







ORIGINAL RESEARCH

Thrombolytic Treatment in Wake-Up Stroke: A Propensity Score–Matched Analysis of Treatment Effectiveness in the Norwegian Stroke Registry

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BACKGROUND: Previous clinical trials found improved outcome of thrombolytic treatment in patients with ischemic wake-up stroke (WUS) selected by advanced imaging techniques. The authors assessed the effectiveness of thrombolytic treatment in patients with WUS in a nationwide stroke registry.

METHODS AND RESULTS: Using propensity score matching, the authors assessed the effectiveness and safety of thrombolytic treatment versus no thrombolytic treatment in 726 patients (363 matched pairs) with WUS in the Norwegian Stroke Registry in 2014 to 2019. Thrombolytic treatment in WUS versus known-onset stroke was compared in 730 patients (365 matched pairs). Functional outcomes were assessed by the modified Rankin Scale (mRS) at 3 months. A significant benefit of thrombolytic treatment in WUS was seen in ordinal analysis (odds ratio [OR], 1.48 [95% CI, 1.15–1.91]; $P=0.003$) and for mRS 0 to 2 (OR, 1.81 [95% CI, 1.29–2.52]; $P=0.001$) but not for mRS 0 or 1 (OR, 1.32 [95% CI, 1.00–1.74]; $P=0.050$). The proportion of patients with mRS 0 or 1 was lower in patients with WUS who underwent thrombolysis versus those with known-onset stroke (50.4% versus 59.5%; OR, 0.69 [95% CI, 0.52–0.93]; $P=0.013$), while outcomes were similar between groups for mRS 0 to 2 and ordinal analysis. Symptomatic intracranial hemorrhage after thrombolytic treatment occurred in 4.4% of patients with WUS and 3.9% of patients with known-onset stroke (OR, 1.14 [95% CI, 0.54–2.41]; $P=0.726$).

CONCLUSIONS: Thrombolytic treatment in patients with WUS was associated with improved functional outcome compared with patients with no thrombolytic treatment and was not associated with increased rates of symptomatic intracranial hemorrhage compared with known-onset stroke. The results indicate that thrombolytic treatment is effective and safe in WUS in a real-life setting.

Key Words: cerebrovascular disease/stroke ■ epidemiology ■ ischemic stroke ■ thrombolytic treatment ■ wake-up stroke

Wake-up stroke (WUS) is known to occur in 1 in 5 ischemic strokes.¹ These patients have traditionally represented an unprivileged subgroup of patients with stroke as they have been considered ineligible for intravenous thrombolysis (IVT) based on uncertain time of symptom onset. Results from recent randomized controlled trials have shown benefit of

IVT in patients with WUS who have ischemic lesions on diffusion-weighted imaging and absence of visible hyperintense signal in the corresponding region on fluid-attenuated inversion recovery series on magnetic resonance imaging (magnetic resonance imaging/diffusion-weighted imaging/fluid-attenuated inversion recovery mismatch) or signs of salvageable tissue on

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This article was sent to Meng Lee, MD, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.032309>

For Sources of Funding and Disclosures, see page 8.

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CLINICAL PERSPECTIVE

What Is New?

- In this study, based on data from a nationwide stroke registry, intravenous thrombolysis for wake-up stroke was associated with improved functional outcome compared with no intravenous thrombolysis.
- The proportions of symptomatic intracranial hemorrhage after thrombolysis were similar in patients with wake-up stroke and those with known-onset stroke.

What Are the Clinical Implications?

- Our findings from clinical practice support the results from previous randomized trials showing that thrombolysis is beneficial and safe in patients with wake-up stroke.

Nonstandard Abbreviations and Acronyms

IVT	intravenous thrombolysis
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
sICH	symptomatic intracranial hemorrhage

computed tomography or magnetic resonance imaging perfusion imaging.^{2,3} Consequently, IVT with alteplase in patients with magnetic resonance imaging/diffusion-weighted imaging/fluid-attenuated inversion recovery mismatch was recommended in the American 2018 and 2019 Ischemic Stroke Clinical Practice Guidelines, and, in 2021, European guidelines recommended IVT in WUS with either diffusion-weighted imaging/fluid-attenuated inversion recovery mismatch or presence of salvageable tissue on magnetic resonance imaging or computed tomography perfusion imaging.^{4,5}

Results from clinical trials with strictly controlled settings may differ from those obtained in clinical practice. The aim of the present study was to assess effectiveness and safety of IVT in patients with WUS in a real-world clinical setting using data from a high-quality nationwide stroke registry.

MATERIALS

Access to data from the Norwegian Stroke Registry can be obtained by application to Helsedata (<https://helsedata.no>).

A total of 44 439 ischemic stroke cases (*International Classification of Diseases, Tenth Revision* [ICD-10]

code I63) were registered in the Norwegian Stroke Registry from 2014 through 2019. Of these, only patients who presented with either new-onset symptoms on awakening (WUS) or with known time of onset (known-onset stroke [KOS]) were included in the study. Patients with unknown time of onset other than on awakening (n=8055) or missing information about mode of onset (n=1) were excluded, as were those with recurrent stroke (n=8154) or missing information about this variable (n=177). We further excluded patients treated with thrombectomy (n=1178) or with missing information about thrombectomy (n=73). Information on functional outcome at 3 months after stroke onset was missing in 6452 patients, leaving 20 350 patients with first-ever ischemic stroke with either WUS or KOS to be included in the study (Figure 1). Of these, 4967 patients had WUS and 15 383 patients had KOS. The registry is a nationwide quality registry to which it is mandatory for all hospitals providing acute stroke care in Norway to report data on all patients hospitalized with acute stroke. The registry has excellent coverage and has been found to be adequately complete and correct to serve as a source of data for stroke research with a high reliability.^{6–8} The stroke diagnosis (ICD-10 code) is assigned by a treating physician, not a clinical coder, and data are registered manually via a web-based form by trained nurses and physicians. Details on diagnostic criteria used in the registry are described in Data S1. Information on date of death is collected from the Norwegian National Population Register.

Propensity score matching was used to define 2 matched samples generated for comparison of functional outcome at 3 months: one sample of 726 patients (363 matched pairs) for comparison of IVT and no IVT in patients with WUS, and one sample of 730 patients (365 matched pairs) for comparison of the effectiveness of IVT in patients with WUS and those with KOS (details are described in the Statistical Analysis section below).

Patient characteristics included were age, sex, prestroke modified Rankin Scale (mRS), presence of atrial fibrillation, prior myocardial infarction or transient ischemic attack, use of antihypertensive medication prior to admission, living arrangement, and National Institutes of Health Stroke Scale (NIHSS) on admission. In patients with WUS, the time of admission was defined on a scale from 0 to 23, where 1 represents admission from 01:00 to 01:59 a.m. and so on. The time from symptom onset to IVT was calculated for patients with KOS. Door-to-needle time was calculated as the time from admission to the start of IVT.

Hospitals were analyzed by caseload, defined by frequency of ischemic strokes admitted per year, and grouped into high (>300 cases per year), medium (100–300 cases per year), and low (<100 cases per year) volume centers.

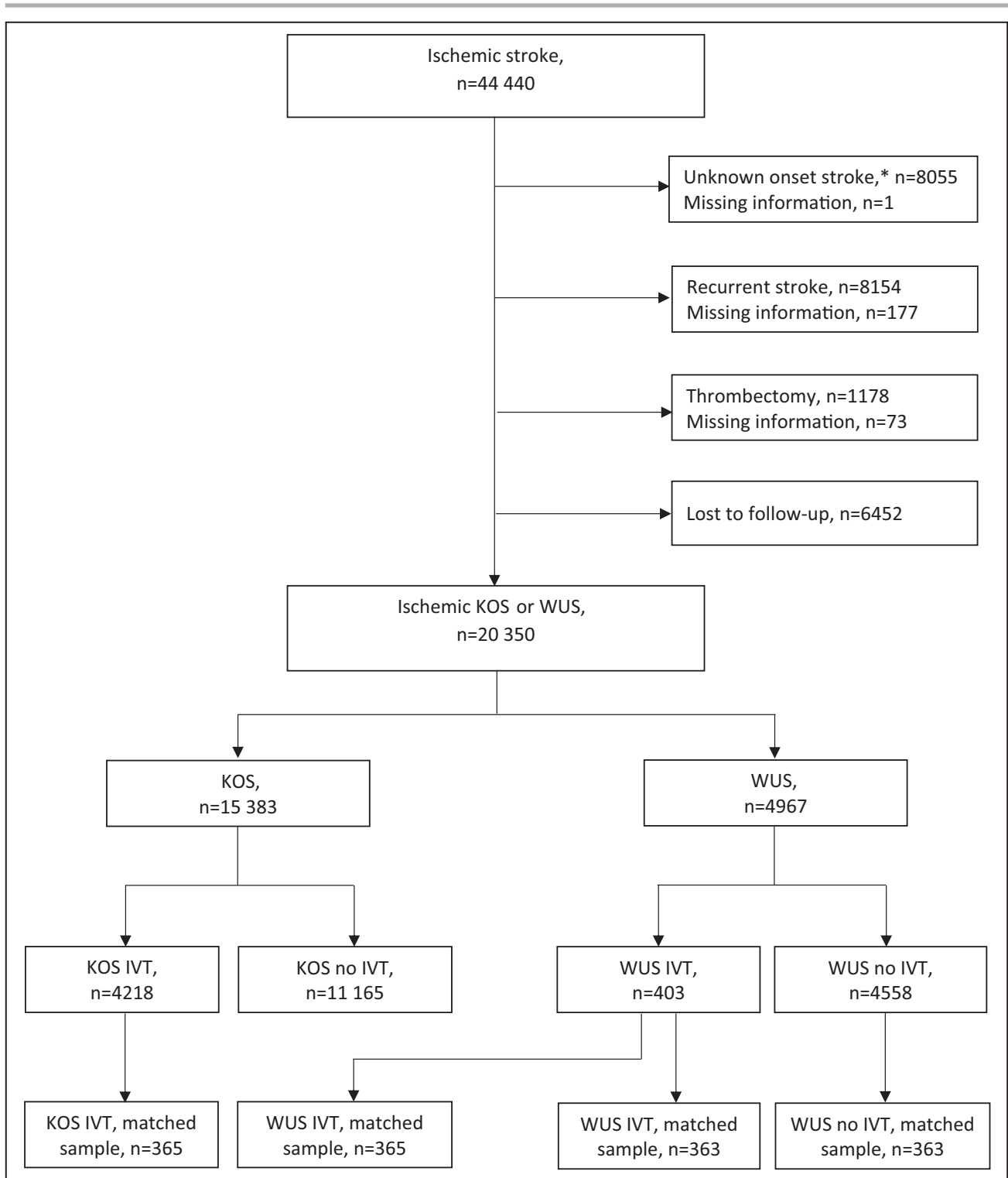


Figure 1. Flow chart of study participation.

*Unknown onset other than wake-up stroke (WUS). IVT indicates intravenous thrombolysis; and KOS, known-onset stroke.

Information on criteria used for selection of patients to IVT, such as imaging modality, is not available in the Norwegian Stroke Registry. Information about type or dose of thrombolytic agent used is only available for 2019 and was therefore not included in the study.

Outcome Measures

The effect of IVT was assessed by mRS at 3 months. The mRS ranges from 0 to 6, with a score of 0 representing no disability, 1 to 5 increasing degree of disability, and 6 death. The primary outcome was

Table 1. Baseline Characteristics in Matched and Unmatched Populations

	Unmatched samples		Matched samples		Unmatched samples		Matched samples	
	WUS, thrombolysis, n=403	WUS, no thrombolysis, n=4558	WUS, thrombolysis, n=363	WUS, no thrombolysis, n=363	WUS, thrombolysis, n=403	KOS, thrombolysis, n=4218	WUS, thrombolysis, n=365	KOS, thrombolysis, n=365
Age, y	70.3 (14.3)	73.1 (13.3)	69.9 (13.6)	70.0 (14.1)	70.3 (14.3)	72.3 (13.9)	70.0 (14.1)	70.5 (13.9)
Women	37.5	43.7	39.1	39.7	37.5	45.1	39.5	41.4
Atrial fibrillation	15.4	22.8	16.0	16.3	15.4	21.2	16.2	15.6
Prior myocardial infarction	13.0	13.6	14.1	13.8	13.0	12.8	13.7	14.0
Prior TIA	9.3	8.2	9.6	9.6	9.3	9.4	9.6	11.2
Diabetes	13.2	17.7	12.7	17.4	13.2	13.5	12.6	11.5
Use of medication								
Antihypertensive drugs	47.5	51.5	45.5	45.7	47.5	49.4	45.5	46.3
Platelet inhibitors	31.8	32.7	31.0	30.9	31.8	35.5	31.1	35.3
Oral anticoagulants	3.8	11.7	3.6	7.5	3.8	4.0	3.6	3.0
Living alone	27.1	36.5	29.8	27.3	27.1	31.1	27.1	27.1
Living in institution	2.5	3.0	1.4	0.8	2.5	4.0	1.4	1.6
Prestroke mRS score								
0	76.0	65.3	75.5	77.7	76.0	68.8	77.8	79.7
1	11.9	15.9	11.9	11.9	11.9	13.9	11.8	11.5
2	5.9	9.4	7.2	5.0	5.9	7.9	4.9	5.5
3	4.7	6.4	4.4	4.1	4.7	6.3	4.1	2.5
4	1.3	2.5	1.1	1.1	1.3	2.9	1.1	0.6
5	0.2	0.4	0.0	0.3	0.2	0.3	0.3	0.3
NIHSS on admission	5 (3–9)	2 (1–5)	4 (2–10)	5 (3–9)	5 (3–9)	5 (3–10)	5 (3–9)	5 (2–9)
Hour of admission*	8 (6–11)	12 (9–15)	9 (7–11)	8 (6–11)	8 (6–11)	14 (11–18)	8 (6–11)	14 (10–17)
Door-to-needle time, min	40 (26–60)	...	40 (26–60)	...	40 (26–60)	32 (22–49)	40 (26–60)	33 (22–50)
Hospital stroke volume								
>300 cases/y	51.1	39.5	56.2	54.3	51.1	42.1	54.5	53.2
100–300 cases/y	42.3	45.3	39.9	41.3	42.3	44.2	41.1	41.9
<100 cases/y	6.6	15.2	3.9	4.4	6.6	13.7	4.4	4.9

Age is presented as mean (SD) and prestroke modified Rankin Scale (mRS), National Institutes of Health Stroke Scale (NIHSS) on admission, hour of admission, and door-to-needle time as median (interquartile range). All other values are percentages. KOS indicates known-onset stroke; TIA, transient ischemic attack; and WUS, wake-up stroke.

*Values for hour of admission indicate times according to a 24-hour clock.

functional improvement in mRS by at least 1 point, assessed by ordinal logistic regression analysis. Secondary outcome measures were excellent functional outcome defined as an mRS score 0 or 1 and good functional outcome as an mRS 0 to 2.

Safety outcomes included death within 28 days and within 3 months after stroke, as well as symptomatic intracranial hemorrhage (sICH). The definition of sICH is a clinical deterioration corresponding to an increase of ≥ 4 points on the NIHSS and a radiologically confirmed intracranial hemorrhage within 36 hours of treatment, perceived to

be associated with the clinical deterioration. Information on intracranial hemorrhage after the index stroke was not available for patients who did not receive IVT.

The study was approved by the Regional Committee for Medical and Health Research Ethics as well as by the data protection officials at the Hospital of Southern Norway. The Norwegian Stroke Registry is a mandatory register, thus individual patient consent is not required. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Table 2. Effectiveness and Safety of Thrombolysis Versus No Thrombolysis in Propensity Score–Matched Samples of Patients With WUS

	Thrombolysis, n=363	No thrombolysis, n=363	OR (95% CI)	P value
Effectiveness outcomes				
Improved functional outcome			1.48 (1.15–1.91)	0.003
Excellent functional outcome	184 (50.7)	159 (43.8)	1.32 (1.00–1.74)	0.050
Good functional outcome	282 (77.7)	239 (65.8)	1.81 (1.29–2.52)	0.001
Safety outcomes				
Death within 28 d	19 (5.2)	27 (7.4)	0.69 (0.37–1.27)	0.230
Death within 3mo	24 (6.6)	36 (9.9)	0.64 (0.37–1.12)	0.117
Symptomatic intracranial hemorrhage	16 (4.4)

Results are presented as number (percentage). OR indicates odds ratio; and WUS, wake-up stroke. Improved functional outcome represents a shift in modified Rankin Scale (mRS) score in the direction of improved outcome. Excellent functional outcome was defined as an mRS score 0 or 1 after 3 months, and good functional outcome as an mRS score 0 to 2 after 3 months.

Statistical Analysis

We used propensity score matching to generate 2 comparable groups for assessing functional outcome at 3 months. Groups were generated within WUS to compare patients receiving IVT with those not treated, and within thrombolized cases to compare patients with WUS and those with KOS. To generate the matched groups we used the *ps-match2* command in Stata (StataCorp LLC) with 1:1 matching, using the nearest neighbor with caliper 0.2 and no replacement. The covariates used for matching were age, sex, prestroke mRS, NIHSS on admission, atrial fibrillation, prior myocardial infarction or transient ischemic attack, use of blood pressure medication, living arrangement, and hospital caseload. For WUS, 2-hour categories of hour of admission were included as a matching criterion for the comparison of IVT versus no IVT. Standardized difference was used to compare distribution of baseline characteristics between groups. Adequate

balance was defined as a standardized difference of ≤ 0.1 . The matching was adequate for all covariates, except for a small imbalance for the covariates prestroke mRS and time of admission in the analysis of IVT vs no IVT in WUS, where the standardized difference was 0.12 and 0.2, respectively, and for the analysis of thrombolized WUS versus thrombolized KOS, where the standardized difference for prestroke mRS was 0.11.

Baseline characteristics are presented for both matched and unmatched cases. Results are shown with total number of cases for all characteristics, average and SD for age, median and interquartile range (IQR) for NIHSS on admission, time of admission and door-to-needle time, and percentages for the remaining variables. The nonparametric Mann–Whitney *U* test was used to compare door-to-needle time in WUS and KOS due to nonnormal distribution.

Logistic regression analyses were used to compare functional outcome at 3 months between IVT and no

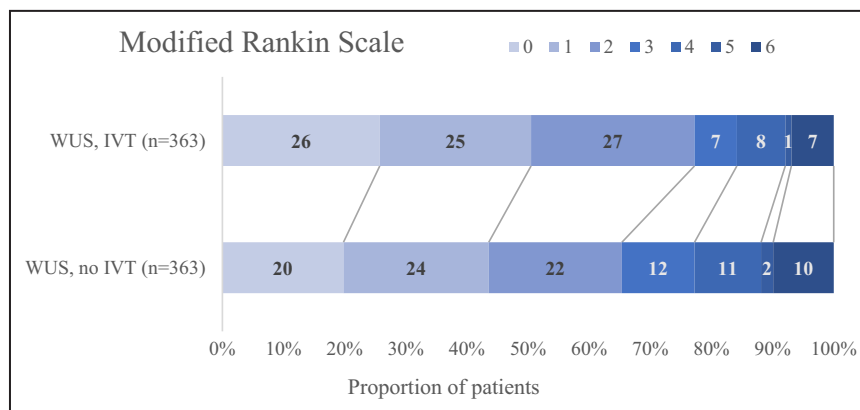


Figure 2. Distribution of modified Rankin Scale (mRS) scores at 3 months in patients with wake-up stroke (WUS) treated with or without intravenous thrombolysis (IVT; propensity score–matched sample). Percentages are not equal to 100% because of rounding.

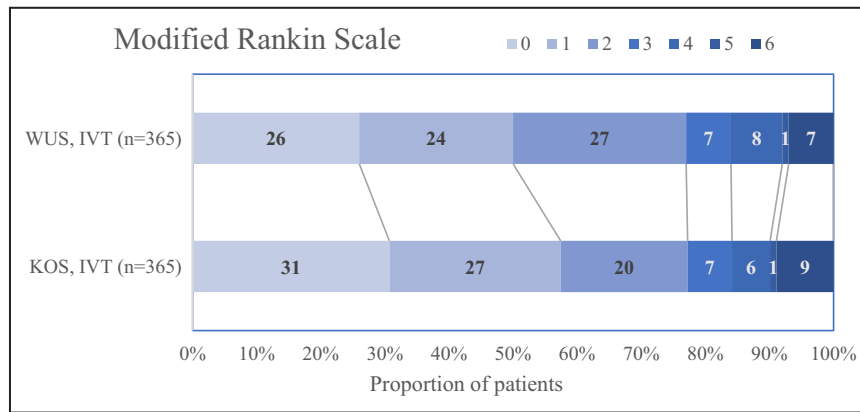


Figure 3. Distribution of modified Rankin Scale (mRS) at 3 months in patients with wake-up stroke (WUS) or known-onset stroke (KOS; propensity score-matched samples) who underwent intravenous thrombolysis (IVT). Percentages are not equal to 100% because of rounding.

IVT within WUS, as well as between patients who underwent thrombolysis with WUS and those with KOS. Ordinal logistic regression analyses were used to assess change across the full mRS scale (0–6) and results are presented as ORs with 95% CIs for a change in the direction of improved outcome on the mRS score. Standard logistic regression analyses were used for the dichotomized mRS outcomes. Analyses on propensity score-matched data were performed with robust standard error for clustered data to account for the matched nature of the data. Since the proportional odds assumption, assessed by use of the *omodel* command in Stata, was not met for ordinal regression analysis comparing thrombolysis in WUS with KOS (matched samples), we used generalized OR analysis for this comparison. One hundred bootstrapped samples were selected to estimate 95% CI for the generalized OR.

Sensitivity analyses were performed for the comparison of thrombolysed WUS and KOS where time

of admission to hospital was included in the selection of patients. For these analyses, only patients with WUS admitted before 12:00 p.m. and patients with KOS within 4.5 hours of symptom onset were included.

To test for hidden bias and unmeasured covariates, we performed sensitivity analyses for the effect outcomes by use of the Rosenbaum bounds approach (*rbounds* command in Stata).⁹

The safety of IVT was assessed as the OR for death within 3 months for both comparisons, and as the OR for sICH in thrombolysis of WUS versus KOS.

There was <2% missing data for all variables except for prestroke mRS, NIHSS on admission, and sICH in included patients (Table S1).

Statistical analyses were conducted using Stata/SE version 17.0 (StataCorp LLC). Generalized ORs with bootstrapped 95% CIs were calculated in SAS version 9.4 (SAS Institute Inc).

Table 3. Comparison of Effectiveness and Safety of Thrombolysis in Propensity Score-Matched Samples of Patients With WUS and Patients With KOS

	WUS, n=365	KOS, n=365	OR (95% CI)	P value
Effectiveness outcomes				
Improved functional outcome			0.85 (0.66–1.10)	0.215
Excellent functional outcome	184 (50.4)	217 (59.5)	0.69 (0.52–0.93)	0.013
Good functional outcome	283 (77.5)	276 (75.6)	1.11 (0.81–1.53)	0.507
Safety outcomes				
Death within 28 d	19 (5.2)	22 (6.0)	0.86 (0.45–1.62)	0.632
Death within 3mo	24 (6.6)	28 (7.7)	0.85 (0.48–1.51)	0.572
Symptomatic intracranial hemorrhage	16 (4.4)	14 (3.9)	1.14 (0.54–2.41)	0.726

Results are presented as number (percentage). OR indicates odds ratio; KOS, known-onset stroke; and WUS, wake-up stroke. Improved functional outcome represents a shift in modified Rankin Scale (mRS) score in the direction of improved outcome. Excellent functional outcome was defined as an mRS score 0 or 1 after 3 months, and good functional outcome as an mRS score 0 to 2 after 3 months.

RESULTS

The proportion of patients treated with IVT was 8.1% (403 of 4961) among patients with WUS, and 27.4% (4218 of 15375) among patients with KOS in the unmatched population. The proportion of patients with WUS receiving IVT in Norway increased from 5.0% in 2014 to 11.8% in 2019, equivalent to a >2-fold increase over time.

Patients with WUS who underwent thrombolysis were slightly younger, less frequently female, and living alone, and the proportion with atrial fibrillation and use of oral anticoagulant drugs was lower compared with both patients with WUS who did not undergo thrombolysis and patients with KOS who underwent thrombolysis (Table 1). The median door-to-needle time was generally longer in patients with WUS compared with those with KOS (40 minutes [IQR, 26–60 minutes] versus 33 minutes [IQR, 22–50 minutes]; $P < 0.001$).

Effectiveness of Thrombolytic Treatment

In ordinal analysis of matched samples, IVT was associated with better functional outcome at 3 months compared with no IVT (common OR, 1.48 [95% CI, 1.15–1.91]; $P = 0.003$; Table 2, Figure 2). The proportion who attained an excellent outcome was 50.7% in patients with WUS who received IVT versus 43.8% in patients who did not receive IVT (OR, 1.32 [95% CI, 1.00–1.74]; $P = 0.050$), while the corresponding figures for good functional outcome was 78% versus 66%, respectively (OR, 1.81 [95% CI, 1.29–2.52]; $P = 0.001$). Results from the unmatched samples revealed similar findings (Table S2).

Patients with WUS who underwent thrombolysis were less likely to have an excellent outcome compared with patients with KOS who underwent thrombolysis (OR, 0.69 [95% CI, 0.52–0.93]; $P = 0.013$), while no significant differences were found in ordinal analysis (OR, 0.85 [95% CI, 0.66–1.10]; $P = 0.215$) or for a good outcome (OR, 0.90 [95% CI, 0.77–1.05]; $P = 0.507$) (Figure 3). Sensitivity analyses including only patients with WUS admitted before 12:00 and patients with KOS treated within 4.5 hours of symptom onset ($n = 588$, 294 in each group) yielded similar results (Table S3). Analyses on the unmatched samples also produced similar results (Table S4).

Sensitivity analyses for the comparison of IVT vs no IVT in patients with WUS using the Rosenbaum bounding approach revealed $\Gamma = 1.2$ for the ordinal analysis, $\Gamma = 1.05$ for the excellent outcome analysis, and $\Gamma = 1.35$ for the good outcome analysis.

Safety of Thrombolytic Treatment

There was no significant difference in the proportion of patients who died within 28 days or within 3 months in patients with thrombolysed compared with non-thrombolysed WUS: 5.2% versus 7.4% (OR, 0.69 [CI,

0.37–1.27]; $P = 0.230$) and 6.6% versus 9.9% (OR, 0.64 [CI, 0.37–1.12]; $P = 0.117$), respectively.

Likewise, in patients with thrombolysed WUS and those with thrombolysed KOS, there was no significant difference in either the proportion of patients who died within 28 days (5.2% versus 6.0%; OR, 0.86 [CI, 0.45–1.62]; $P = 0.632$) or within 3 months (6.6% versus 7.7%; OR, 0.85 [95% CI, 0.48–1.51]; $P = 0.572$).

Symptomatic intracranial hemorrhage was seen in 4.4% of patients with WUS and 3.9% of patients with KOS (OR, 1.14 [CI, 0.54–2.41]; $P = 0.726$; Table 3). The corresponding numbers for the unmatched population was 4.6% and 4.3%, respectively (Table S4).

DISCUSSION

In this nationwide registry-based study, IVT in WUS was associated with improved functional outcome compared with no IVT. The benefit from IVT was smaller in patients with WUS than in those with KOS when measuring excellent functional outcome (mRS 0 or 1), but similar when assessing good functional outcome (mRS 0–2) and in ordinal analysis. There was no increased risk of death within 28 days or 3 months in patients with WUS who underwent thrombolysis. The risk of sICH was similar in patients with WUS and those with KOS.

Our results are in line with results from an individual participant meta-analysis of 4 previous trials of IVT in unknown-onset stroke (89% WUS), although the benefit of thrombolysis in our real-life data tended to be somewhat weaker. In the meta-analysis, 47% of patients who underwent thrombolysis and 39% of patients who did not undergo thrombolysis achieved an mRS score of 0 or 1 (OR, 1.49 [95% CI, 1.10–2.03]; $P = 0.01$),¹⁰ compared with 50.7% versus 44% in the current study (OR, 1.32 [95% CI, 1.00–1.74]; $P = 0.05$). A previous study from the Austrian Stroke Unit Registry found more frequent improvement in NIHSS from admission to discharge in patients with WUS who underwent thrombolysis compared with patients who did not undergo thrombolysis (38.7% versus 16.3%), while the proportion of patients who attained an mRS score of 0 to 1 after 3 months was lower in patients with WUS who underwent thrombolysis compared with those who did not (42.1% versus 48.5%).¹¹ After exclusion of endovascular treatment from the analysis, IVT was significantly associated with mRS score 0 to 1 at 3 months (adjusted OR, 1.3 [95% CI, 1.04–1.5]).¹¹

The current study supports the growing knowledge on the safety of IVT in WUS. There was no significant difference between the proportions of sICH in patients with WUS who underwent thrombolysis and those with KOS (4.4% versus 3.9%). Similar results were found in the Austrian Stroke Unit Registry (4.1% versus 4%).¹¹ Also, the rate of sICH in patients with WUS who

underwent thrombolysis found in our study is similar to those reported in randomized controlled trials.^{10,12} While the proportions of deaths at 3 months in patients who underwent thrombolysis were similar in the meta-analysis and in our study (6.6% and 6%, respectively), the proportion of deaths in patients who did not undergo thrombolysis was higher in our study than in the meta-analysis (9.9% versus 3%), probably reflecting the stricter selection criteria of the randomized controlled trials.

The strengths in our study include the large sample size, the nationwide real-life quality of the data, and the use of propensity score matching, which balances baseline characteristics between compared groups for the purpose of reducing bias due to confounding variables. A challenge, however, is the reduction in sample size, which this method causes. We have therefore presented analyses on the unmatched population samples for comparison, and found similar results in matched and unmatched cases.

There are several limitations to our study. The results of the sensitivity analyses to check for hidden bias or unmeasured covariates showed that an unmeasured covariate would need to increase the odds of treatment by more than a factor of 1.2 to explain away the effect of thrombolysis on improved functional outcome (ordinal analysis). The effect size needed to influence good functional outcome was 1.35 but for the excellent outcome the effect size needed was only 1.05. Information on imaging modality and criteria used for selection of patients to IVT, which is not available in the Norwegian Stroke Registry, may have influenced selection to treatment and the effect outcome. With the majority of the cases being from the time prior to guideline recommendations for IVT in WUS we primarily looked at off-label use, which may also contribute to selection bias. Furthermore, 20% of patients registered with ischemic stroke in the national registry were lost to follow-up at 3 months. Patients lost to follow-up were slightly older, more likely to live in a nursing home and to have a pre-stroke mRS score of 2 to 4, and less likely to receive IVT than those with available information at 3 months (Table S5). Another important limitation is the lack of information on sICH in the patients with WUS who did not undergo thrombolysis, making direct comparison of sICH risk between treatment groups of WUS impossible.

CONCLUSIONS

In conclusion, IVT for WUS in routine clinical practice was associated with improved functional outcome compared with no IVT. Furthermore, the proportions of sICH after IVT were similar in patients with WUS

and those with KOS; thus, the results from the current study indicate that IVT is safe and improves functional outcome in patients with WUS.

ARTICLE INFORMATION

Received October 24, 2023; accepted January 3, 2024.

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Acknowledgments

The authors would like to thank Hugo Pripp, Oslo Centre for Biostatistics & Epidemiology, and Tom Wilsgaard, UiT The Arctic University of Norway, for statistical support.

Sources of Funding

Søyland is supported by the South-Eastern Norway Regional Health Authority.

Disclosures

None.

Supplemental Material

Data S1.
Tables S1–S5.

REFERENCES

- Søyland MH, Tveiten A, Eltoft A, Øygarden H, Varmdal T, Indredavik B, Mathiesen EB. Wake-up stroke and unknown-onset stroke; occurrence and characteristics from the nationwide Norwegian Stroke Register. *Eur Stroke J*. 2022;7:143–150. doi: [10.1177/23969873221089800](https://doi.org/10.1177/23969873221089800)
- Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, Cheripelli B, Cho TH, Fazekas F, Fiehler J, et al. MRI-guided thrombolysis for stroke with unknown time of onset. *N Engl J Med*. 2018;379:611–622. doi: [10.1056/NEJMoA1804355](https://doi.org/10.1056/NEJMoA1804355)
- Roaldsen MB, Lindekleiv H, Mathiesen EB, Berge E. Recanalisation therapies for wake-up stroke. *Cochrane Database of Syst Rev*. 2018;8:CD010995. doi: [10.1002/14651858.CD010995.pub2](https://doi.org/10.1002/14651858.CD010995.pub2)
- Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50:e344–e418. doi: [10.1161/STR.0000000000000211](https://doi.org/10.1161/STR.0000000000000211)
- Berge E, Whiteley W, Audebert H, De Marchis GM, Fonseca AC, Padiglioni C, Pérez de la Ossa N, Strbian D, Tsvigoulis G, Turc G. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J*. 2021;6:I–LXII. doi: [10.1177/2396987321989865](https://doi.org/10.1177/2396987321989865)
- Varmdal T, Bakken IJ, Janszky I, Wethal T, Ellekjær H, Rohweder G, Fjærtøft H, Ebbing M, Bønaa KH. Comparison of the validity of stroke diagnoses in a medical quality register and an administrative health register. *Scand J Public Health*. 2016;44:143–149. doi: [10.1177/1403494815621641](https://doi.org/10.1177/1403494815621641)
- Varmdal T, Ellekjær H, Fjærtøft H, Indredavik B, Lydersen S, Bønaa KH. Inter-rater reliability of a national acute stroke register. *BMC Res Notes*. 2015;8:1–7. doi: [10.1186/s13104-015-1556-3](https://doi.org/10.1186/s13104-015-1556-3)
- Varmdal T, Løchen M-L, Wilsgaard T, Njølstad I, Nyrnes A, Grimsgaard S, Mathiesen EB. Data from national health registers as endpoints for the Tromsø study: correctness and completeness of

-
- stroke diagnoses. *Scand J Public Health*. 2023;51:1042–1049. doi: [10.1177/14034948211021191](https://doi.org/10.1177/14034948211021191)
9. Liu W, Kuramoto SJ, Stuart EA. An introduction to sensitivity analysis for unobserved confounding in nonexperimental prevention research. *Prev Sci*. 2013;14:570–580. doi: [10.1007/s11121-012-0339-5](https://doi.org/10.1007/s11121-012-0339-5)
 10. Thomalla G, Boutitie F, Ma H, Koga M, Ringleb P, Schwamm LH, Wu O, Bendszus M, Bladin CF, Campbell BC. Intravenous alteplase for stroke with unknown time of onset guided by advanced imaging: systematic review and meta-analysis of individual patient data. *Lancet*. 2020;396:1574–1584. doi: [10.1016/S0140-6736\(20\)32163-2](https://doi.org/10.1016/S0140-6736(20)32163-2)
 11. Krebs S, Posekany A, Ferrari J, Lang W, Sommer P, Gatteringer T, Boehme C, Sykora M, Collaborators ASUR. Intravenous thrombolysis in wake-up stroke: real-world data from the Austrian Stroke Unit Registry. *Eur J Neurol*. 2019;26:754–759. doi: [10.1111/ene.13884](https://doi.org/10.1111/ene.13884)
 12. Roaldsen MB, Eltoft A, Wilsgaard T, Christensen H, Engelter ST, Indredavik B, Jatužis D, Karelis G, Kõrv J, Lundström E. Safety and efficacy of tenecteplase in patients with wake-up stroke assessed by non-contrast CT (TWIST): a multicentre, open-label, randomised controlled trial. *Lancet Neurol*. 2023;22:117–126. doi: [10.1016/S1474-4422\(22\)00484-7](https://doi.org/10.1016/S1474-4422(22)00484-7)