Clinical selection strategies to identify ischemic stroke patients with large anterior vessel occlusion– Results from SITS-ISTR

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Word count: 5572 abstract: 248

Cover title: Prediction of large anterior vessel occlusion

Abstract

Background and Purpose: The National Institutes of Health Stroke Scale (NIHSS) correlates with presence of large anterior vessel occlusion (LAVO). However, the application of the full NIHSS in the prehospital setting to select patients eligible for treatment with thrombectomy is limited. Therefore, we aimed to evaluate the prognostic value of simple clinical selection strategies.

Methods: Data from the Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Registry (2012-May 2014) were analyzed retrospectively. Patients with complete breakdown of NIHSS scores and documented vessel status were included. We assessed the association of prehospital stroke scales and NIHSS symptom profiles with LAVO (internal carotid artery, carotid-terminus or M1-segment of the middle cerebral artery).

Results: Among 3505 patients, 23.6% (n=827) had LAVO. Pathological finding on the NIHSS item 'best gaze' was strongly associated with LAVO (adjusted OR 4.5, 95%CI 3.8-5.3). All three Face-Arm-Speech Time test (FAST) items identified LAVO with high sensitivity. Addition of abnormal 'gaze' to FAST (G-FAST) or high scores on other simplified stroke scales increased specificity. The NIHSS symptom profiles representing total anterior syndromes showed a 10-fold increased likelihood for LAVO compared to a non-specific clinical profile. If compared to an NIHSS threshold of >=6, the prehospital stroke scales performed similarly or even better without losing sensitivity.

Conclusions: Simple modification of the FAST score or evaluating the NIHSS symptom profile may help to stratify patients' risk of LAVO and to identify individuals who deserve

rapid transfer to comprehensive stroke centers. Prospective validation in the prehospital setting is required.

Introduction

The beneficial effects of endovascular treatment (EVT) in addition to intravenous thrombolysis (IVT) have been proven in patients with acute ischemic stroke caused by large anterior vessel occlusion (LAVO).[1-5] Given the time-dependent effects of revascularization,[6,7] rapid recognition of potentially eligible patients for such treatment is critical, both in the prehospital and the early in-hospital triage stage. Because EVT and complex diagnostic imaging resources often have limited availability outside of comprehensive stroke centers (CSC) or clinical trial settings, there is a pressing need to develop strategies to identify patients that need bypass of a primary stroke center (PSC) and transfer to CSCs with EVT capability. These strategies should balance well between sensitivity to capture the majority of LAVO and appropriate specificity to avoid overwhelming the CSCs with patients that do not require EVT.

A high National Institutes of Health Stroke Scale (NIHSS) score is strongly associated with presence of LAVO.[8-10] Therefore, the NIHSS is frequently recommended to select patients for EVT.[11,12] Due to the complexity of a complete NIHSS examination, simple stroke recognition scores like the Face-Arm-Speech Time (FAST) test are commonly used by paramedics to evaluate patients with suspected stroke in the field. Moreover, certain NIHSS items or symptom patterns may be more informative of LAVO compared to simply a score reflecting the overall severity of deficits. Recently, six profiles of NIHSS symptoms have been proposed and shown to improve the clinical value of the overall NIHSS concerning prediction of functional outcome and mortality.[13-15] In order to evaluate different simple triage strategies beyond the total NIHSS sum score, we aimed to analyze the value of the common prehospital stroke scales and the NIHSS item profiles to predict LAVO in acute stroke patients.

Methods

Data source, design, patients, and outcomes

We conducted a retrospective analysis on individual patient data obtained from the Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Registry (SITS-ISTR) between January 2012 and May 2014. SITS-ISTR is a multinational open registry of acute ischemic stroke patients who received reperfusion therapies.[16,17] Patients from 132 participating centers with complete breakdown of NIHSS scores and status of vessel occlusion were included. Baseline characteristics included data on age, sex, stroke severity according to the NIHSS, onset-to-treatment time, pre-stroke modified Rankin Scale (mRS), and medical history (i.e. previous stroke, current smoking, hypertension, diabetes, atrial fibrillation, and chronic heart failure).

Our outcome of interest was the presence of LAVO (i.e., occlusion within the internal carotid artery, carotid-T and M1 segment of the middle cerebral artery). The definition of LAVO was in accordance to the recent positive endovascular treatment trials in patients with anterior circulation stroke.[18,19] Vessel imaging was usually performed before treatment with thrombolysis or shortly after application of bolus dose.

Two sensitivity analyses were conducted. First, we added basilar artery occlusion (BAO) to the definition of large vessel occlusion. Although currently EVT is not covered by Class I recommendation in BAO, guidelines recommend clinical evaluation of patients with BAO in CSCs.[11] Thus, prehospital detection of patients with BAO is important. Second, we confined the analysis to patients with moderate stroke severity (NIHSS 6-11). This group constitutes a relevant subgroup because most false positive or false negative identifications of LAVO occurs and the majority of patients evaluated in the field have overall moderate stroke severity. The upper limit of NIHSS 11 was chosen for consistency with optimal cut-off for prediction of LAVO in the previous studies.[9,20-22] The lower threshold of NIHSS 6 was chosen as this cutoff showed at least 90% sensitivity for LAVO in the present cohort and previous reports.[20,21] Stroke with NIHSS score <6 is often considered mild stroke, with low probability of LAVO.[23]

Common prehospital stroke scales and NIHSS item profiles

We evaluated prehospital stroke recognition scales that could be derived directly from the individual breakdown of NIHSS items at baseline (i.e., Face Arm Speech Time [FAST] test) and simplified NIHSS scores that have been shown to be associated with LAVO (i.e., 3-item Stroke Scale [3I-SS], the Rapid Arterial Occlusion Evaluation Scale [RACE], the Cincinnati Stroke Triage Assessment Tool [C-STAT], and the Prehospital Acute Stroke Severity scale [PASS]).[24-26] Supplemental Table I summarizes components of the prehospital stroke scales that were analyzed. As the NIHSS item 'best gaze' is missing in the typical FAST algorithm but strongly associated with LAVO,[21,26,27] we tested the hypothesis that adding the abnormal gaze to FAST (G-FAST) may improve its predictive value.

The NIHSS item profiles that were recently described and validated may prove useful for clinical stroke prognostication and research studies.[13-15] The profiles grouped the 15 individual attributes of NIHSS, using latent class analysis, into six clinical symptom profiles.[13-15] We applied the probabilities of profile membership generated by Sucharew et al to our cohort. Profile A represents a total anterior circulation syndrome (TACS) of the dominant hemisphere, Profile B a TACS of the non-dominant hemisphere, Profile C a partial anterior circulation syndrome (PACS) of the dominant hemisphere with predominant language deficits, Profile D a PACS of dominant hemisphere without predominant language deficits, Profile E a PACS of the non-dominant hemisphere, and Profile F a mild clinical syndrome with low probability of abnormal findings on all NIHSS items (Supplementary Table II).

Statistical methods

Continuous variables were compared using the t-test or Mann–Whitney U test and were presented as mean± standard deviation (SD) or median (interquartile range, IQR), where appropriate. Categorical variables were compared using the Pearson χ2 test and presented as percentages (n). Multivariable logistic regression analysis was performed to assess the association of single NIHSS items, the prehospital stroke scales, and the NIHSS profiles with LAVO. Adjustment was made for variables significantly associated with LAVO in the univariable comparison (sex, atrial fibrillation, onset-to-treatment time). We also adjusted the analysis for age, pre-stroke mRS >2 (i.e. being dependent from others in activities of daily living) and history of previous stroke, because pre-stroke disability and residual neurological deficits from a previous stroke may affect the NIHSS. For the prehospital stroke scales, the lowest score was used as the reference. For the NIHSS item profiles, profile F (stroke with low probabilities of abnormal findings on all 15 items) was used as reference. Regarding single NIHSS items, we applied forward stepwise regression analysis to identify the NIHSS item that improves the model most.

We computed area under the receiver operating characteristics (ROC) curve (AUC) and the respective 95% confidence intervals (CI) to assess the global performance of the prehospital stroke scales and NIHSS symptom profiles to predict LAVO. AUC values were compared using the method of DeLong et al.[28] The ROC-derived optimal cut-off for the scores was determined at the maximal Youden-Index.[29] Finally, we calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy for the prediction of LAVO, at high-sensitivity (>85%) and high-specificity (>75%) cut-offs of the common prehospital stroke scales. For consistency with the sensitivity of the widely-accepted FAST and CPSS scores for recognition of stroke patients in the field, a sensitivity >85% was considered as the high-sensitivity threshold.[30,31] The target specificity of >75% is even higher than the average specificity of common stroke recognition tools to discriminate strokes from stroke mimics and suggests rate of futile transfers of less than one out of four.[31,32] Data analysis was performed using SPSS (version 22, IBM, New York, USA) or MedCalc (Version 16.2, Ostend, Belgium).

Results

During the study period, 3505 patients with complete breakdown of NIHSS items and data on vessel occlusion site were available for analysis. LAVO was present in 23.6% (n=827) of patients. Baseline characteristics of patients with or without LAVO are shown in Table 1. Baseline NIHSS was strongly associated with LAVO (adjusted OR 1.15, 95%CI 1.13-1.16, per point). Sensitivity, specificity, PPV and NPV at different NIHSS cut-offs are shown in supplemental table III.

As shown in Table 2, there was a graded relationship between prehospital stroke scales scores and NIHSS item profiles with presence of LAVO. Compared to a FAST score of 0 or 1, patients with all three FAST items being positive had an adjusted OR of 7.9 (95% CI 5.2-11.9) for LAVO (sensitivity 84%, specificity 44%, PPV 32%, NPV 90%). Forward stepwise multiple regression analysis suggested 'best gaze' to be the single NIHSS item with strongest association with LAVO (adjusted OR 4.5, 95% CI 3.8-5.3). Addition of 'abnormal gaze' to FAST improved specificity (table 2) and resulted in significant improvement of the AUC for LAVO compared to FAST alone (p<0.001, supplemental table IV).

The six NIHSS symptom profiles that represent different clinical phenotypes were reproduced from previous analyses.[13-15] Patients allocated to NIHSS symptom profiles representing TACS (profile A and B) had a more than 6-fold increased of LAVO compared to all other profiles combined (OR 6.2, 95%CI 5.1-7.5).

Table 3 shows sensitivity, specificity, PPV and NPV for presence of LAVO of different cut-offs of the entire NIHSS, the prehospital stroke scales and NIHSS item profiles. High sensitivity was observed for FAST>=2, G-FAST >=3, C-STAT >=1, 3I-SS >=1, PASS>=1, RACE >=3 and clinical signs of at least a PACS (NIHSS symptom profiles A to E), while high specificity was observed for G-FAST=4, C-STAT>=3, 3I-SS=3, PASS=3, RACE >=6 and clinical signs of TACS (NIHSS symptom profile A and B).>

The AUC of the prehospital stroke scales and NIHSS item profiles to predict LAVO was similar and nearly as good as the entire NIHSS (supplemental table IV), especially in patients presenting with moderate stroke severity. When compared to the NIHSS cut-off >=6 which is recommended by current AHA/ASA guidelines to select patients for thrombectomy (AUC 0.60, 95%CI 0.58-0.62), AUC of the G-FAST>=3 (AUC 0.64, 95%CI 0.62-0.66) and C-STAT>=1 (AUC 0.63, 95%CI 0.61-0.65) were significantly higher (p<0.001), but the cut-offs showed similar sensitivity (89-91%, table 3).

Sensitivity analyses

Similar results were obtained after addition of 93 patients with basilar artery occlusion (BAO) to the large vessel occlusion definition (n=920, 26.2%), although the overall strength of the association was slightly weaker (Supplemental table V). The optimal NIHSS cut-off was also >=12 (sensitivity 70%, specificity 70%, PPV 45%, NPV 87%) and the cut-off showing at least 85% sensitivity was >=7 (sensitivity 88%, specificity 39%, PPV 34%, NPV 90%). The optimal cut-offs for detection of LVO including BAO were FAST=3, G-FAST=4, C-STAT>=2, 3I-SS>=2, and RACE >=5 (supplemental table VI).

When we focused our analysis to patients with moderate stroke severity (NIHSS 6-11, n=1257 patients), frequency of LAVO was 12.6% (19.2% of all observed LAVO within the cohort, 159 of 827). The common prehospital stroke scales' performances for prediction of LAVO did not differ from the overall total NIHSS score (supplemental table III), with the highest absolute AUC value for the C-STAT. Similar to the entire cohort, increasing integer values of the common prehospital stroke scales showed disparate associations with LAVO (supplemental table VII). Profiles A and B (left and right TACS) were associated with a nearly 3-fold increased risk of LAVO compared to all other profiles (C-F combined, adjusted OR 2.8, 95%CI 2.0-4.0).

Discussion

One of the major challenges of the current stroke care is to translate the implications of the endovascular stroke trials into clinical practice. Non-invasive vessel imaging and rapid transfer of eligible patients to CSCs with EVT treatment option need to be organized effectively. Since no triage strategy performs perfectly, some patients with LAVO will be inevitably missed and many patients without LAVO will be transferred to CSCs.[22] It is a political issue to decide what range of false negatives and false positives are acceptable from the perspective of society as a whole. Local circumstances should also influence the choice of selection criteria.

In general, prehospital triage tools for detection of LAVO should be as simple as possible and easily repeatable by EMS staff. In addition, the ideal scores are supposed to discriminate stroke patients from stroke mimics. In our cohort, the simple prehospital stroke scales performed nearly as well as the entire NIHSS in identifying LAVO, and at least as well as the entire NIHSS in patients with overall moderate severity. Importantly, highly sensitive cut-offs of the prehospital scores performed as well as or even better than NIHSS cut-off >=6, which is recommended to select patients for thrombectomy according to the current AHA/ASA guidelines.[12] Thus, our findings emphasize the potential of simplified NIHSS scores to detect LAVO in the prehospital setting. Our sensitivity analysis demonstrated comparable findings when basilar artery occlusion was included in the large vessel occlusion category.

Several stroke recognition tools have been validated for prehospital evaluation of patients with suspected strokes.[30-32] The FAST score is already widely used and shows the best sensitivity for correct diagnosis of stroke together with the similar CPSS.[30,31] In order to identify stroke patients with underlying LAVO in the field, it seems reasonable to use a two-step screening process starting with the FAST score. FAST has the advantage of using the item 'facial palsy' that has been shown to be the NIHSS item with best capability to discriminate between strokes and mimics.[33] In a second step, another tool is needed for the triage regarding vessel imaging and facilitate transfer to EVT centers. Ideally, this secondary score should be deduced from the initial score but require addition of only a few more items with higher sensitivity and specificity for presence of LAVO. In line with previous studies,[21,27](HASTRUP) we found that gaze deviation was the most sensitive clinical sign suggestive of LAVO. Thus, a simple expansion of the typical FAST score by the NIHSS item 'best gaze' was developed in our study (G-FAST or 'Go FAST'). G-FAST would fulfill the criteria mentioned above and has the advantage of mentioning all tested signs as an acronym. The C-STAT follows a similar concept and also seems promising at the second stage as cortical signs (especially gaze) strengthen the score, but still it maintains simplicity.[18] By using the questions and commands from the NIHSS instead of the language and speech items which are complex for many emergency medical services, the C-STAT makes the rating objective, rather than subjective. Satz ergänzen zu (HASTRUP)??

Importantly, the optimal prehospital triage strategy depends on various time variables. Besides time from symptom onset until first evaluation by paramedics, transport time to next CSC has to be considered. Our analysis adds relevant findings in at least three different clinical scenarios:

First, we consider a patient with suspected stroke who is evaluated by paramedics early after onset of symptoms or with short transfer time to a CSC. In this case, a high sensitivity for LAVO (ideally close to 90%) should be achieved. This was observed in different symptom combinations in our study, namely: at least two FAST items being positive, all three FAST items or abnormal NIHSS item 'best gaze', G-FAST >=3, C-STAT >=1, 3I-SS >=1, PASS>=1, RACE >=3 and clinical signs of at least a PACS (NIHSS symptom profiles A to E).

Second, we consider a patient with suspected stroke who is evaluated by paramedics at the end of IVT time-window or with long transfer time to the nearest CSC. In this case a high specificity (>75%) for LAVO is warranted with less than one out of four futile transfers. This was observed for patients with abnormal gaze and all three FAST items being positive (G-FAST=4), C-STAT>=3, 3I-SS=3, PASS=3, RACE >=6 and clinical signs of TACS (NIHSS symptom profile A and B).

Third, we consider a patient who arrives at a PSC and is evaluated by trained stroke physicians. In this case full examination of the NIHSS is feasible. It has been shown that no single variable beyond the NIHSS is able significantly to improve prediction of LAVO.[10] Current recommendations by the European Stroke Organisation are based on the statistically optimal NIHSS cut-point observed in the large Bernese stroke registry (NIHSS>=9 within 3h, NIHSS>=7 within 6h).[8,11] Our findings suggest that lower NIHSS cut-offs could be used to improve sensitivity (>90% with NIHSS >=6 and >95% with NIHSS >=5).

Yet, there are certain constellations in which application of highly specific LAVO scores or the highly specific NIHSS symptom profiles A or B could be helpful. Amongst others these are: late arrival close to 6 hours, relative contraindications to CT-A like severely impaired kidney function or uncontrolled hyperthyroidism, and to avoid expenses of screening failures in a randomized controlled trial.

Although all NIHSS items contribute equally to the sum score, certain items and item constellations may reflect larger ischemic lesions that carry a high attributable risk of an underlying LAVO. Not surprisingly, we observed a graded association of the NIHSS item profiles with LAVO. The two symptom profiles with the highest risks, Profiles A and B, represent left and right total hemispheric syndrome, respectively. Thus, our findings suggest that patterns of deficit rather than simply scores reflecting severity of deficit will be more useful in triage. Although the exact concept of the NIHSS symptom profiles may be difficult to conduct by paramedics, our findings support the notion that patients with a total anterior clinical syndrome, even if mild to moderate, should prompt an urgent neurovascular imaging and consideration for a transfer to a dedicated stroke center capable of EVT. Given that right-hemispheric symptoms are under-represented in the NIHSS, patients with right LAVO might be missed in case of mild to moderate stroke severity based on NIHSS scoring alone.

Our study has limitations. While the overall extent and accuracy of data collected within SITS-ISTR allow for statistically robust analyses, the retrospective and observational design inherits potential for bias. Our cohort consists of patients who received revascularization treatments after a clinical diagnosis of acute ischemic stroke was already established and hemorrhagic stroke was ruled out by brain imaging. Consequently, sensitivity and specificity of the simplified NIHSS scores for LAVO might differ in prehospital cohorts with suspected stroke that include stroke mimics and hemorrhagic strokes. Majority of data were derived from primary stroke centers with limited availability of vessel-imaging compared to comprehensive stroke centers. Moreover, data on LAVO status were obtained from assessment by local radiologists at the respective centers (not necessarily neuroradiologists). It is reassuring that 96% of patients within the ESCAPE trial had the correct target-vessel occlusion status by using similar LAVO definition as per our analysis, after review from central adjudication laboratory.[2] In addition, it is possible that residual deficits related to prior stroke or other reasons may affect baseline NIHSS score, consequently led to incorrect ratings. We have accounted for this by adjusting the analysis for pre-stroke mRS and previous stroke. Finally, we were not able to evaluate other established stroke recognition tools (e.g. LAMS, LAPSS, MASS, ROSIER),[31,32] because 'grip strength' was not part of the NIHSS recording and some scores require additional information other than the NIHSS (e.g. history of seizures).

In summary, we found that the common simplified NIHSS scores may be useful to stratify patients' risk of LAVO in the prehospital setting. Certain cut-offs were suggested to give guidance in clinical settings that require either high sensitivity (>85%) or high specificity (>75%). In general, patients with abnormal findings on all three FAST items, and, especially patients with additional gaze deviation (G-FAST) may be considered for urgent neurovascular imaging and transfer to comprehensive stroke centers. This subset of patients may be readily identifiable by paramedics during the prehospital stage. Our findings deserve prospective validation, ideally in the prehospital setting. The upcoming specialized stroke ambulances seem to be one of the promising settings to validate our findings and the feasibility of triage tools.

Acknowledgments: None.

Sources of funding: J.F.S. is a participant in the Charité Clinical Scientist Program funded by the Charité Universitätsmedizin Berlin and the Berlin Institute of Health. The research was done with support from European Academy of Neurology via a Research Fellowship grant awarded to Dr. Scheitz. M.E. receives funding from the DFG (Excellence cluster NeuroCure; SFB TR43, KFO 247, KFO 213), Bundesministerium für Bildung und Forschung (BMBF, Center for Stroke Research Berlin), European Union (European Stroke Network, Wake-Up, Counterstroke), Volkswagen Foundation (Lichtenberg Program).

Conflicts of interest/Disclosures: None

References

1. Berkhemer OA,Fransen PS,Beumer D,van den Berg LA,Lingsma HF,Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med.* 2015;372:11-20.

2. Goyal M,Demchuk AM,Menon BK,Eesa M,Rempel JL,Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med.* 2015;372:1019-1030.

3. Campbell BC,Mitchell PJ,Kleinig TJ,Dewey HM,Churilov L,Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med.* 2015;372:1009-1018.

4. Saver JL,Goyal M,Bonafe A,Diener HC,Levy EI,Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med.* 2015;372:2285-2295.

5. Jovin TG,Chamorro A,Cobo E,de Miquel MA,Molina CA,Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med.* 2015;372:2296-2306.

6. Emberson J,Lees KR,Lyden P,Blackwell L,Albers G,Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet.* 2014;384:1929-1935.

7. Sheth SA,Jahan R,Gralla J,Pereira VM,Nogueira RG,Levy EI, et al. Time to endovascular reperfusion and degree of disability in acute stroke. *Ann Neurol.* 2015;78:584-593.

8. Heldner MR,Zubler C,Mattle HP,Schroth G,Weck A,Mono ML, et al. National Institutes of Health stroke scale score and vessel occlusion in 2152 patients with acute ischemic stroke. *Stroke.* 2013;44:1153-1157.

9. Cooray C,Fekete K,Mikulik R,Lees KR,Wahlgren N,Ahmed N. Threshold for NIH stroke scale in predicting vessel occlusion and functional outcome after stroke thrombolysis. *Int J Stroke.* 2015; 10:822-829.

10. Vanacker P,Heldner MR,Amiguet M,Faouzi M,Cras P,Ntaios G, et al. Prediction of Large Vessel Occlusions in Acute Stroke: National Institute of Health Stroke Scale Is Hard to Beat. *Crit Care Med.* 2016;44:e336-e343.

11. Wahlgren N,Moreira T,Michel P,Steiner T,Jansen O,Cognard C, et al. Mechanical thrombectomy in acute ischemic stroke: Consensus statement by ESO-Karolinska Stroke Update 2014/2015, supported by ESO, ESMINT, ESNR and EAN. *Int J Stroke.* 2016;11:134-147.

12. Powers WJ,Derdeyn CP,Biller J,Coffey CS,Hoh BL,Jauch EC, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013

Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2015;46:3020-3035.

13. Sucharew H,Khoury J,Moomaw CJ,Alwell K,Kissela BM,Belagaje S, et al. Profiles of the National Institutes of Health Stroke Scale items as a predictor of patient outcome. *Stroke.* 2013;44:2182-2187.

14. Abdul-Rahim AH,Fulton RL,Sucharew H,Kleindorfer D,Khatri P,Broderick JP, et al. National institutes of health stroke scale item profiles as predictor of patient outcome: external validation on independent trial data. *Stroke.* 2015;46:395-400.

15. Abdul-Rahim AH,Fulton RL,Sucharew H,Kleindorfer D,Khatri P,Broderick JP, et al. National Institutes of Health Stroke Scale Item Profiles as Predictor of Patient Outcome: External Validation on Safe Implementation of Thrombolysis in Stroke-Monitoring Study Data. *Stroke.* 2015;46:2779-2785.

16. Mazya MV,Lees KR,Collas D,Rand VM,Mikulik R,Toni D, et al. IV thrombolysis in very severe and severe ischemic stroke: Results from the SITS-ISTR Registry. *Neurology.* 2015;85:2098-2106.

17. Mazya MV,Ahmed N,Ford GA,Hobohm C,Mikulik R,Nunes AP, et al. Remote or extraischemic intracerebral hemorrhage--an uncommon complication of stroke thrombolysis: results from the safe implementation of treatments in stroke-international stroke thrombolysis register. *Stroke.* 2014;45:1657-1663.

18. Demchuk AM,Goyal M,Menon BK,Eesa M,Ryckborst KJ,Kamal N, et al. Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times (ESCAPE) trial: methodology. *Int J Stroke.* 2015;10:429-438.

19. Saver JL,Goyal M,Bonafe A,Diener HC,Levy EI,Pereira VM, et al. Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) trial: protocol for a randomized, controlled, multicenter study comparing the Solitaire revascularization device with IV tPA with IV tPA alone in acute ischemic stroke. *Int J Stroke.* 2015;10:439-448.

20. Scheitz JF,Erdur H,Tutuncu S,Fiebach JB,Audebert HJ,Endres M, et al. National Institutes of Health Stroke Scale for prediction of proximal vessel occlusion in anterior circulation stroke. *Int J Stroke.* 2015;10:E60.

21. Fischer U,Arnold M,Nedeltchev K,Brekenfeld C,Ballinari P,Remonda L, et al. NIHSS score and arteriographic findings in acute ischemic stroke. *Stroke.* 2005;36:2121-2125.

22. Turc G,Maier B,Naggara O,Seners P,Isabel C,Tisserand M, et al. Clinical Scales Do Not Reliably Identify Acute Ischemic Stroke Patients With Large-Artery Occlusion. *Stroke.* 2016;47:1466-1472.

23. Heldner MR,Jung S,Zubler C,Mordasini P,Weck A,Mono ML, et al. Outcome of patients with occlusions of the internal carotid artery or the main stem of the middle cerebral artery with NIHSS score of less than 5: comparison between thrombolysed and non-thrombolysed patients. *J Neurol Neurosurg Psychiatry.* 2015;86:755-760.

24. Singer OC,Dvorak F,du Mesnil de RR,Lanfermann H,Sitzer M,Neumann-Haefelin T. A simple 3-item stroke scale: comparison with the National Institutes of Health Stroke Scale and prediction of middle cerebral artery occlusion. *Stroke.* 2005;36:773-776.

25. Perez de la Ossa N,Carrera D,Gorchs M,Querol M,Millan M,Gomis M, et al. Design and validation of a prehospital stroke scale to predict large arterial occlusion: the rapid arterial occlusion evaluation scale. *Stroke.* 2014;45:87-91.

26. Katz BS,McMullan JT,Sucharew H,Adeoye O,Broderick JP. Design and validation of a prehospital scale to predict stroke severity: Cincinnati Prehospital Stroke Severity Scale. *Stroke.* 2015;46:1508-1512.

27. Singer OC,Humpich MC,Laufs H,Lanfermann H,Steinmetz H,Neumann-Haefelin T. Conjugate eye deviation in acute stroke: incidence, hemispheric asymmetry, and lesion pattern. *Stroke.* 2006;37:2726-2732.

28. Hastrup…

28. DeLong ER,DeLong DM,Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics.* 1988;44:837-845.

29. Youden WJ. Index for rating diagnostic tests. *Cancer.* 1950;3:32-35.

30. Kleindorfer DO,Miller R,Moomaw CJ,Alwell K,Broderick JP,Khoury J, et al. Designing a message for public education regarding stroke: does FAST capture enough stroke? *Stroke.* 2007;38:2864-2868.

31. Purrucker JC,Hametner C,Engelbrecht A,Bruckner T,Popp E,Poli S. Comparison of stroke recognition and stroke severity scores for stroke detection in a single cohort. *J Neurol Neurosurg Psychiatry.* 2015;86:1021-1028.

32. Brandler ES,Sharma M,Sinert RH,Levine SR. Prehospital stroke scales in urban environments: a systematic review. *Neurology.* 2014;82:2241-2249.

33. Ali SF,Viswanathan A,Singhal AB,Rost NS,Forducey PG,Davis LW, et al. The TeleStroke mimic (TM)-score: a prediction rule for identifying stroke mimics evaluated in a Telestroke Network. *J Am Heart Assoc.* 2014;3:e000838.

Table 1 - Baseline characteristics of the cohort according to presence of LAVO

	Entire cohort N=3505	LAVO N=827	No LAVO N=2678	p
Age, years, mean (± SD)	68.1 (±13.6)	68.3 (±13.5)	68.1 (±13.6)	0.631
Sex, male, % (n)	56.1 (1967)	52.6 (435)	57.2 (1532)	0.020
Pre-mRS>2, % (n), 164 missings	4.0 (134)	3.7 (29)	4.1 (105)	0.577
NIHSS sum, median (IQR)	9 (6-16)	16 (11-20)	8 (5-13)	<0.001
Endovascular treatment, % (n)	8.0 (282)	26.6 (220)	2.3 (62)	<0.001
Atrial fibrillation, % (n), 16 missings	18.9 (661)	22.8 (188)	17.7 (473)	0.001
Chronic Heart Failure, % (n), 21 missings	7.7 (268)	8.6 (71)	7.4 (197)	0.255
Current Smoker, % (n) , 121 missings	17.5 (593)	18.2 (143)	17.3 (450)	0.560
Diabetes, % (n) , 13 missings	18.5 (645)	16.9 (139)	19.0 (506)	0.187
Hyperlipidemia, % (n) , 34 missings	29.6 (1028)	31.5 (257)	29.1 (771)	0.188
Hypertension, % (n) , 12 missings	64.6 (2258)	64.8 (533)	64.6 (1725)	0.935
Previous Stroke, % (n) , 20 missings	12.0 (417)	11.1 (91)	12.2 (326)	0.358
Onset-to-needle, min, median (IQR)	150 (119-195)	145 (115-190)	150 (120-195)	0. 028

Abbreviations: LAVO – large anterior vessel occlusion, mRS – modified Rankin Scale, NIHSS - National Institutes of Health Stroke Scale

Table 2 - Association of NIHSS categories, NIHSS symptom profile, and simplified NIHSS scores with LAVO

Score name	Score result	LAVO n/N	Number needed to screen*	Adjusted OR for LAVO†
NIHSS categories	0-5	72/828	11.5	1 (Reference)
	6-10	128/1107	8.7	1.40 (1.02-1.92)
	11-15	191/679	3.6	4.29 (3.15-5.83)
	>15	436/891	2.1	10.72 (8.00-14.37)
NIHSS symptom profile	A	318/793	2.5	10.24 (6.40-16.38)
	B	310/775	2.5	9.95 (6.22-15.92)
	C	38/352	9.3	1.85 (1.05-3.25)
	D	70/644	9.2	1.62 (0.97-2.72)
	E	68/591	8.7	1.87 (1.12-3.13)
	F	23/350	15.2	1 (Reference)
FAST	0	3/63	20.8	1 (Reference)
	1	25/429	17.2	1.65 (0.38-7.18)
	2	104/806	7.8	4.19 (1.01-17.45)
	3	695/2207	3.1	12.29 (2.99-50.57)
G-FAST‡	0	3/56	18.6	1 (Reference)

	1	22/398	18.2	1.37 (0.31-6.05)
	2	68/686	10.0	2.85 (0.68-11.99)
	3	265/1334	5.0	5.96 (1.44-24.68)
	4	468/1029	2.2	20.52 (4.97-84.99)
C-STAT	0	92/1091	11.9	1 (Reference)
	1	145/953	6.6	1.85 (1.38-2.48)
	2	108/410	3.8	4.17 (3.04-5.74)
	3	266/606	2.3	8.81 (6.65-11.66)
	4	216/445	2.1	10.58 (7.82-14.32)
PASS	0	23/296	12.8	1 (Reference)
	1	153/1446	9.4	1.38 (0.86-2.24)
	2	333/1074	3.2	5.63 (3.53-8.97)
	3	318/689	2.2	11.16 (6.92-18.00)
RACE	0-1	55/781	14.2	1 (Reference)
	2	63/587	9.3	1.75 (1.18-2.60)
	3	55/368	6.7	2.35 (1.54-3.57)
	4	65/327	5.0	3.42 (2.27-5.14)

	5-6	153/590	3.9	4.79 (3.38-6.79)
	7-9	436/852	2.0	15.18 (10.96-21.02)
3I-SS§	0	68/803	11.8	1 (Reference)
	1	221/1419	6.4	1.90 (1.41-2.56)
	2	367/900	2.5	7.47 (5.56-10.00)
	3	171/383	2.2	8.44 (6.03-11.81)

Abbreviations: 3I-SS - 3-item Stroke Scale, C-STAT - Cincinnati Stroke Triage Assessment Tool, FAST – face, arm, speech and time test, G-FAST – Go FAST score, LAVO – large anterior vessel occlusion, NIHSS - National Institutes of Health Stroke Scale, PASS – Prehospital Acute Stroke Severity scale, RACE - Rapid Arterial Occlusion Evaluation Scale.

* number needed to screen with the respective test result to identify a LAVO, per 100 patients. † adjusted for age, sex, atrial fibrillation, pre-mRS, prior stroke and onset-to-treatment time. ‡ In G-FAST the item 'best gaze' was added to the FAST score (→ G-FAST).§ in contrast to the original version only one point was assigned per pathological item.

Table 3 - Sensitivity, specificity, PPV, and NPV for presence of LAVO at certain cut-offs of the NIHSS, simplified NIHSS scores and NIHSS symptom profiles.

Cut-offs of scores with >85% sensitivity and highest possible specificity						
	n/N (%)	Sensitivity	Specificity	PPV	NPV	Accuracy
NIHSS>=8	2183/3505 (63.2)	85.6	44.9	28.2	91.3	54.5
NIHSS>=6*	2677/3505 (76.4)	91.3	28.2	28.2	91.3	43.1
FAST>=2	3013/3505 (86.0)	96.6	17.3	26.5	94.3	36.0
FAST=3 OR abnormal item 'Best Gaze'	2410/3505 (68.8)	89.1	37.5	30.6	91.8	49.7
G-FAST>=3	2363/3505 (67.5)	88.7	39.1	31.0	91.8	50.8
C-STAT>=1	2414/3505 (68.9)	88.9	37.3	30.4	91.6	49.5
3I-SS>=1	2702/3505 (77.1)	91.8	27.5	28.1	91.5	42.7
PASS >=1	3209/3505 (91.6)	97.2	10.2	25.1	92.2	xx
RACE>=3	2137/3505 (61.0)	85.7	46.7	33.2	91.4	55.9
NIHSS profile A-E (at least PACS or worse) vs profile F	3155/3505 (90.0)	97.2	12.2	25.5	93.4	32.3
Cut-offs of scores with specificity >75% and highest possible sensitivity						
NIHSS >=14	1133/3505 (32.3)	63.1	77.2	46.1	87.1	73.9
G-FAST=4	1029/3505 (29.4)	56.7	79.0	45.5	85.5	73.7

C-STAT>=3	1051/3505 (30.0)	58.3	78.8	45.9	85.9	73.9
3I-SS=3	383/3505 (10.9)	20.7	92.1	44.6	79.0	75.3
PASS =3	689/3505 (19.7)	38.5	86.2	46.2	81.9	cc
RACE>=6	1154/3505 (32.9)	62.2	76.1	44.5	86.7	72.8
NIHSS profile A	793/3505 (22.6)	38.5	82.3	40.1	81.2	72.0
NIHSS profile B	775/3505 (22.1)	37.5	82.6	40.0	81.1	72.0
Statistically optimal cut-offs						
NIHSS >=12	1420/3505 (40.5)	72.1	69.2	42.0	88.9	69.9
FAST=3	2207/3505 (63.0)	84.0	43.5	31.5	89.9	53.1
G-FAST>=3	2363/3505 (67.5)	88.7	39.1	31.0	91.8	50.8
C-STAT>=2	1461/3505 (41.7)	71.3	67.5	40.4	88.4	68.4
3I-SS>=2	1283/3505 (36.6)	65.0	72.2	41.9	87.0	70.5
PASS >=2	1763/3505 (50.3)	78.7	58.5	36.9	89.9	
RACE>=5	1442/3505 (41.1)	71.2	68.2	40.8	88.5	68.9
NIHSS symptom profile A or B	1568/3505 (44.7)	75.9	64.9	40.1	89.7	67.5

Abbreviations: 3I-SS - 3-item Stroke Scale, C-STAT - Cincinnati Stroke Triage Assessment Tool, FAST – face, arm, speech and time test, G-FAST – Go FAST score, NIHSS - National Institutes of Health Stroke Scale, PASS – Prehospital Acute Stroke Severity scale, RACE - Rapid Arterial Occlusion Evaluation Scale.

* NIHSS>=6 is an inclusion criterion for endovascular treatment with stent retrievers according to current "AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment"[12]