

## Tables and figure legends

### **Table 1: Baseline characteristics comparing patients treated with IVF vs SoC**

Comparison of patients who received intraventricular fibrinolysis(IVF) vs standard of care(SoC) presented for the entire IPD cohort. Absolute differences are provided in percent for frequency data and for scales or continuous variables as absolute differences according to the measurement unit(negative values indicate a decreased frequency or unit of measurement from the reference, i.e patients treated as standard of care).

### **Figure 1: Flow Diagram of Study Population and Data Analysis**

Flow diagram providing, screening, eligibility, exclusion, and generation of the study population available for IPD-contribution, based on the PRISMA-IPD guidelines.

### **Figure 2: modified Rankin Scale distribution at 6 Months(A) & Intracranial Adverse Events(B)**

A), Graphical comparison of the mRS distribution at 6 months in patients who received IVF vs SoC presented for the ps-matched IPD cohort(n=1,150). For details of the matching procedure and balance, supplement, **TableS9** and **FigureS5**).

B), Intracranial adverse events within 30 days of the ictus comparing intraventricular fibrinolysis(IVF) vs standard of care(SoC) presented for the entire IPD cohort(n=1,501, **TableS10**).

### **Figure 3: Exploratory sub-group analyses of the primary outcome**

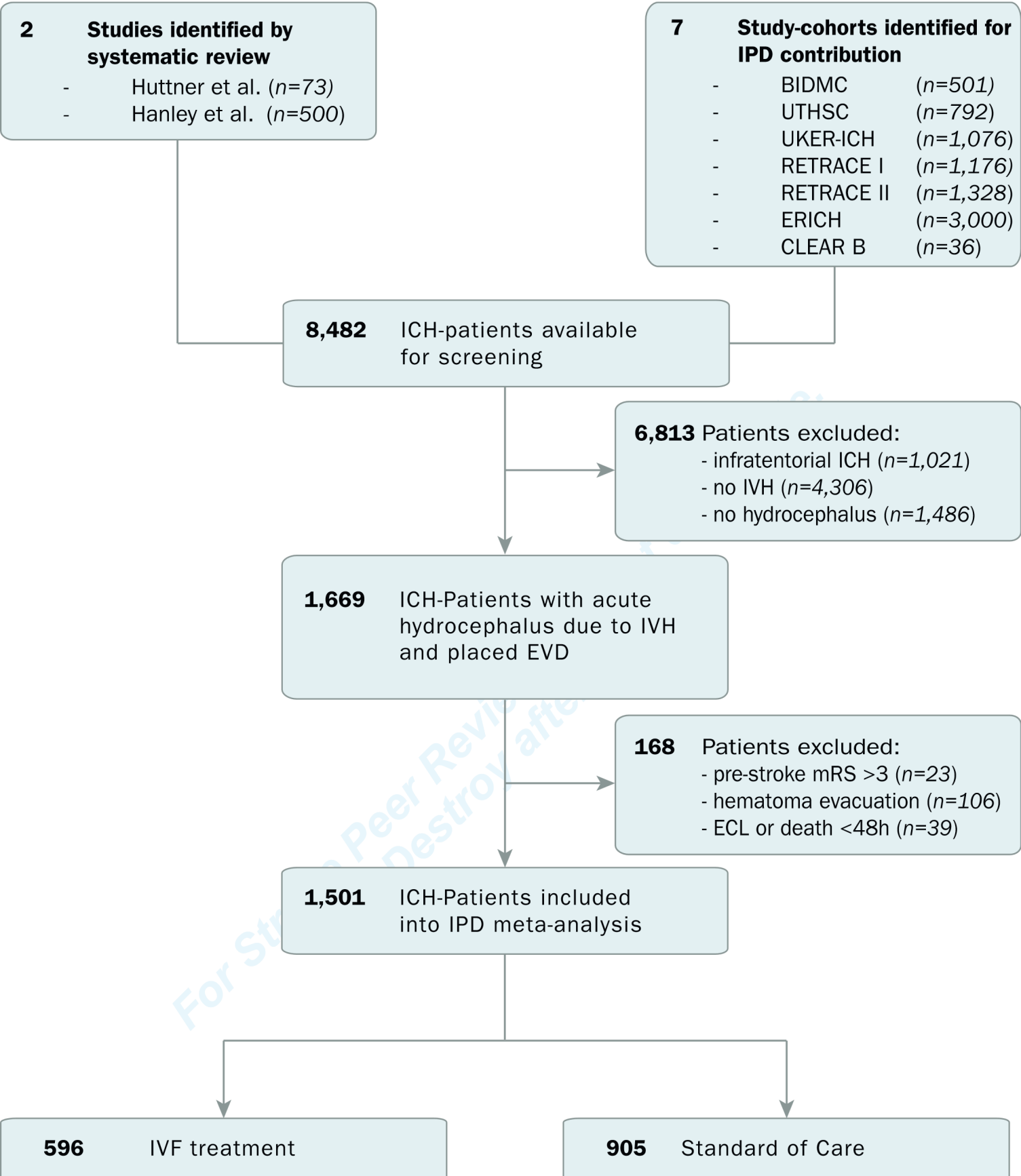
Results for the primary outcome(mRS 0-3) are presented as crude frequency data, adjusted odds ratios, and adjusted absolute treatment effects(for the entire cohort, n=1,501). Adjusted models(GLM, AIPW) were conducted as aforementioned. Interactions of exploratory subgroup analyses were tested using the subgroup-defining variable(variable\*intervention) and was considered significant for p-values<0.05.

### **Figure 4: Threshold analysis for the primary outcome using the predictor (time from symptom onset to treatment)**

Analysis was conducted as generalized linear mixed-effects(GLM) model to analyze all studies simultaneously, accounting for clustering of treatment effects across participating studies with a random effect and adjustments for confounders associated with the primary outcome. Confounders comprised: age, pre-stroke mRS, oral anticoagulation, GCS, thalamic ICH location, ICH volume, IVH volume. The adjusted odds ratio used fractional polynomials and was presented on a log-odds scale.

**Table 1. Baseline characteristics comparing patients treated with IVF vs SoC**

| IPD cohort (n=1,501)                            | IVF (n= 596)    | SoC (n= 905)    | Absolute difference, (95%CI) | SMD   |
|-------------------------------------------------|-----------------|-----------------|------------------------------|-------|
| Age, mean(SD), y                                | 61.0(12.4)      | 61.6(12.9)      | -0.5(-1.9 to 0.7)            | -0.05 |
| Female sex, No.(%)                              | 246(41.3%)      | 358(39.6%)      | 1.7(-3.4 to 6.7)             | 0.03  |
| Medical History, No.(%)                         |                 |                 |                              |       |
| Pre-stroke mRS[0-1]                             | 539(90.4%)      | 801(88.5%)      | 1.9(-1.2 to 5.1)             | 0.06  |
| Hypertension                                    | 465(78.0%)      | 737(81.4%)      | -3.4(-7.6 to 0.7)            | -0.08 |
| Diabetes Mellitus                               | 116(19.5%)      | 205(22.7%)      | -3.2(-7.4 to 1.0)            | -0.08 |
| Coronary artery disease                         | 47(7.9%)        | 95(10.5%)       | -2.6(-5.6 to 0.3)            | -0.09 |
| Prior Stroke                                    | 87(14.6%)       | 154(17.0%)      | -2.4(-6.1 to 1.3)            | -0.07 |
| Prior oral anticoagulation                      | 116(19.5%)      | 235(26.0%)      | -6.5(-10.7 to -2.2)          | -0.16 |
| Antiplatelet use                                | 109(18.3%)      | 158(17.5%)      | 0.8(-3.1 to 4.8)             | 0.02  |
| Glasgow Coma Scale <sup>a</sup> , median(IQR)   | 9(6-13)         | 9(6-13)         | 0.0(-0.6 to 0.6)             | -0.08 |
| 1 <sup>st</sup> tertile [GCS 3-7], No.(%)       | 236(39.6%)      | 332(36.7%)      | 2.9(-2.1 to 7.9)             | -0.11 |
| 2 <sup>nd</sup> tertile [GCS 8-12], No.(%)      | 211(35.4%)      | 292(32.3%)      | 3.1(-1.7 to 8.0)             |       |
| 3 <sup>rd</sup> tertile [GCS 13-15], No.(%)     | 149(25.0%)      | 281(31.0%)      | -6.0(-10.6 to -1.4)          |       |
| Stability Imaging <sup>c</sup> , No.(%)         |                 |                 |                              |       |
| Primary IVH                                     | 51(8.6%)        | 58(6.4%)        | 2.1(-0.6 to 4.9)             | 0.08  |
| Deep ICH location                               | 486(81.5%)      | 701(77.5%)      | 4.1(-0.1 to 8.2)             | 0.10  |
| Thalamic ICH location(No. 1,292)                | 276(52.5%)      | 379(49.5%)      | 3.0(-2.6 to 8.5)             | 0.06  |
| ICH volume, median(IQR), cm3                    | 8.5(3.1-17.8)   | 14.5(5.3-33.5)  | -6.0(-7.9 to -4.1)           | -0.54 |
| 1 <sup>st</sup> tertile [0.0-6.3 cm3], No.(%)   | 250(42.0%)      | 250(27.6%)      | 14.3(9.4 to 19.2)            | -0.42 |
| 2 <sup>nd</sup> tertile [6.4-19.1 cm3], No.(%)  | 216(36.2%)      | 284(31.4%)      | 4.8(0.0 to 9.7)              |       |
| 3 <sup>rd</sup> tertile [≥19.2 cm3], No.(%)     | 130(21.8%)      | 371(41.0%)      | -19.2(-23.8 to -14.6)        |       |
| IVH volume, median(IQR), cm3                    | 26.6(15.6-45.2) | 20.6(10.5-36.6) | 6.0(3.3 to 8.7)              | 0.30  |
| 1 <sup>st</sup> tertile [0.5-15.9 cm3], No.(%)  | 155(26.1%)      | 347(38.3%)      | -12.3(-17.1 to -7.6)         | 0.27  |
| 2 <sup>nd</sup> tertile [16.0-33.3 cm3], No.(%) | 207(34.7%)      | 292(32.3%)      | 2.5(-2.4 to 7.3)             |       |
| 3 <sup>rd</sup> tertile [≥33.4 cm3], No.(%)     | 234(39.3%)      | 266(29.4%)      | 9.9(4.9 to 14.7)             |       |
| Time-windows(median(IQR),h, No.1,303)           |                 |                 |                              |       |
| Ictus to ED-arrival                             | 2.0(1.0-4.5)    | 1.9(1.0-4.3)    | 0.1(-1.9 to 2.6)             | 0.05  |
| Ictus to 1. CT                                  | 3.0(1.6-6.8)    | 3.0(1.6-7.0)    | 0.0(-3.3 to 3.9)             | 0.06  |
| Ictus to stability CT                           | 30.2(18.3-47.1) | 30.0(16.2-48.0) | 0.2(-2.9 to 3.3)             | 0.07  |
| ED-arrival to 1. CT                             | 0.6(0.3-1.0)    | 0.7(0.4-1.2)    | -0.1(-0.2 to 0.0)            | -0.09 |
| 1. CT to stability-CT                           | 23.3(13.2-41.5) | 23.3(11.0-39.7) | -0.1(-2.9 to 2.8)            | -0.03 |



### Primary Outcome

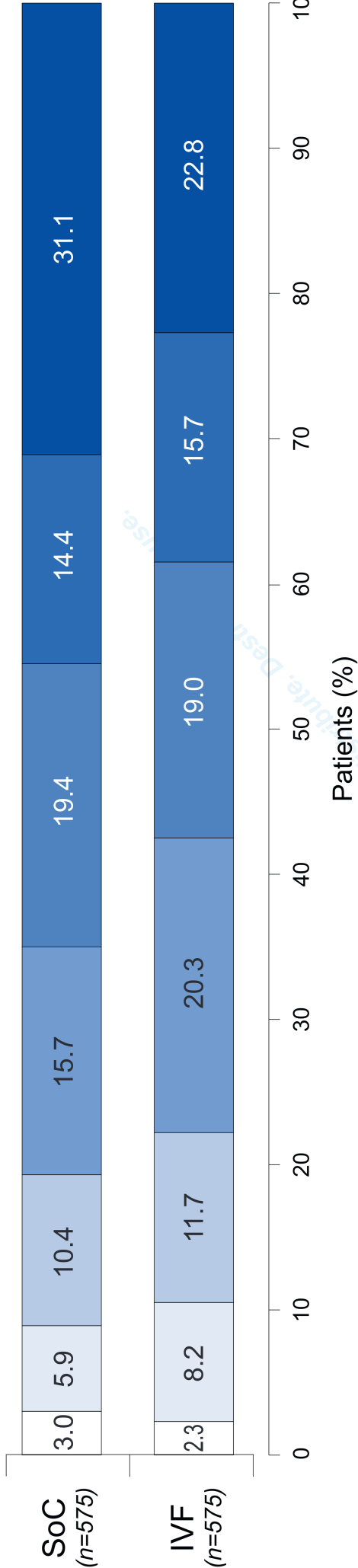
- Proportion of patients with modified Rankin scale 0-3 at 6 months

### Secondary Outcomes

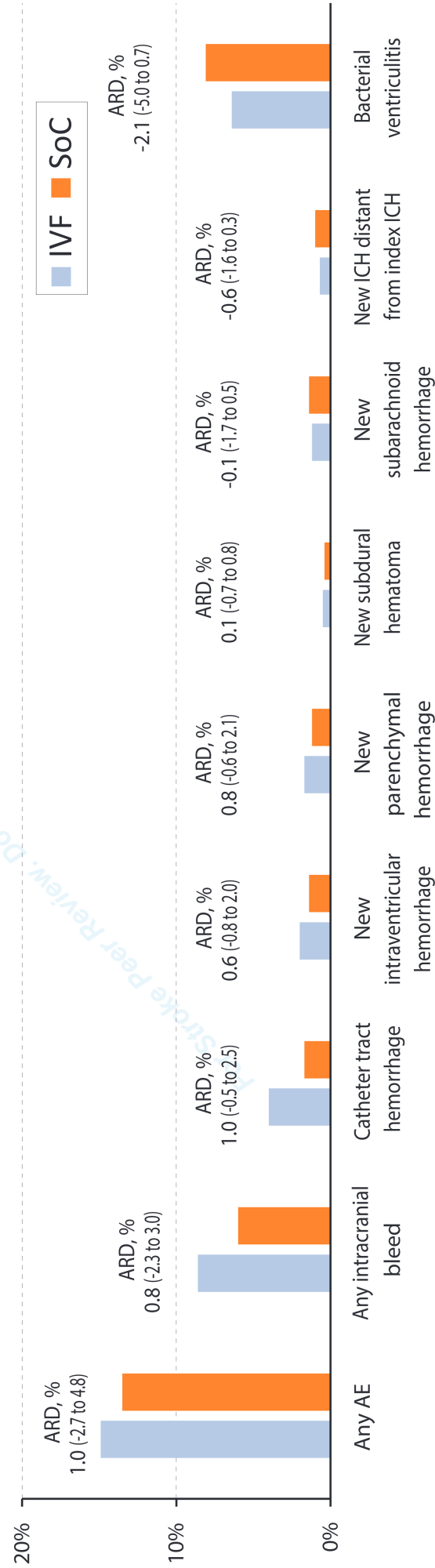
- Shift analysis: modified Rankin scale at 6 months
- Mortality at 6 months
- Intracranial adverse events within 30 days

A

0 1 2 3 4 5 6  
favorable unfavorable



B



Primary Outcome  
Total No.: 1,501

IVF  
No./total (%)

Standard of Care  
No./total (%)

Odds Ratio  
(95% CI)

Absolute Treatment Effect  
% (95% CI)

P  
interaction

## Age (years)

|                                 |                 |                 |                  |                    |      |
|---------------------------------|-----------------|-----------------|------------------|--------------------|------|
| 1 <sup>st</sup> tertile (23-55) | 113/190 (59.5%) | 140/318 (44.0%) | 1.98 (1.24-3.18) | 13.4 (5.5 to 21.3) | 0.23 |
| 2 <sup>nd</sup> tertile (56-68) | 94/236 (39.8%)  | 88/278 (31.7%)  | 1.31 (0.83-2.05) | 5.3 (-2.9 to 13.6) |      |
| 3 <sup>rd</sup> tertile (69-89) | 44/170 (25.9%)  | 48/309 (15.5%)  | 2.04 (1.16-3.60) | 8.7 (0.5 to 16.8)  |      |

## Glasgow Coma Scale

|                                 |                 |                 |                  |                    |      |
|---------------------------------|-----------------|-----------------|------------------|--------------------|------|
| 1 <sup>st</sup> tertile (3-7)   | 67/236 (28.4%)  | 56/332 (16.9%)  | 1.87 (1.15-3.05) | 12.1 (5.0 to 19.3) | 0.10 |
| 2 <sup>nd</sup> tertile (8-12)  | 89/211 (41.2%)  | 87/292 (29.8%)  | 1.48 (0.94-2.36) | 8.2 (0.5 to 15.8)  |      |
| 3 <sup>rd</sup> tertile (13-15) | 149/170 (63.8%) | 133/281 (47.3%) | 1.89 (1.07-3.34) | 9.6 (0.8 to 18.3)  |      |

## ICH Location

|          |                 |                 |                  |                    |      |
|----------|-----------------|-----------------|------------------|--------------------|------|
| Deep     | 200/486 (41.2%) | 209/701 (29.8%) | 1.83 (1.37-2.46) | 9.7 (4.8 to 14.6)  | 0.27 |
| Non-deep | 51/110 (46.4%)  | 67/204 (32.8%)  | 1.71 (0.91-3.23) | 10.4 (0.8 to 23.1) |      |

Thalamic

|                 |                 |                  |                    |      |
|-----------------|-----------------|------------------|--------------------|------|
| 101/276 (36.6%) | 114/379 (30.1%) | 1.44 (0.98-2.28) | 6.3 (0.2 to 13.0)  | 0.45 |
| 121/250 (48.4%) | 146/387 (37.7%) | 1.76 (1.17-2.66) | 12.6 (5.4 to 19.8) |      |

## ICH Volume (mL)

|                                    |                 |                 |                  |                    |      |
|------------------------------------|-----------------|-----------------|------------------|--------------------|------|
| 1 <sup>st</sup> tertile (<6.4)     | 140/250 (56.0%) | 126/250 (50.4%) | 1.74 (1.14-2.68) | 9.5 (2.1 to 16.9)  | 0.33 |
| 2 <sup>nd</sup> tertile (6.4-19.1) | 83/216 (38.4%)  | 94/284 (33.1%)  | 1.58 (1.04-2.38) | 8.6 (0.6 to 16.5)  |      |
| 3 <sup>rd</sup> tertile (≥19.2)    | 28/130 (21.5%)  | 56/371 (15.1%)  | 2.55 (1.43-4.54) | 10.9 (2.8 to 19.0) |      |

## IVH Volume (mL)

|                                     |                |                 |                  |                    |      |
|-------------------------------------|----------------|-----------------|------------------|--------------------|------|
| 1 <sup>st</sup> tertile (<16.0)     | 93/155 (60.0%) | 139/347 (40.1%) | 1.53 (0.98-2.39) | 7.8 (-0.5 to 16.1) | 0.79 |
| 2 <sup>nd</sup> tertile (16.0-33.3) | 87/207 (42.0%) | 91/292 (31.2%)  | 1.86 (1.18-2.93) | 10.6 (3.0 to 18.2) |      |
| 3 <sup>rd</sup> tertile (≥33.4)     | 71/234 (30.3%) | 46/266 (17.3%)  | 2.01 (1.27-3.22) | 9.5 (2.4 to 16.5)  |      |

## Treatment Time Window (h)

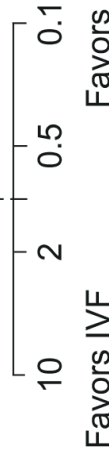
|                                     |                |                 |                  |                     |      |
|-------------------------------------|----------------|-----------------|------------------|---------------------|------|
| 1 <sup>st</sup> tertile (<29.9)     | 51/116 (44.0%) | 82/332 (24.7%)  | 3.00 (1.59-5.86) | 23.0 (12.8 to 33.2) | 0.09 |
| 2 <sup>nd</sup> tertile (29.9-52.8) | 83/185 (44.9%) | 79/264 (29.9%)  | 1.89 (1.15-3.11) | 10.0 (1.3 to 18.7)  |      |
| 3 <sup>rd</sup> tertile (≥52.8)     | 90/200 (45.0%) | 105/249 (42.2%) | 1.35 (0.84-2.16) | 5.6 (-2.0 to 13.2)  |      |

## Oral Anticoagulation

|         |                 |                 |                  |                    |      |
|---------|-----------------|-----------------|------------------|--------------------|------|
| Present | 32/116 (27.6%)  | 44/235 (18.7%)  | 1.98 (0.97-4.07) | 8.9 (-1.4 to 19.4) | 0.13 |
| Absent  | 219/480 (45.6%) | 232/670 (34.6%) | 1.67 (1.23-2.27) | 9.0 (3.7 to 14.3)  |      |

## Total

|                 |                 |                  |                   |  |
|-----------------|-----------------|------------------|-------------------|--|
| 251/596 (42.1%) | 276/905 (30.5%) | 1.69 (1.26-2.23) | 9.3 (4.4 to 14.1) |  |
|-----------------|-----------------|------------------|-------------------|--|



Favors IVF

Favors SoC

