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Intravenous thrombolysis and thrombectomy decisions in acute ischemic stroke: An interrater and intrarater agreement study

C. Ducroux^{a,b}, R. Fahed^{a,b}, N.N. Khoury^c, G. Gevry^b, E. Kalsoum^d, M.-A. Labeyrie^e, D. Ziegler^f, C. Sauve^f, M. Chagnon^g, T.E. Darsaut^h, J. Raymond^{b,*} FAMOUS collaborative group¹

^a Interventional Neuroradiology Department–Fondation Ophthalmologique Adolphe de Rothschild Hospital, 75019 Paris, France

^b Radiology Department–Centre Hospitalier de l'Université de Montréal (CHUM), Notre-Dame Hospital, H2X 3E4 Montreal, Canada

^c HSHS Neuroscience Center - HSHS St. John's Hospital, 62769 Springfield, IL, USA

^d Neuroradiology Department–Henri Mondor Hospital, 94010 Créteil, France

^e Neuroradiology Department–Lariboisière Hospital, 75010 Paris, France

^f CHUM Library - Centre Hospitalier de l'Université de Montréal (CHUM), Notre-Dame Hospital, H2X 3E4 Montreal-Québec, Canada

^g Department of Mathematics and Statistic–Université de Montréal, H2X 3E4 Montreal-Québec, Canada

^h Department of Surgery, Division of Neurosurgery - University of Alberta Hospital, Mackenzie Health Sciences Centre, T6G 2B7 Edmonton-Alberta, Canada

* Corresponding author at: CHUM, Notre-Dame Hospital, Department of Radiology, 1051 Sanguinet street, Montreal, Quebec, H2X 0C1, Canada.

E-mail address: jean.raymond@umontreal.ca (J. Raymond).

¹ FAMOUS collaborative group members (90 physicians): Philippe NICLOT, Alain AMERI, Jérôme HODEL, Jean-Christophe GENTRIC, François-Mathias MERRIEN, Aurore JOURDAIN, François ROUHART, Irina VIAKHIREVA, Serge TIMSIT, Frédéric CLARENÇON, Silvia PISTOCCHI, Charlotte ROSSO, Chiara ZAVANONE, Emmanuel HOUDART, Marc-Antoine LABEYRIE, Peggy REINER, Benjamin GORY, Roberto RIVA, Norbert NIGHOGHOSSIAN, Tae-Hee CHO, Laurent DEREK, François EUGÈNE, Jean-Christophe FERRÉ, Anthony LE BRAS, Stéphane VANNIER, Maria LASSALLE, Cyril CHIVOT, Audrey ARNOUX, Philippe ALLA, Jean-Brice VEYRIERES, Gaultier MARNAT, Jérôme BERGE, Stéphane OLINDO, Igor SIBON, Bertrand LAPERGUE, Adrien WANG, Arturo CONSOLI, Federico DI MARIA, Michael OBADIA, Candice SABBEN, Mikael MAZIGHI, Hocine REDJEM, Michel PIOTIN, William BOISSEAU, Lilia RAZLOG, Raoul POP, Rémy BEAUJEUUX, Dan MIHOC, Sébastien RICHTER, Monica MANISOR, Valérie WOLFF, Véronique QUENARDELLE, Lisa ZINGHENKO, Mihaela DIACONU, Marion YGER, Stephen DELORME, Christina IOSIF, Thierry MOULIN, Hatem ZEKRI, François LALLEMENT, Olivier VERCRUYSE, Christanthi PAPAGIANNAKI, Ozlem OZKUL-WERMESTER, Cyril DARGAZANLI, Vincent COSTALAT, Nicolas GAILLARD, Caroline ARQUIZAN, Mireille CAYRE-CASTEL, Serge BRACARD, Anne-Laure DERELLE, Sébastien RICHARD, Lisa HUMBERTJEAN, Yann HERVÉ, Pascal FAVROLE, Patrick LE COZ, Thomas DE BROUKER, Marie-Isabelle FORCE, Serge AKONO, Serkan CAKMAK, Alexandru FLOREA, Thibault LALU, Grégory TAURIN, Duc Long DUONG, Marie-Laure CHADENAT, Fernando PICO, Rémi ALLIBERT, Sarah EVAIN, Philippe TASSAN, Eric BERTHIER, Xavier DUCROCQ, Matthieu RIGAL, Marion BOULANGER.

Abbreviations: AIS, Acute Ischemic Stroke; DWI-ASPECTS, Diffusion-Weighted-Imaging-Alberta-Stroke-Program-Early-CT-Score; IV tPA, IntraVenous Tissue Plasminogen Activator; MT, Mechanical Thrombectomy; RCT, Randomized Controlled Trial.

Purpose. – We aimed to assess agreement on intravenous tissue-plasminogen activator (IV tPA) and mechanical thrombectomy (MT) management decisions in acute ischemic stroke (AIS) patients. Secondary objectives were to assess agreement on Diffusion-Weighted-Imaging-Alberta-Stroke-Program-Early-CT-Score (DWI-ASPECTS), and clinicians' willingness to recruit patients in a randomized controlled trial (RCT) comparing medical management with or without MT.

Materials and Methods. – Studies assessing agreement of IV tPA and MT were systematically reviewed. An electronic portfolio of 41 AIS patients was sent to randomly selected providers at French stroke centers. Raters were asked 4 questions for each case: (1) What is the DWI-ASPECTS? (2) Would you perform IV tPA? (3) Would you perform MT? (4) Would you include the patient in a RCT comparing standard medical therapy with or without MT? Twenty responders were randomly selected to study intrarater agreement. Agreement was assessed using Fleiss' Kappa statistics.

Results. – The review yielded two single center studies involving 2–5 raters, with various results. The electronic survey was answered by 86 physicians (60 vascular neurologists and 26 interventional neuroradiologists). The interrater agreement was moderate for IV tPA treatment decisions ($\kappa = 0.565$ [0.420–0.680]), but only fair for MT ($\kappa = 0.383$ [0.289–0.491]) and for combined treatment decisions ($\kappa = 0.399$ [0.320–0.486]). The intrarater agreement was at least substantial for the majority of raters. The interrater agreement for DWI-ASPECTS was fair ($\kappa = 0.325$ [0.276–0.387]). Physicians were willing to include a mean of 14 ± 9 patients ($33.1\% \pm 21.7\%$) in a RCT.

Conclusion. – Disagreements regarding the use of IVtPA or MT in the management of AIS patients remain frequent. Further trials are needed to resolve the numerous areas of uncertainty.

1. Introduction

Intravenous thrombolysis with tissue plasminogen activator (IV tPA) and mechanical thrombectomy (MT) have been proven effective in reducing morbidity in AIS patients in multiple randomized controlled trials (RCTs) [1,2]. Most RCTs have used restrictive selection criteria, leaving multiple clinical uncertainties in spite of published guidelines [3,4]. This uncertainty may translate into diverging clinical practices.

Agreement in making clinical decisions on individual AIS patients has rarely been studied [5]. Our first aim was to assess the inter- and intrarater agreement on the use of IV tPA and/or MT in the management of diverse AIS patients using a portfolio of selected cases.

More inclusive future trials may address remaining uncertainties; a secondary aim was to document how often clinicians would propose participation in a RCT comparing standard medical therapy (including IV tPA) with or without MT.

Finally, computed tomography (CT) and the Alberta-Stroke-Program-Early-CT-Score (ASPECTS) [6] were used in most thrombectomy trials. However, in the “THrombectomie des Artères CErébrales” (THRACE) trial [7], most patients underwent brain MRI, thought to be more reliable for the detection and grading of early ischemic lesions, [8] in accordance with French guidelines [9]. Another secondary aim of this study was to evaluate the inter- and intrarater

agreement of the Diffusion-Weighted-Imaging-ASPECTS (DWI-ASPECTS) [10] in AIS candidates for IV tPA or MT.

2. Methods

2.1. Literature systematic review

We initially performed a systematic review on management decisions regarding AIS patients. The protocol and search strategy, written in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA), [11] are provided in Appendix A. We included all articles that met the following selection criteria:

- original research (review articles, abstracts, editorials and letters were excluded);
- estimates of reliability or agreement of IV tPA or MT decisions for a group of individual AIS patients (surveys of opinions on general indications were excluded).

2.2. Agreement study

The present report is written in compliance with the Guidelines for Reporting Reliability and Agreement studies [12]. The French Agreement study on the Management Of acUte ischemic Stroke (FAMOUS) was a national, multi-centric

Table 1 – Summary of patients’ characteristics. Data are presented as n (%), mean ± SD, or median [IQR].

	Patients (n = 41)
Male	24 (58.5%)
Mean age ± SD	65.2 ± 15.3
Age > 80 years old, n (%)	7 (17.1%)
Unknown time of symptom onset, n (%)	8 (19.5%)
Median (IQR) delay between symptoms onset and MRI (minutes)	120 (78.7–180)
Median (IQR) initial NIHSS	11 (5–17)
Low initial NIHSS (< 10), n (%)	18 (43.9%)
Very low initial NIHSS (< 6), n (%)	14 (34.1%)
Right hemispheric stroke, n (%)	18 (43.9%)
Median (IQR) initial DWI-ASPECTS	8 [6–9]
Low DWI-ASPECTS (< 6), n (%)	8 (19.6%)

agreement study. An electronic survey (available in Appendix C) was used to assess agreement of multiple primary and comprehensive stroke center clinicians on multiple individual patients.

2.3. Patients

Two authors (R.F and C.D) screened the databases of 2 primary and 2 comprehensive stroke centers to select 41 patients with anterior-circulation AIS confirmed by MRI. Since kappa statistics are sensitive to prevalence and to minimize potential paradoxes, [13,14] the spectrum of cases was meant to include approximately 1/3 indications for IVtPA and/or MT according to French guidelines, [9,15] 1/3 contraindications and 1/3 “grey zone” cases. Clinical characteristics of the 41 patients are summarized in Table 1.

There were 24 men (58.5%, mean age ± SD = 65.2 ± 15.3), with a median [IQR] initial NIHSS of 11 [5–17] and a median [IQR] DWI-ASPECTS of 8 [6–9]. The total number of patients was selected to set the lower boundary of the confidence interval at $\kappa > 0.4$, assuming substantial agreement ($\kappa > 0.6$) between raters [16].

2.4. Raters

Raters were fully qualified staff clinicians routinely caring for AIS patients in 15 comprehensive (offering both IV tPA and MT on site) and 20 primary stroke centers (offering IV tPA only) randomly selected from all the 37 comprehensive stroke centers and 95 primary French stroke centers listed in [17,18]. Twenty clinicians were randomly selected to assess intrarater agreement by independently reviewing the same 41 cases presented in different order at least 2 months later.

2.5. Electronic survey

Raters experience and practice characteristics were addressed in the first part of the survey: specialty (neurologist or radiologist), experience in the management of AIS patients (0–5 years, 6–10 years, 11–20 years, > 20 years), proficiency in the use of IV tPA/MT/DWI-ASPECTS, and whether MT is available at their center. Senior clinicians were defined as

individuals with more than 10 years experiences in managing AIS patients.

For each case, a brief clinical synopsis was provided, including patient gender, age, time of symptom onset (when known), initial NIHSS, a summary of the neurological symptoms, and the time of brain MRI, in addition to either 5 (37/41 patients) or 6 (4/41 patients) MR images (the two main ASPECTS slices [6] in DWI and fluid-attenuation-inversion-recovery [FLAIR], and 1 or 2 time-of-flight [TOF] images of the circle of Willis, for a total of 209 images).

For each patient, raters were asked to answer the 4 following questions:

- what is the DWI-ASPECT score (0 to 10, or NA if the rater doesn’t routinely use the DWI-ASPECTS);
- would you prescribe IV tPA?;
- would you perform MT/refer the patient for MT?;
- would you include the patient in a randomized trial comparing standard medical therapy with or without MT?

2.6. Statistical analysis

Inter- and intrarater agreement was assessed using Fleiss’ Kappa with 95% bias-corrected confidence intervals obtained by 1000 bootstrap resampling. For a supplementary assessment of the DWI-ASPECTS score reliability the Krippendorff’s alpha intercoder reliability coefficient is also reported with 95% confidence intervals based on 1000 bootstrap resamples.

The mean proportion of answers among subgroups of responders were compared using a Student t-student test or a one-way ANOVA when 3 or more groups were compared. All analyses were done with Stata version IC 14.0 and a significance level of 5%. Slight, fair, moderate, and substantial agreement categories were defined according to Landis and Koch [19].

3. Results

3.1. Systematic review

Two pertinent studies [20,21] were identified (flow diagram provided in Fig. 1): one study involving 5 raters and 25 confirmed AIS patients found a fair-to-moderate agreement for the decision to perform MT; [20] while the other, involving 2 to 3 raters and 60 patients with a suspected AIS found substantial agreement for IV tPA and MT decisions [21].

3.2. Agreement study

The electronic survey was distributed and answered between November 2016 and April 2017. Eighty-six clinicians participated in the study (60 vascular neurologists and 26 interventional neuroradiologists [INRs]) from 15 comprehensive and 20 primary stroke centers. There were 49 junior (0–10 years) and 37 senior raters (> 10 years of experience).

The kappa values of the interrater agreement for all raters, by specialty, for IV tPA decision, for MT decision, and for the combined treatment decision (i.e. the combination of IV tPA

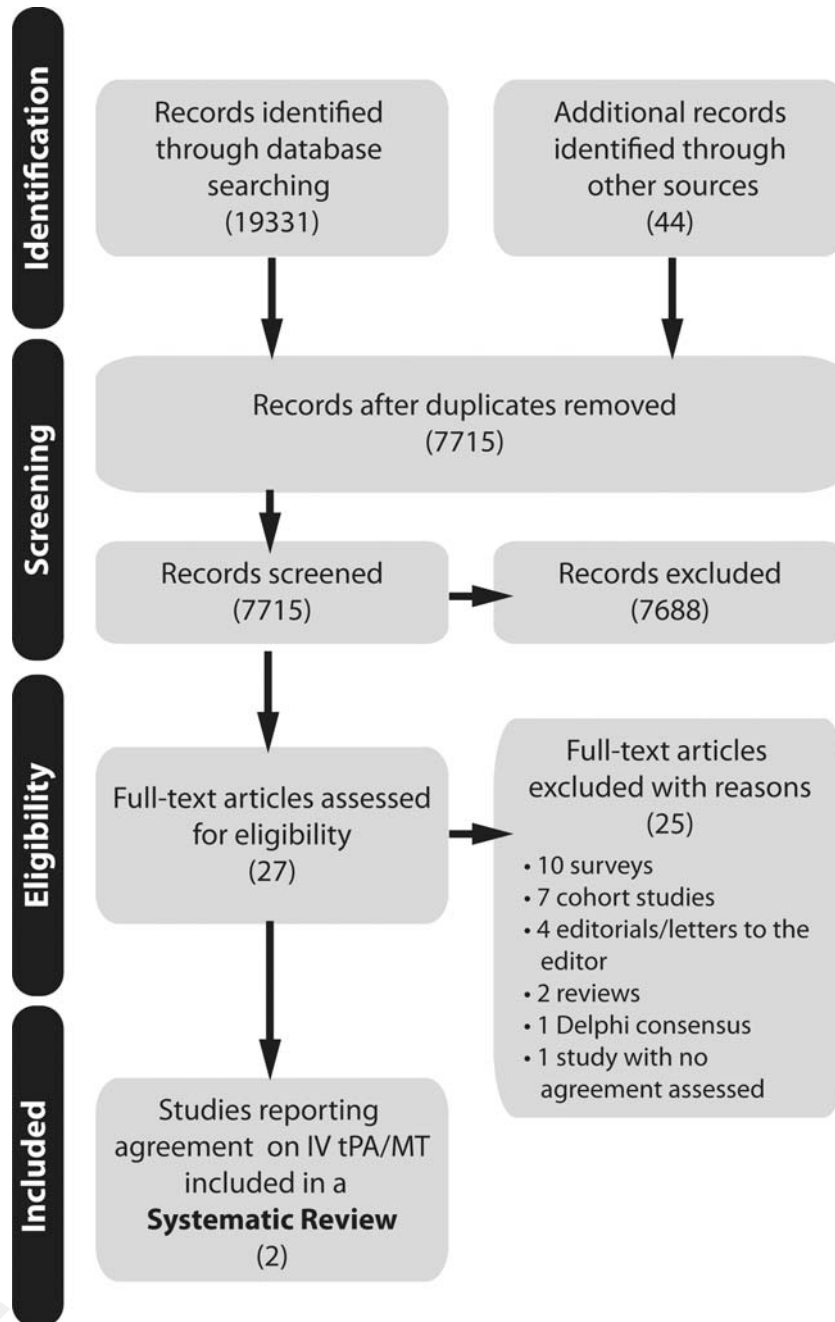


Fig. 1 – Flow diagram of systematic review.

and MT decisions, resulting in the following options: no IV tPA/MT, IV tPA only, MT only, and bridging therapy [IV tPA + MT]) are displayed in Fig. 2A and Table 2.

Interrater agreement was similar for primary and comprehensive stroke centers, for junior and senior raters. Interrater agreement for combined treatment decision was fair ($\kappa = 0.399$, 95% confidence interval [0.320–0.486]). In more than half of the patients (24/41 cases [58.6%]), at least 25% of physicians did not agree on the combined treatment decision.

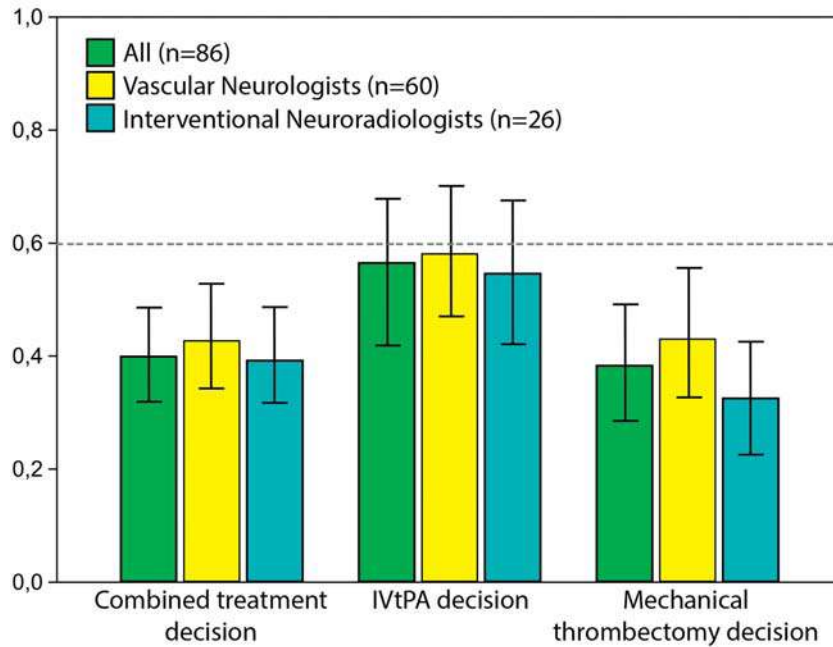
Interrater agreement for IV tPA decision was moderate for all raters ($\kappa = 0.565$ [0.420–0.680]). In 12/41 cases (29.3%), at least 25% of physicians did not agree on the decision to administer IVtPA.

Interrater agreement for MT decision was fair ($\kappa = 0.383$ [0.289–0.491]). In 16/41 cases (39%), at least 25% of physicians did not agree on the decision to perform or refer the patient for MT.

INRs were willing to perform MT more often than neurologists (mean \pm SD number of decisions to perform MT = 29.1 \pm 5.8 vs. 23.3 \pm 5.6, $P = 0.0001$). Neurologists working in comprehensive stroke centers prescribed MT more often than those working in primary stroke centers (mean \pm SD number of MT prescriptions = 26.7 \pm 5.9 vs. 21.5 \pm 5.3, $P = 0.0001$).

Agreement regarding management decisions within each comprehensive stroke center was higher for IV tPA than for

A Interrater agreement (Fleiss' Kappa) for treatment decisions



B Interrater Agreement (Fleiss' Kappa) within each comprehensive stroke center

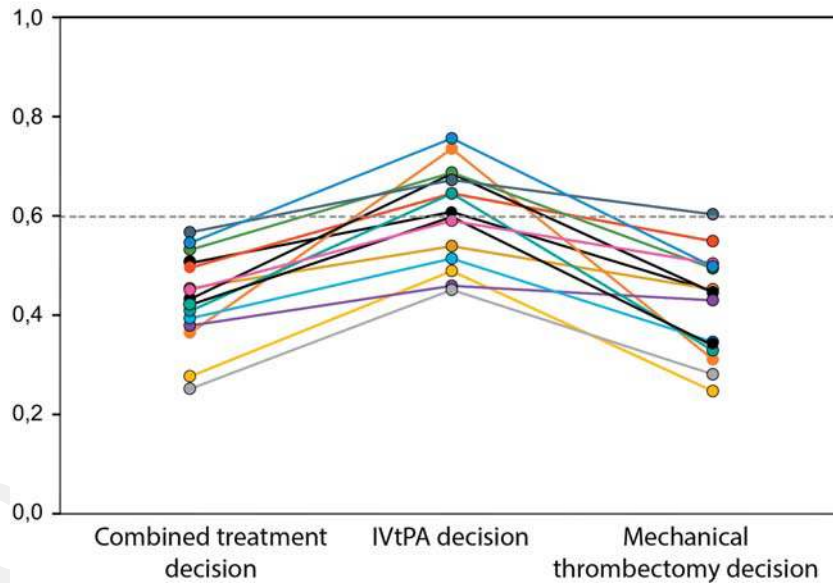


Fig. 2 – Interrater agreement for treatment decisions. (A) Graphic display of interrater agreement for combined treatment decision, IV tPA decision, and mechanical thrombectomy decision, for all raters, and for each specialty. (B) Graphic representation of interrater agreement for combined treatment decision, IV tPA decision, and MT decision, within each of the 15 comprehensive stroke centers. In each center, at least 1 vascular neurologist and 1 INR answered the survey independently.

MT (Fig. 2B and Appendix B). Eight comprehensive centers (53.3%) reached a substantial interrater agreement for IV tPA decision, and 1 center (6.7%) for MT decision.

Agreement and proportions of positive answers for IV tPA and MT for various subgroups of patients are displayed in Fig. 3 (details provided in Appendix B). There were more than 90%

positive answers for IV tPA and MT in subgroups of patients who should receive these treatments according to current French recommendations [9,15]. Treatment decisions were more variable for patients > 80 years old, for patients with unknown symptom onset, and patients with a low (< 10) or very low initial NIHSS (< 6).

Table 2 – Summary of interrater agreement values (Fleiss’Kappa [95% confidence intervals]) for combined treatment decision, IV tPA decision, and MT decision, for all raters, by specialty, and by stroke center category.

	Combined treatment decision	IV tPA decision	MT decision
All (n = 86)	0.399 [0.320-0.486]	0.565 [0.420-0.680]	0.383 [0.289-0.491]
By specialty			
Vascular neurologists (n = 60)	0.427 [0.341-0.527]	0.581 [0.471-0.701]	0.430 [0.331-0.552]
Interventional Neuroradiologists (n = 26)	0.392 [0.317-0.486]	0.546 [0.422-0.677]	0.325 [0.229-0.425]
By stroke center category			
Primary stroke centers (n = 26)	0.446 [0.357-0.538]	0.600 [0.467-0.715]	0.443 [0.348-0.557]
Comprehensive stroke centers (n = 60)	0.401 [0.325-0.491]	0.561 [0.428-0.693]	0.378 [0.284-0.495]
Neurologists in comprehensive stroke centers (n = 34)	0.431 [0.350-0.543]	0.575 [0.433-0.702]	0.441 [0.321-0.570]
By experience			
0-5 years (n = 16)	0.370 [0.288-0.462]	0.543 [0.391-0.674]	0.334 [0.234-0.484]
6-10 years (n = 33)	0.396 [0.325-0.497]	0.572 [0.445-0.711]	0.369 [0.277-0.487]
11-20 years (n = 21)	0.453 [0.367-0.561]	0.570 [0.441-0.690]	0.468 [0.345-0.598]
> 20 years (n = 16)	0.396 [0.312-0.490]	0.567 [0.451-0.711]	0.377 [0.272-0.495]

Proportion of positive answers ('yes') for all patients and specific subgroups

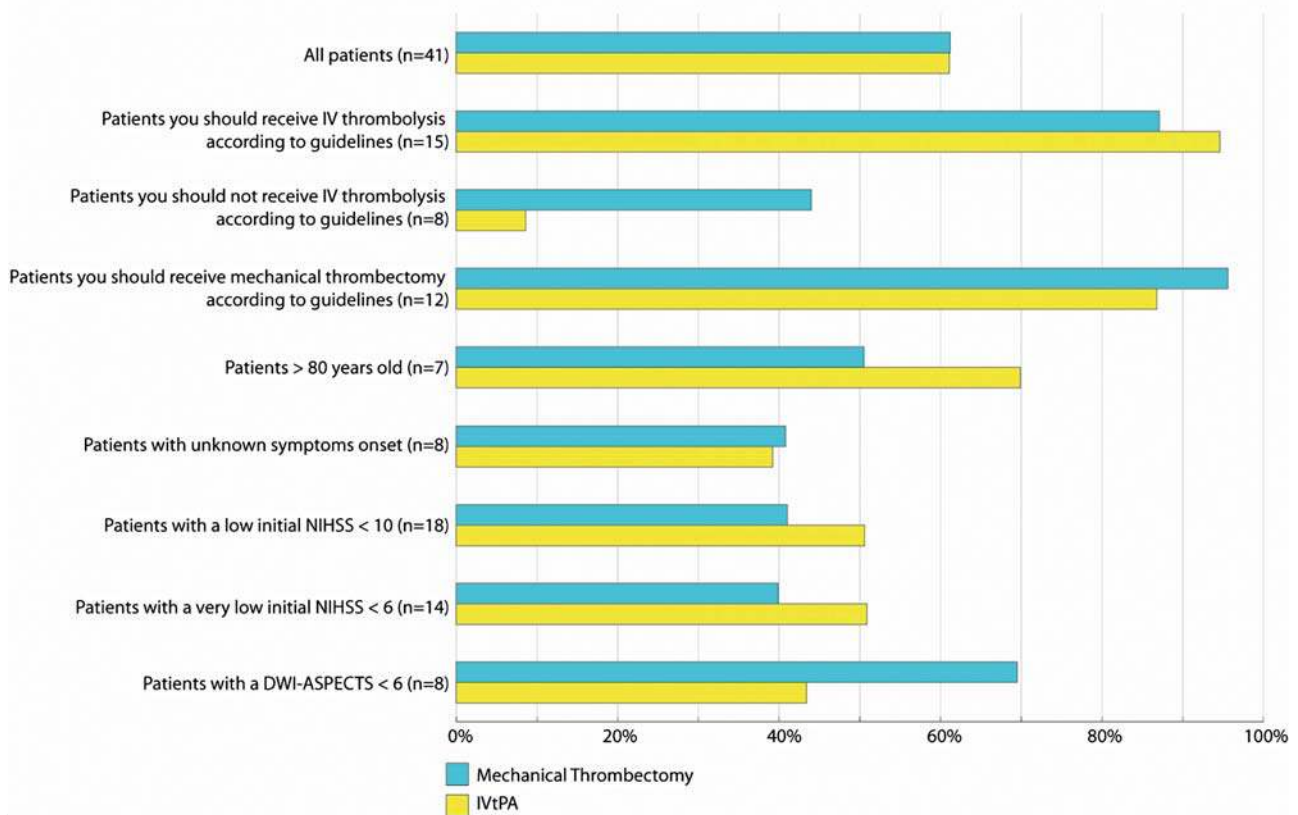


Fig. 3 – Graphic representation of positive answers for IV tPA and MT, for all patients and for subgroups of patients.

Intrater agreement is displayed in Fig. 4 (details provided in Appendix B). Intrater agreement was at least substantial for 18/20 physicians (90% [68.3%–98.8%]) for IV tPA; and 13/20 physicians (65% [40.8%–84.6%]) for MT decisions. In practical terms, at least 5/20 clinicians (25%) changed their own decision regarding IV tPA and MT in 9.7% (4/41) and 17.1% (7/41) of cases, respectively.

3.3. Inclusion in a randomized controlled trial

Physicians were willing to include a mean of 14 ± 9 patients (33.1% \pm 21.7%) in a randomized trial comparing medical treatment with or without MT. Trial participation was more frequently offered by INRs than by vascular neurologists (mean = 17.3 ± 11.0 patients versus 11.9 ± 7.4 , $P = 0.009$). There

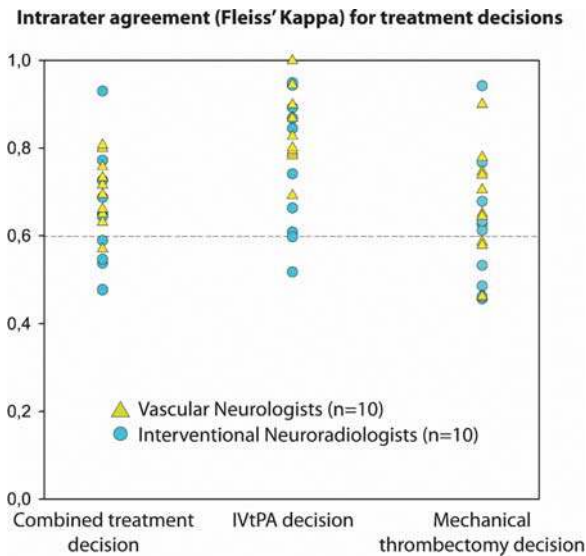


Fig. 4 – Intrater agreement for treatment decisions.

was no significant difference with experience or between comprehensive and primary stroke centers.

3.4. DWI-ASPECT score

Thirty four of 86 physicians (39.5% [29.2%–50.7%]) routinely used the DWI-ASPECTS. Interrater agreement for all 34 raters, and by specialty, are displayed in Fig. 5A (details provided in Appendix B). When considered as a categorical variable, agreement for DWI-ASPECTS was fair for all raters, specialties, and categories of stroke centers. The alpha coefficient was excellent for all raters, and at least substantial within each specialty and each category of stroke centers. There was no significant difference with experience.

Intrater agreement ($n = 9$) is displayed in Fig. 5B (details provided in Appendix B). The intrater agreement of DWI-ASPECTS was at least substantial for 3/9 raters (33.3% [7.5%–70.1%]).

4. Discussion

This study found that disagreements are frequent in the management of AIS patients. Clinicians were more likely to disagree on decisions that concerned categories of patients that were excluded from past trials, and clinicians were willing to offer participation in a new RCT in approximately one third of patients. Agreement on the DWI-ASPECTS was moderate at best, raising concerns regarding its use for making clinical recommendations.

There have been few agreement studies on the management of AIS individual patients. Other than surveys of general opinions, [22,23] the systematic review yielded only two articles: one study, performed in real-time at the bedside, found substantial-to-excellent agreement regarding IV tPA and MT, but there were only 2–3 raters and 41.7% of patients were stroke mimics [21]. Another 5-raters study, focusing on

imaging, showed insufficient agreement for MT decision, whether decisions were based on CT or CT-perfusion [20].

Our study shows moderate agreement only for IV tPA, even when considering the decisions made by vascular neurologists alone. For patients with straightforward indications or obvious exclusions for IV tPA, most decisions complied with current guidelines, but decisions were more variable for patients aged > 80 years old, patients with minor symptoms (NIHSS < 6), or with unknown time of onset, who were excluded from previous IV tPA RCTs and are still the subjects of controversies [3].

The lower agreement for MT decisions was expected, since evidence in favor of therapy is more recent [2]. Again, agreement was higher with straightforward patients according to guidelines. Our study suggests that, even after multiple positive trials, uncertainty remains a source of variability in practice, mainly because of the lack of evidence regarding the results of MT in many kinds of patients, such as patients with proximal arterial occlusion and low baseline stroke severity or low DWI-ASPECTS score.

Clinicians from secondary stroke centers proposed MT to a smaller proportion of patients, perhaps because they took into consideration the habitual delays entailed by a ‘drip-and-ship’ procedure [24]. The therapeutic window for MT remains controversial. Recent trials extending MT up to 24 hours showed clear benefits, but brain imaging criteria were very restrictive [25,26].

Magnetic resonance imaging, recommended for AIS in France, [8] has a higher sensitivity for early ischemic lesions than CT. According to some authors, a DWI-FLAIR mismatch may identify, among patients with an unwitnessed stroke, those that might be within 6 hours of symptoms onset [27]. If the WAKE-UP trial convincingly showed that some patients with acute stroke with DWI-FLAIR mismatch and an unknown time of onset could benefit from IV tPA, [28] the judgment whether such mismatch was present or not has been shown to be poorly repeatable, at least for thrombectomy candidates [29]. Agreement on the DWI-ASPECTS was moderate at best, raising concerns regarding the dogmatic use of poorly repeatable DWI verdicts to propose or deny validated and effective treatments to individual AIS patients. These MRI features have not been assessed in most MT trials, in which patients typically underwent CT rather than MR imaging. Agreement for DWI-ASPECTS was sub-optimal, as we have previously found on both CT and MRI [29,30].

Variability in decision making may be related to the way particular clinicians interpret available guidelines or selection criteria of past clinical trials and how they apply results or recommendations to individual patients. Many past RCTs excluded patients based on pre-set, somewhat arbitrary limits (regarding age, time, NIHSS or ASPECT scores). A recent study showed that the proportion of patients eligible for MT could vary between 5 and 50% depending on which trial criteria are applied [5]. The variability we have documented in making clinical decisions concerning the same AIS patients reflects the uncertainty of physicians in making clinical decisions in the absence of scientific evidence. Restrictive selection in practice could perhaps improve agreement but at the potential cost of denying treatment to patients that could benefit. Our study shows that many clinicians are willing to propose a new

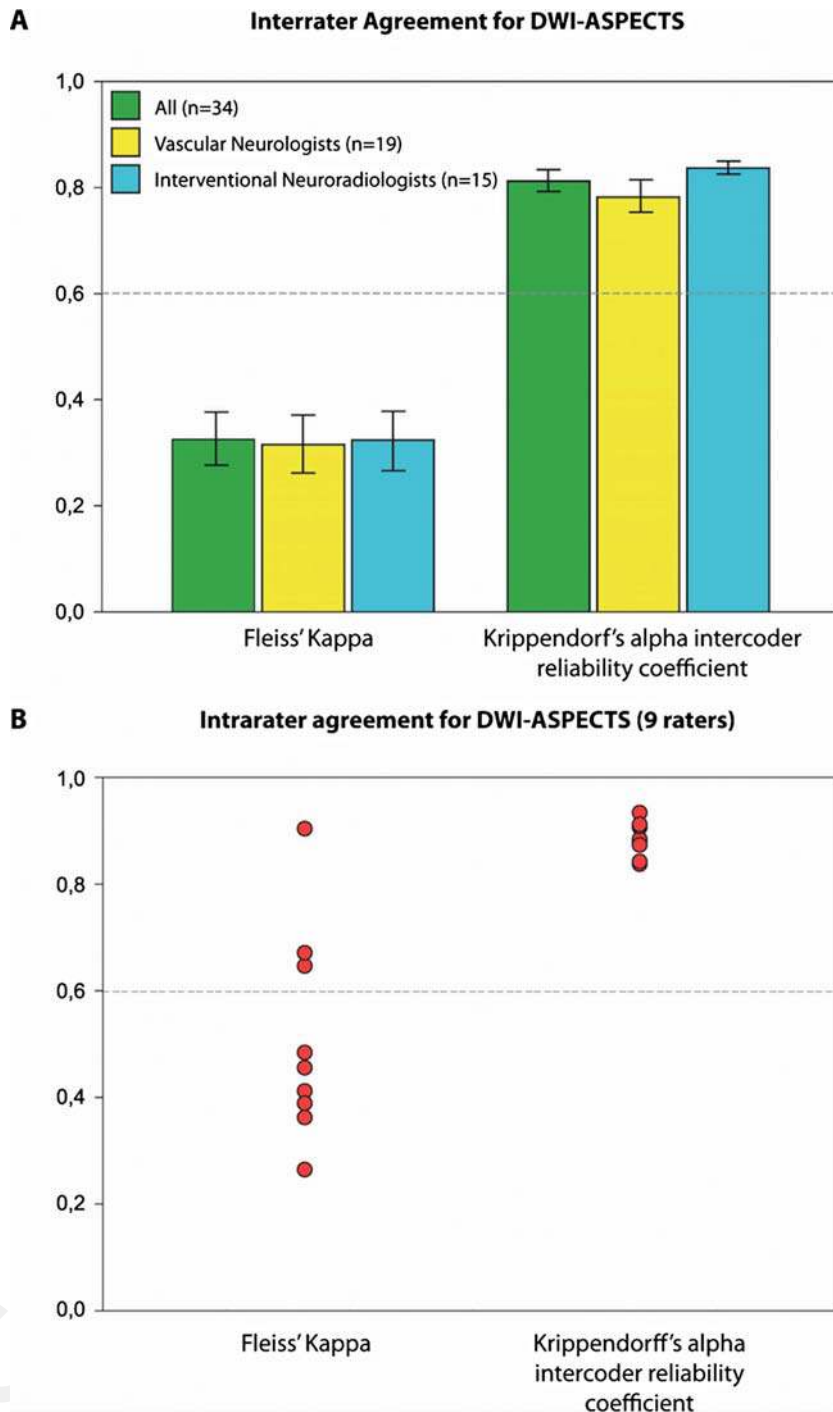


Fig. 5 – Agreement on DWI-ASPECT score. (A) Graphic display of interrater agreement for DWI-ASPECTS, for all raters, and for each specialty. Fleiss' kappa evaluates the DWI-ASPECTS as a categorical variable, and Krippendorff's alpha intercoder reliability index evaluates the DWI-ASPECTS as an ordinal variable. (B) Graphic display of intrarater agreement (Fleiss' kappa and Krippendorff's alpha intercoder reliability coefficient).

trial to a substantial number of patients, suggesting that more inclusive trials could perhaps address remaining uncertainties.

Our study has several limitations. The present agreement study was completed prior to the publication of some recent trials [25,26,28]. Disagreements could be less frequent for certain patients, such as patients with unknown onset stroke

time, if the survey were answered now. An electronic portfolio of past cases was used to study clinicians' decisions. Answering a questionnaire and actually caring for patients are very different contexts. The decisions made in this study were based on limited clinical information, as compared to actual decisions at the bedside. It is uncertain, however, whether providing additional data regarding pre-stroke

comorbidities or concomitant treatments would have improved or worsened agreement between clinicians. The number of patients was limited to take into consideration rater fatigue. Real life practice involves shared decision making between a vascular neurologist and an INR, while in our study those specialists were interrogated separately. As raters were not queried regarding the arterial occlusion site (internal carotid artery-middle cerebral artery), some variability in decision making might have been caused by disagreement on arterial occlusion sites. All patients underwent MRI, and results could have been different had they undergone CT, the main imaging modality used in IV tPA and MT trials. The portfolio was emailed to the heads of each stroke center and then disseminated secondarily, so we cannot record precisely how many clinicians were asked to complete the questionnaire. We can only speculate that responders were self-selected participants interested in the research question, which means that results obtained may not be “representative” of French stroke physicians in general. Finally, the study concerned clinicians from a single country and results may not apply to other practice sites with diverging diagnostic and treatment guidelines [31].

5. Conclusion

Disagreements regarding the use of IV tPA or MT in the management of AIS patients remain frequent. Further trials are needed to resolve the numerous areas of uncertainty.

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Disclosure of interest

The authors declare that they have no competing interest.

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APPENDIX A: Literature systematic review protocol and search strategy

Two authors (X.X and Y.Y) screened all articles (titles and abstracts) up to December 2017, with no starting date specification. Any article mentioning agreement or discrepancies among physicians regarding IVtPA or MT management decisions in AIS was retained, excluding expert opinions written in editorials or letters. The full texts were then reviewed by two authors for the final selection of pertinent articles reporting case-by-case agreement studies.

<u>Database</u>	
Database	MEDLINE
Interface	PubMed
Research date	December 12 th , 2017
Filters	-

<u>Syntax</u>	
[MeSH Terms]	Medical Subject Heading
OR, AND	Boolean operators
*	Truncation
[Other Term] / [ot]	Include Author's Keywords
[Title/Abstract] / [tiab]	Title, abstract

Search strategy

"Stroke"[Mesh] **OR** stroke[tiab] **OR** stroke[ot] **OR** Cerebrovascular Accident*[tiab] **OR** Cerebrovascular Accident*[ot] **OR** "Stroke, Lacunar"[Mesh]

AND

agreement*[Title/Abstract] **OR** agreement*[Other Term] **OR** kappa[Other Term] **OR** kappa[Title/Abstract] **OR** scale*[Title/Abstract] **OR** scale*[Other Term] **OR** score*[Title/Abstract] **OR** score*[Other Term] **OR** survey*[Title/Abstract] **OR** survey*[Other

Term] OR reliability[Other Term] OR reliability[Title/Abstract] OR "Consensus"[Mesh] OR "Reproducibility of Results"[Mesh] OR "Health Surveys"[Mesh] OR "Surveys and Questionnaires"[Mesh] OR "Health Care Surveys"[Mesh]

AND

"Mechanical Thrombolysis"[Mesh] OR thromboly*[tiab] OR thromboly*[ot] OR thrombectom*[tiab] OR thrombectom*[ot] OR "Thrombectomy"[Mesh] OR "Fibrinolytic Agents"[Mesh] OR "Thrombolytic Therapy"[Mesh] OR "Tissue Plasminogen Activator"[Mesh] OR tPA[tiab] OR tPA[ot] OR Plasminogen Activator[tiab] OR Plasminogen Activator[ot]

Total references: 5289

Database

Databases	CINAHL Complete
Interface	EBSCO
Research date	December 12 th , 2017
Filters	-

Syntax

MH	Exact Subject Headings
MM	Exact Major Subject Headings
TI	Title
AB	Abstract
S (1, 2, 3...)	Search
OR, AND	Boolean operators

Search strategy

#	Question	Résultats
S1	(MH "Stroke") OR (MH "Stroke, Lacunar")	59,969
S2	TI Cerebrovascular Accident* OR AB Cerebrovascular Accident* OR TI Stroke OR Stroke OR SU Stroke OR SU Cerebrovascular Accident*	88,109
S3	S1 OR S2	88,109
S4	(MH "Consensus") OR (MH "Reproducibility of Results") OR (MH "Surveys") OR (MH "Questionnaires")	424,790

S5	TI (agreement* or kappa or scale* or score* or survey* or reliability) OR AB (agreement* or kappa or scale* or score* or survey* or reliability) OR SU (agreement* or kappa or scale* or score* or survey* or reliability)	734,461
S6	S4 OR S5	898,180
S7	(MH "Thrombolytic Therapy") OR (MH "Fibrinolytic Agents") OR (MH "Thrombectomy") OR (MH "Tissue Plasminogen Activator") OR (MH "Plasminogen Activators")	12,498
S8	TI (thromboly* or thrombectom* or tpa or plasminogen activator) OR AB (thromboly* or thrombectom* or tpa or plasminogen activator) OR SU (thromboly* or thrombectom* or tpa or plasminogen activator)	14,363
S9	S7 OR S8	17,190
S10	S3 AND S6 AND S9	2,382
S11	S3 AND S6 AND S9 / publication date : 20170401-20180131	222

<u>Database</u>	
Databases	EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 7, 2017 EBM Reviews - ACP Journal Club 1991 to November 2017, EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016, EBM Reviews - Cochrane Central Register of Controlled Trials November 2017, EBM Reviews - Cochrane Methodology Register 3rd Quarter 2012, EBM Reviews - Health Technology Assessment 4th Quarter 2016, EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016
Interface	OvidSP
Research date	December 12th, 2017
Filters	-

<u>Syntax</u>	
/	Exact Subject Heading
kw	Keywords
tw	Includes Title, Abstract, Caption Text and Full Text fields.
or, and	Boolean operators
*	Truncation
adj2	The Adjacent operator

Search strategy

- 1 blood clot lysis/ (0)
- 2 mechanical thrombectomy/ (0)
- 3 fibrinolytic therapy/ (1622)
- 4 thrombectomy/ or mechanical thrombectomy/ or surgical thrombectomy/ or rheolytic thrombectomy/ (202)
- 5 fibrinolytic agent/ (2036)
- 6 tissue plasminogen activator/ (1486)
- 7 (thromboly* or thrombectom* or tpa or plasminogen activator).tw,kw. (8195)

- 8 **or/1-7 (9672)**
- 9 cerebrovascular accident/ (3)
- 10 (stroke or Cerebrovascular Accident*).tw,kw. (37162)
- 11 **9 or 10 (37162)**
- 12 consensus/ (47)
- 13 reproducibility/ (0)
- 14 health survey/ (812)
- 15 health care survey/ (357)
- 16 questionnaire/ (8)
- 17 reliability/ (0)
- 18 (agreement* or kappa or scale* or score* or survey* or reliability).tw,kw. (241601)
- 19 **or/12-18 (241932)**
- 20 **8 and 11 and 19 (1255)**
- 21 **limit 20 to yr="2017 - 2018" [Limit not valid in DARE; records were retained] (236)**



Database	
Database	Embase 1980 to December 11, 2017
Interface	OvidSP
Research date	December 12th, 2017
Filters	-

Syntax	
/	Exact Subject Heading
*/	Focus on Exact Subject Heading
tw	Text word field in EMBASE includes Title (TI), Abstract (AB) and Drug Trade Name (TN).
kw	Keywords
or, and	Boolean operators
*	Truncation

Search strategy

- 1 blood clot lysis/ (34877)
- 2 mechanical thrombectomy/ (3980)
- 3 fibrinolytic therapy/ (21774)
- 4 thrombectomy/ or mechanical thrombectomy/ or surgical thrombectomy/ or rheolytic thrombectomy/ (14487)
- 5 fibrinolytic agent/ (24300)
- 6 tissue plasminogen activator/ (25990)
- 7 (thromboly* or thrombectom* or tpa or plasminogen activator).tw,kw. (110164)
- 8 or/1-7 (145772)**
- 9 cerebrovascular accident/ (156380)
- 10 (stroke or Cerebrovascular Accident*).tw,kw. (320477)
- 11 9 or 10 (363575)**
- 12 consensus/ (51661)
- 13 reproducibility/ (186945)
- 14 health survey/ (180465)
- 15 health care survey/ (13250)
- 16 questionnaire/ (557954)
- 17 reliability/ (121947)
- 18 (agreement* or kappa or scale* or score* or survey* or reliability).tw,kw. (2602119)
- 19 or/12-18 (3139539)**

20 8 and 11 and 19 (10000)
21 limit 20 to embase (5163)
22 limit 21 to yr="2017 - 2018" (594)



<u>Database</u>	
Database	Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Interface	OvidSP
Research date	December 12 th , 2017
Filters	-

<u>Syntax</u>	
/	Exact Subject Heading
*/	Focus on Exact Subject Heading
tw	Text word field in MEDLINE includes Title (TI) and Abstract (AB)
kw	Keywords
or, and	Boolean operators
*	Truncation

Search strategy

- 1 Stroke/ or Stroke, Lacunar/ (90788)
- 2 (stroke or Cerebrovascular Accident*).tw,kw. (225170)
- 3 1 or 2 (238907)**
- 4 Consensus/ (9373)
- 5 "Reproducibility of Results"/ (386094)
- 6 Health Surveys/ (61607)
- 7 "Surveys and Questionnaires"/ (429444)
- 8 Health Care Surveys/ (31721)
- 9 (agreement* or kappa or scale* or score* or survey* or reliability).tw,kw. (2178386)
- 10 or/4-9 (2666151)**
- 11 Mechanical Thrombolysis/ or Thrombolytic Therapy/ (24300)
- 12 Thrombectomy/ (5356)
- 13 Fibrinolytic Agents/ (30374)
- 14 Tissue Plasminogen Activator/ (18936)
- 15 (thromboly* or thrombectom* or tpa or plasminogen activator).tw,kw. (88962)

16 or/11-15 (116393)
17 3 and 10 and 16 (5601)
18 limit 17 to yr="2017 - 2018" (716)



APPENDIX B: SUPPLEMENTAL TABLES

Table B.1: Summary of interrater agreement values (Fleiss'Kappa [95% confidence intervals]) for combined treatment decision, IV tPA decision, and MT decision within each of the 15 comprehensive stroke centers.

	Combined treatment decision	IV tPA decision	MT decision
Comprehensive stroke center #1 (5 physicians)	0.505 [0.369-0.641]	0.608 [0.408-0.767]	0.448 [0.291-0.641]
Comprehensive stroke center #2 (2 physicians)	0.496 [0.295-0.711]	0.645 [0.407-0.884]	0.549 [0.274-0.825]
Comprehensive stroke center #3 (4 physicians)	0.277 [0.179-0.407]	0.489 [0.329-0.668]	0.247 [0.108-0.421]
Comprehensive stroke center #4 (4 physicians)	0.454 [0.333-0.612]	0.539 [0.376-0.710]	0.452 [0.230-0.662]
Comprehensive stroke center #5 (2 physicians)	0.365 [0.202-0.571]	0.735 [0.520-0.949]	0.311 [0.068-0.554]
Comprehensive stroke center #6 (2 physicians)	0.433 [0.267-0.623]	0.685 [0.455-0.916]	0.446 [0.226-0.665]
Comprehensive stroke center #7 (4 physicians)	0.379 [0.245-0.516]	0.459 [0.270-0.650]	0.430 [0.260-0.626]
Comprehensive stroke center #8 (9 physicians)	0.394 [0.311-0.486]	0.514 [0.367-0.653]	0.346 [0.249-0.475]

Comprehensive stroke center #9 (6 physicians)	0.409 [0.304-0.526]	0.645 [0.490-0.783]	0.329 [0.195-0.495]
Comprehensive stroke center #10 (2 physicians)	0.252 [0.104-0.421]	0.451 [0.183-0.718]	0.281 [0.079-0.482]
Comprehensive stroke center #11 (5 physicians)	0.532 [0.389-0.664]	0.687 [0.517-0.851]	0.494 [0.313-0.684]
Comprehensive stroke center #12 (4 physicians)	0.421 [0.307-0.560]	0.598 [0.418-0.779]	0.339 [0.166-0.538]
Comprehensive stroke center #13 (4 physicians)	0.567 [0.453-0.698]	0.672 [0.488-0.828]	0.603 [0.403-0.779]
Comprehensive stroke center #14 (5 physicians)	0.451 [0.327-0.586]	0.590 [0.423-0.775]	0.504 [0.355-0.675]
Comprehensive stroke center #15 (2 physicians)	0.546 [0.358-0.745]	0.756 [0.555-0.956]	0.498 [0.228-0.767]
Centers with a substantial agreement, n(%)	0	8 (53.3 %)	1 (6.7 %)

Table B.2: Number of positive answers and interrater agreement for IV tPA and MT for various subgroups.

	IV tPA decision		MT decision	
	Proportion of positive answers ("yes")	Kappa values [95% CI]	Proportion of positive answers ("yes")	Kappa values [95% CI]
All patients (n=41) 3526 decisions	2155/3526 (61.1%)	0.565 [0.420–0.680]	2158/3526 (61.2%)	0.383 [0.289–0.491]
Patients who should receive IV tPA according to guidelines (n=15) 1290 decisions	1220/1290 (94.6%)	0.056 [0.048–0.064] *	1123/1290 (87.1%)	0.451 [0.442–0.459]
Patients who should not receive IV tPA according to guidelines (n=8) 688 decisions	59/688 (8.6%)	0.075 [0.063–0.087] *	303/688 (44.0%)	0.230 [0.218–0.242]
Patients who should receive MT according to guidelines (n=12) 1032 decisions	896/1032 (86.8%)	0.488 [0.478–0.497]	987/1032 (95.6%)	0.063 [0.054–0.073] *
Patients >80 years old (n=7) 602 decisions	421/602 (69.9%)	0.139 [0.044–0.299]	304/602 (50.5%)	0.132 [0.043–0.249]
Patients with unknown symptom onset (n=8) 688 decisions	270/688 (39.2%)	0.411 [0.203–0.603]	281/688 (40.8%)	0.327 [0.094–0.553]
Patients with a low initial NIHSS <10 (n=18) 1548 decisions	784/1548 (50.6%)	0.457 [0.288–0.616]	635/1548 (41.0%)	0.181 [0.089–0.330]
Patients with a very low initial NIHSS <6 (n=14) 1204 decisions	613/1204 (50.9%)	0.458 [0.250–0.645]	480/1204 (39.9%)	0.190 [0.074–0.347]
Patients with a DWI-ASPECTS<6 (n=8)	299/688 (43.4%)	0.667 [0.483–0.856]	478/688 (69.5%)	0.348 [0.081–0.600]

688 decisions				
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*: The low kappa values obtained despite the high proportion of similar answers is due to kappa statistics paradox.



Table B.3: Summary of intrarater agreement values (Fleiss'Kappa [95% confidence intervals]) for combined treatment decision, IV tPA, and MT.

	Combined treatment decision	IV tPA decision	MT decision
INR #1	0,772 [0,568-0,948]	0,892 [0,745-1,000]	0,626 [0,239-1,000]
INR #2	0,589 [0,369-0,793]	0,943 [0,834-1,000]	0,457 [0,176-0,737]
INR #3	0,687 [0,473-0,864]	0,868 [0,692-1,000]	0,485 [0,134-0,836]
INR #4	0,477 [0,289-0,685]	0,608 [0,364-0,851]	0,462 [0,191-0,734]
INR #5	0,930 [0,810-1,000]	0,949 [0,851-1,000]	0,942 [0,831-1,000]
INR #6	0,537 [0,286-0,749]	0,517 [0,261-0,772]	0,532 [0,068-0,997]
INR #7	0,546 [0,368-0,738]	0,597 [0,330-0,865]	0,612 [0,382-0,843]
INR #8	0,726 [0,534-0,880]	0,845 [0,675-1,000]	0,767 [0,556-0,978]
INR #9	0,650 [0,465-0,822]	0,663 [0,417-0,909]	0,678 [0,446-0,910]
INR #10	0,644 [0,440-0,824]	0,741 [0,529-0,953]	0,633 [0,394-0,871]
Vascular neurologist #1	0,630 [0,438-0,819]	0,800 [0,614-0,985]	0,579 [0,286-0,872]
Vascular neurologist #2	0,806 [0,643-0,958]	0,900 [0,765-1,000]	0,778 [0,538-1,000]
Vascular neurologist #3	0,732	1,000	0,645

	[0,552-0,895]	[1,000-1,000]	[0,414-0,876]
Vascular neurologist #4	0,800 [0,607-0,942]	0,827 [0,640-1,000]	0,747 [0,539-0,954]
Vascular neurologist #5	0,716 [0,542-0,882]	0,868 [0,640-1,000]	0,741 [0,529-0,953]
Vascular neurologist #6	0,650 [0,466-0,823]	0,790 [0,596-0,984]	0,705 [0,497-0,913]
Vascular neurologist #7	0,694 [0,521-0,862]	0,795 [0,604-0,986]	0,651 [0,417-0,886]
Vascular neurologist #8	0,660 [0,474-0,852]	0,945 [0,838-1,000]	0,584 [0,332-0,836]
Vascular neurologist #9	0,571 [0,354-0,775]	0,784 [0,584-0,983]	0,462 [0,191-0,734]
Vascular neurologist #10	0,758 [0,588-0,896]	0,693 [0,466-0,919]	0,900 [0,765-1,000]
Substantial or higher intrarater agreement, n(%)	15 (75%)	18 (90%)	13 (65%)

Table B.4: Summary of interrater agreement values (Fleiss'Kappa [95% confidence intervals] and Krippendorff's alpha inter coder reliability coefficient [95% CI]) for DWI-ASPECTS for all raters, by specialty, and by stroke center category.

	Fleiss' Kappa	Krippendorff's alpha intercoder reliability coefficient
All (n=34)	0.325 [0.276-0.387]	0.809 [0.793-0.824]
By specialty		
Vascular neurologists (n=19)	0.315 [0.267-0.386]	0.782 [0.760–0.803]
Interventional Neuroradiologists (n=15)	0.324 [0.271-0.394]	0.837 [0.824–0.849]
By stroke center category		
Primary stroke centers (n=5)	0.285 [0.213-0.366]	0.754 [0.710–0.796]
Comprehensive stroke centers (n=29)	0.330 [0.282-0.394]	0.815 [0.799–0.830]
Neurologists in comprehensive stroke centers (n=14)	0.325 [0.271-0.393]	0.786 [0.762–0.808]
By experience		
0-5 years (n=5)	0.329 [0.255-0.436]	0.839 [0.808–0.869]
6-10 years (n=12)	0.314 [0.249-0.387]	0.807 [0.789–0.823]
11-20 years (n=10)	0.363 [0.305-0.445]	0.814 [0.792–0.832]
>20 years (n=7)	0.293 [0.229-0.373]	0.787 [0.760–0.812]

Table B.5: Summary of intrarater agreement values (Fleiss'Kappa [95% confidence intervals] and Krippendorff's alpha inter coder reliability coefficient [95% CI]).

	Fleiss' Kappa	Krippendorff's alpha intercoder reliability coefficient
Physician #4	0,647 [0,465–0,799]	0,936 [0.897–0.969]
Physician #5	0,263 [0,106–0,422]	0,839 [0.771–0.902]
Physician #10	0,411 [0,249–0,582]	0,881 [0.803–0.946]
Physician #12	0,455 [0,278–0,636]	0,908 [0.849–0.950]
Physician #15	0,484 [0,292–0,658]	0,886 [0.840–0.932]
Physician #17	0,906 [0,790–1,000]	0,844 [0.539–1.000]
Physician #38	0,388 [0,224–0,574]	0,875 [0.825–0.925]
Physician #44	0,361 [0,188–0,534]	0,910 [0.873–0.946]
Physician #52	0,672 [0,514–0,824]	0,914 [0.825–0.977]
Substantial or higher intrarater agreement, n(%)	3 (33%)	9 (100%)