TITLE

Arterial collateral status and treatment effect of intravenous alteplase thrombolysis prior to endovascular treatment in patients with anterior circulation large vessel occlusion: prespecified analysis of the MR CLEAN-NO IV trial

AUTHORS

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ABSTRACT

Background and purpose Collateral blood flow to the affected cerebral territory in acute ischemic stroke may modify the effect of intravenous alteplase treatment (IVT) prior to endovascular treatment (EVT). We assessed whether an interaction effect between arterial collateral status, assessed by both a visual and quantitative collateral score (CS), and administration of IVT plus EVT was present in the MR CLEAN-NO IV trial.

Methods Baseline CT or MR angiography (CTA and MRA) from patients included in MR CLEAN-NO IV was assessed using both a visual and automated quantitative score for arterial collateral status. We included 526 patients with visual CS and 401 with quantitative CS in this prespecified analysis. The primary outcome was functional outcome measured as the modified Rankin Scale score at 90 days. Interaction terms of treatment allocation (IVT plus EVT vs EVT alone) and collateral scores were included in regression models to assess whether the treatment effect of IVT differed by arterial collateral status.

Results IVT plus EVT was not statistically significantly associated with better functional outcome compared with EVT alone (adjusted common odds ratio 1.14; 95% CI 0.84 to 1.55). There was no statistically significant modification of IVT treatment effect on functional outcome by either visual or quantitative CS (adjusted p-interaction=0.34; adjusted p-interaction=0.57, respectively).

Conclusion In the MR CLEAN-NO IV trial, we did not find evidence that arterial collateral status measured with a visual score or quantitative score can inform treatment decisions regarding IVT plus EVT for patients with acute ischemic stroke due to large vessel occlusion in the anterior circulation within 4.5 hours.

INTRODUCTION

Endovascular treatment (EVT) with prior intra-venous alteplase treatment (IVT) has become the standard of care for patients with acute ischemic stroke due to anterior circulation large vessel occlusions without IVT contraindications.1 2 Since IVT was shown to be of limited value in patients with a large vessel occlusion,3 the additional value of IVT is debated and was studied in six recent randomized trials,4–10 including the multicenter randomized clinical trial of direct endovascular treatment versus intravenous alteplase followed by endovascular treatment in patients with acute stroke due to a large vessel occlusion (MR CLEAN-NO IV trial).7 A pooled analysis of all trials failed to demonstrate non-inferiority of EVT alone compared with IVT plus EVT. No evidence of superiority of the

combined strategy was found in the overall population either.10 Thus, it is of interest to further study factors that might modify the effect of IVT in order to further individualize stroke treatment.

Collaterals can provide compensatory blood flow to the cerebral territory affected by an acute vessel occlusion. The treatment effect of EVT on clinical outcomes varied across patients with different collateral grades, with or without significant interaction found in previous studies.11–14 Theoretically, a robust collateral filling may improve delivery of alteplase to the thrombus and promote dissolution.15 Further, it has been suggested that through collaterals, alteplase can reach the capillary bed of the brain territory at risk up to systemic levels, reducing microvascular thrombosis.16 These processes may increase the rate of tissue reperfusion and subsequently improve clinical outcomes after IVT administration in patients with higher degrees of collateral filling.

The aim of this prespecified analysis was to evaluate whether the effect of IVT administration prior to EVT in patients with acute ischemic stroke due to anterior circulation large vessel occlusion presenting directly to an EVT-capable center is modified by collateral filling as assessed on baseline CT angiography (CTA) and MR angiography (MRA) in the MR CLEAN-NO IV trial.

METHODS

Study design and patient selection

We used data from the MR CLEAN-NO IV trial. Details of the study methods and inclusion criteria have previously been reported. In short, the MR CLEAN-NO IV trial was an open-label, multicenter, randomized clinical trial of EVT alone (intervention group) versus IVT plus EVT (control group) in patients with acute ischemic stroke due to large vessel occlusion in the anterior circulation shown on vessel imaging, eligible for EVT and IVT within 4.5 hours after symptom onset. Patients were only included if they presented directly at an EVT-capable center. The MR CLEAN-NO IV trial was conducted with ethical approval from central ethical committees of each participating country (The Netherlands, Belgium, France) and the research boards of each participating center. Deferred informed consent was obtained from all participants. This study was approved by all relevant institutional review boards.

Imaging assessment and collateral scores

We used two methods to determine the degree of collateral filling of the territory affected by the large vessel occlusion on baseline imaging acquired directly prior to randomization: the visual categorical collateral score (CS) by Tan et al based on baseline CTA or MRA17 and an automated quantitative CS (StrokeViewer by Nicolab, Amsterdam, The Netherlands; www. nicolab.com) based on baseline CTA.18 Both scores compared the collateral flow in the affected target downstream territory to the contralateral side. The visual categorical CS ranged from 0 to 3, with a score of 0 indicating absent collaterals (0%), 1 indicating poor collaterals (1–50%), 2 moderate collaterals (51–99%), and 3 good collat-erals (100%). The visual CS was assessed by an independent core laboratory, blinded for treatment allocation and all clinical information, including outcomes. Patients with improper contrast timing, noise, movement, an incomplete field of view, or absent axial angiography images were not included in the visual assessment based on CTA or MRA.

For the quantitative CS, the vessels downstream of the occlusion were segmented, and the ratio of the volume of vessels of the affected side and the contralateral side was

calculated, ranging from 0% to 100%. Only patients with a CTA were included in the automated quantitative assessment, and patients with poor CTA image quality (eg, noise, movement), thick-slice (>2 mm) axial CTA images, incomplete field of view, and incorrectly detected vessel occlusion location were excluded. As the quantitative score was dependent on the occlusion location, one reviewer assessed whether the large vessel occlusion detection by the StrokeViewer software was correct.

Outcome measures

The primary outcome was the distribution of modified Rankin Scale (mRS) score expressing functional outcome, assessed at 90 days. The mRS is an ordinal scale ranging from 0 (no disability) to 6 (death).19 Secondary outcomes included functional independence (mRS 0–2 vs 3–6) at 90 days; National Institutes of Health Stroke Scale (NIHSS) score at 5–7 days20; early recanalization (absence of a treatable occlusion on the initial angiogram); successful reperfusion (extended Thrombolysis in Cerebrovascular Infarction (eTICI) scores of 2b-3 on the final angiogram)21; and final infarct volume on follow-up non-contrast CT or MRI (in milliliters). Safety outcomes were death within 90 days; any intracranial hemorrhage; symptomatic intracranial hemorrhage (sICH) ; hemorrhagic transformation (subtypes) according to the Heidelberg Bleeding Classification22; and stroke progression (defined as neurological deterioration of 4 points or more on the NIHSS, or 2 points or more on one item, not explained by intracranial hemorrhage).

Statistical analysis

Data were analyzed according to the intention-to-treat principle. We reported baseline variables per visual CS. Counts and percentages were reported for categorical variables and medians with 25th and 75th percentiles for (semi)-continuous variables. Baseline variables of dichotomized visual CS (score 0–1 and score 2–3) were also reported.
Visual CS was used in the analyses as a categorical variable, and quantitative CS as a continuous variable. The Spearman rank correlation coefficient assessed the correlation between the visual and quantitative CS. After the quantitative CS was converted into the category of the visual CS, quadratic weighted kappa analysis was calculated to determine the agreement between the visual and categorized quantitative CS.
First, we determined the overall effect of IVT plus EVT compared with EVT alone on the primary outcome in the study population. Then, in patients with available visual CS, we assessed whether the visual CS was associated with the primary outcome. Potential modification of the effect of IVT plus EVT on clinical outcomes by the visual CS was subsequently assessed with the inclusion of multiplicative interaction terms between visual CS and treatment allocation. We also report the effect of IVT plus EVT in subgroups per visual CS, though these analyses were exploratory in case of a non-statistically significant inter-action. Additionally, the potential modification of the treatment effect of IVT plus EVT on all clinical outcomes by the dichotomized visual CS was reported in the online supplemental mate-rial, reducing statistical validity due to the small sample sizes in some subgroups.
For patients with available automated quantitative CS, we assessed the association between the quantitative CS and primary outcome. Since the quantitative CS is a semi-continuous scale (range 0–100%), it allowed us to assess nonlinear associations. To determine whether a nonlinear term improved model fit, we compared logistic regression

models with and without restricted cubic splines using a likelihood ratio test. Nonlinear terms were only used if there was a significantly better model fit compared with nonlinear terms. Subsequently, we assessed the potential modification of the effect of IVT plus EVT on primary outcome by the quantitative CS with the inclusion of multiplicative interaction terms between quantitative CS and treatment allocation. Odds ratios (ORs), common ORs, and beta coefficients with 95% confidence intervals (CIs) were estimated with logistic regression, ordinal logistic regression, and linear regression and reported for dichotomous, ordinal, and continuous outcomes, respectively. The proportional odds assumption was tested and met in the ordinal logistic regression model. All regression analyses were adjusted for age, sex, baseline mRS, time from onset to randomization, occlusion location, presence of carotid tandem lesion, and systolic blood pressure as potential confounders.7 23 Missing data were imputed with multiple imputation by chained equations for the regression analyses only. A two-sided P-value<0.05 was considered statistically significant. All statistical analyses were performed with SPSS software for Windows (version 25.0; IBM Corp., Armonk, NY, USA) and R (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

Five hundred and thirty-six patients from the MR CLEAN-NO IV trial with valid consent were included in this prespecified substudy, with 272 randomized to the EVT alone group and 264 to the IVT followed by EVT group. Visual CS was available in 526 (98%) of all cases, based on CTA (n=512) and MRA (n=14). Baseline characteristics across the visual CS and the dichotomized visual CS subgroups were summarized in table 1 and online supplemental table 1. The automated quantitative CS based on CTA was available in 401 (75%) of 536 patients. Figure 1 shows the patient inclusion flowchart.

Agreement between visual CS and quantitative CS

The correlation between the quantitative and visual CS was strong and statistically significant, with a Spearman □ of 0.66. When turning the quantitative CS into ordinal variables corresponding to the four-point scale of visual CS, the quadratic weighted kappa value was moderate at 0.54 (95% CI 0.41 to 0.66) between the visual and quantitative CS.

Primary outcome

In the overall population, IVT plus EVT was not statistically significantly associated with better functional outcome compared with EVT alone (adjusted common OR 1.14, 95% CI 0.84 to 1.55) (figure 2). Higher visual CS was significantly associated with improved functional outcome (adjusted common OR compared with good collaterals: absent collaterals 0.08, 95% CI 0.03 to 0.17; poor collaterals 0.31, 95% CI 0.20 to 0.49; moderate collaterals 0.76, 95% CI 0.50 to 1.15). We did not observe a significant effect modification between the visual CS and the effect of IVT plus EVT versus EVT alone on functional outcome (unadjusted p-interaction=0.39; adjusted p-interaction=0.34, respectively). Furthermore, we found no evidence of statistically significant differences in functional outcome between patients treated with and without prior IVT in any of the visual CS strata (table 2, figures 2 and 3).

The quantitative CS was also associated with clinical outcome (p<0.0001), and this association was better explained by a nonlinear function (figure 4). Models with a nonlinear term for the quantitative CS (restricted cubic spline with three knots) yielded better fits (p=0.001). This indicated that higher quantitative CS was associated with better functional outcomes in patients who underwent EVT. However, this association was no longer evident with a CS of 78 or higher (figure 4).
Similar to the visual CS, the quantitative CS was not found to significantly modify the effect of IVT plus EVT on functional outcome (unadjusted p-interaction=0.86; adjusted p-interaction=0.57, respectively).

Secondary outcomes
We also did not observe a statistically significant IVT treatment effect modification by visual CS for any of the secondary outcomes (table 2). In patients with a visual CS of 0, a statistically significant effect was observed with smaller final lesion volumes in patients receiving IVT plus EVT than those receiving EVT alone (table 2). However, this result was not reliable due to the limited number of patients in this subgroup and because of the not-significant interaction. No other statistically significant results were observed. The unadjusted and adjusted results were consistent (online supplemental table 4).

Safety outcomes and serious adverse events
There was a statistically significant difference in 90-day mortality across the four and two visual collateral grades, with less mortality for higher grades (p<0.01, table 3 and online supplemental table 3). No significant differences were found per the four and two visual collateral grades for any of the other safety outcomes.

Dichotomized visual CS on primary and secondary outcomes In the exploratory analysis for poor collateral status (visual CS of 0–1) the statistically significant effect was observed with better functional outcome at 90 days and lower NIHSS score at 5–7 days and smaller final lesion volumes in patients receiving IVT plus EVT than those receiving EVT alone. We also did not observe statistically significant IVT treatment effect modification by dichotomized visual CS on all clinical outcomes, either in the unadjusted or adjusted results (online supplemental table 2). Caution should be used in interpreting the significant differences between subgroups.

DISCUSSION
In this prespecified analysis of the MR CLEAN-NO IV trial, we found no statistically significant modification by either visual or quantitative CS on the effect of IVT plus EVT as compared with EVT alone. These results suggest that arterial collateral status does not offer additional value for individualized treatment decisions with regard to IVT administration prior to EVT.
After six recent randomized trials found similar outcomes after EVT alone or IVT plus EVT, investigators have been exploring which factors contribute to the observed treatment effect hetero-geneity.4–7 For example, earlier time from onset to expected IVT administration was shown to be associated with the benefit of prior IVT.24 Previous studies found that arterial collateral status had a significant association with clinical outcomes after IVT, such as tissue reperfusion, functional outcome, and hemorrhagic transformation.25–27 We hypothesized that arterial collateral status could be another

effect modifier and could thereby help identify patients with more or less benefit from IVT plus EVT.

Although higher CTA collateral grades were associated with improved outcomes in this study, in line with previous findings, no statistically significant effect modification of IVT administration prior to EVT by arterial collateral status on the functional outcome was observed.11 28 As such, we did not find evidence for our hypothesis. These results are consistent with the prespecified subgroup analyses of the other randomized trials on this topic.4 7 While the DIRECT-MT subgroup analysis of dichotomous collateral grade suggested potential benefits from IVT administration with better collaterals, no statistically significant interaction was observed. No statistically significant interaction was observed either. A result from the ETIS Registry, an observational, non-randomized trial, indicated that arterial collateral status evaluated by pre-thrombectomy angiogram did not modify the effect of IVT plus EVT.29

Of note, we quantified baseline arterial collateral status in this study with the quantitative CS to assess any interactions between collaterals and IVT administration prior to EVT in a more precise, granular approach. Quantitative CS was nonlinearly correlated with functional outcome. After a certain level, better quantitative CS no longer increased the odds of better outcomes. Still, no interaction was found between the quantitative CS and prior IVT on the functional outcome.

Strengths and limitations

We used randomized data from the MR CLEAN-NO IV trial, enabling analyses without large concerns regarding confounding by indication, in contrast to observational data. Potential confounders for the association between CS and functional outcome were added to our study for a more unbiased estimate. In addition, the CS effect modification analysis was prespecified in the statistical analysis plan of the MR CLEAN-NO IV trial.

Several limitations of our study should be noted. First, 14 of 526 collateral scores assessed by MRA were included in this analysis. Although the percentage is small, it may lead to a bias of the results. Second, approximately 25% of patients were excluded from the quantitative CS analysis, mainly based on imaging requirements. This limits the practical value of automated collateral scoring and may have introduced a selection bias for centers with CT-based, high-quality imaging protocols. Third, single-phase CTA used in this study may lead to an underestimation of the arterial collateral status due to the limited information captured by a snapshot model and could be influenced by contrast timing. Multiphase CTA and dynamic CTA-based collateral scoring could circumvent this problem.30–32 Fourth, interobserver variability of the visual CS could have affected the consistency and generalizability of our results, although a high interobserver agreement was reported by Tan et al.17 Fifth, only patients presenting directly at an EVT-capable center were included in the MR CLEAN-NO IV trial, so our results are not applicable to transfer (drip-and-ship) patients. In these patients, IVT usually has more time to work, and they should receive IVT if eligible before transfer. Finally, our results only include data from the MR CLEAN-NO IV trial, with a limited sample size. Repeating this analysis in the pooled data of all randomized clin-ical trials could offer additional insights.

CONCLUSIONS

In the MR CLEAN-NO IV trial we found no evidence that arterial collateral status modified the effect of IVT prior to EVT on functional outcome, neither for a visual score nor for a

quantitative assessment of arterial collateral status. Arterial collateral status may not be of additional value for individualization of IVT administration prior to EVT for patients with acute large vessel occlusion stroke in the anterior circulation within 4.5 hours.