Neurological Deficits in Stroke Patients that May Impede the Capacity to Provide Informed Consent for Endovascular Treatment Trials

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Background: We assessed the occurrence of neurological deficits that may impede the capacity to provide consent for trial participation in patients with an acute stroke, who are eligible for endovascular treatment (EVT). *Methods:* We used data from the Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands Registry, a prospective observational cohort study. We included 1526 patients with an anterior large vessel occlusion, undergoing EVT between March 2014 and June 2016. We based our assessment of decision-making capacity for trial participation on neurological symptoms influencing conditions concerning informed consent as stated in the declaration of Helsinki. We formulated a strict and a mild capacity assessment rule, using 2 different cut points in item scores on the National Institutes of Health Stroke Scale (NIHSS). *Results:* Applying the strict and mild rule, respectively 1469 (96%) and 1220 (80%) patients deemed not capable of decision-making for trial participation on admission, and 1077 (79%) and 825 (60%) patients at 24-48 hours after admission. Highest frequencies of predefined scores suggesting incapacity based on the strict rule were on the NIHSS items "Level of Consciousness Questions" (59%), "Best Gaze" (68%), and "Best Language" (58%). Patients who were considered incapable were older (median 71 versus 66 years, $P = .043$), had higher NIHSS scores (median 16 versus 8, $P < .001$), and had more often left hemisphere strokes (55% versus 28%, $P < .001$) than patients who were presumably capable. *Conclusions:* In the majority of patients with an anterior circulation stroke who are eligible for EVT, neurological deficits are present that may impede the capacity to provide informed consent for trial participation.

Key Words: Stroke—acute stroke treatment—endovascular treatment—thrombectomy—medical decision making

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Introduction

Endovascular treatment (EVT) for acute ischemic stroke has been proven safe and effective for selected patients and is recommended in international guidelines.[1-3] More randomized trials are needed to refine or expand patient selection, and to improve outcome. Execution of these trials is challenging because it may be difficult to obtain informed consent from a patient with neurological deficits within a limited time window in an emergency setting. Whether informed consent by proxy, deferred informed consent, or exception from informed consent is allowed, depends on national or state regulations.[4,5]

Judgement of the capacity to provide informed consent for trial participation is often left to the discretion of the physician. Previous studies reported aphasia, denial of deficit, and impaired consciousness as reasons for not getting informed consent from patients in person.[6-9] However, the same neurological symptoms have also been reported in patients who were considered able to provide informed consent for trial participation.[8-12] Assessing the decision-making capacity for trial participation in stroke patients may be difficult, since no specific and valid assessment instruments exist. In general, assessment of a patient's capacity to make a decision on medical treatment can be supported by the use of a structured interview.[13,14] A modified, stroke-specific, version of 1 of these instruments showed a low specificity, resulting in an often incorrect assessment of incapacity.[15] However, decision-making on trial participation is more complex than decision-making on medical treatment. Information on the frequency of clinical factors that impede decision-making capacity for trial participation in stroke patients is needed to support researchers and institutional review boards in proposing or approving trial procedures to obtain consent. We aimed to assess these factors in stroke patients eligible for EVT using data from the Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry.[16]

Methods

Study Population and Design

The MR CLEAN Registry is an ongoing, multicenter, observational cohort study—which started directly after the final MR CLEAN trial randomization—and includes all consecutive acute ischemic stroke patients undergoing EVT in the Netherlands.[16] From its start in March 2014 until December 2014, enrollment was retrospective, and from January 2015 enrollment has been prospective. The present analysis included patients enrolled in the MR CLEAN Registry until June 2016 (n = 1628). Sixteen centers also participated in the MR CLEAN trial. Two non-MR CLEAN centers started performing EVT later on and added patients to the MR CLEAN Registry, but these patients were not included in this analysis. Other inclusion criteria for this observational cohort study were: age of 18 years and older, a clinical diagnosis of ischemic stroke with intracranial hemorrhage ruled out with CT or MRI, and presence of an intracranial large vessel occlusion in the anterior circulation (intracranial carotid artery or middle [M1/M2] or anterior cerebral artery [A1/A2]) demonstrated by computed tomography angiography, magnetic resonance angiography, or digital subtraction angiography. The National Institutes of Health Stroke Scale (NIHSS) was assessed on admission and at 24-48 hours after admission in the intervention center.

Assessment of Decision-Making Capacity for Trial Participation

Informed consent forms the basis of research involving humans. Ethical principles concerning informed consent are stated in the declaration of Helsinki.[17] The declaration states that each potential subject must be adequately informed of the aims, methods, and the anticipated benefits and potential risks of a study. The declaration also states that the physician must seek the potential subject's freely given informed consent, but only after ensuring that the potential subject has understood the information. Since the method of determining the capacity to provide informed consent is not described in the declaration, we based our assessment of the decision-making capacity on neurological deficits influencing these stated conditions. We formulated 2 decision-making capacity assessment rules, reflected by the scores on the individual items of the NIHSS, a widely used systematic assessment tool that provides a quantitative measure of stroke related neurological deficits.[18] The NIHSS consists of 11 items assessing level of consciousness, horizontal eye movements, visual fields, motor function, limb coordination, sensory function, language, speech, and extinction and inattention. Scores range from 0 to 42, with higher scores indicating more severe neurological deficits.

Our 2 predefined capacity assessment rules—1 strict rule and 1 mild rule—consist of predefined scores on individual NIHSS items interfering with decision-making capacity, with different cut points for each item (Table 1). We considered patients with at least 1 of the scores above the predefined threshold incapable of decision-making for trial participation. Patients without any of the predefined scores were considered capable to make a decision on trial participation. The decision-making capacity was assessed for each patient with both decision-making capacity assessment rules, on admission and at 24-48 hours after admission. These predefined capacity assessment rules were formulated after patients were included in the MR CLEAN Registry.

In the first decision-making capacity assessment rule, we interpreted the conditions for obtaining informed consent described in the declaration of Helsinki very strictly. Patients who are not fully able to understand information,

Table 1. *Strict and mild decision-making capacity assessment rules using predefined scores on individual NIHSS items suggesting decision-making incapacity for trial participation*

Strict capacity assessment rule	Mild capacity assessment rule
1a. LOC; score > 0 (not alert, not arousable by minor or repeated stimulation, or unresponsive)	1a. LOC; score > 1 (not alert, requires repeated stimulation to respond, or unresponsive)
1b. LOC Questions; score > 0 (answers 1 of 2 questions, or neither question correctly)	1b. LOC Questions; score > 1 (answers neither question correctly)
1c. LOC Commands; score > 0 (performs 1 of 2 tasks, or neither task correctly)	1c. LOC Commands; score > 0
2. Best Gaze; score > 0 (partial or total gaze paresis)	-
3. Visual; score = 3 (bilateral hemianopia, blindness)	-
9. Best Language; score > 0 (any degree of aphasia)	9. Best Language; score > 1 (mild-to-moderate aphasia)
10. Dysarthria; score = 2 (severe dysarthria)	10. Dysarthria; score = 2
11. Extinction and inattention; score > 0 (extinction or inattention to 1 or more sensory modalities)	11. Extinction and inattention; score > 1 (extinction or inattention to more than 1 sensory modality)

Abbreviations: LOC, level of consciousness; NIHSS, National Institutes of Health Stroke Scale.
Patients with at least one of the predefined scores were considered incapable of decision-making for trial participation.

to discuss this information with the physician in order for the physician to ensure understanding, and then to give voluntary informed consent, were considered incapable for decision-making on trial participation. For example, patients with any degree of aphasia were considered incapable in this strict rule, since physicians cannot be completely sure that a patient understands all provided complex information on trial participation, and can express all their considerations. Not being able to read trial information due to a sudden bilateral hemianopia forces the patient to gather the extensive information only by listening. Gaze palsy and inattention or extinction both decrease the awareness of the current disease and can influence a patient's estimation of possible intervention benefits and risks.

The second proposed decision-making capacity assessment rule was a milder interpretation of the conditions for obtaining informed consent described in the declaration of Helsinki. We considered patients who were not completely alert but could be aroused by minor stimulation to obey, answer or respond; who made 1 mistake in the level of consciousness questions; had partial or complete gaze palsy, bilateral hemianopia, mild-to-moderate aphasia, or inattention or extinction in at most one of the sensory modalities as likely capable of decision-making for trial participation.

Statistical Analysis

We evaluated the proportion of patients who were considered incapable to make a decision concerning trial participation using both our formulated capacity assessment rules, and the distribution of individual NIHSS item scores indicating decision-making incapacity. We compared clinical and imaging characteristics at baseline between patients considered incapable of decision-making and those who were presumably capable. We used descriptive statistics providing median (interquartile range) or mean (standard deviation) for continuous data, and percentages for categorical data. For intergroup comparison, we used the Chi-squared test, Fisher's exact test, Student's t test, or Mann-Whitney's U test as appropriate. All P values were 2-sided ($\alpha = .05$). We used Stata/SE statistical package version 15.1 (StataCorp, College Station, TX) for all analyses.

Results

The MR CLEAN Registry enrolled 1628 patients between March 16, 2014 and June 15, 2016. A total of 1526 patients met the inclusion criteria and were included in the current analysis (Fig 1). Data on the scores of the individual NIHSS items was complete on admission, and missing for 162 patients at 24-48 hours after admission. These 162 patients were excluded from the analysis of the decision-making capacity at 24-48 hours after admission. Thirty-two patients with missing data had died at 24-48 hours after admission. The reason for incompleteness of the data of the remaining 130 patients is unclear.

Based on the scores on the individual NIHSS items, 1469 of 1526 patients (96%) were considered incapable to make decisions concerning trial participation on admission using the strict capacity assessment rule, and 1220 (80%) based on the mild assessment rule. Highest frequencies of predefined scores indicating decision-making incapacity on admission using the strict capacity assessment rule were on the NIHSS items "Level of Consciousness Questions" (59%), "Best Gaze" (68%), and "Best Language" (58%) (Fig 2). The frequency of all individual scores on all NIHSS items on admission is shown in Table 2.

At 24-48 hours after admission, 1077 of 1364 patients (79%) were considered incapable of decision-making for trial participation based on the strict rule, and 825 of 1364 patients (60%) were considered incapable when we applied the mild rule. Figure 1 shows the proportion of capable and incapable patients based on each rule at both assessment times.

Baseline characteristics of patients considered incapable and those presumably capable of decision-making

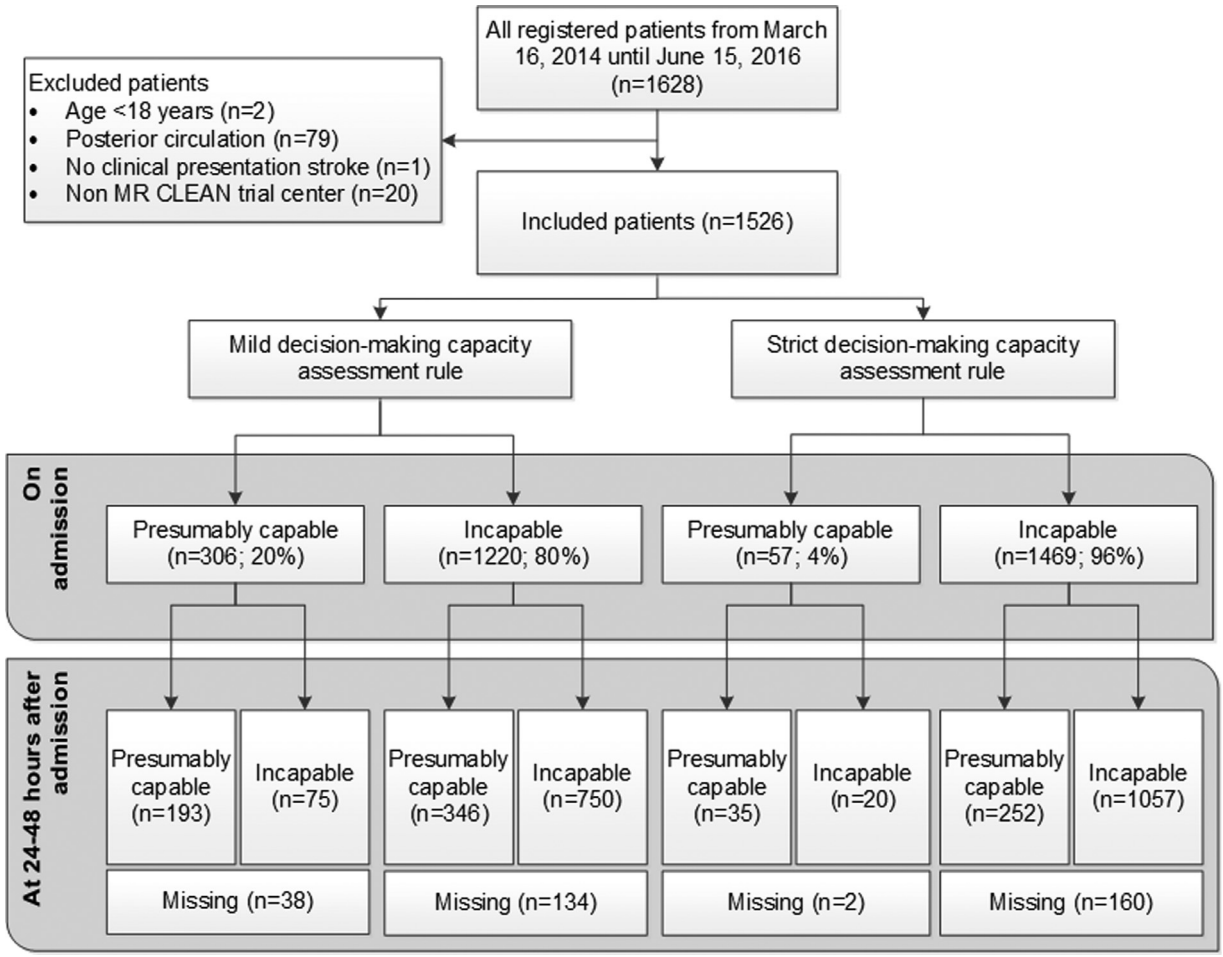

Figure 1. *Assessment of decision-making capacity for trial participation of stroke patients eligible for endovascular treatment.*

concerning trial participation based on the strict rule are shown in Table 3. Patients who lacked decision-making capacity on admission were older (median 71 versus 66 years, $P = .043$), had higher total NIHSS scores on admission (median 16 versus 8, $P < .001$), more often left hemisphere strokes (55% versus 28%, $P < .001$), more often proximal arterial occlusions ($P = .021$), lower collateral grade ($P = 0.038$), and lower Alberta Stroke Program Early Computed Tomography Score (ASPECTS) ($P = .001$) than patients presumably capable of decision-making. These differences in baseline characteristics between incapable and capable patients were also found when we applied the mild rule, except for age (median 71 versus 70, $P = .489$) and myocardial infarction (17% versus 11%, $P = .006$).

Discussion

In our cohort of acute ischemic stroke patients with an intracranial large vessel occlusion in the anterior circulation eligible for EVT, the vast majority of patients would not be capable of making a decision concerning trial participation considering their neurological deficits. A large proportion of patients had a lowered level of consciousness and/or aphasia, resulting in difficulty to understand information and/or to express questions and preferences. Several other deficits, such as neglect and severe dysarthria, added to the presumed incapacity for decision-making on trial participation early after stroke onset.

Little is known about the capacity to provide informed consent in stroke patients eligible for EVT, both in routine clinical practice as well as in trials. Baseline characteristics of included patients in our study were comparable with those of patients included in 7 large EVT trials.[19] For these trials, the distribution of consent by patients and informed consent provided by legal representatives has not been reported.[20-26] The proportion of patients deemed incapable to provide informed consent for trial participation was larger in our study compared to acute stroke trials on intravenous thrombolytic agents or neuroprotective agents.[7-9,11,12,27] The presence of an intracranial large vessel occlusion in all patients in our cohort might explain the high frequency of symptoms indicating cortical function deficits and thus a larger proportion of patients considered incapable to provide informed consent. Patients are considered eligible for EVT in the Netherlands since March 2014 when meeting the inclusion and exclusion criteria of the MR CLEAN trial, which turned out to be equal to conditions described in the current international

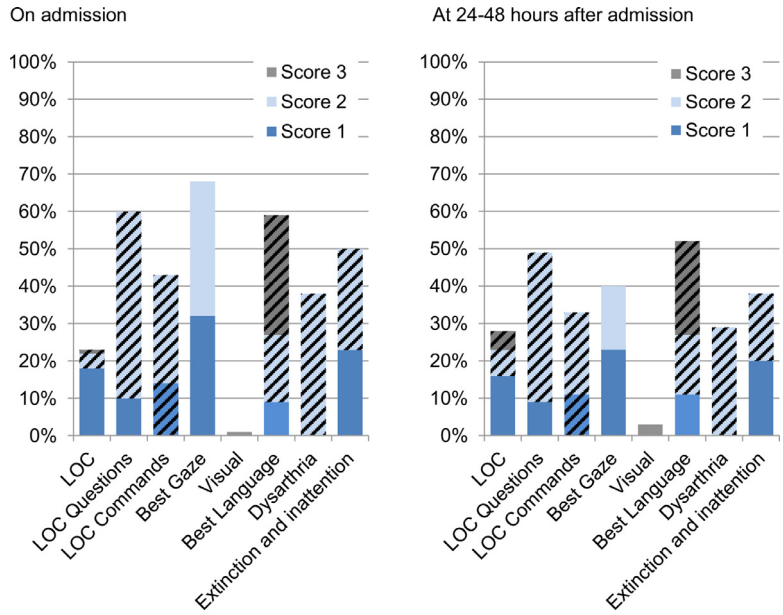

Figure 2. *Distribution of the predefined individual NIHSS item scores suggesting decision-making incapacity for trial participation. Frequency of NIHSS item scores on admission and at 24-48 hours after admission for the strict (all bars) and mild capacity assessment rule (shaded bars only). Abbreviations: LOC, level of consciousness; NIHSS,National Institutes of Health Stroke Scale.*

guidelines.[1,2] All patients with anterior circulation stroke in the Netherlands who are treated with EVT are being included in the MR CLEAN Registry.[16] Since our analysis includes nearly all registered patients, we assume that the patients in our study cohort are representative for patients eligible for EVT in current routine clinical practice and thus representative as candidates for future EVT trials aimed

at refining patient selection and improving outcome. The low proportion of patients presumably capable to provide consent for trial participation would significantly reduce trial recruitment rates.

Not surprisingly, patients considered incapable to make a decision on trial participation differed from those presumed capable. They had more severe strokes, more often a left hemisphere stroke, a proximal arterial occlusion, a lower collateral grade, and lower ASPECTS. These findings are consistent with observations in 2 randomized controlled trials, showing that patients not able to provide written consent had total anterior circulation strokes or left hemisphere

Table 2. *Frequency of all individual scores on all NIHSS items on admission*

NIHSS items (n = 1526)	Score 0, No. (%)	Score 1, No. (%)	Score 2, No. (%)	Score 3, No. (%)	Score 4, No. (%)
1a. LOC	1184 (78%)	267 (17%)[a]	57 (3.7%)[b]	18 (1.2%)[b]	NA
1b. LOC Questions	625 (41%)	146 (9.6%)[a]	755 (49%)[b]	NA	NA
1c. LOC Commands	867 (57%)	211 (14%)[b]	448 (29%)[b]	NA	NA
2. Best Gaze	495 (32%)	480 (31%)[a]	551 (36%)[a]	NA	NA
3. Visual	680 (45%)	266 (17%)	564 (37%)	16 (1.0%)[a]	NA
4. Facial palsy	172 (11%)	291 (19%)	928 (61%)	135 (8.8%)	NA
5a. Motor left arm	822 (54%)	104 (6.8%)	88 (5.8%)	98 (6.4%)	414 (27%)
5b. Motor right arm	760 (50%)	109 (7.1%)	85 (5.6%)	106 (7.0%)	466 (31%)
6a. Motor left leg	856 (56%)	129 (8.5%)	155 (10%)	132 (8.7%)	254 (17%)
6b. Motor right leg	808 (53%)	101 (6.6%)	128 (8.4%)	137 (9.0%)	352 (23%)
7. Limb ataxia	1409 (92%)	79 (5.2%)	38 (2.5%)	NA	NA
8. Sensory	798 (52%)	450 (29%)	278 (18%)	NA	NA
9. Best Language	635 (42%)	131 (8.6%)[a]	276 (18%)[b]	484 (32%)[b]	NA
10. Dysarthria	434 (28%)	507 (33%)	585 (38%)[b]	NA	NA
11. Extinction and Inattention	760 (50%)	350 (23%)[a]	416 (27%)[b]	NA	NA

Abbreviations: LOC, level of consciousness; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale.

[a]Predefined item scores suggesting decision-making incapacity for trial participation according to the strict capacity assessment rule.

[b]Predefined item scores suggesting decision-making incapacity for trial participation according to both the strict and mild capacity assessment rule.

Table 3. *Baseline characteristics of patients considered incapable and patients presumably capable using the strict decision-making capacity assessment rule on admission*

	Incapable (n = 1469)	Presumably capable (n = 57)	*P* value
Age, y, median (IQR)	71 (60-80)	66 (48-77)	.043
Male sex, no. (%)	780 (53%)	29 (51%)	.742
SBP, mm Hg, mean (SD) [n]	150 (25) [1428]	152 (23) [55]	.543
DBP, mm Hg, mean (SD) [n]	82 (16) [1423]	82 (17) [55]	.854
Transferred, no. (%)	797 (54%)	25 (44%)	.122
Onset to door intervention ER for nontransferred patients, min, median (IQR) [n]	58 (39-108) [636]	56 (45-102) [30]	.748
Onset to door intervention ER for transferred patients, min, median (IQR) [n]	171 (138-215) [761]	200 (162-236) [25]	.084
NIHSS score at baseline, median (IQR)	16 (12-20)	8 (5-10)	<.001
Medical history, no. (%)			
Atrial fibrillation	324/1447 (22%)	11/57 (19%)	.582
Diabetes mellitus	254/1460 (17%)	8/57 (14%)	.510
Hypercholesterolemia	424/1420 (30%)	18/57 (32%)	.781
Hypertension	734/1450 (51%)	31/57 (54%)	.577
Myocardial infarction	223/1438 (16%)	10/57 (18%)	.678
Peripheral arterial disease	130/1440 (9%)	8/56 (14%)	.182
Previous ischemic stroke	241/1460 (17%)	12/57 (21%)	.366
Smoking	336/1131 (30%)	15/47 (32%)	.746
Pre-stroke mRS, No. (%)			.745
0	976/1444 (68%)	41/55 (75%)	
1	188/1444 (13%)	7/55 (13%)	
2	112/1444 (7.8%)	3/55 (5.5%)	
>2	168/1444 (12%)	4/55 (7.3%)	
Imaging			
Occlusion side on CTA, no. (%)			<.001
Left hemisphere	803/1469 (55%)	16/57 (28%)	
Right hemisphere	653/1469 (44%)	41/57 (72%)	
Neither[a]	13/1469 (0.9%)	0/57 (0%)	
Occlusion location on CTA, no. (%)			.021
ICA	82/1402 (5.9%)	3/56 (5.4%)	
ICA-T	318/1402 (23%)	4/56 (7.1%)	
M1	799/1402 (57%)	43/56 (77%)	
M2	176/1402 (13%)	5/56 (8.9%)	
Other[b]	27/1402 (1.9%)	1/56 (1.8%)	
Collateral grade, no. (%)			.038
Grade 0 (absent)	98/1361 (7.2%)	0/56 (0%)	
Grade 1 (poor)	453/1361 (33%)	14/56 (25%)	
Grade 2 (moderate)	519/1361 (38%)	28/56 (50%)	
Grade 3 (good)	291/1361 (21%)	14/56 (25%)	
ASPECTS, median (IQR) [n]	9 (7-10) [1404]	9 (8-10) [55]	< .001

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CTA, computed tomography angiography; DBP, diastolic blood pressure; ER, emergency room; ICA, internal carotid artery; ICA-T, terminal internal carotid artery; IQR, interquartile range; M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; SD, standard deviation.

[a]No occlusion on CTA is visible on evaluation by the imaging core lab.

[b]Occlusion in segment 1 or 2 of the anterior cerebral artery (A1, n = 3; A2, n = 3), or segment 3 of the middle cerebral artery (M3, n = 9), or no occlusion visible (n = 13) on CTA on evaluation by the imaging core lab.

strokes more often.[8,11] In our study cohort, patients with assumed impaired decision-making capacity (when using the strict capacity assessment rule) were older and had a higher total NIHSS score, which was consistent with observations in 5 acute stroke studies using the NIHSS and 1 study using the Scandinavian Stroke Scale.[7,9-12,27] The higher total NIHSS in patients considered incapable in our cohort was influenced by the use of NIHSS item scores to indicate decision-making incapacity. However, this only partially explains the difference in median NIHSS (16 versus 8; strict

rule) between both groups. The most logical explanation could be that the higher scores on the NIHSS are a reflection of the more severe strokes, as indicated by a proximal arterial occlusion, lower collateral grade, and lower ASPECTS. Excluding patients incapable to provide informed consent from stroke trials—in which the outcome of the studied intervention can be affected by the location of the large vessel occlusion, collateral grade, and ASPECT—can lead to selection bias and reduced generalizability of trial results.

A limitation of our study is the retrospective application of 2 new decision-making capacity assessment rules. Since no specific and valid instruments exist to assess the decision-making capacity on trial participation in acute stroke patients, we used neurological symptoms influencing conditions needed for a proper informed consent as stated in the declaration of Helsinki. Several structured interviews to assess the capacity of medical decision-making have been reported, using similar conditions, but do not describe how to deal with specific neurological deficits.[13-15] Precisely due to these deficits, the use of these structured interviews is challenging in most acute stroke patients. The interobserver agreement for assessing decision-making capacity in acute stroke patients for trial participation is unknown. A stroke-specific version of a structured interview to assess the capacity to make a decision on medical treatment, showed a low specificity to detect capacity compared with psychiatric assessment as well as compared with neuropsychological assessment.[15] Ideally, 1 would investigate the decision-making capacity for example by scoring videos of an informed consent dialogue by multiple assessors, and use this as a gold standard for other scoring rules. Our analysis should be considered as exploratory. We aimed to assess the occurrence of neurological deficits that may impede the capacity to provide consent. This study was not designed to determine whether the NIHSS item scores alone could be used to assess the capacity to provide consent. We used the scores on the individual items of the NIHSS, of which its interobserver reliability has been demonstrated in several studies.[18,28,29] Neurological examination of an acute stroke patient using the NIHSS is standard practice and costs little extra time. The main difference between our strict and mild capacity assessment rule is whether extra time and enhanced communication skills can overcome some of the neurological deficits influencing the informed consent procedure. In this study we did not address time as a factor for reduced decision-making capacity. The minimum time required to make a decision on trial participation is not mentioned in the declaration of Helsinki. It is however reasonable that patients need more than an hour to process a multiple paged patient information form with text concerning extensive information on trial participation. Taking additional time for the consent procedure will have an adverse effect on functional outcome after EVT.

Although many neurological functions are assessed by the NIHSS, other parameters influencing the capacity of decision-making, such as emotions and stress, are not measured by this scale. In addition, cognitive impairment is also associated with decision-making incapacity.[10,30] Our predefined criteria were formed to indicate decision-making incapacity rather than decision-making capacity. Therefore, we considered a patient without any of the predefined scores of the individual NIHSS items to be presumably capable of making a decision on trial participation.

This study suggests that we need to allow and apply alternative ways to obtain informed consent for acute stroke trial participation, for example by obtaining informed consent from the legal representative. However, even the decision-making capacity of a healthy legal representative may be affected by the combination of a restricted time window for randomization and treatment with the stress induced by a vitally endangered family member as well. These factors need further study. Exception from informed consent can be another option, although this is not accepted in every country and state. The specific condition of a patient in which exception from consent can be applied, has to be stated in the research protocol, and approved by a research ethics committee. The consent to remain in the study should then be obtained as soon as possible from the patient or a legal representative (deferred consent). This deferred consent procedure may be the preferred option in EVT trials. In our cohort, only about one-fifth of patients considered incapable of decision-making on admission, regained the capacity to make a decision concerning trial participation at 24-48 hours after admission. This suggests that, in most cases, deferred consent can only be obtained from the legal representative. Results from this study can support researchers and institutional review boards in determining appropriate procedures for obtaining consent.

Conclusions

In the majority of patients with an anterior circulation ischemic stroke who are eligible for EVT, neurological deficits are present that may impede the capacity to provide informed consent for trial participation.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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