Hansen CK, Christensen A, Rodgers H, Havsteen I, Kruuse C, Christensen H.
Does the Primary Imaging Modality—Computed Tomography or Magnetic Resonance Imaging—Influence Stroke Physicians' Certainty on Whether or Not to Give Thrombolysis to Randomized Acute Stroke Patients?
***Journal of Stroke and Cerebrovascular Diseases* 2017**
DOI: https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.10.035

Does the primary imaging modality - CT or MRI – influence stroke physicians' certainty about whether or not to give thrombolysis to randomized acute stroke patients?

Christine Krarup Hansen (MD, Ph.D)[1], Anders Christensen (MD, Ph.D)[2], Helen Rodgers (MBChB)[3], Inger Havsteen (MD)[2], Christina Kruuse (MD, Ph.D)[4], Hanne Christensen (MD, Ph.D, DMSc)[1].

[1]Department of Neurology, Bispebjerg-Frederiksberg-Hospital, University of Copenhagen, Denmark
[2]Department of Radiology, Bispebjerg-Frederiksberg-Hospital, University of Copenhagen, Denmark
[3] Stroke Research Group, Institute of Neuroscience, Newcastle University, Newcastle, United Kingdom
[4] Department of Neurology, Neurovascular Research Unit, Herlev-Gentofte-Hospital, University of Copenhagen, Denmark

Authors' contributions:
CKH, AC, HR, IH, CK and HC were all involved in the study design.
HC is the chief-investigator and CKH managed the trial and conducted the statistical analysis. CKH, HC, CK and HR drafted the manuscript. All authors have thoroughly reviewed the manuscript and have given final approval to this version.

Disclosures: None.

Corresponding author:
Christine Krarup Hansen, MD, Ph.D.
Bispebjerg-University-Hospital, Department of Neurology, Bispebjerg-Bakke 23, 2400 Copenhagen NV, Denmark
christinekraruphansen@gmail.com, Telephone +45 22705664

Abstract:

Background: Door-needle-times of 20 minutes to stroke-patients with intravenous-tissue-Plasminogen-Activator (iv-tPA) are feasible when Computer Tomography (CT) is used as first-line of brain-imaging. Magnetic Resonance Imaging (MRI)-based assessment is more time-consuming but superior in detecting acute ischaemia. The certainty with which stroke-physicians prescribe or refrain from iv-tPA-treatment to CT versus MRI-examined patients has not previously been studied. The aim was to determine the effect of a primary imaging-strategy of CT or MRI upon clinicians' certainty to prescribe or refrain from giving patients with suspected acute stroke iv-tPA.

Method: Consecutive patients with suspected stroke were quasi-randomized to either CT or MRI-based assessment prior to potential iv-tPA-treatment.
The influence of 1) the clinical-findings and 2) the image-findings and 3) the certainty at which the stroke-physician prescribed or refrained from giving iv-tPA-treatment were assessed with Visual-Analogue-Scales.
Predictors of treatment-certainty were identified with a random-effect-model.

Results: Four-hundred-forty-four consecutive patients were quasi-randomized. MRI influenced the final treatment-decision more than CT (p=0.002). Compared to CT-examined patients (mean VAS-score 8.6, SD± 1.6) stroke-physicians were significantly more certain when prescribing or refraining from giving iv-tPA to MRI-examined patients (mean VAS-score 9.0, SD ±1.2) (p=0.014). No differences in modified Ranking Scale or mortality were detected at three months in CT versus MRI-examined iv-tPA-treated patients.

Conclusions: Stroke-physicians were significantly more certain when prescribing iv-tPA to MRI-examined stroke-patients and MRI influences the final treatment-decision significantly more compared with CT— though no difference in mortality and functional outcome at three months were detected between CT and MRI-examined patients treated with iv-tPA.

Introduction:

Stroke-teams have worked assiduously to reduce Door-Needle-Time (DNT) from hospital-admission to administration of intravenous-thrombolysis (iv-tPA) for acute stroke-patients (1-8) as the treatment-efficacy is time-dependent hence the saying “time is brain” (9).
Compared to Computer Tomography (CT), Magnetic Resonance Imaging (MRI) is more likely to show early signs of acute cerebral ischemia (10, 11) but is more time-consuming and unfeasible in patients with ferromagnetic-implants, pacemakers, claustrophobia, physical unrest and large body-size (12). As the efficacy of iv-tPA is time-dependent (13), MRI must impart clinical benefits to justify as primary image-modality prior to iv-tPA-administration.

As MRI-based-assessment is superior in confirming early signs of ischaemia and identifying some stroke-mimics it could add clinical information especially in situations with diagnostic uncertainty. If MRI were to be used as first-line imaging prior to iv-tPA then one could speculate that stroke-physicians would feel more certain about their decision to prescribe iv-tPA to these patients.

Although physicians’ clinical decisions-making have been studied (14-19), studies on factors which influence stroke-physicians’ decision-making about whether or not to give iv-tPA-treatment are scarce (20). The certainty with which they prescribe or refrain from iv-tPA-treatment has not previously been studied in a clinical setting.

We conducted a randomized clinical trial to answer the question; is CT or MRI-head-scan the best radiological image-modality to use prior to iv-thrombolysis for acute stroke-patients? Image-feasibly and DNT for CT and MRI-based iv-tPA-treatment have been reported (12); the median DNT for MRI-examined patients was 11 minutes longer than for CT-examined patients and 42.0% of the MRI allocated patients were not eligible for MRI due to contraindications or unstable medical conditions.

The aims of this sub-study were to assess the certainty with which stroke-physicians prescribed or refrained from giving iv-tPA-treatment to acute stroke-patients randomized to CT or MRI-based assessment and to evaluate the influence of the clinical and radiological information available upon the iv-tPA-decision.

Method:

Setting:

All patients from the Region of Copenhagen (1.7 million inhabitants) presenting with symptoms of acute stroke within 4.5-hours from symptom-onset were brought to Bispebjerg-Frederiksberg-University-Hospital on even dates after pre-notification by the emergency-service. Patients were treated with iv-tPA and endovascular-treatment if eligible. The patients were brought directly to a dedicated stroke-room within the Department of Radiology, bypassing the Emergency-Department. Upon arrival, the patients were evaluated by a pre-notified stroke-team working according to a

fast-track-setup and comprising a stroke-physician, a stroke-nurse, a porter, a neuro-radiologist and two radiographers. The stroke-physician was either a neurological resident in the final six month of training (n=14, assessing 12.6% of the patients), a neurological consultant (n=4, assessing 12.8% of the patients) or a senior-stroke-neurological consultant (n=6, assessing 74.5% of the patients).
The stroke-physician initiated all examinations, informed the patients about iv-tPA-related benefits/risks and advised the patients to accept the iv-tPA-treatment if eligible. For patients who were able to consent, the final decision of accepting the treatment was their choice.

Randomization:
From December 2013 to November 2015, all consecutive patients (>17 years) with suspected acute stroke and admission during daytime on weekdays (8am-3pm) were quasi-randomized based on the day of admission to receive CT or MRI as the initial imaging-strategy. An equal number of days were predefined as CT and MRI-days and posted in the Department of Radiology at least 6 months in advance.
A radiological Standard-Operational-Procedure (SOP) was followed but allowed for cross-over between the CT and MRI in case of predefined contraindications, absolute medical need of the non-allocated image-modality, physical unrest or patients in a critical condition not enabling MRI.
All MRI-allocated patients were systematically assessment for MRI-eligibility.
Due to the clinical setup, blinding of neither patients nor stroke-team-members was possible.

Sample size:
As no previous comparable studies have been conducted, sample-size was estimated based on expected differences in DNT of CT-and MRI-based examination. With a least clinically relevant difference of 10 minutes, Standard-Deviation at 20 minutes, alpha two-tailed at 0.05 and beta at 90%, the total number of participants was estimated at 172 patients. Nevertheless, the sample-size was extended in order to allow for analysis of secondary outcome-measures.

Outcome:
For each patient, the stroke-physicians completed an anonymous questionnaire using Visual-Analogue-Scales (VAS) to indicate 1) the influence of the clinical information obtained on the final decision to prescribe or refrain from giving iv-tPA-treatment 2) the influence of the radiological image-information obtained on the final decision to prescribe or refrain giving from iv-tPA-treatment and 3) the level of certainty of prescribing or refraining from iv-tPA.
The VAS was constructed as 10-cm horizontal-lines. The two extremes were placed at each end of the lines; zero indicated the lowest possible influence/most pronounced uncertainty while 10 indicated the highest possible influence/certainty. To answer the three questions, the stroke-physicians marked each line.

Imaging:

If allocated to CT, patients had a non-contrast head-CT followed by CT-angiography and if allocated to MRI a head-DWI, T2-FLAIR, GRE-T2* and an arterial Time-of-Flight (TOF)-angiography.
MRI were performed in 1.5T (GE-Sigma) or 3T (Siemens-Magnetom-Verio) scanners according to availability and CT on a Philips Brilliance 64-slice scanner. MRI-safety was adhered to according to International guidelines.

The imaging was assessed twice; first prior to iv-tPA-administration to rule out pathology contraindicating iv-tPA-treatment and later systematically according to a predefined research-plan.

In order to categorize the image-findings which either supported or discouraged use of iv-tPA three binary radiological scores were constructed and assessed for each patient of; 1) radiological signs for iv-tPA-treatment, 2) radiological signs against iv-tPA-treatment and 3) radiological signs of increased risk of iv-tPA-induced Intracranial Hemorrhage (ICH). This constituted the basis of the stroke-image-reading and replicates what was available prior to the stroke-physician' treatment-decision. For MRI-examined patients, the first score was positive in case of DWI-positivity and/or a large-vessel-occlusion of clinical relevance combined with FLAIR-negativity and for CT-examined patients in case of lack of deep hypoattentuation and/or large-vessel-occlusion or a dense-artery of clinical relevance.
The second score was positive in case of ICH, hemorrhagic-transformed infarct, signs of tumor, ischaemia involving >1/3 of the middle-cerebral-artery-territory or MRI-FLAIR-positivity. Further arteriovenous-malformations, aneurysms, subacute infarctions and signs of traumatic brain-injury were included as radiological contraindications.
The third score assessing signs of increased risk of iv-tPA-induced ICH included moderate to severe leucoaraiosis (Fazekas 2-3) that has been shown to double the risk of iv-tPA-induced ICH (21). Though lack of association between intracerebral microbleeds and iv-tPA-induced symptomatic ICH recently has been reported (22), microbleeds are still considered a risk-factor of iv-tPA-induced ICH by many clinicians (23) and were thus included as a risk-factor.

Statistical analysis:
Continuous data were compared with students-t-tests and categorical with Chi-square tests. A random-effect-model allowing for the cluster-effect of the stroke-physicians each seeing more than one patient was constructed to identify predictors of increasing treatment-certainty.
Patients with missing VAS-scores were not included when VAS-scores were compared or predictors of treatment-certainty were tested.
Tests were done according to the conducted imaging (per-protocol) and not according to allocation (intention-to-treat) as the stroke-physicians' decisions were based on the conducted imaging.
The following predictors were tested; age/gender of the patient, conducted image-modality, NIHSS, pre-onset modified-Rankin-Scale (mRS), seniority(late neurological resident, neurological consultant or senior-neurological-stroke consultant), the time-interval to arrival of the next patient and the number of patients evaluated during the shift (accounting for the work-intensity), if iv-tPA was

prescribed, the image and clinical influence on the treatment-decision (VAS-scores) and finally the three previous mentioned constructed binary radiological scores.
A two-sided P-value <0.05 were considered significant.

Statistical analyses were performed using IBM-SPSS-Statistics (Version 20.0, IBM-Corp, Armonk, NY, USA) and SAS-Enterprise (Version 7.11, Cary, NC, USA).

The registry was approved by the Copenhagen-Regional-Ethics-Committee (H-4-2013-118), the Danish-Data-Protection-Agency (2007-58-0015) and registered at clinicalTrials.gov (NCT02780843).

Results:

Four-hundred-forty-four patients were admitted with suspected stroke within 4.5 hours from symptom-onset; 225 patients were quasi-randomized to CT and 219 patients to MRI (fig 1.).
Due to cross-overs between CT and MRI, 310 patients had a CT-scan and 134 patients had MRI.
MRI was not performed in 48.9% of MRI-allocated patients due to: MRI-contraindications (23.7%), physical agitation (7.8%), unstable medical conditions (6.4%) and organizational issues (6.8%); further details have been published elsewhere (12). Twenty-two (9.8%) of the CT-allocated patients had MRI; 6 (2.7%) patients due omission of X-ray-exposure of pregnant/very young patients and 16 (7.1%) in need of diagnostic clarification of suspected stroke-mimics due to atypical clinical presentation.

The median DNT for MRI-examined were 11 minutes longer than for CT-examined patients (table 1); further details on DNT has been reported elsewhere (12).

A total of 140/444 patients received iv-tPA-treatment corresponding to 33.5% of the male patients and 29.7% of the female patients, (p=0.449).

Baseline-characteristics according to allocation are presented in table 2 and conducted imaging in table 3.

The median NIHSS on admission did not differ between CT (6 IQR 9.25) and MRI-allocated (6 IQR 10) iv-tPA-treated patients, p=0.773. But the NIHSS on admission was significantly higher for the iv-tPA treated CT-examined (7 IQR 10) than for the MRI-examined patients (4 IQR 4), p=0.007.
For CT versus MRI-examined iv-tPA-treated patients, mortality, median mRS and chance of independent living at 3 months did not differ (table 4). The frequencies of symptomatic ICH (sICH) at 24 hours are further reported (table 4).

For 111 (25.0%) patients, the stroke-physicians did not fill-out the questionnaires with the three VAS-based questions (fig. 1); no significant difference in missing questionnaires were detected between CT (61 patients=27.1%) versus MRI-allocated patients (50 patients=22.8%) (p=0.352) nor between CT (81 patients=26.1%) versus MRI-examined patients (30 patients=22.4%) (p=0.474). The uncompleted questionnaires were not associated with the seniority of the stroke-physicians - (p=0.363).

The image and clinical contribution:

The stroke-physicians indicated that MRI compared with CT had a significantly larger influence on the final decision to prescribe or refrain from iv-tPA-treatment (p=0.002) (table 5).

When asked to indicate the influence of the clinical information available on the final decision, no significant difference were detected between the CT and the MRI-examined patients, p=0.915 (table 5); indicating that the clinical information available for CT-examined patients did not gain compensatory relevance in spite of the less pronounced influence of imaging in CT-examined patients.

The certainty to prescribe or refraining from iv-tPA:

The stroke-physicians were significantly more certain when they prescribed or refrained from thrombolysis in MRI-examined patients compared to CT-examined patients, p=0.014 (table 5).

However, when the treatment-certainty was adjusted for; age/gender of the patient, NIHSS, pre-onset mRS, seniority of the stroke-physician, work-intensity of the shift, if thrombolysis was prescribed, the VAS-based imaging and clinical contribution on the final treatment-decision and the three binary radiological scores, the image-modality no longer predicted the level of treatment-certainty (p=0.125) (table 6). Further stroke-physicians were significantly more certain when treating male patients (p=0.046) and were more doubtful if iv-tPA had been prescribed (p=0.001) (table 6). An increasing VAS-score of the radiological image-contribution (p=0.0001) as well as the clinical information obtained (p=0.0001) on the final decision both predicted increasing levels of treatment-certainty (table 6). Seniority of the stroke-physician did not predict the treatment-certainty (table 6).

Discussion:

In this quasi-randomized study, MRI contributed with significantly more diagnostic value than CT-scans to help stroke-physicians decide whether or not to prescribe iv-tPA-treatment. Stroke-physicians further felt significantly more certain when they prescribed or refrained from giving iv-tPA-treatment to MRI-examined patients though no difference in mortality and functional outcome at three months were detected between CT and MRI examined patients.

This randomized trial was conducted in a stroke-unit with a well-established iv-tPA-service performing approximately 300 iv-tPA-treatments annually.

We are not aware of any previous randomized studies comparing the level of treatment-certainty in CT versus MRI-examined patients.

The strengths of this study include the novelty of comparing CT and MRI in an acute randomized clinical setting, the substantial number of included consecutive patients and the prospectively collected data regarding the treatment-decision.

Apart from a significantly higher number of male patients in the MRI-allocated group, the quasi-randomization allocated the patients into two well-balanced groups. But due to cross-overs between CT and MRI, the CT and MRI-examined groups differed in both numbers, baseline-characteristics and long-term outcome; a scenario that reflects a true clinical setting with patients with diverse clinical presentations and inherent MRI-contraindications. For this sub-study only a lower age-limit were applied to secure a true consecutive and unselected cohort of patients presenting with symptoms of acute stroke; with discharge-diagnosis of stroke as well as stroke-mimicking conditions.

Due to MRI-contraindications, physical agitation, unstable medical conditions and organizational issues MRI was not feasible in 48.9% of the MRI-allocated patients, consistent with Singer et al (24); details has been published elsewhere (12). To accommodate the need for cross-over, the degree of certainty is reported as per-protocol and not as intention-to-treat. Due to the need for cross-overs there is a selection-bias.

There is a non-response-bias as for 111 (25%) patients whose VAS-based-questionnaires were not filled out by the stroke-physicians. No significant difference in missing VAS-formularies was detected between CT versus MRI allocated/examined patients or between young and more experienced stroke-physicians. We did not identify whether missing questionnaires in particular occurred on busy shifts or the patients for whom the questionnaires were not filled out differed from the patients with completed questionnaires. We are not able to establish why the questionnaires were not replied.

The trial was conducted in a comprehensive acute stroke-unit in a Danish public hospital treating patients with mixed socioeconomic-status. No private acute stroke-services exist.
We believe that our results generalize to acute stroke settings outside Denmark as two important decisions have to be made in patients presenting with symptoms of acute stroke, regardless of the institutional set-up. First, is the patient suffering from acute cerebral ischaemia and second is the patient eligible for iv-tPA-treatment?
Our patient-cohort consists of a higher number of patients with mild strokes as well as stroke-mimics which potentially induces a higher degree of treatment-uncertainty compared to a cohort of severe strokes with a higher iv-tPA-treatment-related benefit/risk-ratio. The reported difference in treatment-certainty might have been different if the trial had been conducted in a setting with more selected patients: i.e a higher frequency of severe strokes and less stroke-mimics.

A general presupposition of MRI as golden-standard (10, 11) may have affected the stroke-physicians' perception of MRI compared to CT. In case of MRI-allocation, both the assessment for MRI-specific radiological signs as well as the psychological-effect of knowing that "the best" available radiological examination had been conducted could have enhanced the perceived certainty. It would have been relevant to include each stroke physician's general perception of whether MRI or CT scan is the best imaging-modality for iv-tPA-decision.

We could have included well-established CT-specific predictors of early ischaemia (30, 31); but our population presented early after onset and predominantly with mild strokes. However, of the three radiological predictors only image confirmed contraindications differed significantly between the two groups (table 3), caused by MRI-detected FLAIR-lesions which indicated potential non-hyper-acute cerebral ischaemia.

Due to the clinical setup, blinding of neither patients nor stroke-team-members was possible. In addition, the quasi-randomized setup did not allow for concealment.

Although the VAS-based questions were not pre-validated, VAS is widely used for anxiety (25), pain (26) and headache (27), the latter daily used by Danish neurologists. We assumed that the daily use of VAS would easily facilitate the usage of the VAS-based questions. As physicians may not always be as certain as patients presume them to be (17, 28), we had not anticipated the high mean reported VAS-scores (table 4). The stroke-physicians marked the VAS-scales anonymously and should thus unimpeded be able to answer the questions truthfully.
Similar to our high degree of treatment-certainty, a Canadian survey reported that iv-tPA-prescribing physicians recognized the importance of diagnostic uncertainty though only 4% frequently experienced uncertainty (29).

Decision-making not only relies on the presentation of symptoms and the probability of disease but is also influenced by non-medical factors regarding the patient, the physician, the staff and the practical setting (14, 15, 29). Our study was not designed to test further predictors.

Although male and female patients were equally likely to receive iv-tPA-treatment, male gender predicted a significantly higher level of treatment-certainty. Female patients are significantly less likely to accept iv-tPA-treatment and less certain when involved in the treatment-decision (30). If the female patients were more doubtful, the hesitation may have affected the stroke-physicians' certainty. We did not register socioeconomic-status or language-barriers caused by ethnicity, reduced consciousness or aphasia/dysarthria; conditions that potentially affect the communication and thus the treatment-decision. Nor did we register if the patient accepted the advised treatment, if the patient participated in the decision-making or was so severely affected that the treatment-decision was at the discretion of the stroke-physician alone.
The stroke-physicians were significantly more certain when the iv-tPA-decision followed a MRI-examination; but when adjusted for baseline-characteristics and the radiological detectable CT and MRI-pathology available in the acute setting undertaking a MRI no longer predicted a significantly higher level of certainty.

Use of MRI as first-line of imaging induced a median treatment-delay of 11 minutes compared to when patients had a CT-scan prior to iv-tPA-treatment. Despite the MRI-induced treatment-delay, we did not detect a difference in mortality or functional outcome at three months between CT and MRI-examined patients. Table 1 reports DNT according to allocation and the actual imaging

performed. The median DNT for all MRI-allocated patients were 30 minutes but four minutes longer for the subgroup of MRI-allocated patients who had MRI as first-line of imaging. Cross-over from MRI to CT on average decreased DNT —likely due to a shorter image protocol and lack of MRI-safety procedures.
When comparing patient-baseline-characteristics according to allocation and actual imaging performed (table 2 +3), it is evident that the subgroup of MRI-allocated patients who had crossover to CT in general were of increased age and stroke severity, of poorer pre-onset functional status and to a higher extend were suffering from hypertension. Though lack of balance in baseline-characteristics between CT and MRI-examined patients is in favor of a better outcome for the MRI-examined patients, no differences in long-term outcome were reported (table 4).

The treatment-delay in MRI-examined patients might leave more time for the treatment-decision and could thus potentially contribute to a high level of treatment-certainty in MRI-examined patients — though the majority of the additional time spend was attributed to MRI-safety procedures involving the stroke-physician. The random-effect-model further indicates that the work-intensity of the stroke-physician did not affect the degree of treatment-certainty reported.

Our study was not designed to assess whether the results of the imaging in fact changed the stroke-physicians' treatment-decisions. We are only able to assess their level of certainty of the final treatment-decision.
The mechanisms of refraining from treatment versus prescribing treatment may be different but due to lack of power certainty to give iv-tPA and certainty to refrain from iv-tPA was condensed into a single category.

Further one must consider the moderate difference of 0.4 VAS score of certainty between the CT and MRI-examined patients; although statistical significant on group level, the difference is small. The question remains, are the differences of clinical relevance?

A borderline-significant higher frequency of CT-examined patients had iv-tPA-treatment compared to MRI-examined patients but in addition also presented with significantly higher stroke-severity on admission (table 3).
Our patient-cohort consists of relatively mild strokes and thus perhaps represents the type of patients in whom most uncertainty exists regarding the iv-tPA-treatment-decisions. The benefit-harm-ratio in patients with mild strokes is less favorable than in patients with more severe neurological symptoms. Mild strokes thus potentially introduces a higher degree of uncertainty on whether one should prescribe or refrain from treatment in order to prevent treatment-induced complications. Due to cross-overs, the patients who had MRI presented with less pronounced neurological symptoms and a significantly higher frequency of stroke-mimics (table 3). Consequently it is reasonable that fewer MRI-examined patients received iv-tPA treatment compared to CT-examined patients.
Our trial was not designed to establish the decisive diagnostic cause of the treatment-decision.

It would be interesting to know whether MRI mostly reinforces the decision not to treat patients who otherwise would have been treated if examined with CT. The frequency of relative radiological iv-tPA-contraindications were significantly higher in the MRI-examined group of patients (table 3) which potentially could have induced a reluctance to administration of iv-tPA.

As the MRI-examined patients presented with a more heterogeneous clinical profile and thus potentially posed an increased diagnostic challenge, one would expect that the stroke-physicians would indicate a low degree of treatment-certainty. But as indicated by the significantly higher contribution of MRI on the treatment-decision (table 5), it is likely that MRI-detectable signs of disease (e.g lack/presences of acute intracranial ischemia) induced a feeling of making the correct – treatment-decision.
We do not know what the increase in treatment-certainty means in terms of the adequacy of treatment-decision and how the increased certainty translates into treatment-outcome potentially affecting complication rates and long-term physical outcome.
Mortality and mRS at 3 three month did not differ between iv-tPA-treated CT versus MRI-examined patients.
Due to lack of power, a direct group-comparison of sICH in our CT and MRI-examined patients is not applicable but the reported frequency for both CT and MRI-examined patients elaborates previously reported frequencies (1.8-9.5% (4, 31-38)) of sICH in iv-tPA-treated patients.
We may thus buy certainty with MRI, but what do we gain with certainty and what is the cost? Our trial was not designed to fully account for this aspect.

To conclude stroke-physicians were significantly more certain when prescribing iv-tPA to MRI-examined stroke-patients and MRI influences the final treatment-decision significantly more compared with CT— though no difference in mortality and functional outcome at three months were detected between CT and MRI examined patients treated with iv-tPA.

Acknowledgment:

The trial was fully funded by the Danish Tryg Foundation.
The authors declare that they have no competing interests.
We are very grateful for the dedicated participation and support from all members of the stroke team at Bispebjerg Hospital.

References:

1. Meretoja A, Strbian D, Mustanoja S, Tatlisumak T, Lindsberg PJ, Kaste M. Reducing in-hospital delay to 20 minutes in stroke thrombolysis. Neurology. 2012;79(4):306-13.
2. Tai YJ, Weir L, Hand P, Davis S, Yan B. Does a 'code stroke' rapid access protocol decrease door-to-needle time for thrombolysis? Intern Med J. 2012;42(12):1316-24.
3. Ford AL, Williams JA, Spencer M, McCammon C, Khoury N, Sampson TR, et al. Reducing door-to-needle times using Toyota's lean manufacturing principles and value stream analysis. Stroke; a journal of cerebral circulation. 2012;43(12):3395-8.

4. Meretoja A, Weir L, Ugalde M, Yassi N, Yan B, Hand P, et al. Helsinki model cut stroke thrombolysis delays to 25 minutes in Melbourne in only 4 months. Neurology. 2013;81(12):1071-6.
5. Van Schaik SM, Van der Veen B, Van den Berg-Vos RM, Weinstein HC, Bosboom WM. Achieving a door-to-needle time of 25 minutes in thrombolysis for acute ischemic stroke: a quality improvement project. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2014;23(10):2900-6.
6. Van Schaik SM, Scott S, de Lau LM, Van den Berg-Vos RM, Kruyt ND. Short Door-to-Needle Times in Acute Ischemic Stroke and Prospective Identification of Its Delaying Factors. Cerebrovasc Dis Extra. 2015;5(2):75-83.
7. Kendall J, Dutta D, Brown E. Reducing delay to stroke thrombolysis--lessons learnt from the Stroke 90 Project. Emerg Med J. 2015;32(2):100-4.
8. Busby L, Owada K, Dhungana S, Zimmermann S, Coppola V, Ruban R, et al. CODE FAST: a quality improvement initiative to reduce door-to-needle times. J Neurointerv Surg. 2016;8(7):661-4.
9. Saver JL. Time is brain--quantified. Stroke; a journal of cerebral circulation. 2006;37(1):263-6.
10. Fiebach JB, Schellinger PD, Jansen O, Meyer M, Wilde P, Bender J, et al. CT and diffusion-weighted MR imaging in randomized order: diffusion-weighted imaging results in higher accuracy and lower interrater variability in the diagnosis of hyperacute ischemic stroke. Stroke; a journal of cerebral circulation. 2002;33(9):2206-10.
11. Chalela JA, Kidwell CS, Nentwich LM, Luby M, Butman JA, Demchuk AM, et al. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. Lancet. 2007;369(9558):293-8.
12. Hansen CK, Christensen A, Rodgers H, Havsteen I, Kruuse C, Nybing J, et al. CT and MRI-based door-needle-times for acute stroke patients a quasi-randomized clinical trial. Clin Neurol Neurosurg. 2017;159:42-9.
13. Saver JL, Fonarow GC, Smith EE, Reeves MJ, Grau-Sepulveda MV, Pan W, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. JAMA. 2013;309(23):2480-8.
14. McKinlay JB, Potter DA, Feldman HA. Non-medical influences on medical decision-making. Soc Sci Med. 1996;42(5):769-76.
15. McKinlay JB, Lin T, Freund K, Moskowitz M. The unexpected influence of physician attributes on clinical decisions: results of an experiment. J Health Soc Behav. 2002;43(1):92-106.
16. McKinlay JB, Burns RB, Feldman HA, Freund KM, Irish JT, Kasten LE, et al. Physician variability and uncertainty in the management of breast cancer. Results from a factorial experiment. Med Care. 1998;36(3):385-96.
17. Kaplan RM, Frosch DL. Decision making in medicine and health care. Annu Rev Clin Psychol. 2005;1:525-56.
18. Hajjaj FM, Salek MS, Basra MK, Finlay AY. Non-clinical influences on clinical decision-making: a major challenge to evidence-based practice. J R Soc Med. 2010;103(5):178-87.
19. Brown DL, Barsan WG, Lisabeth LD, Gallery ME, Morgenstern LB. Survey of emergency physicians about recombinant tissue plasminogen activator for acute ischemic stroke. Ann Emerg Med. 2005;46(1):56-60.
20. Boissy AR. IV tissue plasminogen activator use in acute stroke: What are neurologists thinking? Neurology. 2013;81(13):1110-1.

21. Neumann-Haefelin T, Hoelig S, Berkefeld J, Fiehler J, Gass A, Humpich M, et al. Leukoaraiosis is a risk factor for symptomatic intracerebral hemorrhage after thrombolysis for acute stroke. Stroke; a journal of cerebral circulation. 2006;37(10):2463-6.
22. Turc G, Sallem A, Moulin S, Tisserand M, Machet A, Edjlali M, et al. Microbleed Status and 3-Month Outcome After Intravenous Thrombolysis in 717 Patients With Acute Ischemic Stroke. Stroke; a journal of cerebral circulation. 2015;46(9):2458-63.
23. Charidimou A, Shoamanesh A, Wilson D, Gang Q, Fox Z, Jager HR, et al. Cerebral microbleeds and postthrombolysis intracerebral hemorrhage risk Updated meta-analysis. Neurology. 2015;85(11):927-4.
24. Singer OC, Sitzer M, du Mesnil de Rochemont R, Neumann-Haefelin T. Practical limitations of acute stroke MRI due to patient-related problems. Neurology. 2004;62(10):1848-9.
25. Hornblow AR, Kidson MA. The visual analogue scale for anxiety: a validation study. Aust N Z J Psychiatry. 1976;10(4):339-41.
26. Gallagher EJ, Bijur PE, Latimer C, Silver W. Reliability and validity of a visual analog scale for acute abdominal pain in the ED. Am J Emerg Med. 2002;20(4):287-90.
27. Lundqvist C, Benth JS, Grande RB, Aaseth K, Russell MB. A vertical VAS is a valid instrument for monitoring headache pain intensity. Cephalalgia. 2009;29(10):1034-41.
28. Anderson N, Fuller R, Dudley N. 'Rules of thumb' or reflective practice? Understanding senior physicians' decision-making about anti-thrombotic usage in atrial fibrillation. QJM. 2007;100(5):263-9.
29. Shamy MC, Jaigobin CS. The complexities of acute stroke decision-making: a survey of neurologists. Neurology. 2013;81(13):1130-3.
30. Kapral MK, Devon J, Winter AL, Wang J, Peters A, Bondy SJ. Gender differences in stroke care decision-making. Med Care. 2006;44(1):70-80.
31. Mokin M, Kass-Hout T, Kass-Hout O, Zivadinov R, Mehta B. Blood pressure management and evolution of thrombolysis-associated intracerebral hemorrhage in acute ischemic stroke. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2012;21(8):852-9.
32. Seners P, Turc G, Tisserand M, Legrand L, Labeyrie MA, Calvet D, et al. Unexplained early neurological deterioration after intravenous thrombolysis: incidence, predictors, and associated factors. Stroke; a journal of cerebral circulation. 2014;45(7):2004-9.
33. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke. The New England journal of medicine. 2015.
34. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. The New England journal of medicine. 2015;372(11):1009-18.
35. Does time of day or physician experience affect outcome of acute ischemic stroke patients treated with thrombolysis? A study from Finland. International journal of stroke : official journal of the International Stroke Society. 2012;7(6):511-6.
36. Seet RC, Rabinstein AA. Symptomatic intracranial hemorrhage following intravenous thrombolysis for acute ischemic stroke: a critical review of case definitions. Cerebrovascular diseases. 2012;34(2):106-14.
37. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372(1):11-20.

38. Mazya M, Egido JA, Ford GA, Lees KR, Mikulik R, Toni D, et al. Predicting the risk of symptomatic intracerebral hemorrhage in ischemic stroke treated with intravenous alteplase: safe Implementation of Treatments in Stroke (SITS) symptomatic intracerebral hemorrhage risk score. Stroke; a journal of cerebral circulation. 2012;43(6):1524-31.

Figure legends

Figure 1, Flow-chart.

Table 1, Median Door-to-needle-times

Table 2, Baseline-characteristics according to image-allocation.

Table 3, Baseline-characteristics according to conducted-imaging.

Table 4, Symptomatic ICH (sICH) detected at 24 hours and mRS and mortality at 3 month. *The same patient fulfilling all three sICH-criteria

Table 5, Visual-Analogue-Scale scores for CT and MRI-examined patients.

Table 6. Random-effect-model predicting the iv-tPA-treatment-certainty-level.

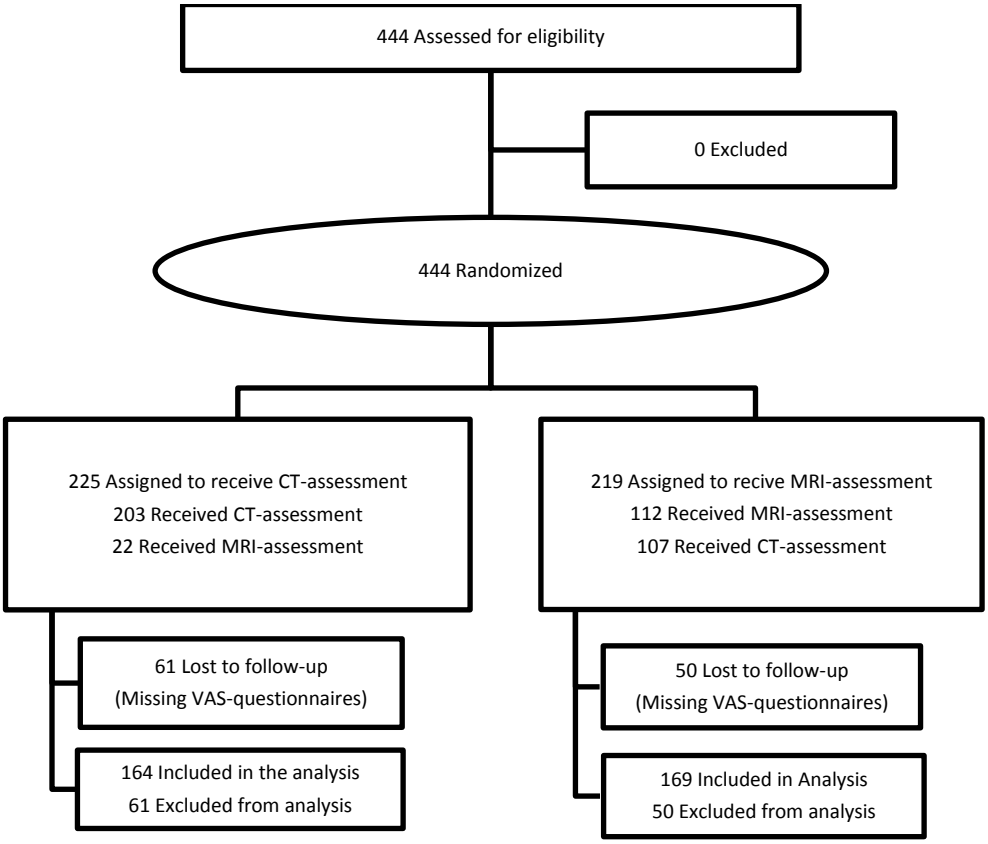

Figure 1, Flow-chart

Allocation			Conducted imaging			Allocation, cross-overs excluded		
CT (n=75)	MRI (n=65)	p	CT (n=107)	MRI (n=33)	p	CT (n=73)	MRI (n=31)	p
22 (15.5)	30.0 (14.0)	0.004	23.0 (16.5)	34 (14.0)	0.001	22 (15.0)	34 (14.0)	0.001

Table 1. Median Door-to-needle-times (DNT) in minutes (IQR) according to allocation, actually conducted image-modality (after cross-over) and according to allocation (not including cross-overed patients).

	CT-allocated (n= 225)	MRI-allocated (n= 219)	p
Age, years*	70 (26)	70 (24)	0.757
Male gender	97 (44.1%)	118 (53.9%)	0.030
NIHSS admission*	3 (7)	3 (6)	0.838
mRS before onset*	1 (2)	1 (2)	0.743
mRS at 3 month (median, IQR)	2 (3.0)	2 (2.0)	0.398
Independent living at 3 months (mRS<3)	116 (51.6%)	110 (50.2%)	0.891
Mortality at 3 months	26 (10.2%)	19 (8.7%)	0.477
Atrial fibrillation	35 (15.6%)	40 (18.3%)	0.552
Hypertension	91 (40.4%)	86 (39.3%)	0.876
Hypercholesterolemia	56 (24.9%)	47 (22.4%)	0.457
Diabetes melitus	19 (8.4%)	26 (11.9%)	0.299
Previous stroke/TCI	52 (23.1%)	54 (24.7%)	0.787
Alcohol abuse	23 (10.2%)	21 (9.6%)	0.974
Use of tobacco	47 (20.9%)	42 (19.2%)	0.777
Thrombolysis	75 (33.3%)	65 (29.7%)	0.468
Door-needle-time	22 (15.5)	30 (14)	0.004
Discharge diagnosis			
Ischemic stroke	96 (43.6%)	89 (40.6%)	0.736
Transient Ischaemic Attack	40 (17.8%)	42 (19.2%)	0.797
ICH	15 (6.7%)	22 (10.0%)	0.264
Stroke-mimic	74 (32.9%)	66 (30.1%)	0.502
Radiological scores:			
Relative signs of iv-tPA treatable hyper acute ischemia	28 (12.4 %)	37 (16.9 %)	0.233
Relative radiological iv-tPA contraindications	30 (13.3 %)	37 (16.9 %)	0.360
Findings considered to increase the risk of iv-tPA treatment	82 (36.4 %)	83 (37.9 %)	0.827

Table 2, Baseline-characteristics according to image-allocation (intention-to-treat), *median (IQR)

	CT performed n= 310	MRI performed n= 134	p
Age*	73.5 (22)	63.5 (29.25)	0.001
Male gender	148 (47.7%)	67 (50%)	0.739
NIHSS admission*	4 (10)	2 (5)	0.001
mRS before onset*	1 (3)	0 (1)	0.001
Atrial fibrillation	56 (18.1%)	19 (14.2%)	0.387
mRS at 3 month (median, IQR)	2 (3.0)	1 (2.25)	0.001
Independent living at 3 months (mRS<3)	149 (48.1%)	77 (57.5%)	0.001
Mortality at 3 months	40 (12.9%)	5 (3.7%)	0.009
Hypertension	134 (43.2%)	43 (32.1%)	0.036
Hypercholesterolemia	76 (24.5%)	27 (20.1%)	0.380
Diabetes melitus	36 (11.6%)	9 (6.7%)	0.162
Previous stroke/TCI	77 (24.9%)	29 (21.6%)	0.546
Alcohol abuse	32 (10.3%)	12 (9.0%)	0.798
Use of tobacco	62 (20.0%)	77 (57.5%)	0.980
Thrombolysis	107 (34.5%)	33 (24.6%)	0.051
Door-needle-time	23 (16.5)	34 (14)	0.001
Discharge diagnosis:			
Ischemic stroke	140 (45.2%)	45 (33.6%)	0.030
Transient Ischaemic Attack	54 (17.4%)	28 (20.9%)	0.463
ICH	29 (9.4%)	8 (6.0%)	0.319
Stroke-mimic	87 (28.1%)	53 (39.6%)	0.023
Radiological scores:			
Relative signs of iv-tPA treatable hyper acute ischemia	43 (13.9 %)	22 (16.4 %)	0.582
Relative radiological iv-tPA contraindications	39 (12.6 %)	28 (20.9%)	0.036
Findings considered to increase the risk of iv-tPA treatment	120 (38.7%)	45 (33.6%)	0.358

Table 3, Baseline-characteristics according to conducted-imaging (per protocol), *median (IQR)

		CT-examined iv-tPA-treated patients (n=107)	MRI-examined iv-tPA-treated patients (n=33)	p
Mortality within 3 months		15 (14.0 %)	4 (12.1 %)	0.787
mRS < 3 at 3 months		63 (58.9 %)	24 (72.7 %)	0.184
Median mRS (IQR) at three months		2 (3)	1 (2)	0.068
Any ICH detected on control imaging 24 hours after iv-tPA-treatment		5 (4.7 %)	1 (3.0 %)	NA
sICH at 24 hours				
	NINDS criteria	1*(0.9 %)	1 (3.0 %)	NA
	ECASS criteria	1*(0.9 %)	0	NA
	SITS-MOST criteria	1*(0.9 %)	0	NA

Table 4, Symptomatic ICH (sICH) detected at 24 hours and mRS and mortality at 3 month. *The same patient fulfilling all three sICH-criteria

	CT-examined patients n=229 (310)	MRI-examined patients n=104 (134)	p
Image-contribution	7.5 (2.5)	8.2 (1.9)	0.002
Clinical-contribution	8.3 (2.1)	8.3 (2.0)	0.915
Certainty of prescribing or refraining from iv-tPA-treatment	8.6 (1.6)	9.0 (1.2)	0.014

Table 5, Visual-Analogue-Scale scores for CT and MRI-examined patients.

According to conducted imaging (per-protocol). Patients with missing VAS-scores are not included into this analysis equalizing the difference between n and the (bracket total number of patients). Mean, standard-deviation.

			95.0 % Confidence interval		
	Estimate	Std. Error	Lower	Upper	Sig.
Intercept	1.361	0.561	0.556	2.466	.016
CT-examination #	.260	.169	-0.072	0.583	.125
Age	-0.001	.004	-.072	.593	.758
Female gender	-0.410	.144	-.692	-.128	**.046**
NIHSS on admission	0.002	.014	-.024	.0291	.862
Pre-onset mRS	0.002	.005	-.008	.013	.677
Thrombolysis not prescribed	0.965	.166	0.634	1.205	**.001**
Neurological consultant*	0.496	.379	-.309	1.301	.209
Neurological resident*	-0.047	.343	-.753	0.659	.892
Number of patients per shift	-.093	.062	-.223	.037	.160
Minutes to arrival of next patient§	-0.011	.020	-.050	.029	.588
Image-findings(VAS score)	.458	.030	.040	.516	**.0001**
Clinical-findings (VAS score)	.532	.030	.474	.591	**.0001**
No radiological signs for iv-tPA-treatment	-.390	.223	.828	0.048	.081
No radiological signs against iv-tPA-treatment	-.263	.224	-.704	0.178	.241
Radiological signs of increased risk of iv-tPA-induced ICH	-.156	.161	-.474	.162	.336

Table 6. Random-effect-model predicting the level of iv-tPA treatment-certainty.

The analysis allows for the cluster-effect of the 24 stroke-physicians each seeing more than one patient.

#Versus MRI-examination
*Versus a Senior-Neurological-Stroke Consultant
§Intervals of 20 minutes