Stroke

CLINICAL AND POPULATION SCIENCES

# Association of Intraventricular Fibrinolysis With Clinical Outcomes in Intracerebral Hemorrhage: An Individual Participant Data Meta-Analysis

Joji B. Kuramatsu, MD*; Stefan T. Gerner, MD*; Wendy Ziai, MD*; Jürgen Bardutzky, MD; Jochen A. Sembill, MD; Maximilian I. Sprügel, MD; Anne Mrochen, MD; Kathrin Kölbl, MD; Malathi Ram, PhD; Radhika Avadhani, MS; Guido J. Falcone, MD; Magdy H. Selim, MD; Vasileios-Arsenios Lioutas, MD; Matthias Endres, MD; Sarah Zweynert, MD; Peter Vajkoczy, MD; Peter A. Ringleb, MD; Jan C. Purrucker, MD; Jens Volkmann, MD; Hermann Neugebauer, MD; Frank Erbguth, MD; Peter D. Schellinger, MD; Ulrich J. Knappe, MD; Gereon R. Fink, MD; Christian Dohmen, MD; Jens Minnerup, MD; Heinz Reichmann, MD; Hauke Schneider, MD; Joachim Röther, MD; Gernot Reimann, MD; Michael Schwarz, MD; Hansjörg Bäzner, MD; Joseph Claßen, MD; Dominik Michalski, MD; Otto W. Witte, MD; Albrecht Günther, MD; Gerhard F. Hamann, MD; Hannes Lücking, MD; Arnd Dörfler, MD; Muhammad Fawad Ishfaq, MD; Jason J. Chang, MD; Fernando D. Testai, MD; Daniel Woo, MD; Andrei V. Alexandrov, MD; Dimitre Staykov, MD; Nitin Goyal, MD; Georgios Tsivgoulis, MD; Kevin N. Sheth, MD; Issam A. Awad, MD; Stefan Schwab, MD†; Daniel F. Hanley, MD†; Hagen B. Huttner, MD†

**BACKGROUND:** In patients with intracerebral hemorrhage (ICH), the presence of intraventricular hemorrhage constitutes a promising therapeutic target. Intraventricular fibrinolysis (IVF) reduces mortality, yet impact on functional disability remains unclear. Thus, we aimed to determine the influence of IVF on functional outcomes.

**METHODS:** This individual participant data meta-analysis pooled 1501 patients from 2 randomized trials and 7 observational studies enrolled during 2004 to 2015. We compared IVF versus standard of care (including placebo) in patients treated with external ventricular drainage due to acute hydrocephalus caused by ICH with intraventricular hemorrhage. The primary outcome was functional disability evaluated by the modified Rankin Scale (mRS; range: 0–6, lower scores indicating less disability) at 6 months, dichotomized into mRS score: 0 to 3 versus mRS: 4 to 6. Secondary outcomes included ordinal-shift analysis, all-cause mortality, and intracranial adverse events. Confounding and bias were adjusted by random effects and doubly robust models to calculate odds ratios and absolute treatment effects (ATE).

**RESULTS:** Comparing treatment of 596 with IVF to 905 with standard of care resulted in an ATE to achieve the primary outcome of 9.3% (95% CI, 4.4–14.1). IVF treatment showed a significant shift towards improved outcome across the entire range of mRS estimates, common odds ratio, 1.75 (95% CI, 1.39–2.17), reduced mortality, odds ratio, 0.47 (95% CI, 0.35–0.64), without increased adverse events, absolute difference, 1.0% (95% CI, −2.7 to 4.8). Exploratory analyses provided that early IVF treatment (≤48 hours) after symptom onset was associated with an ATE, 15.2% (95% CI, 8.6–21.8) to achieve the primary outcome.

**CONCLUSIONS:** As compared to standard of care, the administration of IVF in patients with acute hydrocephalus caused by intracerebral and intraventricular hemorrhage was significantly associated with improved functional outcome at 6 months. The treatment effect was linked to an early time window <48 hours, specifying a target population for future trials.

**GRAPHIC ABSTRACT:** A graphic abstract is available for this article.

**Key Words:** fibrinolysis ■ hydrocephalus ■ intracerebral hemorrhage ■ mortality ■ standard of care

Correspondence to: Hagen B. Huttner, MD, Department of Neurology, University of Erlangen-Nuremberg, Germany, Schwabachanlage 6, 91054 Erlangen, Germany. Email hagen.huttner@uk-erlangen.de

*J.B. Kuramatsu, S.T. Gerner, and W. Ziai contributed equally.

†S. Schwab, D.F. Hanley, and H.B. Huttner contributed equally.

This manuscript was sent to Theresa A. Jones, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.121.038455.

For Sources of Funding and Disclosures, see page 2885.



*Stroke* is available at www.ahajournals.org/journal/str

## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **AD** | absolute difference |
| **ATE** | absolute treatment effects |
| **CLEAR III** | Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III |
| **ERICH** | Ethnic/Racial Variations of Intracerebral Hemorrhage |
| **GCS** | Glasgow Coma Scale |
| **ICH** | intracerebral hemorrhage |
| **IPD** | individual participant data |
| **IVF** | intraventricular fibrinolysis |
| **mRS** | modified Rankin Scale |
| **OR** | odds ratio |
| **RETRACE** | German-Wide Multicenter Analysis of Oral Anticoagulation Associated Intracerebral Hemorrhage Study |
| **SMD** | standardized mean difference |
| **SoC** | standard of care |
| **UKER** | Observational Cohort Study Spontaneous ICH Conducted at the University Hospital Erlangen |

Intraventricular fibrinolysis (IVF) is a treatment strategy in patients with intracerebral hemorrhage (ICH) and severe ventricular involvement (IVH).[1,2] Several studies demonstrated hastened intraventricular clot resolution by IVF and the randomized controlled CLEAR-III trial (Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III) verified prior demonstration of safety (bleeding complications and infections) compared to placebo treatment in an ICH population with smaller parenchymal but larger intraventricular hemorrhage volumes.[3,4] Mortality rates were reduced, but the primary efficacy analysis for functional outcome was neutral.[3,5] Questions remain whether improved patient selection may provide functional benefit and establish this therapy with greater certainty.[3,6,7]

Two important subgroups have been identified from CLEAR-III, patients with intermediate-sized IVH volumes and time from symptom onset to randomization.[3] Hence, individualizing a treatment strategy suggests that threshold-based selection of lesion volumes and timing from symptom onset to IVF treatment may provide functional benefit. Only availability of a large sample with highly granular data would allow quantification of patient characteristics predictive of favorable functional outcome.[8–10] We thus conducted an individual participant data (IPD) meta-analysis integrating published studies on IVF and eligible ICH patients from large observational cohort studies.[11]

# METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request and after approval of the data coordinating centers of the participating trials and studies.

## Search Strategy and Data Synthesis

We performed a systematic review searching the Cochrane Library, Pubmed, and Scopus databases, and international trial registries, without language restrictions for clinical studies from inception to July 30, 2019. For full details of search criteria for the systematic review, aggregate data meta-analysis, and statistical analysis plan, please see Supplemental Methods, Table S1, and Figure S1–S3. The systematic review identified 8 studies of which 3 fulfilled prespecified criteria for IPD contribution and after invitation 2 contributed IPD.[3,12,13] Hence, decision was made by the lead investigators (J.B.K., W.Z., S.T.G., S.S., D.F.H., H.B.H.) to complement the present analysis by integrating further IPD from existing large studies of general ICH populations with availability of highly granular data.[3,12,14–19] This decision was based on the fact that with these few available specific studies analytical methodology would have been limited by restricting appropriate adjustments for bias and confounding as well as leading to an inability to conduct sufficient exploratory analyses (Supplemental Methods). Identification of observational studies was performed by screening registries (ClinicalTrials.gov, European Clinical Trials Database), complemented by our systematic review, and by contacting established investigative teams. All findings are reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis of Individual Participant Data.[20]

The present IPD meta-analysis (Figure S1) incorporated 9 studies (Table S2): (1) the randomized controlled CLEAR-III trial (https://www.clinicaltrials.gov; Unique identifier: NCT00784134), (2) CLEAR-B phase-II trial (https://www.clinicaltrials.gov; Unique identifier: NCT00650858),[3,4] (3) the multicenter, prospective, case-control ERICH study (Ethnic/Racial Variations of Intracerebral Hemorrhage; https://www.clinicaltrials.gov; Unique identifier: NCT01202864),[15] (4 and 5) 2 multicenter cohorts from the German-wide multicenter analysis of oral anticoagulation associated intracerebral hemorrhage, RETRACE-study (German-Wide Multicenter Analysis of Oral Anticoagulation Associated Intracerebral Hemorrhage Study) part-I (https://www.clinicaltrials.gov; Unique identifier: NCT01829581)[14] and part-II (https://www.clinicaltrials.gov; Unique identifier: NCT03093233),[16,21] (6) the single-center observational cohort study (UKER [Observational Cohort Study Spontaneous ICH Conducted at the University Hospital Erlangen]) for primary spontaneous ICH conducted at the University Hospital Erlangen, Germany (https://www.clinicaltrials.gov; Unique identifier: NCT03183167),[17] (7) single-center observational cohort study in adult nontraumatic ICH patients conducted at the University of Tennessee Health Science Center,[18] (8) single-center observational cohort study in adult patients with spontaneous supratentorial ICH conducted at Beth Israel Deaconess Medical Center,[19] (9) single-center matched-pair cohort study conducted at University Hospital Heidelberg, Germany.[12] Informed consent was obtained from all participants or their legal representatives within each participating study if not waived by the respective ethical committees. Institutional review boards or ethical committees reviewed and approved all study protocols.

## Data Extraction and Study Population

Eligibility for IPD inclusion comprised the following: (1) supratentorial primary ICH or IVH with IVH causing acute hydrocephalus treated with an external ventricular drainage, (2) patient age ≥18 years, (3) premorbid modified Rankin Scale (mRS) score ≤3, (4) >10 patients treated with IVF within each study framework, (5) no evidence of early care limitations or death within 48 hours after admission,[22] (6) no evidence of secondary ICH causes, (7) no other competing treatment intervention (eg, craniectomy, minimal invasive surgery), (8) use of validated methods for imaging assessment, (9) standardized scoring of neurological status (Glasgow Coma Scale [GCS] ranging from 3, comatose, to 15, alert), and (10) availability of standardized functional outcome assessed by the mRS (ranging from 0, no functional deficit to 6, death) recorded between 3 and 12 months after the index event. For methodology of data acquisition and description of included studies, please see Table S3. Complete data sets were available for patient identification; that is, the entire ICH cohort within each study framework was available for identification of patients eligible for IPD contribution according to the predefined eligibility criteria. Baseline data on demographics, prior comorbidities, prior medication exposures, timing measures, and neurological status upon hospital admission were obtained.[16] Imaging analyses were conducted at imaging cores within each study framework by investigators blinded to clinical information (Table S3). The IPD-set was compiled and centrally analyzed by the coordinating center (University Hospital Erlangen, Germany).[16]

## Intervention and Outcomes

The investigated intervention (intraventricular fibrinolysis, IVF) consisted of the instillation of alteplase (1 mg/mL) through an external ventricular drainage until the stopping point was achieved. The stopping point was defined as radiographic opening of the third and fourth ventricles or relieved mass effect of IVH or reached maximum dose according to individual study protocols.[3,4,12] IVF was compared to either placebo treatment (CLEAR-III) or external ventricular drainage management according to American or European ICH guidelines, both referred to as standard of care (SoC) throughout the article.[23,24]

The primary outcome was predefined as the proportion of patients achieving favorable functional outcome at 6 months mRS score of 0 to 3 dichotomously compared with mRS score of 4 to 6. Secondary outcomes comprised (1) ordinal-shift analysis of mRS values at 6 months, (2) all-cause mortality at 6 months, and (3) adverse events defined as any intracranial bleeding complication or bacterial infection occurring within 30 days after ictus. Follow-up information was obtained according to individual study protocols by personnel blinded to clinical data (Table S3).

## Risk of Bias Assessment

All included studies were evaluated for risk of bias using the ROBINS-I tool (Risk of Bias in Nonrandomized Studies of Interventions)[25] by consensus of the lead authors (Table S4).

## Statistical Analysis

Full details of the prespecified statistical analysis plan of this IPD meta-analysis are provided Supplemental Methods. Each IPD-set was checked for completeness, consistency, and queries were resolved with participating investigators. We standardized coding, format, and units of measurement for scale or continuous variables to maximize data completeness.[26] Missing outcome information (5.4%, complete IPD-dataset) was handled by multiple imputations (Supplemental Methods; Table S4).[27] Sensitivity analyses involved interstudy variance of treatment effects across participating studies with clinical outcomes at 6 months, confounding due to excluded patients determined by interaction analysis (IVF×excluded patients), and evaluation of unmeasured confounding (*E* values).[9,28] Heterogeneity was evaluated by Cochran-Q testing, calculated $I^2$-values, considered significant $P<0.1$, and inconsistency of results were determined according to the GRADE-Handbook (Grading of Recommendations Assessment, Development and Evaluation).[29] Analyses for interactions of treatment effect (IVF×interaction term) were considered significant for $P<0.05$. All tests were 2-sided with significance level at $\alpha=0.05$. The systematic review and aggregate meta-analysis were conducted using RevMan (Version5.4) and IPD meta-analysis was conducted with STATA (version 14.2).

Statistical analyses of primary and secondary outcomes used pooled IPD (N=1501) comparing IVF treatment, as per-protocol basis, to SoC as reference. To rigorously address bias and confounding, we used 3 different confounder-adjusted methods conducted as one-stage approach to calculate adjusted odds ratios (OR) and adjusted absolute treatment effects (ATE). (1) Conventional OR-model calculated using generalized linear mixed-effect to analyze all studies simultaneously, accounting for clustering of treatment effects (between-study differences) across participating studies with random effects and adjustments for confounders associated with the investigated outcomes. (2) Doubly robust estimations to calculate ATE using logistic regression by a technique (augmented inverse probability weighting), which was identified as most conservative model after sensitivity analyses. Adjustments were performed in 2 ways (1) confounders associated with an increased propensity to receive IVF treatment, that is, oral anticoagulation, GCS, deep ICH location, ICH volume, IVH volume and (2) validated confounders associated with functional outcome and mortality, that is, age, prestroke mRS, oral anticoagulation, GCS, thalamic ICH location, ICH volume, IVH volume. (3) For graphical analyses only, we used a propensity-matched cohort (n=1150) using the aforementioned confounders associated with an increased treatment propensity, calculated by balanced, parallel (1:1) nearest neighbor approach (caliper. 0.2).[30] Analyses comprised the mRS distribution at 6 months and exploratory threshold regression analyses of nonlinear treatment effect modifiers (age, GCS, ICH volume and IVH volume, symptom onset to treatment) calculated using the multivariable fractional polynomials interaction approach with OR presented on a log-odds scale.[31]

In general, confounders were identified based on sensitivity analyses of each investigated outcome and considered relevant by a standardized mean difference larger than 10%. Primary and secondary outcome analyses comprised binary regression for the primary end point (mRS score of 0–3), mortality, and adverse events as well as ordinal-shift analyses (presented as common odds ratio, after checking the proportional odds assumption, as appropriate) across the entire mRS within generalized linear mixed-effect- and augmented inverse probability weighting modeling. Exploratory subgroup analyses followed





*Stroke.* 2022;53:2876–2886. DOI: 10.1161/STROKEAHA.121.038455

the same methodology. Subgroup categories of continuous or scale variables were grouped into tertiles or scored as present or absent and were tested for interactions (IVF×subgroup category) considered significant for $P<0.05$.

# RESULTS

## Systematic Review and Aggregate Data Meta-Analysis

The systematic review of published studies analyzing associations of IVF with mortality at discharge, mortality, and functional outcome at ≥3 months identified 2 trials and 6 observational cohort studies (Table S1 and Figure S1). Results provided significant heterogeneity and substantial data inconsistency for functional outcome (Figure S2). Risk of bias due to baseline confounding was judged high or unclear in 6 out of 8 studies (Figure S3).

## Study Population of IPD Meta-Analysis

We screened 9 datasets with 8482 ICH patients for eligibility, pooling IPD data from one randomized controlled trial (CLEAR-III, including n=500), from one phase-II trial (CLEAR-B, including n=35), from one observational study (including n=52), and additionally integrated IPD from large observational cohort studies (ERICH, including n=388; RETRACE-I, including n=115; RETRACE-II, including n=144; UKER, including n=170; University of Tennessee Health Science Center, including n=80; Beth Israel Deaconess Medical Center, including n=17). Hence, the IPD study cohort consisted of 1501 patients of which 596 patients received IVF compared to 905 patients with SoC (Figure 1). Sensitivity analyses of excluded patients did not show significant interactions (Table S5).

## Risk of Bias Assessment

Statistical heterogeneity was not significant and inconsistency of results across participating studies with respect to interstudy variance of treatment associations was determined low ($I^2$-fluctuation span, 0%–47%; Figure S4). Risk of bias was judged low to moderate risk across all participating studies (Figure S4 and Table S4).

## IPD Meta-Analysis

Baseline characteristics are provided in the Table. Patients with IVF received the first dose at a median of 47.8 hours interquartile range (31.0–64.5) after symptom onset with a median cumulative dose of 5 mg alteplase interquartile range (3–8) and 95% CI (0–12). We identified significant imbalances in IVF treated patients compared to SoC, that is, less frequent prior use of oral anticoagulation (absolute difference [AD], 6.5% [95% CI, −10.7 to −2.2]), standardized mean difference [SMD], 0.16), more frequent deep ICH location (AD, 4.1% [95% CI, −0.1 to 8.2]; SMD, 0.10), less frequent higher GCS (values=13–15, AD, 6.0% [95% CI, −10.6 to −1.4]; SMD, −0.11), smaller ICH volumes (AD, −6.0 mL [95% CI, −7.9 to −4.1]; SMD, −0.54), and larger IVH volumes (AD, 6.0 mL [95% CI, 3.3–8.7]; SMD, 0.30). Sensitivity analyses dichotomized according to functional outcome (mRS score: 0–3 at 6 months; Table S6) showed more frequent IVF-use (AD, 12.2% [95% CI, 6.8–17.4]; SMD, 0.25), younger age (AD, −7.5 years [95% CI, −8.8 to −6.2]; SMD, −0.62), higher GCS values (AD, 3.0 [95% CI, 2.3–3.7]; SMD, 0.57), less frequent thalamic ICH (AD, −9.7% [95% CI, −15.3 to −4.1]; SMD, −0.19), lower ICH volumes (AD, −9.7 mL [95% CI, −11.5 to −8.0]; SMD, −0.59), and lower IVH volumes (AD, −8.0 mL [95% CI, −10.9 to −5.1], SMD, −0.45) in patients with favorable outcome. Sensitivity analyses according to adverse events showed more frequent prior oral anticoagulant use (AD, 9.2% [95% CI, 2.5–15.8]; SMD, 0.21) and larger IVH volumes (AD, 3.8 mL [95% CI, 0.2–7.4]; SMD, 0.10; Table S7).

## Analyses of the Primary Outcome

The adjusted absolute treatment effect of IVF to achieve a favorable functional outcome at 6 months using the entire IPD cohort (N=1501) was 9.3% (95% CI, 4.4–14.1), $P<0.001$, according to the most conservative model identified by sensitivity analyses (all models, ATE-range, 9.3%–10.0%; Table S8). The adjusted-OR to achieve favorable functional outcome was 1.69 (95% CI, 1.26–2.23), $P<0.001$; (*E* values, point-estimate, 1.92, CI, 1.50) and the crude difference for the entire cohort (N=1501) was 42.1% (251/596) versus 30.5% (276/905). Graphical representation of the mRS distribution at 6 months using the propensity-matched cohort (N=1150) is shown in Figure 2A, with a difference in proportions of favorable functional outcome of 42.4% (244/575) versus 35.0% (201/575), for sensitivity analyses of the propensity-matched cohort (Table S9 and Figure S5).

## Analyses of Secondary Outcomes

IVF treatment was associated with a significant shift towards improved functional outcome across the entire range of mRS, common-OR, 1.75 (95% CI, 1.39–2.17), $P<0.001$; (*E* values, point-estimate, 1.98, CI, 1.64). Mortality at 6 months was significantly reduced with IVF treatment compared with SoC, adjusted-OR, 0.47 (95% CI, 0.35–0.64), $P<0.001$; (*E* values, point-estimate, 2.28, CI, 1.81), with an ATE, −10.0% (95% CI, −14.5 to −5.4), $P<0.001$. Focusing on safety Figure 2B provides an overview of evaluated adverse events. In total 14.9% (89/596), adverse events in IVF treated patients were detected compared to 13.5% (122/905) in patients who received SoC, with an adjusted AD, 1.0% (95% CI,

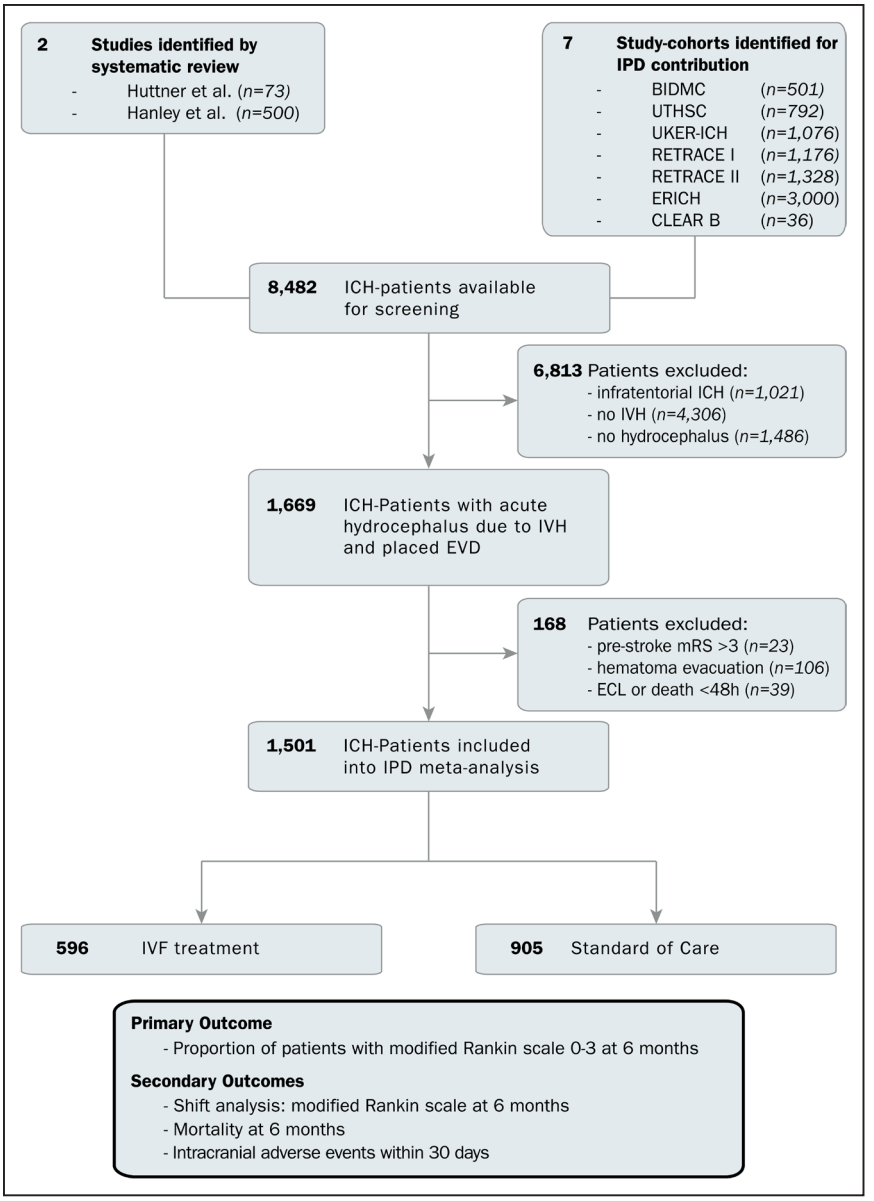


**Figure 1. Flow diagram of study population and data analysis.**
Flow diagram providing, screening, eligibility, exclusion, and generation of the study population available for individual participant data (IPD) contribution, based on the Preferred Reporting Items for Systematic Review and Meta-Analysis of Individual Participant Data guidelines. BIDMC indicates Beth Israel Deaconess Medical Center; CLEAR, Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage; ECL, early care limitations; ERICH, Ethnic/Racial Variations of Intracerebral Hemorrhage; EVD, external ventricular drainage; ICH, intracerebral hemorrhage; IVF, intraventricular fibrinolysis; IVH, intraventricular hemorrhage; RETRACE, German-Wide Multicenter Analysis of Oral Anticoagulation Associated Intracerebral Hemorrhage Study; UKER, Observational Cohort Study Spontaneous ICH Conducted at the University Hospital Erlangen; and UTHSC, University of Tennessee Health Science Center.

−2.7 to 4.8). New intracranial hemorrhagic complications were present in 8.6% (51/596) of IVF treated patients compared to 6.0% (54/905), a difference that was not statistically different, with an adjusted AD, 0.8% (95% CI, −2.3 to 3.0; Table S10).

## Exploratory Subgroup Analyses

For associations of IVF with the primary outcome (Figure 3), significant ATE were found in younger patients aged 23 to 55 years, ATE, 13.4% (95% CI, 5.5–21.3), in patients with lower GCS (3–7) values, ATE, 12.1% (95% CI, 5.0–19.3), in nondeep ICH, ATE, 10.4% (95% CI, 0.8–23.1), or nonthalamic ICH, ATE, 12.6% (95% CI, 5.4–19.8), as well as in patients with larger ICH volumes (≥19.2 mL), ATE, 10.9% (95% CI, 2.8–19.0), and moderate IVH volumes (16.0–33.3 mL), ATE, 10.6% (95% CI, 3.0–18.2). The largest ATE was observed for symptom onset to treatment, especially in the earliest time window (treatment started within first tertile<29.9 hours after onset), ATE, 23.0% (95% CI, 12.8–33.2). The following time window (29.9–52.8 hours) remained significantly associated but revealed a lower ATE, 10.0% (95% CI, 1.3–18.7). Significant interactions between treatment and subgroup categories were not detected, all $P$>0.05. Similar associations were appreciated for the secondary outcomes (ordinal-shift analysis, mortality, and adverse events, Tables S11 through S13). Early IVF treatment (<29.9 hours) was associated with the largest shift towards improved functional outcomes, common-OR, 2.70 (95% CI, 1.67–4.35). Mortality reduction was most distinct in patients with GCS (3–7) values, ATE, −19.6% (95% CI, −26.9 to −12.2), and larger ICH volumes (≥19.2 mL) ATE, −19.3% (95% CI, −28.2 to −10.3). Upon exploratory analyses of IVF treatment with adverse events, the only significant association was observed in




*Stroke.* 2022;53:2876–2886. DOI: 10.1161/STROKEAHA.121.038455

**Table. Baseline Characteristics Comparing Patients Treated With IVF Versus SoC**

| IPD cohort (N=1501) | 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, N (%) | 246 (41.3%) | 358 (39.6%) | 1.7 (−3.4 to 6.7) | 0.03 |
| Medical history, N (%) | | | | |
| Prestroke 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 | 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, median (IQR) | 9 (6–13) | 9 (6–13) | 0.0 (−0.6 to 0.6) | −0.08 |
| First tertile [GCS 3–7], N (%) | 236 (39.6%) | 332 (36.7%) | 2.9 (−2.1 to 7.9) | −0.11 |
| Second tertile [GCS 8–12], N (%) | 211 (35.4%) | 292 (32.3%) | 3.1 (−1.7 to 8.0) | |
| Third tertile [GCS 13–15], N (%) | 149 (25.0%) | 281 (31.0%) | −6.0 (−10.6 to −1.4) | |
| Stability imaging, N (%) | | | | |
| 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 (n=1292) | 276 (52.5%) | 379 (49.5%) | 3.0 (−2.6 to 8.5) | 0.06 |
| ICH volume, median (IQR), $cm^3$ | 8.5 (3.1–17.8) | 14.5 (5.3–33.5) | −6.0 (−7.9 to −4.1) | −0.54 |
| First tertile [0.0–6.3 $cm^3$], N (%) | 250 (42.0%) | 250 (27.6%) | 14.3 (9.4 to 19.2) | −0.42 |
| Second tertile [6.4–19.1 $cm^3$], N (%) | 216 (36.2%) | 284 (31.4%) | 4.8 (0.0 to 9.7) | |
| Third tertile [≥19.2 $cm^3$], N (%) | 130 (21.8%) | 371 (41.0%) | −19.2 (−23.8 to −14.6) | |
| IVH volume, median (IQR), $cm^3$ | 26.6 (15.6–45.2) | 20.6 (10.5–36.6) | 6.0 (3.3–8.7) | 0.30 |
| First tertile [0.5–15.9 $cm^3$], N (%) | 155 (26.1%) | 347 (38.3%) | −12.3 (−17.1 to −7.6) | 0.27 |
| Second tertile [16.0–33.3 $cm^3$], N (%) | 207 (34.7%) | 292 (32.3%) | 2.5 (−2.4 to 7.3) | |
| Third tertile [≥33.4 $cm^3$], N (%) | 234 (39.3%) | 266 (29.4%) | 9.9 (4.9 to 14.7) | |
| Time windows (median [IQR], h, n=1303) | | | | |
| 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 scan | 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 scan | 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 scan | 0.6 (0.3–1.0) | 0.7 (0.4–1.2) | −0.1 (−0.2 to 0.0) | −0.09 |
| 1. CT scan to stability CT scan | 23.3 (13.2–41.5) | 23.3 (11.0–39.7) | −0.1 (−2.9 to 2.8) | −0.03 |

Comparison of patients who received IVF vs 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, that is, patients treated as SoC). CT indicates computed tomography; ED, emergency department; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IPD, individual participant data; IQR, interquartile range; IVF, intraventricular fibrinolysis; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale; SMD, standardized mean difference; and SoC, standard of care.

patients with thalamic ICH, adjusted-OR, 1.74 (95% CI, 1.04–2.93), $P$=0.04 (Tables S11 through S13).

## Threshold Analyses for the Primary Outcome

Exploratory threshold analysis of treatment effect modifiers with the primary outcome showed significant treatment effects of IVF almost across the entire range of age and GCS levels (Figure S6A and S6B) as well as for patients with intermediate-sized ICH (above 8–67 mL) and IVH (above 12–69 mL) volumes (Figure S6C and S6D). The most clear-cut threshold for treatment effects associated with favorable functional outcome was identified for the predictor: time from symptom onset to initiation of IVF treatment (Figure 4). Translating this threshold (IVF treatment received ≤48 hours compared with SoC) resulted in an ATE of 15.2% (95% CI, 8.6–21.8), $P$<0.001, to achieve the primary outcome (for the entire cohort analysis 78.5% (1179/1501) of patients were analyzed within the 48-hour time frame). Validating this time window threshold exclusively with CLEAR trial data resulted in an ATE of 13.3% (95% CI, 3.3–23.4), $P$=0.009 to achieve favorable functional outcome (for the CLEAR trial cohort analysis 68.4% [366/535] of patients were analyzed within the 48-hour time frame).

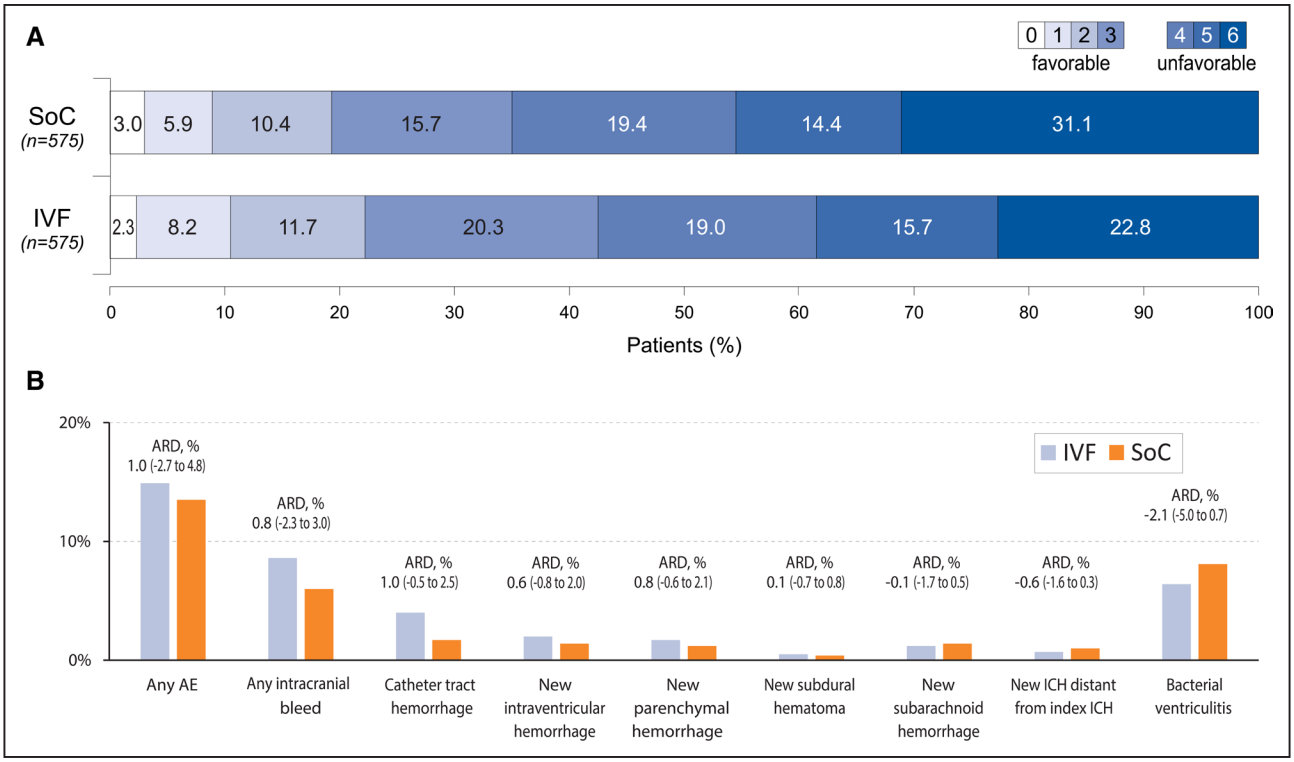


**Figure 2. Modified Rankin Scale (mRS) distribution at 6 mo and intracranial adverse events.**
**A**, Graphical comparison of the mRS distribution at 6 mo in patients who received intraventricular fibrinolysis (IVF) vs standard of care (SoC) presented for the propensity score-matched individual participant data (IPD) cohort (n=1150). For details of the matching procedure and balance, see Table S9 and Figure S5. **B**, Intracranial adverse events within 30 d of the ictus comparing IVF vs SoC presented for the entire IPD cohort (N=1501, Table S10). ARD indicates absolute risk difference; and ICH, intracerebral hemorrhage.

## DISCUSSION

The present IPD meta-analysis incorporated trial and observational data and represents the largest analysis of patients treated with IVF to date. We provide that the use of IVF in this pooled analysis of 9 studies was related to improved functional outcome, specifically in an early time window <48 hours with an effect size of 15% using the IPD cohort, which was validated using only CLEAR trial data (effect size, 13%). Furthermore, we extend prior observations that the intervention is safe, feasible, and was significantly associated with improved survival.

What may be the reason that this analysis provided positive associations while a trial showed neutral results on functional outcome? Possible explanations refer to differences in patient selection and treatment characteristics among observational- compared with trial data. In observational studies, patient selection was most likely based upon expertise and individual protocols. A priori selection bias was rigorously addressed by sophisticated statistical means in this current study, yet important differences in patient selection compared to trial data were apparent. The latter involved more patients with thalamic ICH (59% versus 46%), a location with worse prognosis.[6] Trial inclusion criteria lead to significantly less patients treated with larger ICH volumes (≥19.2 mL) compared with nontrial patients (14% versus 44%) potentially associated with our results. Specifically, IVF treatment in these patients provided robust associations with reduced mortality (ATE, 19%) and increased favorable outcome (ATE, 11%). One general question refers to the conflict between internal versus external validity of randomized controlled trials.[32] CLEAR-III was aimed at addressing both as large international multicenter trial recruiting patients from 73 sites in 8 countries.[3] Yet, IVF represents a technical strategy disruptive to usual clinical practice and therefore not always fully applied in each clinical situation. We have learned from various randomized trials, for example, mechanical thrombectomy or carotid endarterectomy in ischemic stroke that hallmarks are crucial to demonstrate a clinical net benefit, such as patient selection, experience, and timing.[33] Similarly, our data suggest optimized patient selection, possibly higher center-experience, and most strikingly identified time from symptom onset to IVF as therapeutic window for treatment benefit up to 48 hours.

This hypothesis-generating analysis provides background evidence to justify exploring new questions. What may be the mechanistic concept behind rapid IVH resolution benefiting patients? Severe IVH leads to mass effect on ependymal, midbrain, and brain stem structures, along with obstructive hydrocephalus leading to direct damage and global brain hypoperfusion.[34,35] In various studies, IVH appears to exert independent effects on outcome beyond



 *Stroke.* 2022;53:2876–2886. DOI: 10.1161/STROKEAHA.121.038455

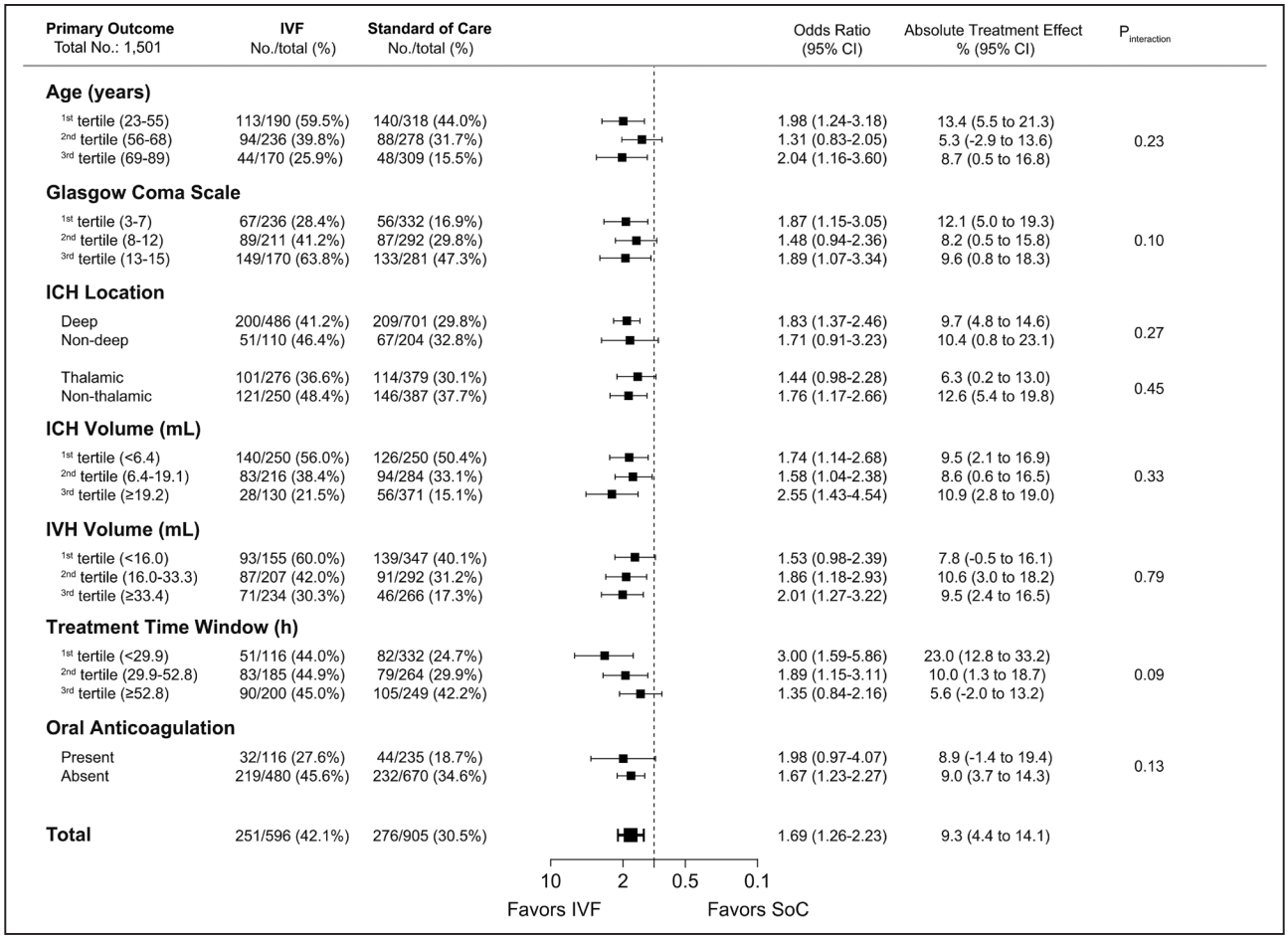


**Figure 3. Exploratory subgroup analyses of the primary outcome.**
Results for the primary outcome (modified Rankin Scale score 0–3) are presented as crude frequency data, adjusted odds ratios, and adjusted absolute treatment effects (for the entire cohort, N=1501). Adjusted models (generalized linear mixed-effect, augmented inverse probability weighting) were conducted as aforementioned. Interactions of exploratory subgroup analyses were tested using the subgroup-defining variable (variable×intervention) and were considered significant for $P<0.05$. ICH indicates intracerebral hemorrhage; IVF, intraventricular fibrinolysis; IVH, intraventricular hemorrhage; and SoC, standard of care.

ICH volume. Acute injury may be related to exaggerated neuroinflammation, yet causal relationships between outcome and acute inflammation, disturbed autoregulation, and the glymphatic system need to be determined.[36,37] Rapid clot removal by IVF limits exposure to blood-related toxins and harbors the potential to improve pathophysiology. However, IVF is not modifying parenchymal lesions suggesting that functional benefit may be driven by similar mechanisms influencing survival or otherwise by unknown factors which need to be elucidated. Specific analyses of CLEAR-III control group data suggest that instillation of saline only, that is, mechanical clot manipulation, neither led to rapid IVH resolution nor to a time-dependent association on clinical outcomes.[3] Hence, rapid clot removal achieved by alteplase is linked to improved functional outcome, presumably by multifactorial mechanisms stated above in a time-dependent manner. Regarding a subsequent randomized trial design, our findings support the evolving belief that "time is brain" not only in ischemic stroke. Current ICH trials have started to target early time windows (https://www.clinicaltrials.gov; Unique identifiers: NCT03385928, NCT03209258, NCT04434807).[38] Although time scales for ICH may be different than for ischemic stroke, our data suggest that early treatment with IVF is safe, feasible, and may positively influence outcomes.

Our results should be cautiously understood within the context of limitations pertaining to observational data (selection bias) from multiple cohorts as only 2 of 9 studies represented trials. Moreover, all observational studies were conducted by academic centers located in the United States and Germany with specialized neurointensive care units. The generalizability to hospitals without such capability is not addressed, but this may represent a potential avenue for quality improvement and implementation research. This study represents by far the largest investigation, tripling the size of the CLEAR-III, yet random sequence generation and allocation concealment were largely not present. Data derived from multiple cohorts required data harmonization to increase inferential equivalence.[26] Bias due to confounding was addressed by robust statistical methodologies and

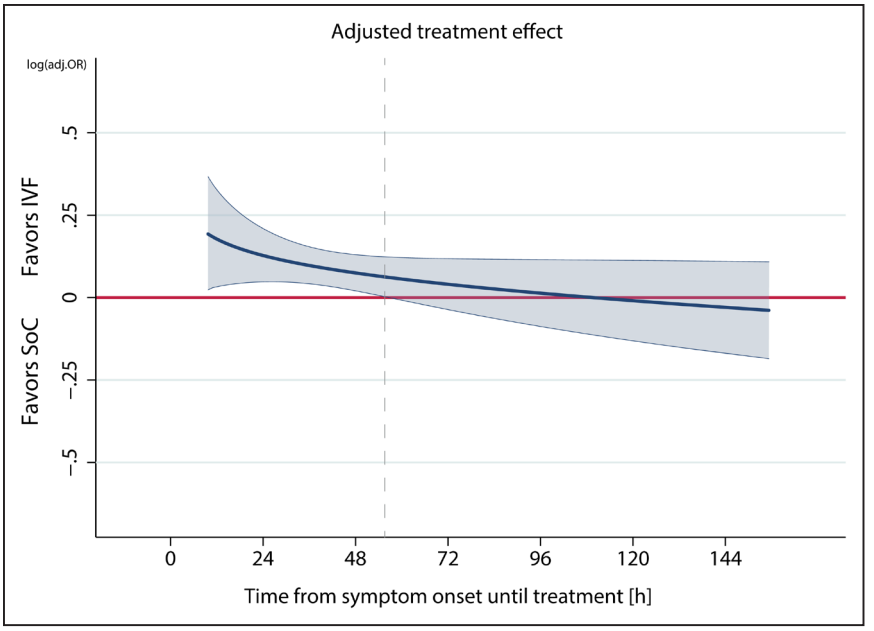


**Figure 4. Threshold analysis for the primary outcome using the predictor (time from symptom onset to treatment).**
Analysis was conducted as generalized linear mixed-effects model to analyze all studies simultaneously, accounting for clustering of treatment effects across participating studies with a random effect and adjustments for confounders associated with the primary outcome. Confounders comprised: age, prestroke modified Rankin Scale, oral anticoagulation, Glasgow Coma Scale, thalamic intracerebral hemorrhage (ICH) location, ICH volume, intraventricular hemorrhage volume. The adjusted odds ratio used fractional polynomials and was presented on a log-odds scale. IVF indicates intraventricular fibrinolysis; and SoC, standard of care.

sensitivity analyses included unmeasured confounding yet may not have completely compensated for this bias. Patients included into this study spanned a time frame from 2004 to 2015 with potential adaptations of ICH management. Imaging analysis was not centralized and lesion volume evaluation used validated but not standardized methodologies across all patients, which may have resulted in overestimation or underestimation. In addition, outcome was scored according to individual study protocols and may have been influenced by variability in time-point estimation or assessment methodology. We updated our systematic review search on May 25, 2021, which resulted in one more cohort study eligible for inclusion with a sample size of 80 patients representing a theoretical increase of 5% to the current investigation, and therefore, omission was considered sensible.[39]

## CONCLUSIONS

As compared to SoC, the administration of IVF in patients with intracerebral and intraventricular hemorrhage was significantly associated with improved functional outcome at 6 months. The treatment effect was linked to an early time window of <48 hours, specifying a target population for future trials.

## ARTICLE INFORMATION

Received December 26, 2021; final revision received April 20, 2022; accepted April 26, 2022.
Presented in part at the European Stroke Organisation Conference, Lyon, France, May 4–6, 2022.

### Affiliations

Department of Neurology (J.B.K., S.T.G., J.A.S., M.I.S., A.M., K.K., D.S., S.S., H.B.H.) and Department of Neuroradiology (H.L., A.D.), University of Erlangen-Nuremberg, Germany. Division of Brain Injury Outcomes, Johns Hopkins University, Baltimore, MD (W.Z., M.R., R.A., D.F.H.). Department of Neurology, University of Freiburg, Germany (J.B.). Department of Neurology (G.J.F.), Department of Neurosurgery (G.J.F., K.N.S.), Yale University School of Medicine, New Haven, CT. Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA (M.H.S., V.A.L.). Department of Neurology (M.E., S.Z.), and Department of Neurosurgery (P.V.), Charité–Universitätsmedizin Berlin, Germany. Center for Stroke Research Berlin, Germany (M.E.). German Centre for Cardiovascular Research (DZHK) (M.E.). German Center for Neurodegenerative Diseases (DZNE) (M.E.). Department of Neurology, Heidelberg University Hospital, Germany (P.A.R., J.C.P.). Department of Neurology, University of Würzburg, Germany (J.V., H.N.). Department of Neurology, University of Ulm, Germany (H.N.). Department of Neurology, Nuremberg General Hospital, Germany (F.E.). Department of Neurology and Neurogeriatry (P.D.S.), and Department of Neurosurgery (U.J.K.), Johannes Wesling Medical Center Minden, Germany. Department of Neurology, University of Cologne, Germany (G.R.F., C.D.). Department of Neurology, LVR-Hospital Bonn, Germany (C.D.). Department of Neurology, University of Münster, Germany (J.M.). Department of Neurology, University of Dresden, Germany (H.R., H.S.). Department of Neurology, Klinikum Augsburg, Germany (H.S.). Department of Neurology, Asklepios Klinikum Hamburg Altona, Germany (J.R.). Department of Neurology, Klinikum Dortmund, Germany (G.R., M.S.). Department of Neurology, Klinikum Stuttgart, Germany (H.B.). Department of Neurology, University of Leipzig, Germany (J.C., D.M.). Department of Neurology, University of Jena, Germany (O.W.W., A.G.). Department of Neurology and Neurological Rehabilitation, Bezirkskrankenhaus Günzburg, Germany (G.F.H.). Department of Neurology, University of Tennessee Health Science Center, Memphis (M.F.I., A.V.A., N.G., G.T.). Department of Critical Care Medicine, MedStar Washington Hospital Center, Washington, DC (J.J.C.). Department of Neurology and Rehabilitation, University of Illinois College of Medicine, Chicago (F.D.T.). Department of Neurology and Rehabilitation Medicine, University of Cincinnati, OH (D.W.). Second Department of Neurology, Attikon University Hospital, School of Medicine, Greece (G.T.). Department of Neurosurgery, University of Chicago, IL (I.A.).

### Acknowledgments

Additional Information: Collaborator Wolfgang Müllges, MD, died February 7, 2021.

### Sources of Funding

This work was partly supported by research grants from the Johannes & Frieda-Marohn Foundation (FWN/Zo-Hutt/2011) and from the Erlanger Anschubfinanzierung (ELAN) fonds (ELAN 12.01.04.1), University of Erlangen, Germany; the Jeffrey and Harriet Legum Professorship in Acute Neurological Medicine at Johns Hopkins University; and grants from the US National Institutes of Health (NINDSU01NS080824; NCATSU24TR001609). Dr Endres received funding from DFG under Germany´s Excellence Strategy–EXC-2049–390688087, Bundesministerium für Bildung und Forschung (BMBF), Deutsches Zentrum

für Herz-Kreislauf-Forschung (DZNE), Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK), European Union (EU), Corona Foundation, and Fondation Leducq. The funding entities had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the article; and decision to submit the article for publication.

## Disclosures

None of the authors report conflicts of interest related to the contents of the article. Outside the submitted work the following authors reported conflicts of interests: Dr Kuramatsu reports compensation from Biogen Idec for other services and grants from Alexion Pharmaceuticals. Dr Ziai reports compensation from BARD Pharmaceuticals Ltd for consultant services and compensation from Neurocritical Care Society for consultant services. Dr Selim reports grants from National Institutes of Health (NIH)/National Institute on Aging (NIA); grants from NIH/National Institute of Neurological Disorders and Stroke (NINDS); and compensation from MedRhythms, Inc, for consultant services. Dr Lioutas reports compensation from Qmetis for consultant services. Dr Endres reports compensation from Amgen for other services; compensation from Pfizer for other services; compensation from Daiichi Sankyo Company for other services; compensation from Bristol-Myers Squibb for other services; grants from Bayer Healthcare; compensation from AstraZeneca for other services; compensation from Bayer Healthcare for other services; compensation from Boehringer Ingelheim for other services; compensation from Novartis for other services; compensation from SANOFI-AVENTIS US LLC for other services; and grants from Deutsche Forschungsgemeinschaft. Dr Ringleb reports travel support from Bayer Healthcare; compensation from Boehringer Ingelheim for consultant services; travel support from Bristol-Myers Squibb; and compensation from Daiichi Sankyo Company for consultant services. Dr Erbguth reports grants from Boehringer Ingelheim. Dr Schellinger reports compensation from AstraZeneca for consultant services; compensation from Bayer Healthcare for consultant services; compensation from Daiichi Sankyo Europe GmbH for consultant services; compensation from Boehringer Ingelheim for consultant services; and compensation from Bristol-Myers Squibb for consultant services. Dr Röther reports compensation from AstraZeneca for consultant services and compensation from AstraZeneca for other services. Dr Günther reports compensation from PFIZER PHARMA GMBH for other services; compensation from Ipsen Pharma SAS for other services; compensation from Daiichi Sankyo Company for other services; and compensation from Boehringer Ingelheim for other services. Dr Testai reports grants from National Institutes of Health. Dr Alexandrov reports compensation from Genentech, Inc. for other services; compensation from AstraZeneca for consultant services; and employment by Health Science Center, University of Tennessee. Dr Sheth reports grants from Hyperfine; compensation from ZOLL Medical Corporation for data and safety monitoring services; compensation from CSL Behring for consultant services; grants from Novartis; compensation from Cerevasc for consultant services; a patent pending for Stroke wearables licensed to Alva Health; grants from Biogen; compensation from Rhaeos for consultant services; service as President for Advanced Innovation in Medicine; compensation from Sense for data and safety monitoring services; compensation from Certus for consultant services; and grants from BARD. Dr Awad reports grants from NIH/NINDS, compensation from Medicoegal consulting for expert witness services; compensation from Neurelis, Inc. for consultant services; and grants from Stridebio. Dr Hanley reports grants from National Institute of Neurological Disorders and Stroke; gifts from Jeffrey and Harriet Legum Professorship in Acute Neurological Medicine at Johns Hopkins University; and grants from National Center for Advancing Translational Sciences. Dr Huttner reports compensation from Boehringer Ingelheim for consultant services. Dr Kuramatsu and Dr Huttner had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The other authors report no conflicts.

## Supplemental Material

Supplemental Methods
Tables S1–S13
Figures S1–S6
PRISMA-IPD Checklist
References 40–42

# APPENDIX

## Collaborators

Lauren Sansing, MD (Department of Neurology, Yale University School of Medicine); Charles C. Matouk, MD (Department of Neurology, Yale University School of Medicine); Audrey Leasure, MD (Department of Neurology, Yale University School of Medicine); Jan Sobesky, MD (Department of Neurology, Charité–Universitätsmedizin Berlin, Germany and Center for Stroke Research Berlin, Germany); Miriam Bauer, MS (Center for Stroke Research Berlin, Germany); Johannes Schurig, MD (Center for Stroke Research Berlin, Germany); Timolaos Rizos, MD (Department of Neurology, Heidelberg University Hospital, Germany); Karl Georg Haeusler, MD (Center for Stroke Research Berlin, Germany; German Centre for Cardiovascular Research (DZHK), Germany; Department of Neurology, University of Würzburg, Germany); Wolfgang Müllges, MD (Department of Neurology, University of Würzburg, Germany); Peter Kraft, MD (Department of Neurology, University of Würzburg, Germany); Anna-Lena Schubert, MD (Department of Neurology, University of Würzburg, Germany); Sebastian Stösser, MD (Department of Neurology, University of Ulm, Germany); Albert Christian Ludolph, MD (Department of Neurology, University of Ulm, Germany); Martin Nueckel, MD (Department of Neurology, Nuremberg General Hospital, Germany); Jörg Glahn, MD (Department of Neurology and Neurogeriatry, Johannes Wesling Medical Center Minden, Germany); Henning Stetefeld, MD (Department of Neurology, University of Cologne, Germany); Jan Rahmig, MD (Department of Neurology, University of Dresden, Germany); Anna Lena Fisse, MD (Department of Neurology, University of Münster, Germany); Peter Michels, MD (Department of Neurology, Asklepios Klinikum Hamburg Altona, Germany); Henning Schwert, MD (Department of Neurology, Klinikum Stuttgart, Germany); Georg Hagemann, MD (Department of Neurology, Helios Klinikum Berlin-Buch, Germany); Florian Rakers, MD (Department of Neurology, Helios Klinikum Berlin-Buch, Germany); Johannes C. Wöhrle, MD (Department of Neurology, Klinikum Koblenz, Germany); Fahid Alshammari (Department of Neurology, Klinikum Koblenz, Germany), Markus Horn, MD (Department of Neurology, Klinikum Bad Hersfeld, Germany); Dirk Bahner, MD (Department of Neurology, Klinikum Bad Hersfeld, Germany), Christian Urbanek, MD (Department of Neurology, Klinikum der Stadt Ludwigshafen am Rhein, Germany); Frederick Palm, MD (Department of Neurology, Klinikum der Stadt Ludwigshafen am Rhein, Germany); Armin Grau, MD (Department of Neurology, Klinikum der Stadt Ludwigshafen am Rhein, Germany)

# REFERENCES

1. Baker AD, Rivera Perla KM, Yu Z, Dlugash R, Avadhani R, Mould WA, Ziai W, Thompson RE, Staykov D, Hanley DF. Fibrinolytic for treatment of intraventricular hemorrhage: a meta-analysis and systematic review. *Int J Stroke*. 2018;13:11–23. doi: 10.1177/1747493017730745
2. Cordonnier C, Demchuk A, Ziai W, Anderson CS. Intracerebral haemorrhage: current approaches to acute management. *Lancet*. 2018;392:1257–1268. doi: 10.1016/S0140-6736(18)31878-6
3. Hanley DF, Lane K, McBee N, Ziai W, Tuhrim S, Lees KR, Dawson J, Gandhi D, Ullman N, Mould WA, et al; CLEAR III Investigators. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. *Lancet*. 2017;389:603–611. doi: 10.1016/S0140-6736(16)32410-2
4. Naff N, Williams MA, Keyl PM, Tuhrim S, Bullock MR, Mayer SA, Coplin W, Narayan R, Haines S, Cruz-Flores S, et al. Low-dose recombinant tissue-type plasminogen activator enhances clot resolution in brain hemorrhage: the intraventricular hemorrhage thrombolysis trial. *Stroke*. 2011;42:3009–3016. doi: 10.1161/STROKEAHA.110.610949
5. Khan NR, Tsivgoulis G, Lee SL, Jones GM, Green CS, Katsanos AH, Klimo P Jr, Arthur AS, Elijovich L, Alexandrov AV. Fibrinolysis for intraventricular hemorrhage: an updated meta-analysis and systematic review of the literature. *Stroke*. 2014;45:2662–2669. doi: 10.1161/STROKEAHA.114.005990
6. Eslami V, Tahsili-Fahadan P, Rivera-Lara L, Gandhi D, Ali H, Parry-Jones A, Nelson LS, Thompson RE, Nekoobakht-Tak S, Dlugash R, et al. Influence of intracerebral hemorrhage location on outcomes in patients with severe intraventricular hemorrhage. *Stroke*. 2019;50:1688–1695. doi: 10.1161/STROKEAHA.118.024187
7. Casolla B, Cordonnier C. is hyperselection of patients the right strategy? *JAMA Neurol*. 2019;76:1426–1427. doi: 10.1001/jamaneurol.2019.0213
8. Tierney JF, Vale C, Riley R, Smith CT, Stewart L, Clarke M, Rovers M. Individual Participant Data (IPD) meta-analyses of randomised controlled trials: guidance on their use. *PLoS Med*. 2015;12:e1001855. doi: 10.1371/journal.pmed.1001855
9. Kuramatsu JB, Sheth KN, Huttner HB. Unmeasured confounding in observational studies of management of cerebellar intracranial hemorrhage-reply. *JAMA*. 2020;323:666. doi: 10.1001/jama.2019.20857
10. McGuinness LA, Higgins JPT, Sterne JAC. Assessing the credibility of findings from nonrandomized studies of interventions. *JAMA Cardiol*. 2018;3:905–906. doi: 10.1001/jamacardio.2018.2267
11. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies

in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008–2012. doi: 10.1001/jama.283.15.2008
12. Huttner HB, Tognoni E, Bardutzky J, Hartmann M, Köhrmann M, Kanter IC, Jüttler E, Schellinger PD, Schwab S. Influence of intraventricular fibrinolytic therapy with rt-PA on the long-term outcome of treated patients with spontaneous basal ganglia hemorrhage: a case-control study. *Eur J Neurol*. 2008;15:342–349. doi: 10.1111/j.1468-1331.2008.02077.x
13. Dunatov S, Antoncic I, Bralic M, Jurjevic A. Intraventricular thrombolysis with rt-PA in patients with intraventricular hemorrhage. *Acta Neurol Scand*. 2011;124:343–348. doi: 10.1111/j.1600-0404.2010.01481.x
14. Kuramatsu JB, Gerner ST, Schellinger PD, Glahn J, Endres M, Sobesky J, Flechsenhar J, Neugebauer H, Jüttler E, Grau A, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. *JAMA*. 2015;313:824–836. doi: 10.1001/jama.2015.0846
15. Woo D, Rosand J, Kidwell C, McCauley JL, Osborne J, Brown MW, West SE, Rademacher EW, Waddy S, Roberts JN, et al. The Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study protocol. *Stroke*. 2013;44:e120–e125. doi: 10.1161/STROKEAHA.113.002332
16. Kuramatsu JB, Biffi A, Gerner ST, Sembill JA, Sprügel MI, Leasure A, Sansing L, Matouk C, Falcone GJ, Endres M, et al. Association of surgical hematoma evacuation vs conservative treatment with functional outcome in patients with cerebellar intracerebral hemorrhage. *JAMA*. 2019;322:1392–1403. doi: 10.1001/jama.2019.13014
17. Sprügel MI, Kuramatsu JB, Volbers B, Saam JI, Sembill JA, Gerner ST, Balk S, Hamer HM, Lücking H, Hölter P, et al. Impact of statins on hematoma, edema, seizures, vascular events, and functional recovery after intracerebral hemorrhage. *Stroke*. 2021;52:975–984. doi: 10.1161/STROKEAHA.120.029345
18. Chang JJ, Khorchid Y, Dillard K, Kerro A, Burgess LG, Cherkassky G, Goyal N, Chapple K, Alexandrov AW, Buechner D, et al. Elevated pulse pressure levels are associated with increased in-hospital mortality in acute spontaneous intracerebral hemorrhage. *Am J Hypertens*. 2017;30:719–727. doi: 10.1093/ajh/hpx025
19. Lioutas VA, Wu B, Norton C, Helenius J, Modak J, Selim M. Cerebral small vessel disease burden and functional and radiographic outcomes in intracerebral hemorrhage. *J Neurol*. 2018;265:2803–2814. doi: 10.1007/s00415-018-9059-5
20. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF; PRISMA-IPD Development Group. Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. *JAMA*. 2015;313:1657–1665. doi: 10.1001/jama.2015.3656
21. Gerner ST, Kuramatsu JB, Sembill JA, Sprügel MI, Endres M, Haeusler KG, Vajkoczy P, Ringleb PA, Purrucker J, Rizos T, et al; RETRACE II (German-Wide Multicenter Analysis of Oral Anticoagulation-Associated Intracerebral Hemorrhage II) Investigators. Association of prothrombin complex concentrate administration and hematoma enlargement in non-vitamin K antagonist oral anticoagulant-related intracerebral hemorrhage. *Ann Neurol*. 2018;83:186–196. doi: 10.1002/ana.25134
22. Sembill JA, Castello JP, Sprügel MI, Gerner ST, Hoelter P, Lücking H, Doerfler A, Schwab S, Huttner HB, Biffi A, et al. Multicenter validation of the max-ICH score in intracerebral hemorrhage. *Ann Neurol*. 2021;89:474–484. doi: 10.1002/ana.25969
23. Steiner T, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, Forsting M, Harnof S, Klijn CJ, Krieger D, et al; European Stroke Organisation. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. *Int J Stroke*. 2014;9:840–855. doi: 10.1111/ijs.12309
24. Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, Fung GL, Goldstein JN, Macdonald RL, Mitchell PH, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46:2032–2060. doi: 10.1161/STR.0000000000000069
25. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919. doi: 10.1136/bmj.i4919
26. Fortier I, Raina P, Van den Heuvel ER, Griffith LE, Craig C, Saliba M, Doiron D, Stolk RP, Knoppers BM, Ferretti V, et al. Maelstrom research guidelines for rigorous retrospective data harmonization. *Int J Epidemiol*. 2017;46:103–105. doi: 10.1093/ije/dyw075
27. Chevret S, Seaman S, Resche-Rigon M. Multiple imputation: a mature approach to dealing with missing data. *Intensive Care Med*. 2015;41:348–350. doi: 10.1007/s00134-014-3624-x
28. Haneuse S, VanderWeele TJ, Arterburn D. Using the E-value to assess the potential effect of unmeasured confounding in observational studies. *JAMA*. 2019;321:602–603. doi: 10.1001/jama.2018.21554
29. Schünemann HBJ, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group. Accessed March 30, 2020. https://gdt.guidelinedevelopment.org/app/handbook/handbook.html.
30. Leisman DE. Ten pearls and pitfalls of propensity scores in critical care research: a guide for clinicians and researchers. *Crit Care Med*. 2019;47:176–185. doi: 10.1097/CCM.0000000000003567
31. White IR, Kaptoge S, Royston P, Sauerbrei W; Emerging Risk Factors Collaboration. Meta-analysis of non-linear exposure-outcome relationships using individual participant data: a comparison of two methods. *Stat Med*. 2019;38:326–338. doi: 10.1002/sim.7974
32. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet*. 2005;365:82–93. doi: 10.1016/S0140-6736(04)17670-8
33. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, Campbell BC, Nogueira RG, Demchuk AM, Tomasello A, et al; HERMES Collaborators. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA*. 2016;316:1279–1288. doi: 10.1001/jama.2016.13647
34. Abdelmalik PA, Ziai WC. Spontaneous intraventricular hemorrhage: when should intraventricular tPA be considered? *Semin Respir Crit Care Med*. 2017;38:745–759. doi: 10.1055/s-0037-1607991
35. Reinhard M, Neunhoeffer F, Gerds TA, Niesen WD, Buttler KJ, Timmer J, Schmidt B, Czosnyka M, Weiller C, Hetzel A. Secondary decline of cerebral autoregulation is associated with worse outcome after intracerebral hemorrhage. *Intensive Care Med*. 2010;36:264–271. doi: 10.1007/s00134-009-1698-7
36. Ziai WC, Thompson CB, Mayo S, McBee N, Freeman WD, Dlugash R, Ullman N, Hao Y, Lane K, Awad I, et al; Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III) Investigators. Intracranial hypertension and cerebral perfusion pressure insults in adult hypertensive intraventricular hemorrhage: occurrence and associations with outcome. *Crit Care Med*. 2019;47:1125–1134. doi: 10.1097/CCM.0000000000003848
37. Nedergaard M, Goldman SA. Glymphatic failure as a final common pathway to dementia. *Science*. 2020;370:50–56. doi: 10.1126/science.abb8739
38. Mayer SA. Intracerebral hemorrhage: natural history and rationale of ultra-early hemostatic therapy. *Intensive Care Med*. 2002;28 Suppl 2:S235–S240. doi: 10.1007/s00134-002-1470-8
39. Luong CQ, Nguyen AD, Nguyen CV, Mai TD, Nguyen TA, Do SN, Dao PV, Pham HTM, Pham DT, Ngo HM, et al. Effectiveness of combined external ventricular drainage with intraventricular fibrinolysis for the treatment of intraventricular haemorrhage with acute obstructive hydrocephalus. *Cerebrovasc Dis Extra*. 2019;9:77–89. doi: 10.1159/000501530
40. Ducruet AF, Hickman ZL, Zacharia BE, Grobelny BT, Narula R, Guo KH, Claassen J, Lee K, Badjatia N, Mayer SA, et al. Exacerbation of perihematomal edema and sterile meningitis with intraventricular administration of tissue plasminogen activator in patients with intracerebral hemorrhage. *Neurosurgery*. 2010;66:648–655. doi: 10.1227/01.NEU.0000360374.59435.60
41. Volbers B, Wagner I, Willfarth W, Doerfler A, Schwab S, Staykov D. Intraventricular fibrinolysis does not increase perihemorrhagic edema after intracerebral hemorrhage. *Stroke*. 2013;44:362–366. doi: 10.1161/STROKEAHA.112.673228
42. Ziai W, Moullaali T, Nekoovaght-Tak S, Ullman N, Brooks JS, Morgan TC, Hanley DF. No exacerbation of perihematomal edema with intraventricular tissue plasminogen activator in patients with spontaneous intraventricular hemorrhage. *Neurocrit Care*. 2013;18:354–361. doi: 10.1007/s12028-013-9826-1