Endovascular treatment versus no endovascular treatment after 6-24 h in patients with ischaemic stroke and collateral flow on CT angiography (MR CLEAN-LATE) in the Netherlands

Endovascular treatment versus no endovascular treatment after 6–24 h in patients with ischaemic stroke and collateral flow on CT angiography (MR CLEAN-LATE) in the Netherlands: a multicentre, open-label, blinded-endpoint, randomised, controlled, phase 3 trial

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Summary

Background Endovascular treatment for anterior circulation ischaemic stroke is effective and safe within a 6 h window. MR CLEAN-LATE aimed to assess efficacy and safety of endovascular treatment for patients treated in the late window (6–24 h from symptom onset or last seen well) selected on the basis of the presence of collateral flow on CT angiography (CTA).

Methods MR CLEAN-LATE was a multicentre, open-label, blinded-endpoint, randomised, controlled, phase 3 trial done in 18 stroke intervention centres in the Netherlands. Patients aged 18 years or older with ischaemic stroke, presenting in the late window with an anterior circulation large-vessel occlusion and collateral flow on CTA, and a neurological deficit score of at least 2 on the National Institutes of Health Stroke Scale were included. Patients who were eligible for late-window endovascular treatment were treated according to national guidelines (based on clinical and perfusion imaging criteria derived from the DAWN and DEFUSE-3 trials) and excluded from MR CLEAN-LATE enrolment. Patients were randomly assigned (1:1) to receive endovascular treatment or no endovascular treatment (control), in addition to best medical treatment. Randomisation was web based, with block sizes ranging from eight to 20, and stratified by centre. The primary outcome was the modified Rankin Scale (mRS) score at 90 days after randomisation. Safety outcomes included all-cause mortality at 90 days after randomisation and symptomatic intracranial haemorrhage. All randomly assigned patients who provided deferred consent or died before consent could be obtained comprised the modified intention-to-treat population, in which the primary and safety outcomes were assessed. Analyses were adjusted for predefined confounders. Treatment effect was estimated with ordinal logistic regression and reported as an adjusted common odds ratio (OR) with a 95% CI. This trial was registered with the ISRCTN, ISRCTN19922220.

Findings Between Feb 2, 2018, and Jan 27, 2022, 535 patients were randomly assigned, and 502 (94%) patients provided deferred consent or died before consent was obtained (255 in the endovascular treatment group and 247 in the control group; 261 [52%] females). The median mRS score at 90 days was lower in the endovascular treatment group than in the control group (3 [IQR 2–5] *vs* 4 [2–6]), and we observed a shift towards better outcomes on the mRS for the endovascular treatment group (adjusted common OR 1·67 [95% CI 1·20–2·32]). All-cause mortality did not differ significantly between groups (62 [24%] of 255 patients *vs* 74 [30%] of 247 patients; adjusted OR 0·72 [95% CI 0·44–1·18]). Symptomatic intracranial haemorrhage occurred more often in the endovascular treatment group than in the control group (17 [7%] *vs* four [2%]; adjusted OR 4·59 [95% CI 1·49–14·10]).

Interpretation In this study, endovascular treatment was efficacious and safe for patients with ischaemic stroke caused by an anterior circulation large-vessel occlusion who presented 6–24 h from onset or last seen well, and who were selected on the basis of the presence of collateral flow on CTA. Selection of patients for endovascular treatment in the late window could be primarily based on the presence of collateral flow.

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Introduction

Before 2018, stroke guidelines recommended endovascular treatment for patients with ischaemic stroke due to anterior circulation large-vessel occlusions within 6 h from symptom onset or last seen well, with the highest level of evidence.[1,2] This therapeutic window was based on five randomised controlled trials.[3] The HERMES pooling of these trials did not indicate a significant treatment benefit of endovascular treatment after 7·3 h.[4] However, as only two of the trials in HERMES included patients treated 6–24 h from symptom onset or last seen well (referred to as the late window), the number of patients treated in the late window was too small to draw conclusions.[4–6]

The exact time after which recanalisation therapies are futile differs between individuals. Therefore, in the late window, we should identify and treat those patients who could potentially still benefit from endovascular treatment.[7] In 2018, the DEFUSE-3 trial[8] and DAWN trial[9] showed benefit of endovascular treatment up to 16 h (DEFUSE-3) and 24 h (DAWN) from symptom onset or last seen well in patients who had an ischaemic stroke and were selected on the basis of a combination of clinical criteria and perfusion imaging (estimating

Research in context

Evidence before this study

We searched PubMed for randomised controlled trials published between Jan 1, 2015, and Feb 17, 2023, using medical subject headings terms: "((((Ischemic Stroke) AND (Therapy/Broad[filter])) OR anterior circulation brain infarction OR brain infarction OR cerebral infarction OR cerebral ischemia OR acute stroke OR brain ischemia OR brain embolism) AND (((Endovascular Procedures) AND (Therapy/Broad[filter])) OR endovascular procedure OR thrombectomy OR embolectomy OR thrombectomies OR embolectomies)) NOT (infarction, posterior cerebral artery)". No language restriction was applied. We found nine randomised controlled trials in total that included patients with ischaemic stroke who had endovascular treatment in the late window (ie, 6–24 h from symptom onset or last seen well). The ESCAPE (0–12 h), REVASCAT (0–8 h), and RESILIENT (0–8 h) trials selected patients on the basis of small ischaemic cores (assessed with Alberta Stroke Program Early CT Score [ASPECTS]). ESCAPE additionally required collateral grades 2–3 on CT angiography (CTA), and RESILIENT required collateral grades 1–3. For RESILIENT, perfusion mismatch criteria were also applied (if available), whereas REVASCAT used perfusion imaging-derived ASPECTS for patient selection 4·5 h or longer from symptom onset or last seen well. The HERMES collaboration pooled the data from REVASCAT, ESCAPE, and three other landmark trials and showed a non-significant effect of endovascular treatment when treatment started after 7·3 h. However, because only few patients in these trials presented in the late window (49 in ESCAPE, 20 in REVASCAT, and 26 in RESILIENT), no conclusions can be drawn from these data. More recently, three trials were published that specifically included patients treated in the late window. The DAWN and DEFUSE-3 trials showed treatment benefits for patients treated between 6–24 h (DAWN) and 6–16 h (DEFUSE-3) from symptom onset or last seen well who were selected on the basis of perfusion imaging combined with clinical criteria. The POSITIVE trial included 12 patients between 6 h and 12 h selected with perfusion imaging but stopped enrolment after publication of DAWN and DEFUSE-3. Data from patients treated in the late window included in all the aforementioned trials were pooled in the AURORA meta-analysis (n=505) and showed improved modified Rankin Scale scores at 90 days (adjusted common odds ratio 2·54 [95% CI 1·83–3·54]). Three large core trials (RESCUE-Japan LIMIT, ANGEL-ASPECT, and SELECT2) showed benefit of endovascular treatment in patients with low ASPECTS (3–5) presenting between 0 and 24 h. A post-hoc analysis of the MR CLEAN trial showed that for patients treated within 6 h, better collateral grades were associated with larger treatment benefits, and a post-hoc analysis of DAWN showed that 97% of included patients had collateral flow on CTA. However, we did not find published randomised controlled trials that primarily used collaterals to select patients for endovascular treatment in the late window.

Added value of this study

This study showed efficacy and safety of endovascular treatment in patients with anterior circulation ischaemic stroke who were treated within 6–24 h from onset or last seen well and selected on the basis of the presence of collateral flow on CTA and not being eligible for endovascular treatment according to the national guidelines (based on criteria for endovascular treatment derived from DAWN and DEFUSE-3). Besides this pragmatic and simple approach to selecting patients for endovascular treatment in the late window, these results also favour extending the indication for late-window endovascular treatment to a larger group of patients than currently recommended by guidelines. Furthermore, CTA is more widely available than perfusion imaging modalities. Therefore, our results promote late-window endovascular treatment for patients in centres or countries that have limited access to perfusion imaging.

Implications of all the available evidence

Our results, in addition to previous literature, support the notion that the selection of patients for endovascular treatment in the late window could be primarily based on the presence of collateral flow. Future and ongoing late-window trials are warranted to confirm our results in different populations.

ischaemic core and penumbra volumes) criteria. Because of the relatively strict selection criteria and the large treatment effects observed in these trials, we expected that more patients presenting in the late window who are currently excluded from endovascular treatment could benefit from this treatment.

In patients with good intracranial collateral blood supply, brain tissue in the affected vascular territory might be viable for a longer period before it turns into the ischaemic core.[7] A post-hoc analysis of the MR CLEAN trial showed larger treatment benefits of endovascular treatment in patients with better collateral grades on CT angiography (CTA).[10] Therefore, we hypothesised that the presence of collaterals might offer a more inclusive and pragmatic tool to select patients for late-window endovascular treatment than currently used criteria.

The MR CLEAN-LATE trial aimed to assess the efficacy and safety of endovascular treatment in addition to best medical treatment compared with best medical treatment alone in patients who had an ischaemic stroke and presented 6–24 h from stroke onset or last seen well with an intracranial large-vessel occlusion in the anterior circulation and the presence of collateral flow on baseline CTA.

Methods

Study design

The MR CLEAN-LATE was an investigator-initiated, multicentre, open-label, blinded-endpoint, randomised, controlled, phase 3 trial (PROBE design). The trial was done at 18 stroke intervention centres in the Netherlands (appendix p 7).

This trial was approved by a central medical ethics committee at Erasmus MC, University Medical Center Rotterdam (Rotterdam, Netherlands). Written deferred informed consent was obtained from patients or their legal representatives as soon as deemed reasonable after randomisation. If a patient died before consent could be obtained, we informed their representatives of trial participation. The research protocol, statistical analysis plan, and format of the informed consent forms can be accessed online and a protocol summary has previously been published.[11]

Participants

Patients with the following criteria were eligible for inclusion: age 18 years or older; ischaemic stroke due to a proximal occlusion in the anterior circulation (ie, the distal intracranial internal carotid artery, first segment of the middle cerebral artery [M1], or the proximal second segment of the middle cerebral artery [M2]) as confirmed by CTA or magnetic resonance angiography (MRA); endovascular treatment could start within 6–24 h from symptom onset or last seen well; the presence of collateral flow in the middle cerebral artery territory of the affected hemisphere on CTA (single-phase CTA or the arterial phase of multiphase CTA), defined as grade 1 (collateral filling ≤50%, but >0%), grade 2 (collateral filling >50%, but <100%) or grade 3 (100% collateral filling) scored in comparison to the entire contralateral middle cerebral artery territory;[12,13] and a neurological deficit score of at least 2 on the National Institutes of Health Stroke Scale (NIHSS). Exclusion criteria were intracranial haemorrhage on baseline imaging; pre-stroke dependency defined as a modified Rankin Scale (mRS) score of 3 or higher; ischaemic stroke within the previous 6 weeks with persistent neurological symptoms; clinical evidence of haemorrhagic diathesis; clearly demarcated hypodensity of more than a third of the middle cerebral artery territory consistent with current symptoms; and participation in medical or surgical intervention trials other than the current trial (exceptions are listed in the protocol). The inclusion of patients with grade 1 collaterals was halted after a predetermined number of 100 patients was reached, in accordance with the research protocol, to avoid over-representation of patients with collateral grade 1 (as we expected this group to have poorer treatment responses than patients with grade 2 or 3).

Before the first patient was included in the MR CLEAN-LATE trial, the positive results of the DAWN and DEFUSE-3 trials were published.[8,9] On the basis of these trials, the Dutch guidelines for endovascular treatment were revised, recommending endovascular treatment for patients with clinical and imaging profiles similar to the study populations of these trials.[14] This profile was defined by the following criteria: occlusion of the internal carotid artery terminus or M1; an NIHSS score of at least 10; an ischaemic core of 25 mL or less (based on the 75th percentile in the DEFUSE-3 trial); and a total ischaemic volume/ischaemic core ratio of at least 2 assessed on CT perfusion or magnetic resonance perfusion or diffusion. Patients meeting these criteria were therefore treated with endovascular treatment and were not included in MR CLEAN-LATE. Detailed methods and inclusion and exclusion criteria are described in our research protocol. A summary of the protocol has been previously published.[11]

Randomisation and masking

Treating physicians assessed patient eligibility and randomly assigned (1:1) patients to receive endovascular treatment or no endovascular treatment (control group), in addition to best medical treatment. Randomisation was web based using permuted blocks of varying block sizes (eight to 20) and stratified by centre. Local investigators, treating physicians, and patients were aware of the assigned treatment. The primary outcome and other clinical outcomes at 90 days were centrally assessed by certified research nurses masked to treatment allocation using standardised interview forms and procedures. Adjudication of the primary outcome (based on these interview reports) was performed by members of the outcome committee and that of serious adverse events (based on serious adverse

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See **Online** for appendix

For the **protocol and statistical analysis plan** see https://www.mrclean-late.nl/

event reports) was performed by members of the adverse event committee; all committee members were unaware of treatment allocation (appendix pp 2–5). Neuroimages were assessed by a core imaging laboratory of experienced radiologists who were masked to all clinical data.

Procedures

All CE-marked endovascular treatment devices were allowed. Treatment technique and device choices were left to the discretion of the treating interventionist. All patients, regardless of treatment allocation, underwent neurological assessment by trained assessors at baseline (not masked to treatment allocation), 24 h after randomisation, and 5–7 days after randomisation or before hospital discharge. Non-contrast CT combined with CTA was performed at baseline and at 24 h. Additionally, non-contrast CT was repeated at 5–7 days or discharge. Participating stroke intervention centres could opt for replacing CT as the follow-up modality for a single MRI combined with MRA at 24–48 h after randomisation. To avoid bias, centres were expected to adhere to their choice of imaging modality, unless patients had contraindications rendering one of these modalities unsuitable.

All patients underwent follow-up until the final central assessment of clinical outcomes at 90 days by means of standardised telephone interviews (by a research nurse masked to treatment allocation). If a patient was incapable of being interviewed, their representative (eg, a relative or carer) was interviewed instead.

Outcomes

The primary outcome measure was the distribution of scores on the mRS at 90 (±14) days after randomisation. The mRS scores were used to assess functional outcomes, ranging from 0 (no disability) to 6 (death).[15] Secondary outcomes were dichotomised mRS scores of 0–1 versus 2–6, 0–2 versus 3–6, and 0–3 versus 4–6 at 90 days; interference with self-care activities scored with the Barthel Index at 90 days, ranging from 0 (severe disability) to 100 (no disability); quality of life scored at 90 days with utility values based on the EQ-5D 5-Levels (EQ-5D-5L) self-report questionnaire, ranging from –0·446 to 1·0 (full health; deceased patients have a utility of 0); stroke severity scored on the NIHSS at 24 h and at 5–7 days after randomisation or discharge ranging from 0 (no deficit) to 42 (maximum deficit); recanalisation on CTA or MRA at 24 h after randomisation, defined as a modified arterial occlusive lesion score of at least 2, a score ranging from 0 (no recanalisation) to 3 (complete recanalisation); and infarct volume (mL) assessed on follow-up CT or MRI (for details on this method, see the appendix p 6).[16]

Safety outcomes were the occurrence of any intracranial haemorrhage; occurrence of intracranial haemorrhage according to the European Cooperative Acute Stroke Study classification, which includes haemorrhagic infarction type 1, haemorrhagic infarction type 2, parenchymal haematoma type 1, and parenchymal haematoma type 2;[17] occurrence of symptomatic intracranial haemorrhage according to the Heidelberg bleeding classification;[18] all-cause mortality at 90 days; post-procedural occurrence of groin haematoma; post-procedural occurrence of femoral-artery pseudoaneurysm; embolisation in a new cerebral territory during the procedure; and clinical evidence of infarction in a new cerebral territory in the first 7 days of randomisation, according to local investigators, and adjudicated by the adverse event committee.

Statistical analysis

Statistical analyses were performed according to the prespecified statistical analysis plan by the trial statistician. To determine the sample size, in a simulation with 5000 runs, the proportion of positive trials was computed for a given sample size, with the mRS score distribution in the control group based on the MR CLEAN trial.[19] A sample size of 670 provided 84% power to detect a true treatment effect in case of an underlying common odds ratio (OR) of at least 1·52 (two-sided α value of 0·05). We planned on using covariate adjustments, which reduces the required sample size by approximately 25%.[20] A sample size of 500 was therefore deemed to be sufficient.

The primary, secondary, and safety outcome analyses assessed the superiority of endovascular treatment compared with no endovascular treatment according to the assigned treatment allocation in the modified intention-to-treat population. All patients who provided deferred consent or died before consent could be obtained comprised the modified intention-to-treat population. The primary effect parameter was the adjusted common OR, with a common OR of more than 1 representing a shift towards better outcomes on the full distribution of the mRS at 90 days, estimated with multivariable ordinal logistic regression analysis. Secondary and safety outcomes were analysed with binary logistic and linear regression analyses to estimate ORs or β-coefficients. All estimates were adjusted for the following prespecified prognostic variables: age; pre-stroke mRS score; time from symptom onset or last seen well to randomisation; baseline NIHSS score; collateral grade; and whether stroke onset was witnessed. Variables with a non-Gaussian distribution were log-transformed to perform linear regression analyses ($^{e}\log[\text{var}+1]$). For interpretation, we exponentiated their β-coefficients ($[\exp(\beta)-1]\times 100$) and expressed the results as the difference between groups in percentages. We performed two prespecified sensitivity analyses: first, we repeated the main analyses comparing treatment groups based on the received treatment (as-treated analyses), defining treated as undergoing artery puncture for endovascular treatment; and second, we analysed in-hospital mortality and symptomatic intracranial haemorrhage in the safety

cohort, which included all randomly assigned patients, irrespective of whether consent was obtained, and in which we only recorded the study number, treatment allocation, in-hospital symptomatic intracranial haemorrhage, and in-hospital mortality.

Treatment effect on the mRS was further analysed in prespecified subgroups based on age, sex, baseline systolic blood pressure, baseline NIHSS, time from onset or last seen well to randomisation, time from onset or first noticed symptoms to randomisation, diabetes, atrial fibrillation, tandem occlusion, occlusion location, Alberta Stroke Program Early CT Score (ASPECTS), collateral grade, witnessed stroke onset, and treatment with intravenous alteplase. We tested for an interaction between these variables and treatment effect on the primary outcome using a two-sided α value of 0·05.

For all analyses, adjusted effect estimates with their corresponding 95% CIs were reported. p values and 95% CIs of effect estimates in our secondary, safety, and subgroup analyses were not corrected for multiplicity.

Safety and prespecified efficacy interim analyses were performed by an independent data safety monitoring board after every 100th randomisation. None of these interim analyses showed any safety issues. All investigators were masked to the results of these analyses.

For secondary outcomes, we assigned the worst possible scores on clinical outcomes for patients who died before this outcome could be assessed. All other missing values were imputed using multiple imputations by chained equations. All analyses were performed using R (version 4.2.1).

This trial was registered with the ISRCTN, ISRCTN19922220.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit the manuscript for publication.

Results

Between Feb 2, 2018, and Jan 27, 2022, 535 eligible patients (who were all included in the safety cohort) were randomly assigned to the endovascular treatment group (n=268) or the control group (n=267). 502 (94%) patients provided deferred consent or died before consent could be obtained and comprised the modified intention-to-treat population. Of these 502 patients, 255 (51%) were in the endovascular treatment group and 247 (49%) were in the control group (figure 1). As no patients were lost to follow-up, data on the primary outcome were available for all 502 patients. Details on inclusion rates during the study period and the number of inclusions per centre are described in the appendix (pp 7, 17).

The median age was 74 years in both the endovascular treatment group (IQR 64–80) and control group (64–81). 148 (58%) patients in the endovascular treatment group and 113 (46%) patients in the control group were female (table 1). The appendix reports additional baseline characteristics (p 8) and endovascular treatment details (p 9).

The median mRS score at 90 days was lower in the endovascular treatment group (3 [IQR 2–5]) than in the control group (4 [2–6]; table 2). Ordinal regression analyses (shift analyses) showed that patients allocated to the intervention group had a significantly better score on the mRS at 90 days in both the unadjusted (common OR 1·42 [95% CI 1·04–1·93]; appendix p 10) and adjusted analysis (adjusted common OR 1·67 [95% CI 1·20–2·32]; table 2; figure 2).

Effect estimates of prespecified mRS dichotomisations were all similar to the primary effect estimate (table 2). In the endovascular treatment group, the baseline-adjusted NIHSS score at 24 h decreased by 16% (95% CI –27 to –5) compared with the control group, and the baseline-adjusted NIHSS score at 5–7 days or discharge decreased by 27% (–38 to –13) compared with the control group (table 2). Patients in the endovascular treatment group had higher EQ-5D-5L utility scores (adjusted

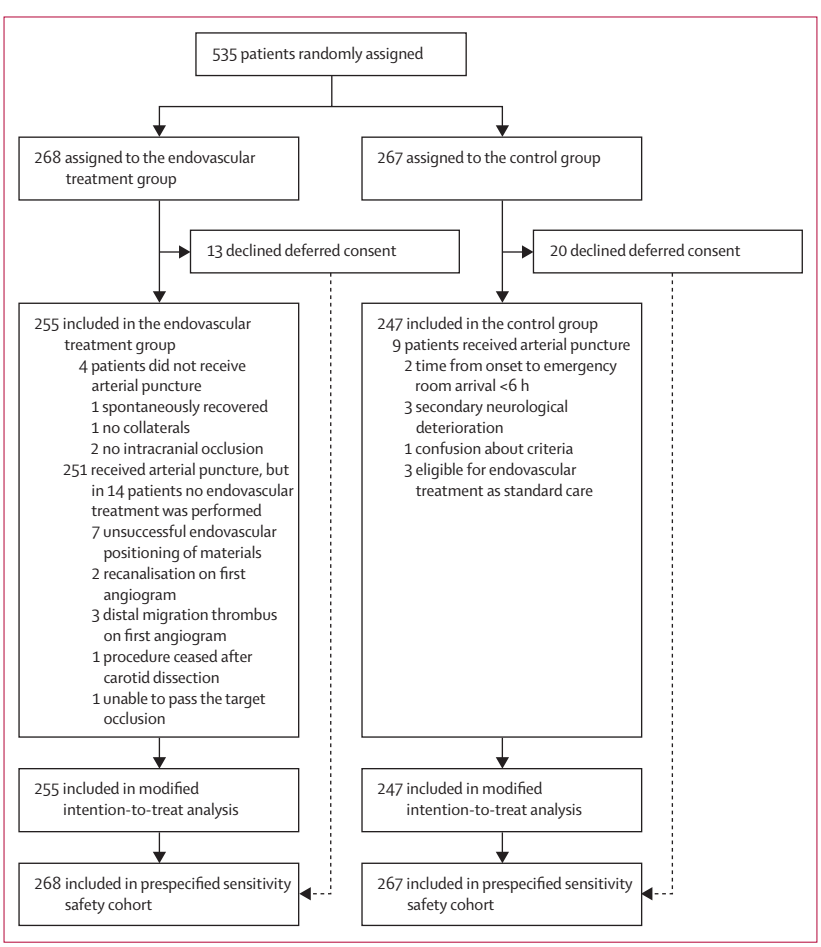

Figure 1: **Trial profile**

β=0·08 [95% CI 0·01 to 0·14]) and a higher Barthel Index (8·2 [2·0 to 14·5]) at 90 days than the control group (table 2). Recanalisation on follow-up CTA occurred more often in the endovascular treatment group than in the control group (adjusted OR 3·14 [95% CI 2·15 to 4·58]) and follow-up infarct volume was 36% (–52 to –16) smaller in the endovascular treatment group than in the control group (table 2).

	Endovascular treatment group (n=255)	Control group (n=247)
Age, years	74 (64–80)	74 (64–81)
Sex		
Female	148 (58%)	113 (46%)
Male	107 (42%)	134 (54%)
NIHSS score*	10 (6–17)	10 (6–18)
Medical history		
Ischaemic stroke	51/254 (20%)	40/246 (16%)
Atrial fibrillation	51/254 (20%)	53/246 (22%)
Diabetes	35/254 (14%)	39/246 (16%)
Hypertension	142/254 (56%)	118/245 (48%)
Pre-stroke modified Rankin Scale score†		
0	145/254 (57%)	159 (64%)
1	66/254 (26%)	47 (19%)
2	38/254 (15%)	36 (15%)
≥3	5/254 (2%)	5 (2%)
Systolic blood pressure, mm Hg‡	155 (136–176)	154 (140–174)
Proximal target occlusion§		
Intracranial internal carotid artery	5 (2%)	7 (3%)
Internal carotid artery terminus	32 (13%)	32 (13%)
First segment of middle cerebral artery	135 (53%)	126 (51%)
Second segment of middle cerebral artery	80 (31%)	76 (31%)
Other or none¶	3 (1%)	6 (2%)
Tandem lesion	51/248 (21%)	57/236 (24%)
ASPECTS§‖	9 (7–10)	8 (7–9)
Collateral grade§**		
0 (absent collateral filling)	11/251 (4%)	15/246 (6%)
1 (filling ≤50%, but >0%)	67/251 (27%)	73/246 (30%)
2 (filling >50%, but <100%)	109/251 (43%)	96/246 (39%)
3 (filling 100%)	64/251 (25%)	62/246 (25%)
Time from symptom onset or last seen well to randomisation, min	709 (542–910)	682 (532–887)
Time from symptom onset or last seen well to door of endovascular treatment centre, min	665 (485–862)	630 (478–851)
Treatment with intravenous thrombolytics	12 (5%)	19 (8%)
Witnessed stroke onset	35 (14%)	21 (9%)

Data are median (IQR), n (%), or n/N (%). ASPECTS=Alberta Stroke Program Early CT Score. NIHSS=National Institutes of Health Stroke Scale. *NIHSS scores range from 0 (no deficits) to 42 (worst deficits in all items). NIHSS scores are missing or incomplete for nine patients in the endovascular treatment group and four patients in the control group. †The modified Rankin Scale ranges from 0 (no symptoms) to 6 (death), with higher scores indicating more severe functional disability. ‡Systolic blood pressure was missing for two patients in the control group. §Scored by the core imaging laboratory and assessment could therefore differ from the baseline assessment of local radiologists. ¶For two patients in the control group, no anterior circulation occlusions were identified. Three patients (one in the endovascular treatment group and two in the control group) had an occlusion of the anterior cerebral artery. For four patients (two in the endovascular treatment group and two in the control group), the occlusion was more distal than the second segment (ie, third or fourth) of the middle cerebral artery. ‖ASPECTS range from 0 to 10. Lower scores indicate early ischaemic changes in more brain areas on CT. For one patient in the control group, the score was missing. **Collateral filling in the middle cerebral artery territory of the affected hemisphere is expressed as a percentage of the collateral filling in the contralateral middle cerebral artery territory.

Table 1: **Baseline characteristics of the modified intention-to-treat population**

All-cause mortality at 90 days was lower in the endovascular treatment group than in the control group (62 [24%] of 255 patients *vs* 74 [30%] of 247 patients), but this difference was not significant (adjusted OR 0·72 [95% CI 0·44–1·18]; table 3). Symptomatic intracranial haemorrhage occurred more often in the endovascular treatment group than in the control group (17 [7%] *vs* four [2%]; adjusted OR 4·59 [95% CI 1·49–14·10]), as did any intracranial haemorrhage (119 [54%] of 222 *vs* 67 [36%] of 188; 1·88 [1·24–2·85]; table 3). There were no significant differences between groups in the occurrence of infarctions in a new territory within the first 7 days (adjusted OR 1·08 [95% CI 0·21–5·62]; table 3). The appendix presents unadjusted safety outcomes (p 11) and descriptive data on the occurrences of serious adverse events and procedural complications (p 12).

Point estimates of treatment effects on the primary outcome in the prespecified subgroup analyses all favoured endovascular treatment. We observed an interaction between tandem lesions and treatment effect ($p_{interaction}$=0·0085), with a higher effect estimate in favour of endovascular treatment for patients with a tandem lesion. We found a lower effect estimate in patients presenting with an occlusion of M2 or the third segment of the middle cerebral artery (M3) than in patients with other occlusion locations ($p_{interaction}$=0·0069). Furthermore, an interaction between collateral grades and treatment effect ($p_{interaction}$=0·035) was observed, with a higher effect estimate for grade 1 collaterals (2·55 [95% CI 1·33–4·88]) than for grade 2 collaterals (1·73 [1·02–2·92]) and grade 3 collaterals (1·03 [0·54–1·97]). No interactions were observed between treatment effect and any of the other prespecified subgroups (appendix p 18).

Notably, in the subgroup of patients with grade 3 collaterals the incidence of M2 or M3 occlusions was higher (51 [40%] of 126) than in the group of patients with grade 1 collaterals (31 [22%] of 140; appendix p 13).

The as-treated sensitivity analyses showed similar treatment effects on the primary outcome (mRS score at 90 days: adjusted common OR 1·58 [95% CI 1·14–2·20]), secondary outcomes, and safety outcomes (appendix pp 14–15). For in-hospital mortality and occurrence of symptomatic intracranial haemorrhage, we observed similar results in the sensitivity analyses of the safety cohort as in the modified intention-to-treat population (table 3; appendix p 16).

Discussion

In this trial, patients with ischaemic stroke caused by an anterior circulation large-vessel occlusion selected based on the presence of collateral flow on CTA in the late window, and allocated to receive endovascular treatment

	Endovascular treatment group (n=255)	Control group (n=247)	Measure of effect	Adjusted value (95% CI)*
Primary outcome				
Modified Rankin Scale score at 90 days after randomisation†	3 (2 to 5)	4 (2 to 6)	Common odds ratio	1·67 (1·20 to 2·32)
Secondary outcomes‡				
Dichotomised scores on the modified Rankin Scale at 90 days after randomisation				
0–1 *vs* 2–6	54 (21%)	39 (16%)	Odds ratio	1·63 (0·99 to 2·68)
0–2 *vs* 3–6	100 (39%)	84 (34%)	Odds ratio	1·54 (0·98 to 2·43)
0–3 *vs* 4–6	129 (51%)	103 (42%)	Odds ratio	1·73 (1·11 to 2·69)
NIHSS score§				
At 24 h after randomisation	7 (3 to 16)	10 (4 to 18)	β-coefficient	−0·18 (−0·31 to −0·05)
At 24 h after randomisation			Difference¶	−16% (−27 to −5)
At 5–7 days after randomisation or discharge	3 (1 to 10)	7 (3 to 14)	β-coefficient	−0·31 (−0·48 to −0·14)
At 5–7 days after randomisation or discharge			Difference¶	−27% (−38 to −13)
EQ-5D-5L-based utility scores at 90 days after randomisation‖	0·53 (0·00 to 0·88)	0·28 (0·00 to 0·83)	β-coefficient	0·08 (0·01 to 0·14)
Barthel Index at 90 days after randomisation**	100 (81 to 100)	95 (55 to 100)	β-coefficient	8·2 (2·0 to 14·5)
Recanalisation (mAOL ≥2) at 24 h after randomisation on CTA or MRA††	154/190 (81%)	84/160 (53%)	Odds ratio	3·14 (2·15 to 4·58)
Follow-up infarct volume on non-contrast CT or MRI, mL‡‡	28 (6 to 87)	43 (13 to 121)	β-coefficient	−0·45 (−0·73 to −0·17)
			Difference¶	−36% (−52 to −16)

Data are median (IQR), n (%), or n/N (%) unless otherwise specified. The modified intention-to-treat population included all patients who provided deferred consent or died before consent could be obtained. CTA=CT angiography. EQ-5D-5L=EQ-5D 5-Levels. mAOL=modified arterial occlusive lesion. MRA=magnetic resonance angiography. NIHSS=National Institutes of Health Stroke Scale. *All treatment effects were adjusted for age; pre-stroke modified Rankin Scale score; time from onset or last seen well to randomisation; baseline NIHSS score; collateral grade; and whether stroke onset was witnessed. †The modified Rankin Scale ranges from 0 (no symptoms) to 6 (death), with higher scores indicating more severe functional disability. ‡Reported 95% CIs of secondary outcomes were not corrected for multiplicity; therefore, inferences drawn from the intervals might not be reproducible. §NIHSS scores range from 0 (no deficits) to 42 (worst deficits in all items) and were scored for survivors only and missing in case of death before assessment. NIHSS scores at 24 h were missing or incomplete for six patients in the endovascular treatment group and 16 patients in the control group. NIHSS scores at 5–7 days or discharge were missing or incomplete for 37 patients in the endovascular treatment group and 32 patients in the control group. ¶β-coefficients of non-Gaussian variables were calculated on ᵃlog(var + 1) to perform linear regression and thereafter exponentiated ([exp(β) − 1] × 100) to express the difference in percentages between groups. ‖Higher EQ-5D-5L-based utility scores indicate better quality of life; scores range from −0·446 to 1·00. Values were missing for 22 patients in the endovascular treatment group and 21 patients in the control group. **The Barthel Index measures performance on self-care activities of daily living and ranges from 0 (severe disability) to 100 (no disability). The Barthel Index was scored for survivors only and missing in case of death before assessment. Scores were missing for 89 patients in the endovascular treatment group and 95 patients in the control group. ††mAOL ranges from 0 (no recanalisation) to 3 (complete recanalisation). ‡‡ Follow-up infarct volumes were missing for 46 patients in the endovascular treatment group and 75 patients in the control group.

Table 2: **Primary and secondary outcomes in the modified intention-to-treat population**

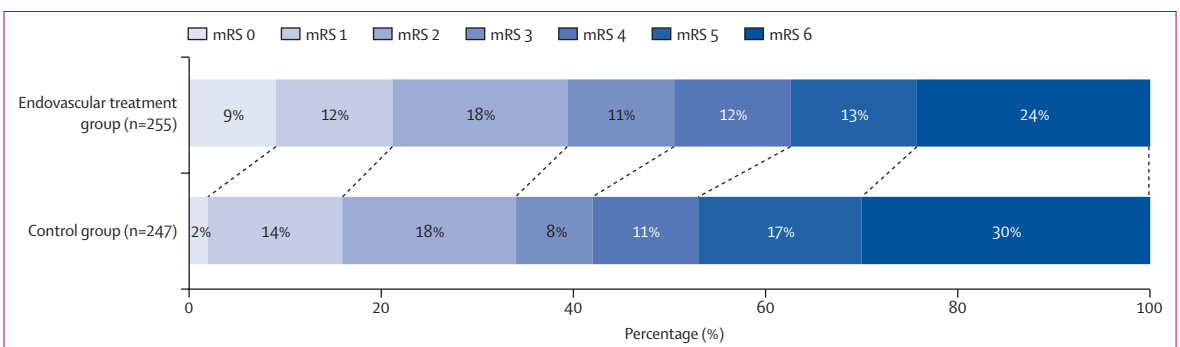

Figure 2: **Distribution of mRS scores at 90 days after randomisation in the modified intention-to-treat population**
The modified intention-to-treat population included all patients who provided deferred consent or died before consent could be obtained. mRS=modified Rankin Scale.

in addition to best medical treatment, had significantly better functional outcomes at 90 days than patients allocated to receive best medical treatment alone. Additionally, post-treatment neurological deficits were less severe and follow-up infarct volumes were lower in patients in the endovascular treatment group compared

	Endovascular treatment group (n=255)	Control group (n=247)	Adjusted odds ratio (95% CI)*
All-cause mortality at 90 days after randomisation	62 (24%)	74 (30%)	0·72 (0·44–1·18)
Symptomatic intracranial haemorrhage†	17 (7%)	4 (2%)	4·59 (1·49–14·10)
Any intracranial haemorrhage†	119/222 (54%)	67/188 (36%)	1·88 (1·24–2·85)
Haemorrhagic infarction type 1	31/222 (14%)	35/188 (19%)	0·59 (0·33–1·07)
Haemorrhagic infarction type 2	26/222 (12%)	19/188 (10%)	1·10 (0·57–2·11)
Parenchymal haematoma type 1	29/222 (13%)	8/188 (4%)	2·31 (1·04–5·12)
Parenchymal haematoma type 2	16/222 (7%)	3/188 (2%)	2·17 (0·73–6·43)
Embolisation in new territory on digital subtraction angiography‡	46/245 (19%)	0/246	NA
Infarction in new territory within first 7 days of randomisation§	4 (2%)	3 (1%)	1·08 (0·21–5·62)
Femoral-artery pseudoaneurysm‡	3 (1%)	1 (<1%)	NA
Groin haematoma‡	9 (4%)	0	NA

Data are n (%) or n/N (%) unless otherwise specified. NA=not applicable. The modified intention-to-treat population included all patients who provided deferred consent or died before consent could be obtained. *All treatment effects were adjusted for age; pre-stroke modified Rankin Scale score; time from onset or last seen well to randomisation; baseline score on the National Institutes of Health Stroke Scale; collateral grade; and whether stroke onset was witnessed. Reported 95% CIs were not corrected for multiplicity; therefore inferences drawn from the intervals might not be reproducible. †Haemorrhages were scored by the core imaging laboratory. Haemorrhagic infarction type 1 indicates scattered small petechiae without mass effect; haemorrhagic infarction type 2 indicates confluent petechiae without mass effect; parenchymal haematoma type 1 indicates haematoma occupying less than 30% of the infarcted tissue without substantive mass effect; and parenchymal haematoma type 2 indicates haematoma occupying 30% or more of the infarcted tissue with obvious mass effect. Symptomatic intracranial haemorrhages were additionally assessed by the adverse event committee according to the Heidelberg criteria. ‡Embolisation in new territory on digital subtraction angiography, femoral-artery pseudoaneurysm, and groin haematoma could have occurred in treated patients only. In the control group, this could occur for cross-overs only; therefore, the odds ratio is not applicable. §Infarction in new territory within 1 week was clinically assessed by the treating physician.

Table 3: **Safety outcomes in the modified intention-to-treat population**

with those in the control group. These results were observed in a population that did not include patients who received endovascular treatment directly according to national guidelines (based on the following criteria derived from DAWN and DEFUSE-3:[8,9] occlusion of the internal carotid artery terminus or M1; NIHSS score ≥10; ischaemic core ≤25 mL [based on the 75th percentile in the DEFUSE-3 trial]; and a total ischaemic volume/ischaemic core ratio ≥2 assessed on CT perfusion or MR perfusion or diffusion).[8,9] This study thus identified an additional population eligible for late-window endovascular treatment. The effect estimates observed in MR CLEAN-LATE were lower than those observed in AURORA,[21] which pooled late-window randomised controlled trial data including DAWN and DEFUSE-3.[8,9,22,23] This difference might be explained by the exclusion of patients with a relatively high chance of treatment benefit based on these DAWN and DEFUSE-3-derived criteria.[8,9]

Regarding safety, we did not find a significant difference in mortality between groups, although the risk of symptomatic intracranial haemorrhage was higher for patients in the endovascular treatment group than in the control group. We note that the percentage of symptomatic intracranial haemorrhages in the endovascular treatment group was, however, similar to that in the intervention groups of the DAWN and DEFUSE-3 trials.[8,9]

Subgroup analyses showed a greater effect estimate for patients with collateral grade 1 than for patients with collateral grade 2 or 3. This finding was unexpected based on the positive relationship between collateral grades and treatment effect observed in the post-hoc analysis of the MR CLEAN trial.[10] It could be due to chance, but might also be the result of the selection that occurred by exclusion of patients who met criteria derived from DAWN and DEFUSE-3 because these patients are assumed to have high collateral grades.[8,9,24] Therefore, patients with favourable collaterals in the MR CLEAN-LATE trial were presumably ineligible for direct endovascular treatment based on DAWN and DEFUSE-3-derived criteria other than core and penumbra volumes. These criteria were probably also predictive of smaller treatment benefits. For example, this phenomenon applied to M2 occlusions, which were over-represented within the groups of patients with better collateral grades. This over-representation of M2 occlusions could also, in part, be consequent to the collateral scoring method applied (comparing the middle cerebral artery territory in the affected hemisphere to the contralateral side), which in most cases, leads to higher collateral grade scores for patients with M2 occlusions. This method was, however, preferred because of its pragmatism. Despite the observed treatment interactions in this study, we do not recommend excluding any subgroups from treatment because point estimates of treatment effects all favoured endovascular treatment, the small sample sizes within these subgroups increase the probability that these interactions were due to chance, and inferences drawn from safety and subgroup analyses might not be reproducible because we did not adjust for multiplicity.

Using perfusion imaging, the DAWN and DEFUSE-3 trials provided important evidence that patients who have had a stroke in the late window can still benefit from endovascular treatment.[8,9] Unfortunately, because the selection criteria differed in these late-window trials, it is difficult to derive uniform and pragmatic selection criteria that are suitable for the emergency setting from their results. This led to different interpretations of late-window selection criteria in national and international guidelines and centre-specific approaches.[1,2,14,25,26]

In our trial population, perfusion imaging (if performed) preceded collateral-based selection. However, patients selected by either one of these selection strategies—ie, populations that overlap—should all receive endovascular treatment according to the current evidence and our results.[24,27] Hence, the order of selection should not result in differences regarding the eventually treated population. Patients could, therefore, be primarily selected for endovascular treatment on the basis of the presence of collateral flow on CTA, which should result in the selection of a larger population than is recommended by current guidelines. Moreover, selection based on collaterals does

not seem to exclude patients whose profiles meet DAWN and DEFUSE-3 criteria.[24,27] Furthermore, it is unlikely that CT perfusion would identify patients without collateral flow who still benefit from endovascular treatment, although we should be careful with interpreting these post-hoc analyses of the DAWN trial (which was more selective than the DEFUSE-3 trial).[24] Another advantage is that CTA, compared with CT perfusion is more widely available, especially in emergency situations.[26,28] Therefore, centres with limited access to perfusion imaging will also be able to select patients for endovascular treatment in the late window.

An important strength of the current study is its pragmatic and inclusive approach. In contrast to other (late-window) trials, we did not use an upper age limit and we included patients with mild neurological deficits (NIHSS ≥2), and more distal occlusions (proximal M2). Furthermore, we did not select patients on the basis of ASPECTS (we did exclude patients with clearly demarcated hypodensity of more than a third of the middle cerebral artery territory, which is not to be confused with early ischaemic changes on which ASPECTS is based). Three recently published trials showed benefit of endovascular treatment in patients with large cores (ASPECTS 3–5) presenting between 0 h and 24 h since stroke onset or last seen well. On the basis of these results, it does not seem justifiable to exclude patients from endovascular treatment based on ASPECTS.[29–31] Besides expanding treatment eligibility for late-window endovascular treatment, we therefore also expect our results to be broadly generalisable to clinical practice. Moreover, our selection method should be easy to implement in daily clinical practice, because our results only call for the distinction between absent (grade 0) and present (grade 1–3) collaterals.

We also need to acknowledge certain limitations. Most patients in our study had an unknown time of symptom onset (eg, in the case of wake-up stroke), although the subgroup analyses on witnessed versus unwitnessed stroke onset and the subgroup analyses on time to treatment (assessed using last seen well and the moment patients first noticed their symptoms) do not seem to imply that treatment effect was driven by patients treated in the early window with unknown stroke onset. Furthermore, a small percentage of patients in our trial did not fulfil the inclusion criteria based on their occlusion location or collateral grade. This is partly due to inter-rater variability, as inclusion criteria were assessed by treating physicians at the time of randomisation, and reported (baseline) imaging variables were scored by the core imaging laboratory. Unfortunately, we are unable to assess the inter-rater variability because no record was kept of the imaging assessment at the time of randomisation.

In conclusion, in this study endovascular treatment was efficacious and safe for patients with ischaemic stroke caused by an anterior circulation large-vessel occlusion who presented 6–24 h from onset or last seen well and had collateral flow on CTA. Our results, in addition to previous literature, support that the selection of patients for endovascular treatment in the late window could be primarily based on the presence of collateral flow.

Contributors

The trial was designed by WHvZ, RJvO, and HFL. All authors contributed to data collection. Data were verified by MAAvW, GJLàN, MU, WJS, P-JvD, BR, JS, JMC, HBvdW, THL, RPHB, EIvD, HDB, MJHW, JHvT, HGJK, RARG, LSFY, J-AV, KFdL, LCvD, IRvdW, JH, JMM, PJAMB, TB, MJMR, TEAMdJ, HMdH, YBWEMR, BJE, BAAMvH, ADR, OEHE, BvdV, DRS, CBLMM, WHvZ, RJvO, DWJD, AvdL, ACGMvE, SGHO, FAVP, WHH, and R-JBG. SGHO, RJvO, WHvZ, and HFL wrote the statistical analysis plan, and DN performed the statistical analysis with input from SGHO, RJvO, WHvZ, and HFL. DN, SGHO, and RJvO had direct access to the data and verified the underlying data reported in the manuscript. SGHO wrote the first draft with input from FAVP, IRdR, JS, RJvO, and WHvZ. All authors contributed to manuscript writing and critical reviewing of the manuscript and had full access to all the study data. All authors had final responsibility for the decision to submit the manuscript for publication.

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Data sharing

With publication, collected data including de-identified participant data and a data dictionary defining each field in the set, will be made available upon reasonable request. Requests can be made by submitting a proposal via the CONTRAST website.

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For the **CONTRAST website** see https://www.contrast-consortium.nl

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