The efficacy of thrombolysis in lacunar stroke – evidence from the Austrian Stroke Unit Registry

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Background and purpose: Intravenous thrombolysis (ivT) with recombinant tissue plasminogen activator is established in acute ischaemic stroke. Little is known, however, about its efficacy in different stroke subtypes.

Methods: A retrospective analysis of 128 733 patients from the Austrian Stroke Unit Registry was performed. Patients were classified as lacunar (LacS) or non-lacunar ischaemic stroke (nonLacS) by use of the clinical syndrome and technical findings. Outcome parameters were the short term improvement in the stroke unit [the difference of the National Institutes of Health Stroke Scale (NIHSS) score at admission and at discharge] and the modified Rankin Scale (mRS) score at 3 months. Patients were assigned to four groups according to thrombolysis and stroke subtype. To control for confounding, patients were matched for variables identified with impact outcome and for variables of general interest (NIHSS at admission, mRS before stroke and general risk factors).

Results: There were four matched groups of 401 cases each. In LacS median short term improvement was 3 [interquartile range (IQR) 2–5] NIHSS points in the thrombolysed patients and 2 (IQR 1–4) in the non-thrombolysed patients (P < 0.001). In the nonLacS groups median short term improvement was 3 (IQR 1–5) in the thrombolysed and 2 (IQR 0–4) in the non-thrombolysed patients (P < 0.001). At 3-month follow-up, ivT was significantly associated with a better functional outcome in LacS (P < 0.001) and nonLacS patients (P < 0.001). Taking magnetic resonance imaging as a requirement for stroke subtyping led to similar results.

Conclusions: Patients with both lacunar and non-lacunar stroke benefitted from ivT. The degree of improvement was similar in both groups.
compared only thrombolysed patients of different stroke subtypes [9–12]. The European Cooperative Acute Stroke Study (ECASS) ivT trials did not differentiate between different stroke subtypes [13,14]. Most importantly, in the two large randomized rtPA studies (NINDS and IST-3 [6,7]) the assignment of the patients to the different stroke subtypes was done at admission prior to ivT [15]. Thus, classification was based on clinical information only, neglecting technical, e.g. radiological, findings. This approach leads to misclassification in one-fifth of cases [16].

In this work the efficacy of ivT in LacS was studied. By using data from a nationwide stroke registry and by employing a strict definition of LacS, thrombolysed versus non-thrombolysed patients with LacS and non-LacS were compared.

Methods

The Austrian Stroke Unit Registry

Since 2003, a network of stroke units covering the whole country (Austrian Stroke Unit Network) prospectively has been collecting data on standard characteristics and acute management of all stroke patients admitted to 33 of 34 stroke units. Data collection and ratings are performed by experienced stroke neurologists using standardized variable definitions and scores. Evaluations are done at the time of admission to and discharge from the stroke unit and are supplemented by a 3-month follow-up (3MoFU) call. To ensure high data quality, immediate data entry is obligatory. The web-based database features online plausibility checks. The scoring procedures and variable assessment are regularly discussed in national meetings. Details on the registry have been reported previously [17]. The modified Rankin Scale (mRS) score from before stroke was assessed on admission, and the mRS score was again done at discharge from the stroke unit as well as at the 3MoFU. The National Institutes of Health Stroke Scale (NIHSS) score was evaluated on admission to and at discharge from the stroke unit.

Hypertension, diabetes mellitus and hyperlipidaemia were diagnosed according to international criteria. Atrial fibrillation, if not already known before stroke, was diagnosed on the admission electrocardiogram (ECG) or during ECG monitoring on the stroke unit. Risk factors were coded at the time of discharge from the stroke unit.

For thrombolysis, rtPA alteplase was administered according to the NINDS trial [6] at a dose of 0.9 mg/kg body weight, not exceeding a total of 90 mg, with 10% given as a bolus.

Definition of terms

In the registry ischaemic strokes are classified at the time of discharge from the stroke unit when the results of ancillary diagnostic findings and all relevant historical details are available. The aetiology is classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [18]. For this study patients were assigned to two groups of stroke aetiology: ‘lacunar’ (LacS) and ‘non-lacunar’ (non-LacS), where the nonLacS group excluded patients with an unknown cause of stroke. This resulted in the exclusion of unclassifiable cases, which is why the relative proportion of stroke subtypes covered in this work differs from the numbers published in epidemiological studies on stroke subtypes.

Symptomatic intracerebral haemorrhage (SICH) was rated according to the National Institute of Neurological Disorders and Stroke criteria [any bleeding documented by CT or magnetic resonance imaging (MRI) with clinical deterioration of ≥1 point on the NIHSS or leading to death in <7 days] [6].

The filtering process, building of groups and statistics

The whole dataset of patients in the registry was filtered by a set of selection criteria (Fig. 1). These were as follows: acute stroke, yes; syndrome, ischaemia; NIHSS at admission between 1 and 16 inclusive; age between 18 and 89 inclusive; mRS prior to the event ≤2; onset-to-door time (ODT) ≤240 min in those subjects undergoing thrombolysis; being treated on the stroke unit for between 1 and 9 days inclusive; not undergoing catheter-based intra-arterial recanalizing procedures; the possibility of assigning the patient’s stroke to either LacS or non-LacS; and the availability of the full dataset including the 3MoFU. Patients with a pre-stroke mRS of ≥3 were excluded in the main analysis because any improvement of neurological deficits on the background of pre-stroke disability is difficult to discern. A sensitivity analysis included patients with all ranges of pre-stroke disability.

The resulting population (group I) was then divided into four subgroups according to stroke subtype and to treatment status (thrombolysis versus non-thrombolysis): LacS–Lysis, LacS–noLysis, nonLacS–Lysis and nonLacS–noLysis (Table 1).

Patients were matched from the smallest of the subgroups to patients of the other three subgroups according to the following variables: age, stroke severity (measured by the NIHSS), pre-stroke disability (measured by the mRS), sex, hypertension, diabetes and hypercholesterolaemia.
As MRI increases the diagnostic certainty in stroke subtyping, group I was further refined by requiring an MRI as part of the diagnostic work-up. The resulting group II was then subjected to the same matching process as group I, again yielding four subgroups.

The variable age was treated as continuous numeric variable, computed as days between birth and stroke event divided by 365.25. Concerning the stroke severity (NIHSS), for values ≤3 an exact match was required whilst for higher values a match using the square root

Figure 1  Flow diagram of the filtering process of the total registry population.
of the NIHSS score was used. All other variables were on an ordinal scale (pre-stroke disability) or on a dichotomous level of measurement (sex, hypertension, diabetes), and exact matching was required.

Group comparisons of continuous (age, NIHSS) or ordinal (mRS) variables were performed with the Kruskal–Wallis rank sum test. Correlations between categorical variables were tested with the chi-squared contingency table test or Fisher’s exact test as appropriate. All data were processed using the statistical environment R, version 2.15.2 [19].

Results
By November 2015 the database contained 128 733 patients with acute ischaemic stroke. Application of the selection criteria yielded a final study population of 10 632 cases (group I). Amongst these an MRI was available for 6744 (group II) (Fig. 1).

Patient characteristics
Within group I of 10 632 patients 3988 (37.5%) of the strokes were categorized as lacunar (LacS). Of these, 496 (12.4%) patients underwent ivT. 6644 (62.5%) patients were classified to have a non-lacunar type of stroke (nonLacS) and, of these, 1220 (18.7%) patients underwent ivT.

Patients with LacS were younger than their nonLacS counterparts [71.1 years (interquartile range IQR 62.5–78.4) vs. 72.2 (IQR 62.7–79.7), \( P = 0.003 \)] and, at admission, were neurologically less affected [NIHSS at admission 3 (IQR 2–5) vs. 4 (IQR 2–7), \( P < 0.001 \)].

Outcome according to stroke type
Matching within group I yielded four subgroups of 401 patients each who were comparable with regard to variables possibly confounding the outcome (Table 1). The ODT, however, was considerably shorter in the thrombolysed patients (median 80 and 75 min for the LacS/C0 Lysis and nonLacS/C0 Lysis groups, respectively, and 242 and 160 min for their non-thrombolysed counterparts) (Table 1). The onset-to-treatment time was practically the same in the LacS/C0 Lysis group as in the nonLacS/C0 Lysis group [median 130 min (IQR 100–170) vs. 130 (IQR 99.5–170.5), \( P = 0.63 \)].

In non-thrombolysed patients, short term improvement in the NIHSS (i.e. during the stay in the stroke unit) was seen both in LacS and nonLacS, but patients with LacS improved slightly more (2 points, IQR 1–4) than nonLacS patients (2 points, IQR 0–4, \( P = 0.044 \)) (Fig. 2). At the 3MoFU, the non-thrombolysed LacS patients had a marginally lesser degree of handicap as compared to their nonLacS peers (\( P = 0.054 \)) (Fig. 3).

Outcome according to thrombolysis
Short term improvement in the NIHSS was more pronounced in the subgroups undergoing ivT. In LacS median improvement was 3 (IQR 2–5) in the thrombolysed and 2 (IQR 1–4) in the non-thrombolysed

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<th>Table 1 Demographic and stroke-associated data of the four groups that resulted after matching</th>
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<td>Symptomatic intracranial haemorrhage, n (%)</td>
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<td>IQR, interquartile range; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.</td>
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<td>aAtrial fibrillation was an exclusion criterion for lacunar stroke.</td>
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patients ($P < 0.001$). In the nonLacS groups median improvement was 3 (IQR 1–5) in the thrombolysed and 2 (IQR 0–4) in the non-thrombolysed patients ($P < 0.001$) (Fig. 2).

Concerning the mRS at 3MoFU ivT was significantly associated with a better functional outcome in both LacS ($P < 0.001$) and nonLacS patients ($P < 0.001$) (Fig. 3).

Neurological dysfunction generally improves early after stroke. Therefore, a longer stay on the stroke unit might allow for more improvement of the NIHSS (which was determined at discharge from the stroke unit) and might thereby confound the outcome. Duration of stay at the stroke unit, however, was somewhat shorter for the LacS patients (median 3 days, IQR 2–4) than for the nonLacS patients (median 3, IQR 2–5; $P = 0.001$). Length of stay was very similar for thrombolysed and non-thrombolysed patients (for both, median 3, IQR 2–5, $P = 0.335$). Therefore, an excess of improvement of the LacS over the nonLacS patients due to a longer stay on the stroke unit can be ruled out.

Results with stricter definition of stroke type by use of MRI

Amongst group II of 6744 with MRI available, 2472 patients were classified as LacS (36.6%) and 4272 as nonLacS (63.4%). Thus, incorporating the MRI into the criteria for stroke subtyping did not change the relative proportion of LacS versus nonLacS.

Matching yielded four subgroups of 229 patients each. Here, the results were in line with those of the larger population. In LacS median short term improvement was 3 (IQR 2–5) in the thrombolysed and 2 (IQR 0–4) in the non-thrombolysed patients ($P < 0.001$). In the nonLacS groups median short term improvement was 3 (IQR 2–5) in the thrombolysed and 2 (IQR 1–4) in the non-thrombolysed patients ($P < 0.001$).

With respect to the mRS at 3MoFU, ivT was associated with a better functional outcome in both LacS ($P < 0.001$) and nonLacS patients ($P < 0.001$).

Results with inclusion of all ranges of pre-stroke disability

The exclusion of a pre-stroke disability grade of mRS $>2$ was done to allow for improvement after the stroke. As this selection criterion might introduce bias a sensitivity analysis was done with all ranges of pre-stroke disability including patients without MRI which now increased the subgroups to 413 patients each. Again, the results were very similar to the analyses described above. In LacS median short term improvement was 3 (IQR 2–5) in the thrombolysed and 2 (IQR 1–4) in the non-thrombolysed patients ($P < 0.001$). In the non-LacS groups median short term improvement was 3 (IQR 1–5) in the thrombolysed and 2 (IQR 0–4) in the non-thrombolysed patients ($P < 0.001$). At the 3MoFU thrombolysed patients had lower mRS with both LacS ($P < 0.001$) and nonLacS ($P < 0.001$).

Intracranial haemorrhage

The rate of SICH as a possible side effect of ivT was determined from the 49401 matched patients from group I. Amongst the LacS group SICH occurred in 1.0% of the thrombolysed and 0.2% of the non-thrombolysed patients ($P = 0.02$, Fisher’s exact test).

Discussion

In this study of a nationwide stroke registry the clinical outcome of LacS versus nonLacS and the effect of ivT on different subtypes of stroke were investigated. The very large database allowed for the generation of matched patient groups, thereby adjusting for confounding variables.

It was first shown that, irrespective of ivT, patients with LacS did better than their nonLacS counterparts both in terms of short term improvement and at the
3MoFU. This is in line with other non-randomized studies [8–12] that found better or comparable short and/or long term outcomes of LacS versus other stroke types. As our patient samples were matched for confounding variables our finding of more improvement in LacS versus nonLacS seems to be attributable to the type of stroke rather than, for example, age or pre-existing handicap. Smaller infarct volumes and differences in neuronal plasticity may play a role in this phenomenon.

Concerning the effect of ivT our analyses show that patients with both LacS and nonLacS significantly benefitted from ivT, and that the magnitude of this benefit is no less in LacS than in nonLacS.

The NINDS [6] and IST-3 [7] were randomized trials comparing ivT to placebo, and both found ivT to be effective in LacS [15]. However, in these studies the assignment to stroke subtype was done at admission and was merely based on clinical judgement, neglecting the results of, for example, imaging studies. This has been shown to lead to misclassification in one-fifth of cases [16]. In contrast, our classification was based on technical studies (including neuroimaging, vascular and cardiological studies) in addition to the clinical syndrome and on the clinical course during the first days. It is therefore assumed that the rate of misclassification in our study is low enough for our results to be valid. This assumption is supported by the fact that our results remain the same when MRI was required for the assignment to stroke subtype, as lacunar infarcts can be more reliably diagnosed by MRI than by CT.

In our study, SICH occurred more frequently in thrombolysed than in non-thrombolysed patients and in nonLacS than in LacS patients. In patients receiving ivT the Austrian stroke units perform follow-up neuroimaging some 24 h after treatment, whilst this is not routinely done in non-thrombolysed patients. Bleeding is recorded if clinically relevant, and no distinction between parenchymal mass bleeding and microbleeds is made. Therefore, the registry is not adequately designed to compare the type and relative rate of bleeding after ivT. Hence, it was not possible to draw any meaningful conclusions on the risk and the type of bleeding associated with ivT in LacS. As SICH, by definition, affects neurological functioning, however, any clinically relevant bleeding would be accounted for by the clinical outcome parameters.

Hwang et al. raised concern about potentially higher rates of early neurological deterioration in LacS after ivT [20]. This phenomenon was not seen in our study. However, since ivT afforded a better long term clinical outcome in the LacS patients, and since SICH rates were low in these subjects, early neurological deterioration may rather reflect the natural history of gradual deterioration and fluctuation known for LacS.

Our study has limitations. The matching process does not account for unknown variables that might impact the outcome. One such variable was the ODT that, as expected, was much longer in the groups not given ivT. The registry does not capture the reasons for not administering ivT to an individual patient. However, the ODT as a main contributor to the onset-to-treatment time along with other factors such as oral anticoagulation, recent surgery, recent bleeding etc. is probably the most pertinent reason for forgoing ivT. Clinical deterioration after admission to the hospital, as measured by the NIHSS, is often observed in acute stroke patients. In embolic stroke this may be due to collapsing collaterals, and in lacunar stroke progressive narrowing of the vessel lumen in the hours after stroke onset may be the cause. Earlier presentation after stroke onset (i.e. shorter ODT) may therefore imply a higher potential for further worsening, and thereby a worse outcome. It is therefore thought that the differences in the ODT between groups does not invalidate the result on the efficacy of ivT in LacS.

Although our study is non-randomized and therefore does not represent the study design desired to firmly prove the efficacy of ivT in LacS, it is quasi population-based, is multi-centric, features prospective data
collection, has a large number of patients and allows for matching to adjust for known confounding variables.

Studies on the relative efficacy of ivT in different types of stroke are subject to restrictions inherent to the biology of stroke. At least theoretically, ivT may lead to recanalization before irreversible brain damage occurs and may let the clinical syndrome appear as transitory ischaemic attack. In this case neuroimaging would not show acute infarction. In addition, infarcts of lacunar shape on imaging might theoretically result after ivT-induced recanalization of embolically occluded intracranial vessels. Therefore, ivT by itself might lead to misclassification of the stroke aetiology. This limitation could only be overcome if the aetiology of the patient’s stroke were reliably determined before ivT by, for example, perfusion imaging and angiography. Whilst for large embolic territorial infarcts this is well established, the spatial resolution of the current techniques is only rarely sufficient to reliably catch perfusion deficits due to the occlusion of small vessels [21].

In conclusion, our study strongly supports the notion that ivT is beneficial for patients not only with embolic but also with lacunar ischaemic stroke.

Ethical approval
The Austrian Stroke Unit Registry is part of a governmental quality assessment programme for stroke care in Austria sponsored by the Federal Ministry of Health. It is based on federal law promoting quality in health care. Anonymized data are centrally administered by the Gesundheit Österreich GmbH, and scientific analyses are approved and supervised by an academic review board. This was a non-interventional study using anonymized data.

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Disclosure of conflicts of interests
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