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Early Neurologic Deterioration in Lacunar Stroke: Clinical and Imaging Predictors and Association With Long-term Outcome

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Abstract

Objective. To determine the rate and predictors of early neurological deterioration (END) in patients with lacunar strokes as well as its implications for management and outcome.

Methods. We enrolled consecutive patients with MRI-defined lacunar stroke who presented within 12 hours after symptom onset from a prospective stroke database (2015-2019). END was defined as any persisting increase in National Institutes of Health Stroke Scale (NIHSS) score of ≥2 points within 24 hours after admission and favorable outcome as modified Rankin Scale (mRS) of 0-2 at 90 days. We assessed the association of END with clinical and imaging variables, acute treatment and outcome using multivariable regression, calculating adjusted odds ratios.

Results. Sixty-one of 365 (16.7%) patients with acute lacunar stroke (median age 71.8 years, 39.5% female, median NIHSS score on admission 3) had END. Lower NIHSS score on admission (per point, aOR 0.81, p=0.006), capsular warning syndrome (aOR 7.00, p<0.001), ventral pontine infarct (aOR 3.49, p=0.008) and hypoperfusion on imaging (aOR 2.13, p=0.026) were associated with END. Acute dual antiplatelet therapy was associated with reduced risk of END (aOR 0.10, p=0.04). Patients with END had less favorable outcome at 90 days (aOR 0.13 p<0.001), but intravenous thrombolysis (IVT) was associated with favorable outcome at 90 days (aOR 3.95, p=0.002).

Conclusion. One in six patients with lacunar stroke has END and patients at high risk of END can be identified using radiological and clinical variables. Targeted therapeutic trials for this population seem justified.

Classification of evidence. This study provides Class II evidence that early neurologic deterioration in patients with acute lacunar stroke predicts poorer functional outcome at 90 days as determined by the modified Rankin Scale.

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Glossary

END = early neurological deterioration; IVT = intravenous thrombolysis; mRS = modified Rankin scale; NIHSS = National Institutes of Health Stroke Scale

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Introduction.

Lacunar strokes constitute up to 20% of all ischemic strokes.[1] The outcome for patients with lacunar stroke is generally fair, but some are affected by early neurological deterioration (END), which is associated with an unfavorable outcome.[2] Classically, END is defined as an increase in the National Institute of Health Stroke Scale (NIHSS) score of 4 points or more. The usefulness of this definition in lacunar stroke is questionable, however, as it was originally developed for use in recanalization trials in stroke patients with large vessel occlusion, and lacunar strokes are thought to arise from small vessel occlusions.[3,4]

Research in patients with lacunar strokes in the acute setting has been hampered because CT imaging and clinical scores lacked diagnostic accuracy.[5–10] Recently, new definitions were agreed, using MRI as the gold standard, allowing for more targeted research in this field.[11]

The exact rate of END and whether it translates into poor long-term outcome has not been extensively studied in large cohorts of patients with advanced imaging-based diagnosis of lacunar stroke. Furthermore, evidence-based rescue therapies have not yet been established, although dual antiplatelet therapy showed promising results in one case series.[12] Therefore, we aimed to elucidate the rate of END in patients with lacunar stroke and to assess its impact on functional outcome. We also aimed to identify clinical and imaging variables associated with END and potential treatment effects, in order to identify potential strategies for prevention and treatment of END.

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Methods

Patient population

This single-center, imaging-based, cross-sectional cohort study with 90 days of clinical follow-up, included patients from the Swiss Stroke Registry consecutively admitted to the comprehensive university stroke center in Bern between January 2015 and December 2019. To ensure diagnostic certainty, we included only patients who underwent MRI on admission. From this group, we identified patients with lacunar stroke through manual review of clinical records and MRI data. We defined lacunar stroke as evidence of an acute small subcortical infarction in the territory of a perforating arteriole[11] but without an upper limit for the maximal diameter[13]. We excluded patients with visible large or medium-sized vessel occlusions, multiple or cortical lesions, Percheron infarct[14], stroke mimics or MRI-negative strokes and patients who presented >12 hours after symptom onset.

Clinical data collection

The Swiss Stroke Registry prospectively collected information on pre-defined variables using electronic case report forms and a secured web-based databank. We extracted the following from the databank: demographic variables (age, sex, pre-stroke modified Rankin Scale), cardiovascular risk factors, medical history, clinical parameters (systolic and diastolic blood pressure on admission, NIHSS score on admission, at 24 hours and at discharge), intake of antithrombotic, antihypertensive and lipid-lowering medication before admission, laboratory values (glucose, cholesterol and D-dimer levels). Acute treatment (first treatment after admission) was classified as: a) intravenous thrombolysis (IVT), b) loading dose of dual antiplatelet therapy (i.e. 250 mg of aspirin and/or 300-600 mg of clopidogrel), c) loading dose of single antiplatelet therapy (i.e. 250 mg of aspirin), d) low-dose single antiplatelet therapy (e.g. single antiplatelet therapy started/continued without loading dose), or e) oral anticoagulant started/continued. In addition, two authors (JV and BM) retrospectively reviewed patient files to determine maximal and minimal NIHSS scores during the first 24

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hours of hospitalization and the presence of capsular warning syndrome, which was defined as a fluctuating one-sided weakness in the 48h preceding admission.[15]

Radiological assessment

All admission MRI in our center was performed on a 1.5 or 3 Tesla MRI scan unit from Siemens (1.5T MAGNETOM Avanto/Aera; 3T MAGNETOM Verio/Skyra/Vida). The routine stroke protocol included at a minimum: diffusion weighted imaging (DWI), susceptibility-weighted imaging (SWI), fluid attenuation inversion recovery (FLAIR) and time-of-flight (TOF) images. Perfusion imaging using the dynamic susceptibility contrast technique was also performed routinely. Perfusion maps were automatically postprocessed using Olea Sphere v2.3 (Olea medical. La ciotat, France), including quantitative analysis of Tmax. DWI sequences were acquired at baseline and follow-up with two b values of 0 and 1000 s/mm2 using four MR scanners which included two 1.5 T Magnetom Avanto and two 3 T Magnetom Verio (Siemens, Erlangen Germany). Scanner parameters for DWI were repetition time 3000–4500 ms, echo time 64–94 ms, flip angle 90° or 180°, voxel spacing (dx, dy, dz): [1.2x1.2 or 1.3x1.3]x6.5 mm3, or repetition time 3500 ms, echo time 89 ms, flip angle 90°, voxel spacing (dx, dy, dz): 1.8x1.8x[5.2 or 6.0 or 6.5] mm3, for 1.5 T and 3 T, respectively. A trained vascular neurologist (JV) and a neuroradiologist (LG) reviewed all imaging and performed the analysis. Infarct location was rated according to visual assessment as follows: supratentorial internal capsule, basal ganglia, thalamus, striatocapsular, thalamocapsular, ventral pons, dorsal pons, medulla oblongata, and midbrain. Maximal axial infarct diameter was measured on DWI at baseline, and at 24 hours, if repeat imaging was obtained. A hypoperfusion lesion was defined as a visually evident decrease in cerebral blood flow with Tmax > 6s, corresponding to the location of the DWI lesion. The following MRI small vessel disease markers were rated according to international consensus criteria[11] using validated scales and scores whenever applicable: deep and periventricular white matter hyperintensities (Fazekas scale),[16,17] presence of cerebral microbleeds,[18] old lacunes, and enlarged perivascular spaces,[19] to calculate total small-vessel disease scores[20].

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Outcome assessment

The primary endpoint of this analysis was the rate of END, defined as any persisting increase in NIHSS score of ≥2 in the first 24 hours.[3,21,22] A permanent or non-permanent deterioration of only 1 point on the NIHSS was not considered as END as this is within the expected inter-rater variability of the NIHSS. Secondary outcomes were clinical and imaging variables associated with END and good functional outcome at 90 days defined as a modified Rankin scale (mRS) of 0-2. Safety outcomes were hemorrhagic transformation and symptomatic intracranial hemorrhage on follow-up imaging, defined according to the ECASS 3 trial definition.[23] The primary research question was if END in patients with acute lacunar stroke could predict poorer functional outcome at 90 days as determined by the modified Rankin scale (Class II level of evidence).

Statistical analysis

We used medians with interquartile ranges (IQR) or means with standard deviation as appropriate, as well as percentages with 95% confidence intervals (CI) to present the distribution of continuous, ordinal and categorical variables, respectively. For the comparison of baseline group characteristics we used the Pearson chi-squared or Fischer's exact test for categorical variables, the Wilcoxon rank sum or Kruskal-Wallis test for non-normally distributed continuous and ordinal variables, and the t-test for normally distributed data. Cohen's kappa score was calculated for interrater agreement.

First, we assessed the association of different clinical and radiological baseline variables with END using uni- and multivariable regression models with variables of interest based on previous literature[3] as well as plausibility. The clinical variables were: sex; medical history; antihypertensive, lipid-lowering, and antithrombotic medication; capsular warning syndrome; first systolic, diastolic, and mean arterial blood pressure; time from onset to admission; lacunar syndrome, and NIHSS score on admission. The radiological variables were: lesion location, hypoperfusion lesion, total small-vessel disease score, presence of cerebral

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microbleeds, and the presence of concomitant large artery stenosis. We then performed multivariable logistic regression analysis to calculate adjusted odds ratios. As a sensitivity analysis, we performed the same regression comparing patients with END with those whose NIHSS never rose during the entire hospitalization period ("neurologically entirely stable").

Second, we assessed the association of acute treatment with END using a multivariate regression model adjusted for known predictors reported in the literature and pathophysiologically plausible variables that reached $p<0.10$ in the univariable regression.

Third, we determined the association of END with outcome at 90 days by performing multivariable logistic regression analysis, adjusted for pre-stroke mRS, age, sex, acute treatment, NIHSS score on admission and glucose level on admission. Patients with missing outcome data were excluded from this analysis. Model selection was based on known predictors reported in the literature and pathophysiologically plausible variables that reached significance in univariable analysis. As a sensitivity analysis we performed the same analysis comparing those patients with END to those who remained neurologically entirely stable and an analysis in those not treated with anticoagulants before the index event.

All statistical analyses were performed using STATA (StataCorp. 2019. *Stata Statistical Software: Release 16.* College Station, TX: StataCorp LLC) including the table1_mc package. All reported p-values are two-sided, with $p< 0.05$ considered statistically significant and without adjustments for multiple testing.

Standard Protocol Approvals, Registrations, and Patient Consents

Ethical approval was obtained from the cantonal ethics committee ("Kantonale Ethikkommission" Bern) for the correlation of clinical and imaging parameters with outcome in cerebrovascular diseases (KEK 231/14, PB_2016-01905). The patient data used came from the Swiss Stroke Registry, which allows for all patients treated at our stroke centers to be enrolled in a quality registry, according to Swiss legislation (Law on highly specialized

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medicine - “Hochspezialisierte Medizin” HSM; Art. 39 Abs. 2bis KVG) Patients who refused to allow their data to be used for scientific purposes were excluded from this analysis.

Data availability

Anonymized data will be shared upon reasonably justified written request from any qualified investigator.

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Results

Of 4611 patients admitted with an acute ischemic stroke, 393 (9%) had a lacunar stroke presenting within 12 hours after symptom onset and 365 of these patients (92.9%) were included in our final analysis (see *Figure 1* for patient selection process). The median age was 72 years (IQR 61-80) and 144 (39.5%) of patients were female. Baseline characteristics are shown in table 1. Median NIHSS score was 3 (IQR 1-5) on admission, 3 (IQR 1-4) at 24 hours and 2 (IQR 0-3) at discharge. The evolution of NIHSS scores during hospitalization is depicted in *Figure 2* (24 hours NIHSS available in 98.8% of patients). Median hospital stay in days was 3 (IQR 2-5). A total of 61 (16.7%) patients experienced END, whereas 239 (65.5%) remained entirely neurologically stable and 65 (17.8%) had transient fluctuations (permanent or non-permanent deterioration of 1 point on the NIHSS score). The distribution of the infarct location is depicted in *Figure 3*. Cohen's kappa for interrater agreement was good to excellent for infarct location (0.74) and affected perforator (0.76), respectively.

Clinical and radiological predictors of END

Baseline characteristics were similar in patients with END and clinically stable patients (table 1). Patients with END had a lower median NIHSS scores on admission (p<0.001) and tended to have a history of hypertension slightly more often (p=0.06). In univariable analysis, the following variables were associated with END: presentation with capsular warning syndrome (OR 9.37, [95% CI 4.37-20.08], p<0.001), higher mean arterial pressure on admission (OR 1.01,[95% CI 0.99-1.03], p=0.07), infarct location in the ventral pons (OR 2.17, [95% CI 1.01-4.64], p=0.046) and hypoperfusion lesion on perfusion weighted imaging (OR 2.02, [95% CI 1.11-3.66], p=0.021). In a multivariable logistic regression model, the following variables remained independently predictive of END: NIHSS score on admission (per 1 point increase aOR 0.81, [95% CI 0.70-0.94], p=0.006), presentation with a capsular warning syndrome (aOR 7.00, [95% CI 2.85-17.21], p<0.001), infarct location in the ventral pons (aOR 3.49, [95% CI 1.39-8.73], p=0.008) and hypoperfusion lesion on imaging (aOR 2.13, [95% CI 1.10-4.14], p=0.026). The results are shown in table 2. The sensitivity analysis

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comparing patients with END to those who were entirely neurologically stable showed similar results.

Acute treatment and lesion growth

One hundred and nineteen (33%) patients received acute treatment with IVT, 25 (7%) were treated with a loading dose of dual antiplatelet therapy, and 110 (30%) with a loading dose of single antiplatelet therapy. In 71 (19%), low-dose antiplatelet therapy was implemented and in 41 (11%) oral anticoagulation was continued. None of the patients developed a symptomatic intracranial hemorrhage.[21] Nine patients had an asymptomatic hemorrhagic transformation[22] on imaging, all of whom received IVT.

In the multivariable analysis, dual antiplatelet loading-dose therapy was associated with a reduced risk of END (aOR 0.10, [95% CI 0.01-0.89], *p*=0.04) but this was not seen with IVT or high dose single antiplatelet therapy. The distribution of END across treatment groups is shown in figure 4.

Initial lesion diameter was 9.9 mm (6.9-13) in the clinically stable vs 10.1 mm (8-14.4) in the group with END (p=0.11). Follow up with MRI at 24±12 hours was available for 176 (48%) of patients. In these patients, presentation with capsular warning syndrome was associated with lesion growth (OR 2.65, [95% CI 1.03-6.81], *p*=0.04). There was no statistically significant association between infarct growth on imaging (defined as any increase in maximal axial diameter at 24 hours as compared to baseline) and END (OR 1.79, [95% CI 0.84-3.84], *p*=0.13). Infarct growth was, however, inversely associated with the use of intravenous antihypertensive treatment (OR 0.35, [95% CI 0.13-0.96], *p*=0.04) and associated with use of IVT (OR 0.33 [95% CI 0.16-0.68], *p*=0.002).

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Functional outcome at 90 days

mRS at 90 days was available for 331 of 365 patients (90.6%). After adjustment for confounders, END was associated with a less favorable outcome at 90 days (aOR 0.13 [95% CI 0.05-0.30] $p<0.001$) for good functional outcome (table 3). Moreover, when compared to low-dose antiplatelet therapy, IVT was independently associated with better functional outcome (aOR 3.95, [95% CI 1.68-9.34], $p=0.002$) as was high-dose single antiplatelet therapy (aOR 2.73, [95% CI 1.08-6.90], $p=0.03$). In the group treated with dual antiplatelet therapy with loading dose, the association did not reach statistical significance (aOR 20.71 [95% CI 0.89-482.31], $p=0.06$). A sensitivity analysis comparing END patients with entirely neurologically stable patients and a second sensitivity analysis excluding patients with previously treated with oral anticoagulation yielded similar results.

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Discussion

Our prospectively collected dataset of patients with MRI-proven lacunar stroke, shows the following main findings: 1) END is common in patients with lacunar stroke and occurs in one in six patients presenting within 12 hours after symptom onset; 2) Low NIHSS on admission, preceding capsular warning syndrome, an infarct location in the ventral pons and a hypoperfusion lesion are predictive of END; 3) END is associated with worse functional outcome at 90 days.

Rates of neurological deterioration

The rate of 16.7% of END seen in our cohort is in line with previous studies of patients with lacunar stroke.[21,22,25–29] Most of these studies, however, used CT and clinical syndromes for patient selection, making our MRI-based cohort more reliable concerning the diagnosis of a single lacunar infarct. Moreover, to the best of our knowledge, our cohort represents the largest consecutive dataset of patients with an acute lacunar stroke assessed with MRI and only the second one looking at END specifically in such a number of patients.[30]

Predictors of END

Patients with infarcts in the ventral pons had END much more frequently than those with infarcts in any other location. This may constitute a basilar branch disease with progression rather than a true lacunar stroke[31]. Furthermore, due to the anatomical organization in the ventral pons, there is a high probability of the infarct affecting the corticospinal tract when infarct growth occurs, thus rapidly increasing the NIHSS score. This hypothesis is in line with the findings of a previous study using sequential DWI in highly selected supratentorial lacunar infarcts, where END was accompanied by an extension of the lesion encompassing the corticospinal tract,[27] and a study of 105 patients with pure motor stroke in which a pontine lesion was also predictive of END.[32] Furthermore, capsular warning syndrome before admission was highly predictive of END and was correlated with infarct growth on imaging, giving further support to this hypothesis.

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In our cohort, neither systolic nor mean arterial blood pressure on admission was significantly associated with END. This is in contrast to the findings of a previous study showing systolic hypertension on admission to be independently associated with END.[33] However, the time window in that study was less clearly defined, also including patients who showed clinical deterioration before admission, which hampers a true comparison.

Normal perfusion imaging was associated with a clinically stable course in a previous smaller study using perfusion MRI,[34] and decreased cerebral blood flow and increased mean transit time were associated with worsening in a CT perfusion-based trial[35]. We confirmed this result with our finding of hypoperfusion lesions being independently associated with END. Given the plausible pathophysiological link as well as results from previous in-depth perfusion imaging analysis in lacunar infarcts,[36] further targeted analyses are warranted. Both hypoperfusion and mean arterial pressure are associated with cerebral perfusion pressure and autoregulation. A possible pathophysiological link between early infarct growth – subsequently causing clinical deterioration – and failure of autoregulation of the cerebral vascular bed may well exist. In patients with chronically elevated blood pressure, for example, cerebral perfusion curves are shifted to the right,[37] and there might be a negative effect of acute blood pressure reduction on the delivery of oxygen to the neuronal and glial cells at risk during the acute phase of the lacunar infarction. Our finding that the use of intravenous antihypertensive treatment was associated with infarct growth on follow-up imaging could point in the same direction.

The efficacy of IVT in patients with lacunar stroke has been the subject of non-randomized trials in the last few years.[38–41] In our cohort, the use of IVT appeared to be safe in both clinically stable and END patients with lacunar stroke. Most notably, none of the patients had a symptomatic intracerebral hemorrhage after IVT. Although the group treated with dual antiplatelet therapy with a loading dose was small in absolute numbers (25/365 or 7% of the

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population), this type of therapy was the only one associated with a clinically stable course. This is in line with one retrospective cohort study, which showed better outcomes with dual antiplatelet therapy as a rescue therapy in patients who had already experienced END, again without increasing the risk of symptomatic intracranial hemorrhage.[12]

Impact of END on outcome

Although the prognosis of patients with lacunar stroke is generally considered to be fair, we were able to demonstrate that those patients who experience END have a worse functional outcome and are more frequently dependent in the long term, confirming the findings of previous studies.[12,22,30,33] Across treatment groups, patients treated with IVT as well as high-dose single antiplatelet therapy, fared better than those treated with low-dose antiplatelet monotherapy. The effect of dual antiplatelet therapy with loading dose did not reach statistical significance but the point estimate does suggest that it could be a valuable treatment option in this patient group, especially as it is the only therapy that was associated with a decreased rate of END. However, our study was neither powered nor specifically targeted at this treatment effect, and the results should therefore be interpreted with great caution. Given the recent evidence that, in strokes with a minor non-disabling deficit, aspirin was not inferior to IVT,[42] as well as for short-term dual antiplatelet therapy in minor strokes,[43,44] more targeted studies in lacunar stroke patients are clearly warranted, to determine the usefulness of different acute therapy strategies. This is especially true for the subgroup of patients who are at a high risk of END.

Strengths and limitations

The advantages of our study are the large number of patients included in our database and the use of multimodal MRI as the acute imaging type in more than 90% of cases, ensuring diagnostic confidence that the advent stroke was truly the result of a perforator vessel infarction. Furthermore, despite being retrospective in nature, because of the prospective

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collection of data and the highly standardized workflow in our center for the treatment of acute ischemic strokes, the data are reliable and robust.

Our study has several limitations. First, because of its retrospective nature, we cannot exclude a certain selection bias especially with respect to acute treatments (decision for/against thrombolysis, dual antiplatelet therapy and loading). Second, because we opted for an imaging-based approach and used a practical definition of deep perforator infarction, this cohort could represent a heterogeneous group of patients with different pathophysiological mechanisms underlying their stroke. Third, we cannot exclude that more advanced imaging analysis such as lesion volumetric analysis might be better predictors than the readily available imaging parameters we used. Fourth, the analysis of the association of acute clinical worsening with outcome should be interpreted with caution because of the incompleteness of the outcome data. Fifth, because detailed information on the pre-hospital course was not available, we cannot exclude any effects of pre-hospital blood pressure management on the outcome. Sixth, follow-up imaging was only available in 48% of patients and we therefore urge caution in the interpretation of the results on lesion growth. Last, the group of patients with END was too small to perform further subanalyses to identify predictors of clinical outcome at 3 months in this subgroup.

Conclusion

One in six patients with lacunar stroke experiences early neurological deterioration. This occurs both in patients treated with IVT and in those who were not. Clinical and imaging predictors are capsular warning syndrome before admission, infarct location in the ventral pons, a hypoperfusion lesion on imaging, lower NIHSS on admission. The phenomenon of END in these patients is important, as it is associated with unfavorable long-term outcome. Dual antiplatelet therapy, but not IVT, reduced the risk of END, but only IVT improved functional outcome at 90 days. Lacunar stroke patients at high risk for END on admission should be included in future targeted trials of novel acute treatment options.

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Figure legends.

Figure 1. Flowchart of study population selection.

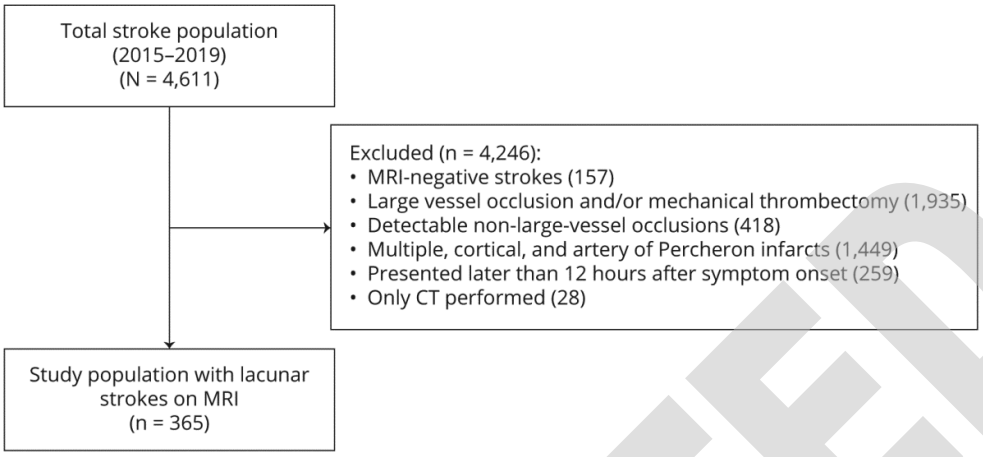

Figure 2. Evolution of the total NIHSS score in the total population during hospitalization. Peak refers to the maximal total NIHSS score whereas the trough refers to the minimal total NIHSS score within the first 24 hours of hospital stay.

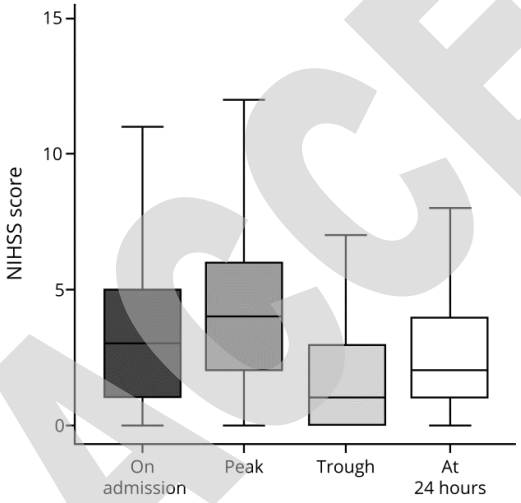

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Figure 3. Distribution of lacunar infarct location. Panel A shows the entire population, the patients with END are depicted in Panel B.

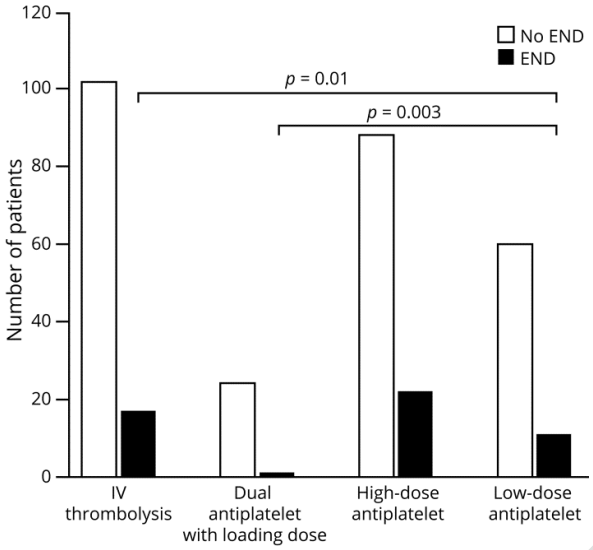
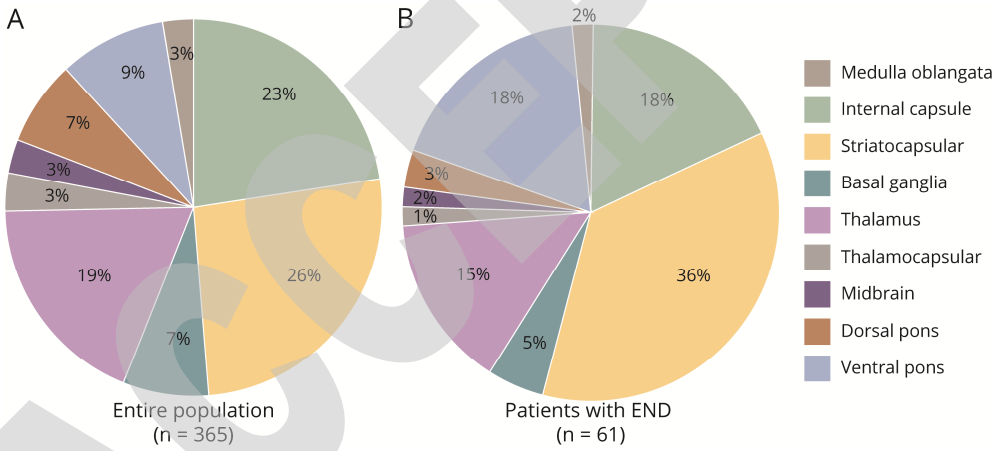


Figure 4. Number of patients with END across acute treatment groups. P-values are depicted for adjusted analysis using Bonferroni method to compare for multiple treatment means after regression analysis.



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Tables

	Clinically stable (N = 304)	END (N = 61)	Total (N = 365)	p-value
Demographics				
Age (years)	71 (60-80)	74 (64-81)	72 (61-80)	0.18
Female	122 (40.1%)	22 (36.1%)	144 (39.5%)	0.55
Pre-stroke modified Rankin scale	0 (0-0)	0 (0-0)	0 (0-0)	0.29
Medical history				
Body mass Index (kg/m2)	26 (24-29)	25 (23-28)	26 (24-29)	0.55
Previous stroke	49 (16.1%)	9 (14.8%)	58 (15.9%)	0.79
Previous transient ischemic attack	23 (7.6%)	5 (8.2%)	28 (7.7%)	0.87
Previous intracerebral hemorrhage	3 (1.0%)	0 (0.0%)	3 (0.8%)	0.44
Hypertension	231 (76.0%)	53 (86.9%)	284 (77.8%)	0.062
Smoker	80 (26.3%)	14 (23.0%)	94 (25.8%)	0.58
Diabetes	55 (18.1%)	16 (26.2%)	71 (19.5%)	0.14
Dyslipidemia	212 (69.7%)	42 (68.9%)	254 (69.6%)	0.89
Coronary heart disease	40 (13.2%)	5 (8.2%)	45 (12.3%)	0.28
Peripheral arterial disease	12 (3.9%)	2 (3.3%)	14 (3.8%)	0.80
Atrial fibrillation	36 (11.8%)	10 (16.4%)	46 (12.6%)	0.33
Prior Medication				
Antiplatelet	91 (29.9%)	19 (31.1%)	110 (30.1%)	0.85
Anticoagulant	31 (10.2%)	10 (16.4%)	41 (11.2%)	0.16
Antihypertensive treatment	150 (49.3%)	35 (57.4%)	185 (50.7%)	0.25
Lipid-lowering drugs	68 (22.4%)	14 (23.0%)	82 (22.5%)	0.92
Clinical features				
National Institute of Health Stroke Scale score on admission	3 (2-5)	2 (0-4)	3 (1-5)	**<0.001**
Time from onset to treatment (min)	250 (155-503)	300 (175-519)	252 (159-508)	0.34
Small-vessel disease imaging markers				
Lacunes present	86 (30.4%)	21 (36.8%)	107 (31.5%)	0.34
Cerebral microbleeds present	73 (25.8%)	19 (33.3%)	92 (27.1%)	0.25
White matter hyperintensities*	90 (31.8%)	16 (28.1%)	106 (31.2%)	0.64
Perivascular spaces[+]	66 (23.3%)	17 (29.8%)	83 (24.4%)	0.30
Total small-vessel disease score	1 (0-2)	1 (0-2)	1 (0-2)	0.68
Laboratory values				
Glucose on admission (mmol/L)	6.3 (5.6-7.3)	6.2 (5.6-7.6)	6.3 (5.6-7.4)	0.93
D-dimer level on admission (mmol/L)	0.49 (0.30-0.81)	0.36 (0.24-0.59)	0.48 (0.29-0.78)	0.24

Table 1 Baseline variables. Data are presented as median (IQR) for continuous measures and n (%) for categorical measures.

** Defined according to Fazekas scale: periventricular Fazekas 3 and/or deep white matter hyperintensities Fazekas 2-3.*[20]

[+] Defined as moderate to severe perivascular spaces in the basal ganglia (≥11 on either side).[19]

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	Adjusted Odds ratio	95% Confidence Interval	p-value
National Institutes of Health Stroke Scale score on admission (per point increase)	0.81	0.70-0.94	**0.006**
Mean arterial pressure on admission (per mm Hg)	1.01	0.99-1.03	0.14
Capsular warning syndrome	7.00	2.85-17.21	**<0.001**
Acute therapy*			
Intravenous thrombolysis	0.92	0.39-2.16	0.85
Dual antiplatelet with loading dose	0.10	0.01-0.89	**0.04**
High-dose single antiplatelet	0.80	0.37-1.77	0.59
Ventral pontine lesion	3.49	1.39-8.73	**0.008**
Hypoperfusion lesion	2.13	1.10-4.14	**0.026**

Table 2. Results of multivariable regression analysis for predictors of END. Effects are presented as adjusted odds ratios (aOR) with 95% confidence intervals. The pseudo-R2 of the model is 0.187 with 8 degrees of freedom.
** Low-dose single antiplatelet therapy as the reference therapy.*

	Adjusted Odds ratio	95% Confidence Interval	p-value
Early neurological deterioration	0.13	0.05-0.30	**<0.001**
Age (years)	0.93	0.09-1.06	**<0.001**
National Institutes of Health Stroke Scale score on admission (per point increase)	0.74	0.65-0.85	**<0.001**
Acute therapy*			
Intravenous thrombolysis	3.95	1.68-9.34	**0.002**
Dual antiplatelet with loading dose	20.71	0.89-482.31	0.06
High-dose single antiplatelet	2.73	1.08-6.90	**0.03**
Glucose level on admission	0.95	0.92-1.10	0.48

Table 3. Results of multivariable regression analysis for good functional outcome (modified Rankin Scale 0-2) at 90 days. Effects are presented as adjusted odds ratios (aOR) with 95% confidence intervals.The pseudo-R2 of the model is 0.404 with 10 degrees of freedom.
** Low-dose single antiplatelet therapy as the reference therapy.*

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Appendix 1. Authors

Name	Location	Contribution
Jan Vynckier	Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Switzerland	Drafting/revision of the manuscript for content, including medical writing for content Major role in the acquisition of data Study concept or design Analysis or interpretation of data
Basel Maamari	Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Switzerland	Major role in the acquisition of data Study concept or design
Lorenz Grunder	Department of Diagnostic and Interventional Neuroradiology, Department of Diagnostic Interventional and Pediatric Radiology and Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Switzerland	Major role in the acquisition of data Study concept or design
Martina Goeldlin	Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Switzerland	Drafting/revision of the manuscript for content, including medical writing for content Analysis or interpretation of data
Thomas Raphael Meinel	Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Switzerland	Drafting/revision of the manuscript for content, including medical writing for content Study concept or design Analysis or interpretation of data

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Marcel Arnold	Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Switzerland	Analysis or interpretation of data
Jan Gralla	Department of Diagnostic and Interventional Neuroradiology, Inselspital, Bern University Hospital and University of Bern, Switzerland	Major role in the acquisition of data
David J Seiffge	Department of Neurology, Inselspital, Bern University	Drafting/revision of the manuscript for content, including medical writing for content Study concept or design

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	Hospital and University of Bern, Switzerland	Analysis or interpretation of data
Urs Fischer	Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Switzerland	Drafting/revision of the manuscript for content, including medical writing for content Study concept or design Analysis or interpretation of data

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