
Adherence in a randomised controlled trial comparing liberal and restrictive red blood cell transfusion thresholds after cardiac surgery

Pike K, Brierley R, Rogers CA, Murphy GJ, Reeves BC

Background

- There is a lack of evidence regarding optimal red blood cell (RBC) transfusion practice following cardiac surgery – transfusion rates are reported to vary between 40% and 90%
- Blood is an increasingly scarce resource and the donor pool is reducing, therefore identifying best practice is critical
- Any findings from cardiac surgery could help guide practice in other medical areas with high blood usage

TITRe2 trial

- Multi-centre RCT comparing:
 - Restrictive group: transfuse if Hb <9 g/dL (or Hct <27%)
 - Liberal group: transfuse if Hb <7.5 g/dL (or Hct <22%)
- Composite primary outcome: any serious infectious OR ischaemic event in first 3 months after randomisation
- Pragmatic trial:
 - Eligibility criteria are as inclusive as possible
 - Clinicians can opt out of transfusing, or can transfuse outside of protocol but must document the reason

Patient pathway

PRE-SURGERY

Consent obtained



Patient pathway

PRE-SURGERY

Consent obtained

POST-SURGERY

Hb monitored



Patient pathway

PRE-SURGERY

Consent obtained



POST-SURGERY

Hb monitored



Hb falls below 9 g/dL?

Patient pathway

PRE-SURGERY

Consent obtained

POST-SURGERY

Hb monitored

Hb falls below 9 g/dL?

NO

Patient not
randomised

YES

Randomise

Patient pathway

PRE-SURGERY

Consent obtained



POST-SURGERY

Hb monitored



Hb falls below 9 g/dL?

NO

Patient not
randomised



YES

Randomise



Liberal group
(transfuse if Hb <9 g/dL)

Restrictive group
(transfuse if Hb <7.5 g/dL)



Patient pathway

PRE-SURGERY

Consent obtained



POST-SURGERY

Hb monitored



Hb falls below 9 g/dL?

NO

Patient not
randomised



YES

Randomise



Liberal group
(transfuse if Hb <9 g/dL)

Restrictive group
(transfuse if Hb <7.5 g/dL)

Transfuse

Continue to monitor Hb and
transfuse if necessary



Patient pathway

PRE-SURGERY

Consent obtained



POST-SURGERY

Hb monitored



Hb falls below 9 g/dL?

NO

Patient not
randomised

YES

Randomise

Liberal group
(transfuse if Hb <9 g/dL)



Transfuse



Continue to monitor Hb and
transfuse if Hb <9 g/dL

Restrictive group
(transfuse if Hb <7.5 g/dL)



Continue to monitor Hb and
transfuse if Hb <7.5 g/dL

TITRe2 trial

- Target sample size 2000 (3500) patients from 14 UK centres
- With complete adherence the transfusion rates should be 100% in the liberal group and ~30% in the restrictive group:
 - Convergence of these rates severely threatens the power of the trial
 - Concern about differential non-adherence, with transfusion being withheld or delayed in the liberal group
- Monitoring this adherence is difficult

TRICC trial (NEJM, 1999)

- Multi-centre RCT comparing restrictive (Hb <7 g/dL) and liberal (Hb <10 g/dL) thresholds in 838 patients in 25 **general ICU units** in Canada
- Non-adherence indicated by reported Hb below threshold for at least 48 hours:
 - 6 (1.4%) patients in restrictive group
 - 18 (4.3%) patients in liberal group

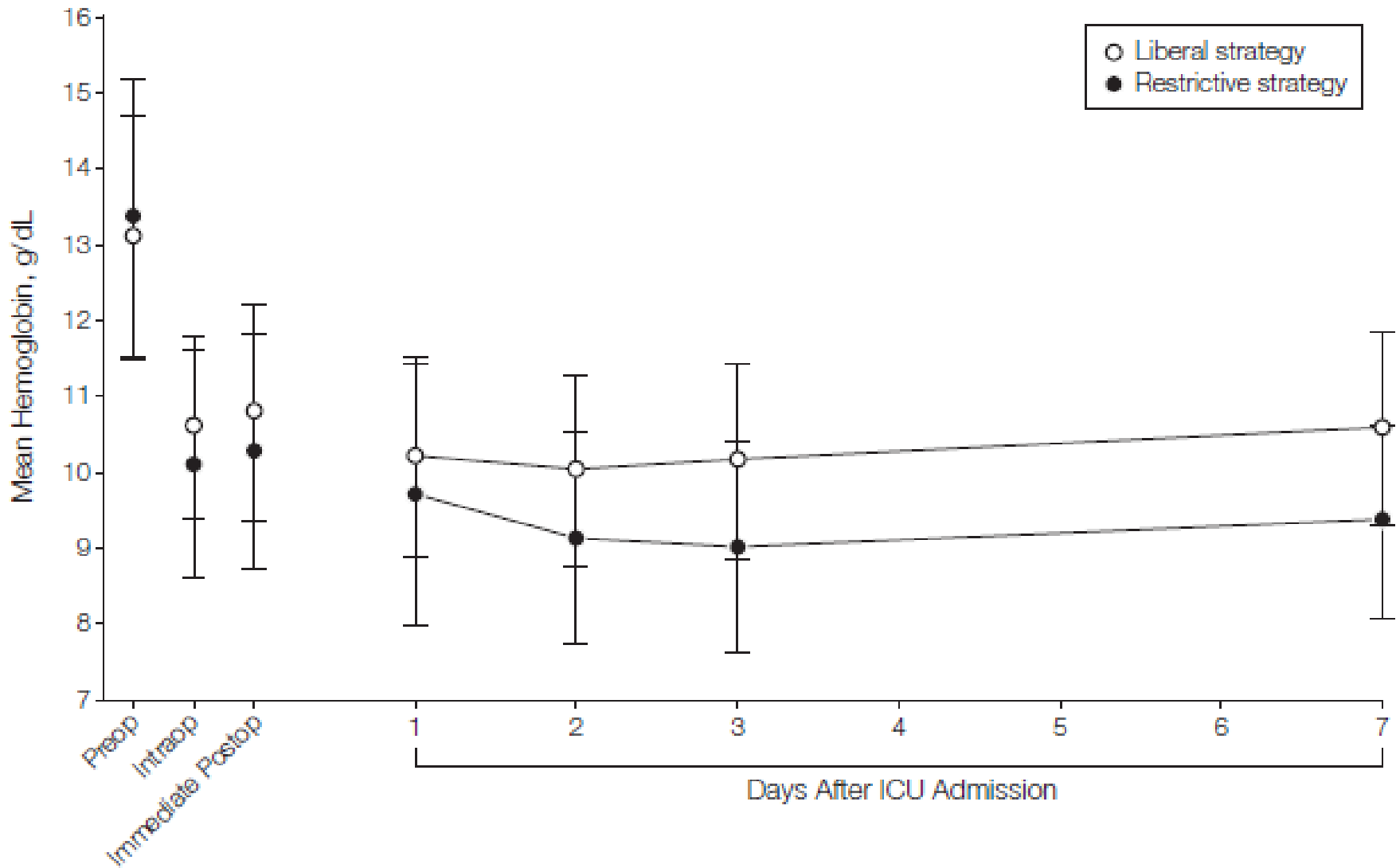
	Restrictive group (n=418)	Liberal group (n=420)
Mean (SD) Hb g/dL	8.5 (0.7)	10.7 (0.7)
Patients receiving any RBC	67%	100%
Mean (SD) units transfused	2.6 (4.1)	5.6 (5.3)

TRACS trial (JAMA, 2010)

- Single-centre RCT comparing restrictive (Hb <8 g/dL) and liberal (Hb <10 g/dL) thresholds in 502 patients undergoing elective cardiac surgery in Brazil
- Reported non-adherence rate of 0.8%:
 - 4 patients in restrictive group received 1 RBC outside of protocol
 - No patients in liberal group were non-compliant
 - “Hct concentrations were maintained above or at the threshold for 95% of the time”

	Restrictive group (n=249)	Liberal group (n=253)
Mean (95% CI) Hb g/dL	9.1 (9.0-9.2)	10.5 (10.4-10.6)
Patients receiving any RBC	47%	78%
Mean units transfused	2.2	3.1

TRACS trial (JAMA, 2010)

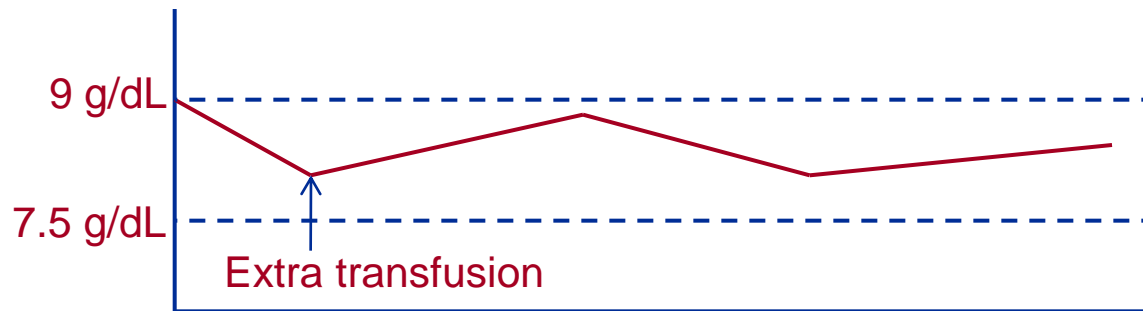


TITRe2 non-adherence

- **Randomisation protocol:** patient should be randomised within 24 hours of Hb breaching 9 g/dL threshold:
 - Failure to randomise
 - Randomised >24 hours after breaching threshold
 - Randomised without or before breaching threshold
- **Transfusion protocol:** patient should be transfused within 24 hours of Hb breaching allocated threshold:
 - **“Extra” transfusion:** transfusion given when allocated threshold NOT breached
 - **“Withheld” transfusion:** transfusion NOT given when allocated threshold breached
 - Instances are classified as mild, moderate or severe

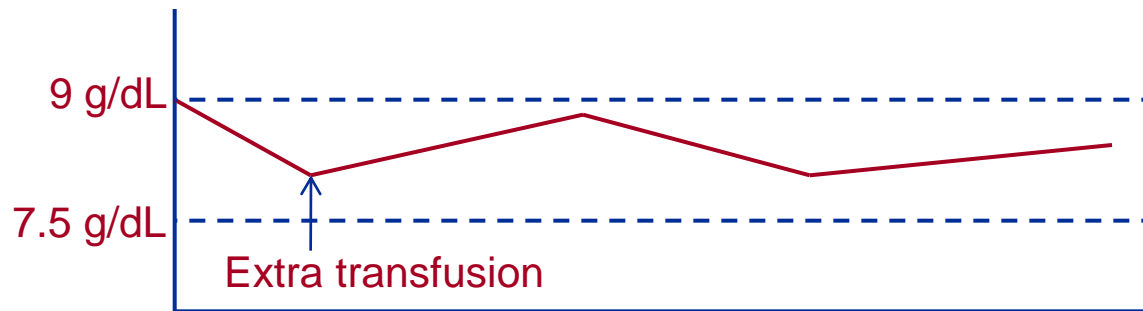
Severe non-adherence

- Severe extra transfusions: Transfused despite allocated threshold not being breached at ANY point

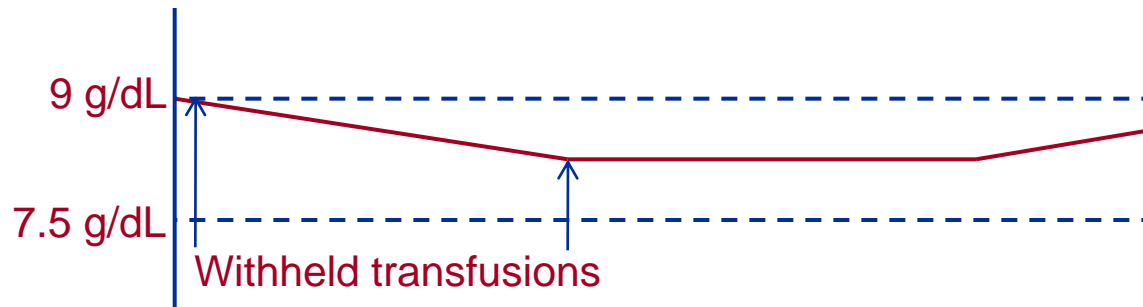


Severe non-adherence

- Severe extra transfusions: Transfused despite allocated threshold not being breached at ANY point



- Severe withheld transfusions: Not transfused despite allocated threshold being breached, and was not transfused at ANY point



Data collection for adherence

Date, time and Hb at
randomisation

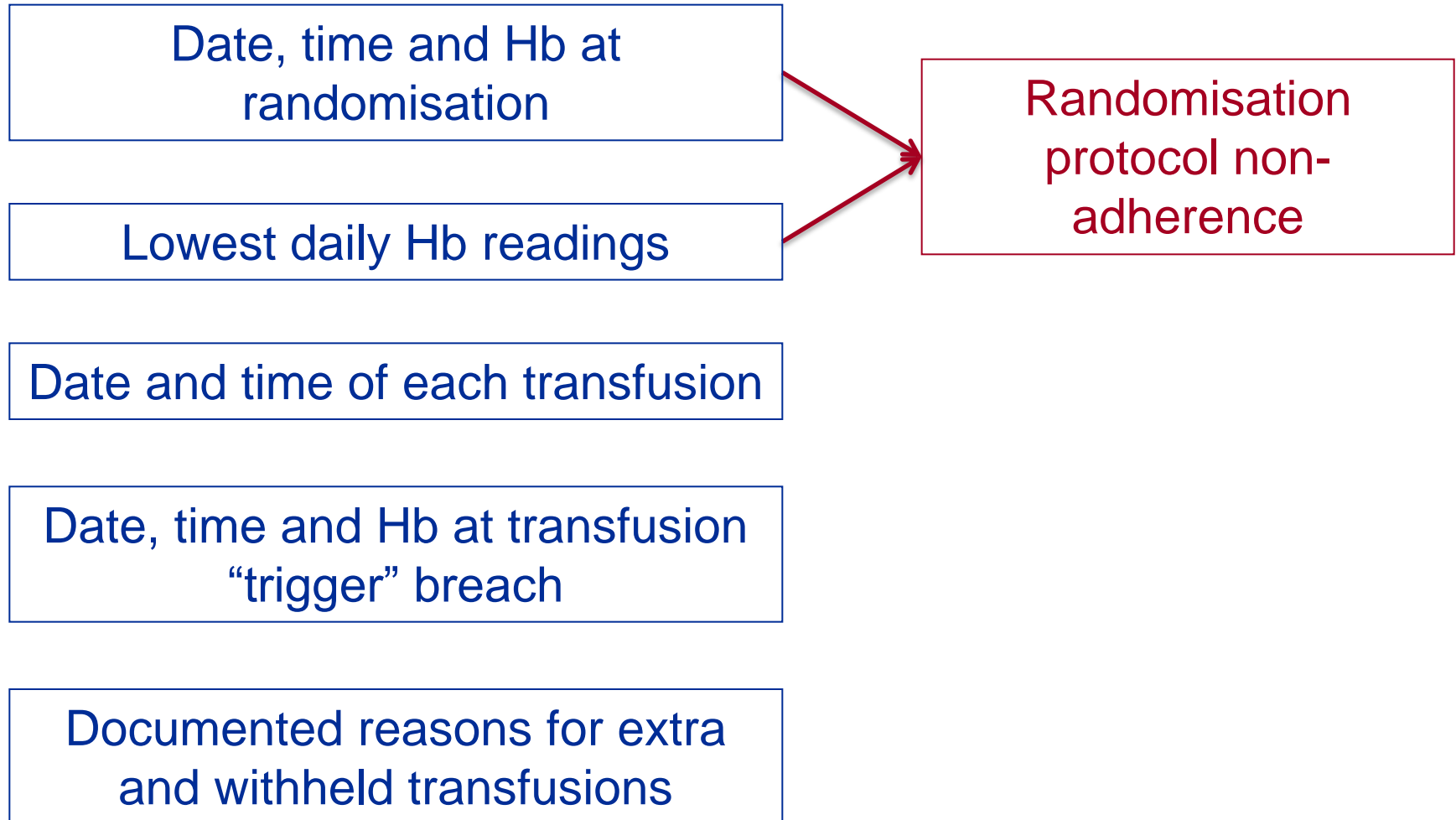
Lowest daily Hb readings

Date and time of each transfusion

Date, time and Hb at transfusion
“trigger” breach

Documented reasons for extra
and withheld transfusions

Data collection for adherence



Data collection for adherence

Date, time and Hb at randomisation

Lowest daily Hb readings

Date and time of each transfusion

Date, time and Hb at transfusion “trigger” breach

Documented reasons for extra and withheld transfusions

Withheld transfusions

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graph LR; A[Date, time and Hb at randomisation] --- B[Lowest daily Hb readings]; B --- C[Date and time of each transfusion]; C --- D[Date, time and Hb at transfusion “trigger” breach]; D --- E[Documented reasons for extra and withheld transfusions]; B --- F[Withheld transfusions]; C --- F; D --- F; E --- F;
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Data collection for adherence

Date, time and Hb at randomisation

Lowest daily Hb readings

Date and time of each transfusion

Date, time and Hb at transfusion
“trigger” breach

Documented reasons for extra
and withheld transfusions

Extra transfusions

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graph LR; A[Date, time and Hb at randomisation] --- B[Lowest daily Hb readings]; B --- C[Date and time of each transfusion]; C --- D[Date, time and Hb at transfusion "trigger" breach]; D --> E[Extra transfusions]; F[Documented reasons for extra and withheld transfusions] --> E;
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Overall adherence rates

- From the first 1033 consented patients, 582 (56%) have been randomised
- Adherence with randomisation protocol:

Randomised patients (n=582)

Randomised according to protocol	563 (97%)
Randomised late	19 (2%)
Randomised without or before breaching threshold	0 (0%)

Non randomised patients (n=451)

9 g/dL threshold not breached	414 (92%)
9 g/dL threshold breached	37 (8%)

Overall adherence rates

- Adherence with transfusion protocol:

	Randomised patients (n=576)
Any non-adherence	186 (32%)
Any “severe” non-adherence	37 (6%)
Extra transfusions	98 (17%)
Withheld transfusions	108 (19%)

- Patients can be classified as having both withheld and extra transfusions
- Group specific rates are confidential to the DMSC

Conclusions

- Data collection is intensive but satisfactory
- The DMSC has recommended that the trial should continue and judged the transfusion rates to be consistent with the sample size
- Site-specific adherence rates are being fed back and initiatives have been launched to try and improve adherence