

Magnetic Resonance Imaging or Computed Tomography for Suspected Acute Stroke: Association of Admission Image Modality with Acute Recanalization Therapies, Workflow Metrics, and Outcomes

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Objective: To examine rates of intravenous thrombolysis (IVT), mechanical thrombectomy (MT), door-to-needle (DTN) time, door-to-puncture (DTP) time, and functional outcome between patients with admission magnetic resonance imaging (MRI) versus computed tomography (CT).

Methods: An observational cohort study of consecutive patients using a target trial design within the nationwide Swiss-Stroke-Registry from January 2014 to August 2020 was carried out. Exclusion criteria included MRI contraindications, transferred patients, and unstable or frail patients. Multilevel mixed-effects logistic regression with multiple imputation was used to calculate adjusted odds ratios with 95% confidence intervals for IVT, MT, DTN, DTP, and good functional outcome (mRS 0–2) at 90 days.

Results: Of the 11,049 patients included (mean [SD] age, 71 [15] years; 4,811 [44%] women; 69% ischemic stroke, 16% transient ischemic attack, 8% stroke mimics, 6% intracranial hemorrhage), 3,741 (34%) received MRI and 7,308 (66%) CT. Patients undergoing MRI had lower National Institutes of Health Stroke Scale (median [interquartile range] 2 [0–6] vs 4 [1–11]), and presented later after symptom onset (150 vs 123 min, $p < 0.001$). Admission MRI was associated with: lower adjusted odds of IVT (aOR 0.83, 0.73–0.96), but not with MT (aOR 1.11, 0.93–1.34); longer adjusted DTN (+22 min [13–30]), but not with longer DTP times; and higher adjusted odds of favorable outcome (aOR 1.54, 1.30–1.81).

Interpretation: We found an association of MRI with lower rates of IVT and a significant delay in DTN, but not in DTP and rates of MT. Given the delays in workflow metrics, prospective trials are required to show that tissue-based benefits of baseline MRI compensate for the temporal benefits of CT.

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Introduction

According to the American Heart Association/American Stroke Association guidelines, both computed tomography (CT) and magnetic resonance imaging (MRI), including CT and MR angiography, may be used for initial imaging in patients with suspected acute stroke, and these are the most frequently used diagnostic tests in neurology.¹ The primary purpose of neuroimaging in stroke patients is to differentiate ischemia from hemorrhage, and to confirm the suspected diagnosis of an acute ischemic stroke. In addition, acute stroke imaging assists with several other key tasks: These include selection of patients for intravenous thrombolysis (IVT), mechanical thrombectomy (MT), and guidance of early secondary prevention and etiological work-up (Table 1).

Because of its broad availability and rapid acquisition time, CT is the most widely used diagnostic tool. However, MRI offers certain advantages over CT. Diffusion-weighted imaging is more sensitive in detecting acute ischemia, especially in the posterior circulation,^{2,3} and MRI is more suitable for differentiating cerebrovascular causes from stroke mimics.^{4,5} The main disadvantage of MRI is the delay of 15–30 minutes from admission to treatment in real-world patients.⁶

No reliable data are available on the impact of the initial imaging modality on IVT and MT rates, procedure times, and outcome in an unselected nationwide population of patients with suspected acute stroke. We therefore sought to compare rates of IVT, MT, door-to-needle (DTN) time, door-to-puncture (DTP) time, and outcome between patients with admission MRI and admission CT. Analyses aimed to assess potential differences in the overall cohort of patients with suspected stroke, and in subgroups of patients with high likelihood of subsequent IVT and MT (presenting

early with severe deficits), as well as the subgroup with large uncertainty (mild or transient deficits).

Materials and Methods

We used data from the compulsory prospective nationwide Swiss Stroke Registry (SSR) for this analysis. Details have been described previously.^{7,8} Briefly, all consecutive patients with suspected stroke hospitalized in stroke units and comprehensive stroke centers since January 2014 were enrolled. For this analysis, we applied inclusion and exclusion criteria for participation in a hypothetical randomized controlled target trial to all consecutive patients (Table 2, Table S1 for exclusions at each point and imaging choice approach of each center). The target trial design was proposed by Hernan to minimize bias in observational datasets.⁹ The SSR steering committee designed and approved this project in cooperation with the clinical trials units of Bern (data analysis) and Basel (data management).

Local investigators at the study sites collected data on prespecified baseline variables using electronic case report forms. We performed a plausibility check with restrictions for age, blood pressure, National Institutes of Health Stroke Scale (NIHSS), and symptom onset to hospital time, and implausible data items were set as missing.

Patients were grouped according to initial imaging modality (MRI or CT). The outcomes assessed were: (1) DTN; (2) DTP; (3) rates of IVT (admission IVT at any dose), and MT (admission intra-arterial treatment: aspiration or stent retriever or intra-arterial thrombolysis); (4) occurrence of symptomatic intracranial hemorrhage (sICH) before discharge (ECASS-II definition¹⁰); (5) favorable functional outcome at 3 months (modified Rankin Scale 0–2); and (vi) futile MT/IVT defined as use of

TABLE 1. Role of Neuroimaging for Suspected Acute Stroke

Role of Imaging
Exclude hemorrhage
Patient selection for thrombolysis
Patient selection for endovascular treatment
Helping to establish the diagnosis, especially in patients with transient and mild symptoms
Excluding stroke mimics
Estimation of the time elapsed if onset time is unknown or unwitnessed
Collateral assessment
Etiological clues (eg, multiple infarctions)
Predicting stroke recurrence and guiding secondary prevention
Diffusion-weighted imaging positivity in (low risk) transient ischemic attacks guides treatment and surveillance
Predicting stroke recurrence and guiding secondary prevention
Large baseline ischemia guides treatment
Posterior fossa infarction guides treatment
Prediction of hemorrhage risk

MT/IVT followed by severe dependency or death at 3 months (modified Rankin Scale 5–6).

SSR patients underwent standardized follow-up assessments by local investigators for in-hospital and 3-month outcomes. All follow-up checks were performed by certified stroke neurologists or trained research staff during clinic visits, or by structured telephone interviews.

Statistical Analysis

We prespecified the statistical analysis plan and used standard descriptive methods: medians (interquartile ranges [IQRs]) or means (with standard deviation [SD]), as appropriate, as well as percentages to present the distribution of continuous, ordinal, and categorical variables, respectively. We compared baseline variables between MRI and CT patients using Pearson's χ^2 test for categorical variables, and the Kruskal–Wallis test for continuous and ordinal variables.

For the primary analysis, we used multilevel mixed-effects logistic regression models with multiple imputation (imputing baseline variables with <25% missing data items) to calculate adjusted odds ratios (aOR) with 95% confidence intervals

(CI) for the association of MRI (as compared with the reference CT) with the main outcomes (IVT, MT, sICH, and favorable outcome at 3 months). Model selection was based on obligatory covariates of previously published differences between MRI and CT patients influencing those outcomes, and facultative least absolute shrinkage and selection operator of pathophysiologically plausible factors identified using univariate comparisons (see supplement for full models). Centers were handled in the model as a random effect. As a post-hoc analysis, we used inverse probability weighting as an alternative model correcting for the same confounders.

To assess the association of MRI with DTN and DTP, we used quantile regression models to calculate adjusted coefficients with 95% CI for the association of MRI (as compared with the reference CT) with log-transformed time points. Those coefficients were then back-transformed and presented as adjusted time intervals (minutes).

For the subgroup analysis, we defined the following subgroups: (1) patients with a high likelihood of MT, including only patients presenting with a NIHSS ≥ 8 , for this subgroup an early time window was defined as admission 0–6 hours after symptom onset; (2) patients with a high likelihood of IVT, including only patients with a NIHSS ≥ 4 , for this subgroup an early time window was defined as admission 0–4.5 hours after symptom onset; and (iii) large uncertainty cohort, including only patients with a NIHSS ≤ 2 , for this subgroup an early time window was defined as admission 0–4.5 hours after symptom onset. See Table S3 for prespecified outcomes for each subgroup. Further post-hoc analysis included bridging patients (receiving both IVT and MT); patients actually receiving IVT; patients actually receiving MT, patients presenting within 3 hours from onset to the hospital, and patients with a vessel-occlusion detected on imaging.

We calculated (adjusted) odds ratios and corresponding 95% CI. All statistical analyses were performed using Stata (Stata Statistical Software: Release 16; StataCorp, College Station, TX, USA). The p -values were two-sided, without adjustments for multiple testing, and $p < 0.05$ was considered statistically significant.

Ethics

The registry and this analysis were approved by the responsible ethics committee (KEK Bern 2019–01010). In accordance with Swiss law, patients who—after being informed about the collection of their biological data—refused to allow its use for research purposes were excluded from the analysis.

Results

Overall Population

Of 65,942 patients screened in the SSR, the final target trial population included 11,049 patients (mean [SD] age, 71 [15] years; 4,811 women [44%]). Final diagnosis was: 69% ischemic stroke, 16% transient ischemic attack, 8% stroke mimics, 6% intracranial hemorrhage, and 1% other (amaurosis fugax/retinal infarction, spinal ischemia,

TABLE 2. Target Trial Inclusion and Exclusion Criteria

Target trial (hypothetical randomized controlled trial)	Swiss Stroke Registry (SSR) criteria
Inclusion criteria	Inclusion criteria (=analysis population)
Suspected acute vascular event (“stroke”)	All event categories of patients enrolled in the SSR, including mimics and hemorrhages
Time from symptom onset <24 h	Time from symptom onset <24 h
Any age	Any age
Both neuroimaging modalities available at site	Centers that perform at least 10% of acute stroke imaging with the less used modality
Exclusion criteria	Exclusion criteria
MRI contraindicated (e.g. agitation, vomiting, presence of metal, claustrophobia)	Exclusion of patients with a prosthetic heart valve, exclusion GCS <8
	Body mass index >45kg/m ²
	Systolic blood pressure <90 or >230mmHg
	NIHSS >30
Known contraindication for contrast agent of one particular modality	Not possible to exclude patients in whom a particular contrast agent is contraindicated in the SSR
No new image after transfer from another hospital needed	Transfer patients
Severe kidney failure	Severe kidney failure (estimated glomerular filtration rate <30ml/min)
Severe frailty, palliative care decided at admission	Patients from nursing homes and with prestroke modified Rankin Scale >2
Wake-up patients	Exclusion of wake-up patients after publication of wake-up trial (August 2018)
Further exclusion criteria	Missing data on initial imaging modality

GCS = Glasgow Coma Scale; NIHSS = National Institutes of Health Stroke Scale.

cerebral sinus venous thrombosis). Overall, 3,741 (34%) received MRI and 7,308 (66%) CT as baseline imaging modality. Patients undergoing MRI had lower NIHSS (median [IQR] 2 [0–6] vs 4 [1–11]), less frequently had a witnessed onset (72 vs 78%, $p < 0.001$), and presented later after symptom onset (150 vs 123 min, $p < 0.001$) than those who underwent CT. The rate of angiography (93% vs 94%, $p = 0.311$) was similar in both groups, but perfusion imaging (56% vs 67%, $p < 0.001$) was less frequently performed in MRI patients (see Table 3 for further baseline differences and all baseline characteristics).

In unadjusted analysis, IVT was applied in 30% of MRI patients and 41% of CT patients ($p < 0.001$). MT was used in 19% of MRI patients, as compared with 24% of CT patients ($p < 0.001$). After adjustment, and in the

whole target trial population, admission MRI was associated with lower adjusted odds of use of IVT compared with CT (aOR 0.83, 95% CI 0.73–0.96), but had no association with use of MT (aOR 1.11, 95% 0.93–1.34). The association of MRI with lower rates of IVT (aOR 0.89, 95% 0.47–1.69) did not reach significance using inverse probability weighting, with no difference also in the rate of MT (aOR 1.37, 95% 0.74–2.56). In patients presenting within 3 hours to the hospital, admission MRI remained associated with lower adjusted odds of use of IVT compared with CT (aOR 0.79, 0.66–0.94).

The median DTN was 40 minutes (30–60 min) and the median DTP 97 minutes (77–127 min). In the unadjusted analysis, MRI patients had longer admission to image and longer image to IVT needle intervals than CT

TABLE 3. Baseline Characteristics of Patients According to Initial Imaging Modality

	Computed tomography (CT) (N = 7,308)	Magnetic resonance imaging (N = 3,741)
Epidemiology and stroke characteristics		
Age (years)	n = 7,152, 72.1 ± 14.4	n = 3,466, 69.0 ± 15.2
Female sex	n = 7,293, 3,174 (44%)	n = 3,738, 1,637 (44%)
Arrival time window (day/night) (night)	n = 7,308, 1744 (24%)	n = 3,741, 618 (17%)
Known onset time	n = 7,273, 5,682 (78%)	n = 3,716, 2,660 (72%)
Disability on modified Rankin Scale before event	n = 6,683,	n = 3,305,
No symptoms at all (0)	4,831 (72%)	2,512 (76%)
No significant disability (1)	1,066 (16%)	520 (16%)
Slight disability (2)	786 (12%)	273 (8%)
NIHSS on admission	n = 6,393, 4.0 (1.0; 11.0)	n = 3,390, 2.0 (0.0; 6.0)
First systolic blood pressure in hospital (mmHg)	n = 7,112, 155.0 ± 25.9	n = 3,427, 157.6 ± 26.7
Body mass index (kg/m ²)	n = 5,322, 25.6 ± 4.4	n = 3,110, 25.8 ± 4.4
Minutes from onset to arrival at hospital	n = 7,182, 123.0 (64.0; 310.0)	n = 3,524, 150.0 (73.0; 459.8)
Medication		
Antiplatelet therapy	n = 7,308,	n = 3,741,
No antiplatelet agent monotherapy	4,866 (67%)	2,467 (66%)
One antiplatelet agent	2,252 (31%)	1,167 (31%)
Dual antiplatelet therapy (two antiplatelet agents)	190 (3%)	107 (3%)
Anticoagulation (yes)	n = 7,308, 1,178 (16%)	n = 3,741, 433 (12%)
Antihypertensive drugs (yes)	n = 7,271, 4,089 (56%)	n = 3,714, 1,963 (53%)
Lipid lowering drugs (yes)	n = 7,260, 2,050 (28%)	n = 3,712, 1,021 (28%)
Cardiovascular risk factors		
Hypertension	n = 6,969, 4,949 (71%)	n = 3,592, 2,427 (68%)
Diabetes mellitus	n = 6,971, 1,213 (17%)	n = 3,587, 554 (15%)
Hyperlipidemia	n = 6,937, 3,826 (55%)	n = 3,566, 2,219 (62%)
Smoking	n = 6,923, 1,174 (17%)	n = 3,516, 704 (20%)
Atrial fibrillation/flutter	n = 6,963, 1,682 (24%)	n = 3,579, 703 (20%)
Coronary heart disease	n = 6,948, 1,168 (17%)	n = 3,573, 503 (14%)
Peripheral artery disease	n = 6,938, 326 (5%)	n = 3,557, 145 (4%)
Imaging features		
Perfusion imaging on admission	n = 5,721, 3,844 (67%)	n = 3,073, 1,714 (56%)
CT or MR angiography on admission	n = 7,089, 6,660 (94%)	n = 3,639, 3,400 (93%)

NIHSS = National Institutes of Health Stroke Scale.

patients, whereas image to groin puncture intervals were shorter (Table 4). The rate of patients with a DTN up to 45 minutes (62% vs 47%, $p < 0.001$) and up to 60 minutes (79% vs 68%, $p < 0.001$) was higher with CT selection. The rate of patients with a DTP up to 60 minutes (11% vs 8%, $p = 0.133$) did not differ between modalities, but fewer CT patients had a DTP of up to 90 minutes (40% vs 47%, $p = 0.006$).

After adjustment, MRI was associated with longer adjusted DTN (+22 min^{11–16,19–30}) compared with CT, but not with longer DTP times (+6 min [–1 to +14]). The association of MRI with longer DTN remained significant using inverse probability weighting (+27 min [7–52]) without differences in DTP (+4 min [–9 to +20]). Neither MR nor CT angiography, nor perfusion imaging was associated with an adjusted delay in DTN or DTP.

There was no difference in the odds of symptomatic intracranial hemorrhage (aOR 0.86, 95% CI 0.57–1.30), but, compared with CT, MRI was associated with lower odds of death at 3 months (aOR 0.48, 95% CI 0.38–0.60) and higher odds of favorable outcome (aOR 1.54, 95% CI 1.30–1.81, available for 6,435 patients [58%]). Inverse probability weighting showed no statistical significant association of MRI with good favorable outcome (aOR 1.13, 95% CI 0.73–1.74).

Subgroup with a High Likelihood of IVT

In the subgroup of patients with a high likelihood of IVT, there was a significantly longer delay associated with MRI than with CT in adjusted DTN in patients presenting

within 4.5 hours (+17 min, 8–27 min). The numerical delay in adjusted DTN in the late presenting patients did not reach statistical significance. MRI and CT did not differ significantly in terms of rates of IVT, futile IVT in the early time window, or sICH. However, compared with CT, MRI was associated with higher adjusted odds for good outcome (Table 5). In those patients actually receiving IVT, results were very similar (S Table 4).

Subgroup with High Likelihood of MT

In the subgroup of patients with a high likelihood of MT, there was no difference in adjusted DTP between patients who had had MRI and those who had had CT either in the patients presenting within 6 hours (+8 min, –2 to 18 min) or in those presenting after 6 hours (–8 min, –22 to 9 min). Rates of MT did not differ according to whether patients had undergone MRI or CT. However, compared with CT, MRI was associated with higher adjusted odds for good outcome and lower adjusted odds of futile MT in the early time window (Table 5). In those patients receiving MT, the results were very similar (Table S4).

Subgroup with Large Uncertainty

In the cohort of patients presenting with mild or transient deficits, the patients who had undergone MRI were significantly more likely than those who had undergone CT to have a good outcome. MRI was not significantly different from CT in terms of rates of IVT of MT (Table 5).

TABLE 4. Unadjusted Outcomes According to Initial Imaging Modality

	CT (N = 7,308)	Available	MRI (N = 3,741)	Available	p-value
Door to image (minutes, IQR)	32 (20–103)	7,084	40 (22–128)	3,504	<0.001
Image to IVT needle (minutes, IQR)	16 (9–30)	2006/2075	23 (13–36)	773/802	<0.001
Image to IAT puncture (minutes, IQR)	79 (58–107)	1108/1190	67 (53–87)	470/505	<0.001
Intravenous thrombolysis, N (%)	2075 (41%)	5,017	802 (30%)	2,645	<0.001
Door-to-needle time (minutes, IQR)	39 (28–57)	2058/2075	47 (33–68)	785/802	<0.001
Intra-arterial treatment (yes)	1,190 (24%)	5,016	505 (19%)	2,646	<0.001
Door-to-puncture time (minutes)	100 (79–139)	1173/1190	93 (76–120)	482/505	<0.001
Symptomatic intracranial hemorrhage in hospital (yes)	120 (2%)	6,875	42 (1%)	3,552	0.030
Death (follow-up) (yes)	713 (17%)	4,215	157 (7%)	2,288	<0.001
mRS (0–2) at 90 days (mRS 0–2)	2,608 (62%)	4,194	1719 (77%)	2,241	<0.001

CT = computed tomography; IAT = intra-arterial therapy; IQR = interquartile range; IVT = intravenous thrombolysis; MRI = magnetic resonance imaging; mRS = modified Rankin scale.

TABLE 5. Subgroup Analysis

	High likelihood of MT (NIHSS ≥ 8)		High likelihood of IVT (NIHSS ≥ 4)		Large uncertainty (NIHSS ≤ 2)	
	Early time window (0–6 h)	Late time window (>6 h)	Early time window (0–4.5 h)	Late time window (>4.5 h)	Early time window (0–4.5 h)	Late time window (>4.5 h)
<i>N</i>	2,059	522	3,213	1,265	2,585	1,364
% MRI	22	27	24	32	40	49
aDTP, min	8, –2 to 18	–8, –22 to 9				
aDTN, min			17, 8–27	46, –10 to 136		
Good outcome, aOR	1.77, 1.63–1.93	0.96, 0.82–1.13	1.98, 1.83–2.14	1.01, 0.87–1.17	1.31, 1.19–1.44	1.87, 1.09–3.19
sICH*, aOR			0.88, 0.49–1.60	2.14, 0.28–16.4		
MT, aOR	1.06, 0.77–1.46	0.87, 0.38–1.95			1.00, 0.35–2.87	0.82, 0.06–11.3
IVT, aOR			1.00, 0.77–1.31	1.52, 0.61–3.78	0.73, 0.52–1.04	0.82, 0.42–1.63
Futile MT, aOR	0.54, 0.30–0.98	1.02, 0.36–2.87				
Futile IVT, aOR			1.10, 0.58–2.08	Due to low number not calculated		

Note that use of magnetic resonance imaging (MRI) was slightly more frequent in the late time window; however, computed tomography (CT) was still the most frequently used imaging modality for all subgroups. Bold numbers represent results reaching statistical significance.

Analysis for symptomatic intracranial hemorrhage (sICH) and futile therapies restricted to patients receiving IVT.

aDTP = adjusted difference in door-to-puncture time with MRI as compared with CT; aDTN = adjusted difference in door to intravenous thrombolysis (IVT) needle time with MRI as compared with CT.

In the subgroup of patients receiving both bridging IVT and MT, there was a significantly longer delay associated with MRI than with CT in adjusted DTN (+14 min, 2–28 min). In the subgroup of patients with confirmed vessel occlusion on imaging, MRI had no association with use of MT (aOR 0.83, 95% CI 0.62–1.11).

Discussion

The main findings regarding the initial imaging modality for patients with acute suspected stroke, based on this nationwide real-world multicenter target trial analysis of Swiss stroke units and comprehensive stroke centers are as follows.

First, compared with CT, admission MRI was associated with lower adjusted odds of IVT (aOR 0.83, 95% CI 0.73–0.96) in the overall cohort, but showed no association with rates of IVT in patients presenting early with more severe stroke (aOR 1.00, 95% CI 0.77–1.31). Second, use of MT did not differ between MRI and CT patients either in the overall cohort (aOR 1.11, 95% CI

0.93–1.34) or in the sensitivity analysis of patients presenting early with severe stroke (aOR 1.06, 95% CI 0.77–1.46). Third, compared to CT, MRI was associated with a delay 22 minutes longer than that for CT in adjusted DTN times, but not with longer DTP times. Fourth, in the sensitivity analysis considering only patients presenting early with severe stroke, the association of MRI with an adjusted delay of 17 minutes in DTN remained tangible, whereas, again for DTP, no significant association was found. Fifth, despite lower rates of IVT and longer DTN, but not DTP times, mortality was lower and functional outcome better in MRI patients than in CT patients.

Currently, CT and MRI are equally recommended by international guidelines regardless of stroke subtype (ie, stroke severity, suspected hemorrhage, etc.). In clinical routine, the choice between CT and MRI is mainly driven by availability. Centers that can offer both imaging modalities often have institutional protocols, but a survey among tertiary (mostly university) stroke centers in South Korea showed heterogeneity of acute stroke imaging protocols.¹⁷

MRI and CT differ in several diagnostic characteristics, which potentially affect workflow metrics, therapeutic decisions, and thus outcome. We therefore aimed to examine potential differences in key quality indicators for acute stroke care. The dilemma with diagnostic testing in daily clinical practice is that the scientific standards of interventional trials are not applied, even though the choice of tests has significant therapeutic consequences.

Overall, we found that patients undergoing admission MRI had a lower adjusted rate of IVT applied than those who underwent admission CT, whereas no such association was found in patients presenting within 4.5 hours with a NIHSS ≥ 4 points. In a previous small study, the association of MRI with lower IVT rates approached statistical significance.¹⁸ There are several potential explanations for this finding: First, MRI patients arrived later, and more often had an unwitnessed onset, explaining the less frequent use of IVT in the overall cohort despite the restriction of our cohort to patients presenting within 24 hours after symptom onset. Furthermore, MRI took longer, so some patients might have been outside the time window for IVT after imaging. Additionally, there is an increasing awareness that IVT should be withheld in patients with >10 cerebral microbleeds or superficial siderosis, which cannot be detected by CT.¹¹ In addition, very large infarcts seen on DWI, no visible infarction on DWI, or lacunar infarction verified on MRI might lead to deselection of patients from IVT. In fact, such deselection by MRI might actually be harmful to some patients, as evidence for such approaches, especially in the early time window, is currently missing—for example it was recently shown that in wake-up patients there was no evidence of a reduced treatment effect of IVT in patients with more than one microbleed.¹² Additionally, MRI shows fluid-attenuated inversion recovery demarcation in the infarcted tissue within several hours and, hence, IVT might not be given as opposed to CT, where subtle ischemic changes are not as easily visible and selection relies on perfusion mismatch.¹³ In contrast, IVT will be avoided in stroke mimics identified on MRI, so the lower rate of IVT might be justified in some cases. Nevertheless, other studies showed that in certain stroke subgroups, such as stroke chameleons,¹⁴ wake-up stroke,¹⁵ or late time window, MRI might actually be associated with an increase in IVT use. Taken together, in patients with borderline indications for IVT, the use of MRI might have tipped the scale against use of IVT, balancing its risks and benefits, whereas in patients with clear-cut indications, the imaging modality did not seem to affect IVT use significantly.

In patients receiving IVT, the DTN was also significantly delayed in the subgroup of patients in the MRI group who presented early with relevant deficits. This

signal is pertinent, and reflects other studies reporting an increased DTN in MRI patients presenting early^{16,18} or with unknown time of onset.¹⁹ Even though several rapid protocols have been published, there still seems to be a delay in real-world MRI stroke workflows, even in mostly academic stroke centers, and a relevant percentage of patients do not achieve treatment within society-recommended DTN time. Tools to eliminate inefficiencies in DTN workflow have been published,^{20,21} but it remains uncertain whether similar DTN times to those obtained with CT will ever be achieved. In patients undergoing MRI, there is also the question whether to interrupt the protocol for administration of the IVT bolus directly after DWI, T2/fluid-attenuated inversion recovery and SWI/GRE/T2* imaging or to wait until after the whole protocol for application of bolus and perfusion of IVT. The lack of association of angiography or perfusion imaging with a delay in DTN time suggests that the bolus was mostly applied after the native sequences and, hence, the time point of DTN was not delayed by the subsequent perfusion imaging. Nevertheless, given the latest recommendations, routine perfusion imaging—as done in most participating centers during the study timeframe—is not required, and is most useful for selecting candidates for IVT and MT in the extended time window.¹ Recently, stroke patients with late presentation selected by non-contrast CT were found to not differ in clinical outcomes as compared with those selected with CT perfusion or MRI, arguing that advanced imaging might not be necessary—even in the extended time window.²⁵

Whereas MRI was associated with lower rates of IVT, no such association could be found with MT. Other studies have found inconsistent results with higher^{22,23} or lower indication rates for MT.²⁴ This can probably be explained by the specific imaging protocol used, time from symptom onset to imaging, and the downstream decision algorithms. As compared with IVT, indications for MT seem to depend less on the imaging findings in real-world decisions.

In randomized controlled trials, no significant difference in DTP delay was seen in patients undergoing MRI as compared with CT,^{26,27} although perfusion imaging was performed less frequently than in our cohort.²⁷ Studies on real-world cohorts, however, did report increased DTP times.^{6,28,29} In the present study—unlike DTN—DTP times were similar for both modalities. This is probably because the indication for MT is usually established straightforwardly and early on during the MRI protocol,^{22,30–32} and, hence, the subsequent steps (anesthesia call, angio preparation) can be initiated in parallel to finishing the MRI protocol. Fittingly, the image to puncture interval was shorter in MRI patients.

Previous studies showed that MRI-selected patients had a lower risk for sICH after IVT^{33,34} and MT.⁶ This might be because MRI can detect cerebral microbleeds, cortical siderosis, very severe white matter changes, and subtle hemorrhagic changes within the ischemic region,³⁵ as well as providing a better estimation of the time elapsed when time of onset is unknown or unwitnessed. Hence, patients with increased risk for sICH might be excluded from acute recanalization treatments in borderline scenarios. However, this target trial analysis found no difference in sICH between the two modalities after adjustment for confounders.

Other studies demonstrated an overall association of MRI with better outcomes despite longer DTN times in IVT³⁶ and MT-treated patients.^{37,38} However, assignment bias probably influenced those findings, as the choice of imaging was not randomized. In line with previous studies, we found a pronounced association of MRI with better functional outcome and lower mortality, despite lower rates of IVT and longer DTN, but not DTP times. However, residual confounding and assignment bias will probably have influenced this finding, despite application of a target trial design and sophisticated statistical adjustment. Because of the indication bias in observational data, influence on workflow metrics, and complexity of downstream therapeutic decisions, only randomized controlled trials can determine whether the choice of admission imaging modality truly affects IVT or MT indication rates, workflow delays, and outcomes. However, our aim is to raise awareness among stroke physicians that the imaging modality might influence their decisions regarding which patients to treat by IVT, and that treatment delays might arise secondary to the influence of the choice of imaging. For some patient subgroups, such as MT candidates, such trials are already ongoing (NCT03745391), whereas for broad unselected acute stroke populations, we are unaware of such a trial. As our target trial analysis was not able to identify specific subgroups that gained a particular benefit from either modality, a pragmatic trial in unselected populations with suspected acute stroke could identify subgroups that might benefit from a specific modality (e.g. MRI for transient ischemic attack or stroke mimic patients, or CT for MT candidates). Another study design would be a comparison of treatment decisions in patients who received both imaging modalities almost simultaneously. Such a study should determine which factors (ASPECTS, infarct and penumbra volume) influence physicians' treatment decisions to understand why IVT/MT may be offered differentially between the two groups.

Performing MRI on admission in selected patients might have economic benefits, as there is then no need for potential admission or a second examination during

hospitalization (currently in many CT centers, MRI is performed a few days later).

Until further evidence becomes available, clinicians should individualize the imaging modality to suit patient characteristics, respecting locally established workflows. CT including angiography—or even direct flat-panel CT in the angio suite—is ideal for patients with severe stroke, to exclude hemorrhage and shorten DTN. Advanced CT or MRI including perfusion should be used to identify as many patients as possible who would benefit from acute recanalization therapies in borderline scenarios and patients with a high likelihood of stroke mimics or transient ischemic attack.

Strengths and Limitations

Inevitably, this study had the limitations of a retrospective registry. Most importantly, choice of imaging modality—MRI or CT—was center-specific, and the reasons one imaging modality was preferred over another for individual patients were not available. We sought to address this issue by using the target trial design applying the inclusion and exclusion criteria of a potential randomized trial on this topic. Using this design, the participating sites were mostly comprehensive stroke centers, and the study findings might not be generalizable to other settings. Additionally, we used center as a random effect in the model, to correct for center-specific choice of imaging modality. Given the large sample size and good-quality data, we were able to include many relevant confounders in our model. Despite application of the target trial design, MRI patients had an overall favorable risk profile and allocation bias is possible. Hence, other residual confounding variables (frailty, poor general condition, pacemakers, etc.) not captured in the registry likely represent the true reason for worse outcome in those patients, as they would probably be more often in the CT group. The point estimates of the post-hoc inverse probability weighting were consistent with the prespecified analysis, although due to the use of weights, the results had larger confidence intervals, reflecting the accounting for non-randomized assignment (Figs S1 and S2). Even though the association with outcomes is likely biased, the workflow metrics seem to represent a true delay and should be taken seriously. Nevertheless, the present results need to be replicated by other groups and verified in future randomized controlled trials, also because some of the results might be chance findings due to multiple testing.

Conclusion

Compared with CT, initial MRI was associated with lower rates of intravenous thrombolysis in the overall cohort, but had no association with intravenous thrombolysis in patients

presenting early with more severe stroke. MRI had no significant association with rates of mechanical thrombectomy. There was a significant delay in DTN times, but not DTP times in patients undergoing MRI. Despite lower rates of IVT and longer DTN, mortality was lower and functional outcome better in MRI patients than in CT patients—most likely due to assignment bias. Randomized controlled trials are required to clarify whether the tissue-based benefits of MRI compensate for the temporal benefits of CT. Until further evidence becomes available, clinicians should individualize the imaging modality to suit patient characteristics, respecting locally established workflows.

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Author Contributions

U.F., M.B., L.H.B., P.M., J.K., and T.R.M. contributed to the conception and design of the study; U.F., M.B., L.H.B., E.C., M.V., A.P., Z.K., S.W., A.L., D.J.S., M.A., P.M., D.S., V.D., G.M.D.M., L.S., G.A., F.B., N.P., L.F., K.N., C.W.C., G.K., M.B., S.S., R.S., F.M., C.B., S.R., C.B., M.S., M-L.M., B.R., M.P., P.M., J.G., J.K., and T.R.M. contributed to the acquisition and analysis of data; U.F., M.B., J.K., and T.R.M. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

The authors report no relevant disclosures.

Data Availability

Anonymized data will be shared upon reasonable request from any qualified investigator after clearance by the local ethics committee.

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