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Stroke

BRIEF REPORT

Combined Effect of Age and Baseline Alberta Stroke Program Early Computed Tomography Score on Post-Thrombectomy Clinical Outcomes in the MR CLEAN Registry

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BACKGROUND AND PURPOSE: Ischemic brain tissue damage in patients with acute ischemic stroke, as measured by the Alberta Stroke Program Early CT Score (ASPECTS) may be more impactful in older than in younger patients, although this has not been studied. We aimed to investigate a possible interaction effect between age and ASPECTS on functional outcome in acute ischemic stroke patients undergoing endovascular treatment, and compared reperfusion benefit across age and ASPECTS subgroups.

METHODS: Patients with ischemic stroke from the MR CLEAN Registry (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; March 2014–November 2017) were included. Multivariable ordinal logistic regression was performed to obtain effect size estimates (adjusted common odds ratio) on functional outcome (modified Rankin Scale score) for continuous age and granular ASPECTS, with a 2-way multiplicative interaction term (age×ASPECTS). Outcomes in four patient subgroups based on age (< versus ≥ median age [71.8 years]) and baseline ASPECTS (6–10 versus 0–5) were assessed.

RESULTS: We included 3279 patients. There was no interaction between age and ASPECTS on modified Rankin Scale (P=0.925). The highest proportion of modified Rankin Scale 5 to 6 was observed in patients >71.8 years with baseline ASPECTS 0 to 5 (68/107, 63.6%). There was benefit of reperfusion in all age-ASPECTS subgroups. Although the adjusted common odds ratio was lower in patients >71.8 years with ASPECTS 0 to 5 (adjusted common odds ratio, 1.60 [95% CI, 0.66–3.88], n=110), there was no significant difference from the main effect (P=0.299).

CONCLUSIONS: Although the proportion of poor outcomes following endovascular treatment was highest in older patients with low baseline ASPECTS, outcomes did not significantly differ from the main effect. These results do not support withholding endovascular treatment based n a combination of high age and low ASPECTS.

Key Words: odds ratio ■ registries ■ reperfusion ■ thrombectomy ■ tomography

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†A list of all MR CLEAN Registry Investigators is given in the Appendix.

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Nonstandard Abbreviations and Acronyms

ASPECTS	Alberta Stroke Program Early CT Score
EVT	endovascular therapy
MR CLEAN	Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
mRS	modified Rankin Scale
sICH	symptomatic intracranial hemorrhage

Patient age and baseline Alberta Stroke Program Early CT Score (ASPECTS) are both independent predictors of outcome following endovascular therapy (EVT).[1,2] Current American Heart Association/American Stroke Association treatment guidelines restrict their level 1A recommendation for EVT to patients with baseline ASPECTS ≥6. As for age, there is currently no upper limit recommended.

Because of the higher rate of comorbidities, decreased neuronal plasticity,[3] and limited support networks,[4] the impact of ischemic brain tissue damage may be larger for older patients. Possible interaction between age and ASPECTS is not considered in current guidelines and has not been studied yet, although it may be analyzed in future subgroup analyses of the ongoing trials.

We hypothesized there might be an interaction effect between age and ASPECTS on functional outcome in acute ischemic stroke patients with anterior circulation large vessel occlusions undergoing EVT and that the benefit of successful reperfusion is lower in older patients with low ASPECTS.

METHODS

Patients and Imaging

The MR CLEAN Registry (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) is a prospective, multicenter, observational registry that included data on all patients treated with EVT in the Netherlands (see Appendix A in the Data Supplement for more details).[5] Permission from the local ethics board was obtained. The data supporting this study's findings are available from the corresponding author upon reasonable request.

Baseline noncontrast CT, CT-angiography, angiography images, and follow-up CT were centrally assessed by an independent core-laboratory that was blinded to demographic, clinical, and outcome data except for symptom side. ASPECTS (www.aspectsinstroke.com) was scored on baseline noncontrast CT with 1.0- and 5.0-mm slice thickness.

Outcome Measures

The primary outcome was ordinal functional outcome, defined as 90-day modified Rankin Scale (mRS) score. Secondary outcome measures were functional independence (mRS score, 0–2), moderate functional outcome (mRS score, 0–3), poor functional outcome (mRS score, 5–6), mRS score, 5, 90-day mortality (mRS score, 6), and symptomatic intracranial hemorrhage (sICH; death or neurological deterioration of ≥4 points on the National Institutes of Health Stroke Scale with intracranial hemorrhage on follow-up CT). Successful reperfusion was defined as expanded Treatment in Cerebral Infarction score 2b to 3.

Statistical Analysis

Medians and interquartile ranges were reported for patient age and baseline ASPECTS. Logistic regression was performed to obtain adjusted effect size estimates for age and ASPECTS as predictors for primary and secondary outcomes. The analyses were repeated with a multiplicative interaction term between continuous age and granular ASPECTS (age×ASPECTS) to determine possible effect modification of age and ASPECTS on outcomes (see Appendix A in the Data Supplement for more details).

We then formed four subgroups based on median patient age (≥ versus <71.8 years) and baseline ASPECTS (≥ versus <6, based on current American Heart Association/American Stroke Association guidelines). Raw outcomes were reported for all 4 subgroups.

Benefit of successful reperfusion was assessed in each subgroup by obtaining adjusted effect size estimates for successful reperfusion for outcomes in each age/ASPECTS subgroup. In case of nonsignificant interaction, subgroup analyses were exploratory. To assess reliability of observed differences between subgroup from the main effect, 3-way interaction (dichotomized age×dichotomized ASPECTS×successful reperfusion) was tested.

All statistical analyses were performed in Stata 15.1 (StataCorp LLC). All tests were 2-sided and conventional levels of significance (alpha=0.05) were used for interpretation.

RESULTS

Out of 3637 patients included in the MR CLEAN Registry in the specified time period, we included 3279 patients (Table I and Figure I in the Data Supplement).

Interaction Between Age and ASPECTS

No significant interaction between age and ASPECTS was observed on ordinal mRS or dichotomized mRS outcomes (Table II in the Data Supplement). Interaction between age and baseline ASPECTS on sICH was significant (P=0.043). In younger patients, chance of sICH increased minimally with lower ASPECTS. For older patients, however, there was a greater increase in sICH chance (per ASPECTS point increase in patients <71.8 years: adjusted odds ratio, 1.08 [95% CI, 0.95–1.05]; compared with patients ≥71.8 years: adjusted odds ratio, 0.92 [95% CI, 0.83–1.03]).

Stratified Outcomes

Clinical outcomes were worse in patients with low baseline ASPECTS (Figure; Table II in the Data Supplement). In both ASPECTS subgroups, outcomes in patients over

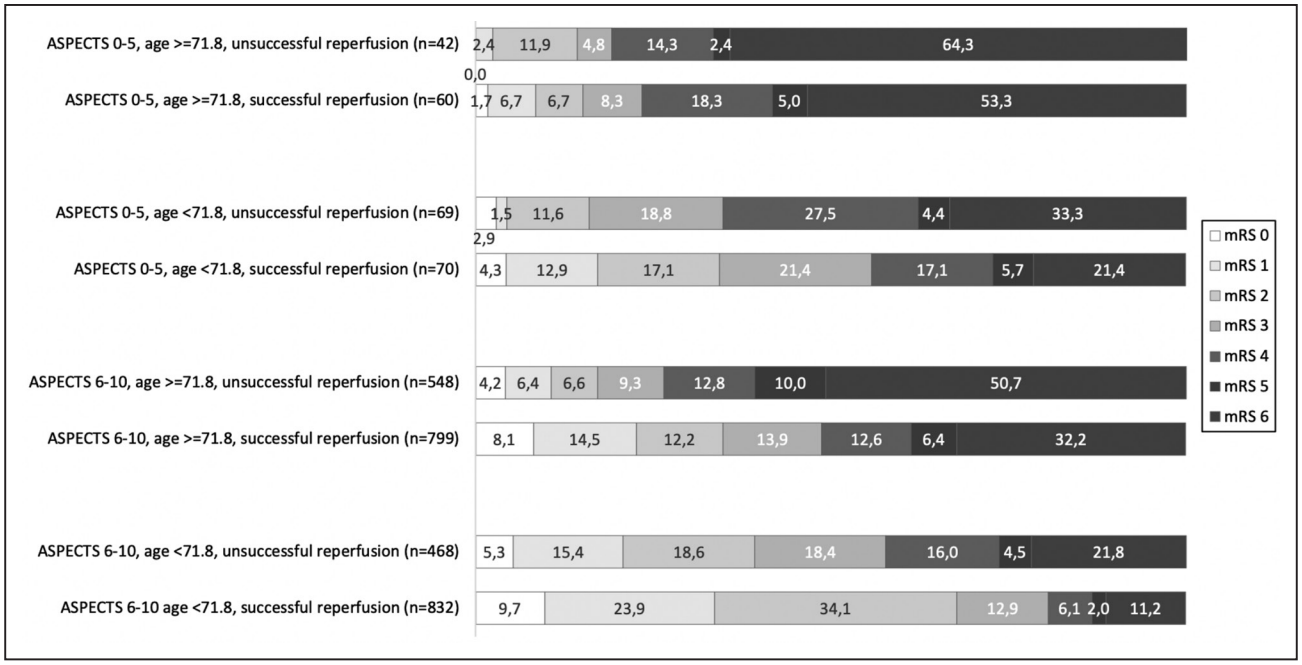

Figure. Ninety-day modified Rankin Scale (mRS) score for age–Alberta Stroke Program Early CT Score (ASPECTS) subgroups, by reperfusion status.
Numbers in bars are percentages. Successful reperfusion: expanded treatment in cerebral infarction score 2B–3.

71.8 years were worse compared with younger patients. Successful reperfusion rates were similar across the 4 groups (53.9%–64.5% expanded Treatment in Cerebral Infarction 2b/3, 31.2%–41.8% expanded Treatment in Cerebral Infarction 2c/3), whereas sICH occurred more often in patients over 71.8 years with low baseline ASPECTS (8.2%) than in the other groups (5.7%–6.4%; Table III in the Data Supplement).

Benefit of Reperfusion

Three-way interaction between dichotomized age, dichotomized ASPECTS, and successful reperfusion for ordinal mRS (P=0.299), functional independence (P=0.214), poor functional outcome (P=0.628), mortality (P=0.530), or sICH (P=0.753) indicated no significant difference of reperfusion benefit among subgroups. Hence, all subgroup analyses regarding reperfusion benefit were exploratory. All 4 age-ASPECTS subgroups showed benefit of reperfusion (Table IV in the Data Supplement). Although this benefit was not significant in older patients with ASPECTS 0 to 5 (n=110), the point estimate was in the direction of benefit. A shift away from mRS score of 5 to mRS scores of 6 and 0 to 4 seemed present with reperfusion in patients with high ASPECTS, with a slightly larger shift in older than younger patients (Figure II and Table IV in the Data Supplement).

DISCUSSION

This study suggests that EVT should not be withheld in patients based on high age and low ASPECTS. All predefined subgroups showed benefit of reperfusion, and although the beneficial effect of successful reperfusion seemed attenuated in older patients with low ASPECTS, results of subgroups did not significantly differ from the main effect.

Our results are the first to report on a possible interaction effect between age and ASPECTS. Although biologically plausible, we could not confirm the hypothesis that older patients would have less reserve to recover from ischemic brain tissue damage, and would hence have poorer outcomes than their younger counterparts for the same ASPECTS.

Interestingly, although mortality rates were high in elderly patients, the proportion of mRS score of 5, often considered a worse outcome than death and the outcome associated with the highest healthcare costs,[6] was relatively low (8% in the ASPECTS 6–10 group and 6% in the ASPECTS 0–5 group), suggesting that EVT could potentially shift patients away from mRS score of 5. This effect was mostly present in patients with baseline ASPECTS 6 to 10 and more pronounced in older patients.

We found a significant interaction between age and ASPECTS on sICH as outcome. This could be an observation due to chance and multiple testing, although age-related changes in the cerebral vascular architecture[7] may increase the hemorrhage risk in low ASPECTS patients.

All age-ASPECTS subgroups showed benefit of reperfusion. Although the high age-low ASPECTS group effect size estimates did not reach statistical significance for any of the outcome measures, reperfusion benefit was not significantly different from the main effect.

Whether such differences really exist should be investigated further in large prospective studies.

Limitations

Our study has limitations. First, our patient sample included few patients in the high age-low ASPECTS group. Second, a possible selection bias could have led to inclusion of relatively fitter old patients. Third, MR CLEAN Registry enrollment comprises several years. With newer devices, reperfusion rates may have improved over time. Fourth, multiple testing effects should be taken into account in the age-ASPECTS interaction on sICH. Finally, the mRS distribution will likely continue to change after the 90-day cutoff, especially for patients with mRS score of 5.

Conclusions

The proportion of poor outcomes following EVT was highest in elderly patients with low baseline ASPECTS. However, benefit of reperfusion in patients with high age and low ASPECTS was not significantly different from the main effect. The current data do not justify withholding EVT based on combined high age and low ASPECTS.

ARTICLE INFORMATION

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Disclosures

Dr Postma reports institutional grants (Siemens, Bayer). Dr Yoo reports the following: personal (Cerenovus, Penumbra, Genentech), equity interest (Insera Therapeutics, Inc, Galaxy Therapeutics, Inc), institutional (Medtronic, Stryker). Dr van der Lugt reports the following grant: institutional (Stryker, Penumbra, Cerenovus, Medtronic). Dr Majoie reports the following: institutional (European Commission, Toegepast Wetenschappelijk Instituut voor Neuromodulatie [TWIN], Stryker, CVON/Dutch Heart Foundation, Dutch Health Evaluation) and shareholder (Nico lab). Dr Goyal reports the following grant: personal (Medtronic, Stryker, Microvention, Mentice). Dr LeCouffe is a coordinating investigator MR CLEAN-NO IV. Dr van Zwam reports the following grant: personal (Stryker, Cerenovus). Dr Roos is a shareholder (Nico lab). The other authors report no conflicts.

APPENDIX

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REFERENCES

1. Goyal M, Menon BK, Coutts SB, Hill MD, Demchuk AM; Penumbra Pivotal Stroke Trial Investigators, Calgary Stroke Program, and the Seaman MR Research Center. Effect of baseline CT scan appearance and time to recanalization on clinical outcomes in endovascular thrombectomy of acute ischemic strokes. *Stroke*. 2011;42:93–97. doi: 10.1161/STROKEAHA.110.594481
2. Castonguay AC, Zaidat OO, Novakovic R, Nguyen TN, Taqi MA, Gupta R, Sun CH, Martin C, Holloway WE, Mueller-Kronast N, et al. Influence of age on clinical and revascularization outcomes in the North American Solitaire Stent-Retriever Acute Stroke Registry. *Stroke*. 2014;45:3631–3636. doi: 10.1161/STROKEAHA.114.006487
3. Sharma JC, Fletcher S, Vassallo M. Strokes in the elderly - higher acute and 3-month mortality - an explanation. *Cerebrovasc Dis*. 1999;9:2–9. doi: 10.1159/000015889
4. Saposnik G, Cote R, Phillips S, Gubitz G, Bayer N, Minuk J, Black S; Stroke Outcome Research Canada (SORCan) Working Group. Stroke outcome in those over 80: a multicenter cohort study across Canada. *Stroke*. 2008;39:2310–2317. doi: 10.1161/STROKEAHA.107.511402
5. Jansen IGH, Mulder MJHL, Goldhoorn RB; MR CLEAN Registry Investigators. Endovascular treatment for acute ischaemic stroke in routine clinical practice: prospective, observational cohort study (MR CLEAN Registry). *BMJ*. 2018;360:k949. doi: 10.1136/bmj.k949
6. Dawson J, Lees JS, Chang TP, Walters MR, Ali M, Davis SM, Diener HC, Lees KR; GAIN and VISTA Investigators. Association between disability measures and healthcare costs after initial treatment for acute stroke. *Stroke*. 2007;38:1893–1898. doi: 10.1161/STROKEAHA.106.472381
7. Leenders KL, Perani D, Lammertsma AA, Heather JD, Buckingham P, Healy MJ, Gibbs JM, Wise RJ, Hatazawa J, Herold S. Cerebral blood flow, blood volume and oxygen utilization. Normal values and effect of age. *Brain*. 1990;113 (pt 1):27–47. doi: 10.1093/brain/113.1.27