Admission systolic blood pressure and effect of endovascular treatment in patients with ischaemic stroke: an individual patient data meta-analysis

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Summary

Background Current guidelines for ischaemic stroke treatment recommend a strict, but arbitrary, upper threshold of 185/110 mm Hg for blood pressure before endovascular thrombectomy. Nevertheless, whether admission blood pressure influences the effect of endovascular thrombectomy on outcome remains unknown. Our aim was to study the influence of admission systolic blood pressure (SBP) on functional outcome and on the effect of endovascular thrombectomy.

Methods We used individual patient data from seven randomised controlled trials (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT, PISTE, and THRACE) that randomly assigned patients with anterior circulation ischaemic stroke to endovascular thrombectomy (predominantly using stent retrievers) or standard medical therapy (control) between June 1, 2010, and April 30, 2015. We included all patients for whom SBP data were available at hospital admission. The primary outcome was functional outcome (modified Rankin Scale) at 90 days. We assessed the association of SBP with outcome in both the endovascular thrombectomy group and the control group using multilevel regression analysis and tested for non-linearity and for interaction between SBP and effect of endovascular thrombectomy, taking into account treatment with intravenous thrombolysis.

Findings We included 1753 patients (867 assigned to endovascular thrombectomy, 886 assigned to control) after excluding 11 patients for whom SBP data were missing. We found a non-linear association between SBP and functional outcome with an inflection point at 140 mm Hg (732 [42%] of 1753 patients had SBP <140 mm Hg and 1021 [58%] had SBP ≥140 mm Hg). Among patients with SBP of 140 mm Hg or higher, admission SBP was associated with worse functional outcome (adjusted common odds ratio [acOR] 0·86 per 10 mm Hg SBP increase; 95% CI 0·81–0·91). We found no association between SBP and functional outcome in patients with SBP less than 140 mm Hg (acOR 0·97 per 10 mm Hg SBP decrease, 95% CI 0·88–1·05). There was no significant interaction between SBP and effect of endovascular thrombectomy on functional outcome (p=0·96).

Interpretation In our meta-analysis, high admission SBP was associated with worse functional outcome after stroke, but SBP did not seem to negate the effect of endovascular thrombectomy. This finding suggests that admission SBP should not form the basis for decisions to withhold or delay endovascular thrombectomy for ischaemic stroke, but randomised trials are needed to further investigate this possibility.

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Introduction

The majority of patients with acute ischaemic stroke caused by large vessel occlusion in the anterior circulation present with high blood pressure in the acute phase.[1] The European Stroke Organisation (ESO) and American Heart Association/American Stroke Association (AHA/ASA) guidelines for acute ischaemic stroke management recommend maintenance of blood pressure below 185/110 mm Hg before reperfusion therapy.[2,3] The recommended blood pressure thresholds are based on the inclusion criteria of randomised controlled trials evaluating the effect of intravenous thrombolysis, in which pretreatment blood pressure thresholds were derived from small pilot studies that observed an association between high diastolic blood pressure and an increased risk of symptomatic intracranial haemorrhage.[4] The association between high blood pressure and worse outcomes following ischaemic stroke has been confirmed by several studies for both intravenous thrombolysis and endovascular thrombectomy, emphasising that blood pressure can be considered as a prognostic factor.[5–7] However, this does not imply that blood pressure influences the effect of intravenous thrombolysis or endovascular thrombectomy on outcome. A large randomised trial of intravenous thrombolysis did not observe an interaction between admission blood pressure and the effect of intravenous thrombolysis.[8] Maintaining blood pressure below 185/110 mm Hg before reperfusion therapy might lead to delay of endovascular

Research in context

Evidence before this study

We did a systematic review of studies evaluating the influence of admission blood pressure on outcome and on the effect of endovascular thrombectomy in patients with anterior circulation ischaemic stroke. We searched PubMed using the search terms "blood pressure", "randomised controlled trial", and either "endovascular therapy" or "mechanical thrombectomy", for articles published in any language between Jan 1, 2010, and Dec 31, 2022. We selected all studies comparing endovascular thrombectomy using second-generation mechanical devices (primarily stent retrievers) with non-endovascular thrombectomy, using vessel imaging to identify patients with proximal anterior circulation ischaemic stroke within 12 h from symptom onset. Several studies observed a non-linear association between admission blood pressure and functional outcome after endovascular thrombectomy. An analysis of individual patient data from randomised trials, concerning the interaction between systolic blood pressure (SBP) and effect of endovascular thrombectomy, was not available. International guidelines advise withholding or delaying of endovascular thrombectomy in patients with admission SBP exceeding 185 mm Hg. However, evidence concerning an interaction between SBP and effect of endovascular thrombectomy is scarce and inconclusive.

Added value of this study

To further investigate interactions between blood pressure and effects of endovascular thrombectomy, we did an individual patient-level meta-analysis that included 1753 patients from seven randomised controlled trials comparing endovascular thrombectomy plus standard care with standard care alone for acute ischaemic stroke due to a large vessel occlusion in the anterior circulation. We found that high SBP on hospital admission was associated with worse functional outcome and larger follow-up infarct volume after stroke treatment, but an interaction between SBP on hospital admission and effect of endovascular thrombectomy was not observed.

Implications of all the available evidence

Our findings suggest that high or low admission SBP should not form the basis for decisions to withhold or delay endovascular thrombectomy for acute ischaemic stroke. If randomised controlled trials confirm our findings, the recommendations by the European Stroke Organisation and the American Heart Association/American Stroke Association for blood pressure management in patients with acute ischaemic stroke eligible for endovascular thombectomy might warrant reconsideration.

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thrombectomy. As the effect of endovascular thrombectomy strongly declines over time, this delay might be deleterious regarding patients' outcome after stroke.[9] In a post-hoc analysis of the MR CLEAN trial (A Multicentre Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands), the beneficial effect of endovascular thrombectomy was observed across the whole range of admission SBP, but the number of patients with blood pressure higher than 185/110 mm Hg treated with endovascular thrombectomy was considered insufficient to recommend performing endovascular thrombectomy in patients with admission blood pressure above this threshold.[10,11] Pooling individual patient data of multiple randomised controlled trials can improve statistical power to accurately assess the influence of admission SBP on effect of endovascular thrombectomy.[12] This information could support guideline recommendations for blood pressure management in the acute setting of ischaemic stroke in patients eligible for endovascular thrombectomy. We evaluated whether admission SBP level modified the effect of endovascular thrombectomy on outcomes in pooled data from the seven randomised controlled trials within the Highly Effective Reperfusion Using Multiple Endovascular Devices (HERMES) collaboration.

Methods

Study population and design

This study, which was done according to the PRISMA guidelines, is a post-hoc analysis of pooled individual patient data from seven randomised controlled trials of endovascular thrombectomy within the HERMES collaboration (MR CLEAN,[13] ESCAPE [Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times],[14] EXTEND-IA [Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial],[15] SWIFT PRIME [Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment],[16] REVASCAT [Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke due to Anterior Circulation Large Vessel Occlusion Presenting Within 8 Hours of Symptom Onset],[17] PISTE [Pragmatic Ischaemic Stroke Thrombectomy Evaluation],[18] and THRACE [Mechanical Thrombectomy After Intravenous Alteplase Versus Alteplase Alone After Stroke][19]). These trials compared endovascular thrombectomy (intervention), using stent retrievers or other second-generation devices, with standard medical care (control) in patients with ischaemic stroke caused by a large vessel occlusion in the anterior circulation. An overview of the individual trial characteristics is provided in the appendix (p 3). The HERMES protocol and main outcomes have been reported previously.[20,21] For this analysis, we included all patients for whom admission SBP values were available.

See Online for appendix

All imaging studies were deidentified at the HERMES central coordinating centre. The imaging datasets were read by independent HERMES core laboratories for baseline CT or MRI, baseline CT angiography, MRI

angiography, follow-up CT or MRI, and conventional angiography. Readers were masked to all clinical information, except side of stroke.

All participants provided informed consent according to each trial protocol and each study was approved by the local ethics board. This meta-analysis was prospectively designed by the HERMES executive committee, but not registered.

Blood pressure measures

In the HERMES trials, admission blood pressure was based on a single measurement on admission at the first hospital (remote centre in "drip-and-ship" patients—ie, patients who receive intravenous thrombolysis in the first hospital they attend before being transferred to a comprehensive stroke centre for endovascular thrombectomy) as part of prerandomisation clinical work-up. How blood pressure was assessed in the individual centres was not available (ie, invasive or non-invasive), but the use of non-invasive blood pressure cuffs (ie, automated or non-automated sphygmomanometer) is common practice in all participating centres. For this analysis, SBP was selected as the blood pressure measure of interest based on the strength of the correlation with functional outcome in previous studies.[10,22]

Outcomes

The primary outcome measure was functional outcome at 90 days, according to the modified Rankin Scale (mRS).[23] Secondary outcomes were functional independence (mRS ≤2) at 90 days, National Institutes of Health Stroke Scale (NIHSS) score at 24 h after randomisation (indicating early neurological deficit), successful reperfusion after endovascular thrombectomy (modified Thrombolysis in Cerebral Infarction score [mTICI] ≥2B), and follow-up infarct volume on non-contrast CT or MRI at 12 h to 2 weeks after randomisation.[24,25] Safety outcomes were mortality within 90 days and any symptomatic intracranial haemorrhage that occurred within this period, defined according to each trial protocol.[21]

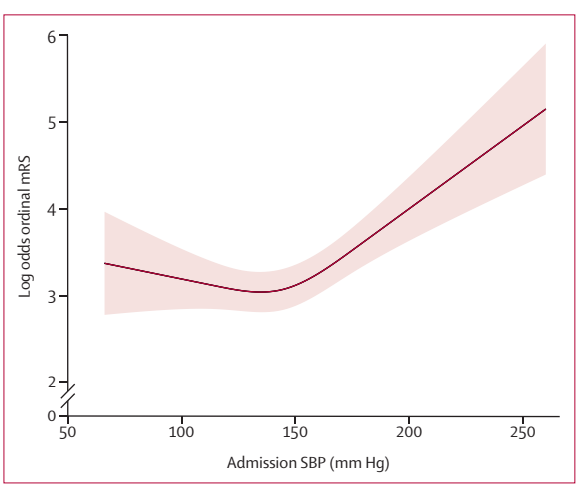

Figure 1: **Association between admission SBP and ordinal mRS at 90 days**
The model was fitted with a restricted cubic spline function with three knots for admission SBP and included the following variables: age, sex, baseline National Institutes of Health Stroke Scale score, baseline Alberta Stroke Program Early CT Score, history of hypertension, collateral score, time from onset to randomisation, and trial (MR CLEAN trial as reference). The graph depicts the log odds for a shift towards worse mRS score, with 95% CI (shaded area), for each level of admission SBP. The range of the curve on the x-axis corresponds to the lowest and highest admission SBP value in the data (62 mm Hg and 261 mm Hg, respectively). Knot locations were default quantiles of admission SBP (0·10 at 115 mm Hg, 0·50 at 142 mm Hg, and 0·90 at 175 mm Hg). mRS=modified Rankin scale. SBP=systolic blood pressure.

Statistical analysis

Patients for whom admission SBP was missing were excluded from this analysis and data were not imputed as it was unclear whether these missing values were randomly distributed. Baseline characteristics of the study population are shown by two subgroups according to SBP categories (SBP <140 mm Hg and SBP ≥140 mm Hg). Continuous variables are expressed as medians with IQRs. Categorical variables are expressed as numbers of patients and percentages. We evaluated linearity of the associations between admission SBP and outcomes by comparing model fit expressed by the log-likelihood of a regression model with a linear SBP term versus a regression model with a restricted cubic spline transformation.[26] The optimal number of knots for the restricted cubic spline transformation was selected within the modelling structure based on best fit. The location of the knots was based on default SBP quantiles.[26] We evaluated the association between admission SBP and outcomes with generalised linear mixed models adjusted for age, sex, NIHSS score on admission, medical history of hypertension, stroke, diabetes, or atrial fibrillation, treatment with intravenous thrombolysis, location of occlusion, Alberta Stroke Program Early CT Score (ASPECTS) on baseline non-contrast CT, collateral score on baseline CT angiogram, time from stroke onset to randomisation, and treatment allocation as fixed effects, and trial as a random effect. The association between endovascular thrombectomy and primary and secondary outcomes for both SBP categories was evaluated with generalised linear mixed models, with a random effect for trial. We estimated the effect of endovascular thrombectomy on functional outcome for both patients with admission SBP lower than 140 mm Hg and patients with admission SBP of 140 mm Hg or higher using multivariable ordinal logistic regression analysis, and reported effect estimates according to the adjusted common odds ratio (acOR) for a shift towards a better functional outcome according to the mRS. Odds ratios greater than 1 indicate better results according to the mRS (ie, mRS score closer to 0); this convention is used in all analyses to represent treatment benefit as an odds ratio greater than 1. We tested for interaction between admission SBP and effect of endovascular thrombectomy by adding multiplicative interaction terms to models used to study the association between SBP and outcomes. We estimated the effect of endovascular thrombectomy on NIHSS and

follow-up infarct volume for both patients with admission SBP less than 140 mm Hg and 140 mm Hg or higher using multivariable linear regression analysis, and reported effect estimates according to the adjusted β-coefficients with corresponding 95% CIs per 10 mm Hg SBP decrease (for SBP <140 mm Hg) or increase (for SBP ≥140 mm Hg).

Post-hoc power was calculated using the observed variability and strength of association observed between admission SBP and the 90-day mRS outcome. The full available sample size of 1753 individuals provided 90% power to detect a true odds ratio of 0·92 (or 1/0·92=1·09) per 10 mm Hg change in SBP using ordinal logistic regression. These calculations assume an SD for baseline SBP of 24 mm Hg and an mRS distribution among the 1735 patients with known mRS at 90 days of 9% (n=155), 14% (n=244), 16% (n=282), 16% (n=274), 20% (n=353), 9% (n=150), and 16% (n=277) for categories 0 to 6, respectively, as observed in the combined HERMES dataset.

The associations of SBP with outcomes were presented per 10 mm Hg change in SBP parameter. For unadjusted and adjusted regression analyses, missing outcome and predictor values were imputed using multiple imputations by chained equations (five sets) to reduce bias in estimates of associations.[27] A p value less than 0·05 was considered significant in all tests. All analyses were performed using R software (version 3.6.1).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

A total of 1753 patients were included in this analysis after excluding 11 patients with missing admission SBP values. The association between admission SBP and functional outcome as assessed with the mRS was non-linear, based on multivariable model fit comparing a linear SBP term with a model allowing three knots for SBP (likelihood-ratio test p=0·0085, knots positioned at default quantiles of admission SBP: 0·10 at 115 mm Hg, 0·50 at 142 mm Hg, and 0·90 at 175 mm Hg; figure 1). Because of this non-linear association, we obtained effect estimates for admission SBP below and above the inflection point at the median value of 140 mm Hg separately. Baseline characteristics of the study population are shown according to the inflection point at 140 mm Hg of the non-linear association between admission SBP and functional outcome (table 1). Patients with admission SBP of 140 mm Hg or higher were on average older and were more likely to have a history of atrial fibrillation, hypertension, and hyperlipidaemia than patients with admission SBP below 140 mm Hg. There were no differences in baseline NIHSS and ASPECTS between patients with admission SBP below 140 mm Hg and patients with admission SBP of 140 mm Hg or higher (table 1). Although patients in the higher SBP category were on average older, the correlation between admission SBP and age was not very strong (correlation coefficient r=0·30, appendix p 9).

In the endovascular thrombectomy group, median mRS at 90 days was lower among patients with admission SBP

	SBP <140 mm Hg (n=732)	SBP ≥140 mm Hg (n=1021)
Patient characteristics		
Age, years	63 (51–73) [n=731]	70 (62–77) [n=1021]
Sex		
Female	357/732 (49%)	427/1021 (42%)
Male	375/732 (51%)	594/1021 (58%)
NIHSS at baseline	17 (13–20) [n=730]	17 (14–21) [n=1018]
Affected hemisphere		
Left hemisphere	351/725 (48%)	511/1006 (51%)
Right hemisphere	374/725 (52%)	495/1006 (49%)
SBP, mm Hg	123 (12) [n=732]	161 (18) [n=1021]
Intravenous thrombolysis	647/732 (88%)	918/1021 (90%)
Medical history		
Previous stroke	71/729 (10%)	117/1015 (12%)
Atrial fibrillation	164/547 (30%)	283/800 (35%)
Hypertension	337/731 (46%)	649/1019 (64%)
Hyperlipidaemia	256/716 (36%)	394/996 (40%)
Diabetes	105/731 (14%)	181/1018 (18%)
Pre-stroke mRS		
0	427/521 (82%)	630/759 (83%)
1	67/521 (13%)	95/759 (13%)
≥2	27/521 (5%)	34/759 (4%)
Imaging		
Occluded segment		
Internal carotid artery	171/685 (25%)	269/958 (28%)
Middle cerebral artery M1	464/685 (68%)	607/958 (63%)
Middle cerebral artery M2	49/685 (7%)	81/958 (8%)
ASPECTS	8 (7–9) [n=723]	8 (7–9) [n=1008]
Collateral score		
0 (absent)	4/528 (1%)	10/759 (1%)
1 (filling ≤50% of occluded area)	78/528 (15%)	120/759 (16%)
2 (filling >50% but <100% of occluded area)	230/528 (44%)	326/759 (43%)
3 (filling 100% of occluded area)	216/528 (41%)	303/759 (40%)
Workflow		
Transfer from primary stroke centre to comprehensive stroke centre (intervention centre)	164/732 (22%)	247/1017 (24%)
Time from stroke onset to randomisation, min	180 (139–244) [n=730]	184 (141–246) [n=1021]
Time from stroke onset to tPA administration, min	115 (81–160) [n=647]	118 (86–159) [n=914]
Time from stroke onset to groin puncture, min	240 (190–300) [n=327]	235 (180–295) [n=456]

Data are n/N (%), median (IQR) [number of patients with available data], or, for SBP, mean (SD) [number of patients with available data]. Admission SBP was categorised according to the inflection point of the association between SBP and functional outcome. Data on race and ethnicity were not reported in this table since these parameters were available for only two of the seven included trials. ASPECTS=Alberta Stroke Program Early CT Score. mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. SBP=systolic blood pressure. tPA=tissue plasminogen activator (alteplase).

Table 1: **Baseline characteristics by admission SBP**

	SBP <140 mm Hg		SBP ≥140 mm Hg	
	Endovascular therapy (n=363)	Control (n=369)	Endovascular therapy (n=504)	Control (n=517)
Clinical outcomes				
mRS at 90 days*	2 (1–4)	3 (2–4)	3 (1–5)	4 (2–5)
mRS 0–2 at 90 days	199/359 (55%)	126/364 (35%)	214/503 (43%)	142/509 (28%)
NIHSS at 24 h	7 (3–15) [n=355]	14 (7–19) [n=359]	10 (4–18) [n=480]	15 (8–20) [n=493]
Imaging outcomes				
mTICI after endovascular thrombectomy†‡				
0	24/299 (8%)	..	36/429 (8%)	..
1	5/299 (2%)	..	14/429 (3%)	..
2A	35/299 (12%)	..	65/429 (15%)	..
2B	209/299 (70%)	..	277/429 (65%)	..
3	26/299 (9%)	..	37/429 (9%)	..
Follow-up infarct volume at 12 h to 2 weeks, mL†	29 (11–79) [n=350]	48 (18–116) [n=349]	38 (11–121) [n=470]	53 (17–148) [n=493]
Safety outcomes				
Mortality at 90 days	34/362 (9%)	53/364 (15%)	93/504 (18%)	97/512 (19%)
Symptomatic intracranial haemorrhage	7/358 (2%)	7/366 (2%)	25/494 (5%)	24/506 (5%)

Data are n/N (%) or median (IQR) [number of patients with available data]. ASPECTS=Alberta Stroke Program Early CT Score. mRS=modified Rankin Scale. mTICI=modified Thrombolysis in Cerebral Infarction. NIHSS=National Institutes of Health Stroke Scale. SBP=systolic blood pressure. *For complete distribution of mRS at 90 days see appendix p 5. †mTICI after endovascular thrombectomy and follow-up infarct volume were read centrally. ‡mTICI after endovascular thrombectomy only available for the endovascular thrombectomy group.

Table 2: **Outcome measures by admission SBP and treatment allocation**

	SBP <140 mm Hg (n=732)		SBP ≥140 mm Hg (n=1021)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Clinical outcomes				
mRS at 90 days, common OR	1·04 (0·95 to 1·14)	0·97 (0·88 to 1·05)	0·83 (0·78 to 0·88)	0·86 (0·81 to 0·91)
mRS 0–2 at 90 days, OR	1·03 (0·93 to 1·14)	0·97 (0·86 to 1·09)	0·84 (0·78 to 0·90)	0·86 (0·79 to 0·93)
NIHSS at 24 h, β-coefficient	–0·05 (–0·44 to 0·35)	0·02 (–0·32 to 0·37)	0·65 (0·39 to 0·91)	0·54 (0·31 to 0·77)
Imaging outcomes				
Successful reperfusion*†, OR	1·08 (0·89 to 1·30)	1·04 (0·88 to 1·23)	0·92 (0·82 to 1·02)	0·92 (0·83 to 1·02)
Follow-up infarct volume at 12 h to 2 weeks*, β-coefficient	–3·84 (–8·78 to 1·11)	–2·38 (–6·67 to 1·92)	4·82 (1·59 to 8·05)	5·96 (3·19 to 8·73)
Safety outcomes				
Mortality at 90 days, OR	1·02 (0·88 to 1·18)	1·15 (0·99 to 1·33)	1·22 (1·13 to 1·32)	1·16 (1·07 to 1·27)
Symptomatic intracranial haemorrhage, OR	0·69 (0·47 to 1·09)	0·78 (0·54 to 1·10)	1·16 (1·02 to 1·32)	1·13 (0·98 to 1·26)

Data are unadjusted and adjusted ORs or β-coefficients with corresponding 95% CIs per 10 mm Hg SBP decrease (for SBP <140 mm Hg) or increase (for SBP ≥140 mm Hg). Adjustments were made for the following fixed effects: age, sex, NIHSS on admission, collateral score, ASPECTS at baseline, time from onset to randomisation, diabetes, previous stroke, atrial fibrillation, history of hypertension, occlusion location, intravenous thrombolysis, treatment allocation, and random effect for trial. ASPECTS=Alberta Stroke Program Early CT Score. FIV=follow-up infarct volume. mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. OR=odds ratio. SBP=systolic blood pressure. *Modified Thrombolysis in Cerebral Infarction score after endovascular thrombectomy and follow-up infarct volume were read centrally. †Reperfusion grade only available for the endovascular thrombectomy group.

Table 3: **Univariable and multivariable associations of admission SBP with outcomes**

below 140 mm Hg than patients with admission SBP of 140 mm Hg or higher (2 [IQR 1–4] *vs* 3 [1–5]; table 2). Also, the proportion of patients with functional independence in the endovascular thrombectomy group was larger among those with admission SBP below 140 mm Hg compared with SBP of 140 mm Hg or higher (199 [55%] of 359 *vs* 214 [43%] of 503; p=0·0002; table 2, appendix p 5). Similarly, the outcomes in the control group (ordinal mRS, mRS ≤2, NIHSS, follow-up infarct volume, mortality, and symptomatic intracranial haemorrhage) were more favourable in patients with admission SBP below 140 mm Hg than in patients with higher SBP (table 2).

Above 140 mm Hg, higher admission SBPs were associated with worse functional outcome (acOR 0·86 [95% CI 0·81–0·91] per 10 mm Hg increment; table 3), but below the median of 140 mm Hg, lower admission SBPs were not (acOR 0·97 [0·88–1·05] per 10 mm Hg decrement). Furthermore, above 140 mm Hg, higher SBPs were associated with less functional independence, larger early neurological deficit, larger follow-up infarct volume, and higher mortality rates (table 3). We did not observe a significant association between admission SBP of 140 mm Hg or higher and symptomatic intracranial haemorrhage or successful reperfusion after endovascular thrombectomy (mTICI ≥2B). There was no association between admission SBP lower than 140 mm Hg and any of the outcomes (table 3).

The median mRS at 90 days was significantly lower in the endovascular thrombectomy group compared with the control group, for both patients with admission SBP below 140 mm Hg (2 [IQR 1–4] *vs* 3 [2–4]; p<0·001) and patients with admission SBP of 140 mm Hg or higher (3 [1–5] *vs* 4 [IQR 2–5]; p<0·001; table 2). The proportion of patients with functional independence at 90 days was larger in the endovascular thrombectomy group compared with the control group for those with SBP less than 140 mm Hg (199 [55%] of 359 *vs* 126 [35%] of 364; p<0·0001) and for those with SBP of 140 mm Hg or higher (214 [43%] of 503 *vs* 142 [28%] of 509; p<0·0001; appendix p 5). Furthermore, follow-up infarct volume was significantly smaller in the endovascular thrombectomy group compared with the control group among both SBP categories (admission SBP <140 mm Hg: median 29 mL [IQR 11–79] *vs* 48 mL [18–116]; p<0·0001; admission SBP ≥140 mm Hg: 38 mL [11–121] *vs* 53 mL [17–148]; p=0·0046). Mortality rates differed between the endovascular thrombectomy and control group only for patients with admission SBP less than 140 mm Hg (34 [9%] of 362 *vs* 53 [15%] of 364; p=0·040), but not for patients with admission SBP of 140 mm Hg or higher (93 [18%] of 504 *vs* 97 [19%] of 512; p=0·87). The association of admission SBP and ordinal mRS per trial is shown in the appendix (p 6).

We did not observe modification of the effect of endovascular thrombectomy by admission SBP for the ordinal mRS ($p_{interaction}$=0·96, figure 2A). The beneficial effect of endovascular thrombectomy on the ordinal mRS

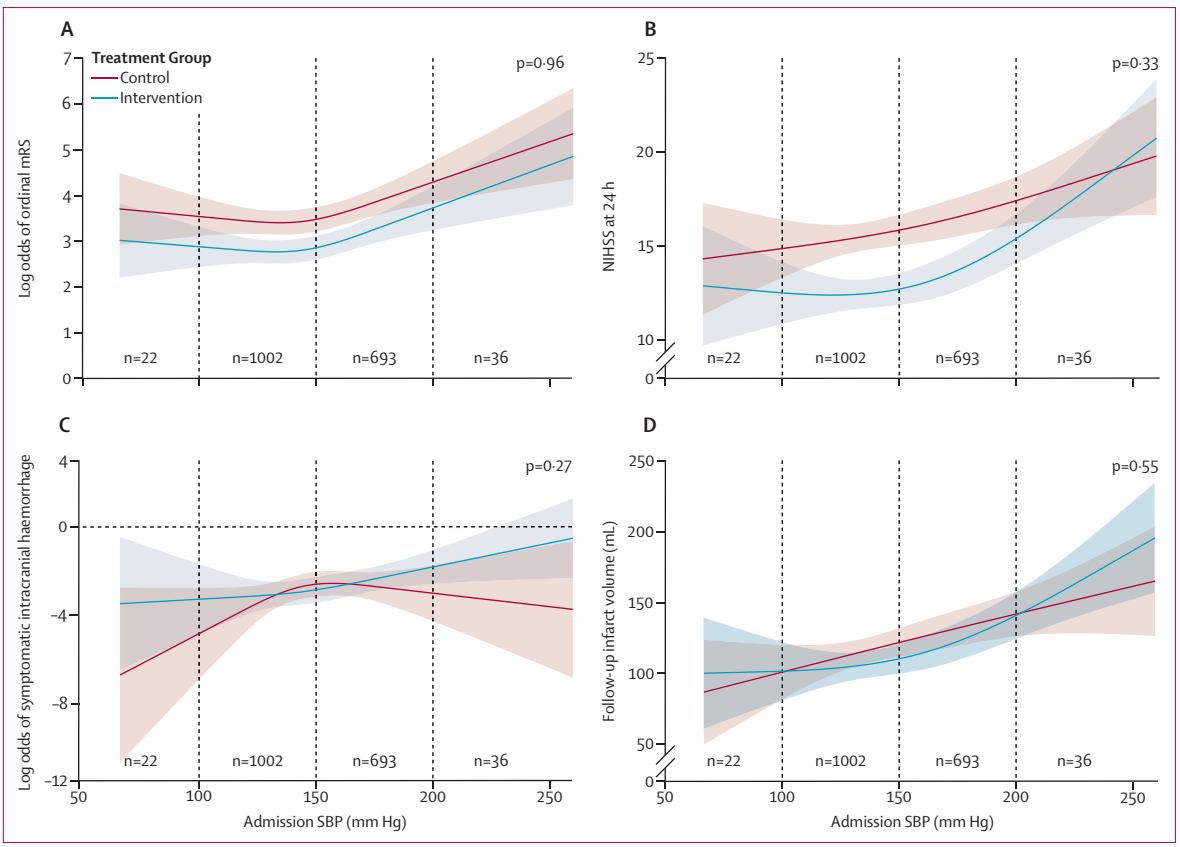

Figure 2: **Effect of endovascular thrombectomy across levels of admission SBP**
Fitted models include a restricted cubic spline transformation of SBP with three knots and included the following variables: age, sex, baseline NIHSS, baseline Alberta Stroke Program Early CT Score, history of hypertension, collateral score, time from onset to randomisation, and trial (MR CLEAN trial as reference). The figures depict the log odds of shift towards worse mRS score (A), NIHSS at 24 h after stroke (B), log odds of symptomatic intracranial haemorrhage (C), and follow-up infarct volume at 12 h to 2 weeks after stroke (D), with 95% CIs (shaded areas), for each level of admission SBP. The p values represent test for interaction (between SBP and effect of endovascular thrombectomy). The total number of patients with pretreatment SBP ≥185 mm Hg (the recommended upper threshold before endovascular thrombectomy) was n=92. mRS=modified Rankin scale. NIHSS=National Institutes of Health Stroke Scale. SBP=systolic blood pressure.

was similar for patients with admission SBP below 140 mm Hg (acOR 2·06 [95% CI 1·56–2·71]) and patients with admission SBP of 140 mm Hg or higher (acOR 1·84 [1·46–2·31]; appendix p 7). Similarly, there was no difference in the effect of endovascular thrombectomy for early neurological deficit ($p_{interaction}$=0·33, figure 2B), symptomatic intracranial haemorrhage ($p_{interaction}$=0·27, figure 2C), and follow-up infarct volume ($p_{interaction}$=0·55, figure 2D). In addition, there was no difference in the effect of endovascular thrombectomy on good functional outcome ($p_{interaction}$=0·96) and mortality ($p_{interaction}$=0·28) between admission SBP groups (appendix p 8).

Discussion

In this individual patient data meta-analysis, which included 1753 patients with ischaemic stroke from centres in multiple countries, the effects of endovascular thrombectomy on clinical, imaging, and safety outcome measures did not differ for low or high levels of admission SBP. Higher admission SBP was associated with worse functional outcome, larger early neurological deficit, and larger follow-up infarct volume.

Our results are in line with findings of a post-hoc analysis of the MR CLEAN trial, in which no interaction between admission blood pressure and the effect of endovascular thrombectomy was observed.[10] Moreover, since pretreatment blood pressure recommendations for endovascular thrombectomy are based on studies of intravenous thrombolysis and the blood pressure targets of several individual endovascular thrombectomy trials, a detailed analysis of treatment effect modification in a large pooled individual patient meta-analysis was warranted. We observed a beneficial effect of endovascular thrombectomy on clinical outcomes up to SBP above 200 mm Hg, based on 92 patients with pretreatment SBP above 185 mm Hg. Given the strongly time-dependent effect of endovascular thrombectomy, we believe that the start of endovascular thrombectomy should not be delayed for the purpose of blood pressure reduction.

This study confirms that admission blood pressure is an independent predictor of poor outcome and larger infarcts after endovascular thrombectomy.[10,22,28] The association between higher admission SBP and larger follow-up infarct volumes contributes to the understanding of the

role of SBP in lesion evolution in patients with ischaemic stroke due to a large vessel occlusion. High SBP might be a marker of tissue damage instead of the cause of poor outcomes. However, it is likely that very low SBP before reperfusion does contribute to lesion extension through a drop in cerebral perfusion via collaterals. The recently published results of the ENCHANTED2 trial indicate that intensive blood pressure management (target SBP <120 mm Hg) following reperfusion caused worse outcomes compared with moderate blood pressure management (target SBP 140–180 mm Hg).[29] These findings suggest that SBP lowering before endovascular thrombectomy, when cerebral perfusion is still severely compromised, could contribute to worse outcomes following stroke by influencing cerebral perfusion pressure, in addition to the detrimental effect of delayed start of endovascular thrombectomy. We observed no significant association between low admission SBP and functional outcome, similar to what has been observed previously.[10,22] Furthermore, we did not find a significant association between lower SBP and symptomatic intracranial haemorrhage, in contrast to results from observational studies. This absence of an association might be caused by the fact that patients with lower admission SBP were more likely to have good outcomes in the randomised trials than in the observational studies due to stricter eligibility criteria for endovascular thrombectomy in the randomised controlled trials. The question on optimal blood pressure management in the acute phase of ischaemic stroke is still not answered. In this study, we found a strong association between admission SBP and outcomes after endovascular thrombectomy and no interaction of admission SBP with the effect of endovascular thrombectomy. Whether these findings also apply to procedural and post-procedural SBP warrants further study. However, these periods of SBP measurements are less relevant for treatment interactions and therefore patient selection than SBP at hospital admission.

Our study has several limitations. First, our analyses were based on a single SBP measurement, and neither diastolic blood pressure nor mean arterial pressure values were available. Second, patients with very high or uncontrollable blood pressure on hospital admission were not included in the endovascular thrombectomy trials. Furthermore, it is well known that age is an important prognostic factor for outcome and is also associated with SBP. Therefore, we adjusted for age, as well as for age-related comorbidities (eg, diabetes, hypertension, atrial fibrillation, previous stroke). Moreover, the correlation between admission SBP and age was not very strong. Still, as vascular health is complex and multifactorial, residual confounding might be present. The included trials differed among several aspects including study population, inclusion and exclusion criteria, and definition of intervention and control groups, which could have introduced some heterogeneity of the association between SBP and outcomes. To account for between-trial differences, we used mixed-effects modelling for all analyses. Furthermore, this analysis has previously been performed in the MR CLEAN dataset, which was also included in this analysis. However, since the effect of endovascular thrombectomy on outcome was similar across all included trials, inclusion of the MR CLEAN data increased the precision of the estimates. Furthermore, accurate evaluation of treatment effect heterogeneity requires a large dataset. Although we performed an individual patient meta-analysis and included a large number of patients, the uncertainty around treatment effects increases for very low and high SBP.

Based on current available evidence and the benefit of early treatment with endovascular thrombectomy in patients with acute ischaemic stroke due to a large vessel occlusion in the anterior circulation, we believe that the recommendations by the ESO and AHA/ASA guidelines to withhold or delay endovascular thrombectomy in patients with admission blood pressure above 185/110 mm Hg deserve revision.[2,3,10,30] High admission SBP is associated with worse functional outcome and larger follow-up infarct volume, but since admission SBP does not influence the effect of endovascular thrombectomy, we believe that high or low admission SBP should not be a reason to withhold or delay endovascular thrombectomy for ischaemic stroke.

Contributors

NS contributed to study design, statistical analysis, interpretation of data, and wrote the paper. DWJD, AvdL, SB, RAvdG, HFL, and MJHLM contributed to the idea for the study and its design, statistical analysis, and interpretation of data. NA contributed to the statistical analysis and interpretation of data. DWJD, MJHLM, BR, PJvD, MG, SB, PMW, LSR, TGJ, MDH, PJM, AMD, AB, TGD, ACGMvE, and AvdL contributed to data acquisition. NS, DWJD, AvdL, SB, and MG verified the data. All authors had full access to all the data in the study, critically reviewed the report, and had final responsibility for the decision to submit for publication.

Declaration of interests

SB reports personal fees from the University of Calgary during the conduct of the HERMES collaboration and membership on a data safety monitoring board (DSMB) for the TESLA trial, no payment accepted. MG reports that Medtronic, NoNO, and Cerenovus provided a grant to the University of Calgary; royalties or licenses from GE Healthcare for systems of acute stroke diagnosis and Microventric for systems of intracranial access; consulting fees from Medtronic, Microvention, Stryker, and Mentice; and holds stock in Circle Neurovascular. KWM reports a grant from Boehringer Ingelheim payed to the institution for support of the ATTEST-2 trial; consulting fees from Boehringer Ingelheim, AbbVie, and Biogen; and BHF-funded DSMB participation (ARREST trial). PMW reports unrestricted grants from Stryker, Medtronic (Covidien), and Penumbra payed to the institution. TGJ reports honoraria from Stryker, Silk Road Medical, Blockade Medical, FreeOx Biomedical, Route 92, Neurotrauma Science, Viz.ai, Corindus, Anaconda, Medtronic, Contego, and Methinks as a consultant; and has consulted for Cerenovus as a steering committee member and Stryker Neurovascular as a principal investigator of DAWN and AURORA. MDH reports a research grant from Medtronic paid to the University of Calgary for the HERMES collaboration; grants all paid to the University of Calgary from Boehringer-Ingelheim (for the TEMPO-2 trial), Biogen, NoNO (for the ESCAPE-NA1 trial, ESCAPE-NEXT trial), Canadian Institutes for Health Research (for the ESCAPE-NA1 trial, ESCAPE-NEXT trial), and Alberta Innovates (for the QuICR Alberta Stroke Program; some of the funds were used for the ESCAPE-NA1 trial). MDH also reports paid work for Sun Pharma and Brainsgate for adjudication of clinical trial outcomes; patents (US Patent 62/086,077 and US Patent 10,916,346) licensed to Circle NVI; and participation as a

DSMB chair for the RACECAT trial (end 2020), Oncovir Hiltonel trial (ongoing), and DUMAS trial (ongoing), and DSMB member for the ARTESIA trial (ongoing) and BRAIN-AF trial (ongoing). MDH is president of the Canadian Neurological Sciences Federation (not for profit), board member of the Canadian Stroke Consortium (not for profit), and holds stock in Circle and PureWeb. PJM reports speaking engagements from Stryker and Medtronic and research institutional support from Stryker Neurovascular and Medtronic. AMD reports honoraria from Medtronic, grants from Cerenovus for the ENDOLOW trial, and participated in a DSMB for the WE-TRUST trial (Philips). DWJD reports unrestricted research grants from the Dutch Heart Foundation, Brain Foundation Netherlands, The Netherlands Organisation for Health Research and Development, Health Holland Top Sector Life Sciences and Health, and unrestricted grants from Medtronic, Penumbra, Stryker, Thrombolytic Science, and Cerenovus (all paid to institution). AvdL reports grants from Dutch Heart Foundation, Brain Foundation Netherlands, The Netherlands Organization for Health Research and Development, Health Holland Top Sector Life Sciences & Health, Stryker, Penumbra, Medtronic, Cerenovus, Thrombolytic Science, GE Healthcare, Siemens Healthineers, and Philips Healthcare (all paid to his institution). AvdL also reports speaking fees from Siemens Healthineers paid to the institution, participation on a DSMB for the ESCAPE-MEVO trial, and is research leader of CONTRAST consortium (unpaid). All other authors declare no competing interests.

Data sharing

Information about analytical methods (R script [Jan 10, 2023]) for the statistical analysis is available from the corresponding author on reasonable request and will be shared by email. Anonymised individual participant data are available in VISTA, the Virtual International Stroke Trials Archive, which is an open access registry, at https://www.virtualtrialsarchives.org/vista/.

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