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ORIGINAL COMMUNICATION

Outcome of patients with large vessel occlusion in the anterior circulation and low NIHSS score

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Abstract

Background Optimal management of patients with large vessel occlusion (LVO) and low NIHSS score is unknown, which was the aim to investigate in this study.

Methods This is a retrospective analysis of a prospective single tertiary care centre 14-year cohort of patients with LVO in the anterior circulation and NIHSS score ≤ 5 on admission. Outcome was analysed according to primary intended therapy.

Results Among 185 patients (median age 67.4 years), 52.4% received primary conservative therapy (including 26.8% secondary reperfusion in case of secondary neurological deterioration), 12.4% IV thrombolysis (IVT) only and 35.1% primary endovascular therapy (EVT). 95 (51.4%) patients experienced neurological deterioration until 3 months. Primary-IVT-only and primary-EVT compared to conservative-therapy patients had better 3 months' outcome (54.5% vs. 30.8%: $_{adjusted}$OR 6.02; $_{adjusted}p = 0.004$ for mRS 0–1 and 54.7% vs. 30.8%: $_{adjusted}$OR 5.09; $_{adjusted}p = 0.002$, respectively). Also mRS shift analysis favored primary-IVT-only and primary-EVT patients ($_{adjusted}$OR 6.25; $_{adjusted}p = 0.001$ and $_{adjusted}$OR 3.14; $_{adjusted}p = 0.003$). Outcome in primary-IVT-only vs. primary-EVT patients did not differ significantly. Patients who received secondary EVT because of neurological deterioration after primary-conservative-therapy had worse 3 months' outcome than primary-EVT patients (20.8% vs. 30.8%: $_{adjusted}$OR 0.24; $_{adjusted}p = 0.047$ for mRS 0–1 and $_{adjusted}$OR 0.31; $_{adjusted}p = 0.019$ in mRS shift analysis). Survival and symptomatic intracranial haemorrhage did not differ amongst groups.

Conclusions Our data indicate that primary IVT and/or EVT may be better than primary conservative therapy in patients with LVO in the anterior circulation and low NIHSS score. Furthermore, primary EVT was better than secondary EVT in case of neurological deterioration. There is an unmet need for RCTs to find the optimal therapy for this patient group.

Keywords Low NIHSS score · Large vessel occlusion · Different therapy modalities · NIHSS score subitems · Outcome

Introduction

Up to 30% of patients with large vessel occlusion (LVO) in the anterior circulation and good collaterals present with NIHSS score ≤ 5 [1–6]. Many of these patients tend to be treated conservatively without thrombolysis and/or thrombectomy, because minor neurological deficits have to be balanced against potential risks of reperfusion therapy. Nevertheless, up to 40% of conservatively treated patients suffer from secondary neurological deterioration (SND) and potentially unfavourable outcome, especially in case of persistent LVO [7–10].

Besides conservative therapy, potential treatment options in patients with LVO and low NIHSS score include intravenous thrombolysis (IVT), endovascular therapy (EVT) or

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IVT followed by EVT. In addition, in case of SND in primary conservatively treated patients secondary reperfusion (=rescue) therapy with IVT and/or EVT may be chosen. There are few mostly retrospective studies addressing different treatment options in limited number of patients and results are conflicting [10–24].

In the RCT EVT trials, only MR CLEAN and EXTEND-IA included patients with NIHSS score ≤ 5. However, number of patients included with low NIHSS score was small and definite conclusions remain open [1].

In a retrospective study of 88 patients with LVO in the anterior circulation and NIHSS score ≤ 5 we found higher rates of SND but similar 3 months' outcome in patients who had been treated conservatively compared to those treated by reperfusion therapy [10]. Nevertheless, our findings were limited due to selection bias, the relatively small number of patients and an unadjusted analysis. Furthermore, we did not analyse IVT and/or EVT separately.

The primary aim of the present study was to perform an analysis according to the primary intended therapy in an enlarged group of patients with LVO in the anterior circulation and low NIHSS score and to compare effectiveness and safety of different treatment regimes.

Methods

We performed a retrospective analysis of consecutive patients with LVO in the anterior circulation and low NIHSS score. We included all patients admitted from 01/2004 to 04/2018 who had been recorded in our prospective Bernese database, if they presented with transient ischaemic attacks (according to the tissue-based ASA/AHA definition) and/or mild symptoms (NIHSS score ≤ 5) at the emergency department [25]. LVO was defined as acute occlusion of the internal carotid artery (ICA), the carotid terminus (ICA-T), the main stem of the middle cerebral artery (M1-segment; MCA) or as tandem occlusion (ICA and MCA). Baseline characteristics, demographic data and vascular risk factors were recorded prospectively. Clinical evaluation was performed by a stroke neurologist using the 15-item version of the NIHSS score, being certified for its scoring [26].

Shortly after initial clinical evaluation, all patients underwent CT-imaging including a native scan, CT-angiography and CT-perfusion and/or multimodal 3T-MR-imaging, including axial fluid-attenuated inversion recovery-images, diffusion-weighted, time-of-flight angiography, perfusion-weighted images and susceptibility-weighted images at the emergency department. All images were reviewed retrospectively by a stroke neurologist and a neuroradiologist blinded to clinical findings.

The treatment decision was made on an individual basis by considering, e.g. time from symptom onset, personal history, IVT contraindications, type of neurological deficits and likely disability. The applied EVT procedure was as follows if feasible: approaching/passing the thrombus with a microwire, application of angioplasty balloon catheters, clot aspiration, retrievable stents (from 2010) and if needed permanent extracranial stent placement. After emergency therapy, patients received intensive monitoring by standard stroke unit care and/or intermediate/intensive care if deemed necessary.

For this analysis we reviewed all patient records and defined therapy modality groups as follows (SND was defined as NIHSS score increase of ≥ 1 point compared to admission):

1. Primary-conservative-therapy patients: Initially treated conservatively and by reperfusion therapy in case of SND by IVT, EVT or both.
2. Primary-IVT-only (=primary reperfusion) patients: Initially treated by IVT only and by EVT in case of SND.
3. Primary-EVT (=primary reperfusion) patients: Initially treated by EVT with or without prior IVT.

Additionally, we analyzed a subgroup of the primary-conservative-therapy group:

1. Secondary-reperfusion patients: Reperfusion therapy using IVT, EVT or both in case of SND.

Patients were followed-up face to face by a stroke neurologist after 1 day, at discharge, at 3 months and at SND. Additionally, they were followed-up by multimodal CT- and/or MR-angiography (CTA/MRA) after 1 day, at 3 months and at SND. Clinical outcome was measured with modified Rankin scale [mRS; excellent outcome (mRS 0–1), favourable outcome (mRS 0–2)] and National Institutes of Health Stroke Scale score (NIHSS score), for which the scoring stroke neurologist was certified [26, 27].

During the 3 months' follow-up period, we recorded all SND confirmed by two independent stroke neurologists and which correlated with a manually outlined increased infarct volume.

Statistical analysis

Baseline characteristics, demographic data, vascular risk factors, baseline imaging findings, therapy details and outcome variables were compared between therapy modality groups, using χ^2-test for categorical variables and Fisher exact test if appropriate and one-way ANOVA and Mann–Whitney U Test if appropriate for continuous and ordinal variables. Binary outcome variables stratified according to therapy modality groups were analysed with logistic regression analysis, continuous outcome variables

and partially NIHSS score with linear regression analysis. For logistic regression, NIHSS subitems were dichotomized in normal vs. pathological findings. NIHSS score, mRS and NIHSS subitems were also analysed with ordinal regression analysis (= shift analysis). Groups were compared as follows: primary-IVT-only vs. primary-conservative-therapy, primary-EVT vs. primary-conservative-therapy, primary-EVT vs. primary-IVT-only and secondary-reperfusion-therapy vs. primary-EVT. Analyses were adjusted for time lapse, precise location of acute vessel occlusion, modified TOAST criteria, vascular risk factors, sex, admission NIHSS score and subitems and chronic co-/pre-existing LVO at an asymptomatic site in logistic, linear and ordinal regression analyses (details of adjustment are listed in the online resource material Methods S1) if they differed significantly ($p < 0.05$) or showed a trend towards a difference ($p < 0.1$) in between-two-group-comparisons. Sensitivity analyses confined to patients with < 4.5 h until time point of first therapy (or its decision if no IVT/EVT performed), to patients with ICA or tandem occlusion, to patients with NIHSS score 0 and also to those admitted after 2010 were carried out. Furthermore, we performed analyses with patients grouped not only as intended-to-treat but also as as-finally-treated. Statistical analysis was performed using SPSS 25.0 (SPSS Inc./Chicago/Illinois/USA).

Results

From 01/2004 to 04/2018, 1621 patients with TIA or acute ischaemic stroke admitted to our Bernese Stroke centre had LVO in the anterior circulation. Of them, 185 (11.4%) had a NIHSS score ≤ 5 and were included in our study. 97 (52.4%) received primary conservative therapy, 23 (12.4%) primary IVT only and 65 (35.1%) primary EVT. 30 (16.2%) patients who suffered SND received secondary reperfusion therapy (every fourth and every fifth patient initially treated conservatively and by IVT only) (Fig. 1). There were differences in time lapse from symptom onset to admission and therapy, in sex, admission NIHSS score, event aetiology, location of acute vessel occlusion and admission NIHSS subitems [facial palsy, motor arm left, motor leg right] amongst groups. Baseline characteristics, demographic data, vascular risk factors, imaging findings and therapy details are listed in Table 1 and admission NIHSS subitems in the online resource material Table S3A.

Outcome overall At 3 months, SND had been observed in 95 (51.4%) patients, a NIHSS score increase of ≥ 4 points in 59 (31.9%), excellent outcome in 72 (40.7%), favourable outcome in 121 (68.4%) and survival in 158

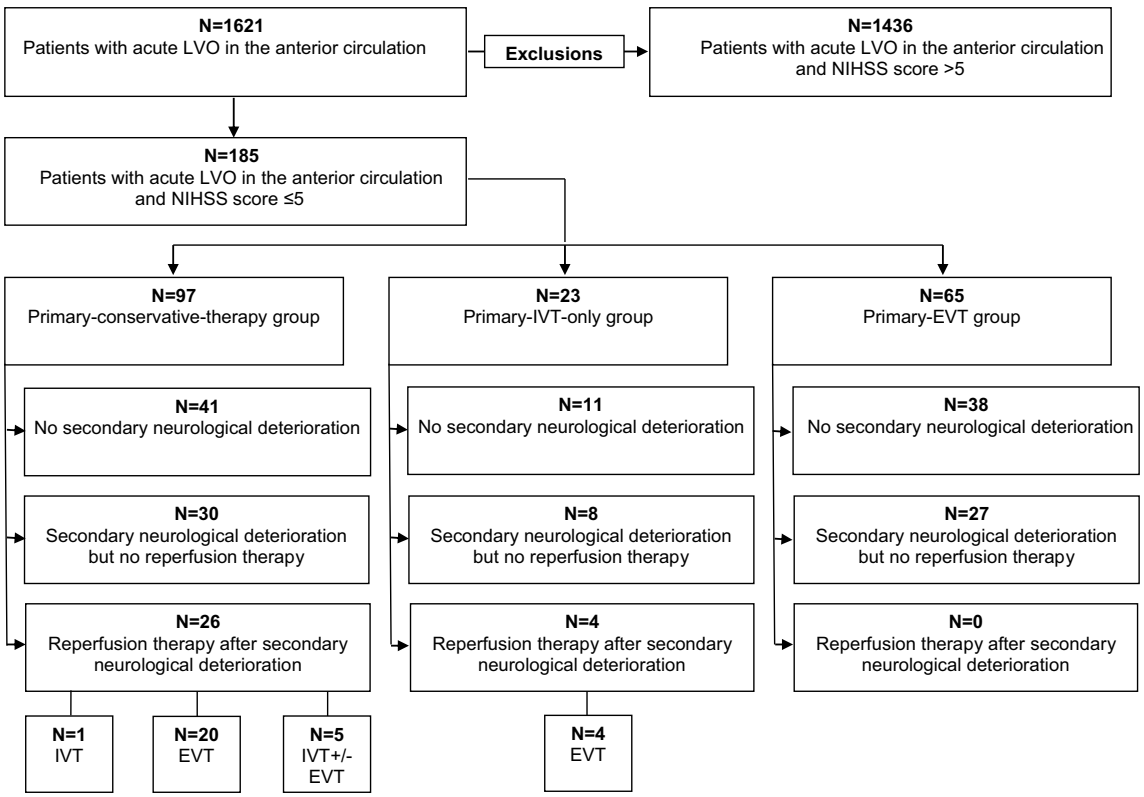

Fig. 1 Flow chart of patients in the study period

Table 1 Baseline characteristics, demographic data, vascular risk factors, imaging findings, therapy details according to therapy modality

	Primary-conservative-therapy group ($n=97$)	Primary-IVT-only group ($n=23$)	Primary-EVT group ($n=65$)	P trend value[a]	Secondary-reperfusion group ($n=26$)	P value[b]
Age (median, range)	66.3 (23.2–93.5)	66.5 (49.1–90.1)	71.0 (19.0–95.5)	0.982	65.4 (42.3–93.2)	0.895
Women	38 (39.2%)	7 (30.4%)	37 (56.9%)	0.030	11 (42.3%)	0.207
Vascular risk factors						
Arterial hypertension	64 (66%)	17 (73.9%)	40 (61.5%)	0.554	18 (69.2%)	0.490
Diabetes mellitus	20 (20.6%)	1 (4.3%)	9 (13.8%)	0.133	7 (26.9%)	0.139
Hypercholesterolaemia	62 (63.9%)	14 (60.9%)	41 (63.1%)	0.963	16 (61.5%)	0.891
Atrial fibrillation	21 (21.6%)	7 (30.4%)	22 (33.8%)	0.214	7 (26.9%)	0.522
Cardiac failure	13 (13.4%)	2 (8.7%)	7 (10.8%)	0.774	5 (19.2%)	0.281
Current smoking	29 (29.9%)	5 (21.7%)	16 (25.8%)	0.687	9 (34.6%)	0.313
Previous smoking	17 (18.7%)	5 (21.7%)	9 (15%)	0.736	4 (16.7%)	0.404
Coronary heart disease	19 (19.8%)	3 (13%)	9 (13.8%)	0.535	6 (24%)	1.000
Previous stroke	14 (14.4%)[c]	0	13 (20%)[c]	0.065	4 (15.4%)[c]	0.247
Premorbid intake of antithrombotics						
Anticoagulants	12 (12.4%)	1 (4.3%)	11 (16.9%)	0.294	5 (19.2%)	0.769
Antiplatelets	30 (30.9%)	7 (30.4%)	15 (23.1%)	0.533	6 (23.1%)	1.000
Event aetiology according to modified TOAST criteria				< 0.0001		0.012
Large artery disease	28 (28.9%)	7 (30.4%)	7 (10.8%)		10 (38.5%)	
Cardioembolism	15 (15.5%)	7 (30.4%)	27 (41.5%)		6 (23.1%)	
Other determined	23 (23.7%)	2 (8.7%)	9 (13.8%)		4 (15.4%)	
Undetermined, evaluation complete	6 (6.2%)	3 (13%)	6 (9.2%)		1 (3.8%)	
Undetermined, evaluation incomplete	8 (8.2%)	4 (17.4%)	12 (18.5%)		1 (3.8%)	
Two or more potential causes	17 (17.5%)	0	4 (6.2%)		4 (15.4%)	
Time delays (median minutes, range)						
From symptom onset to admission	257	92	152	< 0.0001	186	0.617
From symptom onset to therapy	395[d]	180[d]	248[d]	< 0.0001	310[d]	0.311
Symptoms before admission						
Improving	35 (36.1%)	12 (52.2%)	21 (32.3%)	0.232	7 (26.9%)	0.615
Fluctuating	30 (30.9%)	3 (13%)	19 (29.2%)	0.223	10 (38.5%)	0.393
Progressive	9 (9.3%)	1 (4.3%)	4 (6.2%)	0.627	3 (11.5%)	0.403
Admission NIHSS score (median, range)	2 (0–5)	4 (0–5)	4 (0–5)	< 0.0001	3 (0–5)	0.030
Independent (mRS 0–1) before event	89 (91.8%)	22 (95.7%)	58 (89.2%)	0.629	25 (96.2%)	0.292
Admission MRA	80 (82.5%)	19 (82.6%)	55 (84.6%)	0.934	20 (76.9%)	0.384
Location of acute vessel occlusion				< 0.0001		0.001
ICA occlusion	55 (56.7%)	10 (43.5%)	5 (7.7%)		9 (34.6%)	
ICA-T occlusion	2 (2.1%)	0	2 (3.1%)		1 (3.8%)	
M1 occlusion	28 (28.9%)	9 (39.1%)	53 (81.5%)		10 (38.5%)	
ICA and MCA tandem occlusion	12 (12.4%)	4 (17.4%)	5 (7.7%)		6 (23.1%)	

Table 1 (continued)

	Primary-conservative-therapy group ($n=97$)	Primary-IVT-only group ($n=23$)	Primary-EVT group ($n=65$)	P trend value[a]	Secondary-reperfusion group ($n=26$)	P value[b]
Chronic vessel occlusion of ICA or VA	7 (7.2%)	1 (4.3%)	2 (3.1%)	0.506	4 (15.4%)	0.053
Therapy modality				< 0.0001		0.146
Conservative therapy	71 (73.2%)	0	0		0	
Intravenous rt-PA (IVT)	1 (1%)	19 (82.6%)	0		1 (3.8%)	
IA-Urokinase	1 (1%)	0	10 (15.4%)		1 (3.8%)	
Mechanical thrombectomy	18 (18.6%)	0	32 (49.2%)		18 (69.2%)	
IA-Urokinase and thrombectomy	1 (1%)	0	3 (4.6%)		1 (3.8%)	
Bridging	5 (5.2%)	4 (17.4%)	20 (30.8%)		5 (19.2%)	
First therapy decision > 4.5 h	42 (43.3%)	2 (8.7%)	24 (36.9%)	0.173	9 (34.6%)	0.836

Numbers are presented as number (%) unless otherwise specified. Percentages are indicating available data. *MRA* magnetic resonance angiography, *VA* vertebral artery, *IA* intra-arterial

[a]*P* values indicate heterogeneity across all three groups

[b]*P* values compare primary-EVT vs. secondary-reperfusion groups

[c]Three patients in the primary-conservative-therapy, four in the primary-EVT and one in the secondary-reperfusion group suffered the event within 2 months prior to the new event (relative contraindication for IVT and EVT according to our local guidelines)

[d]Time of first therapy (or decision for conservative therapy)

(89.3%). There were no differences in survival, asymptomatic intracerebral haemorrhage (ICH) and symptomatic ICH (sICH) amongst groups. Four of six sICH occurred in primary-EVT patients (all from 2013), of which two (50%) were fatal, one in a patient with underlying endocarditis and one in a patient who bled outside the infarcted tissue in another vessel territory after having received intra-arterial Urokinase. One non-fatal sICH causing SND each occurred in one primary-IVT-only patient (2007) as well as in one primary-conservative-therapy patient after secondary reperfusion therapy (2017). Five asymptomatic iatrogenic ICA dissections occurred in primary-EVT patients (all from 2014), and two craniectomies were performed in primary-conservative-therapy patients after secondary reperfusion (all from 2015). One iatrogenic clot fragmentation was observed in primary-IVT-only (2009) and one in primary-conservative-therapy patients after secondary reperfusion (2015).

Primary-IVT-only vs. primary-conservative-therapy patients showed less SND (52.2% vs. 57.7%): $_{\text{adjusted}}$OR 0.29; $_{\text{adjusted}}p=0.035$, less persistent LVO before first SND (59.1% vs. 85.9%): $_{\text{adjusted}}$OR 0.20; $_{\text{adjusted}}p=0.021$ and less perfusion failure/thrombus growth (39.1% vs. 50.5%): $_{\text{adjusted}}$OR 0.23; $_{\text{adjusted}}p=0.013$. They had a shorter stay in acute care hospital, better 3 months' outcome: excellent (54.5% vs. 30.8%): $_{\text{adjusted}}$OR 6.02; $_{\text{adjusted}}p=0.004$, favourable (81.8% vs. 63.7%): $_{\text{adjusted}}$OR 7.64; $_{\text{adjusted}}p=0.011$, a better 3 months' mRS shift $_{\text{adjusted}}p=0.001$, less 3 months' NIHSS score increases (18.2% vs. 39.5%): $_{\text{adjusted}}$OR 0.17; $_{\text{adjusted}}p=0.011$, more 3 months' NIHSS score decreases (72.7% vs. 40.7%): $_{\text{adjusted}}$OR 5.03; $_{\text{adjusted}}p=0.011$ and a better 3 months' NIHSS score shift ($_{\text{adjusted}}p<0.0001$).

Primary-EVT vs. primary-conservative-therapy patients showed less SND (41.5% vs. 57.7%): $_{\text{adjusted}}$OR 0.26; $_{\text{adjusted}}p=0.004$, less persistent LVO before first SND (12.3% vs. 59.1%): $_{\text{adjusted}}$OR 0.03; $_{\text{adjusted}}p<0.0001$, less perfusion failure/thrombus growth (18.5% vs. 50.5%): $_{\text{adjusted}}$OR 0.15; $_{\text{adjusted}}p<0.0001$, but more recurrent embolism (15.4% vs. 4.1%): $_{\text{adjusted}}$OR 82.90; $_{\text{adjusted}}p<0.15$. They had a shorter hospital stay, better 3 months' excellent outcome (54.7% vs. 30.8%): $_{\text{adjusted}}$OR 5.09; $_{\text{adjusted}}p=0.002$, a better 3 months' mRS shift $_{\text{adjusted}}p=0.003$, less 3 months' NIHSS score increases (21.9% vs. 39.5%): $_{\text{adjusted}}$OR 0.25; $_{\text{adjusted}}p=0.006$, more 3 months' NIHSS score decreases (71.9% vs. 40.7%): $_{\text{adjusted}}$OR 4.39; $_{\text{adjusted}}p=0.002$ and a better 3 months' NIHSS score shift ($_{\text{adjusted}}p=0.002$).

Primary-EVT vs. primary-IVT-only patients did not differ significantly.

Secondary-reperfusion vs. primary-EVT patients showed more multiple (= deteriorated neurologically more than once) SND (61.5% vs. 23.1%): $_{\text{adjusted}}$OR 9.31; $_{\text{adjusted}}p=0.003$, more persistent LVO before first SND (92.3% vs. 12.3%): $_{\text{adjusted}}$OR 519; $_{\text{adjusted}}p<0.0001$, more perfusion failure/thrombus growth (92.3% vs. 50.5%):

$_{adjusted}$OR 68.6; $_{adjusted}p < 0.0001$, more local reocclusion (19.2% vs. 5.2%): $_{adjusted}$OR 25.15; $_{adjusted}p = 0.022$ and higher median peak NIHSS score (17 vs. 5); $_{adjusted}p = 0.009$. They had a longer hospital stay, worse 3 months' excellent outcome (20.8% vs. 30.8%): $_{adjusted}$OR 0.24; $_{adjusted}p = 0.047$, a worse 3 months' mRS shift $_{adjusted}p = 0.019$, more 3 months' NIHSS score increases (62.5% vs. 21.9%): $_{adjusted}$OR 5.73; $_{adjusted}p = 0.006$, less 3 months' NIHSS score decreases (25% vs. 71.9%): $_{adjusted}$OR 0.12; $_{adjusted}p = 0.003$ and a worse 3 months' NIHSS score shift ($_{adjusted}p = 0.001$).

Results including NIHSS subitems analyses and sensitivity analyses confined to patients within < 4.5 h until reperfusion therapy or decision for conservative therapy, to ICA or tandem occlusion, to NIHSS score 0 and including analyses with patients grouped not as intended-to-treat but as-finally treated are presented in Tables 2, 3 and 4 and in the online resource material Tables S1–10 and in the online resource material Fig. S1 and S2.

Discussion

In our study primary reperfusion therapy led to better 3 months' outcome than primary conservative therapy in patients with LVO in the anterior circulation and NIHSS score ≤ 5. In addition, secondary reperfusion therapy after neurological deterioration in patients who had initially been treated conservatively showed worse outcome than primary EVT. Mortality was low and did not differ among primary reperfusion and primary conservative therapy. The comparisons between primary conservative and primary reperfusion therapy are the most important results of our study.

Primary-conservative-therapy patients experienced a remarkably high rate of SND. 56 (57.7%) patients deteriorated (NIHSS score increase of ≥ 1 point), 36 (37.9%) showed a NIHSS score increase of ≥ 4 points. Previous studies have described similar SND rates (mostly defined as NIHSS score increase of ≥ 4 points) of up to 40%. Primary-conservative-therapy patients showed perfusion failure/thrombus growth as the cause of SND in 49 (87.5%) patients and high rates of persistent LVO (85.9%). Therefore, we assume that primary reperfusion therapy may prevent SND in patients with low NIHSS score.

At present, there is limited evidence for the optimal management of patients with LVO and low NIHSS score [10–24]. PRISMS, a RCT in patients with NIHSS score ≤ 5, has addressed effectiveness of IVT. Outcome did not differ between patients treated by IVT compared to those treated conservatively and was favourable in around 80% in both groups. However, vessel occlusion status was not reported. The majority of patients with NIHSS score ≤ 5 have small or no visible vessel occlusions on noninvasive imaging and less than 10% of their strokes are due to LVO [4]. Therefore, it is unlikely that the PRISMS results are meaningful for patients with verified LVO and NIHSS score ≤ 5. Moreover, the PRISMS population had high rates of non-disabling deficits at baseline: sensory deficits in 46%, facial palsy in 39% and dysarthria in 28% making it less likely to find a therapy effect when using mRS as outcome measure [22, 28].

Effectiveness of EVT in patients with LVO and NIHSS score ≤ 5 has been investigated in two retrospective studies and summarized in a recent meta-analysis [15–17]. Of note, LVO definition included anterior cerebral (ACA) and basilar artery (BA) occlusions besides ICA and MCA (M1, M2) occlusions. Patients treated by EVT had a higher chance for favourable 3 to 6 months' outcome [39/40 (97.5%) vs. 81/110 (73.6%); OR 9.27 (1.71–50.29); $p = 0.01$] and similar survival compared to conservatively treated patients. The combined analysis of these two studies is limited by differently defined therapy groups: one study analysed nine rescue-(secondary-reperfusion)-therapy patients within the group of conservative therapy and the other one eight in the EVT group [15, 16]. If analysed separately, only the second study showed significantly differing favourable 3 to 6 months' outcome [29/30 (96.6%) vs. 64/88 (72.7%); OR 10.88 (1.40–84.3); $p = 0.01$] [16].

Messer, Da Ros and Manno et al. have analysed effectiveness of EVT vs. IVT in 48, 56 and 216 patients with ICA, MCA (M1, M2) occlusions and NIHSS score ≤ 5. In Messer et al.'s study two deaths occurred and a numerical difference without statistical significance for excellent 3 months' outcome: 55% after IVT versus 75% after EVT [13]. In Da Ros et al.'s study excellent 3 months' outcome was less frequent after IVT (in 45.8%) than after EVT (in 93.1%) [18]. In Manno et al.'s study there was a trend towards higher mortality (9.3% vs. 2.8%; $p = 0.06$) and three sICH occurred in the EVT vs. none in the IVT group [24].

Other previous studies have investigated conservative therapy vs. IVT or EVT and medical therapy (conservative therapy ± IVT) vs. EVT [10–12, 14–16, 19, 23].

In our present study, survival rates did not differ between groups and were in line with rates of previous studies [11, 14–16]. Although primary-reperfusion-therapy patients had higher admission NIHSS score and primary-EVT patients also more MCA compared to ICA occlusions than primary-conservative-therapy patients, 3 months' outcome (mRS) was better in primary-reperfusion-therapy patients.

Also, it has been questioned whether mRS is reflecting the disability burden of neurological deficits in patients with low NIHSS score well enough. In our previous study, we have investigated 3 months' NIHSS score change (increase of ≥ 1 point in 41.4% of conservatively treated patients vs. 15% of IVT/EVT treated patients; $p < 0.001$) [10]. Haussen et al. showed that patients treated by EVT had a higher chance for a better median NIHSS score change (discharge minus admission score) compared to conservatively treated patients

Table 2 Secondary neurological deterioration and outcome according to therapy modality

At follow-up	Primary-conservative-therapy group ($n=97$) [n (risk %)]	Primary-IVT-only group ($n=23$) [n (risk %)]	Primary-EVT group ($n=65$) [n (risk %)]	Secondary-reperfusion group ($n=26$) [n (risk %)]
Hospital stay (median days, range)				
Stroke centre	8 (0–36)	8 (1–15)	4 (1–28)	8 (1–34)
Acute care	11 (0–45)	9 (3–31)	7 (1–28)	12 (1–34)
Secondary neurological deterioration				
At least once NIHSS score ≥ 4 points	40 (41.2%)	8 (34.8%)	17 (26.2%)	22 (84.6%)
At least once NIHSS score ≥ 1 point	56 (57.7%)	12 (52.2%)	27 (41.5%)	26 (100%)
Twice NIHSS score ≥ 1 point	32 (33%)	5 (21.7%)	15 (23.1%)	16 (61.5%)
Time point of 1st deterioration (median days, range)	0.67 (0.07–42)	0.36 (0.06–10)	0.54 (0.16–52)	0.32 (0.07–2.07)
mRS at 3 months				
0–1	28 (30.8%)	12 (54.5%)	35 (54.7%)	5 (20.8%)
0–2	58 (63.7%)	18 (81.8%)	45 (70.3%)	13 (54.2%)
0–5 (survival)	82 (90.1%)	20 (90.9%)	56 (87.5%)	21 (87.5%)
Vascular death	4 (4.1%)	1 (4.3%)	7 (10.8%)	2 (7.7%)
Peak NIHSS score[a] (median, range)	5 (0–42)	5 (0–42)	5 (1–42)	17 (3–42)
NIHSS score at day 1				
Median change	0 (− 4 to 37)	− 1 (− 4 to 12)	− 2 (− 5 to 31)	6 (− 4 to 37)
Increase	37 (39.4%)	4 (17.4%)	17 (26.2%)	19 (73.1%)
Stable	36 (38.3%)	6 (26.1%)	9 (13.8%)	5 (19.2%)
Decrease	21 (22.3%)	13 (56.5%)	39 (60%)	2 (7.7%)
NIHSS score at discharge				
Median change	0 (− 4 to 39)	− 2 (− 5 to 38)	− 2 (− 5 to 41)	5 (− 4 to 37)
Increase	40 (41.2%)	4 (17.4%)	12 (18.5%)	18 (69.2%)
Stable	21 (21.6%)	2 (8.7%)	6 (9.2%)	5 (19.2%)
Decrease	36 (37.1%)	17 (73.9%)	47 (72.3%)	3 (11.5%)
NIHSS score at 3 months				
Median change	0 (− 4 to 39)	− 2 (− 5 to 38)	− 3 (− 5 to 41)	1 (− 4 to 37)
Increase	34 (39.5%)	4 (18.2%)	14 (21.9%)	15 (62.5%)
Stable	17 (19.8%)	2 (9.1%)	4 (6.3%)	3 (12.5%)
Decrease	35 (40.7%)	16 (72.7%)	46 (71.9%)	6 (25%)
Persistent large vessel occlusion (TICI 0) before first secondary neurological deterioration[b]	79 (85.9%)	13 (59.1%)	8 (12.3%)	24 (92.3%)
Intracranial haemorrhage[c]				
sICH	1 (1.1%)	1 (4.3%)	4 (6.2%)[d]	1 (3.8%)
Asymptomatic ICH	12 (14.6%)	3 (13%)	9 (13.8%)	8 (32%)
Craniectomy	2 (2.1%)	0	0	2 (7.7%)
Iatrogenic ICAD[c]	0	0	5 (7.7%)	0
Iatrogenic clot fragmentation[c]	1 (1%)	1 (4.3%)	0	1 (3.8%)
Perfusion failure/thrombus growth[e]	49 (50.5%)	9 (39.1%)	12 (18.5%)	24 (92.3%)
Recurrent embolism[c]	4 (4.1%)	3 (13%)	10 (15.4%)	2 (7.7%)
Local reocclusion[c]	5 (5.2%)	0	1 (1.5%)	5 (19.2%)

Data are presented as number of events (cumulative risk) unless otherwise specified. Percentages are indicating available data

sICH symptomatic intracranial haemorrhage, defined according to PROACT II criteria. *ICAD* internal carotid artery dissection

[a]Highest NIHSS score overall

[b]Respectively in last image if stable

[c]Evaluation including all images until 3 months follow-up

[d]Two patients suffered an additional subarachnoid haemorrhage

[e]Failure of collaterals, expansion of infarct core, thrombus expansion

Table 3 Adjusted odds ratios and adjusted *p* values of outcome parameters stratified according to therapy modality

At follow-up	Primary-IVT-only vs. primary-conservative-therapy[a] group	Primary-EVT vs. primary-conservative-therapy[a] group	Primary-EVT vs. primary-IVT-only[a] group	Secondary-reperfusion vs. primary-EVT[a] group
Hospital stay (median days, range)				
Stroke centre	0.255[c]	***0.002***[c]	0.234[c]	***0.048***[c]
Acute care	***0.032***[c]	***0.011***[c]	0.328[c]	***0.004***[c]
Secondary neurological deterioration				
At least once NIHSS score ≥ 4 points	***0.30 (0.09–0.99)***	***0.27 (0.11–0.68)***	0.55 (0.15–2.07)	***20.28 (4.12–99.80)***[b]
At least once NIHSS score ≥ 1 point	***0.29 (0.09–0.92)***	***0.26 (0.11–0.66)***	0.58 (0.17–1.95)	3×10^{19} (0.00-NA)
Twice NIHSS score ≥ 1 point	0.37 (0.10–1.37)	0.45 (0.17–1.17)	0.66 (0.15–2.83)	***9.31 (2.13–40.69)***
Time point of 1st deterioration (median days, range)	0.958[c]	0.376[c]	0.340[c]	***0.047***[c]
mRS at 3 months				
0–1	***6.02 (1.76–20.57)***	***5.09 (1.86–13.96)***	0.85 (0.24–3.04)	***0.24 (0.06–0.98)***
0–2	***7.64 (1.59–36.69)***	2.36 (0.88–6.33)	1.21 (0.27–5.47)	0.41 (0.10–1.58)
0–5 (survival)	2.38 (0.31–18.16)	1.24 (0.31–4.96)	1.36 (0.19–9.56)	0.36 (0.05–2.52)
Vascular death	0.60 (0.04–9.32)	2.38 (0.25–22.77)	0.63 (0.05–7.97)	1.82 (0.17–19.62)
Highest NIHSS score (median, range)	0.075[c]	0.084[c]	0.809[c]	***0.009***[c]
NIHSS score at day 1				
Median change	0.052[c]	***0.018***[c]	0.330[c]	***< 0.0001***[c]
Increase	***0.24 (0.07–0.90)***	0.42 (0.17–1.05)	3.37 (0.52–21.92)	***12.13 (2.86–51.42)***
Stable	0.74 (0.20–2.70)	0.35 (0.12–1.00)	0.44 (0.11–1.83)	0.93 (0.19–4.57)
Decrease	***6.10 (1.76–21.15)***	***5.91 (2.15–16.21)***	0.86 (0.25–3.00)	***0.03 (0.00–0.26)***
NIHSS score at discharge				
Median change	0.084[c]	***0.046***[c]	0.394[c]	***0.021***[c]
Increase	***0.12 (0.03–0.45)***	***0.19 (0.07–0.52)***	0.65 (0.12–3.55)	***142 (2.91–48.06)***
Stable	0.82 (0.12–5.88)	0.35 (0.09–1.33)	2.85 (0.16–52.54)	5.15 (0.95–28.06)
Decrease	***7.80 (2.28–26.61)***	***7.51 (2.79–20.23)***	0.82 (0.19–3.57)	***0.02 (0.00–0.15)***[b]
NIHSS score at 3 months				
Median change	0.067[c]	0.188[c]	0.709[c]	0.103[c]
Increase	***0.17 (0.04–0.67)***	***0.25 (0.09–0.57)***	0.68 (0.13–3.52)	***5.73 (1.64–20.08)***
Stable	3.47 (0.19–62.80)	0.50 (0.09–2.70)	1.12 (0.05–25.50)	3.81 (0.32–45.51)
Decrease	***5.03 (1.44–17.56)***	***4.39 (1.70–11.35)***	1.05 (0.24–4.54)	***0.12 (0.03–0.48)***
Persistent large vessel occlusion (TICI 0) before first secondary neurological deterioration	***0.20 (0.05–0.79)***	***0.03 (0.01–0.10)***[b]	0.26 (0.06–1.13)	***519 (17.97–2 × 10^5)***
Intracranial haemorrhage				
sICH	2×10^6 (0.00–NA)	1×10^7 (0–2×10^{21})	0.26 (0.01–5.13)	0.30 (0.01–6.88)
aICH	0.71 (0.13–3.85)	0.77 (0.20–3.01)	1.69 (0.24–12.16)	2.68 (0.67–10.71)
Perfusion failure/thrombus growth	***0.23 (0.07–0.74)***	***0.15 (0.06–0.38)***[b]	0.65 (0.17–2.51)	***68.6 (8.44–558)***[b]
Recurrent embolism	11.32 (0.61–209)	***82.90 (2.15–3189)***	0.63 (0.11–3.56)	0.07 (0.00–3.12)
Local reocclusion	0.00 (0.00–NA)	0.00 (0.00–NA)	1×10^4 (0.00–NA)	***25.15 (1.58–400)***

sICH symptomatic intracranial haemorrhage, defined according to PROACT II criteria. Significance ($p < 0.05$) is indicated with bold and italic numbers. Details of adjustment are listed in the online resource material

[a]Denominator

[b]Adjusted *p* value < 0.0001

[c]Adjusted *p* values according to linear regression

Table 4 Cumulative risks, adjusted odds ratios and shifts of NIHSS subitems stratified according to therapy modality

	All patients	Without dead patients
Primary-IVT-only vs. primary-conservative-therapy[a] group	Right arm paresis:9.1% vs. 20.9%: $_{adjusted}$OR 0.15 (0.03–0.93); $_{adjusted}p=0.041$ Aphasia:13.6% vs. 43%: $_{adjusted}$OR 0.09 (0.02–0.40); $_{adjusted}p=0.002$ Extinction and inattention:9.1% vs. 22.1%: $_{adjusted}$OR 0.14 (0.02–0.93); $_{adjusted}p=0.041$	Aphasia:5% vs. 36.4%: $_{adjusted}$OR 0.05 (0.01–0.52); $_{adjusted}p=0.012$
	Better shift of facial palsy: $_{adjusted}p=0.036$, best language: $_{adjusted}p=0.001$ and of extinction and inattention: $_{adjusted}p=0.022$	Better shift of best language: $_{adjusted}p=0.007$
Primary-EVT vs. primary-conservative-therapy[a] group	Hemianopia:15.6% vs. 20.9%: $_{adjusted}$OR 0.27 (0.08–0.93); $_{adjusted}p=0.039$ Extinction and inattention:15.6% vs. 22.1%: $_{adjusted}$OR 0.28 (0.08–0.92); $_{adjusted}p=0.036$	Hemianopia:3.6% vs. 11.7%: $_{adjusted}$OR 0.02 (0.00–0.58); $_{adjusted}p=0.024$ Facial palsy:37.5% vs. 46.8%: $_{adjusted}$OR 0.28 (0.09–0.89); $_{adjusted}p=0.031$ Hypaesthesia:7.1% vs. 23.4%: $_{adjusted}$OR 0.15 (0.03–0.77); $_{adjusted}p=0.023$ Aphasia:16.1% vs. 36.4%: $_{adjusted}$OR 0.13 (0.04–0.45); $_{adjusted}p=0.001$ Extinction and inattention:3.6% vs. 13%: $_{adjusted}$OR 0.02 (0.00–0.80); $_{adjusted}p=0.037$
	Better shift of visual fields: $_{adjusted}p=0.050$, facial palsy: $_{adjusted}p=0.036$, best language: $_{adjusted}p=0.005$ and of extinction and inattention: $_{adjusted}p=0.027$	Better shift of visual fields: $_{adjusted}p=0.010$, facial palsy: $_{adjusted}p=0.019$, best language: $_{adjusted}p=0.001$ and of extinction and inattention: $_{adjusted}p=0.015$
Secondary-reperfusion vs. primary-EVT[a] group	Facial palsy:66.7% vs. 45.3%: $_{adjusted}$OR 3.81 (1.05–13.84); $_{adjusted}p=0.042$ Right leg paresis:33.3% vs. 17.2%: $_{adjusted}$OR 4.93 (1.09–22.42); $_{adjusted}p=0.039$ Sensory deficits:41.7% vs. 18.8%: $_{adjusted}$OR 4.15 (1.01–16.97); $_{adjusted}p=0.048$ Aphasia:66.7% vs. 26.6%: $_{adjusted}$OR 9.88 (2.39–40.91); $_{adjusted}p=0.002$	Facial palsy: (61.9% vs. 37.5%): $_{adjusted}$OR 4.54 (1.07–19.28); $_{adjusted}p=0.040$ Right leg paresis: (23.8% vs. 5.4%): $_{adjusted}$OR 14.83 (1.06–207); $_{adjusted}p=0.046$ Aphasia: (61.9% vs. 16.1%): $_{adjusted}$OR 17.06 (2.72–107); $_{adjusted}p=0.002$
	Worse shift of facial palsy: $_{adjusted}p=0.032$, motor arm right: $_{adjusted}p=0.024$, motor leg right: $_{adjusted}p=0.032$ and of best language: $_{adjusted}p=0.001$	Worse shift of facial palsy: $_{adjusted}p=0.039$, motor arm right: $_{adjusted}p=0.019$, motor leg right: $_{adjusted}p=0.046$ and best language: $_{adjusted}p=0.001$

Only significantly differing data in between-two-group-comparisons shown here. Further data available in the online resource material

[a]Denominator

[15, 16]. In our present study, primary-reperfusion vs. conservative-therapy patients had not only better 3 months' outcome measured with mRS, but also a better NIHSS score shift, more NIHSS score decreases and in many patients only little remaining disabling deficits at 3 months. Primary-reperfusion patients showed less aphasia in multiple analyses, primary-EVT patients less hemianopia and less extinction/inattention at 3 months, and this despite higher hemianopia and extinction/inattention rates at admission, which likely has influenced the decision for primary EVT. Aphasia may prevent communication and impair higher cognitive functions. Hemianopia as well as extinction/inattention may hamper eating/walking unassisted. Therefore, decreased severity or absence of focal-neurological deficits contribute to a better quality of life post stroke.

In addition to effectiveness, also safety has to be addressed. Does the risk of primary IVT or EVT in patients with LVO and low NIHSS score outweigh the potential benefit? Previous studies have found sICH rates of < 5%, but more sICH in EVT vs. conservative therapy (and/or IVT), significantly differing in one study only [10–17, 22]. There were six sICH in our study. The bleeding rates did not differ among therapy groups, but the small bleeding rates do not allow a meaningful safety conclusion. One iatrogenic clot fragmentation causing SND was observed in both primary-IVT-only as well as in primary-conservative finally secondary-reperfusion-therapy patients. Besides, primary-reperfusion patients were more prone to recurrent embolism in our study.

Moreover, it is unclear whether secondary reperfusion therapy after SND may be superior to primary EVT in the analysed patient group. This issue has only been scarcely addressed so far [13, 15, 19].

In our study, secondary-reperfused patients compared to primary-EVT patients had similar survival, but more multiple SND, more local reocclusions and worse 3 months' outcome ($_{adjusted}p = 0.019$ in mRS shift analysis). As expected, sensitivity analysis confined to patients with < 4.5 h until time point of first therapy (or its decision) showed less differing results as time lapses were more similar between both groups.

Our study has strengths and limitations. The main strength is that we analysed outcome according to primary intended therapy, but in a subgroup analysis also as patients had been treated. In addition, we performed sensitivity analyses and analyses of SND, NIHSS subitems and of NIHSS shifts besides looking at different conventional outcome parameters.

The main limitations are the retrospective study design and an imbalance of baseline variables that potentially could not be adjusted for completely with regression analysis. In addition, the clinical presentation at admission may have caused a selection bias, influenced the treatment decision and contributed to the imbalance of baseline characteristics among the therapy groups. Furthermore, treatment has changed over time. At our centre, before 2010, EVT consisted mainly of aspiration and intra-arterial Urokinase. 2010 marked the advent of stent-retrievers. Though, sensitivity analysis including patients admitted after 2010 only (data not depicted) did not show different results, except five (83.3%) sICH having occurred after 2010. Also, in eight (4.3%) patients mRS and in 14 (7.6%) NIHSS score at 3 months were missing. Moreover, as NIHSS subitems consist of an ordinal scale and as adjustment for multiple variables was needed, we decided to perform a shift analysis by ordinal regression analysis of the total NIHSS score and its subitems even though this has not been performed before. Also, the small sample size is limiting statistical power and increasing risk of model overfitting in some analyses.

Conclusions

Our data suggest that patients with LVO in the anterior circulation and NIHSS score ≤ 5 may benefit from primary reperfusion therapy. Outcome in primary-conservative-therapy was worse than in primary-reperfusion-therapy patients and also outcome in secondary-reperfusion-therapy in case of neurological deterioration was worse than in primary-reperfusion-therapy patients. Published data and our results indicate that there is an unmet need for RCTs to investigate effectiveness and safety of reperfusion therapy in this patient group of LVO and low NIHSS score.

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Ethical standard Patients or their relatives have signed written informed consent for treatment and study participation. The study was approved by the local ethics committee of the canton of Bern (231/14) and has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Data analyses followed EQUATOR reporting guidelines.

Data sharing statement Raw data of all patients included in this study can be made available upon request to the corresponding author and after clearance by the local ethics committee.

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