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# EVT among patients with low nihss: Results from UNAMSK EVT

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# Endovascular treatment decision-making in acute ischemic stroke patients with large vessel occlusion and low National Institutes of Health Stroke Scale: insights from UNMASK EVT, an international multidisciplinary survey

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## Abstract

**Purpose** Many stroke patients with large vessel occlusion present with a low National Institutes of Health Stroke Scale (NIHSS). There is currently no level 1A recommendation for endovascular treatment (EVT) for this patient subgroup. From a physician's standpoint, the deficits might only be slight, but they are often devastating from a patient perspective. Furthermore, early neurologic deterioration is common. The purpose of this study was to explore endovascular treatment attitudes of physicians in acute ischemic stroke patients presenting with low admission NIHSS.

**Methods** In an international cross-sectional survey among stroke physicians, participants were presented the scenario of a 76-year-old stroke patient with an admission NIHSS of 2. Survey participants were then asked how they would treat the patient (A) given their current local resources, and (B) under assumed ideal conditions, i.e., without external (monetary or infrastructural) constraints. Overall, country-specific and specialty-specific decision rates were calculated and clustered multivariable logistic regression performed to provide adjusted measures of effect size.

**Results** Two hundred seventy-five participants (150 neurologists, 84 interventional neuroradiologists, 30 neurosurgeons, 11 affiliated to other specialties) from 33 countries provided their treatment approach to this case scenario. Most physicians favored an endovascular treatment approach, either combined with intravenous alteplase (55.3% under assumed ideal and 52.0% under current working conditions) or as single treatment (11.3% under assumed ideal and 8.4% under current conditions).

**Conclusion** Despite the limited evidence for endovascular therapy in acute stroke patients with low NIHSS, most physicians in this survey decided to proceed with endovascular therapy. A randomized controlled trial seems warranted.

**Keywords** Acute ischemic stroke · Minor stroke · Endovascular therapy · Guidelines

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GS and MG contributed equally to this work.

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## Introduction

Patients with acute ischemic stroke (AIS) due to large vessel occlusion (LVO) usually suffer from severely disabling symptoms [1]. A minority will present with mild symptoms (low National Institute of Health Stroke Scale (NIHSS) scores) [1, 2]. In fact, more than 50% of all LVO patients present with NIHSS scores < 10 [2]. Endovascular therapy (EVT) is a highly effective treatment option for AIS due to LVO and now considered the standard of care [3]. Few data exist on the efficacy of EVT in LVO patients with low NIHSS, since those patients were underrepresented in randomized controlled EVT trials. This lack of empiric data leads to level 1A guideline recommendations for EVT that are currently restricted to LVO patients with NIHSS  $\geq$  6.

It is important to recognize that the NIHSS score is a quantitative estimate of the severity of the neurological deficit and that estimate does not supersede the additional importance of clinical judgment of an individual's context. We may commonly consider AIS with NIHSS < 6 as “mild” and “non-disabling” strokes, but in a specific patient situation the deficits may be devastating. Moderate dysarthria, for instance, formally scores as NIHSS 1 but it can prohibit a teacher or a salesman from earning a living. In one study, more than 30% of patients with untreated supposedly “mild” strokes (NIHSS < 5) were not functionally independent at 90 days [4]. Among AIS patients who initially present with mild symptoms, those with LVO in particular tend to worsen over time: early neurologic deterioration has been reported in 24–38% of LVO patients with low admission NIHSS [5, 6] and presence of LVO is known to be a poor prognostic factor [6–8].

Several non-randomized studies have sought to evaluate the efficacy and safety of EVT in low NIHSS patients with LVO and have reported conflicting results: while some authors reported clear superiority of EVT compared with medical management/intravenous alteplase [9–13], the HERMES meta-analysis only showed a trend towards better outcomes with EVT [14]. Three other studies found no significant benefit of EVT [15–17]. Because the safety profile of EVT is excellent [9–12, 14], randomized controlled trials investigating efficacy and safety of EVT in AIS patients with low NIHSS (ENDO-LOW and In Extremis/MOSTE [18]) are currently in preparation. These trials are predicted to be challenging because of the expected small effect size using traditional 90-day outcomes measured on the modified Rankin Scale.

Currently, endovascular treatment decision-making in AIS patients with LVO and low admission NIHSS is highly variable and mainly based on physicians' personal judgment.

We sought to explore endovascular treatment decisions of physicians in AIS patients presenting with low admission NIHSS using a survey format with a pre-specified case-scenario.

## Methods

### Survey design

An international cross-sectional web-based survey (UNMASK EVT) among stroke physicians was conducted to understand their current treatment practice and endovascular decision-making in acute stroke [19]. Participants were assigned to 10 out of a pool of 22 case scenarios and asked how they would treat the patient in the given scenario (EVT, intravenous alteplase, neither or both). Response data were obtained from November 26, 2017, to March 27, 2018. Approval by the local research ethics board was obtained. Further details of the study were published elsewhere [19–21].

### Survey participants

A total of 1330 stroke physicians (neurologists, interventional neuroradiologists, neurosurgeons, internists, geriatricians and other physicians directly involved in acute stroke care) from 38 countries were invited to participate in this web-based survey. No restrictions with regard to case volume or experience levels were applied, and participants had both academic and non-academic backgrounds. Prior to accessing the case scenarios, the participants provided some personal data (age, gender, years of experience in stroke treatment, geographic region, subspecialty, hospital setting).

### Clinical case scenario

Twenty-two case scenarios were designed to assess participants' treatment practice and particularly endovascular decision-making in acute stroke, one of which involved a patient with an admission NIHSS score of 2 [19]. This scenario was presented to the survey participants as follows:

A 76-year-old, right-handed woman has arrived at your hospital at 2 PM with mild hemiparesis and aphasia. Symptom onset was 3 hours ago. Her stroke severity was measured by **NIHSS of 2**. Alberta Stroke Program Early CT Score (ASPECTS) on non-contrast CT is 10. Baseline CT angiography reveals a proximal M1 occlusion.

Participants were then asked how they would treat the patient (A) under their current local working resources, and (B) under assumed ideal conditions, i.e., without any external (monetary or infrastructural) constraints (for detailed descriptions of the other case-scenarios with corresponding evidence levels, see [Suppl. Material](#)).

## Statistical analysis

Survey data were analyzed using descriptive statistics; differences among subgroups were assessed with chi-square tests. Multivariable logistic regression clustered by respondent was performed to provide adjusted measures of effect size for physician baseline characteristics (physician age and gender, years of experience, personal annual EVT and stroke treatment volume, annual center EVT and intravenous alteplase volume, hospital setting, region of practice, specialty). *p* values < .05 were considered statistically significant. Data analysis was performed in Stata 15.1. Figures were created with Microsoft Power BI desktop 2016 using the Mapbox Visual Plugin.

## Results

### Response rate and respondents' demographic characteristics

Overall, a total number of 607 physicians (97 women, 508 men, 2 who did not wish to disclose their gender) of different subspecialties (326 neurologists, 173 interventional neuroradiologists, 81 neurosurgeons, 5 internists, 2 geriatricians, 20 physicians of other specialties) from 38 countries completed the survey and 6070 responses were obtained for the 22 case scenarios. For the scenario with low admission NIHSS, 275 responses were obtained from physicians of 33 countries. Table 1 provides information about demographic baseline characteristics of the participants who responded to this case-scenario.

### Treatment decision rates for the low NIHSS case-scenario under current local resources and assumed ideal conditions

Figure 1a provides an overview of the treatment decisions of physicians under current local resources and assumed ideal conditions. Under their current local resources, 60.4% ( $n = 166/275$ ) of the participants decided to proceed with EVT. Fifty-two percent ( $n = 143$ ) opted for a combination of EVT and intravenous alteplase, while 8.4% ( $n = 23$ ) decided to proceed with EVT alone. Only 8% ( $n = 22$ ) preferred supportive treatment with either antiplatelets/anticoagulants only. Under assumed ideal conditions, 66.6% ( $n = 183$ ) decided in favor of EVT: 55.3% ( $n = 152$ ) opted for a combined approach and 11.3% ( $n = 31$ ) for EVT only. 9.1% ( $n = 25$ ) decided to treat with antiplatelets/anticoagulants only. The overall resources gap (ideal minus current EVT rate) was 6.19% (Fig. 1a). With regard to intravenous alteplase only, we observed a “negative resources gap”, i.e., participants decided to treat the patient with intravenous alteplase more often under their current

**Table 1** Baseline characteristics of physicians who provided responses to the low NIHSS case-scenario ( $N = 275$ )

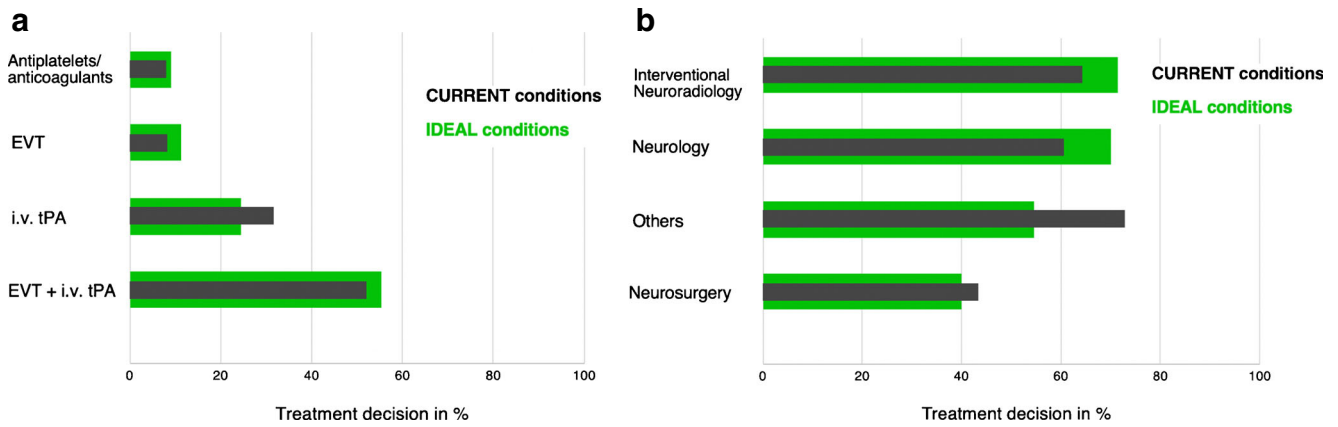
Variable	
Gender– <i>n</i> (%)	
Male	233 (84.7)
Female	41 (14.9)
Do not wish to declare	1 (0.4)
Age–median (IQR)	43 (38–50)
Experience in years–median (IQR)	12 (7–20)
Personal annual stroke treatment volume–median (IQR)	100 (50–300)
Personal annual EVT volume–median (IQR)	25 (15–50)
Annual center alteplase volume–median (IQR)	100 (50–180)
Annual center EVT volume–median (IQR)	65 (30–117)
Hospital setting– <i>n</i> (%)	
Teaching hospital	253 (92.0)
Non-teaching hospital	22 (8.0)
Specialty– <i>n</i> (%)	
Neurosurgery	30 (10.9)
Neurology	150 (54.6)
Interventional Neuroradiology	84 (30.6)
Others	11 (4.0)
Geographic region– <i>n</i> (%)	
East Asia	53 (19.3)
South Asia	15 (5.5)
Australia and New Zealand	17 (6.2)
North America	98 (35.6)
South America	20 (7.3)
Europe	64 (23.3)

*IQR* interquartile range

local resources (83.6%,  $n = 230$ ) than they would like to in an ideal environment (79.6%,  $n = 219$ , Fig. 1a).

### Current and ideal treatment rates for the low NIHSS case-scenario by specialty and country

Current EVT decision rates did not differ significantly between specialties ( $p = .180$ , Fig. 1b). They were highest for physicians affiliated to other subspecialties (72.7%,  $n = 8/11$ ), followed by interventional neuroradiologists (64.3%,  $n = 54/84$ ) and neurologists (60.7%,  $n = 91/150$ ). Neurosurgeons ranked lowest at 43.3% ( $n = 13/30$ ). Ideal EVT rates differed significantly among specialties ( $p = .008$ ). The highest rate was observed among interventional neuroradiologists (71.4%,  $n = 60/84$ ), followed by neurologists (70.0%,  $n = 105/150$ ) and physicians of other specialties (54.6%,  $n = 6/11$ ). The lowest ideal EVT rate was observed among neurosurgeons (40%,  $n = 12/30$ ). For neurosurgeons and physicians of other specialties, current EVT rates were lower than ideal rates (Fig. 1b).



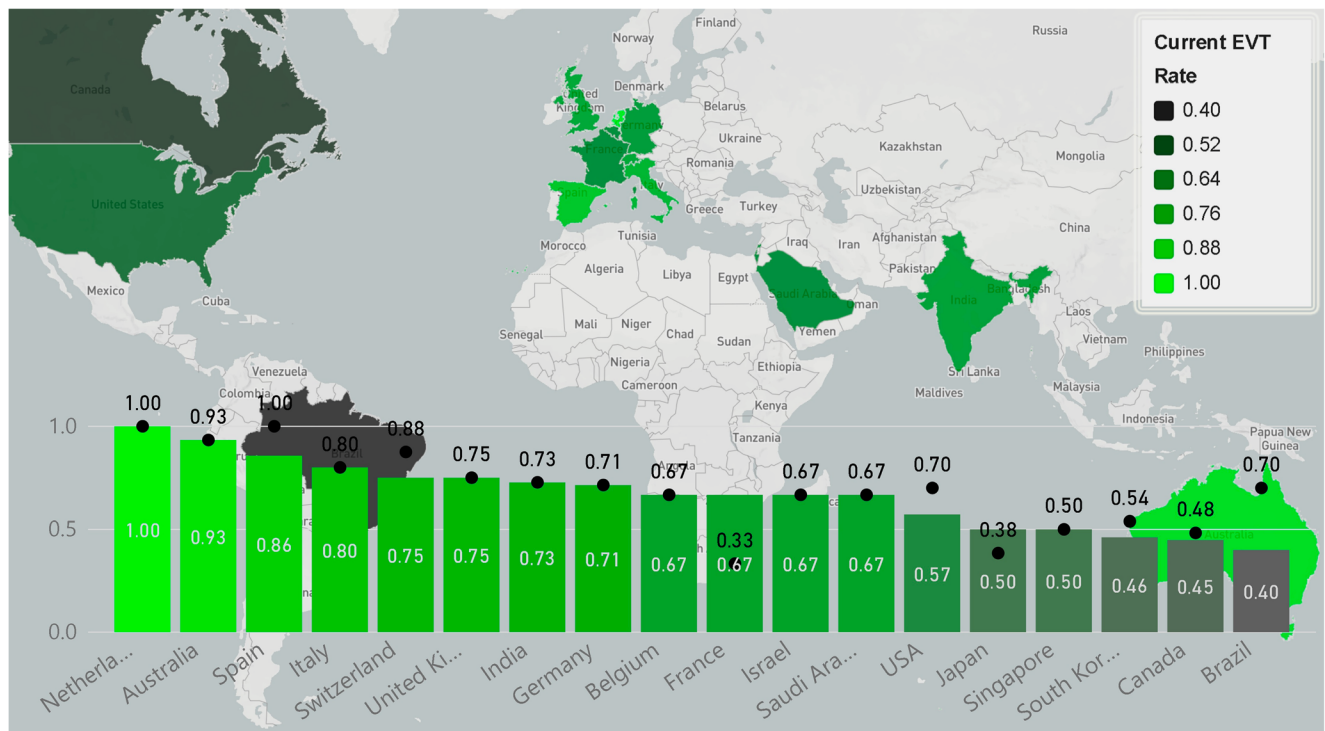
**Fig. 1** Overall current and ideal decision rates for the low NIHSS case-scenario (a) and EVT decision rates by different specialties (b) in percent. Dark bars represent decision rates under physicians' current local

resources, and light bars represent decision rates under assumed ideal conditions. EVT, endovascular therapy; tPA, intravenous alteplase

EVT rates under current local conditions differed significantly among geographic regions ( $p = .006$ ), with Australia's EVT rate being highest (94.1%,  $n = 16/17$ ) and South America ranking lowest (40.0%,  $n = 8/20$ ). Under assumed ideal conditions, EVT rates also differed significantly ( $p = .006$ ) and ranged from 94.1% ( $n = 16/17$ ) in Australia to 47.2% ( $n = 25/53$ ) in East Asia. Figure 2 illustrates current and ideal decision rates across different countries.

### Association of endovascular treatment decision in the low NIHSS case-scenario with physician baseline characteristics

Under participants' current local resources, annual center EVT volume was significantly associated with a decision in favor of EVT (adjusted OR 1.01,  $p = .022$ ). Under assumed ideal conditions, personal annual EVT volume was



**Fig. 2** Current and ideal decision rates in favor of EVT for the low NIHSS case-scenario by country. Bright-colored countries and bars represent high current decision rates in favor of EVT, whereas dark-colored countries and bars represent low current decision rates in favor of EVT.

Black dots illustrate country-specific ideal decision rates in favor of EVT. Note: Countries with less than 3 responses for the low NIHSS scenario were not included in this illustration

significantly associated with a decision in favor of EVT (adjusted OR 1.01,  $p = .036$ ). The remaining physician-specific variables (physician age, gender, years of experience, personal annual stroke treatment volume, annual center alteplase volume) did not reach statistical significance.

## Discussion

In this survey-based study, we explored how physicians approach endovascular treatment decision-making in a given case-scenario with an acute ischemic stroke patient presenting with low admission NIHSS score, but otherwise fulfilling all EVT eligibility criteria. Under their current local resources, the majority of physicians (60.4%,  $n = 166/275$ ) would offer EVT to this patient and the rate was higher under assumed ideal conditions (66.6%,  $n = 183/275$ ). This suggests that the majority of participants considered EVT a safe and effective treatment option, even in LVO patients with “mild” symptoms.

There is a growing body of evidence that AIS due to LVO with low NIHSS carries an increased risk of early neurologic deterioration and, hence, should not be considered “mild stroke” [5]; the high proportion of physicians offering EVT in our survey seems to be consistent with this consideration. However, EVT carries a complication risk that is not negligible and it has to be balanced against the risk of neurologic deterioration in the low NIHSS patient population, in which many patients will do well without treatment. A recent registry study investigated the use of EVT in patients with mild stroke and suggested overall favorable outcomes with EVT; however, they also acknowledged that symptomatic intracerebral hemorrhage and mortality rates were relatively high, at 4% and 5% respectively [22, 23]. This could potentially indicate overtreatment and emphasizes the need for a randomized controlled trial. The TEMPO 1 trial [24] proved safety and feasibility of intravenous tenecteplase for mild strokes, and the ongoing TEMPO 2 trial (NCT02398656) seeks to investigate whether tenecteplase is efficacious in mild stroke patients. The fundamental challenge in both studies was/will be to show a significant treatment effect: even patients in the control arm do relatively well, and thus, overall differences in outcomes are small. This yields true to some degree for a potential EVT trial as well, but neurologic deterioration is more common among mild stroke patients with LVO [5, 6], which is beneficial from a point of view of trial design.

Most participants who opted for EVT in our survey decided in favor of a combined treatment (EVT and intravenous alteplase), thereby adhering to current AHA/ASA treatment guidelines, which recommend alteplase in the above-mentioned case-scenario [3]. While the specialty-specific decision rates under current local resources did not differ significantly, the rates under assumed ideal conditions were significantly different, with interventional neuroradiologists

deciding most frequently (71.4%,  $n = 60/84$ ) and neurosurgeons least frequently (43.3%,  $n = 13/30$ ) in favor of EVT. The low rate among neurosurgeons may reflect a bias arising from general neurosurgical practice, favoring a non-interventional approach to clinically mildly affected patients.

We observed significant differences both in current and ideal EVT rates across geographic regions, with Australia yielding the highest current and ideal rate (94.1%,  $n = 16/17$ ). The lowest rate under current local resources was observed in South America (40.0%,  $n = 8/20$ ), and the lowest rate under assumed ideal conditions in East Asia (47.2%,  $n = 25/53$ ). While the discrepancies under current local resources could be partially explained by external restraints, such as lack of access to endovascular treatment facilities in certain regions, the reasons for the differences under assumed ideal conditions are less obvious. The low number of respondents from some regions (e.g., Australia with only 17 respondents) could have potentially led to misrepresentation of the region's treatment decision rate, thereby exaggerating the region-specific differences. Annual center EVT volume was significantly associated with a treatment decision in favor of EVT under current local resources, suggesting that physicians working in high-volume centers consider EVT a safe and effective treatment option, and their current local working conditions seem to allow them to offer this treatment. Personal annual EVT volume was significantly associated with a decision in favor of EVT under assumed ideal conditions. Higher personal EVT treatment volumes are associated with lower complication rates and better outcomes [25]. Thus, physicians with higher personal annual EVT caseloads in particular might decide in favor of EVT, since they perceive EVT as a safe and effective treatment based on their personal experience.

## Limitations

Our study has several limitations: first of all, the overall response rate of physicians was modest with 45.6%. This is not uncommon when compared with other survey-based studies. The number of responses from certain specialties (e.g., neurosurgeons) and geographic regions (e.g., Australia/New Zealand and South Asia) was relatively small. Since there is no comprehensive international register of stroke physicians, participant enrollment was based on institutional networks and co-operations. Representativeness of the survey results can therefore not be unconditionally assumed. Survey data can only approach but never accurately depict decision-making in clinical routine. However, we tried to design the case scenario as realistic as possible.

Despite its limitations, this study is a first step towards exploring physicians' treatment approaches in AIS patients with LVO and low NIHSS across a broad, international multidisciplinary spectrum.



## Conclusion

The majority of physicians participating in this survey supported an aggressive endovascular treatment approach when facing AIS due to LVO with low NIHSS and would offer EVT despite the limited evidence that is currently available for this patient subgroup. A randomized controlled trial seems justified to build high-level evidence for efficacy and safety of EVT in this patient population.

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## Compliance with ethical standards

**Conflict of interest** GS is supported by the Heart and Stroke Foundation of Canada Career Scientist Award. MG is a consultant for Medtronic, Stryker, Microvention, GE Healthcare, and Mentice. JO is supported by the University of Basel Research Foundation, the Julia Bangerter Rhyner Foundation, and the “Freiwillige Akademische Gesellschaft Basel”. The other authors have nothing to disclose.

**Ethical approval** For this type of study formal consent is not required.

**Informed consent** Since the study did not involve patients, formal consent is not required.

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