

Eligibility and Predictors for Acute Revascularization Procedures in a Stroke Center

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Background and Purpose—Endovascular treatment (EVT) is a new standard of care for selected, large vessel occlusive strokes. We aimed to determine frequency of potentially eligible patients for intravenous thrombolysis (IVT) and EVT in comprehensive stroke centers. In addition, predictors of EVT eligibility were derived.

Methods—Patients from a stroke center–based registry (2003–2014), admitted within 24 hours of last proof of usual health, were selected if they had all data to determine IVT and EVT eligibility according to American Heart Association/American Stroke Association (AHA/ASA) guidelines (class I–IIa recommendations). Moreover, less restrictive criteria adapted from randomized controlled trials and clinical practice were tested. Maximum onset-to-door time windows for IVT eligibility were 3.5 hours (allowing door-to-needle delay of ≤ 60 minutes) and 4.5 hours for EVT eligibility (door-to-groin delay ≤ 90 minutes). Demographic and clinical information were used in logistic regression analysis to derive variables associated with EVT eligibility.

Results—A total of 2704 patients with acute ischemic stroke were included, of which 26.8% were transfers. Of all patients with stroke arriving at our comprehensive stroke center, a total proportion of 12.4% patients was eligible for IVT. Frequency of EVT eligibility differed between AHA/ASA guidelines and less restrictive approach: 2.9% versus 4.9%, respectively, of all patients with acute ischemic stroke and 10.5% versus 17.7%, respectively, of all patients arriving within < 6 hours. Predictors for AHA–EVT eligibility were younger, shorter onset-to-admission delays, higher National Institutes of Health Stroke Scale (NIHSS), decreased vigilance, hemineglect, absent cerebellar signs, atrial fibrillation, smoking, and decreasing glucose levels (area under the curve=0.86).

Conclusions—Of patients arriving within 6 hours at a comprehensive stroke center, 10.5% are EVT eligible according to AHA/ASA criteria, 17.7% according to criteria resembling randomized controlled trials, and twice as many patients are IVT eligible (36.2%). (*Stroke*. 2016;47:1844–1849. DOI: 10.1161/STROKEAHA.115.012577.)

Key Words: cerebral revascularization ■ cerebrovascular occlusion ■ endovascular procedure
■ intravenous thrombolysis ■ stroke

In the last year reporting of 5 positive endovascular thrombectomy trials^{1–3} lead to the publication of new American Heart Association/American Stroke Association (AHA/ASA) guidelines on the early management of patients with acute ischemic stroke (AIS)⁴ and a consensus statement from European societies.⁵ These new recommendations support the use of rapid intravenous thrombolysis (IVT) followed by endovascular treatment (EVT) in well-selected large vessel occlusive strokes.^{6–8}

Implementation of these new guidelines in clinical practice depends on the proportion of patients eligible for this treatment and the organization of the regional health system.^{6,9} However, health systems need to adapt their resource use to the approximate number of revascularization-eligible patients, which also depends on selection criteria that may vary between guidelines, randomized controlled trials, and clinical practice. Whereas the AHA/ASA guidelines recommend a

more focused approach, in some of the randomized controlled trials^{1–3,10} and especially in real-life clinical practice a more liberal approach has been applied.^{11,12}

Independently of the approach chosen, stroke systems of care need estimations of the number of eligible patients for intravenous and endovascular revascularization based on real-world data.¹³ We aimed at providing such numbers from a consecutive series of patients with AIS admitted within more than 10 years to a comprehensive stroke center. We also tried to identify demographic and clinical variables in this population associated with IVT and EVT eligibility.

Methods

Study Design

Data were extracted from Acute Stroke Registry and Analysis of Lausanne (ASTRAL), a large single stroke center AIS registry.¹⁴ It

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contains all patients with AIS presenting within 24 hours of stroke onset or of last proof of usual health who are admitted to the Lausanne University Hospital's stroke unit and intensive care unit. A large set of prespecified data on demographics, past medical history, cerebrovascular risk factors, clinical presentation, acute multimodal imaging (mostly computed tomography (CT) based), physiological and laboratory parameters, and follow-up data were collected in a prespecified manner. For the current analysis, we selected patients from January 2003 to December 2014 with a complete data set allowing calculation of revascularization eligibility according to the AHA/ASA guidelines, that is, age, admission National Institutes of Health Stroke Scale (NIHSS), onset-to-admission delay, prestroke modified Rankin Scale (mRS), use of oral anticoagulants, history of previous strokes and diabetes mellitus, Alberta Stroke Program Early CT Score (ASPECTS) on initial noncontrast CT, and arterial information for all intra- and extracranial vessel sites assessed on CT angiography. The initial NIHSS was performed by NIHSS certified stroke physicians or was supervised by such. Cervical and cerebral CT angiography and cerebral CT perfusion were performed as standard of care if there were no contraindications to iodized contrast, such as known allergy or known renal failure. IVT was usually performed on the CT table immediately after the noncontrast imaging and before vascular imaging was performed and its results were known. Analysis of arterial source images and extra- and intracranial maximum intensity projections was performed by the neuro-radiologist and neurologist on call who were aware of the neurological deficit. Visible vessel occlusion was defined and recorded as described previously.¹⁵ Proximal, endovascular treatable occlusions were defined by the AHA/ASA guidelines as an occlusion of the internal carotid artery (extra and intracranial), and the M1 segment of the middle cerebral artery before its bifurcation, with and without ipsilateral carotid occlusion. The latter motivated additional endovascular revascularization in occasional patients before 2012 according to Swiss guidelines,¹⁶ and according to in-house guidelines that resemble the current European consensus statement.⁵

Patient Selection

Eligibility for acute revascularization therapy was first determined by applying the class I and IIa recommendations stated in the latest AHA/ASA guidelines about IVT and EVT.^{4,17} Following the guidelines accepted hospital arrival delays for IVT and EVT were 3.5 and 4.5 hours, respectively, allowing for door-to-needle times of ≤60 minutes for IVT and for door-to-groin times of ≤90 minutes for EVT. Additional inclusion criteria for IVT beyond 3 hours were used: age ≤80 years, NIHSS ≤25, no history of stroke and diabetes mellitus, no treatment with oral anticoagulants, and no ischemic injury involving more than one third of the middle cerebral artery territory on CT.¹⁷ Other AHA/ASA criteria used for EVT eligibility were an admission NIHSS >6, prestroke mRS score of 0 to 1, ASPECTS of 6 to 10, and presence of an occlusion in the M1 segment of the middle cerebral artery or internal carotid artery.⁴ As the benefits are uncertain, only class IIb evidence⁴ was attributed for endovascular therapy for occlusions of the M2 or M3 portion of the middle cerebral arteries, anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries. Therefore, these occlusion sites were excluded based on their evidence level.^{4,5}

Then, a second set of less stringent EVT criteria was derived, considering the following patients as eligible: NIHSS between 2 and 5, a prestroke mRS score of 2, and ASPECTS of 5. In this more liberal data set, the following arterial sites were considered as reasonable EVT candidates: internal carotid artery (extra and intracranial), M1/M2 segments of the middle cerebral artery, anterior cerebral artery (A1 segment), posterior cerebral artery (P1 segment), and basilar artery occlusion.

The proportion of IVT and EVT actually performed in this center within the recommended time delays was calculated and compared with the eligible proportion of patients.

Statistical Analysis

Univariate logistic regression was performed to identify potential predictors of EVT eligibility, with all relevant clinical, radiological, and

biological data included in the ASTRAL. Imputation of the missing values of the covariates studied was carried out with the method of chained equations, generating 5 imputed data sets. Multiple logistic regression analysis for the identification of predictors that significantly influence the EVT eligibility was performed on each imputed data set, and final results were derived by combining the output of the 5 imputed multiple analyses. Stepwise methods were implemented on each imputed data set to identify significant main effects and interactions. In the multivariate logistic regression analysis, the level of significance was set at 5%. Statistical analysis was performed with R version 3.2.1 software. Collection, analysis, and publication of data in the ASTRAL was approved by the ethics commission for research on humans of the Canton of Vaud, subcommission III.

Results

Patient Characteristics

During the observation period (2003–2014), 3555 patients were entered into the ASTRAL registry. We had to exclude 851 (24%) ASTRAL patients based on their incomplete data sets. Detailed information about the reasons for exclusion is described in the flowchart (Figure 1). These patients were nonsignificantly younger (69 versus 71 years), more often male (57% versus 48%), had a significantly lower median NIHSS (13 versus 16; $P<0.05$), and arrived later at the hospital (median, 392 versus 112 minutes; $P<0.01$) compared with the study cohort. An imputation analysis in the excluded patient cohort identified a significant correlation between inclusion/exclusion and patients' age (odds ratio [OR], 0.96), onset-to-admission time (OR, 0.93), history of diabetes mellitus (OR, 6.38), presence of hemiparesis (OR, 2.60), and visual field defect on admission (OR, 2.79). Our center's patient mix consists of 66.7% ($n=1803$) local referrals, 32.5% ($n=878$) distant referrals from the community or community hospitals for thrombolysis, and 0.9% ($n=23$) referrals from the stroke units for endovascular therapy after thrombolysis had already been started. The majority of patients arrived within the 6- and 12-hour time windows after prove of last seen 67% (18232) and 82% (2227), respectively. The demographics and baseline characteristics of the patients eligible or noneligible for EVT are shown in Table I in the [online-only Data Supplement](#).

Frequency of IVT Eligibility and EVT Eligibility

Almost 1 of 4 (24.6%) patients arriving within 24 hours after symptom onset was eligible for IVT (Figure 2). This proportion increased to more than one third (44.8%) if only those patients arriving within 6 hours were considered. Separated in the local and the referred population, the proportions of IVT eligibility were 24.6% and 24.6% for patients arriving within 24 hours and 40.1% and 56.2% for patients arriving within 6 hours (Figure 3 for the local population), respectively.

For EVT based on the AHA/ASA guidelines, 192 patients fulfilled the criteria (Figure 1). Half of these patients arrived immediately at our emergency department ($n=101$) and the other half ($n=91$) were transfers from the surrounding primary stroke centers.

With the less restrictive approach, 131 additional patients were eligible for EVT because of: an NIHSS 2 to 5 ($n=83$), prestroke mRS score of 2 ($n=19$), ASPECTS of 5 ($n=8$), and an occlusion in the M2, A1 and P1 segments or the basilar artery ($n=21$). Using the 2 different selection criteria, the

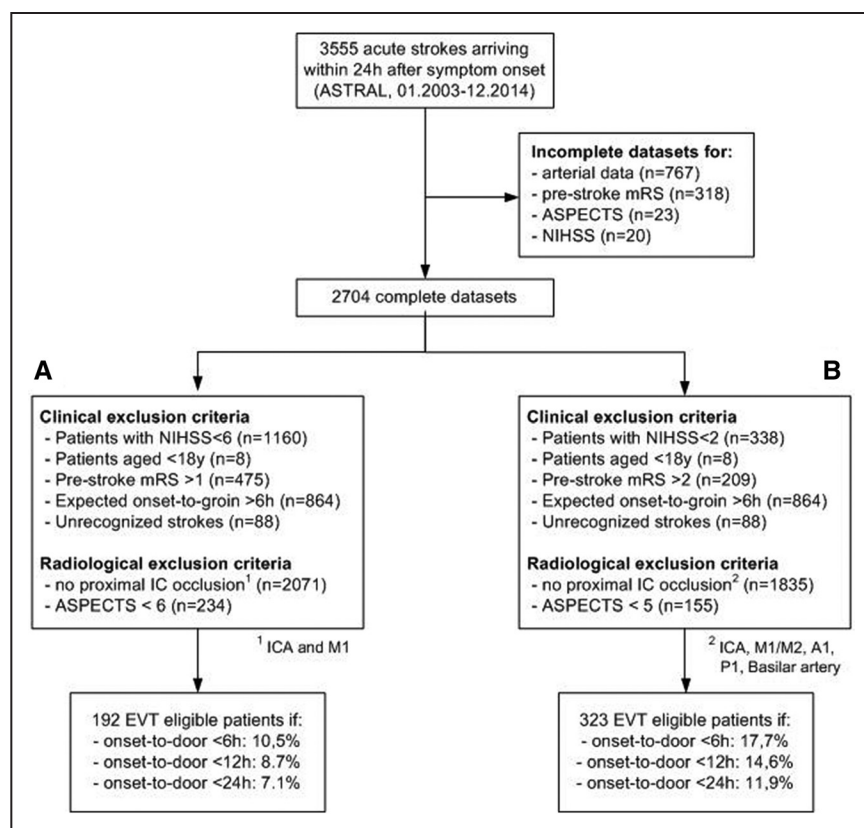


Figure 1. Flowchart of endovascular-eligible patients in the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) registry, based on (A) class I and IIa recommendations of the American Heart Association guidelines 2015 and (B) less restrictive inclusion criteria. One patient may have >1 clinical or radiological exclusion criterion. Only patients with complete data sets were included. ASPECTS indicates Alberta Stroke Program Early CT Score; EVT, endovascular treatment; IC, intracranial; ICA, internal carotid artery; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale International.

proportion of patients with AIS eligible for EVT within 24 hours was 2.9% for the strict and 4.9% for the more liberal approach. Among all patients arriving in <6 hours, these proportions rose to 10.5% and 17.7%, respectively.

Separated in the local and the referred population, the proportions of strict EVT eligibility were 2.5% and 11.3%, for patients arriving within 24 hours and 8.1% and 13.8% for patients arriving within 6 hours (Figure 3), respectively. For more liberal EVT eligibility, the proportions were 16.2 and 21.5%. Globally, 38.7% and 25.4% were eligible for any revascularization treatment according to AHA/ASA criteria of patients arriving within 6 and 24 hours, respectively, and 40.4% and 25.8% according to more liberal criteria.

Predictors of EVT Eligibility

In a multiple analysis, EVT eligibility based on the AHA/ASA recommendations was associated with a younger age (OR, 0.98; 95% confidence interval and *P* values: Table), shorter onset-to-admission interval (OR, 0.79), increasing stroke severity (measured by NIHSS: per point OR, 1.13 for non-decreased vigilance patients and OR, 1.01 for decreased vigilance patients), presence of hemineglect (OR, 1.84), absence of cerebellar signs (OR, 0.51), a history or new detection of atrial fibrillation (OR, 1.73), current smoking (OR, 0.59), and decreasing glucose levels at admission (OR, 0.83 for nondecreased vigilance patients and OR, 1.09 for decreased vigilance patients). The area under the receiver operating characteristic curve of this model for prediction EVT eligibility was 0.86 (95% confidence interval, 0.84–0.89). A second analysis identified the following clinical variables as

independent predictors of EVT eligibility for the local population (Table): time interval onset-to-admission (OR, 0.79), admission NIHSS (OR, 1.13), decreased level of consciousness (OR, 0.60), presence of hemineglect (OR, 1.84), or cerebellar symptoms (OR, 0.51).

Acute Revascularization Procedures Performed in Real Life

Comparing 2003/2004 to 2013/2014, a 2.3-fold increase in IVT and a 40-fold increase in EVT were observed, resulting in a global 3.5-fold increase in acute revascularization treatments in this cohort. In 2013/2014, 20.4% of all patients with AIS arriving within 24 hours after symptom onset were treated by IVT <4.5 hours and 11.0% by EVT <6 hours (Figure I in the [online-only Data Supplement](#)), respectively. When considering only the local population based primarily on our stroke center, these proportions were 11.1% for IVT and 5.8% for EVT.

Discussion

We found that about 1 of 4 patients with AIS arriving within 24 hours at a comprehensive stroke center are eligible for acute recanalization treatments. Using strict AHA/ASA criteria, one third of the IVT-treated patients should receive EVT, and up to 50% of the IVT-treated patients when using more liberal criteria. During the 12-year observation period, our stroke center's recanalization performance approached these theoretical numbers for more liberal criteria, indicating that these may be implemented successfully in clinical practice.

Previously, it has been estimated that ≈5% to 10% of all ischemic strokes and 20% to 30% of IVT-eligible patients

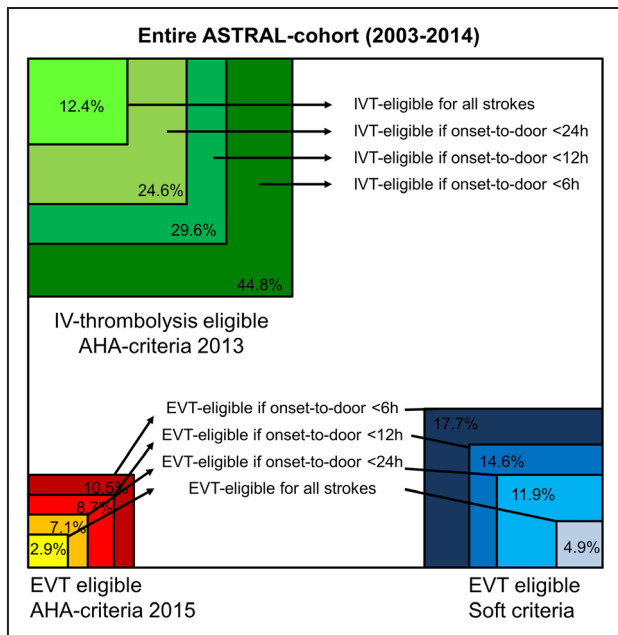


Figure 2. Proportion of all patients with acute ischemic stroke (AIS, locals and referrals) eligible for intravenous thrombolysis (IVT) and endovascular treatment (EVT). Green (left upper corner): proportion of patients eligible for IVT according to the American Heart Association/American Stroke Association (AHA/ASA) criteria¹⁷ when divided by all patients with AIS arriving within 4 different time intervals: within 6 h, 12 h, 24 h, and no time limit. Red (left lower corner): proportion of patients eligible for EVT according to AHA/ASA criteria⁴ when divided by all patients with AIS arriving within the same 4 different time intervals. Blue (right lower corner): proportion of patients eligible for EVT according to more liberal criteria (see text) when divided by all patients with AIS arriving within the same 4 different time intervals.

may be candidates for EVT in well-organized referral centers.^{6,9} With better information on the population, improved prehospital selection and triage, well-organized systems of care, and sufficient institutions offering appropriate recanalization treatments, these estimations may be too low.¹⁸ Indeed, better prehospital identification of patients with large vessel occlusion using the NIHSS¹⁹ or the predictors identified in this publication may be possible. Also, scores associated with a low likelihood of IVT-induced recanalization may be used to select patients for rapid EVT treatment.²⁰ A further increase in eligible patients may stem from broader selection criteria than recommended by the AHA/ASA, as simulated in our analysis with the more liberal criteria. Also, some patients with unknown stroke onset may benefit from such treatment, pending ongoing trials.²¹

We did not calculate the impact of different treatment time windows on patient eligibility because IVT beyond 4.5 hours²² and EVT beyond 6 hours⁷ seem to have no or limited impact on outcome, unless advanced imaging is used.^{2,3}

Stroke severity and site of vessel occlusion were the 2 criteria with the biggest impact on higher eligibility with liberal versus strict criteria. Indeed, the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) subgroup analysis and a meta-analysis found rapid EVT to be effective independently of stroke severity and occlusion location.^{1,10} Although

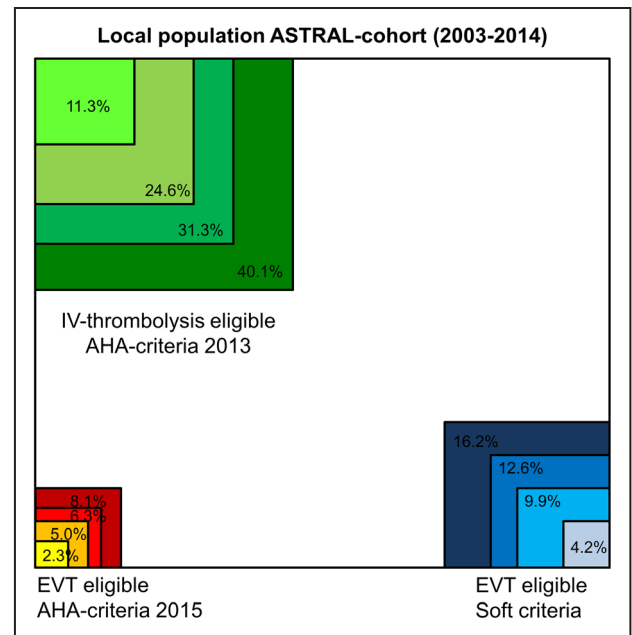


Figure 3. Proportion of all patients with acute ischemic stroke (AIS, only local cohort) eligible for intravenous thrombolysis (IVT) and endovascular treatment (EVT). Green (left upper corner): proportion of patients eligible for IVT according to the American Heart Association/American Stroke Association (AHA/ASA) criteria¹⁷ when divided by all patients with AIS arriving within 4 different time intervals: within 6 h, 12 h, 24 h, and no time limit. Red (left lower corner): proportion of patients eligible for EVT according to AHA/ASA criteria⁴ when divided by all patients with AIS arriving within the same 4 different time intervals. Blue (right lower corner): proportion of patients eligible for EVT according to more liberal criteria (see text) when divided by all patients with AIS arriving within the same 4 different time intervals.

EVT is likely to work also for basilar artery occlusion, results from the ongoing Basilar Artery International Cooperation Study (BASICS) trial will affect further recommendations.²³

Upper age limits were applied in several recent EVT trials but subgroup analyses and a meta-analysis¹ found similar, if not increased, effectiveness of EVT in elderly patients. Similarly, IVT may be effective in patients with a premonitory handicap, despite the fact that such patients have overall higher mortality rates from stroke.²⁴

To date, moderately extensive early ischemic changes on noncontrast CT imaging were considered a contraindication for recanalization treatment. Given that the MR CLEAN trial and other analyses hinted at absent benefit with an ASPECTS of <5, we kept this limit in our more liberal EVT criteria.^{10,25} Imaging of tissue viability or collateral flow is likely to improve patient selection and treatment response.^{2,8} However, complexity and additional time required for such imaging may decrease eligibility further, as hinted at in the imaging-based Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial (EXTEND-IA) trial where only 6.7% of screened IVT patients were eligible for EVT.³ Therefore, and because of insufficient high-quality evidence, imaging of tissue viability was not recommended on a routine basis by AHA/ASA.

Translating EVT recommendations, such as the American⁴ or European ones,⁵ into clinical practice requires major efforts

Table. Independent Predictors of Endovascular Treatment Eligibility in Multivariate Analysis Based on the AHA/ASA Guidelines Class I and IIa Recommendations

Predictors	Entire ASTRAL Population		Local ASTRAL Population	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Age	0.98 (0.97–1.00)	0.02		
Time interval onset-to-admission	0.79 (0.73–0.86)	<0.01	0.78 (0.70–0.87)	<0.01
Admission NIHSS	1.13 (1.09–1.17)	<0.01	1.09 (1.06–1.13)	<0.01
Level of consciousness altered	0.6 (0.07–5.31)	0.64		
Hemineglect	1.84 (1.23–2.75)	<0.01	2.6 (1.47–4.60)	<0.01
Cerebellar symptoms	0.51 (0.28–0.94)	0.03	0.39 (0.16–0.96)	0.04
History of atrial fibrillation	1.73 (1.13–2.66)	0.01		
History of smoking	0.59 (0.35–0.99)	0.04		
Acute glucose level, mmol/L	0.83 (0.74–0.94)	<0.01		

AHA indicates American Heart Association; ASA, American Stroke Association; ASTRAL, Acute Stroke Registry and Analysis of Lausanne; CI, confidence interval; and NIHSS, National Institutes of Health Stroke Scale.

on multiple levels. Although awaiting full and rapid access to EVT in most healthcare networks, IVT needs to be available rapidly, in particular given its generalized efficacy across multiple subgroups of patients when given early.^{1,22,26}

The reasons why the really treated numbers of patients at our center are below eligible ones, in particular in the first few years of the observation period, are several: First, IVT eligible may have not received treatment because of deficiencies in the intrahospital chain of management, such as nonrecognition of stroke,²⁷ CT overload, delays from poor organization or mindset, miscommunication,²⁸ or personal decision by the on call neurologist. Second, eligibility is based on current scientific knowledge on effectiveness IVT and EVT, but real-world treatments were decided on knowledge available at the time. For example, effectiveness of IVT was not proven for the 3- to 4.5-hour window ≤ 2008 , and effectiveness of EVT was not proven at all until recently. Third, the impact of the excluded patient cohort on the estimated proportion of the EVT-eligible patients is not negligible. Because the excluded patients are less likely to be good candidates for EVT, their exclusion overestimated the proportions.

The major strength of our study is the large number of patients in the cohort, the long observation period, and the frequent use of acute vascular imaging since the cohort's beginning in 2003.

Several limitations apply however: First, a substantial percentage (24%) of patients from the original cohort had to be excluded because of lack of data to evaluate EVT eligibility, mainly because of the well-known contraindications for CT angiography (eg, renal reasons and allergy). Main differences between the excluded and the included population were the lower median NIHSS (13 versus 16; $P < 0.05$) and longer delay-to-arrival times (392 versus 112 minutes; $P < 0.05$) compared with the study cohort. Second, there may be disagreement with our decision to exclude class IIb evidence in the AHA/ASA recommendations and our proposed criteria for a more liberal use of EVT. Third, extrapolation of the proportion of eligible patients to other health systems of care may be hampered

by the specific role of our center within a network in which 28% of the patients are referred. Implementation of the AHA/ASA guidelines may even further increase referral rates within our network.

Conclusions

In summary, we found an AHA/ASA guideline-based eligibility for IVT and EVT of 36.2% and 10.5%, respectively, for AIS arriving in our comprehensive stroke center within 6 hours. EVT eligibility increased to 17.7% with less strict criteria, resulting in an overall eligibility of 40.4% for any revascularization treatment in early arriving patients. Constant development of a stroke network and improved intrahospital performance made it possible to achieve these proportions in real life. Our data may allow planning for appropriate resource needs in different settings and identification of EVT-eligible patients in the prehospital setting based on clinical variables.

Acknowledgments

Dr Vanacker studied the concept and design, helped in analysis and interpretation, and preparation of the article. He had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Lambrou carried out data analysis and interpretation and helped in preparation of the article. Dr Eskandari helped in data acquisition and analysis, critical revision of the article for important intellectual content. Dr Mosimann helped in data acquisition and critical revision of the article for important intellectual content. Dr Michel studied the concept and design, and helped in data acquisition, analysis and interpretation, critical revision of the article for important intellectual content, study supervision.

Disclosures

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