

## ORIGINAL RESEARCH

# Too good to intervene? Thrombectomy for large vessel occlusion strokes with minimal symptoms: an intention-to-treat analysis

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/neurintsurg-2016-012633>).

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Received 13 July 2016

Revised 5 August 2016

Accepted 10 August 2016

Published Online First

2 September 2016



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**To cite:** Haussen DC, Bousslama M, Grossberg JA, et al. *J NeuroIntervent Surg* 2017;**9**:917–921.

## ABSTRACT

**Introduction** The minimal stroke severity justifying endovascular intervention remains elusive; however, a significant proportion of patients presenting with large vessel occlusion (LVO) and mild symptoms subsequently decline and face poor outcomes.

**Objective** To evaluate our experience with these patients by comparing best medical therapy with thrombectomy in an intention-to-treat analysis.

**Methods** Analysis of prospectively collected data of all consecutive patients with National Institutes of Health Stroke Scale (NIHSS) score  $\leq 5$ , LVO on CT angiography, and baseline modified Rankin Scale (mRS) score 0–2 from November 2014 to May 2016. After careful discussion with patients/family, a decision to pursue medical or interventional therapy was made. Deterioration (development of aphasia, neglect, and/or significant weakness) triggered reconsideration of thrombectomy. The primary outcome measure was NIHSS shift (discharge NIHSS score minus admission NIHSS score).

**Results** Of the 32 patients qualifying for the study, 22 (69%) were primarily treated with medical therapy and 10 (31%) intervention. Baseline characteristics were comparable. Nine (41%) medically treated patients had subsequent deterioration requiring thrombectomy. Median time from arrival to deterioration was 5.2 hours (2.0–25.0). Successful reperfusion (modified Treatment in Cerebral Infarction 2b–3) was achieved in all 19 thrombectomy patients. The NIHSS shift significantly favored thrombectomy ( $-2.5$  vs  $0$ ;  $p < 0.01$ ). The median NIHSS score at discharge was low with both thrombectomy (1 (0–3)) and medical therapy (2 (0.5–4.5)). 90-Day mRS 0–2 rates were 100% and 77%, respectively ( $p = 0.15$ ). Multivariable linear regression indicated that thrombectomy was independently associated with a beneficial NIHSS shift (unstandardized  $\beta -4.2$  (95% CI  $-8.2$  to  $-0.1$ );  $p = 0.04$ ).

**Conclusions** Thrombectomy led to a shift towards a lower NIHSS in patients with LVO presenting with minimal stroke symptoms. Despite the overall perception that this condition is benign, nearly a quarter of patients primarily treated with medical therapy did not achieve independence at 90 days.

## INTRODUCTION

Endovascular stroke intervention has been recently defined as the standard of care for patients with large vessel occlusion (LVO) strokes who failed to respond to, or are not candidate for, IV thrombolysis. This therapy has one of the largest effects in

the neurosciences with a number-needed-to-treat of only 2.5 for any reduction in disability.<sup>1</sup> However, mechanical thrombectomy carries all the risks and expense inherent to invasive procedures. Thus, the minimal clinical stroke severity justifying endovascular intervention remains to be established. Indeed, the current American Heart Association (AHA) guidelines provide only level 1a evidence for thrombectomy for patients with baseline National Institutes of Health Stroke Scale (NIHSS) score  $\geq 6$ .<sup>2</sup> Nonetheless, a significant number of patients with mild or rapidly improving stroke symptoms on initial presentation subsequently decline and end up with poor outcomes at hospital discharge.<sup>3</sup> In this setting, the presence of an underlying LVO is a strong predictor of neurological deterioration.<sup>4–6</sup> The endovascular approach for low NIHSS emergent LVO has been previously reported; however, data are scarce.<sup>7–8</sup> We sought to evaluate our experience with the treatment of patients with a LVO stroke and low NIHSS score by comparing best medical therapy alone with endovascular thrombectomy in an intention-to-treat analysis.

## PATIENTS AND METHODS

### Patient selection

We prospectively collected data on all consecutive patients who presented directly or were transferred to our comprehensive stroke center with an NIHSS score  $\leq 5$  and an LVO on CT angiography (middle cerebral artery M1/M2, intracranial carotid artery, anterior cerebral artery (ACA), or basilar artery occlusion) from November 2014 to May 2016. Patients who were not independent (modified Rankin Scale (mRS) score  $> 2$ ) at baseline were excluded. The NIHSS score was assessed upon arrival by a certified neurologist and blood pressure levels recorded at the time of the initial neurological examination. This study was approved by the local institutional board.

### Clinical decision analysis

All patients were evaluated upon arrival by the stroke and neurointerventional teams. A careful discussion between the treating physicians and the patients/families about the available medical evidence was routinely performed in order to decide whether intervention or medical therapy would be pursued. The decision of most patients/families was to have medical therapy, which consisted of

## Ischemic stroke

initiating double antiplatelet agents (if not given IV tissue plasminogen activator) and aggressive IV hydration. In addition, the patient's blood pressure was allowed to autoregulate, and the head of the bed was kept flat. All patients were admitted to the neurological intensive care unit and monitored for deterioration with hourly neurological checks by neurointensive care nurses. Deterioration was defined as the development of deficits that could affect function (moderate/severe aphasia or neglect and/or inability to lift limbs antigravity) with worsening of the NIHSS score of at least two points; this automatically triggered reconsideration of thrombectomy. The Alberta Stroke Program Early

CT Score<sup>9</sup> and CT perfusion (RAPID, iSchemaView Inc, California, USA) were used to determine the ischemic core for anterior circulation strokes and perfusion defect. Hemorrhagic transformation was graded by the European Cooperative Stroke Study and reperfusion rates by modified Treatment in Cerebral Infarction (mTICI) criteria.<sup>10 11</sup>

### Outcome analysis

This was an intention-to-treat analysis; patients initially receiving medical therapy alone who subsequently deteriorated and underwent endovascular therapy were analyzed in the

**Table 1** Baseline characteristics of the studied groups

Baseline characteristics	Thrombectomy(n=10)	Medical(n=22)	p Value*
Age (years), mean±SD	60±13.9	68.2±14.4	0.14
Gender (male)	5 (50)	15 (68)	0.43
Hypertension	6 (60)	13 (59)	1.00
Hyperlipidemia	2 (20)	5 (23)	1.00
Atrial fibrillation	3 (30)	8 (36)	1.00
Diabetes	2 (20)	4 (18)	1.00
Smoking	2 (20)	2 (9)	0.57
Anticoagulation	0 (0)	0 (0)	–
Arterial pressure (mm Hg), mean±SD	100.3±20.5	106.7±17.7	0.43
Baseline NIHSS score, median (IQR)	4 (2–5)	2 (1–4)	0.09
Worst NIHSS score, mean±SD	5.8±3.0	7.1±6.8	0.43
NIHSS score fluctuation >4	3 (30)	9 (41)	0.70
Wake-up stroke	2 (20)	7 (32)	0.68
IV t-PA	6 (60)	2 (9)	<b>&lt;0.01</b>
NCCT ASPECTS, mean±SD	8.5±1.0	9.1±0.8	0.14
CT perfusion (cc)			
Ischemic core, mean±SD	8.5±9.9	0.4±1.3	0.06
tMax>4 s, mean±SD	132.1±111.9	177.1±110.8	0.39
tMax>6 s, mean±SD	65.4±52.9	70.7±47.0	0.82
tMax>10 s, mean±SD	24.6±23.9	9.9±12.6	0.16
Times (hours), median (IQR)			
Last-known-normal to arrival	6.25 (3.75–9.12)	10.5 (4.3–15)	0.19
Arrival to deterioration	–	5.2 (2.0–25.0)	
Deterioration to puncture	–	1.5 (0.6–2.1)	
Deterioration to reperfusion	–	2.7 (2.3–3.5)	
Occlusion site			0.62
ACA	1 (10)	0 (0)	
MCA M1	6 (60)	10 (45)	
MCA M2	1 (10)	5 (23)	
Intracranial ICA	0 (0)	3 (14)	
Extracranial ICA	0 (0)	1 (5)	
Basilar	2 (20)	3 (14)	
Tandem	0 (0)	3 (14)	0.53
Procedure	10 (100)	9 (41)	
Stentriever	8 (80)	8 (89)	1.00
mTICI 2b–3	10 (100)	9 (100)	1.00
mTICI 3	5 (50)	6 (67)	0.65
Procedure length (min), mean±SD	67.1±29.6	74.9±31.1	0.58
Etiology			0.19
Cardioembolic	4 (40)	8 (36)	
Large vessel atherosclerosis	1 (10)	7 (32)	
Intracranial atherosclerosis	0 (0)	2 (9)	
Other determined	0 (0)	1 (5)	
Cryptogenic	5 (50)	4 (18)	

Results are shown as number (%) unless stated otherwise.

\*Significant p values are shown in bold.

ACA, anterior communicating artery; ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; mTICI, modified Treatment in Cerebral Infarction; NCCT, non-contrast CT; t-PA, tissue plasminogen activator.

conservative therapy arm. The primary outcome measure was a change in the NIHSS score (discharge NIHSS score minus admission NIHSS score—'NIHSS shift'). This endpoint has been used previously in studies of stroke with a low NIHSS score, and has been associated with poor clinical outcome.<sup>12</sup> For patients who died during hospitalization, the NIHSS score at day 7 was considered the discharge NIHSS score. Secondary efficacy/safety outcomes included the rates of mRS 0–2 (good outcome) at 90 days and parenchymal hematomas.

### Statistical analyses

Continuous variables are reported as mean±SD or median (IQR), as appropriate. Categorical variables are reported as proportions. Between-group comparisons for continuous/ordinal variables were made with the Student t test, Mann–Whitney U test, or analysis of variance, as appropriate. Categorical variables were compared by  $\chi^2$  or Fisher exact test, as appropriate. The overall distribution of 90-day mRS was compared between groups (shift in disability levels) using the Van Elteren test (a Cochran–Mantel–Haenszel test). Scores of 5 and 6 were merged into a single group.<sup>13</sup> Significance was set at  $p < 0.05$  and  $p$  values were two-sided. Multivariable linear regression analysis for predictors of NIHSS shift was performed for variables at the 0.1 level of significance on univariate analysis (enter selection method). Statistical analysis was performed using IBM SPSS Statistics 23 (IBM-Armonk, New York, USA) except for the Van Elteren, which was computed using the FREQ procedure in SAS University Edition (SAS Institute, Cary, North Carolina, USA).

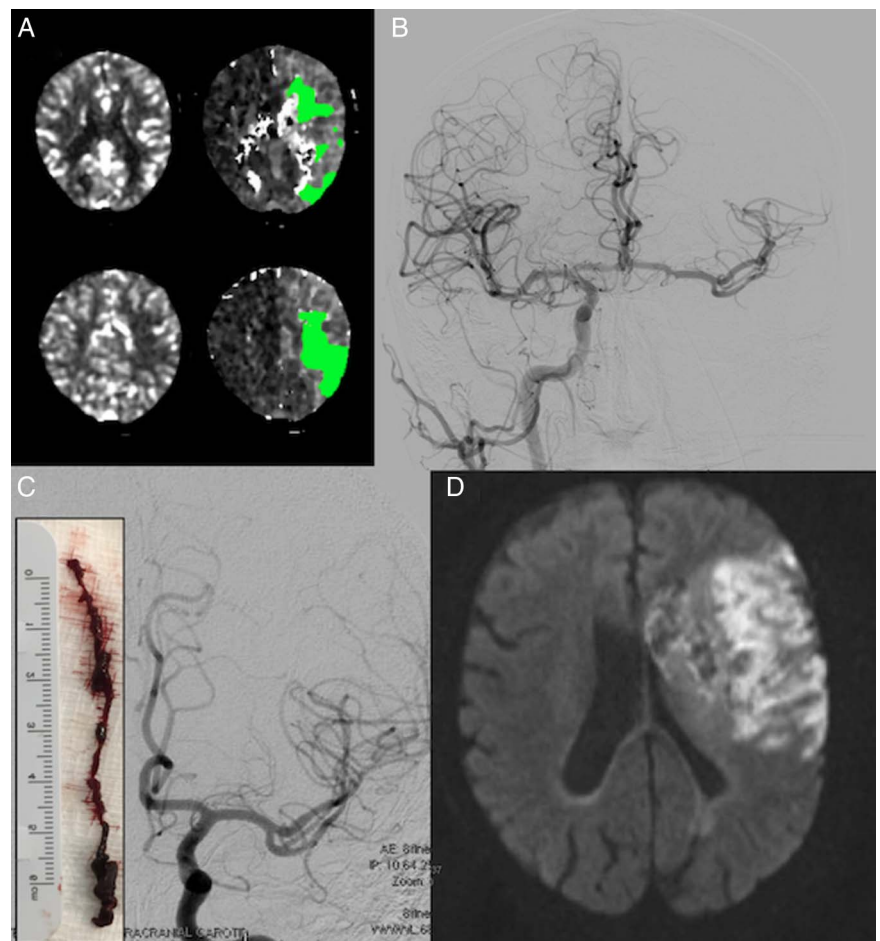
### RESULTS

Thirty-two patients met the inclusion criteria over the 18-month study period and were included in the analysis; 22 (69%) received primary medical therapy alone and 10 (31%) primary interventional therapy. Baseline characteristics were comparable across the two groups (table 1), with the exception of more frequent IV thrombolysis in the primary thrombectomy group.

An orthostatic challenge was performed in 11 patients to evaluate collateral failure by elevating the patient in the stretcher and monitoring their examination. The maneuver was done for a median of 5 min (IQR 5–30) and led to worsening (NIHSS score  $\geq 2$  points) in three (27%) patients; one was taken for intervention and two remained in the medical group and were repositioned with head of the bed flat, without further deterioration.

A total of 9 (41%) of the 22 primary medical therapy patients showed clinical deterioration and were taken for thrombectomy (figure 1). A comparison of the baseline characteristics of medically treated patients who deteriorated with those of patients who remained neurologically stable failed to indicate significant differences (see online supplementary table). The median time from arrival to deterioration was 5.2 hours (2.0–25.0); range 1–48 hours. The median time from deterioration to puncture was 1.5 hours (0.6–2.1); range 0.6–3.5 hours. Of the four patients who deteriorated in  $\leq 3$  hours, three had a good outcome, whereas of the five who deteriorated  $> 3$  hours after arrival, only one had a good outcome.

**Figure 1** Illustrative case of a septuagenarian patient with mild aphasia treated medically who deteriorated 4 hours after presentation. (A) CT perfusion at presentation indicating no ischemic core and a sizeable perfusion (tMax $>6$  s; green) defect in the setting of National Institutes of Health Stroke Scale (NIHSS) score =1; (B) Frontal conventional angiography of the right common carotid upon presentation with cross-flow through the anterior communicating artery confirming an intracranial carotid artery-'I' occlusion; (C) Rescue thrombectomy with full reperfusion at 80 min post-deterioration after one pass of the stent retriever (inset shows the recovered thrombus); (D) final MRI diffusion-weighted imaging showing a large final infarct (modified Rankin Scale score=5 at 90 days).



**Table 2** Outcome data of the studied groups

Outcomes	Thrombectomy (n=10)	Medical (n=22)	p Value*
Parenchymal hemorrhages	0 (0)	0 (0)	1.00
NIHSS score			
NIHSS score at discharge, median (IQR)	1 (0–3)	2 (0.5–4.5)	0.31
NIHSS score worsening >4/death	1 (10)	5 (23)	0.63
NIHSS shift	–2.5	0	<b>0.01</b>
90-Day mRS†			0.19
0	4 (40)	5 (23)	
1	3 (30)	7 (32)	
2	3 (30)	5 (23)	
3	0 (0)	1 (5)	
4	0 (0)	0 (0)	
5–6	0 (0)	4 (18)	
90-Day mRS 0–2	10 (100)	17 (77)	0.15
90-Day mortality	0 (0)	3 (14)	0.53
Discharge home	9 (90)	16 (73)	0.38

Results are shown as number (%) unless stated otherwise.

\*Significant p values are shown in bold.

†The last observation carried forward was used for missing final scores on the mRS.<sup>13</sup>

Only one patient (10%) of the interventional group and one (4%) of the medical therapy group had mRS carried from discharge to 90 days (both with mRS=0 at discharge).

mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Of the 19 patients undergoing thrombectomy (10 primary and 9 rescue), five (26%) had baseline mTICI 1–2a on conventional angiography. All procedures led to successful reperfusion (mTICI 2b–3); stent retrievers were used in 84% of the cases. One procedural complication (microwire perforation) occurred in a patient treated medically who deteriorated.

Outcome data are described in table 2. The NIHSS shift significantly favored thrombectomy (–2.5 vs 0;  $p < 0.01$ ). However, the median NIHSS score at discharge was low in both the thrombectomy (1 (0–3)) and medical therapy (2 (0.5–4.5)) groups. Good outcomes at 90 days were more frequent in the thrombectomy group (100% vs 77%;  $p = 0.15$ ). Three patients in the primary medical therapy group died but none in the primary thrombectomy arm. The multivariable linear regression for predictors of NIHSS shift at discharge indicated that only thrombectomy was independently associated with a beneficial (negative) NIHSS shift (unstandardized  $\beta$  –4.2; 95% CI –8.2 to –0.1;  $p = 0.04$ ). Atrial fibrillation, diabetes, and IV thrombolysis did not reach statistical significance in the multivariable analysis.

## DISCUSSION

We demonstrated that endovascular therapy leads to a statistically significant shift towards a better NIHSS score upon discharge in patients with an LVO stroke and NIHSS score  $\leq 5$ . Moreover, a large proportion of patients with an LVO stroke and mild presentations may deteriorate despite optimized medical management.

Patients with acute ischemic stroke who are felt to be ‘too good to treat’ are not uncommon when presenting early. A population study indicated that 36% of patients presenting within 3 hours of stroke onset were not treated with thrombolysis owing to a mild presentation.<sup>12</sup> Clinical deterioration is common in patients with mild stroke symptoms and underlying LVOs.<sup>5</sup> Although IA therapy has been shown to be feasible for patients

with very low NIHSS score strokes,<sup>7 8 14</sup> the potential risk of harm and the associated expense may attenuate the hypothetical benefits. The best data available originate from a meta-analysis of recent randomized trials that indicates that for the subgroup of patients with an NIHSS score  $\leq 10$ , no benefit could be statistically demonstrated.<sup>1</sup>

In view of the overall high rate of good clinical outcomes in a population of patients with very mild presentation, we preferred not to define ‘deterioration’ as a small change in NIHSS score but rather as a change that could result in a meaningful degree of disability. Since the definition of clinical deterioration, poor outcome, and mild presentation varies among studies, it is difficult to make comparisons. In a study of 136 patients presenting within 24 hours of mild stroke onset, 25% deteriorated, defined by an increase of NIHSS score  $\geq 4$ , and 29% had poor outcomes.<sup>15</sup> In a report of 162 patients within 6 hours of mild stroke onset, 23% had poor outcome (mRS 3–5) with LVO predicting poor prognosis.<sup>5</sup> Another series of 41 patients who were not given IV recombinant tissue plasminogen activator owing to mild symptoms reported that 27% were not discharged home or died.<sup>16</sup> In a study of 204 patients with mild strokes who were treated endovascularly, 62% achieved mRS 0–3 at 90 days.<sup>7</sup> Our study confirms historical data, with a rate of deterioration in the medically treated patients of >40% and a sizeable rate of poor outcomes (despite rescue thrombectomy).

We believe that leptomeningeal collateral failure may have been the cause of the clinical decompensation in the medically treated patients who deteriorated. Repeated neurological examination in orthostasis may challenge tenuous collateralization and precipitate worsening; however, our data are too limited to allow interpretation.

This study has limitations, particularly related to its relatively small sample size and the single-center derivation. The crossover from medical therapy to thrombectomy arms might have influenced the results; however, it is unlikely that this could have affected the medical therapy arm results in light of the current data and recent interventional clinical trials. IV thrombolysis rates were higher in the treatment group; nonetheless, considering that all these patients were successfully endovascularly reperfused, the underlying use of thrombolysis should not be expected to have a significant impact, especially as thrombectomy was found to be independently associated with the primary outcome after adjustments. The fact that the occlusion site was heterogeneous makes the interpretation of the results more challenging.

## CONCLUSIONS

We demonstrate a shift towards a lower NIHSS in patients with a LVO stroke presenting with mild symptoms who underwent primary thrombectomy as compared with those who received best medical therapy alone. Despite the overall perception that this condition is benign, nearly a quarter of patients primarily given medical treatment did not achieve independence at 90 days. Further studies evaluating the role of endovascular reperfusion for acute ischemic stroke with mild symptoms are warranted.

**Contributors** DCH: study conception, design of the work, acquisition of data, statistical analysis, interpretation of data, drafting of the manuscript. MB: data acquisition, statistical analysis, critical revision of manuscript. JAG, AA, SB, MF, NB: interpretation of data and critical revision of manuscript. LCR: data acquisition and critical revision of manuscript. RGN: study conception, critical revision of manuscript. All authors gave final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



**Competing interests** The following authors report no conflicts of interest: DCH/MB/JAG/AA/SB/MF/NB/LCR: no disclosures. RGN: Stryker (PI:Trevo-2 PI/DAWN Trials), Covidien (SWIFT/SWIFT-PRIME Steering Committee, STAR Trial Core-Lab), and Penumbra (3-D Trial Executive Committee).

**Ethics approval** Local institutional review board (IRB)/Emory University IRB.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** The unpublished data from this dataset is held by Grady Memorial Hospital/Emory University and DCH/RGN. Requests for data sharing would have to be discussed with them directly.

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