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Clinical Effect of Thrombolysis in Wake-Up Stroke Compared to Non-Wake-Up Stroke

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ABSTRACT

Background and Aims: In known onset stroke (KOS) cerebral CT is performed to select patients eligible for intravenous thrombolysis (IVT) while MRI (DWI-FLAIR) mismatch aids selection of patients in wake-up stroke (WUPS). In this study, the clinical outcome and safety profile of IVT in WUPS patients is compared to KOS patients.

Methods: IVT treated WUPS patients in the NOR-TEST trial and immediately hereafter and KOS patients also treated at Stavanger University Hospital were included. Retrospective review showed that the traditional MRI mismatch concept in clinical praxis was extended at our center to also treat WUPS patients with partial mismatch and even match. CT excluded intracerebral hemorrhage (ICH) in KOS patients. Clinical improvement was rated by NIHSS and modified Rankin Scale (mRS) at 3 months, while safety analyzed by ICH.

Results: Total 83 WUPS patients and 166 KOS patients were treated with IVT. Patients with pre-stroke mRS < 2 were included in the clinical analysis, giving 73 WUPS patients (44 mismatch, 15 partial mismatch and 14 match) and 158 KOS patients. Comparing each WUPS subgroup with the KOS group, only the partial mismatch group showed significant higher NIHSS at admission; (p=0.007). Comparing to the KOS group, only the mismatch group showed non- inferior NIHSS at discharge; (p=0.385) while all WUPS subgroups were non-inferior with (ΔNIHSS-24h) and (ΔNIHSS-disc). Comparable mRS at 3 months in all groups without any event of ICH.

Conclusion: Compared to the KOS patients, the partial mismatch patients demonstrated comparable and non-inferior neurological improvement and safety profile.

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Introduction

In acute ischemic stroke (AIS) time is of the essence for reperfusion therapy with intravenous thrombolysis within a narrow time window of initially 4.5 hours [1,2]. However, the time window has been extended up to 9 hours based on recent studies showing that some selected patients can profit from IVT treatment beyond the traditional time window [3,4]. Stroke patients awakening with neurological deficit accounts for up to 15-20 %, called wake-up stroke and studies show that majority of these strokes take place in the morning hours close to the time of awakening [5-7]. In WUPS patients the magnetic resonance imaging (MRI) mismatch between positive diffusion-weighted imaging (DWI) and negative Fluid Attenuated Inversion Recovery (FLAIR) indicates that the occurrence of ischemic onset is less than 4-5 hours [8]. Different neuroradiological imaging is also applied in clinical practice to identify patients who might profit from IVT treatment [9-11].

The traditional mismatch concept is an established method for selection of WUPS patients for IVT treatment, however latest studies have indicated that a modified MRI mismatch concept with WUPS patients presenting a partial FLAIR positive signal may benefit from IVT treatment and thereby suggesting that the traditional MRI mismatch concept may exclude patients who might benefit [12-14].

In a previous study, it was investigated how strictly the MRI mismatch concept was practiced in clinical praxis at Stavanger University Hospital and whether patients with partial mismatch profit from IVT [14]. The study showed that only 60% of the WUPS patients treated with IVT at our center had a traditional MRI mismatch, meaning that 40% of WUPS patients were treated although there already was an emerging or complete FLAIR lesion. The study recognized that some selected WUPS patients not fulfilling the classical MRI mismatch criteria might profit from reperfusion treatment with IVT, but the result was not significant. No ICH or death occurred [14].

Available studies, have shown that IVT treatment in WUPS patients guided by traditional MRI mismatch criteria is comparable to the well-established IVT treatment in KOS patients within 4.5 hours of stroke onset [15-18]. However, there is insufficient data available of the comparability of reperfusion therapy with IVT between WUPS patients with a partial mismatch and KOS patients.

In this current study we included, WUPS patients treated with IVT in the NOR-TEST trial and thereafter at Stavanger University Hospital and compared those with KOS patient treated with IVT after the NOR-TEST trial also at our center to determine whether IVT treatment in WUPS patients with a partial mismatch is non-inferior to IVT treatment in KOS patients.

In this study, patients with known onset stroke (KOS) are defined as non-wake-up stroke (non- WUPS) patients, whereas patients with unknown symptom onset or awakening with stroke symptoms are defined as wake-up stroke (WUPS) patients and were divided into three subgroups: mismatch, partial mismatch and match group. Each WUPS subgroup was compared to the KOS group.

Materials and Methods

Study Design and Patients

WUPS patients treated in the NOR-TEST trial (n=40) were included along with all WUPS patients treated with IVT after the NOR-TEST trial at Stavanger University Hospital between Oct 1, 2016, to Nov 30, 2022 (n=43), in total (n=83). In addition to that all KOS patients treated with IVT at Stavanger University Hospital between Jan 1, 2017, to Jul 31, 2021 (n=166) were also included in this study. Patients included had to be >18 years.

Inclusion Criteria for WUPS Patients

The WUPS patients met the following criteria: 1 - last well seen later than 4.5 h, 2 - unknown symptom onset time or awakening with stroke symptoms, 3 - radiologically presenting a diffusion restriction in less than 1/3 of the middle cerebral artery territory on DWI, and 4-fulfilling all other IVT treatment criteria [19]. Patients with a pre-stroke mRS of ≥ 2 were excluded from the clinical analysis.

Inclusion Criteria for KOS Patients

The KOS patients met the following criteria: 1 - last well seen time < 4.5 h, 2 - aware of symptom onset happening in the awake state, 3 - cerebral CT, CT angiography and CT perfusion was performed on admission before the determination of eligibility for thrombolytic treatment, 4 - excluding intracranial hemorrhage or intracranial demarcation of infarct, and 5 - fulfilling all other IVT treatment criteria [19]. Patients with a pre-stroke mRS of ≥ 2 were excluded from the clinical analysis.

Radiological Imaging and Interpretation

Initially, radiological evaluation was performed by the local radiologist on call. At arrival all KOS and WUPS patients were assessed clinically by a neurologist and then went through radiological imaging with either non-contrast cranial computed tomography, Cerebral CT with angiography and CT perfusion (CTAP) or MRI wake- up protocol including DWI, FLAIR, apparent diffusion coefficient (ADC) maps, time of flight MR angiography and gradient echo (GRE) T2*-weighted sequences.

In KOS patients cerebral CT was performed and eligibility for thrombolysis was determined when intracranial hemorrhage and intracranial demarcation of infarct correlating with the presenting clinical symptoms, were excluded. In WUPS patients, if a lesion on MRI was judged visible on DWI but not visible or not visible to the same degree on FLAIR, it was concluded that the patients had a DWI/FLAIR mismatch. If the neurological team on call judged that the WUPS patients would profit from treatment, IVT was then administered. IVT administration was not strictly dependent upon FLAIR negativity, meaning that as well patients with FLAIR lesion were treated, if the clinical symptoms were indicative to a larger penumbra and the intracerebral hemorrhage (ICH) risk was deemed to be low. For the current study all MRI images were reanalyzed by a European certified neuroradiologist blinded to patient demographics, stroke onset, and clinical outcomes. The DWI-FLAIR mismatch was rated visually, and images rated according to the modified DWI-FLAIR mismatch defined in the study by Jakubicek [13].

1. **MRI Mismatch:** an ischemic DWI lesion with no corresponding FLAIR signal change.
2. **Partial MRI Mismatch:** present FLAIR signal change counting by area clearly less than the DWI signal change.
3. **MRI Match:** present lesion is equally visible on both DWI and FLAIR [13].

Clinical Evaluation

Neurological impairment was assessed using the National Institutes of Health Stroke Scale (NIHSS). NIHSS was performed at admission, at 24 hours and at 7 days or at discharge if earlier. Δ-NIHSS at 24 hours (Δ-NIHSS-24h) was defined as the difference between NIHSS at 24 h and NIHSS on admission. Δ-NIHSS at discharge/day7 (Δ-NIHSS- disc) was defined as the difference between NIHSS at day 7 (or at discharge if earlier) and NIHSS on admission.

Functional outcome was assessed using the Modified Rankin Scale (mRS). The assessment was performed at admission and after 3 months via telephone interview by a certified stroke nurse or as an outpatient consultation. The primary endpoint was set as mRS at 3 months as excellent (0–1 points).

Safety Evaluation

Observation of patients treated with IVT the first 24 hours was performed in a specialized ward with high clinical observation expertise. In all patients CT/MRI was performed at 24-48 hours. ICH was classified according to the European Cooperative Acute Stroke Study II (ECASS II) [20]. Symptomatic ICH (sICH) was defined as ICH associated with a four-point or greater NIHSS deterioration.

Statistics

SPSS Statistics version 24 (IBM Cooperation, Armonk, NY, USA) was used for all statistical analysis in order to compare the whole WUPS group and each of following subgroups: MRI DWI/FLAIR mismatch, MRI DWI/FLAIR partial mismatch and MRI DWI/FLAIR match to the KOS group.

Kruskal-Wallis and Mann-Whitney U test was used for comparison between independent quantitative variables, whereas Chi-square test (asymptotic) and Chi-square test (Exact) were used for comparison between independent categorical variables. Clinical outcomes were calculated from Chi-square Test (asymptotic) and Chi square test (exact), while pairwise comparisons were performed by Mann-Whitney U Test. P-values equal to or < 0.05 was considered statistically significant.

Results

In this study a total of 83 WUPS patients and a total of 166 KOS patients were included. Of these only 73 WUPS patients and 158 KOS patients were independent pre-stroke with mRS < 2 and

included in the clinical analysis. After radiological reassessment, 44 MRI investigations were rated as DWI/ FLAIR mismatch (60%), 15 as partial mismatch (21%) and 14 as match (19%). The baseline characteristics including the age, gender and cerebrovascular risk factors of the patients are shown in (Table 1). The median age was 74 years in the WUPS group and 70 years in the KOS group. The distribution of the female patients in the WUPS group and KOS group was respectively (39.7%) and (41.1%); (p=0.839).

Table 1: Baseline Characteristics for Patients with mRS at Baseline < 2

	All KOS and WUPS (n=231)	All KOS (n=158)	ALL WUPS (n=73)	P- Value	MRI DWI/ FLAIR Mismatch (n=44)	MRI DWI/ FLAIR Partial Mismatch (n=15)	MRI DWI / FLAIR Match (n=14)	P- Value
Age - median (IQR)	72.0 (59.0- 80.0)	70.0 (57.0-81.0)	74.0 (63.5-79.0)	0.251[a]	75.0 (64.3-81.3)	72.0 (59.0-79.0)	74.5 (64.3-79.3)	0.725[b]
Female gender	109 (43.8%)	65 (41.1%)	29 (39.7%)	0.839[c]	20 (45.5%)	4 (26.7%)	5 (35.7%)	0.414[c]
Cardiovascular medical history								
Hypertension	115 (49.8%)	86 (54.4%)	29 (39.7%)	**0.038**[c]	20 (45.5%)	2 (13.3%)	7 (50.0%)	0.061[c]
Diabetes mellitus	27 (11.7%)	18 (11.4%)	9 (12.3%)	0.837[c]	4 (9.1%)	4 (26.7%)	1 (7.1%)	0.199[d]
Hypercholesterolemia	74 (32.0%)	57 (36.1%)	17 (23.3%)	0.053[c]	14 (31.8%)	2 (13.3%)	1 (7.1%)	0.098[d]
Atrial fibrillation	15 (6.5%)	10 (6.3%)	5 (6.8%)	0.881[c]	3 (6.8%)	1 (6.7%)	1 (7.1%)	1.000[d]
Previous myocardial infarction	36 (15.6%)	30 (19.0%)	6 (8.2%)	**0.036**[c]	6 (13.6%)	0 (0%)	0 (0%)	0.116[d]
Previous TIA	14 (6.1%)	13 (8.2%)	1 (1.4%)	0.042[c]	1 (2.3%)	0 (0%)	0	1.000[d]
Previous Stroke	33 (14.3%)	18 (11.4%)	15 (20.5%)	0.064[c]	9 (20.5%)	4 (26.7%)	2 (14.3%)	0.715[d]
Smoking	59 (25.5%)	35 (22.2%)	24 (32.9%)	0.213[c]	13 (29.5%)	6 (40.0%)	5 (35.7%)	0.959[c]
mRS Baseline > 1	18 (7.2%)	8 (4.8%)	10 (12.0%)	**0.038**[c]	4 (8.3%)	3 (16.7%)	3 (17.6%)	0.458[d]

Abbreviations: IQ: interquartile range, TIA:transitory ischemic attack, mRS: modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale. If not specified otherwise numbers are shown as n and (%).
P-values calculated from: [a] Mann-Whitney test. [b] Kruskal-Wallis test. [c] Chi square test (asymptotic). [d] Chi square test (Monte Carlo simulated, 10000 samples).

Comparing the WUPS group with the KOS group, significant differences were observed in hypertension; (p=0.038) and previous myocardial infarction; (p=0.036) in favor of the KOS group compared to the WUPS group. The other, baseline variables were similar in both the WUPS and KOS group without exhibiting significant difference (Table 1).

KOS Versus all WUPS

NIHSS at admission was 3.0 (IQR 1.0-5.0) in the KOS group and 4.0 (IQR 2.0-7.0) in the WUPS group, (p=0.016). NIHSS at 24 hours was 0 (IQR 0.0-1.0) in the KOS group and 1.0 (IQR 0.0-2.0) in the WUPS group, (p=0.123). NIHSS at discharge was 0 (IQR 0.0-1.0) in both the KOS and WUPS group, (p=0.157). The difference in NIHSS between admission and 24 hours (Δ-NIHSS-24h): KOS versus WUPS, (p=0.152). The difference in NIHSS between admission and discharge (Δ-NIHSS-disc): KOS versus WUPS, (p=0.076).

KOS Versus Mismatch

NIHSS at admission was 3.0 (IQR 1.0-5.0) in the KOS group and 3.0 (IQR 2.0-5.8) in the mismatch group, (p=0.244). NIHSS at 24 hours was 0 (IQR 0.0-1.0) in both KOS and the mismatch group, (p=0.362). NIHSS at discharge was 0 (IQR 0.0-1.0) in the KOS group and 0 (IQR 0.0-0.8) in the mismatch WUPS group, (p=0.385). (Δ-NIHSS-24h): KOS versus mismatch, (p=0.027) in favor of the mismatch group. (Δ-NIHSS-disc): KOS versus mismatch, (p=0.072).

KOS Versus Partial Mismatch

NIHSS at admission was 3.0 (IQR 1.0-5.0) in the KOS group and 7.0 (IQR 3.0-8.0) in the partial mismatch group, (p=0.007). NIHSS at 24 hours was 0 (IQR 0.0-1.0) in the KOS group and 2.0 (IQR 0.0-5.0) in the partial mismatch group, (p=0.006). NIHSS at discharge was 0 (IQR 0.0-1.0) in the KOS group and 1.0 (IQR 0.0-4.0) in the partial mismatch group, (p=0.019). (Δ-NIHSS-24h): KOS versus partial mismatch, (p=0.420). (Δ- NIHSS-disc): KOS versus partial mismatch, (p=0.068).

KOS Versus Match

NIHSS at admission was 3.0 (IQR 1.0-5.0) in the KOS group and 4.0 (IQR 3.0-5.0) in the match group, (p=0.169). NIHSS at 24 hours was 0 (IQR 0.0-1.0) in the KOS group and 2.5 (IQR 0.0-4.0) in the match group, (p=0.003). NIHSS at discharge was 0 (IQR 0.0-1.0) in the KOS group and 1.0 (IQR 0.0-2.8) in the match group, (p=0.003). (Δ-NIHSS- 24h): KOS versus match, (p=0.198). (Δ-NIHSS-disc): KOS versus match, (p=0.514).

The mRS 0-1 was used to measure the primary outcome at 3 months for the KOS and WUPS group, showing 124 (78.5%) and 48 (65.8%) respectively, (P=0.039) in favor of the KOS group. However, when mRS 0-1 for the KOS group was compared to each of the WUPS subgroups, similar clinical outcome was seen without any significant difference. No ICH was seen in any of the treatment groups. One patient died during the admission due to severe infection in the WUPS group and excluded from the clinical analysis because of pre-stroke mRS of ≥ 2, while two patients died in the KOS group due to a lung disease and cardiac arrest, respectively (Table 2).

Table 2: Clinical Outcome for Patients with mRS at Baseline < 2

	NIHSS inclusion	NIHSS 24h	ΔNIHSS incl to 24h	NIHSS 7 days/ discharge	ΔNIHSS incl to disch	mRS 0-1 (3 months)	Mortality (3 month)	ICH
All KOS and WUPS (n=231)	3.0 (2.0-5.0)	0.0 (0.0-1.0)	-2.0 (-4.0; -1.0)	0.0 (0.0-1.0)	-2.0 (-4.0; -1.0)	172 (74.5%)	2 (0.9%)	0.0 (0.0%)
All KOS (n=158)	3.0 (1.0-5.0)	0.0 (0.0-1.0)	-2.0 (-4.0; -1.0)	0.0 (0.0-1.0)	-2.0 (-4.0; -1.0)	124 (78.5%)	2 (1.3%)	0.0 (0.0%)
All WUPS (n=73)	4.0 (2.0-7.0)	1.0 (0.0-2.0)	-3.0 (-4.0; -1.0)	0.0 (0.0-1.0)	-3.0 (-5.0; -1.0)	48 (65.8%)	0 (0.0%)	0.0 (0.0%)
P	**0.016**[a]	0.123[a]	0.152[a]	0.157[a]	0.076[a]	**0.039**[b]	0.566[c]	NA
All KOS (n=158)	3.0 (1.0-5.0)	0.0 (0.0-1.0)	-2.0 (-4.0; -1.0)	0.0 (0.0-1.0)	-2.0 (-4.0; -1.0)	124 (78.5%)	2 (1.3%)	0.0 (0.0%)
MRI DWI/FLAIR Mismatch (n=44)	3.0 (2.0-5.8)	0.0 (0.0-1.0)	-3.0 (-5.0; -1.3)	0.0 (0.0-0.8)	-3.0 (-5.0; -2.0)	29 (66.0%)	0 (0%)	0 (0%)
P	0.244[a]	0.362[a]	**0.027**[a]	0.385[a]	0.072[a]	0.085[b]	1.000[c]	NA
All KOS (n=158)	3.0 (1.0-5.0)	0.0 (0.0-1.0)	-2.0 (-4.0; -1.0)	0.0 (0.0-1.0)	-2.0 (-4.0; -1.0)	124 (78.5%)	2 (1.3%)	0.0 (0.0%)
MRI DWI/FLAIR Partial Mismatch (n=15)	7.0 (3.0-8.0)	2.0 (0.0-5.0)	-3.0 (-6.0; -1.0)	1.0 (0.0-4.0)	-3.0 (-7.0; -2.0)	11 (73.3%)	0 (0%)	0 (0%)
P	**0.007**[a]	**0.006**[a]	0.420[a]	**0.019**[a]	0.068[a]	0.645[b]	1.000[c]	NA
All KOS (n=158)	3.0 (1.0-5.0)	0.0 (0.0-1.0)	-2.0 (-4.0; -1.0)	0.0 (0.0-1.0)	-2.0 (-4.0; -1.0)	124 (78.5%)	2 (1.3%)	0.0 (0.0%)
MRI DWI/FLAIR Match (n=14)	4.0 (3.0-5.0)	2.5 (0.0-4.0)	-1.0 (-3.0; 0.0)	1.0 (0.0-2.8)	-2.5 (-3.3; -0.8)	8 (57.1%)	0 (0%)	0 (0)
P	0.169[a]	**0.003**[a]	0.198[a]	**0.003**[a]	0.514[a]	0.070[b]	1.000[c]	NA

Abbreviations: NIHSS National Institutes of Health Stroke Scale, mRS modified Rankin Scale, ICH Intracranial Hemorrhage. Statistics given as median (interquartile range, IQR) or count (percentage). P-values calculated from: a Mann-Whitney test. b Chi square test (asymptotic). c Chi square test (exact).

Discussion

Radiological reassessment of all the WUPS patients included in this study showed that only (60%) (n=44) of the WUPS patients treated had a traditional MRI mismatch, implying that (40%) (n=29) of WUPS patients were treated with thrombolysis even though there was already a presentation of an emerging FLAIR lesion (partial mismatch) (n=15, 21%) or complete FLAIR lesion (match) (n=14, 19%) (Table 2).

In this study, WUPS patients with MRI DWI/FLAIR mismatch, partial match and match were each separately compared to the included KOS patients (n=158). Our study confirmed that the clinical outcome and safety profile of WUPS patients treated with thrombolysis guided by traditional MRI DWI/FLAIR mismatch criteria is non-inferior to the KOS patients, which is in line with existing studies [15-18].

MRI DWI/FLAIR is considered to indicate the stroke onset of less than 4–5 hours without visualizing penumbral tissue in the absence of PMI which is a clear limitation [21]. Even though the MRI DWI/FLAIR concept has shortcomings, it is still considered the radiological modality of choice in selecting WUPS patients for reperfusion therapy. In the TWIST trial, selection of the WUPS patients eligible for thrombolysis were experimented with non-contrast CT, showing no increase in ICH events and neither better functional outcome in the treatment group, encouraging more studies of other imaging modalities [22]. Extended criteria for CT perfusion have been used for selection of WUPS patients but showing low sensitivity in posterior strokes and might exclude lacunar stroke syndromes [11].

Recent studies have suggested that by selecting WUPS patients eligible for IVT treatment based on a traditional MRI (DWI/FLAIR) mismatch concept, WUPS patients who might profit are excluded [13]. At our center, a reassessment of MRI examinations showed that the traditional mismatch concept was extended in clinical praxis by also treating WUPS patients with partial mismatch or even match, showing that some patients with partial mismatch might benefit from IVT treatment without any events of ICH, but the result was not significant [14].

In this current study 40 % (n=29) of the WUPS patients treated with IVT, did not have a traditional MRI DWI/FLAIR mismatch. These patients were treated with IVT by our neurologists, even though the MRI DWI/FLAIR mismatch criteria was not fulfilled, based on a clear clinical core mismatch, meaning that the patients clinically presented neurological deficits on the time of treatment without any visible ischemic lesions or considerably minor ischemic lesions on the DWI series not corresponding in size to the larger presented clinical symptoms [9,21].

In this current study, the mismatch group showed an equal clinical improvement with NIHSS at 24h and at discharge when compared with the KOS group. This study was unable to show an equal improvement in NIHSS at 24h and at discharge in the partial mismatch group compared to the KOS group. However, the stroke burden in the partial mismatch group was significantly larger at admission compared to all the other groups, which probably influenced the reduced degree of improvement in NIHSS at 24h and at discharge in the partial mismatch group. The match group showed the poorest clinical outcome even though the NIHSS at admission was similar to the KOS group.

Investigating the neurological improvement with (Δ-NIHSS-24h) and (Δ-NIHSS-disc), none of the WUPS subgroups showed inferiority of neurological improvement compared to the KOS group, surprisingly neither did the match group. However, these findings should be interpreted with caution due to a small sample size in the WUPS group, which also is an obvious limitation of this study.

This study shows that WUPS patients with partial mismatch having a significantly larger stroke burden at admission still exhibit a non-inferior neurological improvement with (Δ-NIHSS-24h) and (Δ-NIHSS-disc) compared to the KOS group. Suggesting comparable clinical effect of WUPS group with the KOS group and indicating that not an insignificant number of WUPS patients presenting a partial mismatch with symptom onset beyond 4.5 hours may profit from IVT treatment as shown in the trials investigating the extended time window [4,23].

ICH was not observed in any of the included patients. Due to a severe infection one patient died during the admission in the WUPS group, while two patients died in the KOS group within a month post-stroke due to lung disease in one patient and cardiac arrest in the second patient.

Our study has several limitations. Primarily, a low number of WUPS patients included in this study which makes it rather challenging to show clinical coherence. Secondly, the included patients have a relatively minor stroke burden presenting a low NIHSS at admission and making it difficult to emphasize clinical effect, because stroke patients with a minor stroke burden have a not negligible tendency of obtaining a good functional outcome spontaneously without any reperfusion therapy [24]. Another limitation is the inclusion of patients treated in NOR-TEST as they were treated with either Alteplase or Tenecteplase. WUPS patients treated in NOR- TEST did not show any clinical difference, why the inclusion of these patients in our study was perceived eligible [25].

In conclusion, the MRI mismatch concept was extended in clinical praxis at our center by allowing thrombolysis in patients without FLAIR negativity. Additionally, it is acknowledged that IVT treatment in selected WUPS patients with a partial mismatch is comparable and non- inferior to IVT treatment in KOS patients, suggesting that traditional MRI mismatch concept may exclude patients systematically from IVT treatment [12-14]. Further clinical and radiological studies are encouraged to improve the modified MRI DWI/FLAIR concept for selection of WUPS patients for IVT beyond the 4.5 hours after symptom onset.

Statement of Ethics

This study was approved by the Regional Committee for Medical and Health Research Ethics, the Norwegian Centre for Research Data and the local hospital authorities. WUPS patients treated with IVT from NOR-TEST trial and consecutively thereafter along with IVT treated KOS patients at Stavanger University Hospital were included in this study. The need for informed consent was waived by the Regional Committee for Medical and Health Research Ethics, the Norwegian Centre for Research Data and the local hospital authorities.

Conflict of Interest Statement

The author declares that there is no conflict of interest.

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Author Contributions

The author has completely contributed to this manuscript. The author has approved the final version of the manuscript.

Data Availability Statement

The data used in this study can be accessed on request.

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