HEMOglobin transfusion threshold in Traumatic brain Injury Optimization: The HEMOTION Trial

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Objective

To evaluate whether a **liberal** RBC transfusion strategy as compared to a **restrictive** strategy could improve clinically important and patient-centered outcomes in **critically ill patients with TBI**

- Funded by the Canadian Institutes of Health Research (CIHR) and Accelerating Clinical Trials Consortium (ACT)
- Sponsor: CHU de Québec-Université Laval and Université Laval
- ClinicalTrials.gov : NCT03260478

HEMOTION TRIAL

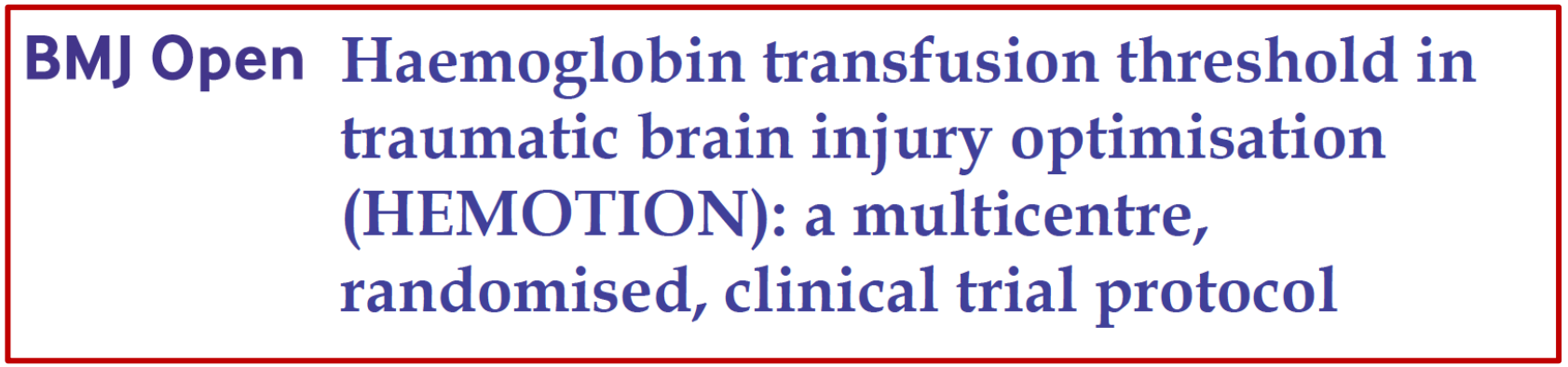
IRSC CIHR
Instituts de recherche en santé du Canada
Canadian Institutes of Health Research

ACT AEC
Accelerating Clinical Trials
Accélérer les Essais Cliniques

Design/Setting

Multicentre open-label randomized controlled trial (**P**ragmatic **R**andomized **O**pen **B**linded **E**ndpoint)

34 centres in 4 countries (Canada/UK/France/Brazil)



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Eligibility Criteria

Inclusion criteria

- Adult patients
- Admitted to an ICU
- Acute moderate or severe blunt TBI (Glasgow Coma Score [GCS] ≤ 12)
- Hb level ≤ 10.0 g/dL

Eligibility Criteria

Exclusion Criteria (at time of randomization)

- Active life-threatening bleeding with hemorrhagic shock or active life-threatening bleeding requiring an urgent surgical procedure
- Contraindications or known objection to transfusions
- RBC transfusion initiated after ICU admission
- Brain-based definition of death
- GCS of 3 with bilateral fixed dilated pupils
- Decision to withhold or withdraw life-sustaining therapies
- No fixed address

Interventions

Study groups

- Liberal strategy (threshold of Hb ≤ 10.0 g/dL) *or*
- Restrictive strategy (threshold of Hb ≤ 7.0 g/dL)

Transfusion strategy

- Within 3 hours after meeting the transfusion threshold
- A single unit at a time
- Until ICU discharge

Primary outcome measure

Glasgow Outcome Scale extended (GOSe) at 6 months

1 = Dead

2 = Vegetative state

Absence of awareness of self & environment

3 = Lower severe disability

Full assistance in activities of daily living

4 = Upper severe disability

Partial assistance in activities of daily living

5 = Lower moderate disability

Independent, but cannot resume work/school or previous social activities

6 = Upper moderate disability

Some disability, but can partly resume work/school or previous social activities

7 = Lower good recovery

Minor physical / mental deficits affecting activities of daily living

8 = Upper good recovery

Full recovery

Secondary outcome measures

Overall functional outcome (Functional Independence Measure-FIM)
Overall quality of life (EQ-5D-5L)
TBI-specific quality of life (Qolibri)
Depression scale (PHQ-9)
Mortality*

Outcome assessment done centrally at 6 months
*Mortality also assessed at ICU and hospital

Tertiary outcome measures

Number of RBC units transfused
Lowest daily Hb
Infections
Duration of mechanical ventilation
ICU and hospital length of stay

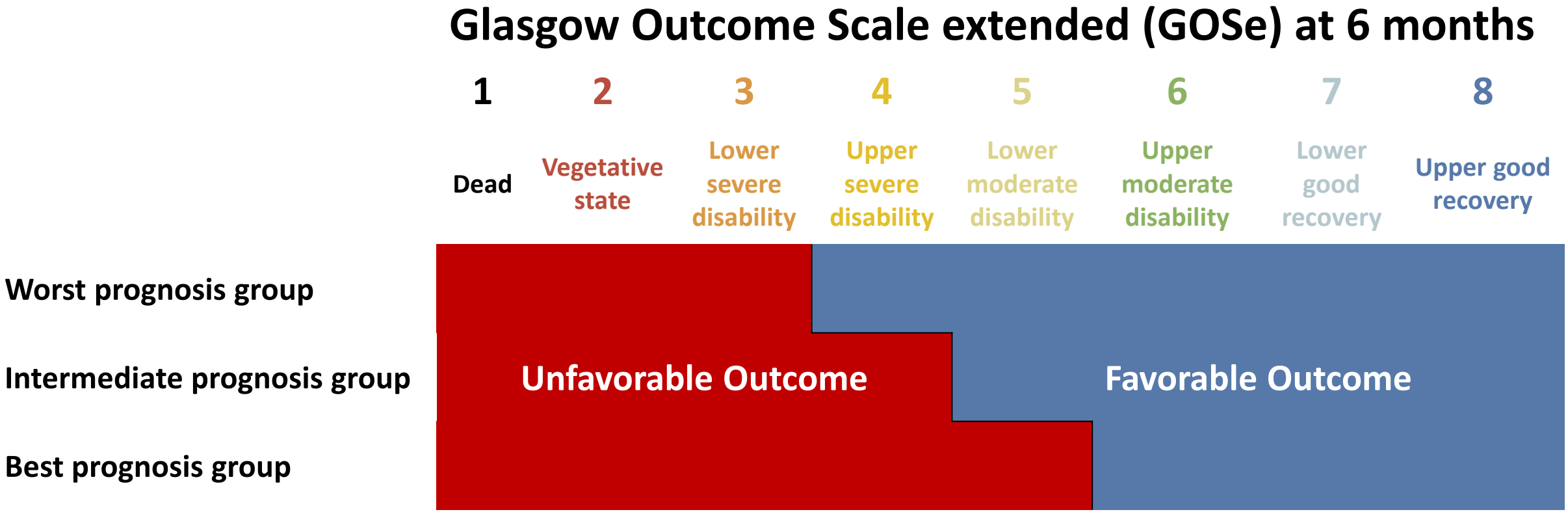
Outcome assessment done at each site
No adjudication of tertiary outcomes or adverse events

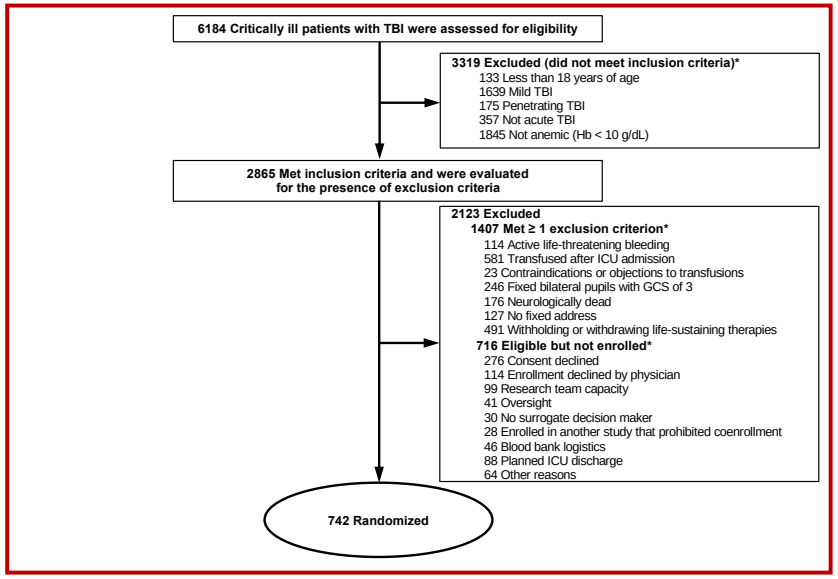
Analytic plan

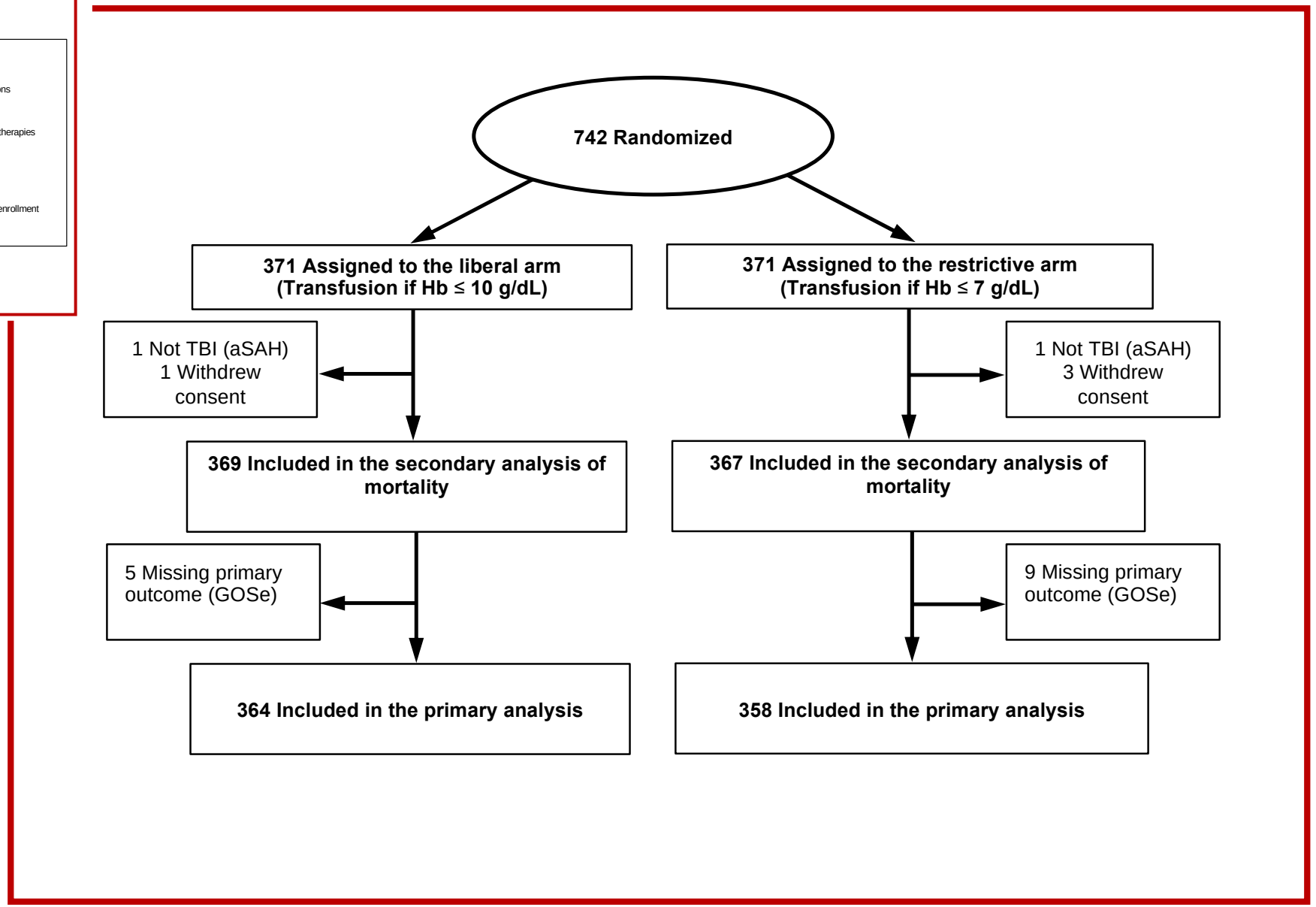
Main analysis of the primary outcome

- Sliding dichotomy approach
  - Baseline prognostic assessed by the TBI-IMPACT prognostic score
    - Age, pupils, GCS motor score, CT scan Marshall score, epidural hematoma, traumatic subarachnoid hemorrhage, hypotension, hypoxemia, Hb, glucose

Sliding dichotomy




6184 Critically ill patients with TBI were assessed for eligibility
3319 Excluded (did not meet inclusion criteria)*
133 Less than 18 years of age
1639 Mild TBI
175 Penetrating TBI
357 Not acute TBI
1845 Not anemic (Hb < 10 g/dL)
2865 Met inclusion criteria and were evaluated for the presence of exclusion criteria
2123 Excluded
1407 Met ≥ 1 exclusion criterion*
114 Active life-threatening bleeding
581 Transfused after ICU admission
23 Contraindications or objections to transfusions
246 Fixed bilateral pupils with GCS of 3
176 Neurologically dead
127 No fixed address
491 Withholding or withdrawing life-sustaining therapies
716 Eligible but not enrolled*
276 Consent declined
114 Enrollment declined by physician
99 Research team capacity
41 Oversight
30 No surrogate decision maker
28 Enrolled in another study that prohibited coenrollment
46 Blood bank logistics
88 Planned ICU discharge
64 Other reasons
742 Randomized


742 Randomized
371 Assigned to the liberal arm (Transfusion if Hb ≤ 10 g/dL)
371 Assigned to the restrictive arm (Transfusion if Hb ≤ 7 g/dL)
1 Not TBI (aSAH)
1 Withdrew consent
1 Not TBI (aSAH)
3 Withdrew consent
369 Included in the secondary analysis of mortality
367 Included in the secondary analysis of mortality
5 Missing primary outcome (GOSe)
9 Missing primary outcome (GOSe)
364 Included in the primary analysis
358 Included in the primary analysis

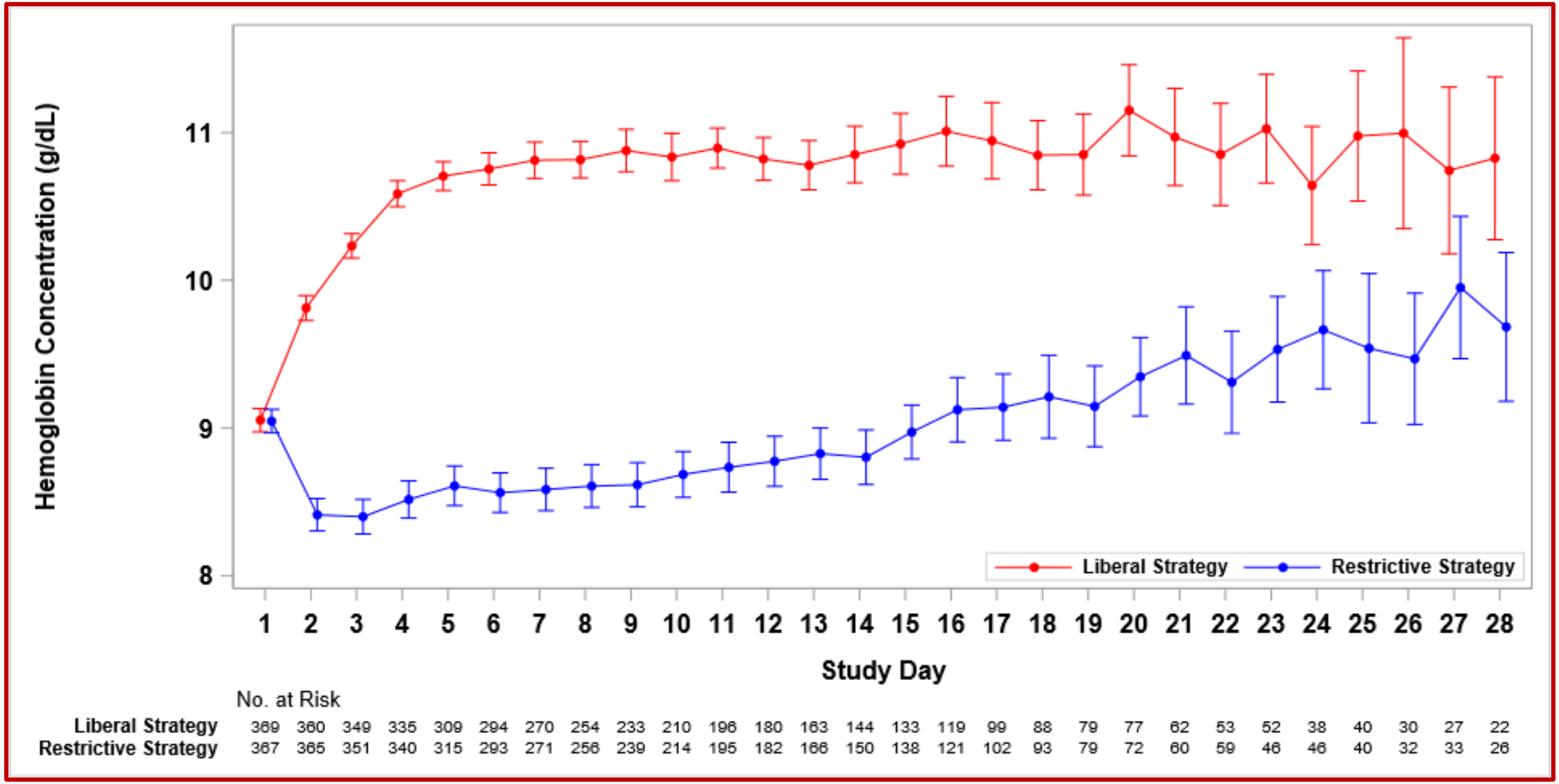
Patient characteristics

Characteristics		Liberal Strategy (N = 369)	Restrictive Strategy (N = 367)
TBI-IMPACT prognostic model variables			
Moderate traumatic brain injury — no./total no. (%)		98/369 (26.6)	99/367 (27.0)
GCS motor score — median (Q1-Q3)		4 (1-5)	4 (1-5)
GCS motor score — no./total no. (%)			
	Normal flexion	79/366 (21.6)	86/367 (23.4)
			93/367 (25.3)
			20/367 (5.4)
Pupil reactivity — no./			
	None	45/362 (12.4)	51/362 (14.1)
	One	32/362 (8.8)	51/362 (14.1)
	Both	285/362 (78.7)	260/362 (71.8)
Hypotension — no./total no. (%)		83/366 (22.7)	105/364 (28.8)
Hypoxemia — no./total no. (%)		94/365 (25.8)	96/361 (26.6)
Injury classification on basis of CT imaging — no./total no. (%)			
	I	5/369 (1.4)	12/367 (3.3)
	II	188/369 (50.9)	192/367 (52.3)
	III or IV	39/369 (10.6)	41/367 (11.2)
	V or VI	137/369 (37.1)	122/367 (33.2)
Traumatic subarachnoid hemorrhage — no./total no. (%)		324/369 (87.8)	324/367 (88.3)
Epidural mass lesion — no./total no. (%)		65/369 (17.6)	67/367 (18.3)
Glucose — mmol/L		9.2±3.6	9.1±3.8
Hemoglobin — g/dL		13.3±1.8	13.1±1.7

TBI-IMPACT probability of unfavourable outcome at 6 months

0.54±0.23 0.55±0.22

Daily hemoglobin levels



Primary outcome

	Liberal Strategy (N = 369)	Restrictive Strategy (N = 367)	Risk Ratio (95% CI)
Primary Outcome — no./total no. (%)			
Sliding dichotomy of the GOSe for unfavorable outcome			
Overall	249/364 (68.4)	263/358 (73.5)	0.93 (0.83 to 1.04)

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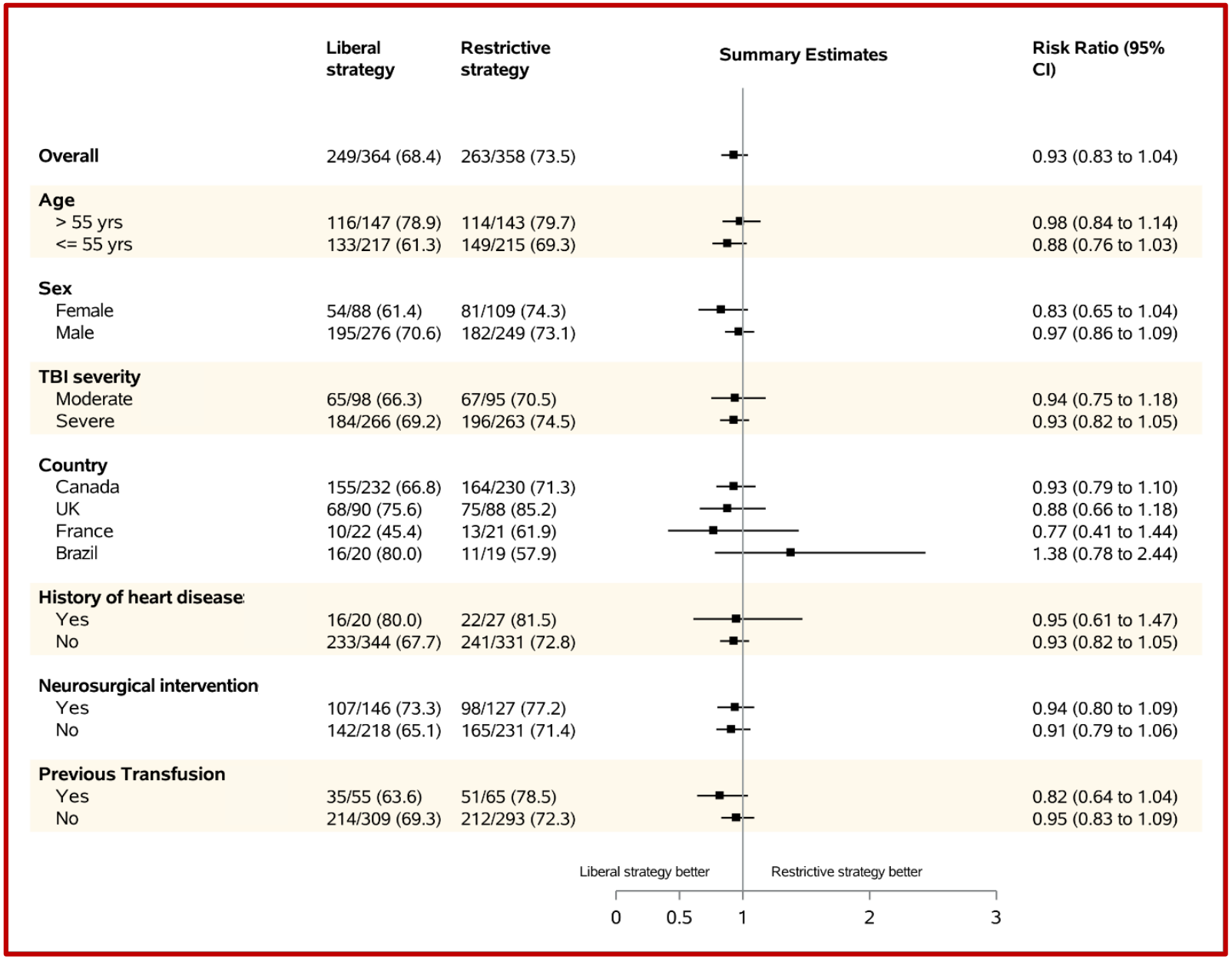
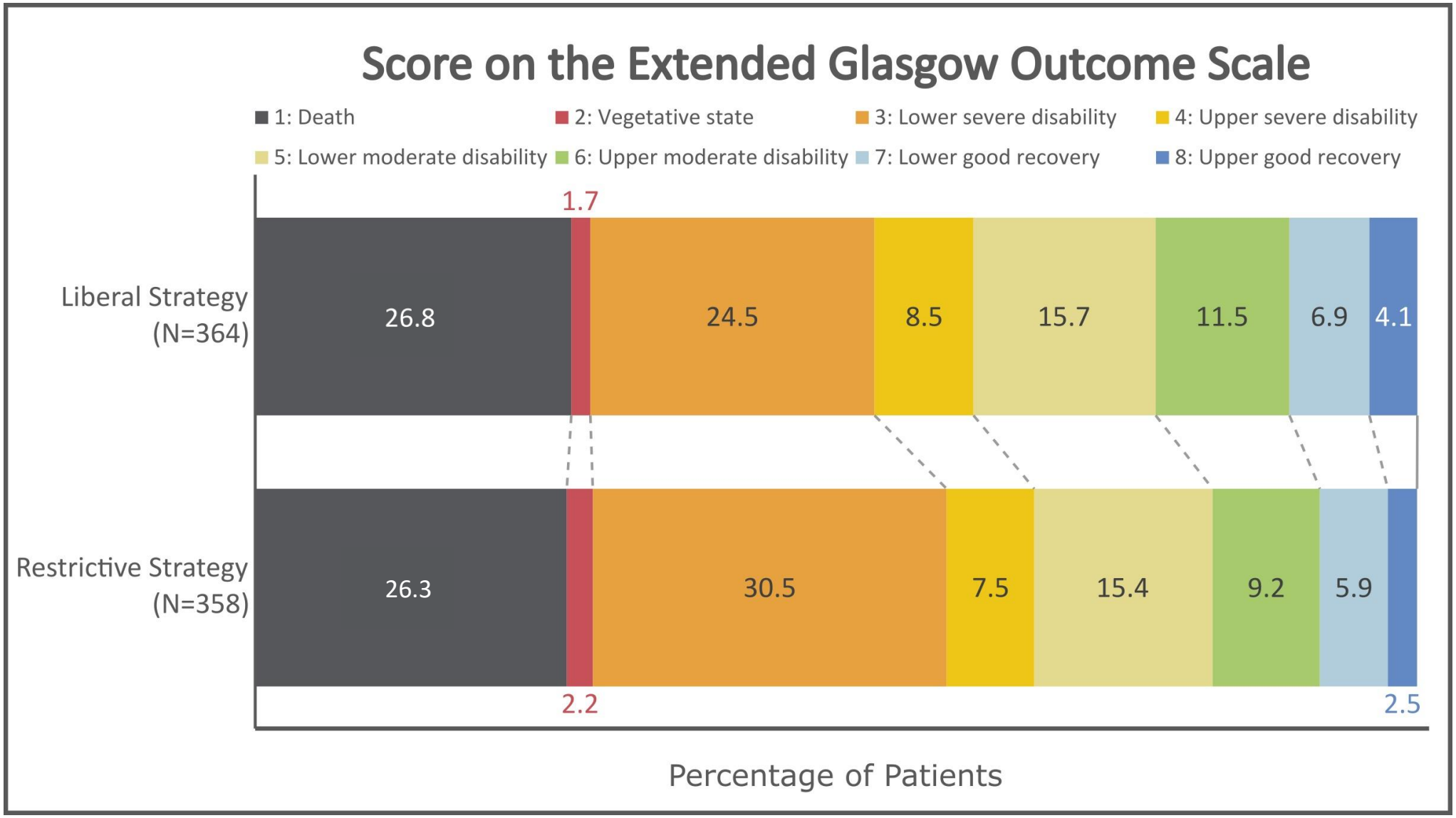
Overall	249/364 (68.4)	263/358 (73.5)	0.93 (0.83 to 1.04)

Adjusted absolute risk reduction 5.4% (95%CI −2.9 to 13.7%)

Subgroup analyses



GOSe distribution



Secondary outcomes

	Liberal Strategy (N = 369)	Restrictive Strategy (N = 367)	Hazard Ratio, Risk Ratio or Median Difference (95% CI)
Secondary Outcomes			
Mortality — no./total no. (%)			
In the ICU	63/369 (17.1)	56/367 (15.3)	1.13 (0.77 to 1.65)
In the hospital	85/369 (23.0)	79/367 (21.5)	1.07 (0.78 to 1.47)
At 6 months	99/369 (26.8)	96/365 (26.3)	1.01 (0.76 to 1.35)
Functional Independence Measure			
Overall	119 (95-125)	115 (76-124)	4.34 (0.22 to 8.45)
Motor	88 (71-91)	86 (50-91)	3.95 (0.63 to 7.27)
Cognitive	32 (24-35)	30 (22-34)	1.15 (-0.16 to 2.46)
EuroQoL Analogue Scale	70 (50-80)	60 (40-75)	5.19 (0.52 to 9.86)
EuroQoL 5-Dimension 5-Level Utility Index	0.74 (0.45-0.87)	0.64 (0.33-0.82)	0.06 (0.01 to 0.10)
Quality of Life after Brain Injury	64 (45-80)	56 (39-77)	3.72 (-1.13 to 8.56)
Patient Health Questionnaire-9			
Median score	7 (3-13)	8 (3-14)	-0.51 (-1.91 to 0.90)
Score ≥ 10	82/227 (36.1)	95/222 (42.8)	0.85 (0.63 to 1.17)

Tertiary outcomes

	Liberal Strategy (N = 369)	Restrictive Strategy (N = 367)	Median Difference (95% CI)
Tertiary Outcomes			
Number of red-cell units transfused	1516	307	
Number of red-cell transfused per patient	3 (2-5)	0 (0-1)	3.0 (3.0 to 10.82)
Any infection	204/369 (55.3)	192/367 (52.3)	1.06 (0.92 to 1.21)
Pneumonia	130/369 (35.2)	121/367 (33.0)	1.07 (0.87 to 1.31)
Bacteremia	24/369 (6.5)	27/367 (7.4)	0.88 (0.52 to 1.50)
Sepsis/septic shock	21/369 (5.7)	28/367 (7.6)	0.75 (0.43 to 1.29)
Ventriculitis/meningitis/brain abscess	12/369 (3.2)	15/367 (4.1)	0.80 (0.38 to 1.68)
Patients with transfusion reactions — no./total no. (%)	6/365 (1.6)	1/141 (0.7)	2.33 (0.35 to 58.32)
Duration of mechanical ventilation— days	12 (8-17)	11 (7-17)	1.00 (-0.52 to 2.52)
Length of ICU stay— days	15 (10-22)	15 (10-22)	0.00 (-1.85 to 1.85)
Length of hospital stay— days	33 (18-50)	33 (19-55)	0.00 (-4.20 to 4.20)

In summary

- We did not observe a statistically significant decrease on the risk of an unfavourable neurological outcome at 6 months in critically ill adult patients with traumatic brain injury, based on the GOSe
  - We cannot exclude the possibility of up to a 13.7% absolute reduction (or 2.9% increase) in the risk of an unfavourable outcome with a liberal transfusion strategy

- A potential beneficial effect was observed with the functional independence measure and quality of life

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ORIGINAL ARTICLE

Liberal or Restrictive Transfusion Strategy in Patients with Traumatic Brain Injury

A.F. Turgeon, D.A. Fergusson, L. Clayton, M.-P. Patton, X. Neveu, T.S. Walsh, A. Docherty, L.M. Malbouisson, S. Pili-Floury, S.W. English, R. Zarychanski, L. Moore, P.L. Bonaventure, V. Laroche, M. Verret, D.C. Scales, N.K.J. Adhikari, J. Greenbaum, A. Kramer, V.G. Rey, I. Ball, K. Khwaja, M. Wise, D. Harvey, F. Lamontagne, R. Chabanne, A. Algird, S. Krueper, J. Pottecher, F. Zeiler, J. Rhodes, A. Rigamonti, K.E.A. Burns, J. Marshall, D.E. Griesdale, L.S. Sisconetto, D.J. Kutsogiannis, C. Roger, R. Green, J.G. Boyd, J. Wright, E. Charbonney, P. Nair, T. Astles, E. Sy, P.C. Hébert, M. Chassé, A. Gomez, T. Ramsay, M. Taljaard, A. Fox-Robichaud, A. Tinmouth, M. St-Onge, O. Costerousse, and F. Lauzier, for the HEMOTION Trial Investigators on behalf of the Canadian Critical Care Trials Group, the Canadian Perioperative Anesthesia Clinical Trials Group, and the Canadian Traumatic Brain Injury Research Consortium*