Risk factors associated with progressive lacunar strokes and benefit from dual antiplatelet therapy

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Background and purpose: Early neurological deterioration (END) occurs in 20%–30% of patients with lacunar stroke and challenges their clinical management. This retrospective cohort study analyzed clinical and neuroimaging risk factors predicting the occurrence of END, the functional outcome after END and potential benefit from dual antiplatelet therapy (DAPT) in patients with lacunar strokes.

Methods: Factors associated with END and benefit from DAPT were retrospectively analyzed in 308 patients with lacunar stroke symptoms and detected lacunar infarction by magnetic resonance imaging. END was defined by deterioration of ≥3 total National Institutes of Health Stroke Scale (NIHSS) points, ≥2 NIHSS points for limb paresis or documented deterioration within 5 days after admission. Patients were treated with DAPT according to in-house standards. The primary efficacy end-point for functional outcome was fulfilled if NIHSS at discharge improved after END at least to the score at admission.

Results: Male gender (odds ratio (OR) 2.08; 95% confidence interval (CI) 1.09–4.00), higher age (OR = 1.65 per 10 years; 95% CI 1.18–2.31), motor paresis (OR = 18.89, 95% CI 4.66–76.57) and infarction of the internal capsule or basal ganglia (OR = 3.58, 95% CI 1.26–10.14) were associated with an increased risk for END. A larger diameter of infarction (OR = 0.85, 95% CI 0.76–0.95), more microangiopathic lesions (OR = 0.75, 95% CI 0.57–0.99) and pontine localization (OR = 0.29, 95% CI 0.12–0.65) were factors associated with unfavorable functional outcome after END occurred. Localization in the internal capsule or basal ganglia was identified as a significant predictive factor for a benefit from DAPT after END.

Conclusions: Identified clinical and neuroimaging factors predicting END occurrence, functional outcome after END and potential benefit from DAPT might improve the clinical management of patients with lacunar strokes.

Introduction

Early neurological deterioration (END) occurs in 20%–30% of patients with lacunar strokes within the first days after stroke onset leading to a high risk for disability [1–3]. Therefore, early identification of these patients might improve their clinical and therapeutic management.

Several clinical risk factors were previously described to be associated with END, e.g. diabetes and severity of motor deficits at admission, pure motor stroke, leg-predominant motor deficits or hypertriglyceridemia [1–6]. Additionally, these risk factors might vary between patients with lacunar...
strokes in different territories [4]. Moreover, high National Institutes of Health Stroke Scale (NIHSS) at admission, leukocytosis and in-hospital infections were associated with poor outcome after lacunar stroke [7]. Neuroimaging risk factors associated with END are a large volume of infarction, conglomerated bead shapes or satellite lesion shaped pattern of ischaemic lesion, localization in the corona radiata, atheromatous vessel occlusion in penetrating artery infarcts or basilar artery branch disease and lower pons lesion in pontine infarction [2,3,8–12]. Although widely studied, these risk factors do not affect therapeutic management. Moreover, none of the studies investigated potential subgroup specific benefits from dual antiplatelet therapy (DAPT).

Based on the results of the POINT trial, the current recommendation is to initiate DAPT for 10–21 days after clinical onset in patients with minor strokes [13]. Interestingly, the POINT trial demonstrated particular efficacy of DAPT within the first 7 days [14], which might be explained by reduction of END occurrence. However, END was not distinguished from stroke recurrence in the trial [15]. Previous data demonstrated that 5 days of DAPT initiated only after END were associated with improved functional outcome without increased risk of symptomatic bleeding in progressive lacunar strokes [16]. As the POINT trial demonstrated an increased risk for hemorrhage after 7 days of DAPT [14], it remains unanswered whether all patients benefit from DAPT or whether it might expose patients who will not deteriorate to an unnecessary increased risk for hemorrhage.

Therefore, the aims of this retrospective study were to analyze clinical and radiographic risk factors predicting the occurrence of END, the functional outcome after END and also a potential benefit from DAPT in patients with lacunar strokes.

Methods

A retrospective observational cohort study in patients with lacunar strokes based on a single-stroke-center hospital database was performed. Data from 1 January 2010 to 31 December 2017 were analyzed.

Inclusion/exclusion criteria

Inclusion criteria were (i) clinical deficits consistent with lacunar ischaemia, (ii) the use of magnetic resonance imaging (MRI) for detection of lacunar infarction, (iii) hyperintensity on diffusion weighted (DWI) sequences on MRI in a subcortical region corresponding to clinical deficit and (iv) largest diameter of ischaemic lesion ≤ 20 mm. Exclusion criteria were proximal vessel occlusion, symptomatic extracranial or intracranial carotid stenosis, evidence of cardioembolism, anticoagulant treatments or contraindications against DAPT. Neuroimaging was performed at admission and upon END to exclude cerebral hemorrhage and new ischaemic lesion.

Measurement of END

Patients were retrospectively screened for occurrence of END within 5 days after stroke onset. END was defined as deterioration of ≥ 3 total NIHSS points, ≥ 2 NIHSS points for limb paresis or description of fluctuating clinical symptoms which might not be well reflected by the NIHSS in electronic medical reports.

Measurement of clinical characteristics

Patients’ characteristics were retrieved from electronic medical reports and laboratory parameters and the clinical outcome from NIHSS documentation, which was performed at least every 6 h mostly for ≥ 72 h or until patients’ discharge by trained physicians on the stroke unit.

Lacunar syndromes were categorized into pure motor paresis, ataxic paresis, senso-motor paresis, pure sensory syndrome and other. The latter consisted mainly in facial paresis and/or dysarthria only and was used as a reference group for statistical analysis. NIHSS was categorized into low (NIHSS < 4) and high (NIHSS ≥ 4) reflecting that the latter mostly included severe paresis.

Measurement of neuroimaging characteristics

Magnetic resonance imaging diagnostics were performed using a 3 T whole body scanner (Magnetom Trio or Verio, Siemens, Germany).

Localization of infarction was categorized into thalamus, corona radiata, internal capsule or basal ganglia and pons. The localization with the lowest percentage of END occurrence in descriptive analysis was used as reference for further analyses. Speckled shape of infarction was defined as an irregular shape of DWI lesions (Fig. S1). The severity of microangiopathy was analyzed according to Fazekas criteria using fluid attenuated inversion recovery and T2 sequences [17].

Efficacy of DAPT

Patients with END were divided into patients with DAPT (aspirin and clopidogrel) or single antiplatelet
therapy only. As the observation time of this study ended before the results of the POINT trial were available, the initiation and duration of DAPT were based on individual decisions of treating physicians and institutional standards, according to which DAPT was allowed as off-label therapy but was not mandatory. If END occurred after systemic thrombolysis, DAPT was initiated after exclusion of cerebral hemorrhage.

For analysis of the efficacy of DAPT in patients with END, the NIHSS was compared between discharge and admission as primary end-point, which was fulfilled if NIHSS at discharge improved after END at least to the score at admission. Secondary end-points were fulfilled if (i) the Rankin score at discharge improved after END at least to the score at admission, (ii) no further clinical fluctuation occurred and (iii) symptomatic hemorrhage was absent.

Analysis investigating the benefit from DAPT depending on risk factors used the primary end-point to determine functional outcome.

**Statistical analysis**

Absolute and relative frequencies were calculated for categorical variables, and medians and interquartile ranges for continuous variables. Univariate and/or multivariable logistic regression models were used to analyze the association between clinical and neuroimaging parameters with END and primary end-point, and corresponding estimates for the odds ratio (OR) with 95% confidence interval (CI) are reported. To identify potential predictive factors for DAPT in patients with END, a logistic regression model with the clinical/neuroimaging parameter, DAPT (yes/no) and the corresponding interaction term was fitted with primary end-point as outcome. All statistical tests were calculated on significance levels of \( p = 0.05 \) using software R3.5 (https://cran.r-project.org/).

**Results**

**Patients’ characteristics**

In all, 308 of 458 patients with lacunar strokes proven by neuroimaging received MRI diagnostics for stroke detection and were included in this study. Patients’ characteristics were comparable between all 458 and the included patients (Table S1). END occurred in 34% (104) of the 308 patients and was associated with a high risk for sustained worsened outcome (Table S2). Detailed patients’ characteristics of all patients and the patients’ subgroups with and without END are given in Tables 1 and S3.

### Table 1 Clinical and neuroimaging characteristics of patients with and without END

| Clinical characteristics       | END \((n = 104)\) | No END \((n = 204)\) |
|-------------------------------|------------------|-------------------|
| Age (median; IQR)             | 68.0 (12.8)      | 68.7 (18.4)       |
| Female gender (n; %)          | 24 (23%)         | 74 (36%)          |
| Hypertension (n; %)           | 89 (86%)         | 190 (93%)         |
| Diabetes mellitus (n; %)      | 25 (24%)         | 55 (27%)          |
| HbA1c (median; IQR)           | 5.8 (0.8)        | 5.7 (0.9)         |
| Hypercholesterolemia (n; %)   | 74 (71%)         | 134 (66%)         |
| LDL-cholesterol (median; IQR) | 127.5 (41)       | 120.5 (48)        |
| Smoker (n; %)                 | 37 (36%)         | 73 (36%)          |
| Lacunar syndrome (n; %)       |                  |                   |
| Pure motor paresis            | 36 (35%)         | 47 (23%)          |
| Ataxic paresis                | 22 (21%)         | 47 (23%)          |
| Senso-motor paresis           | 42 (40%)         | 36 (18%)          |
| Pure sensory symptoms         | 2 (2%)           | 22 (11%)          |
| Other                         | 2 (2%)           | 52 (25%)          |
| NIHSS at admission (median; IQR) | 3 (3)          | 3 (2)             |
| ≥4 (n; %)                     | 51 (49%)         | 69 (34%)          |
| Antipatelet treatment prior to admission (n; %) | 31 (30%) | 50 (25%)  |
| Aspirin                       | 26               | 45                |
| Clopidogrel                   | 5                | 4                 |
| Aspirin + clopidogrel         | –                | 1                 |
| Thrombolysis (n; %)           | 27 (26%)         | 14 (7%)           |
| Right hemisphere (n; %)       | 48 (46%)         | 92 (45%)          |
| Largest diameter (mm) (median; IQR) | 13 (6)     | 10 (6)            |
| Localization of infarction (n; %) |                  |                   |
| Corona radiata                | 25 (24%)         | 59 (29%)          |
| Internal capsule or basal ganglia | 32 (31%)       | 34 (17%)          |
| Pons                          | 39 (38%)         | 69 (34%)          |
| Thalamus                      | 8 (8%)           | 42 (21%)          |
| Speckled DWI lesion (n; %)    | 28 (27%)         | 18 (9%)           |
| Fazekas score (median; IQR)   | 2 (2)            | 3 (2)             |
| 0–3                           | 78 (75%)         | 136 (67%)         |

DWI, diffusion weighted imaging; END, early neurological deterioration; IQR, interquartile range; LDL, low density lipoprotein; NIHSS, National Institutes of Health Stroke Scale. Hypertension, diabetes mellitus or hypercholesterolemia were defined as prior to admission diagnosis or systolic blood pressure ≥140 mmHg, HbA1c ≥ 6.5 or LDL-cholesterol ≥ 120 mg/dl.

**Clinical characteristics associated with END**

Male gender (OR = 2.08; 95% CI 1.09–4.00) and older age (OR = 1.65 per 10 years; 95% CI 1.18–2.31) were significantly associated with increased risks for END (Tables 2 and S4). Patients with hypertension appeared less likely to suffer from END (OR = 0.31, 95% CI 0.11–0.86). Patients presenting with motor paresis with or without additional sensory symptoms (OR = 18.89, 95% CI 4.66–76.57 or OR = 30.00, 95% CI 7.2–124.99) or ataxic paresis (OR = 9.32, 95% CI 2.25–38.66) had substantially higher risks for END compared to patients with other symptoms. Stroke severity was not an independent risk factor for END.
**Neuroimaging characteristics associated with END**

Thalamic lacunar strokes had the lowest risk for END with occurrence in only 16% of patients. Compared to thalamic strokes, those in the internal capsule or basal ganglia were associated with the highest risk for END ($OR = 3.58, 95\% CI 1.26–10.14$, Table 2). Localization in the pons or corona radiata had no significant influence on END occurrence.

Larger diameter ($OR = 1.09, 95\% CI 1.01–1.18$) or speckled shape of DWI lesions ($OR = 2.39, 95\% CI 1.08–5.31$) was associated with significantly increased risks for END, whereas higher Fazekas scores were associated with a lower risk for END ($OR = 0.75, 95\% CI 0.61–0.93$).

**Table 2** Multivariable logistic regression estimates for the association between clinical/neuroimaging risk factors and END

| Explanatory variables | OR (95% CI) | P value |
|-----------------------|-------------|---------|
| Age per 10-year increase | 1.65 (1.18–2.31) | 0.003 |
| Gender Male vs. female | 2.08 (1.09–4.0) | 0.027 |
| Hypertension Yes vs. no | 0.31 (0.11–0.86) | 0.024 |
| Diabetes mellitus Yes vs. no | 0.97 (0.50–1.89) | 0.93 |
| Fazekas score per 1 score | 1.24 (0.66–2.33) | 0.51 |
| Smoker Yes vs. no | 1.12 (0.58–2.14) | 0.74 |
| Lacunar syndrome Other (ref.) | 18.89 (4.66–76.57) | <0.001 |
| Pure motor paresis Ataxic paresis Senso-motor paresis | 9.32 (2.25–38.66) 30.00 (7.20–124.99) | 0.002 0.001 |
| Pure sensory symptoms ≥4 vs. 0–3 | 3.66 (0.53–25.54) | 0.19 |
| NIHSS at admission Thalamus (ref.) | 0.68 (0.34–1.34) | 0.27 |
| Localization Corona radiata Internal capsule or basal ganglia | 1.32 (0.46–3.78) 3.58 (1.29–10.14) | 0.6 0.016 |
| Hemisphere Right vs. left | 2.21 (0.82–5.95) | 0.12 |
| Largest diameter per 1-mm increase | 1.49 (0.82–2.69) | 0.19 |
| Speckled DWI lesion Yes vs. no per 1 score increase | 2.39 (1.08–5.31) 0.75 (0.61–0.93) | 0.03 0.009 |

**Risk factors associated with functional outcome after END**

The occurrence of END does not always result in sustained clinical deterioration. Here, pontine infarction ($OR = 0.29, 95\% CI 0.12–0.65$, Table 3), larger diameter ($OR = 0.85, 95\% CI 0.76–0.95$) or speckled shape of DWI lesions ($OR = 0.12, 95\% CI 0.04–0.33$) or higher Fazekas scores ($OR = 0.75, 95\% CI 0.57–0.99$) were identified as significant prognostic factors for an unfavorable functional outcome after END occurred. In contrast, all patients with thalamic strokes improved after END, although statistical significance could not be proven due to small patient numbers ($n = 8$). Systemic thrombolysis did not influence the

**Table 3** Prognostic factors for improvement of functional outcome after END estimated by univariate logistic regression analysis

| Explanatory variables | OR (95% CI) | P value |
|-----------------------|-------------|---------|
| Age per 10-year increase | 0.91 (0.63–1.31) | 0.596 |
| Gender Male vs. female | 1.49 (0.59–3.7) | 0.392 |
| Hypertension Yes vs. no | 0.67 (0.21–2.10) | 0.492 |
| Diabetes mellitus Yes vs. no | 0.91 (0.37–2.25) | 0.835 |
| Hypercholesterolemia Yes vs. no | 1.07 (0.45–2.51) | 0.885 |
| Smoker Yes vs. no | 1.11 (0.49–2.51) | 0.798 |
| Lacunar syndrome Yes vs. no | 0.53 (0.23–1.19) | 0.124 |
| Pure motor paresis Ataxic paresis Senso-motor paresis | 0.85 (0.33–2.18) 1.56 (0.70–3.49) | 0.731 0.276 |
| NIHSS at admission Per 1-point increase ≥4 vs. 0–3 | 1.13 (0.99–1.30) 1.74 (0.79–3.83) | 0.077 0.165 |
| Localization Yes vs. no | 14.41 (0.68–304.78) 0.91 (0.37–2.25) 2.34 (0.96–5.73) | 0.087 0.835 0.062 |
| Thalamus Corona radiate Internal capsule or basal ganglia | 0.29 (0.12–0.65) 0.90 (0.41–1.96) 2.34 (0.96–5.73) | 0.003 0.785 0.062 |
| Hemisphere Right vs. left | 0.85 (0.76–0.95) | 0.004 |
| Largest diameter Per 1-mm increase | 0.12 (0.04–0.33) 0.75 (0.57–0.99) | <0.001 0.043 |
| Speckled DWI lesion Yes vs. no | 2.78 (1.12–6.94) | 0.028 |
| Fazekas score Per 1 score increase 0–3 vs. 4–6 | 1.63 (0.65–4.06) | 0.297 |
| DAPT Yes vs. no | 2.78 (1.12–6.94) | 0.028 |

CI, confidence interval; DAPT, dual antiplatelet therapy; DWI, diffusion weighted imaging; END, early neurological deterioration; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio. OR indicates the odds ratios compared to the reference group (the latter unit). Bold numbers indicate significant associations. For pure sensory symptoms, an association was not determinable as END occurred in only two patients.
functional outcome after END (OR = 1.63, 95% CI 0.6–4.05) nor prevent the occurrence of END as 27 (66%) of 41 patients treated with systemic thrombolysis at admission presented with END at later time point. The initiation of DAPT after END occurrence was significantly associated with improved functional outcome (OR = 2.78, 95% CI 1.12–6.94, Table 3).

DAPT in patients with END

Seventy-eight (75%) of the 104 patients with END received DAPT after END occurred. DAPT was started within 4 days, mostly on the day of admission or 1 day afterwards (in 31% or 42%) and mainly continued for 5 days (in 88%). The primary end-point was fulfilled in 64% (50) of patients with DAPT compared to 38% (10) of patients with single antiplatelet therapy only (P = 0.038, Table 4). DAPT was associated with significant reductions of further clinical fluctuation in 81% (63) of patients compared to 35% (nine) of patients without DAPT (P < 0.001, secondary end-point). Symptomatic bleeding complications were not observed in any patient regardless of DAPT or not. Median treatment time on the stroke unit was 5 days (range 1–13) in both groups including the same intensity of rehabilitation. No significant imbalances of clinical and neuroimaging parameters, length of stay on the stroke unit or prior antiplatelet treatment were observed between patients receiving/ not receiving DAPT except for thrombolysis which was less often given to patients with later DAPT (Table S5 and S6).

Predictive factors for benefit from DAPT

None of the clinical characteristics or other treatments (prior antiplatelet treatment, systemic thrombolysis, treatment duration on the stroke unit) significantly modified the benefit from DAPT after END occurred (Fig. 1a, Table S7).

Whilst patients with lacunar strokes involving the internal capsule or basal ganglia had the highest risk for END, these patients benefited significantly more from DAPT (fulfilled primary end-point 85% vs. 17% with single antiplatelet therapy, Table S7) than patients with other types of lacunar stroke (54% vs. 45%, interaction P value 0.039, Fig. 1b). Applying DAPT in progressive lacunar strokes located in the corona radiata seemed to have even a negative effect on functional outcome (interaction P value 0.08) which was mainly caused by an over-proportionally high number of patients with improved functional outcome after single antiplatelet therapy only. Response rates to DAPT were similar compared to other stroke localizations (Fig. S2). Patients with pontine or thalamic strokes did not show any DAPT-specific response (Fig. 1b).

Discussion

This study evaluated risk factors predicting the occurrence of END and benefit from DAPT in a large cohort of lacunar stroke patients. It was observed that male gender, older age and presentation with motor deficits at admission were associated with increased risks for END. Accordingly, lacunar strokes in the internal capsule or basal ganglia were those with the highest risk for END, but also with the best response to DAPT.

These data are in line with previously published data demonstrating that pure motor paresis was associated with END [1,3,5]. Regarding imaging risk factors, previous data showed that localization in the corona radiata or pons was associated with END [2,12]. For the latter, the same trend was observed in this study. Furthermore, the data of this study confirmed the association of a speckled shape of DWI lesions, also called conglomerated bead shape, with a high risk for END and poor functional outcome after END [9]. Similar findings were previously reported for satellite lesion shaped patterns of DWI lesions [10]. However, the mechanism underlying this observation is not known so far.

Interestingly, a higher extent of microangiopathic lesions and hypertensive blood pressures reduced the risk for END. Due to the lack of data this remains speculative, but it might indicate that a precondition for ischaemia and hypoperfusion might play a role in the pathomechanism of END. Further research is needed to shed light on these pathomechanisms. Moreover, previously published data indicate that inflammatory parameters and imbalances between

### Table 4 Efficacy of DAPT in progressive lacunar strokes

| DAPT efficacy                  | DAPT (n = 78) | No DAPT (n = 26) | P value |
|-------------------------------|--------------|-----------------|---------|
| Fulfilled primary end-point   | 50 (64%)     | 10 (38%)        | 0.038   |
| Fulfilled secondary end-points|              |                 |         |
| Improvement of Rankin score   | 60 (77%)     | 18 (69%)        | 0.44    |
| No further fluctuation        | 63 (81%)     | 9 (35%)         | <0.001  |
| No bleeding complications     | 78 (100%)    | 26 (100%)       | –       |

DAPT, dual antiplatelet therapy. For efficacy end-points, National Institutes of Health Stroke Scale and Rankin scores were compared between discharge and admission. P values were calculated with Fisher’s exact test.
Figure 1  Benefit from DAPT (versus single antiplatelet therapy only) in subgroups defined by clinical (a) or neuroimaging (b) factors. The figure gives the odds ratio and 95% confidence interval from univariate logistic regression for DAPT (yes versus no) for clinical improvement in clinical/neuroimaging subgroups. DAPT, dual antiplatelet therapy; IA P value, P value of interaction test in logistic regression model testing the difference in DAPT benefit between subgroups.
excitatory and inhibitory neurotransmitters might also be involved in the pathophysiology and outcome of lacunar strokes, but they were not further analyzed in this study [7,18,19].

Furthermore, the POINT trial excluded patients with NIHSS ≥ 4 at admission [14]. However, 39% of all patients and 49% of patients with END presented with NIHSS ≥ 4 in our study and data about END and DAPT efficacy are still rare in this patient population [16].

It was demonstrated recently that 5 days of DAPT after END were associated with improved functional outcomes in progressive lacunar strokes, which was also observed in the patient population of this study [16]. Although the mechanisms of END and DAPT efficacy are not fully understood, atheromatous plaques might play an important role. Here, DAPT might improve functional outcome and reduce further fluctuation by reducing thrombus formation on sub-occlusive plaques. However, it remains unknown whether all patients with END have the same need and benefit from DAPT. In this regard, localization in the internal capsule or basal ganglia was identified as a significant predictive factor for a benefit from DAPT. Additionally, pontine localization, larger diameter, speckled shape of infarction and higher extent of microangiopathy were associated with substantially increased risks for poor functional outcomes after END occurred, whereas thalamic strokes were associated with improved functional outcome after END. These data emphasize the need for early MRI diagnostics to improve treatment decisions according to the predicted outcomes after END and benefit from DAPT.

Still, the results of this study are limited by the retrospective nature of the analysis and small patient numbers for the subgroup analysis of DAPT efficacy. Furthermore, the absence of randomization for different treatments induced potential selection bias and reasons for individual treatment decisions were retrospectively not determinable. For primary efficacy endpoint NIHSS scores were compared between discharge and admission which might underestimate DAPT efficacy but aimed to analyze clinically relevant, reliable and sustained DAPT efficacy. Therefore, prospective studies are necessary to validate identified predictive factors.

Conclusions

This study provides relevant clinical and neuroimaging factors predicting the occurrence of END in patients with lacunar strokes, the functional outcome after END and potential benefit from DAPT, which can easily be translated into clinical routine, and emphasizes the need for early performance of MRI diagnostics. Furthermore, the study provides data for patients with NIHSS ≥ 4 which were excluded from the POINT trial. Thereby, the results might improve the clinical management of patients with lacunar strokes.

Ethical approval

Ethical approval (S-109/2018) was obtained from the local ethics committee; informed consent was waived because this was a retrospective analysis.

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Author contributions

Anne Berberich: Substantial contributions to conception and design of study; acquisition, analysis and interpretation of data; writing and critical revision of manuscript. Christine Schneider: Substantial contributions to acquisition, analysis and interpretation of data; critical revision of manuscript. Christian Herweh: Substantial contributions to concept of study; acquisition, analysis and interpretation of data; critical revision of manuscript. Thomas Hielscher: Substantial contributions to analysis and interpretation of data, particularly the statistical analysis; critical revision of manuscript. Tilman Reiff: Substantial contributions to concept of study; interpretation of data and critical revision of manuscript. Martin Bendszus: Substantial contributions to concept of study and critical revision of manuscript. Christoph Gumbinger: Substantial contributions to conception and design of study; interpretation of data and critical revision of manuscript. Peter Ringleb: Substantial contributions to conception and design of study; acquisition and interpretation of data; writing and critical revision of manuscript.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Speckled DWI lesion.

Figure S2. Clinical improvement for patients with and without DAPT depending on different localizations of lacunar strokes.
Table S1. Baseline characteristics of all patients with detection of lacunar strokes by neuroimaging (computed tomography or MRI) and the subgroup of patients with MRI diagnostics only.

Table S2. Clinical outcome of all patients and of the subgroups of patients with and without END.

Table S3. Clinical and neuroimaging characteristics of all patients included in this study.

Table S4. Univariate logistic regression estimates for the association between clinical/neuroimaging risk factors and END.

Table S5. Baseline data (categorical variables) for the subgroup of patients with progressive lacunar stroke and treatment with or without DAPT.

Table S6. Baseline data (continuous variables) for the subgroup of patients with progressive lacunar stroke and treatment with or without DAPT.

Table S7. Efficacy of dual antiplatelet therapy depending on different clinical and neuroimaging risk factors in patients with progressive lacunar strokes.

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