

## SUPPLEMENTAL MATERIAL

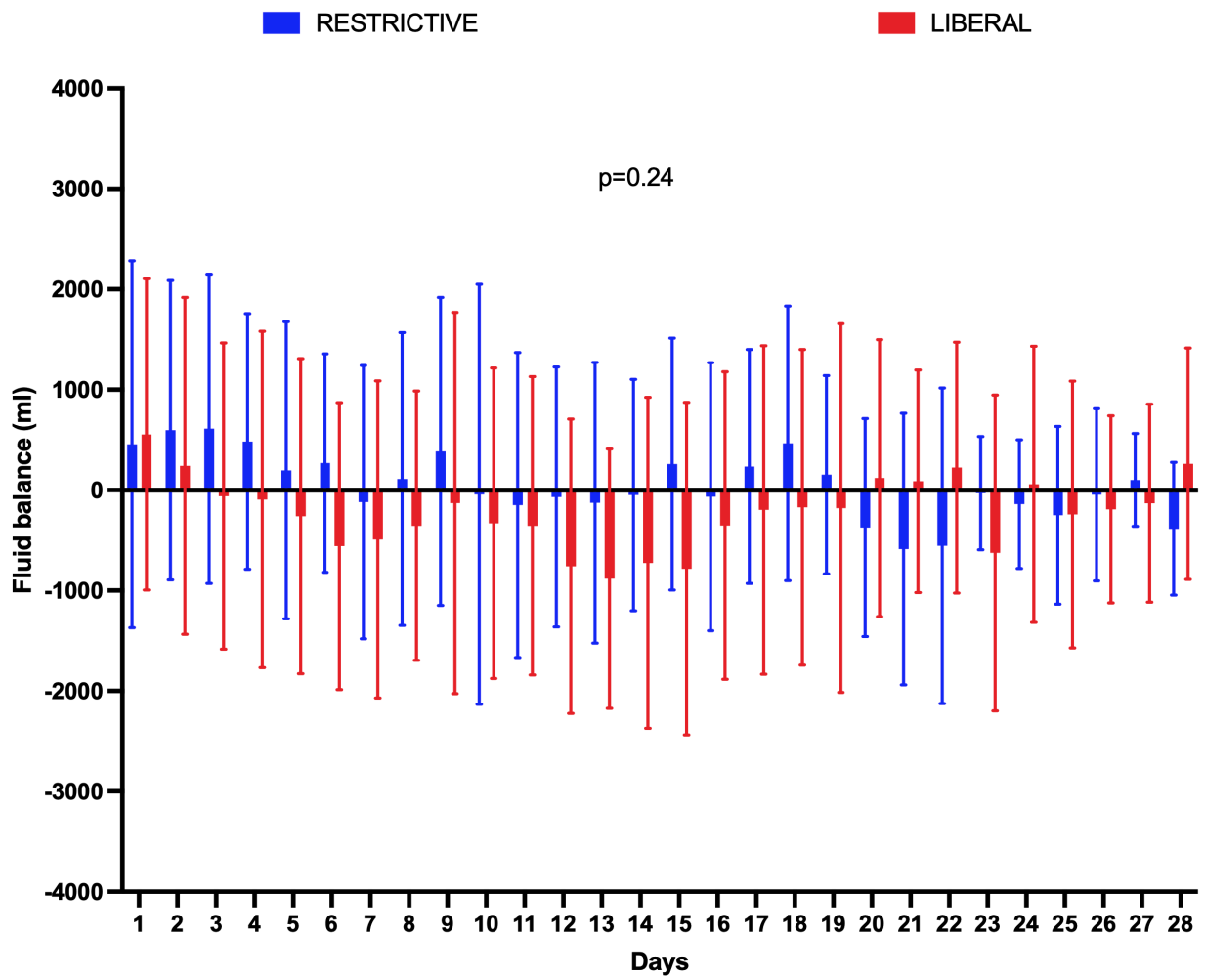
**Supplementary Table S1.** Definitions of serious adverse events (SAE) occurring after randomization, from Taccone et al. [19]

| SAE                                      | DEFINITION   |
|--|--|
| Severe hypertension                      | Mean arterial pressure (MAP) > 130 mmHg for more than 1 hour and needing active therapy, in the absence of vasopressor agents and increased intracranial hypertension.   |
| Severe hypotension                       | MAP < 65 mmHg for at least 1 hour, not responding to fluid therapy and needing vasopressor therapy, in the absence of active bleeding.   |
| Venous thrombotic events                 | Deep vein thrombosis (formation of a blood clot within a deep vein in the legs or arms, which may be associated with non-specific signs, such as pain, swelling, redness, warmth, and engorged superficial veins – it can be diagnosed by echography, venography or CT imaging); pulmonary embolism (formation of a clot within the pulmonary arterial circulation, diagnosed by contrast pulmonary CT-scan or echocardiography).  |
| Acute myocardial ischemia                | Acute myocardial infarction (ST-elevation and non-ST-elevation myocardial infarction) or unstable chest pain diagnosed during current hospital admission, according to specific criteria (i.e., elevated biomarkers of myocardial injury, ischemic signs on electrocardiogram, clinical suspicion) and the patient has received specific treatment (reperfusion strategies such as percutaneous coronary intervention [PCI] or thrombolysis) or initiation/increase of antithrombotic drug treatment during current intensive care unit admission. |
| Cerebral ischemia                        | New (i.e. after randomization) ischemic lesion visible on brain imaging (i.e. either CT-scan or MRI).*   |
| Intestinal ischemia                      | Ischemic lesions confirmed by endoscopy and/or open surgery.   |
| Acute peripheral limb ischemia           | Clinical signs and the need for open or percutaneous vascular intervention, amputation or initiation/increased antithrombotic treatment.   |
| Anaphylactic reaction to RBC transfusion | Muco-cutaneous signs (i.e., urticaria, pruritus) and/or hemolytic anemia within 24 hours after transfusion.  |
| ARDS                                     | Acute hypoxemia with bilateral infiltrates, according to recent definitions. <sup>42</sup>   |
| TRALI                                    | ARDS occurring within 6 hours after RBC transfusion.   |
| TACO                                     | Acute hypoxemia (PaO <sub>2</sub> /FiO <sub>2</sub> < 300 regardless of positive end-expiratory pressure [PEEP] with bilateral lung infiltrates and occurrence within 6 hours after RBC transfusion and increased blood pressure and positive fluid balance.   |
| Sepsis                                   | Presence of an infection and organ failure attributed to it. Septic shock = arterial hypotension (MAP < 65 mmHg) despite adequate fluid resuscitation and necessitating vasopressor therapy.   |
| Infection                                | According to CDC definitions. <sup>43</sup>  |
| Brain tissue hypoxia                     | For those patients with PbtO <sub>2</sub> monitoring, values of < 20 mmHg for at least 1 hour over the previous 24 hours.  |

ARDS = acute respiratory distress syndrome; TRALI = transfusion-related acute lung injury; TACO = transfusion-associated circulatory overload; RBC = red blood cells; CDC = Centers for Disease Control and Prevention; CT = computed tomography; MRI = magnetic resonance imaging.

\* Imaging was decided according to the treating physician and there was no standardized assessment or protocolized imaging. Cerebral ischemia was scored by local research personnel, who filled out the Case Record Form according to the definition provided in the Table.

**Supplementary Figure S1.** Trajectories of the daily fluid balance according to randomization group. Data are reported as median and interquartiles ranges.



**Supplementary Table S2.** Multivariate regression model for predictors of unfavorable neurological outcome (GOS-E from 1 to 5) at 180 days.

| <b>Variable</b>              | <b>Odds Ratio (OR)</b>       | <b>P value</b> |
|------------------------------|------------------------------|----------------|
| Group: Restrictive – Liberal | 2.31 (IC 95%, 0.89 to 5.99)  | 0.085          |
| ICH volume > 30 mL           | 3.87 (IC 95%, 1.47 to 10.17) | 0.006          |
| Hydrocephalus on admission   | 5.91 (IC 95%, 1.89 to 18.41) | 0.002          |
| GCS on admission             | 0.76 (IC 95%, 0.63 to 0.91)  | 0.003          |

**Supplementary Table S3.** Per protocol analysis.

| <b>Outcome</b>                                       | <b>Liberal<br/>(n=66)</b> | <b>Restrictive<br/>(n=72)</b> | <b>Risk Ratio<br/>(95%CI)</b> | <b>P Value</b> |
|--|---------------------------|-------------------------------|-------------------------------|----------------|
| <b>Primary outcome</b>                               |                           |                               |                               |                |
| Unfavorable neurological outcome at 180 days - n (%) | 47/66 (71.2)              | 60/71 (84.5)                  | 0.84 (0.7-1.01)               | 0.06           |
| <b>Secondary outcomes</b>                            |                           |                               |                               |                |
| 28-day mortality - n (%)                             | 17/66 (25.8)              | 17/71 (23.9)                  | 1.08 (0.6-1.93)               | 0.81           |
| ICU length of stay, days – mean (SD)                 | 21.3 (17.3)               | 21.8 (14.1)                   | -                             | 0.87           |
| Hospital length of stay, days – mean (SD)            | 48.7 (46.8)               | 40.1 (33.3)                   | -                             | 0.22           |
| Composite outcome – n (%)                            | 18 (27.3)                 | 23 (31.9)                     | 0.85 (0.51-1.43)              | 0.55           |
| <b>Serious adverse events</b>                        |                           |                               |                               |                |
| - Severe hypotension                                 | 5 (7.6)                   | 9 (12.5)                      | 0.61 (0.21-1.72)              | 0.34           |
| - Severe hypertension                                | 3 (4.5)                   | 7 (9.7)                       | 0.47 (0.13-1.73)              | 0.24           |
| - Venous thromboembolism                             | 4 (6.1)                   | 5 (6.9)                       | 0.87 (0.24-3.11)              | 0.83           |
| - Acute myocardial infarction                        | 0                         | 0                             | -                             | -              |
| - Cerebral ischemia                                  | 2 (3)                     | 2 (2.8)                       | 1.09 (0.16-7.53)              | 0.93           |
| - Intestinal ischemia                                | 1 (1.5)                   | 2 (2.8)                       | 0.55 (0.05-5.88)              | 0.61           |
| - Acute peripheral limb ischemia                     | 0                         | 0                             | -                             | -              |
| - Anaphylaxis  | 0                         | 0                             | -                             | -              |
| - ARDS   | 7 (10.6)                  | 9 (12.5)                      | 0.85 (0.33-2.15)              | 0.73           |
| - TRALI  | 0                         | 0                             | -                             | -              |
| - TACO   | 0                         | 0                             | -                             | -              |
| - Sepsis   | 7 (10.6)                  | 17 (23.6)                     | 0.45 (0.2-1.01)               | 0.05           |
| - Multiple organ failure                             | 7 (10.6)                  | 13 (18.1)                     | 0.47 (0.21-1.07)              | 0.21           |
| - Brain tissue hypoxia*                              | 0                         | 0                             | -                             | -              |

ICU = intensive care unit; ARDS = acute respiratory distress syndrome; TRALI = transfusion-associated acute lung injury; TACO = transfusion-associated cardiovascular overload.

\* The total number of patients undergoing brain tissue oxygenation monitoring was not available

**Supplementary Table S4.** Study outcomes and main adverse events on population presenting with GCS at randomization from 6 to 13.

| <b>Outcomes</b>                                      | <b>Liberal<br/>(n=52)</b> | <b>Restrictive<br/>(n=48)</b> | <b>Risk Ratio<br/>(95%CI)</b> | <b>Absolute risk<br/>reduction (95%CI)</b> | <b>P Value</b> |
|--|---------------------------|-------------------------------|-------------------------------|--|----------------|
| <b>Primary outcome</b>                               |                           |                               |                               |  |                |
| Unfavorable neurological outcome at 180 days - n (%) | 34/52 (65.4)              | 40/47 (85.1)                  | 0.77 (0.61-0.97)              | -19.72 (-36.18 to -3.27)                   | 0.02           |
| <b>Secondary outcomes</b>                            |                           |                               |                               |  |                |
| 28-day mortality - n (%)                             | 12/52 (23.1)              | 12/47 (25)                    | 1.03 (0.83-1.29)              | -2.45 (-19.38 to 14.47)                    | 0.78           |
| ICU length of stay, days – mean (SD)                 | 21.2 (18.1)               | 21.8 (15.5)                   | -                             | -0.6 (-7.31 to 6.11)                       | 0.87           |
| Hospital length of stay, days – mean (SD)            | 47.3 (49.5)               | 39.6 (35.2)                   | -                             | 7.7 (-9.47 to 24.87)                       | 0.38           |
| Composite outcome – n (%)                            | 13/52 (25)                | 17/48 (35.4)                  | 1.16 (0.89-1.51)              | -10.42 (-28.35 to 7.52)                    | 0.26           |
| <b>Serious adverse events</b>                        |                           |                               |                               |  |                |
| - Severe hypotension                                 | 4/52 (7.7)                | 6/48 (12.5)                   | 1.05 (0.92-1.2)               |  | 0.42           |
| - Severe hypertension                                | 2/52 (3.8)                | 5/48 (10.4)                   | 1.07 (0.96-1.2)               |  | 0.2            |
| - Venous thromboembolism                             | 4/52 (7.7)                | 5/48 (10.4)                   | 1.03 (0.91-1.17)              |  | 0.63           |
| - Acute myocardial infarction                        | -                         | -                             | -                             |  | -              |
| - Cerebral ischemia                                  | 2/52 (3.8)                | 0/48 (0)                      | 0.96 (0.91-1.02)              |  | 0.17           |
| - Intestinal ischemia                                | 1/52 (1.9)                | 2/48 (4.2)                    | 1.02 (0.95-1.1)               |  | 0.51           |
| - Acute peripheral limb ischemia                     | -                         | -                             | -                             |  | -              |
| - Anaphylaxis  | -                         | -                             | -                             |  | -              |
| - ARDS   | 7/52 (13.5)               | 8/48 (16.7)                   | 1.04 (0.88-1.23)              |  | 0.65           |
| - TRALI  | -                         | -                             | -                             |  | -              |
| - TACO   | -                         | -                             | -                             |  | -              |
| - Sepsis   | 6/52 (11.5)               | 13/48 (27.1)                  | 1.21 (0.99-1.48)              |  | 0.05           |
| - Multiple organ failure                             | 5/52 (9.6)                | 11/48 (22.9)                  | 1.17 (0.98-1.4)               |  | 0.07           |
| - Brain tissue hypoxia*                              | -                         | -                             | -                             |  | -              |

**Supplementary Table S5.** Comparison of the risk of unfavorable outcome in the liberal compared to restrictive transfusion strategy according to different subgroup.

| Subgroup             | Unfavorable outcome No./total No. (%) |                      | Absolute difference, % (95% CI) | Relative risk (95% CI) | p value for interaction |
|----------------------|---------------------------------------|----------------------|---------------------------------|------------------------|-------------------------|
|                      | Liberal strategy                      | Restrictive strategy |                                 |                        |                         |
| Overall              | 51/71 (71.8)                          | 61/72 (84.7)         | -12.89 (-26.25 to 0.47)         | 0.85 (0.71 to 1.01)    |                         |
| Age, years           |                                       |                      |                                 |                        | 0.3                     |
| <45                  | 5/9 (55.6)                            | 11/12 (91.7)         | -36.11 (-72.15 to -0.1)         | 0.61 (0.32 to 1.11)    |                         |
| ≥45                  | 46/62 (74.2)                          | 50/61 (82)           | -7.77 (-22.32 to 6.78)          | 0.91 (0.75 to 1.09)    |                         |
| GCS at randomization |                                       |                      |                                 |                        | 0.81                    |
| 3 to 5               | 17/19 (89.5)                          | 21/25 (84)           | 5.47 (-14.45 to 25.4)           | 1.07 (0.85 to 1.34)    |                         |
| 6 to 9               | 28/38 (73.7)                          | 33/37 (89.2)         | -15.50 (-32.71 to 1.7)          | 0.83 (0.66 to 1.03)    |                         |
| 10 to 13             | 6/14 (42.9)                           | 7/11 (63.6)          | -30.48 (-64.72 to 3.77)         | 0.67 (0.32 to 1.43)    |                         |
| ICP monitoring       |                                       |                      |                                 |                        | 0.41                    |
| No                   | 14/27 (51.9)                          | 16/23 (69.6)         | -17.71 (-44.34 to 8.91)         | 0.75 (0.47 to 1.17)    |                         |
| Yes                  | 37/44 (84.1)                          | 45/50 (90)           | -5.91 (-19.55 to 7.73)          | 0.93 (0.8 to 1.09)     |                         |
| Salvage therapies    |                                       |                      |                                 |                        | 0.6                     |
| No                   | 41/57 (71.9)                          | 46/56 (82.1)         | -10.21 (-25.6 to 5.17)          | 0.88 (0.71 to 1.07)    |                         |
| Yes                  | 10/14 (71.4)                          | 15/17 (88.2)         | -16.81 (-44.99 to 11.38)        | 0.81 (0.56 to 1.18)    |                         |
| SOFA score           |                                       |                      |                                 |                        | 0.63                    |
| <8                   | 32/46 (69.6)                          | 42/48 (87.5)         | -17.93 (-34.19 to -1.68)        | 0.8 (0.64 to 0.99)     |                         |
| ≥8                   | 18/24 (75)                            | 19/24 (79.2)         | -4.17 (-27.92 to 19.58)         | 0.95 (0.7 to 1.29)     |                         |
| Volume ICH > 30      |                                       |                      |                                 |                        | 0.92                    |
| No                   | 7/17 (41.2)                           | 12/18 (66.7)         | -25.49 (-57.45 to 6.47)         | 0.62 (0.32 to 1.19)    |                         |
| Yes                  | 44/54 (81.5)                          | 49/55 (89.1)         | -7.61 (-20.85 to 5.63)          | 0.91 (0.78 to 1.07)    |                         |
| IVH                  |                                       |                      |                                 |                        | 0.52                    |
| No                   | 19/32 (59.4)                          | 22/29 (75.9)         | -16.49 (-39.56 to 6.58)         | 0.78 (0.55 to 1.11)    |                         |
| Yes                  | 32/39 (82.1)                          | 39/44 (88.6)         | -6.59 (-21.85 to 8.68)          | 0.93 (0.77 to 1.11)    |                         |
| Hydrocephalus        |                                       |                      |                                 |                        | 0.39                    |
| No                   | 26/42 (61.9)                          | 28/38 (73.7)         | -11.78 (-32.07 to 8.51)         | 0.84 (0.62 to 1.14)    |                         |
| Yes                  | 25/29 (86.2)                          | 33/35 (94.3)         | -8.08 (-22.8 to 6.64)           | 0.91 (0.77 to 1.08)    |                         |

**Supplementary Table S6.** Multivariate regression model for predictors of unfavorable neurological outcome (GOS-E from 1 to 5) at 180 days, including sepsis.

| <b>Variable</b>              | <b>Odds Ratio (OR)</b>       | <b>P value</b> |
|------------------------------|------------------------------|----------------|
| Group: Restrictive – Liberal | 2.31 (IC 95%, 0.88 to 6.09)  | 0.09           |
| ICH volume > 30 mL           | 3.87 (IC 95%, 1.47 to 10.19) | 0.006          |
| Hydrocephalus on admission   | 5.92 (IC 95%, 1.86 to 18.86) | 0.003          |
| GCS on admission             | 0.76 (IC 95%, 0.63 to 0.91)  | 0.003          |
| Sepsis                       | 0.99 (IC 95%, 0.22 to 4.48)  | 0.989          |