional” Blood Components



Whole Milk and Component Dairy Products

Dr. James Blundell, 1790-1878

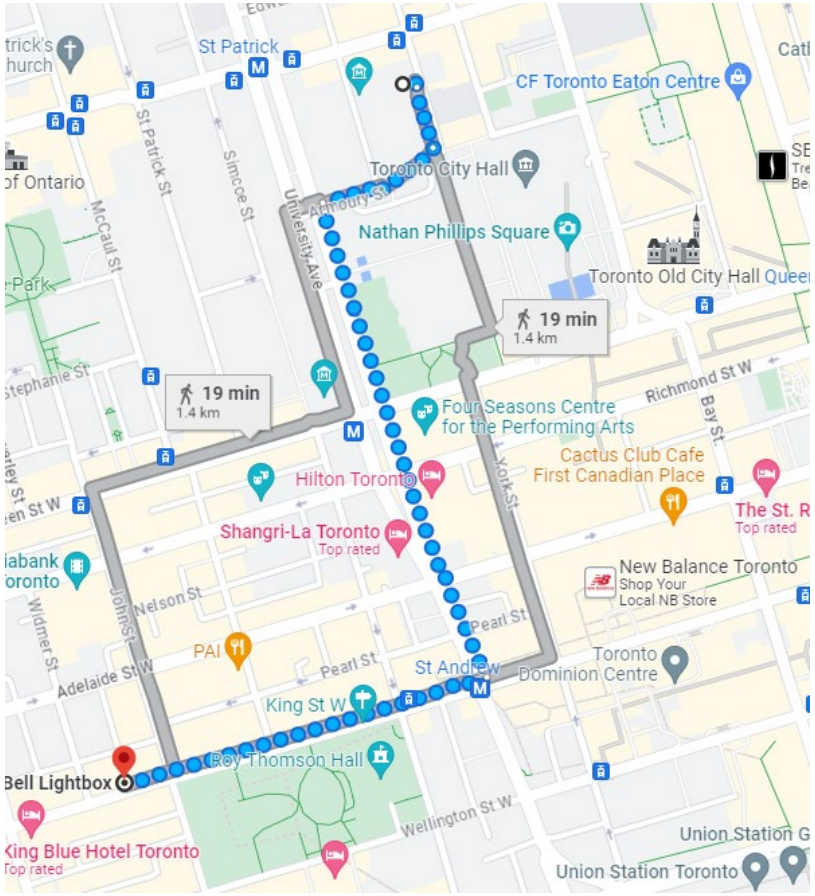


Bovell, J.: On the transfusion of milk, as practised in cholera, at the cholera sheds, Toronto, 1854. Canad. J. 3: 188, 1855.

At I o'clock p.m.—Finding that there was no improvement, but, on the contrary, that the symptoms had not yielded, I proposed to my friend and colleague, Dr. Hodder, to follow out a plan of treatment which had already been discussed between us, namely, that we should transfuse warm fresh milk into the veins. Dr. Hodder coinciding in

opinion was based, readily assented to the operation. Previous, however, to undertaking one of so serious a nature, as we then deemed it to be, I sought the advice of some other medical friends, among the number, Dr. Widmer, who, by message, as I could not see him, requested us to be very cautious as to what we did, least, in case of immediate death, the public mind should become excited. One of my

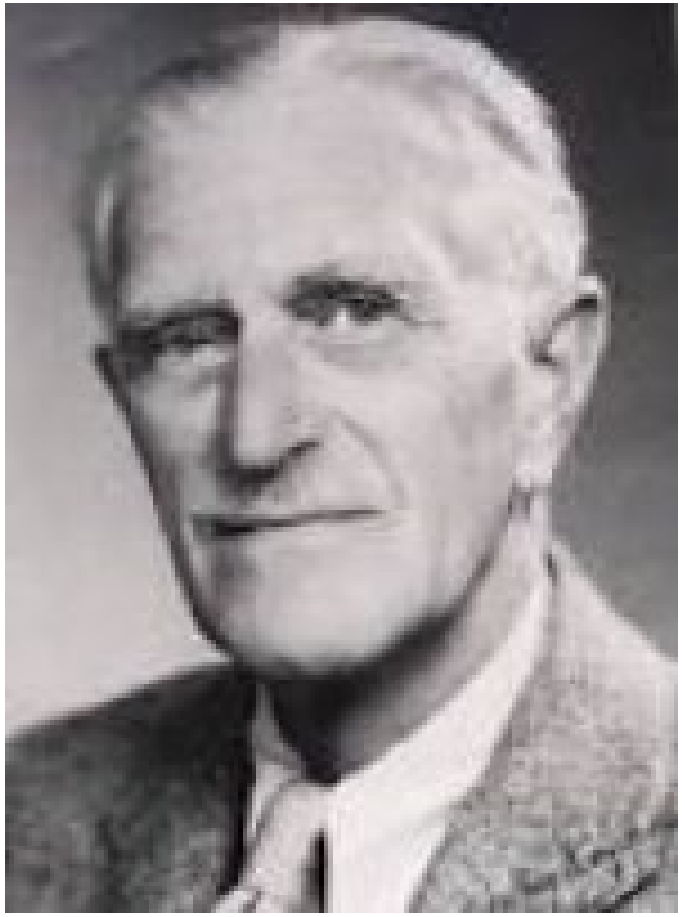
in warm water at the temperature of the blood. A cow, which was grazing close at hand, was brought up to the shed, and the nurse, with great care, keeping the teat close against the side of the vessel, to prevent frothing, drew off the milk in sufficient quantity; the syringe—a



Robertson, Robertson, & Keynes

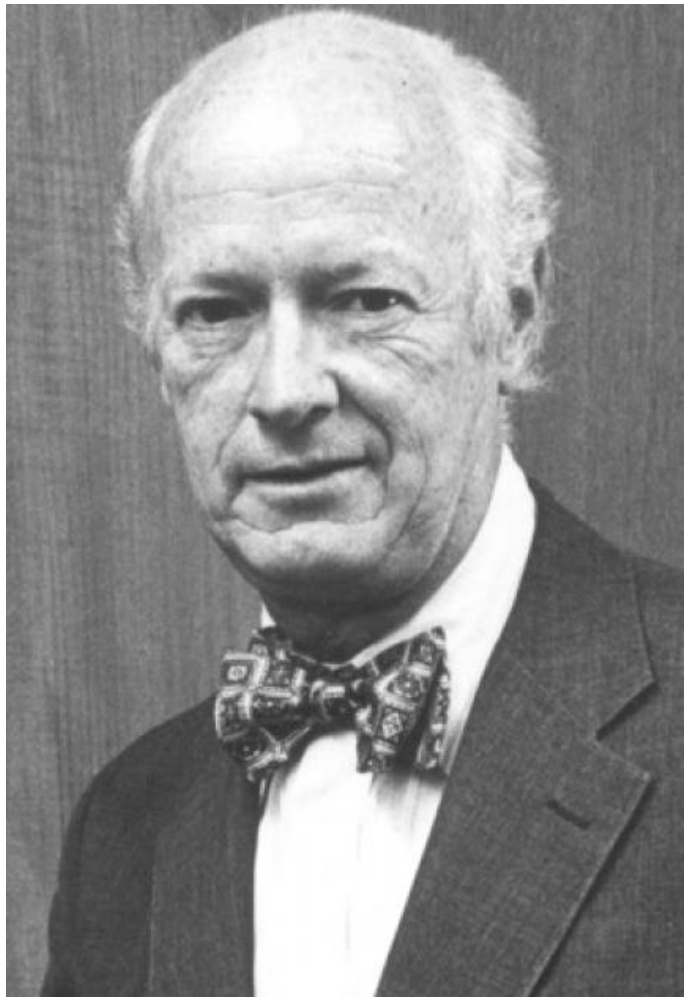
Major Lawrence Bruce Robertson

Captain Oswald Hope Robertson



Sir Geoffrey Keynes

In the bag…a key step in blood component development



Dr. William P. Murphy

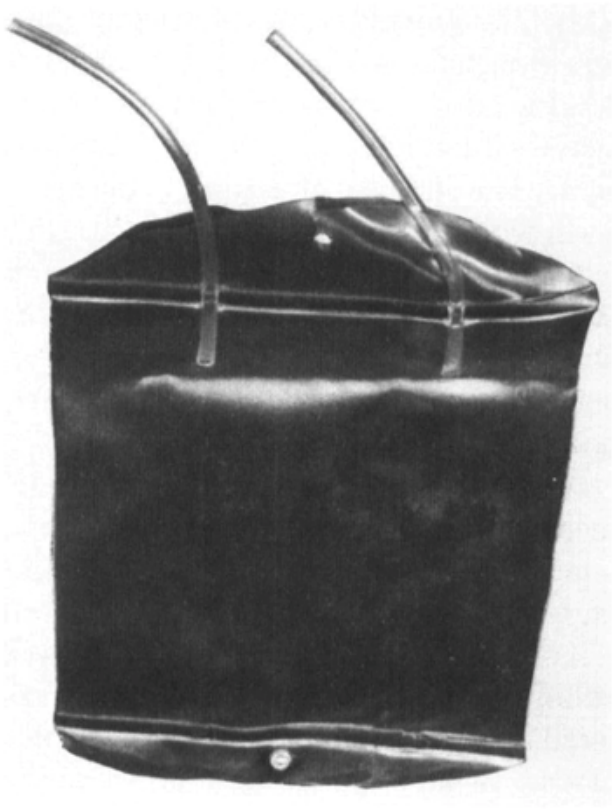


Fig. 1. The Thanksgiving Day blood bag.

Dr. Carl W. Walter

Walter, C. W. and Murphy, W. P., Jr. Surgery Gynec. Obstet. 1952;94: 687-692

Development of a platelet-sparing WBC filter and LrWB

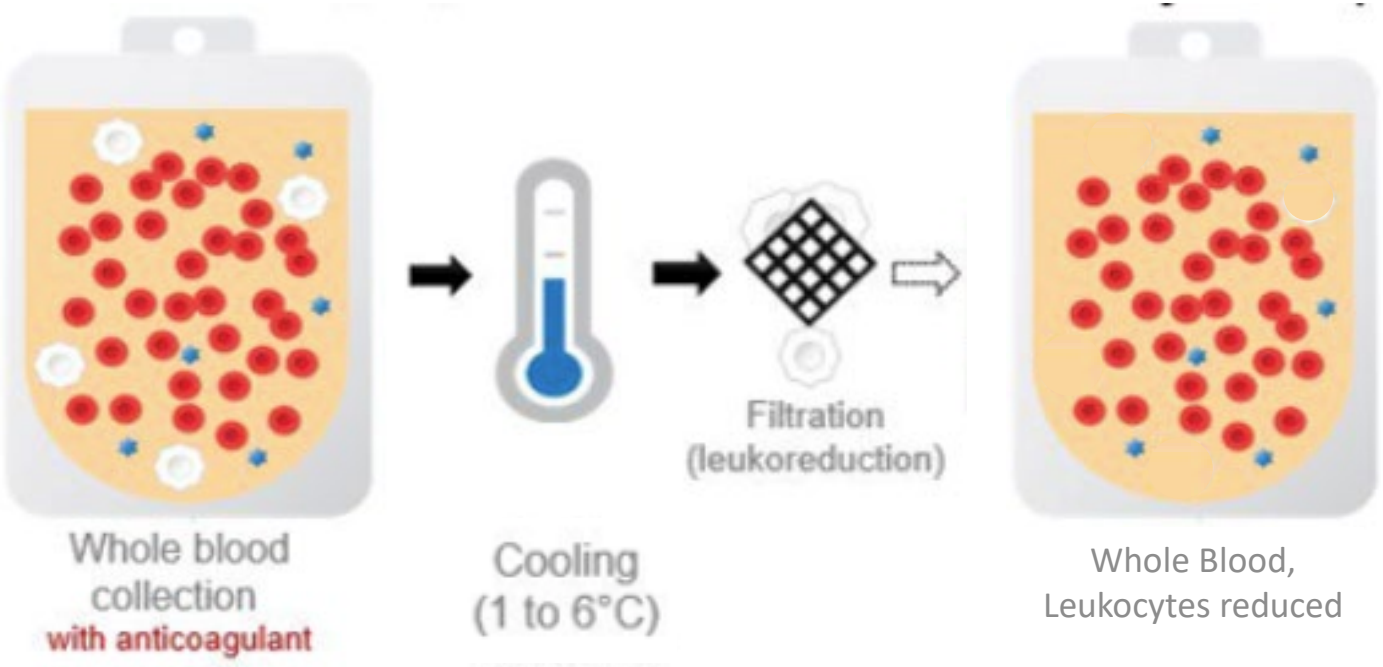


TABLE 1. Recovery of RBCs and platelets after filtration and processing*

Measure	Whole blood	Whole blood after WBC filtration	RBCs after filtration
RBCs (× 10^{12}/unit)	1.99 ± 0.18	1.79 ± 0.15	1.45 ± 0.16
Hb (g/unit)	61 ± 5	55 ± 5	44 ± 5
Platelets (× 10^{9}/unit)	84 ± 22	68 ± 19	ND
Volume (mL)	492 ± 6	449 ± 4	237 ± 10
Hct (%)	36 ± 5	36 ± 1	53 ± 4

* Values are expressed as mean ± SD.

Platelets White blood cells Red blood cells

Larsson S et al. Transfusion. 2002;41:534-539.

LRWB Product Characteristics

LRWB VS CONVENTIONAL COMPONENTS

	LrWB	RBCs	PR PLTs (BC/Aph)	Frozen Plasma
Mean unit volume (mL)	496	287	181/277	289
Anticoagulant	CPD	CPD	CPD/ACD-A	CPD
Hematocrit (%)	0.41	0.67	-	-
Hemoglobin (g)	62	55	-	-
PLT count (x 10^9 per unit)	83	-	243/252	-
Factor VIII (U/mL)	0.78	-	-	0.88

Storage and Shelf-life



Product	Storage Temperature	Shelf-life	Notes
Platelets	20-24˚C	7 days	Agitation required
Whole Blood	**1-6˚C**	**21 days**	-
RBCs	1-6˚C	42 days	-
Frozen Plasma	≤18˚C (frozen) 1-6˚C (thawed)	12 months 120 hours	**Requires thawing**



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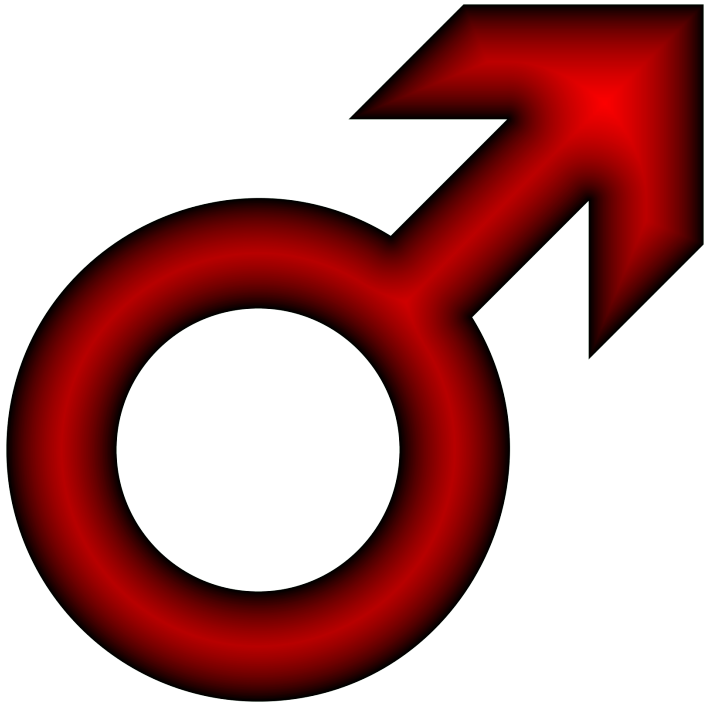
SELECTION OF DONATIONS

Donations used for LRWB

- Male donors (TRALI risk mitigation)
- Group O
- Low-titre anti-A/B isohemagglutinins

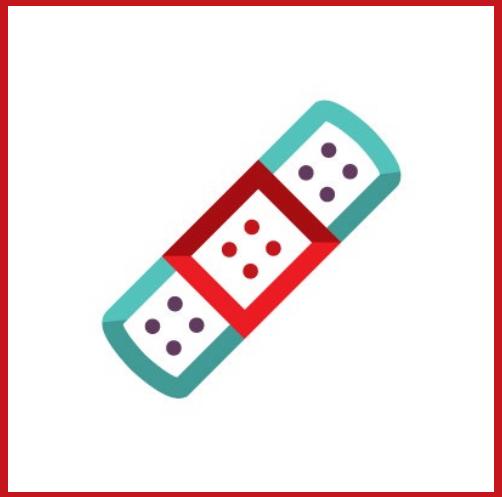


LRWB Indications

Indications

Treatment of clinically significant bleeding.

Benefits and Risks

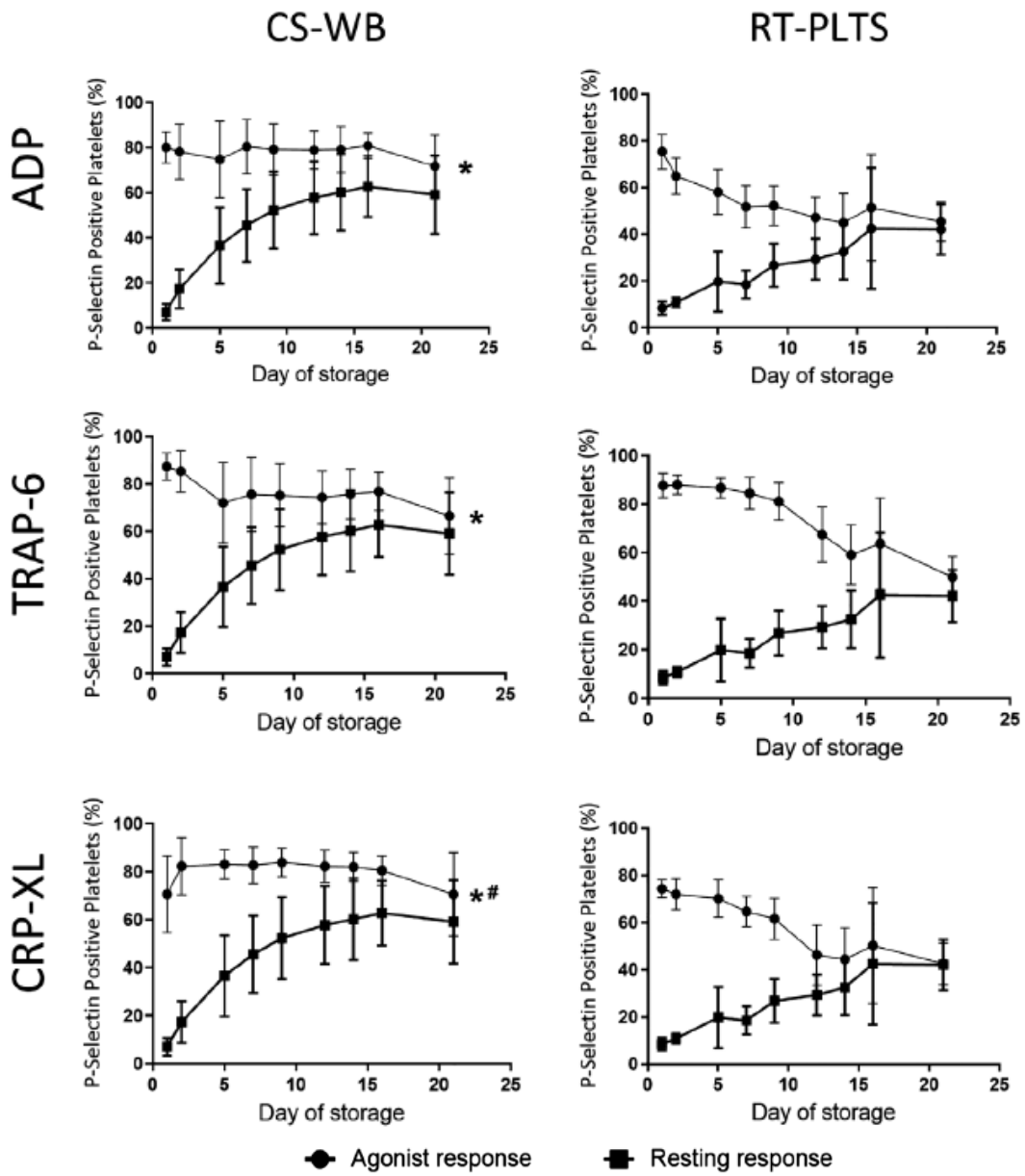


What are possible benefits with leukoreduced whole blood?

Definite Advantage: Logistics/Administration

- Storage simplified: 1-6˚C, no agitation
- Shelf-life: longer compared with platelet concentrates and thawed plasma
- Faster to issue: no thawing required
- Easier to administer: 3 vs 1

Possible Advantage: Cold-Stored Whole Blood vs Platelet Concentrates - platelet activation and response to agonists



Huish et al. Transfusion. 2021;61:3224-3235.

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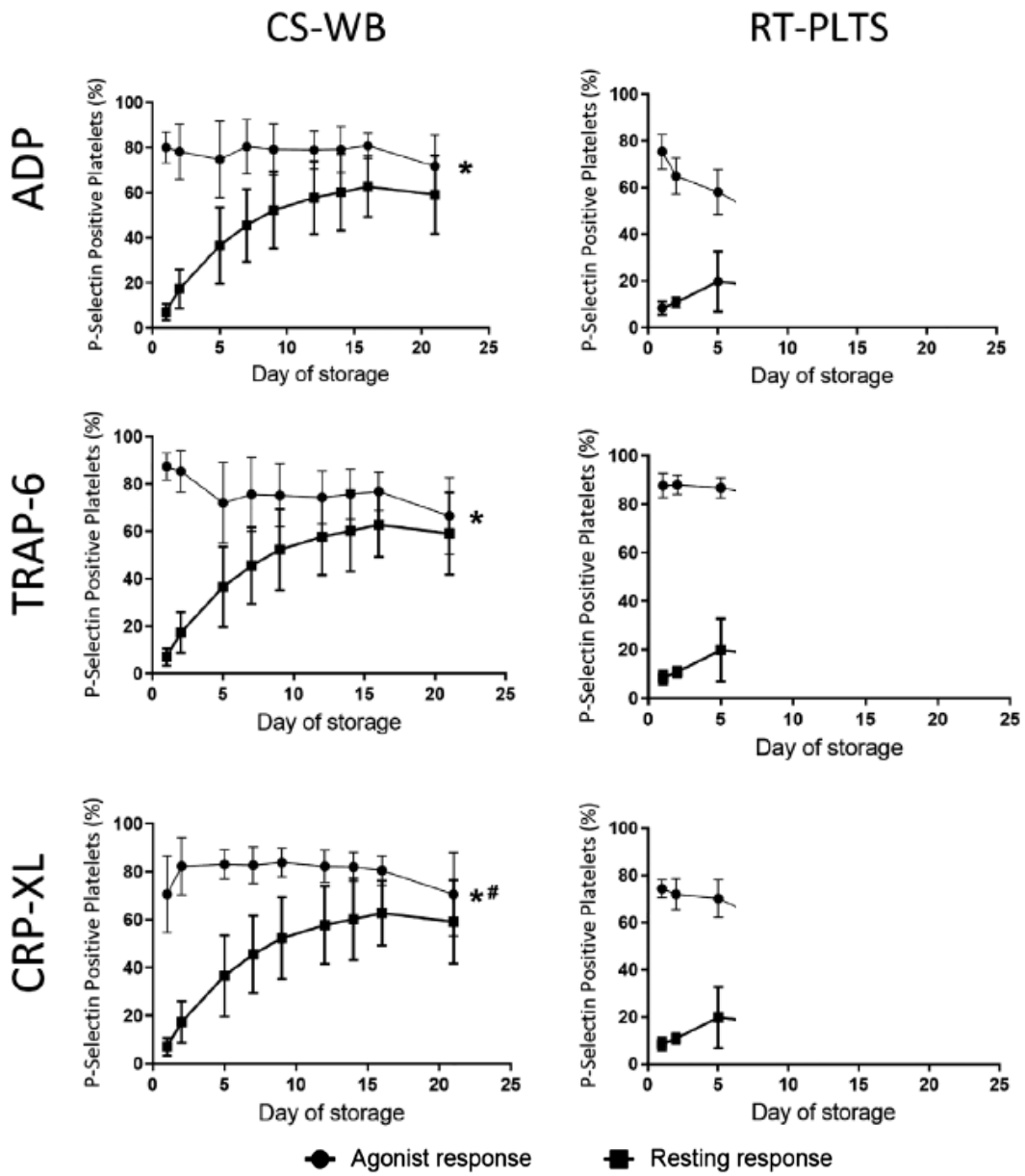

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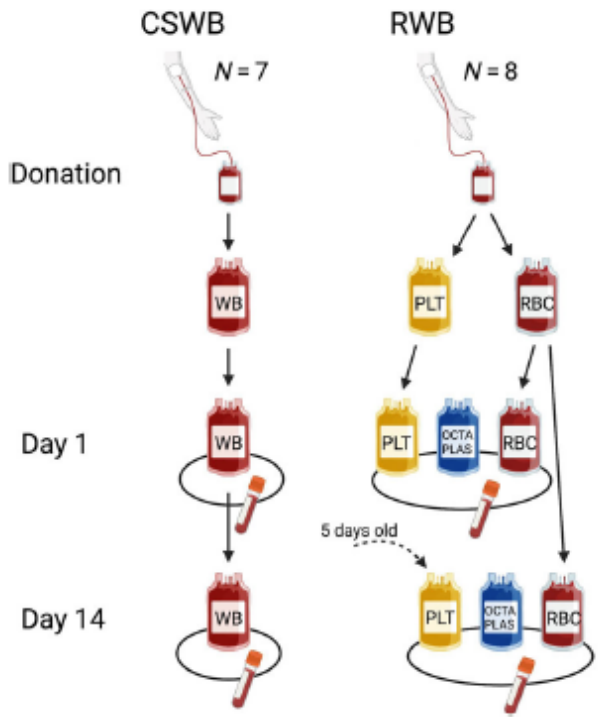
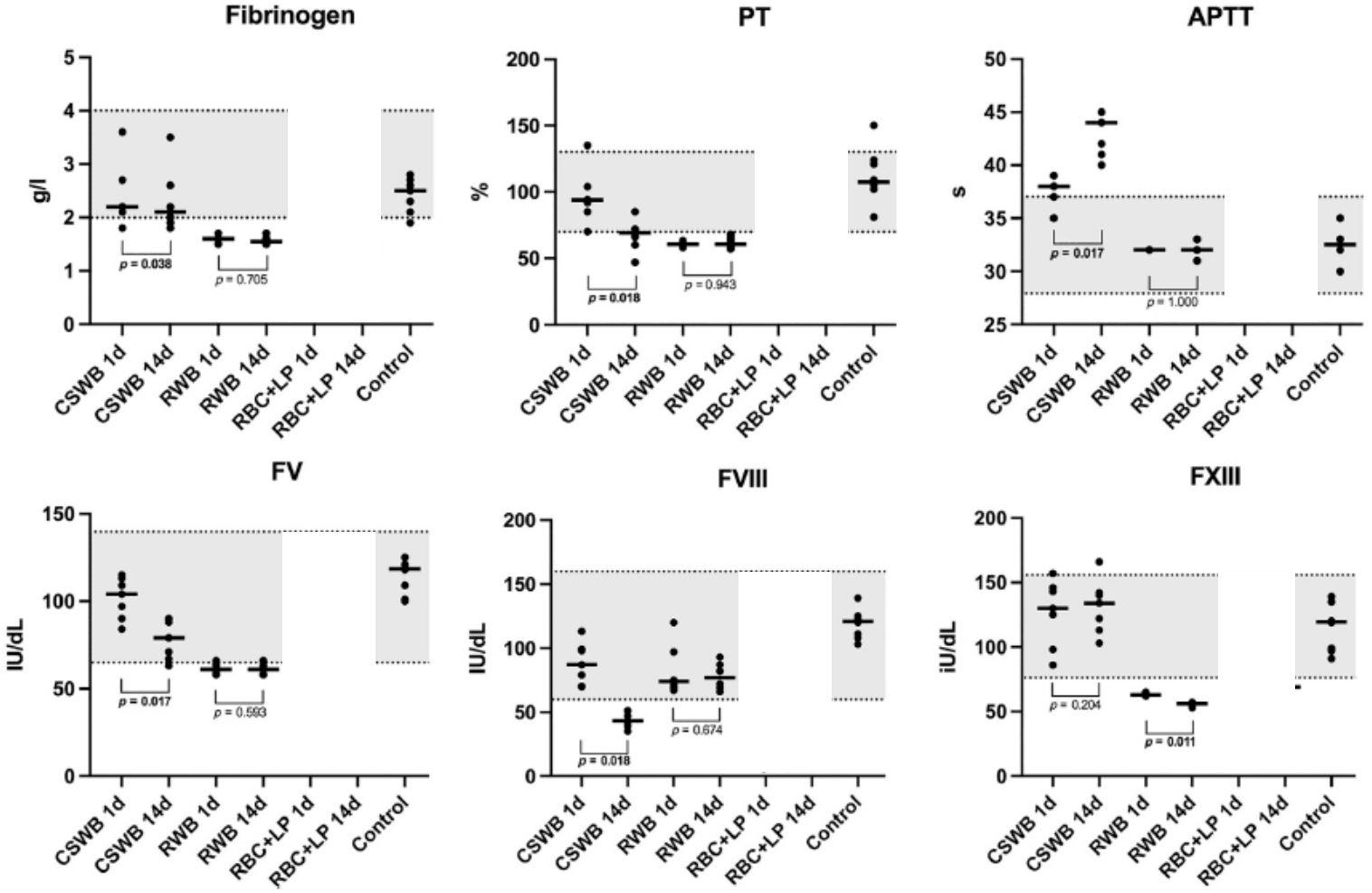
In vitro characteristics of cold-stored whole blood vs reconstituted whole blood





Susila S et al. Vox Sanguinis. 2023;118:523-532.

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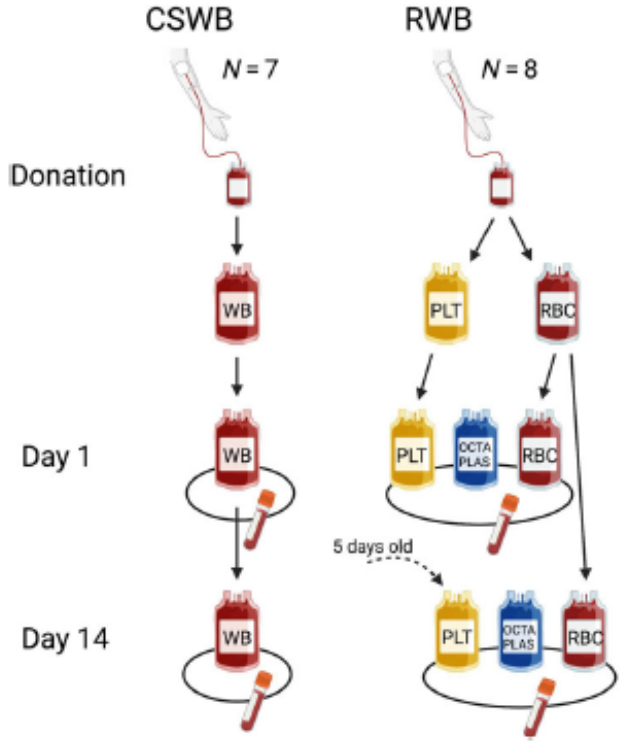

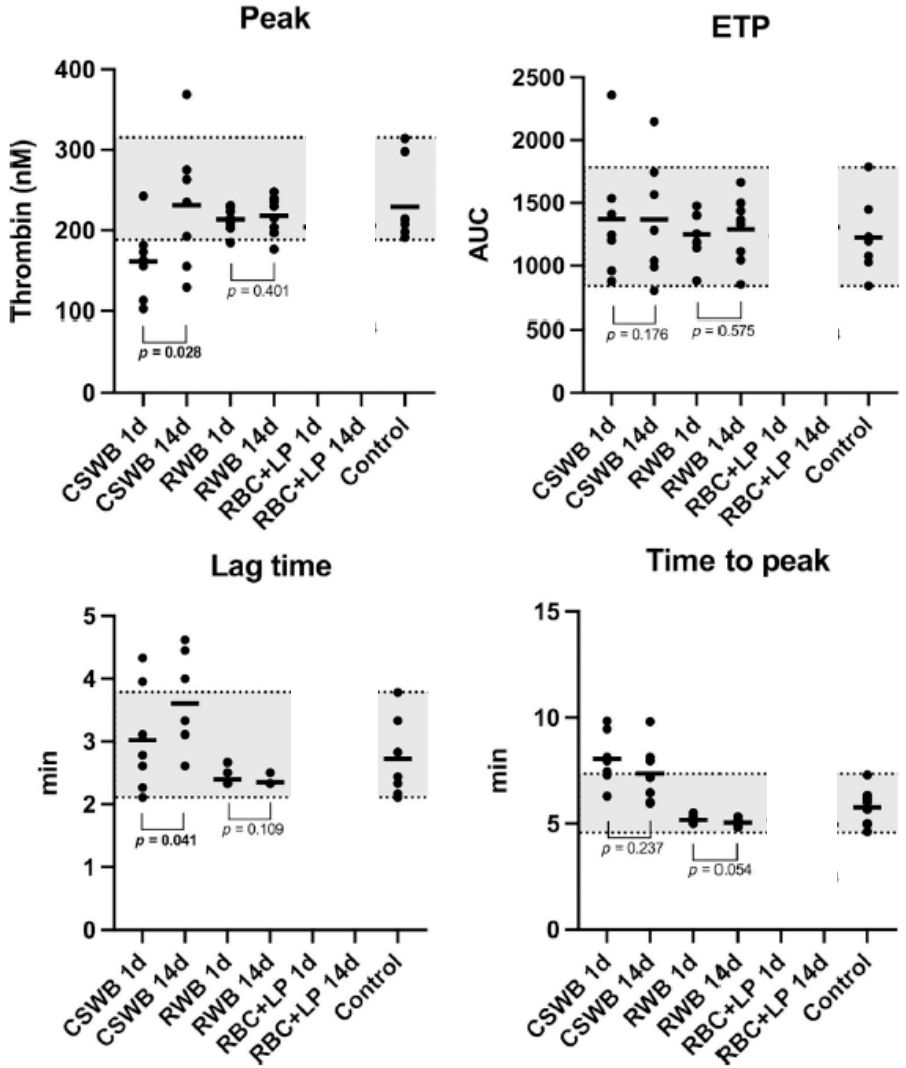

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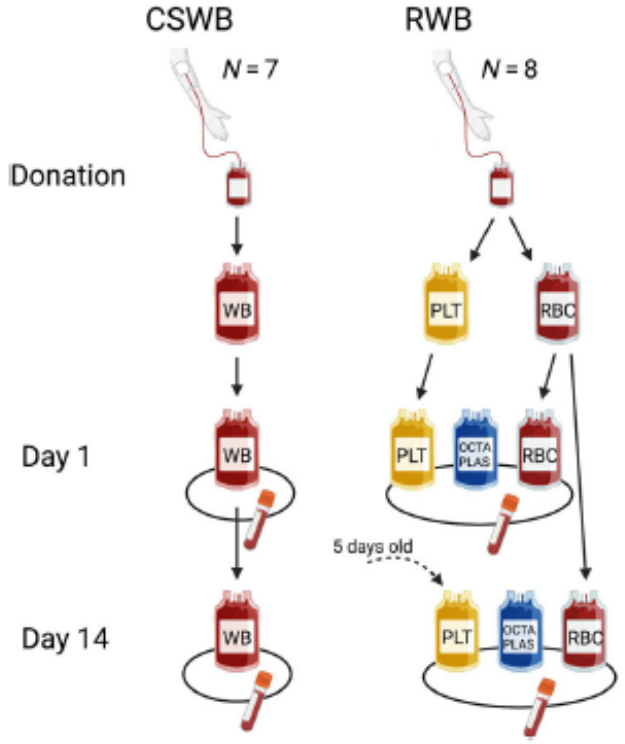

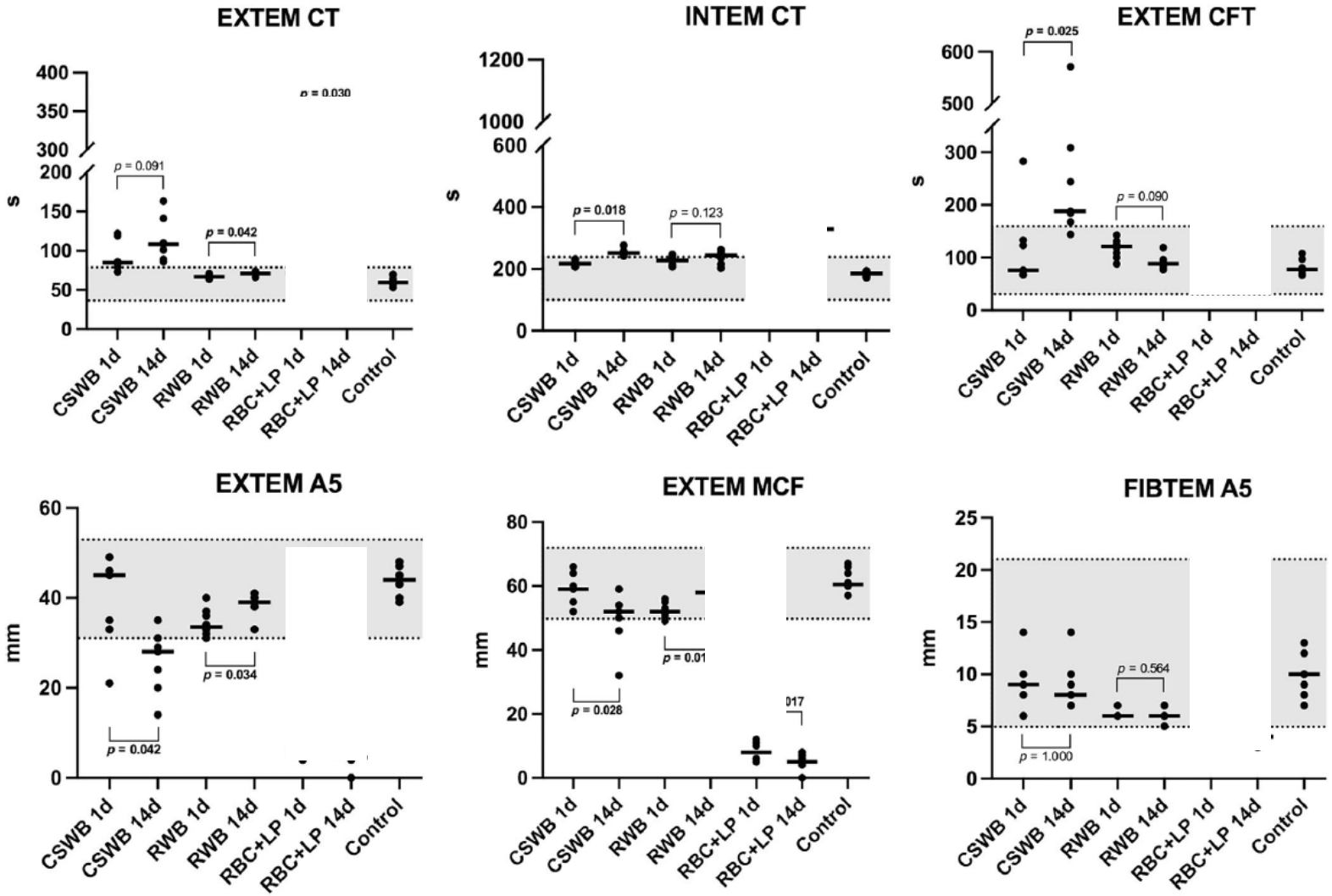

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Susila S et al. Vox Sanguinis. 2023;118:523-532.

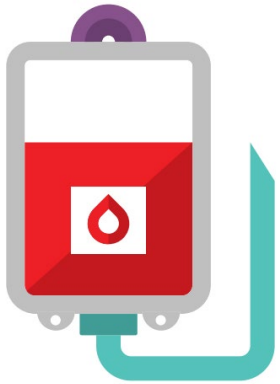
Possible Advantage: Earlier Plasma Administration

Trial	Year	Design	Sample Size	Intervention	Control	Outcome	Results
PAMPer (air, US)	*2014-2017*	*Multi-center cluster-randomized (bases)*	*523, prehosp*	*2 units plasma*	*Crystalloid*	*30-day mortality*	*23.2% vs 33.0%, HR 0.64 (95%CI 0.45-0.91)*
COMBAT (ground, US)	2014-2017	Single center RCT (patients)	144, prehosp	2 units plasma	0.9% saline	28-day mortality	15% vs 10%, RR 1.54 (95%CI 0.60-3.98)
RePHILL (ground, UK)	2016-2021	Multi-center RCT (patients)	509, prehosp	2 RBCs + 2 LyoPlas	0.9% saline	Death prior to discharge and/or failure to clear lactate	64% vs 65%, RR 1.01 (95%CI 0.88-1.17)
PROCOAG (Fr)	2017-2021	Multi-center RCT	324, in-hosp	4F-PCC	0.9% saline	Blood products transfused ≤24h	12 (5-19)U vs 11 (6-19)U, AD 0.2 (95%CI -2.99-3.33)

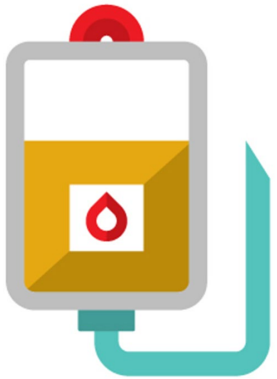
What are possible risks with leukoreduced whole blood?

Leukoreduced Whole Blood and ABO Compatibility

Group O LrWB



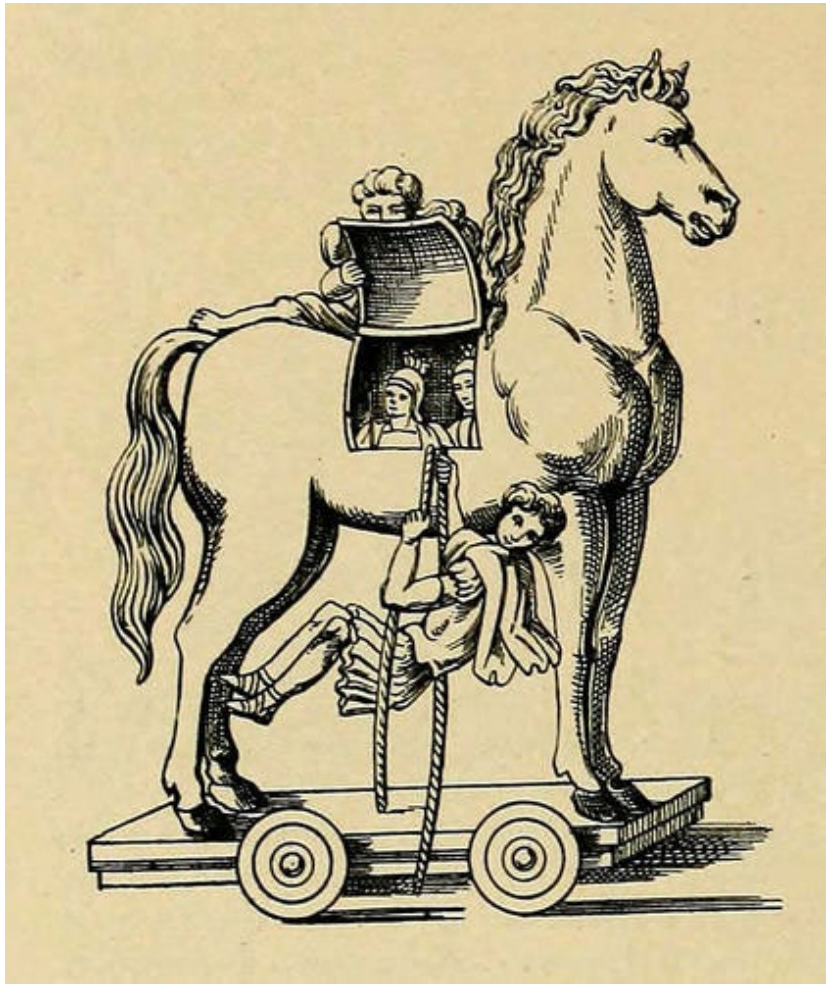
Recipient ABO	RBC Compatibility
O	☺
A	☺
B	☺
AB	☺



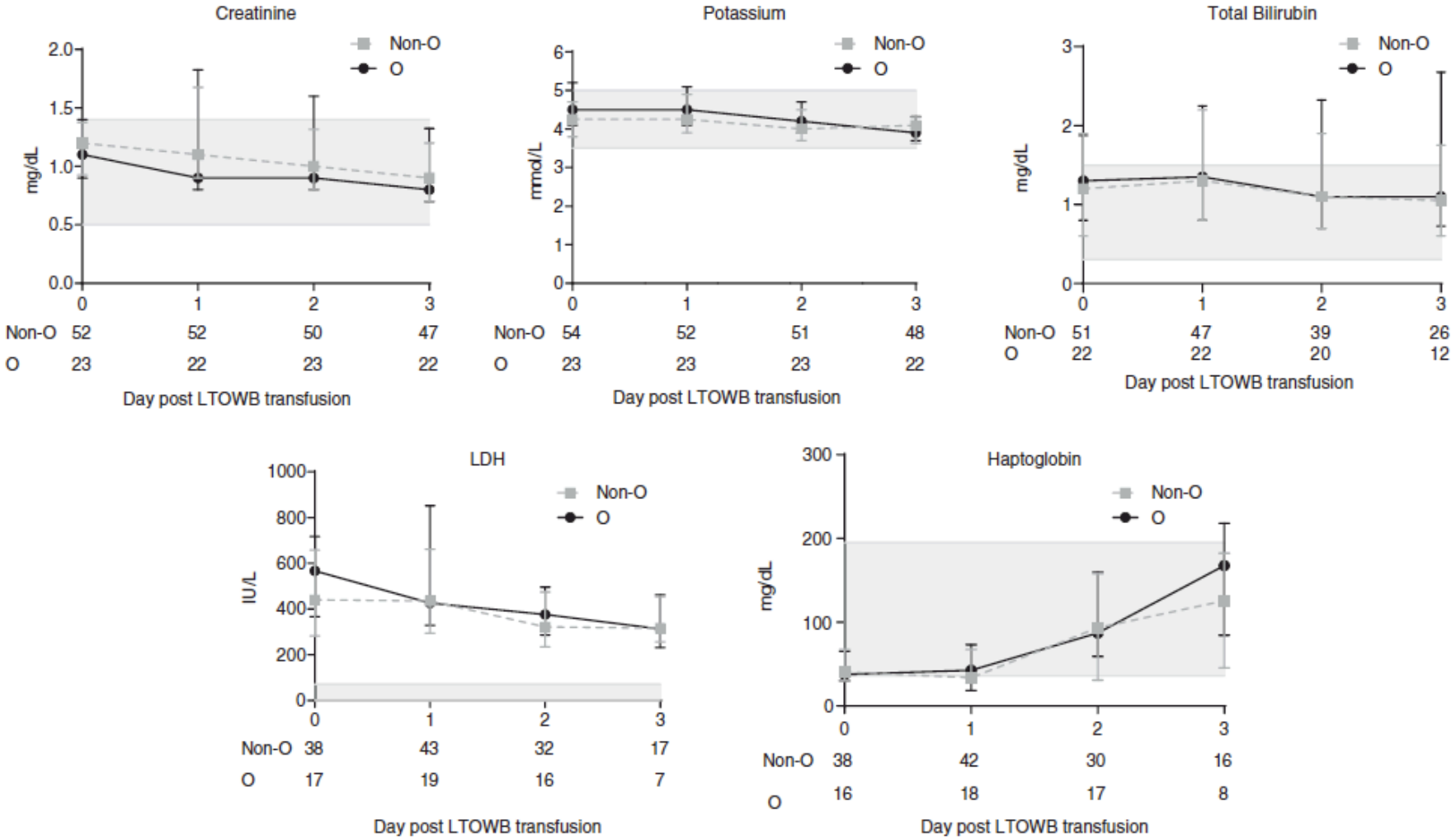
Recipient ABO	Plasma Compatibility
O	☺
A	☹
B	☹
AB	☹

Safety of Group O Whole Blood?

- Obligate incompatibility with either RBCs or plasma, unless using group-specific whole blood
- Group O – universal RBC donor, plasma only compatible with group O
- Use of donors with ‘low-titre’ anti-A/B mitigating factor
- CBS low titre: <1:32 automated (<1:128 manual)



LTOWB and Hemolysis: no difference in Cr, K, Bili, LDH, Haptoglobin for O vs non-O recipients



Harrold IM et al. Transfusion. 2020;60:S24-S30.

Safety of Incompatible Plasma Transfusion

STAT:

TABLE 3. Outcome data between groups*

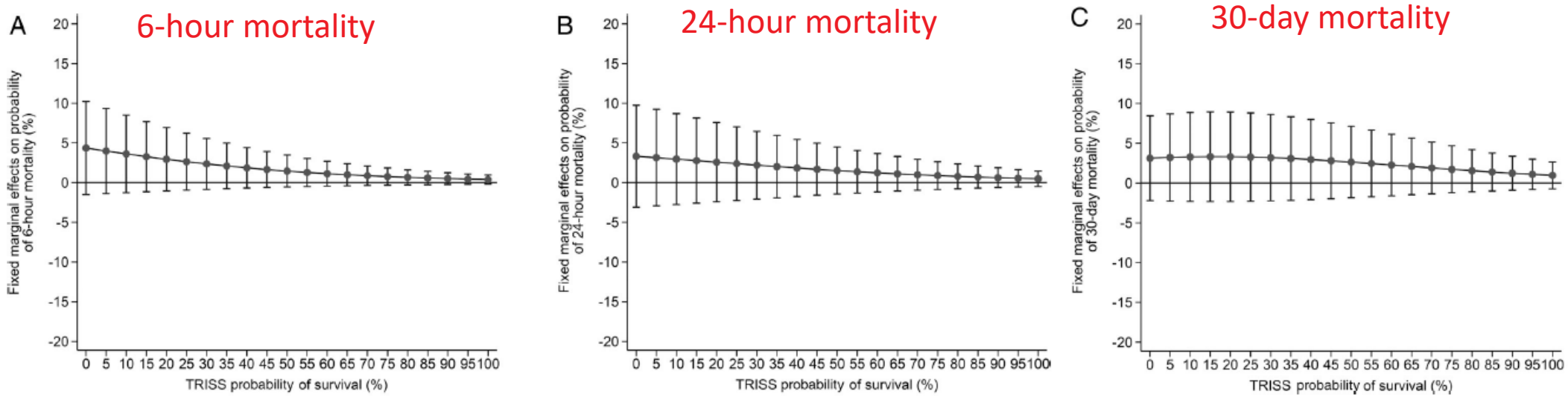
	Identical (n = 809)	Incompatible (n = 354)	p value
In-hospital mortality			
Survival to discharge	572 (71)	253 (71)	0.83
In-hospital death	237 (29)	101 (29)	
Early mortality (<24 hr)			
Yes	114 (14)	59 (17)	0.28
No	695 (86)	295 (83)	
Hospital LOS (days)	14 (0-111, 17)	14 (0-128, 18)	0.89

* Categorical data are reported as number (%), and continuous data are reported as mean (range, SD).

In-hospital death:
29% vs 29%

<24 hour death:
14% vs 17%

MENGO:



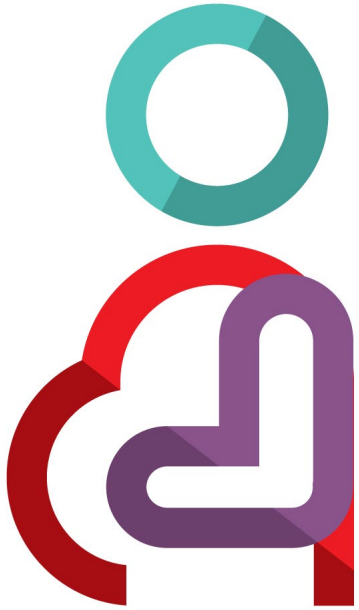
Canadian Blood Services — BLOOD PLASMA STEM CELLS ORGANS & TISSUES

Dunbar N, et al. Transfusion. 2017;57:1879-1884
Seheult J, et al. Transfusion. 2020;60:2517-2528

Safety of Group O-Positive Whole Blood?

Vast majority of donors are RhD positive:

	RhD-positive	RhD-negative
White	85%	15%
Black	92%	8%
Asian	99%	1%
Indigenous North American	99%	1%



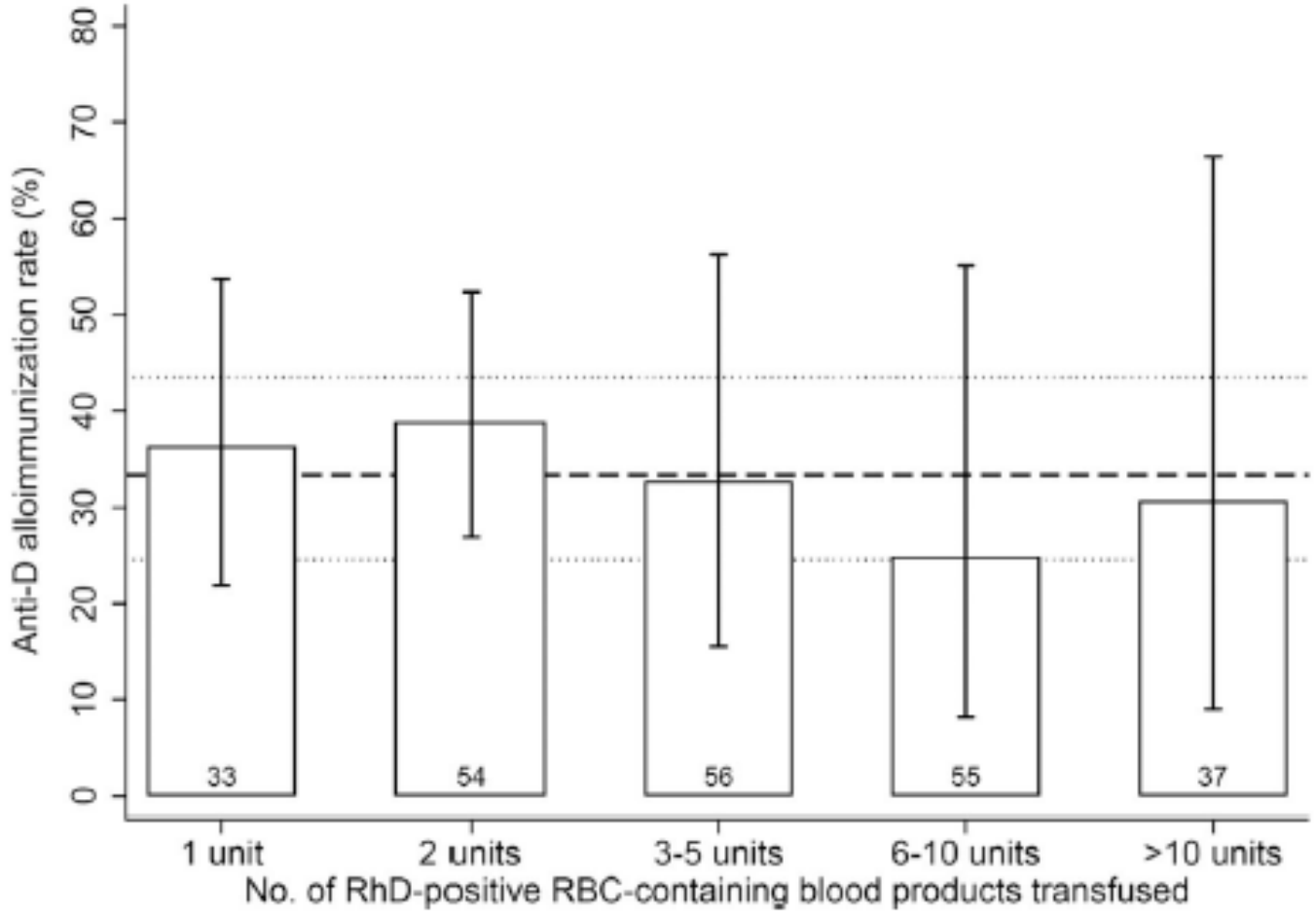
Only ~7% donors in Canada group O-negative

Use of group O-positive LrWB: potential for anti-D formation

Risk of subsequent HDFN for people with child-bearing potential

Risk of hemolytic transfusion reaction if exposed to D-positive RBCs

Risk of D-alloimmunization in trauma



Seheult J et al. Transfusion. 2022;62:S185-S192.

Modeling Harm from RhD Exposure (UK)

Harm	All Recipients (transfusions needed for 1 event)	D-negative females of childbearing potential (transfusions needed for 1 event)
Acute Hemolytic Reaction (Index)	2.7×10^4 (7.6×10^3-3.4×10^5)	6.6×10^3 (1.8×10^3-9.2×10^4)
	TRALI: ~1×10^4	
Acute Hemolytic Reaction (Future)	8.5×10^5 (1.8×10^5-2.1×10^7)	1.4×10^5 (3.1×10^4-3.7×10^4)
	Post-transfusion purpura: ~1×10^5	
Fetal death or permanent disability due to HDFN	2.9×10^4 (1.2×10^4-1.2×10^5)	570 (260-2300)
		Risk of FNHTR: ~300
Any of above	1.4×10^4 (5.6×10^3-4.2×10^4)	520 (250-1700)

Survival increase of ≥1% with LTOWB vs to standard care would lead to life years gained exceeding life years lost

Cardigan R, et al. Vox Sang. 2021;117:701-707.

CAPACITY: LTOWB USE ASSOCIATED WITH INCREASED TOTAL BLOOD USAGE

	pRBC (n = 602)	LTOWB[a] (n = 749)	p-value
0–24 h RBC, U	4.0 (2.0–7.0)	4.0 (2.0–7.0)	.11
0–24 h Plasma, U	0.0 (0.0–3.0)	3.0 (1.0–4.0)	<.0001
0–24 h Platelets, dose[b]	0.0 (0.0–1.0)	0.3 (0.2–0.7)	<.0001
0–24 h Cryoprecipitate, U[c]	0.0 (0.0–0.0)	0.0 (0.0–0.0)	.60
0–24 h Total products, U	4.0 (2.0–12.0)	6.5 (4.2–12.7)	<.0001
0–7 days RBC, U	4.0 (2.0–8.0)	4.0 (2.0–8.0)	.11
0–7 days Plasma, U	0.0 (0.0–4.0)	3.0 (1.0–5.0)	<.0001
0–7 days Platelets, dose[b]	0.0 (0.0–1.0)	0.3 (0.2–0.7)	<.0001
0–7 days Cryoprecipitate, U[c]	0.0 (0.0–0.0)	0.0 (0.0–0.0)	.74
0–7 days Total products, U	5.5 (3.0–13.0)	7.3 (4.3–14.3)	<.0001

Median acquisition cost per patient through 7 days:
RBCs $1110 ($631-$2575 USD) vs LTOWB $1686 ($1068-$3202) USD

Ruby K et al. Transfusion. 2023;63:745-754

WHAT IS THE EVIDENCE FOR CLINICAL OUTCOMES: META-ANALYSIS

Possible Advantage: More Effective Trauma Resuscitation

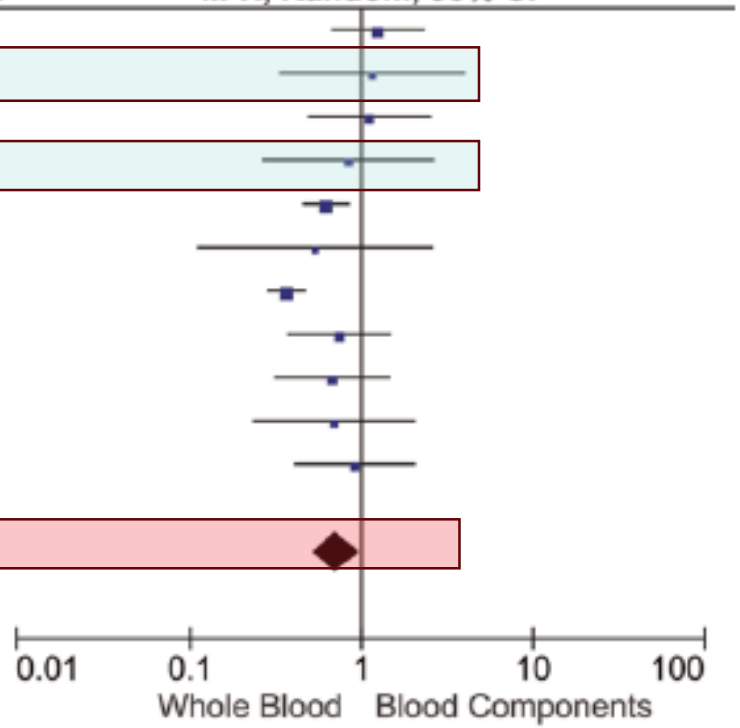
24H mortality

B

Study or Subgroup	Whole Blood Events	Total	Blood Components Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bohan 2021	33	121	22	95	11.1%	1.24 [0.67, 2.32]
Cotton 2014	6	55	5	52	4.8%	1.15 [0.33, 4.03]
Gallahar 2020	12	42	22	83	8.4%	1.11 [0.48, 2.54]
Guyette 2022	6	40	8	46	5.4%	0.84 [0.26, 2.66]
Hanna 2020	48	280	2054	8214	16.4%	0.62 [0.45, 0.85]
Hazelton 2019	2	52	8	115	3.3%	0.54 [0.11, 2.61]
Hazelton 2022	167	1180	138	443	17.3%	0.36 [0.28, 0.47]
Lee 2021	18	169	18	130	10.0%	0.74 [0.37, 1.49]
Seheult 2018	12	135	17	135	8.9%	0.68 [0.31, 1.48]
Shea 2020	7	44	9	42	5.9%	0.69 [0.23, 2.07]
Yazer 2021	13	92	14	92	8.5%	0.92 [0.40, 2.08]
Total (95% CI)		**2210**		**9447**	**100.0%**	**0.71 [0.52, 0.98]**
Total events	324		2315			

Heterogeneity: Tau² = 0.13; Chi² = 24.09, df = 10 (P = 0.007); I² = 58%

Test for overall effect: Z = 2.09 (P = 0.04)



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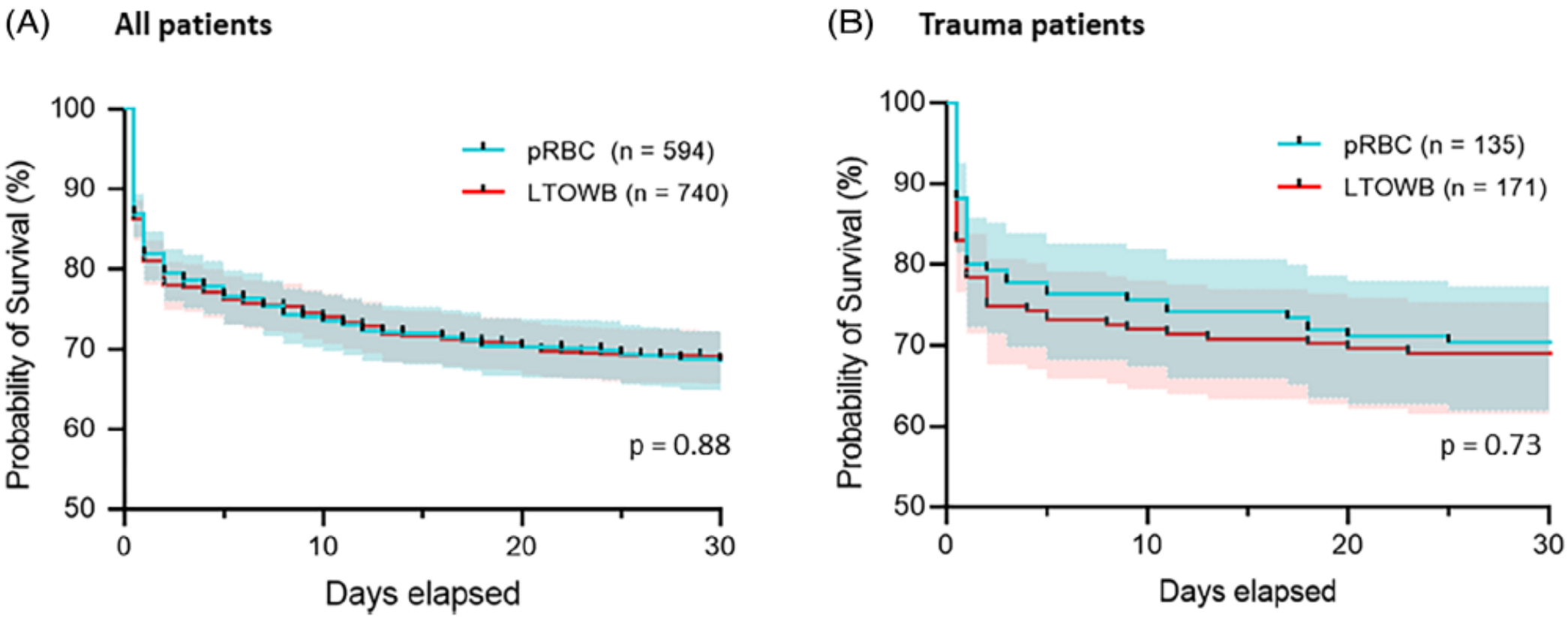
Van der Horst. J Trauma Acute Care Surg. 2023;95(2):256-266

No change in survival at single-center following introduction of LrWB in MHP



Ruby K et al. Transfusion. 2023;63:745-754

Anticipated Clinical Evidence

Name	Setting/Design Country	Comparison	Primary Outcome	Estimated completion
LTO+WB vs Component Therapy for Emergent Transfusion in Trauma Patients	Trauma/RCT USA	LTO+WB vs component	pRBC equivalents transfused in each group in the first 24h	12/2023
SWAT study	Shock, TBI/Obs. USA	WB vs component	4-hour mortality	Completed 03/2022
SWIFT trial	Prehospital trauma/RCT UK	≤2 U WB vs ≤2 U RBCs	24-hour-all-cause mortality and proportion transfused ≥10 U/24H	NA
T-STORHM	Trauma/RCT France	WB vs fractionated blood products	Non-inferiority of coagulopathy correction	09/2024
TOWAR study	Prehospital resuscitation/RCT USA	LTOWB vs standard care (crystalloids ± components)	All-cause 30-d mortality	09/2025
WEBSTER trial	Trauma/RCT Columbia	LrWB vs 1:1:1 components	28-day mortality and SOFA score day 1 and day 5	01/2025

LrWB in Canada…

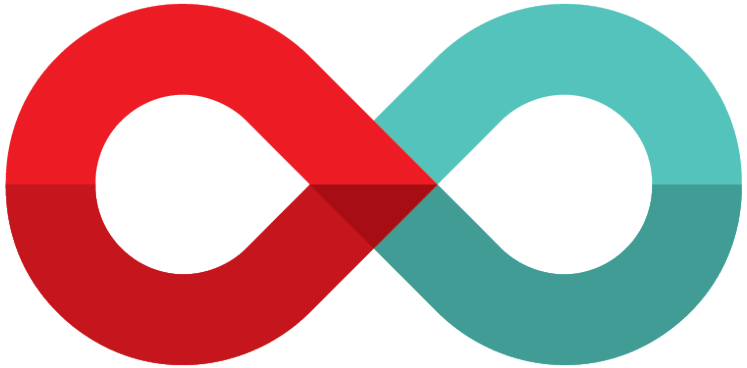
- NAC subcommittee assembled in 2022 to provide recommendations on use of LrWB in Canada
- Capacity to produce LrWB limited and production will impact other components
- Need to ensure that LrWB being used in situations where there is a benefit and that all Canadians who could benefit have access

- https://engage.blood.ca/whole-blood

Summary

- Whole Blood, leukocytes reduced licensed in Canada
- Indication: treatment of clinically significant bleeding
- Currently available for military use only but recommendations on non-military use forthcoming

- Benefits:
  - *Logistic simplification: storage, preparation, shelf-life*
  - *Facilitates earlier, balanced resuscitation*
- Risks:
  - *Hemolysis – safety established with restriction on volume given*
  - *RhD alloimmunization*
- Unknown:
  - *Improved clinical outcomes compared with conventional component*



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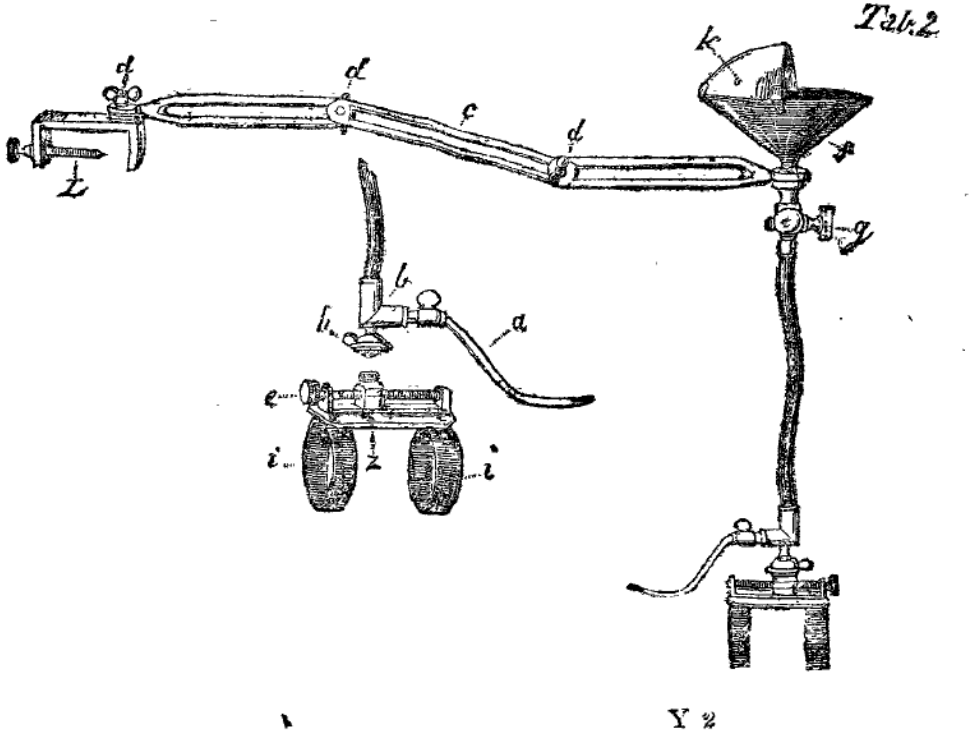
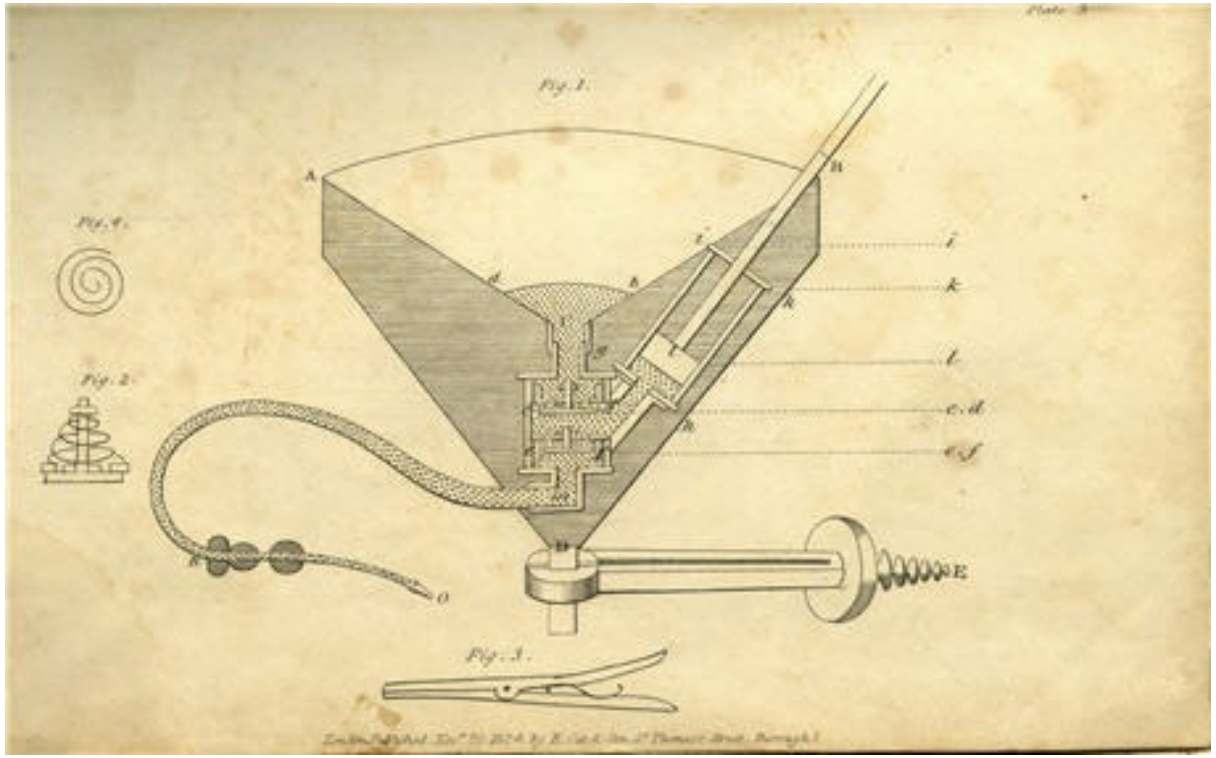
The Gravitator

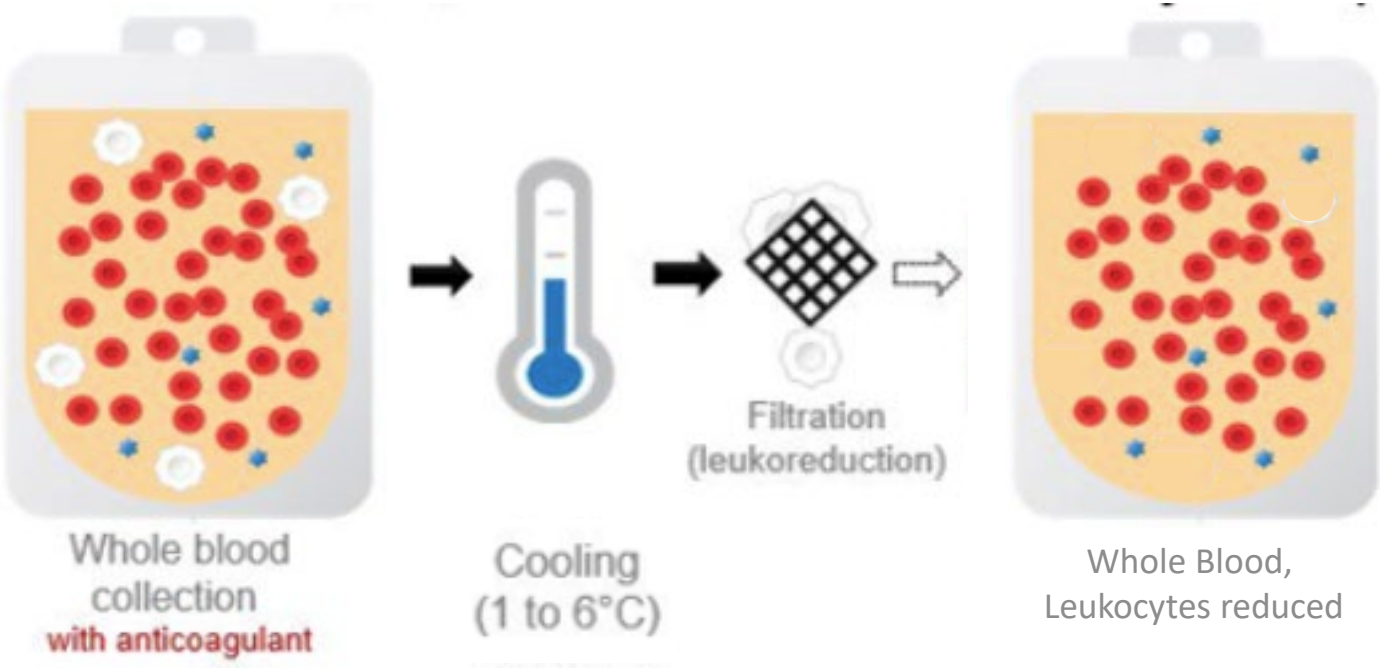




Pinkerton. Transf Med Rev. 2008;22(1):77-86

Science Museum, Science and Society Picture Library

Whole Blood, Leukocytes Reduced Manufacturing



Possible Advantage: More Effective Resuscitation

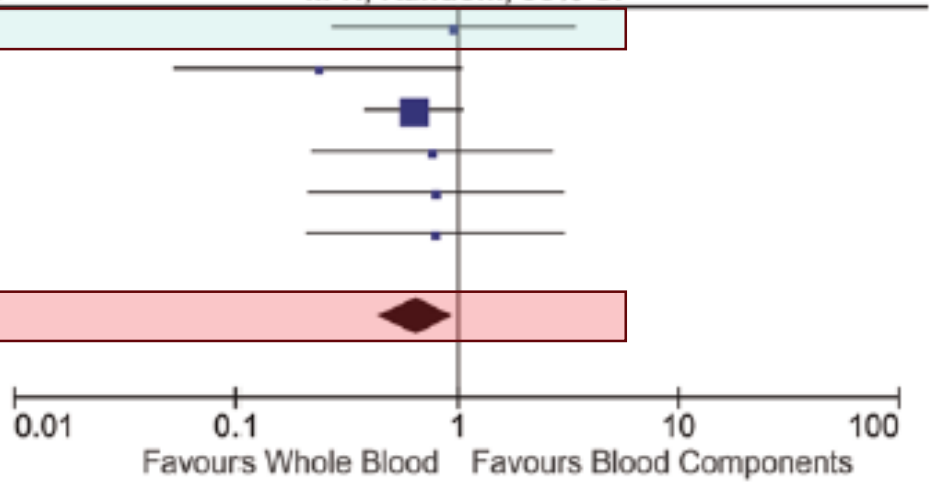
3h, 4h, 6h or ED mortality

A

Study or Subgroup	Whole Blood Events	Whole Blood Total	Blood Components Events	Blood Components Total	Weight	Odds Ratio M-H, Random, 95% CI
Guyette 2022	5	40	6	46	9.4%	0.95 [0.27, 3.39]
Hazelton 2019	2	91	16	182	6.8%	0.23 [0.05, 1.04]
Hazelton 2022	41	1180	24	443	57.2%	0.63 [0.38, 1.05]
Lee 2021	5	169	5	130	9.6%	0.76 [0.22, 2.69]
Seheult 2018	4	135	5	135	8.5%	0.79 [0.21, 3.02]
Yazer 2021	4	92	5	92	8.4%	0.79 [0.21, 3.04]
Total (95% CI)		1707		1028	100.0%	0.65 [0.44, 0.96]
Total events	61		61			

Heterogeneity: Tau² = 0.00; Chi² = 2.44, df = 5 (P = 0.79); I² = 0%

Test for overall effect: Z = 2.19 (P = 0.03)



Van der Horst. J Trauma Acute Care Surg. 2023;95(2):256-266

Possible Advantage: More Effective Resuscitation

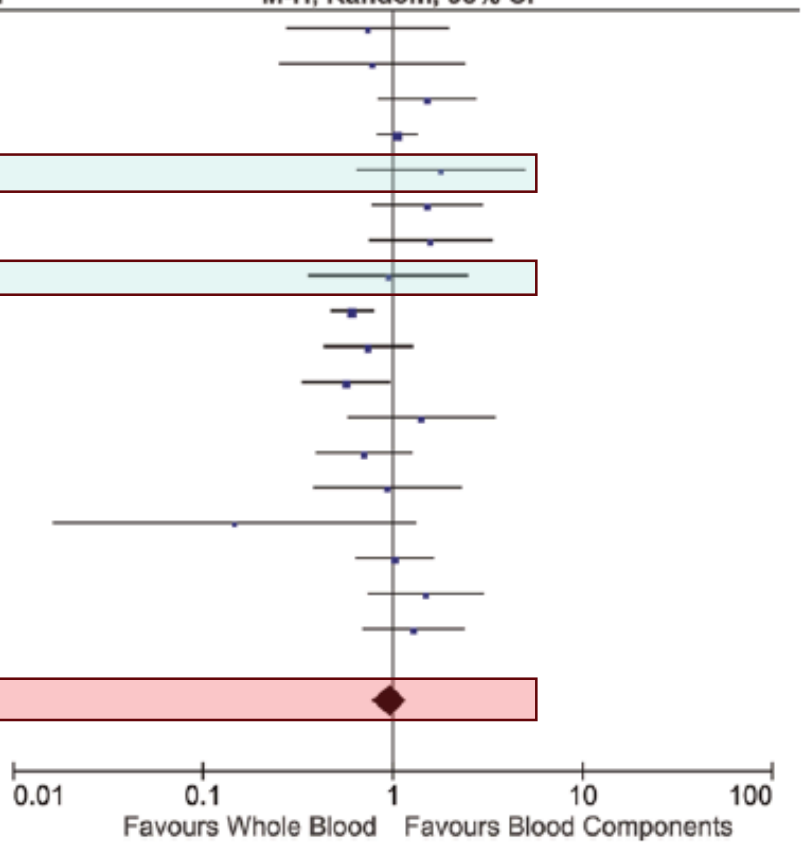
28-30d and in-hospital mortality

C

Study or Subgroup	Whole Blood Events	Total	Blood Components Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Barmparas 2022	13	33	15	32	3.1%	0.74 [0.28, 1.97]
Beckermann 2022	12	29	10	21	2.5%	0.78 [0.25, 2.41]
Bohan 2021	41	121	24	95	6.3%	1.52 [0.83, 2.75]
Brill 2022	210	840	129	537	12.1%	1.05 [0.82, 1.36]
Cotton 2014	12	55	7	52	3.0%	1.79 [0.65, 4.98]
Duchesne 2020	17	73	30	180	5.5%	1.52 [0.78, 2.96]
Gallahar 2020	24	42	38	83	4.7%	1.58 [0.75, 3.34]
Guyette 2022	10	40	12	46	3.2%	0.94 [0.36, 2.50]
Hanna 2020	81	280	3286	8214	11.9%	0.61 [0.47, 0.79]
Jones 2014	17	83	429	1662	7.0%	0.74 [0.43, 1.28]
Lee 2021	33	169	39	130	7.1%	0.57 [0.33, 0.97]
Niemann 2022	8	40	23	153	3.7%	1.41 [0.58, 3.45]
Seheult 2018	25	135	33	135	6.4%	0.70 [0.39, 1.26]
Shea 2020	14	44	14	42	3.6%	0.93 [0.38, 2.30]
Siletz 2021	1	38	5	32	0.8%	0.15 [0.02, 1.32]
Williams 2020	53	198	40	152	8.0%	1.02 [0.63, 1.65]
Yazer 2016	17	47	40	145	5.2%	1.49 [0.74, 2.99]
Yazer 2021	32	92	27	92	6.0%	1.28 [0.69, 2.39]
Total (95% CI)		**2359**		**11803**	**100.0%**	**0.97 [0.80, 1.18]**
Total events	620		4201			

Heterogeneity: Tau² = 0.07; Chi² = 30.59, df = 17 (P = 0.02); I² = 44%

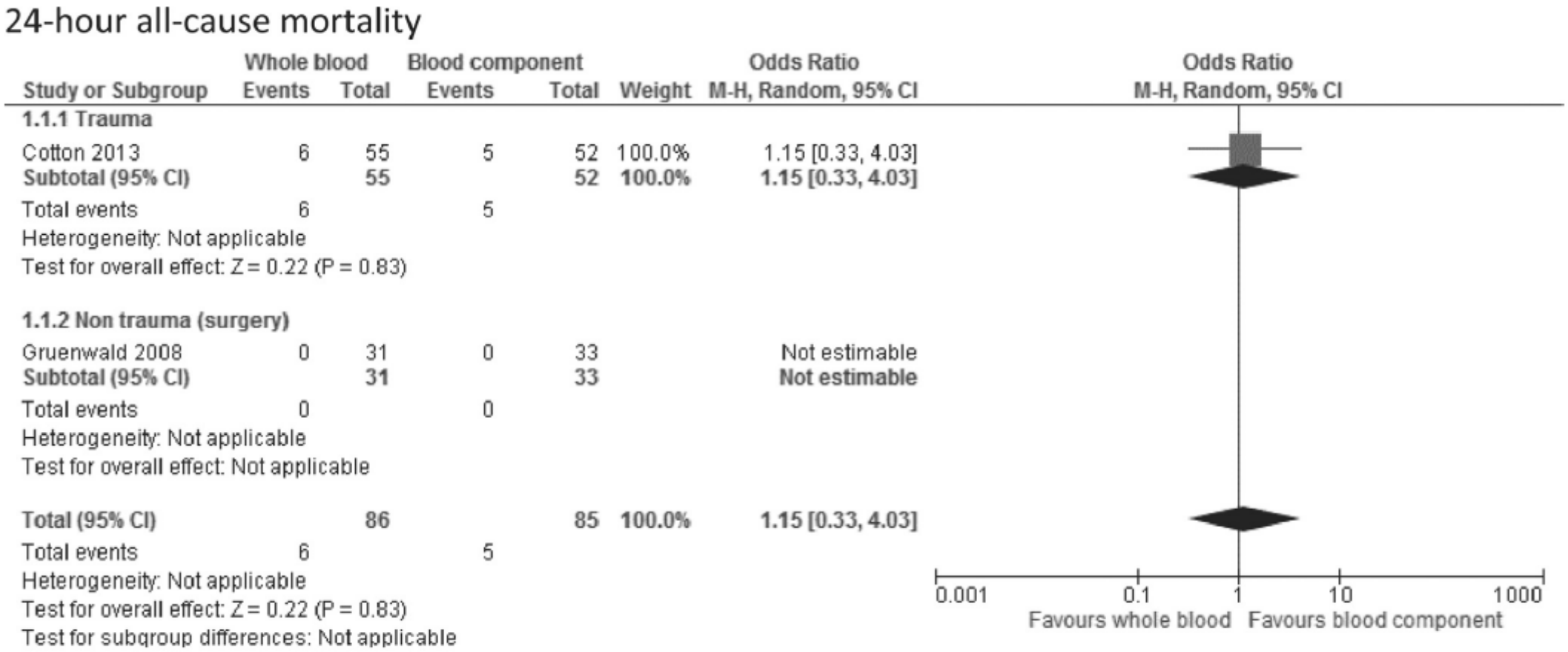
Test for overall effect: Z = 0.33 (P = 0.74)



Canadian Blood Services — BLOOD PLASMA STEM CELLS ORGANS & TISSUES

Van der Horst. J Trauma Acute Care Surg. 2023;95(2):256-266

Meta-analysis including non-trauma populations

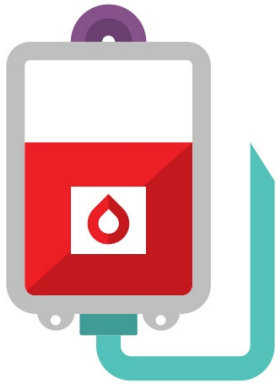


Canadian Blood Services — BLOOD PLASMA STEM CELLS ORGANS & TISSUES

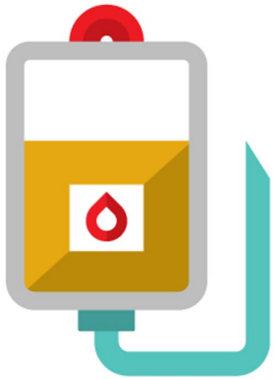
Geneen L. Trans Med Rev. 2022;36:7-15

Leukoreduced Whole Blood and ABO Compatibility

Group AB LrWB



Recipient ABO	RBC Compatibility
O	☹
A	☹
B	☹
AB	☺



Recipient ABO	Plasma Compatibility
O	☺
A	☺
B	☺
AB	☺