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Original research

Influence of time metrics on the treatment effect of intravenous alteplase prior to endovascular treatment in MR CLEAN-NO IV

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ABSTRACT

Background We assessed whether the treatment effect of intravenous alteplase (IVT) prior to endovascular treatment (EVT) on functional outcome is modified by time metrics.

Methods We used data from all patients included in MR CLEAN-NO IV, a randomized trial of IVT followed by EVT versus EVT alone in patients who presented directly to EVT-capable hospitals. The primary outcome was the modified Rankin Scale score at 90 days. We used ordinal regression with a multiplicative interaction term to assess if the effect of IVT is modified by onset-to-randomization (OTR), onset-to-IV-needle (OTN), door-to-groin (DTG) or needle-to-groin (NTG) times. Secondary outcomes included successful reperfusion (extended Thrombolysis In Cerebral Infarction Scale 2b–3) and symptomatic intracranial hemorrhage (sICH).

Results In 539 included patients (266 allocated to IVT+EVT and 273 to EVT alone), median workflow times were OTR: 93 (IQR 71–145) min; OTN: 98 (IQR 75–156) min; DTG: 64 (IQR 51–78) min; and NTG: 28 (IQR 20–41) min. There was a significant association between worse outcomes and longer time intervals for all metrics except NTG. We found no interaction between any of the time metrics and IVT for the effect on functional outcome (p values for interaction: OTR=0.40, OTN=0.39, DTG=0.61, NTG=0.56). We also did not observe any significant interaction for successful reperfusion or sICH.

Conclusion In MR CLEAN-NO IV, the effect of IVT prior to EVT was not modified by OTR, OTN, DTG or NTG times. Our results do not support the use of these metrics to guide IVT treatment decisions prior to EVT in comprehensive stroke centres.

Trial registration number ISRCTN80619088.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Rates of functional outcome after intravenous alteplase treatment (IVT) or endovascular treatment (EVT) for acute ischemic stroke are highly time dependent, but there is a paucity of studies describing whether the effect of IVT prior to EVT is modified by time metrics.

WHAT THIS STUDY ADDS

⇒ We assessed whether the treatment effect of IVT prior to EVT on functional outcome is modified by onset-to-randomization (OTR), onset-to-IV-needle (OTN), door-to-groin (DTG) or needle-to-groin (NTG) times and found no interaction for any of these time metrics (p values for interaction: OTR=0.40, OTN=0.39, DTG=0.61, NTG=0.56).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Our results suggest these time metrics should not be used to guide decisions on IVT prior to EVT in eligible patients presenting directly to comprehensive stroke centers. These findings should be confirmed using data from other randomized trials on IVT prior to EVT.

INTRODUCTION

Rates of functional outcome after intravenous alteplase treatment (IVT) or endovascular treatment (EVT) for acute ischemic stroke are highly time dependent.[1 2] Data of six randomized trials comparing EVT alone with IVT prior to EVT are currently available. The Chinese DIRECT-MT and DEVT trials showed non-inferiority of EVT alone,[3 4] while non-inferiority was not demonstrated in MR CLEAN-NO IV, DIRECT-SAFE, SKIP and SWIFT-DIRECT.[5–9] Treatment-associated time metrics were differently distributed across these trials. Compared with DIRECT-MT and DEVT, MR CLEAN-NO IV reported relatively short onset-to-randomization (OTR), onset-to-needle (OTN) and door-to-groin (DTG) times while needle-to-groin (NTG) times were similar between the trials.[3 4] The delay between symptom onset and administration of IVT, and between IVT and EVT, may influence the effectiveness of IVT and thus the treatment effect of IVT prior to EVT.[10 11] This treatment effect may also be influenced by OTR and DTG times. We therefore aimed to assess whether OTR, OTN, DTG, and NTG times modify the effect of IVT prior to EVT on functional outcome.

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Table 1 Baseline characteristics of the MR CLEAN-NO IV population

	MR CLEAN- NO IV population n=539
Allocated to IVT prior to EVT, n (%)§*	266 (49.4)
Median (IQR) age, years	71 (62–79)
Male sex, n (%)	305/539 (56.6)
Median (IQR) NIHSS score	16 (10–20)
Medical history, n (%)	
Previous ischemic stroke	91/539 (16.9)
Atrial fibrillation	58/539 (10.8)
Diabetes mellitus	90/539 (16.7)
Hypertension	260/538 (48.3)
Pre-stroke mRS score, n (%)	
0	374/538 (69.5)
1	100/538 (18.6)
2	49/538 (9.1)
≥3	15/538 (2.7)
Median (IQR) systolic blood pressure, mmHg	150 (133–169)
Median (IQR) glucose level, mmol/L ¶	6.7 (5.9–7.9)
Median (IQR) ASPECTS	9 (8–10)
Intracranial occlusion location, n (%)*	
Intracranial ICA	4/538 (0.7)
ICA-T	114/538 (21.2)
M1	330/538 (61.3)
Proximal M2	85/538 (15.8)
None	5/538 (0.9)
Tandem lesion, n (%)†	88/507 (17.4)
Collateral score, n (%)	
0	32/526 (6.1)
1	152/526 (28.9)
2	223/526 (42.4)
3	119/526 (22.6)
Adjuvant intra-arterial alteplase administered, n (%)‡	13 (2.4)
Median (IQR) duration, min	
From stroke onset to randomization	93 (71–145)
From door to randomization	27 (20–35)
From stroke onset to start of alteplase**	98 (75–156)
From door to start of alteplase**	31 (24–44)
From stroke onset to groin puncture††	133 (105–180)
From door to groin puncture††	64 (51–78)
From stroke onset to first reperfusion‡‡	174 (144–229)
From door to first reperfusion‡‡	102 (81–129)
From needle to groin§§	28 (20–41)

Missing data for ¶7, **15, ††40, ‡‡157, §§28 patients.
*Five patients had an isolated occlusion of the extracranial ICA and thus were scored as having no intracranial occlusion. For one patient the occlusion location on CT angiography could not be assessed due to motion artifacts.
†Tandem lesion is defined as an intracranial target occlusion with ipsilateral extracranial carotid dissection, significant atherosclerotic stenosis or atherosclerotic occlusion.
‡All 13 patients were allocated to the EVT alone group.
§243/249 (98%) of patients who were treated with IVT prior to EVT received the full dose of IVT.
ASPECTS, Alberta Stroke Program Early CT Score; EVT, endovascular treatment; ICA, internal carotid artery; IVT, intravenous alteplase; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

METHODS

Study design and patient selection

We used data from all patients included in MR CLEAN-NO IV, a multicenter randomized trial of IVT followed by EVT versus EVT alone in patients with anterior circulation large vessel occlusion stroke who were eligible for both interventions and who presented directly to EVT-capable centers within 4.5 hours of stroke onset or last seen well.[6 12] Patients were randomized to receive either IVT with alteplase (0.9 mg/kg) followed by EVT, or EVT alone without prior alteplase. IVT infusion was continued even if successful reperfusion was achieved during EVT prior to complete infusion. Rescue IVT (0.9 mg/kg) was permitted in patients allocated to EVT alone if there was incomplete reperfusion after EVT (score 0, 1, or 2A on the expanded Thrombolysis In Cerebral Infarction (eTICI) scale), and IVT could be administered within 4.5 hours of stroke onset. Adjuvant intra-arterial alteplase was permitted at the discretion of the interventionist. All relevant imaging was analysed by an imaging core laboratory, whose members were blinded to treatment allocation and all clinical data except for symptom side. An outcome committee, whose members were unaware of treatment

Table 2 Association of 30 min increase per time metric of interest with their effect on outcomes including interaction analyses with IVT treatment allocation

	Adjusted (common) OR (95% CI) per 30 min increase	P value for interaction with treatment allocation
Onset-to-randomization		
mRS shift	0.89 (0.83 to 0.95)	0.40
Functional independence*	0.89 (0.81 to 0.97)	0.13
Mortality†	1.17 (1.06 to 1.29)	0.95
Successful reperfusion‡	1.00 (0.90 to 1.11)	0.83
Symptomatic ICH§	1.23 (1.10 to 1.38)	0.53
Recanalization on first angiogram¶	1.01 (0.82 to 1.25)	0.83
Onset-to-needle		
mRS shift	0.88 (0.81 to 0.95)	0.39
Functional independence*	0.87 (0.79 to 0.97)	0.19
Mortality†	1.17 (1.05 to 1.30)	0.88
Successful reperfusion‡	1.00 (0.89 to 1.13)	0.97
Symptomatic ICH§	1.28 (1.10 to 1.49)	0.54
Recanalization on first angiogram¶	1.01 (0.82 to 1.26)	0.85
Door-to-groin		
mRS shift	0.76 (0.62 to 0.94)	0.61
Functional independence*	0.75 (0.57 to 0.99)	0.75
Mortality†	1.66 (1.22 to 2.26)	0.15
Successful reperfusion‡	0.64 (0.49 to 0.86)	0.98
Symptomatic ICH§	1.18 (0.73 to 1.90)	0.65
Recanalization on first angiogram¶	0.75 (0.39 to 1.44)	0.45
Needle-to-groin		
mRS shift	1.03 (0.79 to 1.34)	0.56
Functional independence*	0.98 (0.62 to 1.55)	0.63
Mortality†	1.17 (0.68 to 2.01)	0.58
Successful reperfusion‡	0.58 (0.37 to 0.91)	0.68
Symptomatic ICH§	1.03 (0.57 to 1.87)	0.94
Recanalization on first angiogram¶	0.76 (0.31 to 1.88)	0.95

Functional independence defined as mRS 0–2.
Successful reperfusion defined as expanded Thrombolysis In Cerebral Infarction Scale 2b–3.
Events occurred: *270/539 (50.1%), †98/539 (18.2%), ‡388/480 (80.8%), §30/539 (5.6%), ¶16/495 (3.2%).
ICH, intracranial hemorrhage; mRS, modified Rankin Scale.

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allocation, adjudicated functional outcome data. An adverse event committee evaluated the safety endpoints based on clinical data and reports from the imaging core laboratory.

Outcomes

The primary outcome was functional outcome measured with the modified Rankin Scale (mRS) score at 90 days after stroke (ranging from 0 (no disability) to 6 (death)). Secondary outcomes were mRS dichotomized at 0–2 (indicating functional independence) versus 3–6, mortality, successful reperfusion on the final intracranial angiogram (defined as an eTICI score of 2B, 2C, or 3), recanalization on first angiogram (defined as absence of treatable occlusion on first intracranial angiogram) and occurrence of symptomatic intracranial hemorrhage (sICH) according to the Heidelberg criteria.[13]

Statistical analysis

We assessed the association of the following time metrics with functional outcome: OTR, OTN, DTG and NTG times. We assessed whether the association between the time measures of interest and functional outcome was linear by determining if regression models with a restricted cubic spline transformation allowing three knots for time metrics improved model fit. For the primary outcome, we used ordinal logistic regression with multiplicative interaction terms between the time metrics of interest and treatment allocation to assess whether the association of IVT administration with functional outcome was modified. We assessed binary outcomes using logistic regression. We performed all main analyses in the intention to treat population. All regression analyses were adjusted for the variables pre-specified in the MR CLEAN-NO IV statistical analysis plan[12] (age, pre-stroke mRS, OTR, National Institutes of Health Stroke Scale (NIHSS) score at baseline and collateral score), with the exception of analyses on OTR and OTN times for which we did not adjust for OTR. We additionally plotted the adjusted common OR of EVT alone for the time measures of interest. All time metrics were analysed as continuous variables and the effect of each time metric on outcomes was reported per 30 min increase. Missing data were imputed for the regression analyses only using multiple imputation methods.[14] For regression analyses on OTN and NTG times, imputed data were used for patients in the EVT alone group since IVT-associated time metrics were unavailable due to treatment allocation. We performed an as-treated analysis in which we excluded all patients allocated to the EVT alone group who were treated with IVT as well as all patients allocated to IVT prior to EVT who did not receive full-dose IVT. All analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing 2018, www.r-project.org).

RESULTS

Patient characteristics

Of 539 included patients, 266 (49.4%) were allocated to IVT prior to EVT and 273 (50.6%) to EVT alone (see online supplemental eFigure 1). Baseline characteristics of the trial population are shown in table 1. The median times for the intervals of interest were OTR: 93 (IQR 71–145) min; OTN: 98 (IQR 75–156) min; DTG: 64 (IQR 51–78) min, and NTG: 28 (IQR 20–41) min. All four time measures had a linear association with functional outcome (p value for non-linearity: OTR=0.39; OTN=0.50; DTG=0.63; NTG=0.30).

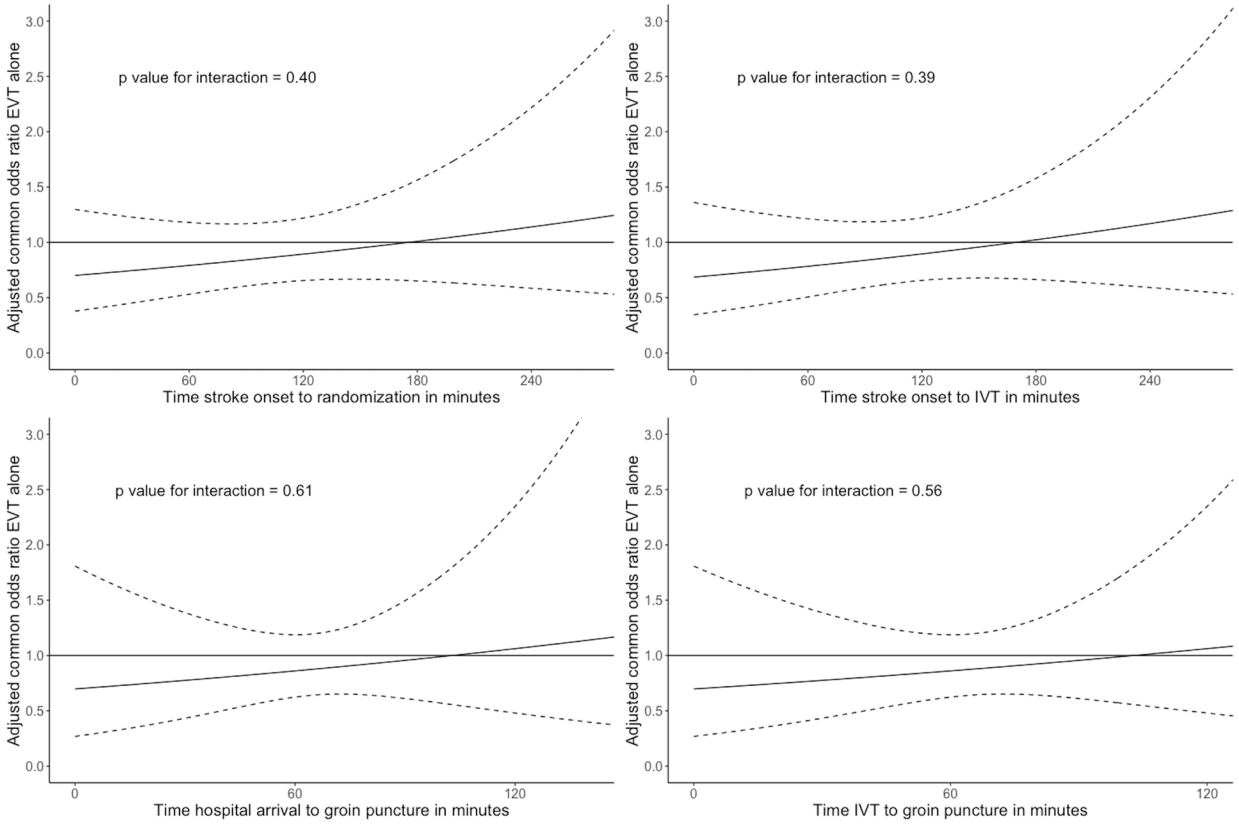

Figure 1 Adjusted common OR for a shift towards better functional outcome for endovascular treatment (EVT) alone versus intravenous alteplase (IVT) prior to EVT for onset-to-randomization (A), onset-to-needle (B), door-to-groin (C) and needle-to-groin times (D). Dashed lines represent 95% CIs.

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Primary outcome

All time metrics were significantly associated with worse functional outcome, except NTG time (table 2). The adjusted common odds ratio (acOR) for functional outcome of EVT alone versus IVT followed by EVT in the trial population was 0.84 (95% CI 0.62 to 1.15). We found no interaction between any of the time metrics and IVT for the effect on functional outcome (p values for interaction: OTR=0.40, OTN=0.39, DTG=0.61, NTG=0.56). We plotted the acOR for functional outcome for EVT alone in relation to the time metrics of interest in figure 1.

Secondary outcomes

A longer DTG (adjusted OR (aOR) 0.64, 95% CI 0.49 to 0.86) and longer NTG (aOR 0.58, 95% CI 0.37 to 0.91) time was associated with lower rates of successful reperfusion after EVT (table 2). Increase in OTR (aOR 1.23, 95% CI 1.10 to 1.38) and in OTN (aOR 1.28, 95% CI 1.10 to 1.49) times were associated with higher rates of sICH. We observed no statistically significant interaction between the treatment effect of IVT prior to EVT and the studied time metrics for any of the secondary outcomes including mortality, successful reperfusion, and sICH.

Results of the as-treated analysis were largely similar to those of the main analysis (online supplemental eTable 2), but we did observe a statistically significant interaction between IVT treatment and OTR for functional independence (p=0.03). This corresponded with better outcomes for EVT alone in patients with longer OTR times (online supplemental eTable 3).

DISCUSSION

In MR CLEAN-NO IV, OTN, OTR and DTG had a significant association with worse functional outcome for every 30 min increase, while we did not find a significant association between NTG time and functional outcome. We observed no modification of the effect of IVT prior to EVT on functional outcome by these time metrics. We also did not find such effect modification for any of the secondary outcomes, including sICH and successful reperfusion.

The DIRECT MT, SKIP, and DEVT trials all reported no heterogeneity of treatment effect of IVT prior to EVT based on OTR times, but reported a non-significant trend that an increase in OTR favoured EVT alone.[3–5] Only the DIRECT MT trial reported additional interaction analyses and assessed onset-to-groin, randomization-to-groin, onset-to-revascularization, and randomization-to-revascularization times, all of which showed no significant interaction.[3]

The effect of IVT for ischemic stroke is highly time dependent.[11 15] Functional outcomes are better for shorter OTN times.[11 16] In the current study we did not observe a significant interaction between treatment allocation of IVT prior to EVT and OTN despite this time dependency for IVT. As the effect of IVT prior to EVT on functional outcome appears to be modest,[8] the sample size of our study may be too low to assess a difference in this effect based on the studied time metrics. A study performed prior to the widespread use of EVT suggested that cohorts including up to 900 patients yielded insufficient power to reliably assess the influence of OTN time on the effect of IVT,[15] indicating that pooling of our results with other trials on EVT alone is important to confirm our findings.

The time interval for OTR was relatively short in our study, with 75% of patients presenting within 145 min after stroke onset, resulting in short OTN times. It may be that the treatment effect of IVT prior to EVT diminishes over time and that patients who present in later time windows benefit less from IVT prior to EVT. This is what we observed for functional independence in the as-treated analysis, although this could have been a chance finding. As such, the interaction between OTR and IVT treatment should be assessed in further analyses which include more patients presenting in a later time window since symptom onset.

We observed no significant interaction between NTG time and IVT treatment allocation. We hypothesized that, when a very fast start of EVT is anticipated following IVT, this would favour EVT alone while longer intervals would favour IVT prior to EVT and that therefore NTG time would modify the effect of IVT. NTG times in our trial were relatively short, which could indicate that there was insufficient time for IVT to have an optimal effect prior to EVT. This is supported by the fact that only 8% of patients allocated to IVT prior to EVT had complete infusion of IVT before the start of EVT.[6] The limited number of patients with longer NTG times in our study could explain why we did not observe such an interaction. It could also be argued that, in patients with short NTG time, IVT has more effect on distal emboli following revascularization with EVT and that we therefore did not observe an effect modification. All in all, we currently have no evidence for an interaction between IVT prior to EVT and NTG times based on both the findings of the current study and the fact that there were differences between the DIRECT MT, DEVT and MR CLEAN-NO IV trials in demonstrating non-inferiority while all reported similar NTG times.

This study has several limitations. First, this was a post-hoc analysis and not a prespecified analysis. Therefore, all results should be considered as exploratory only. Second, the generalizability of our results to other geographical areas with different distributions in time intervals is limited. Third, these results only apply to patients presenting directly to EVT-capable centers and not drip-and-ship patients.

CONCLUSION

In MR CLEAN-NO IV, the effect of IVT prior to EVT was not modified by OTR, OTN, DTG or NTG times. Our results do not support the use of these metrics to guide IVT decisions in eligible patients undergoing EVT in comprehensive stroke centers.

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REFERENCES

1 Fransen PSS, Berkhemer OA, Lingsma HF, *et al*. Time to reperfusion and treatment effect for acute ischemic stroke: a randomized clinical trial. *JAMA Neurol* 2016;73:190.
2 Gumbinger C, Reuter B, Stock C, *et al*. Time to treatment with recombinant tissue plasminogen activator and outcome of stroke in clinical practice: retrospective analysis of hospital quality assurance data with comparison with results from randomised clinical trials. *BMJ* 2014;348:g3429.
3 Yang P, Zhang Y, Zhang L, *et al*. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med* 2020;382:1981–93.
4 Zi W, Qiu Z, Li F, *et al*. Effect of endovascular treatment alone vs intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke: the DEVT randomized clinical trial. *JAMA* 2021;325:234–43.
5 Suzuki K, Matsumaru Y, Takeuchi M, *et al*. Effect of mechanical thrombectomy without vs with intravenous thrombolysis on functional outcome among patients with acute ischemic stroke: the SKIP randomized clinical trial. *JAMA* 2021;325:244–53.
6 LeCouffe NE, Kappelhof M, Treurniet KM, *et al*. A randomized trial of intravenous alteplase before endovascular treatment for stroke. *N Engl J Med* 2021;385:1833–44.
7 Fischer U, Kaesmacher J, Strbian D, *et al*. Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded-outcome, randomised non-inferiority trial. *Lancet* 2022;400:104–15.
8 Podlasek A, Dhillon PS, Butt W, *et al*. Direct mechanical thrombectomy without intravenous thrombolysis versus bridging therapy for acute ischemic stroke: a meta-analysis of randomized controlled trials. *Int J Stroke* 2021;16:621–31.
9 Mitchell PJ, Yan B, Churilov L, *et al*. Endovascular thrombectomy versus standard bridging thrombolytic with endovascular thrombectomy within 4·5 H of stroke onset: an open-label, blinded-endpoint, randomised non-inferiority trial. *Lancet* 2022;400:116–25.
10 Zhu F, Gauberti M, Marnat G, *et al*. Time from i.v. thrombolysis to thrombectomy and outcome in acute ischemic stroke. *Ann Neurol* 2021;89:511–9.

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11 Lees KR, Bluhmki E, von Kummer R, *et al*. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 2010;375:1695–703.
12 Treurniet KM, LeCouffe NE, Kappelhof M, *et al*. MR CLEAN-NO IV: intravenous treatment followed by endovascular treatment versus direct endovascular treatment for acute ischemic stroke caused by a proximal intracranial occlusion- study protocol for a randomized clinical trial. *Trials* 2021;22:141.
13 von Kummer R, Broderick JP, Campbell BCV, *et al*. The Heidelberg bleeding classification. *Stroke* 2015;46:2981–6.
14 van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. 2011. *J Statistical Software* 2011;45:1–67. doi:10.18637/jss.v045.i03
15 Saver JL, Fonarow GC, Smith EE, *et al*. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. *JAMA* 2013;309:2480.
16 Berge E, Whiteley W, Audebert H, *et al*. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J* 2021;6:I–LXII.

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