Journal of Stroke and Cerebrovascular Diseases 34 (2025) 108245

Contents lists available at ScienceDirect

Journal of Stroke and Cerebrovascular Diseases

journal homepage: www.elsevier.com/locate/jstroke

Thrombolysis in lacunar stroke: Comparison of early neurological improvement and 90-day functional outcome with cardioembolic stroke without large-vessel occlusion

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ARTICLE INFO

Keywords:
Lacunar stroke
Cardioembolic stroke
Thrombolysis
Early neurological improvement

ABSTRACT

Introduction: Thrombolysis (IVT) is effective in the treatment of lacunar stroke (LAC). However, most studies compared the outcome of LAC to a heterogenous control group. We aimed to compare early neurological improvement (ENI) and late functional outcomes following thrombolysis for LAC with a homogenous control group of cardioembolic stroke (CE) without large-vessel occlusion (LVO).

Patients and methods: Patient data were obtained from the national multicentre STAY ALIVE Acute Stroke Registry. At each centre, a team of vascular neurologists determined the TOAST classification. ENI was defined as a minimum 4-point decrease in the NIHSS score between admission and discharge, or a complete resolution of symptoms. For late functional outcome, we analysed the dichotomised 90-day mRS scores (good outcome was mRS≤2).

Results: 142 LAC and 156 CE patients were analysed. Following IVT, the percentage of ENI did not differ significantly (LAC 41.1% vs CE 49.7%, p=0.154), and multivariable analysis did not identify any clinical parameters that would predict ENI after IVT in either group. LAC patients had unfavourable, albeit non-significant, odds of having good 90-day functional outcomes compared to CE patients (aOR 0.483, 95% CI 0.201-1.161, p=104).

Conclusions: We report the first analysis of short- and long-term outcomes of IVT in LAC, using a homogenous control group of CE patients without LVO. The prevalence of ENI and 90-day functional outcomes were similar. However, LAC patients had unfavourable odds of achieving good functional outcomes compared to the control group. Therefore, we emphasise that LAC should not be considered a minor stroke subtype.

Abbreviations: aOR, adjusted odds ratio; CE, cardioembolic stroke; CI, confidence interval; CTA, computer tomography angiography; END, early neurological deterioration; ENI, early neurological improvement; HT, haemorrhagic transformation; IQR, interquartile range; IVT, intravenous thrombolysis; LAC, lacunar stroke; LVO, large-vessel occlusion; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NORSTROKE, Norwegian Stroke Research Registry; NIHSS, National Institute of Helath Stroke Scale; NINDS, Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study; SD, standard deviation; TOAST, Trial of Org 10172 in Acute Stroke Treatment; WAKE-UP, Efficacy and Safety of MRI-based Thrombolysis in Wake-up Stroke.

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https://doi.org/10.1016/j.jstrokecerebrovasdis.2025.108245
Received 25 August 2024; Received in revised form 13 January 2025; Accepted 17 January 2025
Available online 29 January 2025

Introduction

Lacunar strokes (LAC) are caused by occlusion of small perforating arteries and account for 15-25 % of all ischaemic strokes.[1, 2] By definition, their diameter is smaller than 20 mm on imaging in an axial plane.[3] Due to their small size and lack of cortical involvement, they usually have milder clinical presentations compared to strokes caused by large-artery atherosclerosis or cardioembolic origin.[4, 5] The pathogenesis of lacunar strokes can be explained by lipohyalinosis of small perforating arteries, branch atheromatous disease or microembolisation.[1, 6]

Although lacunar strokes are usually not caused by a fibrin-rich thrombus, intravenous thrombolysis (IVT) has been shown to be effective in such cases in observational studies, post-hoc subgroup analysis of randomised clinical trials and meta-analysis.[7-10] However, in most studies, the efficacy of IVT in LAC was compared to a heterogenous control group of IVT-treated non-LAC patients.

Our study aimed to better understand the potential beneficial effects of IVT in LAC and predictors of outcome. Therefore, we compared the efficacy of IVT in LAC patients with a homogenous control group of cardioembolic stroke (CE) cases without large-vessel occlusion (LVO). We set out to analyse early neurological improvement (ENI) and 90-day functional outcomes in both groups.

Patients and methods

Patients

Patient data were obtained from the national, multicentre STAY ALIVE Acute Stroke Registry, funded by the Economic Development and Innovation Operative Programme Grant (GINOP 2.3.2-15-2016-00048).[11] Data in the Registry were prospectively collected. All patients or their legal representatives gave informed consent before inclusion in the Registry, and our study was conducted according to the revised Declaration of Helsinki. All patients in our study received IVT with alteplase, which was carried out in accordance with national guidelines.[12] The following data were collected from each patient, where available: demographic characteristics, vascular risk factors, medications pre-stroke, stroke severity (measured by the National Institute of Health Stroke Scale [NIHSS] score) on admission and at discharge, baseline clinical and laboratory parameters, acute and follow-up brain imaging, 90-day functional outcome (measured by the mRS score), stroke and IVT-related serious adverse events and complications (including haemorrhagic transformation, HT). HT was considered symptomatic if the discharge NIHSS score was lower by at least 4 points than the admission NIHSS score.[13] We also analysed early neurological deterioration (END) based on the admission and discharge NIHSS scores. END was present if the NIHSS score decreased by at least 2 points.[14] At each centre, a team of vascular neurologists determined the TOAST classification when imaging and clinical data were entered into the Registry.[15] Our analysis only included patients with LAC and CE without LVO. We excluded LVO cases to focus on the impact of IVT alone, because mechanical thrombectomy is not a treatment option in LAC. We also excluded patients with a pre-stroke mRS>2.

Outcome measures

We analysed baseline and discharge NIHSS and mRS scores 90 days after stroke. We defined ENI similar to the Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study (NINDS) criteria: a minimum 4-point decrease in the NIHSS score between admission and discharge, or a complete resolution of symptoms.[16] For late functional status, we dichotomised 90-day mRS scores into good (mRS≤2), and poor (mRS>2) outcomes.

Statistical analysis

The distribution of continuous variables was tested with the Shapiro-Wilk test. Normally distributed variables were expressed as mean ± standard deviation (SD), and non-normally distributed data as median and interquartile range (IQR). Comparison of continuous variables between LAC and CE groups was made using independent samples t-test for normally distributed data and Mann-Whitney U test for non-parametric data. Pearson's chi-squared test of independence or Fisher's exact test was applied to compare categorical variables. Statistical significance was met when the p-value was <0.05.

The outcome measures of ENI and 90-day mRS were categorical variables. We first applied a univariable binary regression approach in both LAC and CE patient groups to analyse the association between ENI and other clinical parameters. Associations where the p-value was <0.1 (atrial fibrillation, smoking and pre-stroke antiplatelet therapy for LAC, and malignancy and admission glucose for CE) were entered into a multivariable regression model. Statistical significance in the multivariable model was met if the p-value was <0.05.

Furthermore, we used a multivariable binary regression analysis to investigate the connection between ENI and good functional outcomes on the 90-day mRS score with LAC or CE subtypes. We included variables in the model that significantly differed between the two groups (age, smoking, malignancy, atrial fibrillation, coronary artery disease, anticoagulation, systolic blood pressure, baseline NIHSS, door-to-imaging time and door-to-needle time). Statistical significance was met when the p-value was <0.05. Adjusted odds ratios (aOR) and 95% confidence intervals (95% CI) were calculated. Forest plots were drawn to summarise the results. All statistical analyses were performed with IBM SPSS version 22 statistical software (SPSS Inc., Chicago, USA).

Results

At the time of data analysis, the STAY ALIVE Acute Stroke Registry contained 1491 patients. We excluded patients with Trial of Org 10172 in Acute Stroke Treatment (TOAST) classifications of large-artery atherosclerosis, other determined aetiology and undetermined aetiology. Furthermore, we excluded patients with baseline mRS>2, as we aimed to analyse good functional outcomes, defined as mRS≤2. Finally, we excluded CE patients who had LVO. Our final study population included 142 LAC and 156 CE patients. Among the final 298 patients in the study, 114 did not have a pre-stroke mRS recorded in the registry. However, among those with a reported pre-stroke mRS, a score of >2 was very uncommon. Therefore, we did not exclude patients without a pre-stroke mRS from the analysis. Fig. 1 demonstrates the flowchart of patient selection. Seventeen patients in the CE group had distal middle cerebral artery occlusions, one anterior cerebral artery and one vertebral artery occlusion. We did not exclude these patients as, for the time being, there is lack of evidence supporting thrombectomy in these cases. Table 1 presents the demographic, clinical, imaging, and outcome data of our study population. CE patients were significantly older (median age 67.5 [IQR 60.0-74.0] for LAC patients versus 75.0 [IQR 65.0-80.0] for CE patients, $p<0.001$). Smoking prevalence was higher in LAC patients (37.3% versus 19.8%, p=0.001). As expected, atrial fibrillation (7.0% versus 63.5%, p<0.001), coronary artery disease (17.6% versus 30.8%, p=0.010) and pre-stroke anticoagulant treatment (2.2% versus 27.5%, p<0.001) were more common in the CE group. Malignancy was also significantly more prevalent in the CE group (8.0% versus 15.6%, p=0.048). Mean admission systolic blood pressure was significantly higher among LAC patients (172.0±27.2 versus 164.9±26.7 mmHg, p=0.025). Median NIHSS scores at baseline were higher in the CE group (5.0 [IQR 4.0-7.0] versus 7.0 [IQR 4.0-9.0], p=0.007). Median door-to-imaging (14.0 min [IQR 6.0-28.0] versus 25.0 min [IQR 11.0-36.0], p<0.001) and door-to-needle times (52.0 min [IQR 36.5-72.0] versus 64.0 min [IQR 47.0-86.8], p=0.004) were longer in cases of CE. Significantly more computer tomography angiography (CTA) was done

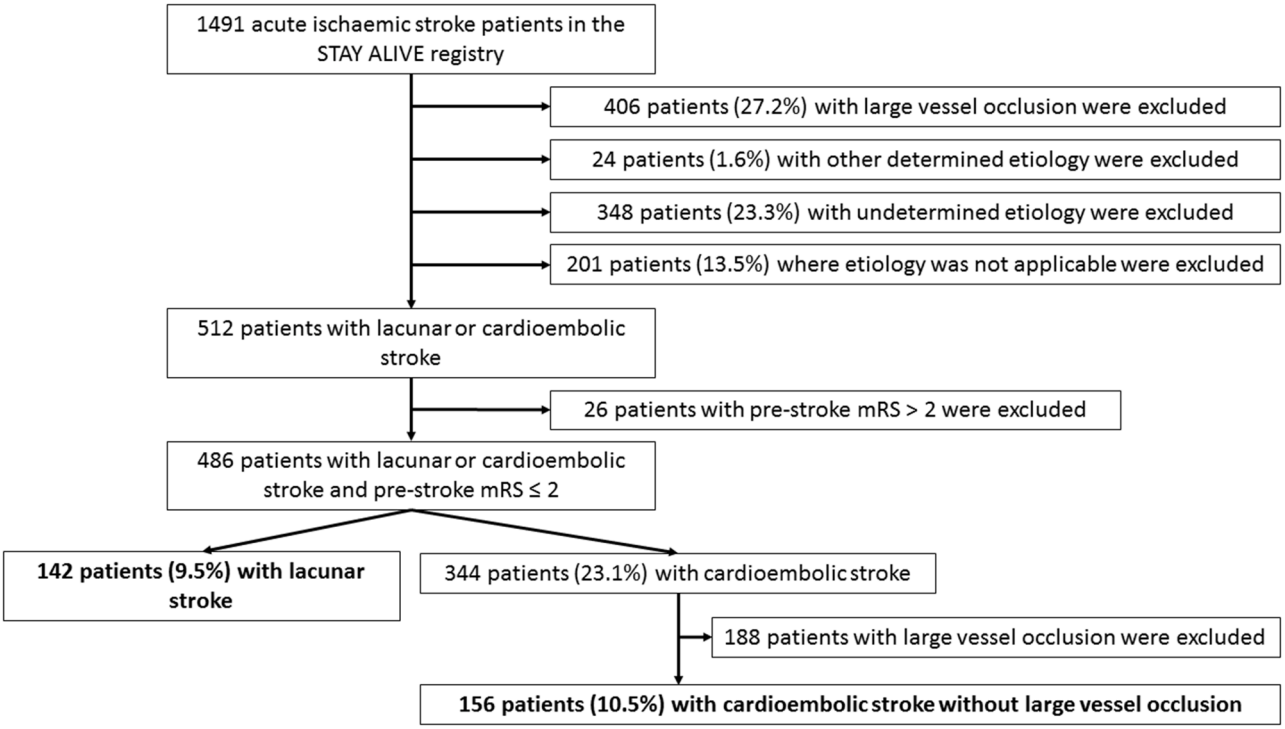

Fig. 1. Flowchart of patient selection for our study from the STAY ALIVE Acute Stroke Registry.

in CE patients (64.1% versus 79.5%, p=0.003), and more non-contrast CTs were performed in the LAC group (26.8% versus 11.5%, p=0.001). A numerical trend toward favouring follow-up magnetic resonance imaging (MRI) was observed in the LAC group (9.9% versus 5.1%, p=0.119).

Regarding outcomes, there was no significant difference between the prevalence of ENI between the two groups (LAC 41.1% versus CE 49.7%, p=0.154). The median NIHSS score at discharge was non-significantly lower in the LAC group (2.0 [IQR 1.0-5.0] versus 3.0 [IQR 1.0-6.0], p=0.310). Median mRS scores at 90 days were similar (LAC 1.0 [IQR 0.0-2.0] versus CE 1.0 [IQR 0.0-2.0], p=0.414). The detailed distribution of mRS scores is presented in Fig. 2. 76.7% and 76.4% of LAC and CE patients achieved good functional outcomes (p=0.943). Adverse events (which included respiratory and urinary tract infections, gastrointestinal bleeding, deep vein thrombosis, acute coronary syndrome, sepsis, acute heart failure, agitation and delirium) were significantly more prevalent in the CE group than in the LAC group (6.5% versus 13.6%, p=0.045). Thrombolysis-related complications (allergic reaction, anaphylaxis, minor and major extra- and intracranial bleeding) were similar in the two groups. (6.3% versus 5.9%, p=0.870).

We analysed which pre-stroke vascular risk factors or other clinical parameters influence ENI. In the univariable analysis, ENI in LAC patients was associated with smoking, atrial fibrillation and pre-stroke antiplatelet treatment (detailed results are presented in the **Supplementary material**). However, the multivariable analysis did not demonstrate a significant association between any parameters and ENI.

In patients with CE, univariable analysis showed an association of ENI with malignancy and admission blood glucose (detailed results are also presented in the **Supplementary material**). However, in the multivariable analysis, none of the variables remained significantly associated with ENI.

In multivariable regression analysis, smoking (aOR 0.407, 95% CI 0.203-0.818, p=0.012) and atrial fibrillation (aOR 0.420, 95% CI 0.203-0.818, p=0.030) were negative predictors of ENI, whereas higher NIHSS scores were associated with ENI (aOR 1.159, 95% CI 1.060-1.268, p=0.001). LAC patients had an unfavourable trend of not achieving ENI compared to CE patients (aOR 0.539, 95% CI 0.264-1.099, p=0.089). The results of the multivariable regression analysis are presented in the forest plot in Fig. 3.

Regarding 90-day outcomes, LAC patients had non-significantly lower odds of achieving good functional outcomes compared to CE patients (aOR 0.483, 95% CI 0.201-1.161, p=104). We found no variables significantly associated with good functional outcomes at 90 days. The results of the multivariable analysis are summarised as a forest plot in Fig. 4.

Discussion

The vascular risk profile of LAC and CE patients differed significantly in our study. CE patients were significantly older. It is well known that the prevalence and incidence of atrial fibrillation and coronary artery disease increase with age.[17, 18]

The prevalence of smoking was higher in LAC patients. Previously, Sacco et al. have reported a higher proportion of cigarette smoking in LAC patients compared to non-LAC patients.[2] A Mendelian randomisation analysis also confirmed an association between smoking and LAC.[19]

As expected, pre-stroke atrial fibrillation, coronary artery disease and prophylactic anticoagulant treatment were more common in the CE group. Malignancy was also significantly more prevalent in the CE group. Embolic-appearing ischaemic stroke is common in tumour-associated cases.[20] Therefore, it can be challenging to decide the aetiology of an embolic-appearing infarct in a cancer patient who also has a potential cardioembolic source. In the Bergen Norwegian Stroke Research Registry (NORSTROKE) Study, 32.7% of ischaemic stroke patients with cancer also had a cardioembolic origin according to the TOAST criteria.[21] In the STAY ALIVE Acute Stroke Registry, the TOAST subtype was determined at the discretion of the treating neurologists.

Mean admission systolic blood pressure was significantly higher among LAC patients. It is well-known that hypertension is one of the most common risk factors in patients with LAC.[1]

Based on our results, LAC patients present with milder stroke symptoms compared to CE patients without LVO. In the study by Mustanoja et al., patients with LAC also had less severe strokes than CE

Table 1
Demographics, clinical characteristics and outcome of the study population.

	Lacunar stroke (n = 142)	Cardioembolic stroke (n = 156)	p-value
Median age (IQR) - year	67.5 (60.0-74.0)	75.0 (65.0-80.0)	**<0.001**
Male sex (%)	78 (54.9%)	85 (54.5%)	0.939
Relevant medical history, vascular risk factors			
Hypertension	122 (87.8%, n=139)	138 (89.0%, n=155)	0.735
Hyperlipidaemia	87 (64.4%, n=135)	89 (60.5%, n=147)	0.499
Diabetes mellitus	55 (39.9%, n=138)	52 (34.0%, n=153)	0.300
Smoking	53 (37.3%)	31 (19.9%)	**0.001**
Excess alcohol consumption	40 (29.6%, n=135)	40 (29.0%, n=138)	0.907
Atrial fibrillation	10 (7.0%)	99 (63.5%)	**<0.001**
Malignancy	11 (8.0%, n=137)	24 (15.6%, n=154)	**0.048**
Previous cerebrovascular event	32 (23.4%, n=137)	39 (25.2%, n=155)	0.720
Coronary artery disease	23 (17.6%, n=131)	45 (30.8%, n=146)	**0.010**
Preventive treatment before stroke			
Anticoagulant	3 (2.2%, n=139)	42 (27.5%, n=153)	**<0.001**
Antiplatelet	53 (37.6%, n=141)	54 (35.3%, n=153)	0.683
Lipid-lowering	29 (20.7%, n=140)	45 (29.0%, n=155)	0.100
Clinical parameters on admission			
Median blood glucose (IQR) - mmol/l	7.0 (5.9-8.1, n=92)	7.05 (5.7-8.5, n=76)	0.654
Mean systolic blood pressure ± SD – Hgmm	172.0±27.2	164.9±26.7	**0.025**
Median diastolic blood pressure (IQR) - Hgmm	91.0 (80.0-102.5, n=141)	90.0 (80.0-100.0, n=151)	0.321
Median C-reactive protein (IQR) - mg/l	3.5 (2.0-7.5, n=136)	3.2 (1.7-6.5, n=147)	0.174
Median white cell count (IQR) - G/l	8.1 (6.6-9.9, n=137)	8.2 (6.9-9.7)	0.807
Median pre-stroke mRS score (IQR)	0.0 (0.0-1.0, n=83)	0.0 (0.0-1.0, n=101)	0.574
Median NIHSS score on admission (IQR)	5.0 (4.0-7.0, n=141)	7.0 (4.0-9.0, n=152)	**0.007**
Time intervals			
Median door-to-imaging time (IQR) - min	14.0 (6.0-28.0, n=137)	25.0 (11.0-36.0, n=151)	**<0.001**
Median door-to-needle time (IQR) - min	52.0 (36.5-72.0, n=141)	64.0 (47.0-86.8, n=152)	**0.004**
Median symptom onset to needle time (IQR) - min	142.5 (114.5-190.0, n=130)	141.0 (109.3-182.5, n=138)	0.478
Median length of hospital stay (IQR) - day	5.0 (3.9-6.7)	5.1 (3.9-8.0, n=155)	0.359
Imaging			
Imaging on arrival			
Non-contrast enhanced CT	38 (26.8%)	18 (11.5%)	**0.001**
CTA	91 (64.1%)	124 (79.5%)	**0.003**
MRI	13 (9.2%)	14 (9.0%)	0.957
Follow-up imaging			
Non-contrast-enhanced CT	125 (88.0%)	147 (94.2%)	0.058
CTA	3 (2.1%)	1 (0.6%)	0.350
MRI	14 (9.9%)	8 (5.1%)	0.119
Outcome			
Median NIHSS score at discharge (IQR)	2.0 (1.0-5.0, n=129)	3.0 (1.0-6.0, n=148)	0.310
Complications of thrombolysis	11 (7.7%)	17 (11.1%, n=153)	0.325
Haemorrhagic transformation	2 (1.4%)	9 (5.8%)	0.064
Symptomatic haemorrhagic transformation	2 (1.4%)	0 (0%)	0.226
Serious adverse event	9 (6.5%, n=139)	21 (13.6%, n=155)	**0.045**
Early neurological improvement according to NINDS criteria	53 (41.1%, n=129)	73 (49.7%, n=147)	0.154
Early neurological deterioration	15 (11.6%, n=129)	14 (9.5%, n=147)	0.570
Median mRS score at 90 days (IQR)	1.0 (0.0-2.0, n=116)	1.0 (0.0-2.0, n=131)	0.414
Good functional outcome at 90 days (%)	89 (76.7%, n=116)	100 (76.4%, n=131)	0.943

patients (median baseline NIHSS scores were 7 [IQR 4.5-10] vs. 11 [IQR 7-17], respectively).[22] However, it is worth highlighting that CE patients with LVO were not excluded in their study. In the post-hoc analysis of the Efficacy and Safety of MRI-based Thrombolysis in Wake-up Stroke (WAKE-UP) trial, where eligibility for endovascular therapy was a contraindication for study enrollment, LAC patients had significantly lower median baseline NIHSS scores than non-LAC participants (5 versus 6, p<0.001).[10] A novelty of our study is that we compared LAC to a homogenous control group in which IVT is known to be efficacious. However, it should be mentioned that data in our Registry might have been biased towards including patients with the most severe LAC symptoms, who were more likely to receive IVT compared to LAC patients with very minor symptoms.

After IVT, the two groups in our study showed similar rates of ENI using the NINDS trial definition. It seems paradoxical that ENI was significantly associated with higher NIHSS scores. Since the median NIHSS scores were relatively low, using the NINDS criteria might not have been the best measure of ENI. In the pivotal NINDS trial, no benefit of IVT was observed compared to placebo in terms of ENI.[16] Unfortunately, the definition of ENI varies significantly in the literature.[23-26] An interesting finding of our study is that LAC patients had an unfavourable trend of not achieving ENI compared to CE patients (p=0.089). This trend could point to IVT being more efficacious in the lysis of relatively small cardioembolic clots compared to its effect in LAC.

Median door-to-imaging and door-to-needle times were longer in cases of CE. These findings may result from significantly more CTAs in CE patients with higher NIHSS scores (to identify LVOs). More non-contrast CTs were performed in the LAC group with lower NIHSS scores.

We analysed whether admission systolic blood pressure or blood glucose levels were independently associated with ENI in LAC. Multivariable regression analysis did not reveal any significant association between ENI and pre-stroke vascular risk factors or clinical parameters in either group.

Based on data from our Registry, significantly more serious adverse events occurred in the CE group. The possible explanation behind this finding is that CE patients were older and had a higher prevalence of heart disease and malignancy.

Regarding long-term outcomes, functional independence was similar in LAC patients compared to CE patients without LVO, 90 days after IVT. However, in the multivariable analysis, LAC patients had worse, albeit non-significant, odds of functional independence, which is a new finding not previously reported. A meta-analysis including 4610 LAC patients and 8451 non-LAC patients demonstrated significantly higher odds for LAC patients to achieve a mRS score of 0-2, 3 months after IVT (aOR 1.12, 95% CI 1.03-1.22, p=0.025).[7] However, this meta-analysis included a heterogenous IVT-treated control group of all non-LAC subtypes of ischaemic stroke patients. Mustanoja et al. reported an independent association between small vessel disease and better 90-day outcomes.[22] They reported that only 52% of CE patients had good

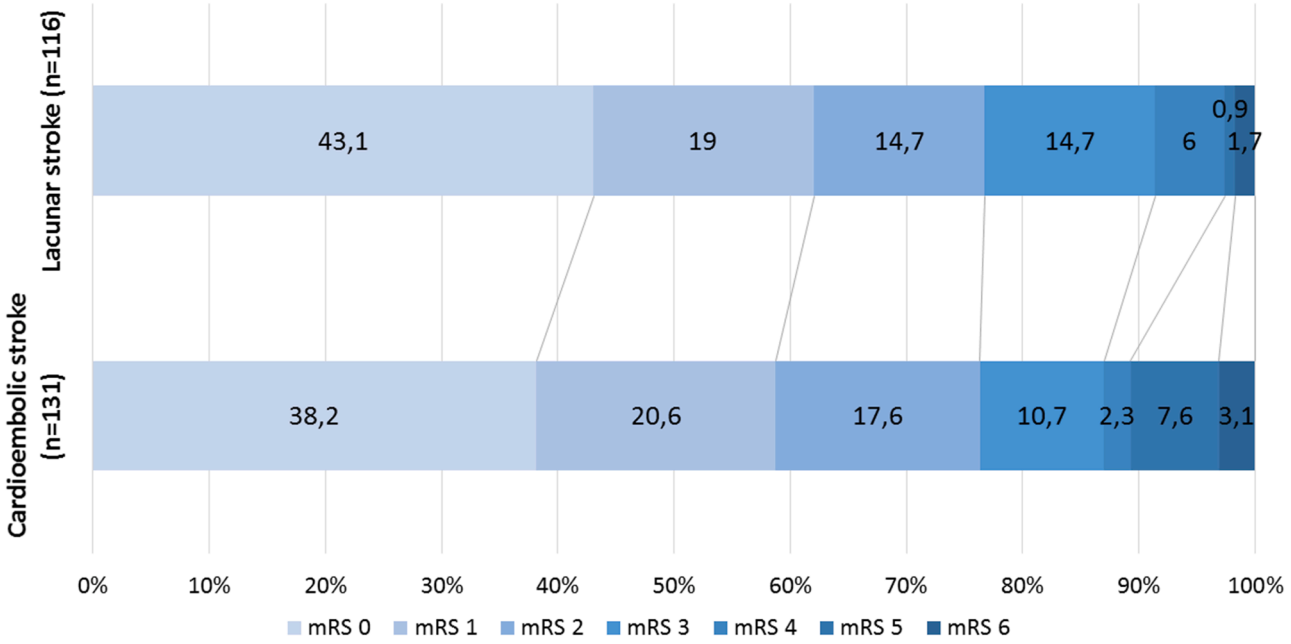

Fig. 2. Distribution of modified Rankin Scale scores 90 days after stroke (numbers in each box highlight percentages).

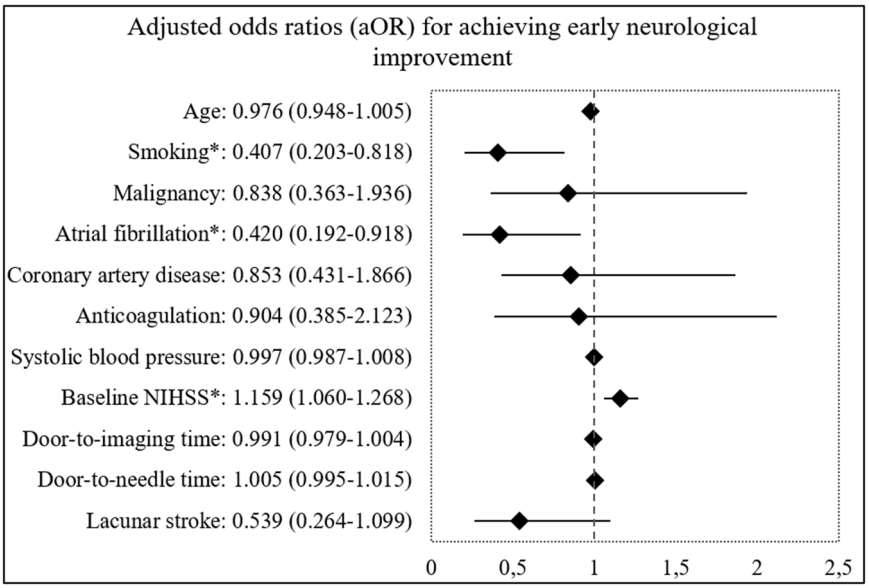

Fig. 3. Forest plot of the binary, multivariable regression analysis demonstrating the adjusted odds ratios (aOR) for achieving early neurological improvement. The diamonds and black lines represent the adjusted odds ratios and 95% confidence intervals.
* Statistically significant association ($p<0.05$)

functional outcomes (mRS≤2). Patients with LVO were included, as thrombectomy was not a treatment option at the time of that study. The rate of good functional outcomes of LAC patients (82%) was similar to our results (76.7%). A limitation of our study is that many patients did not have pre-stroke mRS reported. A few patients might have had a baseline mRS2. However, due to their very low numbers, we do not believe the possible inclusion of such patients had significantly distorted our results.

In our study, only 9.1% of all patients had MRI scans before IVT and 7.4% following treatment. Therefore, in most cases, LAC subtype was determined based on clinical findings (symptoms presenting as classical lacunar syndromes) and CT imaging, which might have led to the misclassification of small embolic strokes not visible on CT as LAC, and vice versa. Previous studies have reported that approximately a fifth of stroke patients have a clinical-imaging dissociation.[27-29]

In a secondary post hoc analysis of the MRI-based WAKE-UP trial, which included 108 patients, 90-day outcomes after IVT were similar in LAC and non-LAC patients. LAC patients had a numerically higher proportion of favourable outcomes, defined as mRS 0-1.[10]

Based on data from the Austrian Stroke Unit Registry, LAC patients had better short-term and 90-day functional outcomes than non-LAC patients, irrespective of IVT.[8] This finding remained the same in a subgroup analysis of this study where MRI-confirmed lacunar infarcts were compared with matched patient groups (n=229).

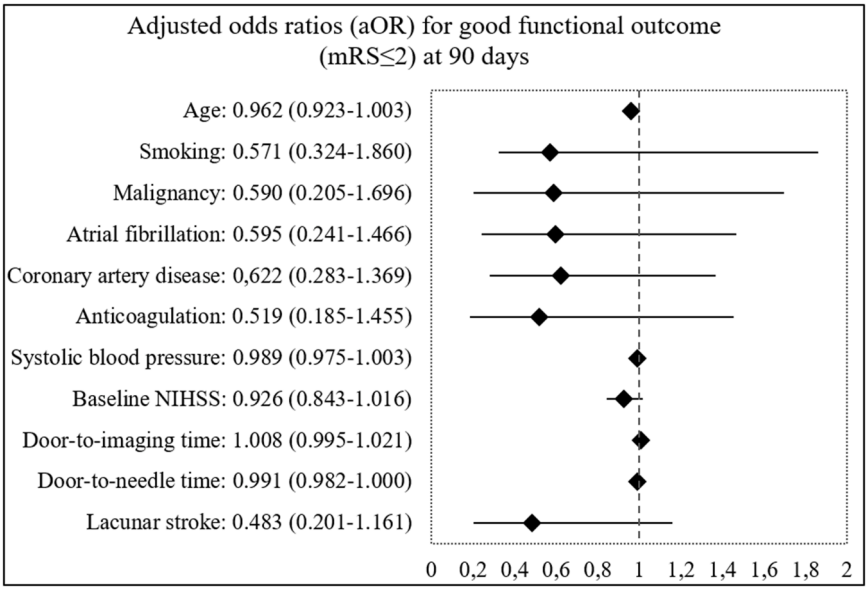

Fig. 4. Forest plot of the binary, multivariable regression analysis demonstrating the adjusted odds ratios (aOR) for good functional outcomes on the modified Rankin Scale 90 days after stroke. The diamonds and black lines represent the adjusted odds ratios and 95% confidence intervals. No statistically significant association ($p<0.05$) was found.

Conclusion

LAC is considered a relatively minor stroke compared to CE or other subtypes. To our knowledge, we report the first analysis of short- and long-term outcomes of IVT in LAC compared to a homogenous control group of patients with CE without LVO. ENI and 90-day functional outcomes were similar in the two groups. However, LAC patients had unfavourable, although non-significant, adjusted odds of achieving good functional outcomes compared to the control group. Therefore, we emphasise that LAC should not be considered a minor stroke subtype.

Funding

The STAY ALIVE Acute Stroke Registry was funded by the Economic Development and Innovation Operative Programme Grant (GINOP 2.3.2-15-2016-00048). This work was also supported by the MTA-SZTE Neuroscience Research Group of the Hungarian Academy of Sciences and the University of Szeged Open Access Fund (Grant ID: 7196). The National Talent Program (NTP-NFTÖ-21-B-0206) supported ÁA.

Informed consent

Written informed consent was obtained from all subjects or legally authorised representatives according to the Good Clinical Practice (GCP) guidelines.

Ethical approval

The STAY ALIVE Acute Stroke Registry was approved by the Hungarian Medical Research Council (35403–2/2017/EKU).

CRediT authorship contribution statement

Ádám Annus: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Nikolett Halmai:** Investigation, Data curation. **Evelin Fehér:** Methodology, Formal analysis, Data curation. **Gábor Tárkányi:** Formal analysis, Data curation. **László Szapáry:** Supervision, Funding acquisition. **István Szegedi:** Data curation. **László Csiba:** Supervision, Funding acquisition. **László Vécsei:** Supervision, Funding acquisition, Conceptualization. **László Sztriha:** Supervision, Methodology, Conceptualization. **Péter Klivényi:** Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to acknowledge the hard work and support of all healthcare workers within the Departments of Neurology at the University of Szeged, the University of Debrecen and the University of Pécs who were involved in the care of acute stroke patients recruited in this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jstrokecerebrovasdis.2025.108245.

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