Title

Methylprednisolone as Adjunct to Endovascular Thrombectomy for Large Vessel Occlusion Stroke: The MARVEL Randomized Clinical Trial

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(3) Supplement 3 – eMethods, eFigures, and eTables

(4) Supplement 4 – Data sharing statement

(5) Supplement 5 – CONSORT Checklist

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Key Points

Question Among patients with large vessel occlusion acute ischemic stroke, does adjunctive intravenous methylprednisolone to endovascular thrombectomy improve clinical outcomes?

Findings In this randomized clinical trial that included 1680 patients, intravenous methylprednisolone, compared with placebo, as adjunct to endovascular thrombectomy resulted in no significant difference in disability severity between groups as measured by the overall distribution of the modified Rankin scale score at 90 days (adjusted generalized odds ratio for a lower level of disability, 1.10).

Meaning Adjunctive methylprednisolone therapy to endovascular treatment for acute ischemic stroke did not significantly improve the degree of overall disability.

Abstract

Importance Methylprednisolone is a pluripotent agent. It remains uncertain whether intravenous methylprednisolone is effective to improve outcomes for patients with large vessel occlusion (LVO) undergoing endovascular thrombectomy (EVT).

Objective To assess the efficacy and safety of adjunctive intravenous low-dose methylprednisolone to endovascular thrombectomy for acute ischemic stroke secondary to large vessel occlusion.

Design, Setting, and Participants This investigator-initiated, randomized, double-blind, placebo-controlled trial was implemented at 82 hospitals in China, enrolling 1680 patients with stroke and proximal intracranial large vessel occlusion presenting within 24 hours of time last known well. Recruitment took place between February 09, 2022, and June 30, 2023, with a final follow-up, on September 30, 2023.

Interventions Eligible patients were randomly assigned with intravenous methylprednisolone (n = 839) at 2mg/kg/day or placebo (n = 841) for 3 days adjunctive to EVT.

Main Outcomes and Measures The primary outcome was disability level at 90 days as measured by the overall distribution of the modified Rankin scale scores from 0 (no symptoms) to 6 (death). Adverse events included mortality at 90 days and the incidence of symptomatic intracranial hemorrhage within 48 hours.

Results Among 1680 patients randomized (median age, 69 years; 727 (43.3%) female), 1673 (99.6%) completed the trial. The median 90-day modified Rankin scale score was 3 (interquartile range, 1-5) in the methylprednisolone group vs 3

(interquartile range, 1-6) in the placebo group. (adjusted generalized odds ratio for a lower level of disability 1.10 [95% CI, 0.96 to 1.25])). In the methylprednisolone group, there was a lower mortality (23.2% vs. 28.5%, adjusted risk ratio 0.84 [95% CI, 0.71 to 0.98], P = 0.03) and a lower rate of sICH (8.6% vs. 11.7%, adjusted risk ratio 0.74 [95% CI 0.55 to 0.99], P = 0.04), compared with placebo.

Conclusions and Relevance Among LVO patients with acute ischemic stroke undergoing EVT, adjunctive methylprednisolone to EVT did not significantly improve the degree of overall disability.

Trial Registration chictr.org.cn, ChiCTR2100051729

Introduction

Adjunctive treatment is needed to complement acute stroke reperfusion therapies which remain unsatisfactory. Over the past decades, preclinical models have revealed potential benefits of corticosteroids in stroke treatment, including the reduction of infarct area, regulation of cerebral flow, improvement of the no-reflow phenomenon, stabilization of the blood-brain barrier, prevention of angiogenic edema, inhibit oxygen free radical-induced lipid peroxidation, and modulation of the immune response[1–9], yet none have been validated by clinical trials. Most of the prior trials investigating corticosteroids were conducted before the advent of mechanical thrombectomy as a viable treatment option, suggesting that many patients may have failed to reperfuse.[10-13] Consequently, corticosteroids were examined under the more challenging conditions of permanent, as opposed to transient, brain ischemia.[14] The presence or lack of reperfusion has been identified as a critical determinant of corticosteroid effectiveness in animal models.[9] In addition, many of the prior trials comprised of patients who did not undergo brain imaging so only had "presumed ischemic stroke" and the sample sizes were limited. In a 2011 Cochrane review, of 24 published stroke trials involving corticosteroids, only 8 were deemed acceptable for meta-analysis synthesis, encompassing a total of 466 patients. Moreover, these studies used high doses and long duration of corticosteroids which may have led to more side effects.[15]

In this study, we sought to determine whether the administration of intravenous low-dose methylprednisolone in patients with acute ischaemic stroke due to LVO is a

safe and effective treatment, in the setting of rapid reperfusion now attainable by endovascular treatment.

Methods

Trial Design and Oversight

The Methylprednisolone as Adjunctive to Endovascular Treatment for Acute Large Vessel Occlusion (MARVEL) trial was an investigator-initiated, multicenter, prospective, randomized, double-blind, placebo-controlled clinical trial. The trial was performed at 82 comprehensive stroke centers in China. It was approved both by the central medical ethics committee and the research board at each site. Signed informed consent was obtained from the patient or their legally authorized representative before enrollment. The study protocol has been published and is available in Supplement 1, and the statistical analysis plan is available in Supplement 2.[16]

The trial was designed and conducted by a steering committee composed of independent academic investigators and was monitored by an independent data and safety monitoring board. All data analyses and end-point adjudication were performed by an independent clinical events committee. The trial was conducted according to the Declaration of Helsinki Harmonization Guidelines. All authors vouch for the fidelity of the trial to the protocol.

Participants

Eligible patients were adults aged 18 years or older with a disabling ischemic stroke at the time of randomization (baseline National Institutes of Health Stroke Scale (NIHSS) $\geqslant$ 6 (range 0 to 42, with higher scores indicating greater stroke severity), who had been able to complete usual activities in daily life without support before the stroke, modified Rankin Scale (mRS) $<$2, range 0 [no symptoms] to 6 [death] for the evaluation of neurological functional disability), and were enrolled up to 24h from the time the patient was last known well. Computed tomographic (CT) angiography, magnetic resonance angiography, or digital subtraction angiography were performed to identify patients with an occlusion of the intracranial internal carotid artery or the first or second segment of the middle cerebral artery. The trial included patients with small-to-large ischemic core (defined as an Alberta Stroke Program Early CT Score[17] [ASPECTS] of 3–10; range 0–10, with 1 point subtracted for early ischemic change in each defined region on the non-contrast CT scan). Detailed inclusion and exclusion criteria are provided in the Supplement 3.

Randomization and Masking

Patients were randomly assigned in 1:1 ratio to receive methylprednisolone or a placebo infusion. We randomly assigned patients using a web-based mobile phone app or computer. Randomization was stratified according to participating center with a permutation block size of 4. Patients were assigned a random serial number according to the time they were enrolled, and corresponding masked and numbered medications were provided. Methylprednisolone and placebo were prepared as white

lyophilized powder in numbered vials. These vials were visually identical, except for a unique vial number. All trial personnel and patients were unaware of the treatment assignment.

Interventions

Patients received either intravenous methylprednisolone or placebo at a dose of 2mg/kg, per day (up to a maximum dose of 160 mg), once daily for 3 days. The study drug was administered as soon as possible after randomization, ideally before arterial access closure but not to be delayed for more than 2 hours after arterial access closure for endovascular treatment. After qualifying imaging, all patients underwent rapid EVT using available devices. Pre-treatment intravenous thrombolysis was allowed. Methylprednisolone and placebo were provided by Chongqing Lummy Pharmaceutical Co., Ltd. The commercial entity had no role in the trial design, data collection, analysis, or preparation of the manuscript. Sites were expected to adhere to stroke national practice guidelines for concomitant medical therapy.[18]

Outcomes

The primary efficacy outcome was the distribution of the modified Rankin Scale (mRS, shift analysis) at 90 days after randomization. The score assessment was based on central evaluation by means of video or audio by evaluators who were unaware of the treatment assignment. If video or audio recordings were unavailable, outcomes

were determined in-person by local investigators, who were also unaware of the treatment assignment.

The secondary efficacy outcomes included the NIHSS score at 5 to 7 days or at early discharge (range, 0 to 42, with higher scores indicating greater stroke severity), health-related quality of life measured with the European Quality Five-Dimension visual-analogue scale (range, 0 to 100, with higher scores indicating better quality of life, and the known MCID for health-related quality of life on a 0-100 scale is 3[19]) at 90 days, and the following prespecified dichotomizations of the modified Rankin score: 0 to 4 versus 5 to 6, 0 to 3 versus 4 to 6, 0 to 2 versus 3 to 6, and 0 or 1 (or return to pre-morbid mRS score) versus 2 to 6 at 90 days.

The primary safety prespecified outcomes were death from any cause within 90 days and symptomatic intracranial hemorrhage, as assessed according to the modified Heidelberg bleeding classification within 48 hours after EVT.[20] Other prespecified safety measures included any intracranial hemorrhage within 48 hours after EVT, adverse events including gastrointestinal bleeding within 7 days after EVT and pneumonia. Other adverse events including new-onset diabetes, hyperosmolar hyperglycemic state, and insulin use in hospital stay were recorded.

Sample Size Calculation

The sample-size calculation was based on previous studies[21,22] with an expected cumulative proportion of patients with mRS score 0-2 (43.0% in the placebo group and 50.0% in the methylprednisolone group, indicating an odds ratio of 1.33). We

expected that a 7% absolute risk difference between the two groups would be appropriate to power the study as it exceeds the reported minimally clinically important difference for a novel stroke treatment, which ranges between 1.1% to 1.5%.[23] We calculated that 794 patients per group would be required to have a power of 80% to show the expected treatment effect with a two-sided alpha of 0.05. Considering an approximate 5% non-adherence or dropout rate, we intended to enroll 1672 patients.

Statistical Analysis

The primary analysis of the primary outcome was based on the as randomized, full analysis set population which included patients according to their randomization assignment, with a valid assessment of mRS at day 90. The primary analyses for all outcomes were based on adjusted analyses for 7 prespecified covariates: age, baseline NIHSS score, pre-stroke modified Rankin Scale score, baseline ASPECTS, use of intravenous thrombolysis, time from onset to randomization, and occlusion location. Per-protocol analyses for the primary and secondary outcomes included patients who received the complete intervention as specified in the protocol. Analyses of adverse events were based on the safety population, which consisted of all randomized participants who received at least 1 dose of the study drug. We also performed some sensitivity analyses of the primary outcome including a per-protocol analysis, imputation of missing primary outcome under best-case, worst-case, and best-worst

case scenarios, and using multiple imputation, and a random effect model to control for possible center effect.

The treatment effect for the primary outcome was measured by generalized odds ratio (GenOR) with 95% confidence intervals (CI).[24] The generalized odds ratio was one the primary statistical method for the primary outcome in the initial statistical analysis plan if the proportional odds assumption not met, and was the final primary analysis of primary outcome in the final statistical analysis plan. Both unadjusted GenOR and adjusted GenOR for prespecified covariates using the inverse probability of treatment weighting (IPTW) method were calculated.[25] Secondary binary outcomes were analyzed by modified Poisson regression model with robust error estimation, from which unadjusted risk ratio (RR) and adjusted RR with their 95% CIs using IPTW were derived. The treatment effects for the non-normal continuous outcomes were measured using unadjusted and adjusted win ratios.[25] Efficacy outcomes were assessed in the as randomized, full analysis set population and repeated in the per-protocol set population. Safety outcomes were assessed in the safety population using modified Poisson regression model and survival analysis methods. Testing for modification of the treatment effect on the primary efficacy and safety outcomes were conducted in ten subgroups: age, sex, NIHSS, prestroke mRS, ASPECTS, intravenous thrombolysis, time to randomization, occlusion location, reperfusion at EVT, and treatment during or outside the peak COVID period. Consistent with regulatory and other guidance to reduce the effect of the COVID-19 pandemic on trial results, a prespecified subgroup analysis was performed. The “control period” included patients

with valid 90-day follow up prior to January 8th, 2023, when the Chinese government downgraded the control of COVID-19 from grade A control (the same level of control as with the plague and cholera) to grade B control.

Formal interaction tests were not performed as there is no reliable technique for calculating the modification effect when generalized odds ratios are analyzed. For the primary and secondary outcomes, a 2-sided *P* value of less than .05 was considered statistically significant. Because of the potential for type I error due to multiple comparisons, findings from analyses of secondary outcomes and subgroups should be interpreted as exploratory. SAS version 9.4 (SAS Institute), and R version 4.3.0 (R Development Core Team; http://www.r-project.org) were used for the statistical analyses.

Results

Characteristics of the Patients

Between February 09, 2022, and June 30, 2023, 1687 patients underwent randomization (839 to the methylprednisolone group and 841 to the placebo group) at 82 centers in China. Seven patients, whose representatives withdrew consent immediately after randomization, could not be included in the as randomized full analysis set (**Figure 1 and eFigure1 and eFigure2 in Supplement 3).** Demographic and clinical characteristics were well balanced in the two study groups (**Table 1, eTable1 in Supplement 3**). The median age was 68 (interquartile range, 59 to 75) in the methylprednisolone group and 69 (59 to 77) in the placebo group. There was 359

of 839 (42.8%) females in the methylprednisolone group and 368 of 841 (43.8%) females in the placebo group. The median baseline NIHSS score was 19.0 (interquartile range, 16.0 to 21.0) in both groups; the median ASPECTS was 6.0 in both groups; the median time from stroke onset to randomization was 354 minutes (interquartile range, 237 to 614) in the methylprednisolone group and 366 minutes (interquartile range, 239 to 590) in the placebo group.

Primary outcome

In the primary analysis, the median 90-day modified Rankin scale score was 3 (interquartile range, 1-5) in the methylprednisolone group vs 3 (interquartile range, 1-6) in the placebo group. There was no significant difference in the distribution of 90-day mRS disability outcomes on the global mRS between the methylprednisolone group and the placebo group, yielding an unadjusted GenOR 1.12 (95%CI, 0.98 to 1.28; P = 0.09), and an adjusted GenOR 1.10 (95%CI, 0.96 to 1.25; P = 0.17). (**Table 2 and Figure 2**). The sensitivity and per-protocol analyses yielded similar results (**eTable 2, eTable 3, eTable 4 and eFigure 3 in the Supplement 3**). A mRS score of 0-4 at 90 days occurred in 597 of 835 patients (71.5%) in the methylprednisolone group and in 555 of 838 patients (66.2%) in the placebo group, and had a significant difference in both unadjusted and adjusted analysis, yielding an unadjusted RR of 1.08 (95%CI, 1.01 to 1.15; P = 0.02) and an adjusted RR of 1.07 (95%, 1.00 to 1.14; P = 0.04). There was no significant difference in other prespecified secondary efficacy end points between the two groups. There were 496 of 835 (59.4%) patients who

achieved mRS 0-3 in the methylprednisolone group, compared with 459 of 838 (54.8%) patients in the placebo group (adjusted RR, 1.07 [95%CI, 0.98 to 1.16], p = 0.11, and adjusted RD, 0.04 [95%CI, 0.01 to 0.07], p = 0.02). The EQ-5D-VAS score was numerically but not significantly higher in the methylprednisolone group than the placebo group (adjusted win ratio 1.11 [95%CI, 0.98 to 1.25], p = 0.11).(**Table 2, and eTable2 in the Supplement 3**).

Adverse Events

As compared to placebo, methylprednisolone was associated with a significantly lower 90-day mortality (23.2% vs. 28.5%), yielding an unadjusted RR of 0.81 (0.69 to 0.94; P = 0.01) and an adjusted RR, 0.84 (95% CI, 0.71 to 0.98; P=0.03) (**Table 2, and eFigure 4 and eFigure 5 in Supplement 3**). Methylprednisolone was associated with a significantly lower rate of symptomatic intracranial hemorrhage at 48 hours (8.6% vs. 11.7%; unadjusted RR 0.74 [95%CI, 0.55 to 0.99], P = 0.04; adjusted RR, 0.74 [95% CI, 0.55 to 0.99] P=0.04), compared with placebo. Pneumonia occurred in 390 of 839 (46.5%) patients in the methylprednisolone and 466 of 841(55.4%) patients in the placebo group (adjusted RR, 0.85 [95%CI 0.77 to 0.93]). The proportion of gastrointestinal bleeding within 7 days after EVT was 33 of 839 patients in the methylprednisolone group and 50 of 841 patients in the placebo group (adjusted RR 1.03, 95%CI [0.91 to 1.16], P = 0.06). Insulin treatment in patients was administered to 165 of 839 patients (19.7%) in the methylprednisolone group and 110 of 841 (13.11%) in the placebo group (P = 0.0003). The incidence of new diabetes

occurred in 40 of 839 patients in the methylprednisolone group and 24 of 841 patients in the placebo group. (P = 0.04)

(**Table 2, eTable 5 and eTable 6in Supplement 3).**

Subgroup and sensitivity analyses of primary endpoint

In the period when COVID-19 was under strict control and no patients caught COVID-19, the adjusted generalized odds ratio for a lower level of disability with methylprednisolone vs placebo was 1.25 (1.04 to 1.50). The genOR was 0.95 (0.79 to 1.15) for the period when the Chinese government downgraded the control of COVID-19. (**Figure 3, eFigures 5, 6 in Supplement 3**).

Discussion

The results of this trial did not support the primary hypothesis that the administration of methylprednisolone 2 mg/kg intravenously as adjunct to EVT in LVO within 24 hours of stroke onset would reduce the overall level of disability at 90 days. However, methylprednisolone treatment was associated with significantly lower rates of symptomatic intracranial hemorrhage within 48 hours and mortality at 90 days as well as a higher proportion of patients who were alive and not bedridden (mRS 0-4) at 90 days.

In contrast to previous trials, our trial provides new insights on the role of corticosteroids in stroke therapy. Use of conventional or large doses of methylprednisolone are currently recommended to be avoided by the current

AHA/ASA guidelines (CLASS III harm), because of a lack of efficacy and the potential to increase the risk of infectious complications.[26] In this study, low-dose methylprednisolone was associated with lower mortality, lower rate of symptomatic intracranial hemorrhage and less pneumonia. Our study is one of the first to provide evidence for the potential role of protective strategies in the setting of endovascular stroke reperfusion.

There are several potential explanations for the neutral result of the primary outcome with respect to methylprednisolone. First, even though this was one of the largest EVT trials performed to date, our sample size was inadequate to capture a smaller but still clinically relevant treatment effect. We modeled our study under a general expectation of a 7% improvement in the rate of mRS 0-2 at 90 days, yet there is expert-derived consensus that the minimal clinically important difference for a safe new acute ischemic stroke treatment may be as low as 1.1% to 1.5%.[23] Second, as our study included a broad range of patients with LVO and small to moderate ischemic core who underwent EVT, the trial population may have encompassed individuals with minimal blood brain barrier disruption who potentially do not respond to corticosteroid treatment.

The secondary outcome findings suggest that corticosteroid therapy has the potential effect of increasing the proportion of patients with outcome of not requiring constant nursing care. The finding may in part reflect the ability of methylprednisolone to lessen blood-brain barrier disruption and vasogenic brain edema[27 28], which is related to fatal brain herniation. [27,28] However, corticosteroids

have less effect on cytotoxic edema due to cellular energetic failure so combination therapy with agents targeting cytotoxic edema merits investigation. The findings of reduced symptomatic intracranial hemorrhage support stabilization of the blood brain barrier as a potential beneficial effect of methylprednisolone. Moreover, the trial's finding of the short-term effect of corticosteroids on decreased incidence of pneumonia and lower incidence of circulation failure is also worth exploring. A similar effect of low-dose corticosteroids has been observed in the prevention of hospital-acquired pneumonia in patients with traumatic brain injury and patients with severe community-acquired pneumonia.[29,30]

Strengths of this trial include assessing a drug that is relatively inexpensive and readily available worldwide. Additionally, the high rates of reperfusion achieved with EVT provided a human ischemia-reperfusion model to test corticosteroid agents.

Limitation

This trial had several limitations. First, the COVID-19 pandemic may have had an influence on trial results. In the prespecified COVID-19 subgroup analysis, a favorable shift in the distribution of scores on the modified Rankin scale toward better outcomes was noted during the period when COVID was under strict control. Second, we did not correct for multiple testing of secondary and safety end points, such as mortality and sICH. Therefore, for these end points, differences and P values should be interpreted with caution. Third, the rate of intravenous thrombolysis was slightly

higher in the placebo group than in the methylprednisolone group, but the results remained robust in the adjusted analysis.

Conclusion

In conclusion, among LVO patients with acute ischemic stroke undergoing EVT, adjunctive methylprednisolone to EVT did not significantly improve the degree of overall disability.

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Author Contributions:

Drs. Qingwu Yang, Changwei Guo, Chengsong Yue, and Jiaxing Song contributed equally as the co-first authors. Drs. Wenjie Zi and Fengli Li had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design:* Wenjie Zi, Qingwu Yang, Jiaxing Song, Chengsong Yue *Acquisition, analysis, or interpretation of data:* All authors. *Drafting of the manuscript:* All authors. *Critical revision of the manuscript for important intellectual content:* Wenjie Zi, Qingwu Yang, Fengli Li, Changwei Guo, Chengsong Yue, Jiaxing Song, Jiacheng Huang, Thanh N. Nguyen, Raul G. Nogueira, and Jeffrey L. Saver. *Statistical analysis:* Duolao Wang, Changwei Guo *Obtained funding:* Qingwu Yang, Wenjie Zi. *Administrative, technical, or material support:* All authors. *Supervision:* Wenjie Zi, Qingwu Yang, and Fengli Li.

Conflict of Interest Disclosures:

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Figure Legends

Figure 1. Flow of Patients in a Study of the Effect of Intravenous Methylprednisolone vs Placebo as Adjunct to Endovascular Thrombectomy

ASPECTS indicates Alberta Stroke Program Early CT Score, NIHSS indicates National Institutes of Health Stroke Scale, ICA denotes intracranial carotid artery, M1 the first segment of middle cerebral artery, M2 the second segment of the middle cerebral artery.

[a] ASPECTS indicates Alberta Stroke Program Early CT Score ranging 0–10, with 1 point subtracted for early ischemic change in each defined region on the non-contrast CT scan.

[b] Randomization was stratified by participating center.

Figure 2. Distribution of Global Disability at 90 Days Based on the Modified Rankin Scale Score.

Shown are the distribution of the modified Rankin scale score among patients in the methylprednisolone group and the placebo group. Scores range from 0 to 6, with 0 indicating no symptoms, 1, no clinically significant disability, 2, slight disability, 3, moderate disability, 4, moderately severe disability, 5, severe disability, and 6, death. Numbers indicate rounded proportions. Data of 7 patients who withdrew consent were not included in the chart. Data of 4 patients in the methylprednisolone group and 3 patients in the placebo group with missing data are not included in the chart.

683 The sum was not 100 because of rounding. Treatment with methylprednisolone was
684 associated with an adjusted generalized odds ratio of 1.10 (95% CI, 0.96 to 1.25; P
685 = .17) for the distribution of the modified Rankin Scale at 90 days.
686
687 **Figure 3. Heterogeneity of Treatment Effect for Less Disability Among**
688 **Prespecified Subgroups.**
689 The figure shows subgroup analysis based on the adjusted generalized odds ratio,
690 indicating the odds that the trial patients assigned to the methylprednisolone group
691 would have better functional recovery at 90 days than patients assigned to receive
692 placebo. NIHSS denotes the National Institutes of Health Stroke Scale, mRS modified
693 Rankin Scale, ASPECTS Alberta Stroke Program Early Computed Tomography
694 Scores, ICA intracranial carotid artery, M1 the first segment of middle cerebral artery,
695 M2 the second segment of the middle cerebral artery. The widths of the confidence
696 intervals were not adjusted for multiple comparisons, and the reported confidence
697 intervals should not be used for hypothesis testing. The age, NIHSS score, and time
698 from stroke onset to randomization were divided at median of the whole population as
699 prespecified in the statistical analysis plan. The sizes of the boxes in the plot
700 correspond to the number of patients in each subgroup. The arrow indicates that the
701 95% confidence interval was beyond the scale. The prespecified subgroup analysis by
702 status of hemorrhage was not represented here because they are post-randomized
703 characteristics.

[a] Scores on the NIHSS range from 0 to 42, with higher scores indicating worse neurologic deficits.

[b] ASPECTS range from 0 to 10, with lower values indicating larger infarction, data were not available for 6 patients. Data for reperfusion was not available for 2 patients.

[c] Scores on the mRS of functional disability range from 0 (no symptoms) to 6 (death).

[d] The Strict COVID control period (Before 08/01/2023) subgroup in the COVID-19 category included all patients who completed their primary outcome assessment around January 8th, 2023 - which marks the beginning of the downgrade in COVID-19 management measures. In the strict COVID control period, no patients had COVID-19 infection. The peak COVID peak period (After 08/01/2023) included patients who completed the primary outcome assessment after January 8th, 2023.

716 **Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.**

Characteristics	Methylprednisolone (N=839)	Placebo (N=841)
Age, median, (IQR), y	68.0 (59.0–75.0)	69.0 (59.0, 77.0)
Female sex, No./total (%)	359 (42.8)	368 (43.8)
Male sex, No./total (%)	480 (57.2)	473 (56.2)
Medical history, No./total (%) [b]		
Hypertension	504 (60.1)	523 (62.2)
Atrial fibrillation	348 (41.5)	353 (42.0)
Hyperlipidemia	267 (31.8)	245 (29.1)
Diabetes mellitus	170 (20.3)	152 (18.1)
Coronary heart disease	147 (17.5)	169 (20.1)
Cerebral ischemia	136 (16.2)	117 (13.9)
Valvular heart disease	114 (13.6)	115 (13.7)
Intracranial hemorrhage	12 (1.4)	10 (1.2)
Transient ischemic attack	6 (0.7)	4 (0.5)
Current Smoke Tobacco	236 (28.1)	241 (28.7)
Pre-stroke Modified Rankin Scale score, No./total (%) [c]		
0	803 (95.7)	817 (97.1)
1	28 (3.3)	14 (1.7)
2	6 (0.7)	8 (1.0)
3	1 (0.1)	1 (0.1)
4	1 (0.1)	1 (0.1)
Glucose level at hospital arrival median (IQR), mmol/liter [d]	7.2 (6.2, 8.9) [N = 736]	7.0 (6.0, 8.6) [N = 736]
Baseline NIHSS score, median, (IQR) [e]	19.0(16.0, 21.0)	19.0(16.0, 21.0)
Baseline ASPECTS, median, (IQR) [f]	6.0 (4.0, 7.0)	6.0 (4.0, 7.0)
TOAST etiology, No./total (%) [g]		
Large artery atherosclerosis	302/838 (36.0)	334/841 (39.7)
Cardioembolic	422/838 (50.4)	393/841 (46.7)
Others	32/838 (3.8)	41/841 (4.9)
Unknown	82/838 (9.8)	73/841 (8.7)
Occlusion site on CT or MR angiography, No./total (%)[h]		
Intracranial internal carotid artery	286 (34.1)	293 (34.8)
M1 middle cerebral artery segment	452 (53.9)	426 (50.7)
M2 middle cerebral artery segment	99 (11.8)	122 (14.5)
Other	2 (0.2)	0 (0.0)
IV thrombolysis, No./total (%)	295 (35.2)	333 (39.6)
Time from last known well, median (IQR), min		
To puncture	346 (232 ,610)	360 (237, 590)
To randomization	354 (237 ,614)	366 (239, 590)
To recanalization[f]	431 (313 ,693)	445 (311, 691) [N = 840]
Time from randomization to initial treatment, median (IQR), min [g]	8.0 (6.0, 14.0)	8.0 (6.0, 13.0) [N = 839]
Systolic blood pressure at hospital arrival, median (IQR), mm Hg	142.0 (126.0,160.0)	145.0 (127.0, 160.0)

Characteristics	Methylprednisolone (N=839)	Placebo (N=841)
Diastolic blood pressure at hospital arrival, median (IQR), mm Hg	83.0 (74.0, 92.0)	84.0 (75.0, 94.0)

Abbreviation: IQR denotes interquartile range, IV intravenous.

[a] Ethnicity group reported by the patient and verified by identification card.

[b] Comorbidities based on family or patient report.

[c] Scores on the mRS of functional disability range from 0 (no symptoms) to 6 (death).

[d] SI conversion factor: To convert glucose values to mmol/L, multiply by 18.15

[e] Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurological deficit.

[f] The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is an imaging measure of the extent of ischemic stroke. Scores range from 0 to 10, with higher scores indicating a smaller infarct core. Listed are values for the core laboratory assessment. Data were missing for 3 patients in the Methylprednisolone group and 3 patients in the Placebo group.

[g] The TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification system is a widely used method for classifying ischemic stroke and transient ischemic attack (TIA). It divides ischemic stroke and TIA into five subtypes based on their likely causes: Large-artery atherosclerosis (LAA), Cardioembolism (CE), Small-artery occlusion (SAO), Other determined etiology (Other), Undetermined etiology (Unknown). Data were missing for 1 patient in the Methylprednisolone group.

[h] 1 patient in the Methylprednisolone group had a basilar artery occlusion.

Table 2. Efficacy and Safety Outcomes in a Study of the Effect of Intravenous Methylprednisolone vs Placebo Before Endovascular Thrombectomy.

Outcome	Methylprednisolone (N=839)	Placebo (N=841)	Treatment Effect	Unadjusted Value (95% CI)	P	Adjusted Value[a] (95% CI)	p
Primary efficacy outcome							
mRS score at 90 days — Win proportion (%)[b]	307623/699730 (44.0)	274681/699730 (39.3)	GenOR[c]	1.12(0.98 to 1.28)	0.09	1.10 (0.96 to 1.25)	0.17
mRS score at 90 days — Median (IQR)	3 (1 to 5)	3 (1 to 6)					
Secondary efficacy outcomes							
mRS score of 0 to 4 at 90 days — no./total no. (%)	597/835 (71.5)	555/838 (66.2)	Risk ratio	1.08 (1.01 to 1.15)	0.02	1.07 (1.00 to 1.14)	0.04
			Risk difference	0.05 (0.01 to 0.1)	0.02	0.05 (0.01 to 0.08)	0.004
mRS score of 0 to 3 at 90 days — no./total no. (%)	496/835 (59.4)	459/838 (54.8)	Risk ratio	1.08 (1 to 1.18)	0.056	1.07 (0.98 to 1.16)	0.11
			Risk difference	0.05 (0 to 0.09)	0.056	0.04 (0.01 to 0.07)	0.02
mRS score of 0 to 2 at 90 days — no./total no. (%)	368/835 (44.1)	343/838 (40.9)	Risk ratio	1.08 (0.96 to 1.20)	0.19	1.07 (0.95 to 1.19)	0.26
			Risk difference	0.03 (-0.02 to 0.08)	0.19	0.03 (-0.01 to 0.06)	0.11
mRS score of 0 to 1 at 90 days — no./total no. (%)	223/835 (26.7)	222/838 (26.5)	Risk ratio	1.01 (0.86 to 1.18)	0.92	0.99 (0.84 to 1.16)	0.89
			Risk difference	0 (-0.04 to 0.04)	0.92	0 (-0.03 to 0.03)	0.85
NIHSS score at 5-7 days or earlier if discharge (IQR)[d]	11.0 (4.0 to 23.0)	12.0 (4.0 to 28.0)	Win Ratio	1.08 (0.96 to 1.21)	0.20	1.07 (0.95 to 1.20)	0.25
EQ-5D-VAS score at 90 days (IQR)[e]	55.0 (5.0 to 80.0)	50.0 (0.0 to 80.0)	Win Ratio	1.13 (1.00 to 1.28)	0.051	1.11 (0.98 to 1.25)	0.11
Primary safety outcomes							
Mortality[f]	194/835 (23.2)	239/838 (28.5)	Risk ratio	0.81 (0.69 to 0.94)	0.01	0.84 (0.71 to 0.98)	0.03
Symptomatic intracranial hemorrhage[g]	71/823 (8.6)	97/830 (11.7)	Risk ratio	0.74 (0.55 to 0.99)	0.04	0.74 (0.55 to 0.99)	0.04
Secondary safety outcomes							

Any radiologic intracranial hemorrhage	314/823 (38.2)	308/830 (37.1)	Risk ratio	1.03 (0.91 to 1.16)	0.66	1.03 (0.91 to 1.16)	0.71
Pneumonia	390 (46.5)	466 (55.4)	Risk ratio	0.84 (0.76 to 0.92)	<.001	0.85 (0.77 to 0.93)	<.001
Gastrointestinal bleeding within 7 days after EVT	33 (3.9)	50 (6.0)	Risk ratio	0.66 (0.43 to 1.02)	0.06	0.66 (0.43 to 1.02)	0.06

Abbreviation: mRS denotes modified Rankin scale, IQR interquartile range, NIHSS National Institutes of Health Stroke Scale, and EQ-5D-VAS EuroQol-5 VAS score. The widths of the confidence intervals for the secondary outcomes were not adjusted for multiple comparisons.

[a] Adjusted values were adjusted for age, baseline NIHSS score, pre-stroke modified Rankin Scale score, baseline ASPECTS score, use of intravenous thrombolysis, time from onset to randomization, and occlusion location using the inverse probability of treatment weighting method.

[b] The modified Rankin Scale of functional disability ranges from 0 (no symptoms) to 6 (death). The Win proportion was calculated by the number of wins in the Methylprednisolone group over Placebo group in mRS among all possible pairs of mRS taking one patient from the Methylprednisolone group and one patient from the Placebo group divided by the total number of pairs. Data was missing for 4 patients in the Methylprednisolone group and 3 patients in the Placebo group.

[c] The GenOR indicated the probability of modified Rankin Scale score was lower than the other group. Generalized Odds Ratio, common odds ratio, risk ratio, and risk difference were adjusted for age, baseline NIHSS score, pre-stroke mRS, baseline ASPECTS score, use of intravenous thrombolysis, time from onset to randomization, and occlusion location using the inverse probability treatment weighting method and were not adjusted for multiple comparisons.

[d] Scores on the NIHSS range from 0 to 42, with higher values reflecting more severe neurologic impairment.

[e] The EuroQoL Group 5-Dimension Self-Report Questionnaire visual-analogue scale((EQ-5D-VAS) is a continuous scale measure of self-reported quality of life. Scores range from 0 to 100, with 0 indicating the worst possible quality of life and 100 the best possible quality of life. Data was missing for 4 patients in the Methylprednisolone group and 3 patients in the Placebo group.

[f] The mortality was analyzed in 835 patients in the Methylprednisolone group and 838 in the placebo group because of loss to follow-up.

[g] Symptomatic intracranial hemorrhage was defined according to the Heidelberg bleeding classification (an increase in the NIHSS score of ⩾4 points or an increase in the score for an NIHSS subcategory of ⩾2 points with any intracranial hemorrhage on imaging). Data were not available for 16 in the methylprednisolone group and 11 in the placebo group.