Thrombolysis in acute ischemic stroke in patients with dementia

A Swedish registry study

OPEN

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ABSTRACT

Objective: To compare access to intravenous thrombolysis (IVT) for acute ischemic stroke (AIS) and its outcomes in patients with and without dementia.

Methods: This was a longitudinal cohort study of the Swedish dementia and stroke registries. Patients with preexisting dementia who had AIS from 2010 to 2014 (n = 1,356) were compared with matched patients without dementia (n = 6,755). We examined access to thrombolysis and its outcomes at 3 months (death, residency, and modified Rankin Scale [mRS] score). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with logistic and ordinal logistic regression.

Results: The median age at stroke onset was 83 years in both groups. IVT was administered to 94 (7.0%) patients with dementia and 639 (9.5%) patients without dementia. The OR of receiving IVT was 0.68 (95% CI 0.54–0.86) for patients with dementia. When the analysis was repeated exclusively among patients independent in everyday activities, dementia status was no longer significant (OR 0.79, 95% CI 0.60–1.06). However, differences persisted in patients ≤80 years of age (OR 0.58, 95% CI 0.36–0.94). In patients who received thrombolysis, the incidence of symptomatic intracerebral hemorrhage (sICH; 7.4% vs 7.3%) and death at 3 months (22.0% vs 18.8%) did not differ significantly between the 2 groups. However, mRS score and accommodation status were worse among patients with dementia after 3 months in adjusted analyses (both $p < 0.001$). Unfavorable outcomes with an mRS score of 5 to 6 were doubled in patients with dementia (56.1% vs 28.1%).

Conclusions: Younger patients with dementia and AIS are less likely to receive IVT. Among patients receiving thrombolysis, there are no differences in sICH or death, although patients with dementia have worse accommodation and functional outcomes at 3 months. ***Neurology*®** **2017;89:1860–1868**

GLOSSARY

ADL = activities of daily living; **AIS** = acute ischemic stroke; **ATC** = Anatomical Therapeutic Chemical; **CI** = confidence interval; **ICD-10** = *International Classification of Diseases, 10th revision*; **IVT** = intravenous thrombolysis; **MMSE** = Mini-Mental State Examination; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **Riksstroke** = Swedish national quality registry for acute vascular diseases of the brain; **RLS** = Reaction Level Scale; **sICH** = symptomatic intracranial hemorrhage; **SveDem** = Swedish Dementia Registry.

Dementia is not a contraindication for intravenous thrombolysis (IVT) in acute ischemic stroke (AIS), but most of the thrombolysis studies to date excluded or underrepresented octogenarians and nonagenarians,[1,2] and guidelines differ in their recommendations for IVT use in this population. According to the American Heart Association/American Stroke Association,

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patients with dementia may benefit from IVT; however, decisions should be made individually with premorbid functional level taken into account.[3] Alteplase is not indicated in patients >80 years of age according to the European Medicines Agency,[4] while it is recommended in selected patients according to European stroke guidelines.[5] Because of this inconsistency and fear of cerebral hemorrhage, physicians may adopt a more conservative approach in patients with dementia.[2,6] Indeed, patients with dementia had increased mortality and poorer functional outcomes after stroke regardless of the use of reperfusion therapy in some[7,8] but not other studies.[9,10] Patients with dementia are less likely to receive IVT,[8,10] even though increased incidence of symptomatic intracranial hemorrhage (sICH) has so far not been reported.[7,9,10]

There is a lack of recent data on use and outcomes of IVT in patients with dementia, and this subject has been identified as a high-priority research area.[3] Our aim is to analyze the use and outcomes of IVT for AIS in patients with preexisting dementia in a large national cohort to determine whether dementia status is associated with lower use or poorer outcomes after IVT.

METHODS

Quality registries and study population. We performed a longitudinal cohort study of patients diagnosed with dementia who subsequently had a first AIS. Patients with dementia were identified from Swedish Dementia Registry (SveDem), which has previously been described.[11,12] Registration occurs at the time of dementia diagnosis with information on dementia type, demographics, and living situation.

Occurrence of AIS was identified with Riksstroke, the Swedish national quality registry for acute vascular diseases of the brain, one of the world's largest stroke registries.[13] All hospitals admitting acute stroke patients participate, and coverage for ischemic stroke is >90%.[14] Information on the registries is available at svedem.se and riksstroke.org.

Data on medication therapy from 2005 were obtained from the Swedish Prescribed Drug Register, including all prescription medications dispensed at Swedish pharmacies, with coverage of ≈100%.[15] Comorbidities were collected from the Swedish National Inpatient Register, available from 1998 and coded according to the ICD-10, at present covering all in-hospital and specialist clinic diagnoses.[16]

Patients with a dementia diagnosis who subsequently had AIS were selected and matched by age (±3 years), sex, year of stroke, and geographic region with controls without dementia from Riksstroke. Controls without dementia were excluded if they ever had a SveDem registration, ever were diagnosed with dementia or confusional syndrome (ICD-10 code F00-F09 or G30-G32), or ever had taken antidementia medication (Anatomical Therapeutic Chemical [ATC] codes N06DX and N06DA, including donepezil, rivastigmine, galantamine, and memantine).

Of 58,154 patients registered in SveDem between May 2007 and December 2014, a total of 2,233 patients with dementia subsequently had AIS and were matched to 8,963 dementia-free controls from Riksstroke. The patient selection process is illustrated in the figure. Because of the changes in the IVT treatment window to 4.5 hours in 2009, data from 2010 to 2014 were used, and a study population of 1,356 AIS patients with dementia and 6,755 AIS controls without dementia was available for analyses.

Variables. From SveDem, we used information on dementia type, date, and cognitive evaluation with the Mini-Mental State Examination (MMSE).

From Riksstroke, we used data on stroke event, demographics, living arrangements, transport to the hospital, activation of stroke code (protocol for management of acute stroke), IVT treatment, symptom-to-needle time (time interval between the symptom onset and initiation of the IVT), follow-up, and death. Independence in activities of daily living (ADL) before and after stroke was defined as independence in mobility, dressing, and toileting. Urban and rural typology was defined for Swedish county councils ("landsting") on the basis of Organisation for Economic Co-operation and Development methodology.[17] We used 2 clinical assessment tools as proxies for stroke severity: level of consciousness at admission to the hospital, determined with Reaction Level Scale (RLS), in which patients with RLS score of 1 are defined as alert, those with RLS score of 2 to 3 are defined as lethargic, and those with RLS score of 4 to 8 are defined as unconscious, and the NIH Stroke Scale (NIHSS). sICH is defined in Riksstroke as clinical worsening with an increase of ≥4 NIHSS points in the presence of intracranial hemorrhage starting <36 hours after the start of thrombolysis (nonsymptomatic intracranial hemorrhage is not recorded). Modified Rankin Scale (mRS) is a scale measuring degree of disability. Because mRS is a standard assessment method in stroke research and is missing in the Riksstroke registry, mRS score was estimated by translation of 5 self-reported Riksstroke functional outcome variables. This previously described conversion method offers high precision but cannot differentiate between functional groups with an mRS score of 0 to 2.[18] Conversion was possible for mRS only after (and not before) stroke.

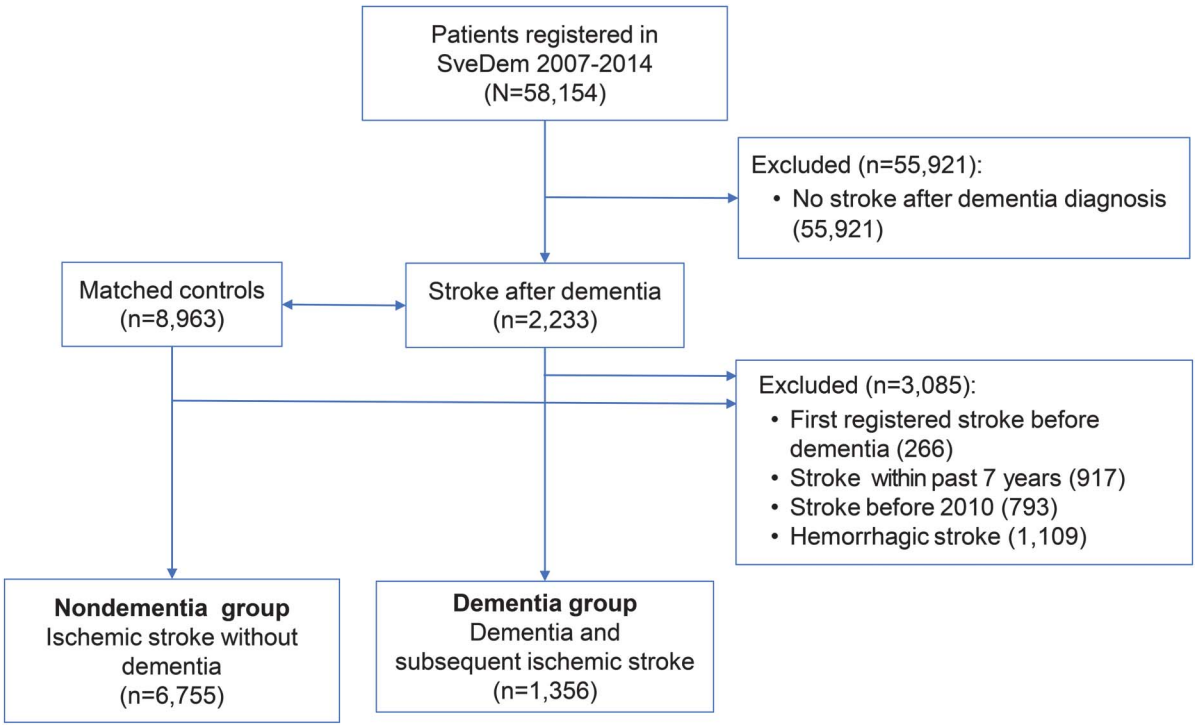
Number of medications was defined as the sum of all prescription drugs dispensed from pharmacies during the 3 months preceding the stroke, obtained from the Swedish Prescribed Drug Register, and was used as a proxy for comorbidity.[12]

Statistical analysis. For categorical variables, data are presented as number of cases and percentages. Continuous variables were summarized as mean ± SD or median (interquartile range). For calculating significant differences, the Student t test and Mann-Whitney U test were used for continuous and χ^2 or Fisher exact tests for categorical variables.

Multivariate logistic regression analyses were used to assess the relationship between dementia status and receiving IVT. We assessed different outcomes after IVT: using multivariate logistic regression for (1) death at 3 months, (2) nursing home placement at 3 months, and (3) mRS score of 4 or 5 (vs mRS score <4) at 3 months and using multivariate ordinal logistic regression for (4) mRS score at 3 months as an ordinal scale of step-wise increase in mRS score. For mRS score, we tested the proportional odds/parallel-lines assumption using the STATA command GOLOGIT2 with a gamma parameterization. No significant violations of the assumptions were found.

Initial regression models were adjusted for age and sex. Next, we tested contraindications to IVT, possible confounding living

Figure Patient selection process



We excluded patients with AIS registered in Riksstroke before dementia, patients who had a history of stroke in the last 7 years according to the National Inpatient Register, patients with stroke before the year 2010 because of incomplete outcome variables and changes in the IVT treatment window to 4.5 hours in 2009, and patients with hemorrhagic stroke. AIS = acute ischemic stroke; IVT = intravenous thrombolysis; Riksstroke = Swedish national quality registry for acute vascular diseases of the brain; SveDem = Swedish Dementia Registry.

arrangements, comorbidities, and medication, adding covariates in a stepwise manner. Covariates were chosen to reflect a burden of comorbidity, which might affect the decision to thrombolyse or, in the case of living situation, could affect time to hospital arrival and obtaining information. Individual drugs were subtracted from total number of medications if also used as separate confounders. We tested several interactions between comorbidities and medication. We tested all variables with $p \leq 0.25$ significance in the univariate models. Variables that did not reach the significance of $p < 0.05$ in a multivariate model, did not change the β coefficient by ≈20%, or did not improve the R^2 of the model were discarded. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) are presented. Post hoc analyses including NIHSS are also shown.

Post hoc propensity score–adjusted models were conducted. The propensity scores were obtained from multiple logistic regression for dementia status including the variables age, sex, smoking, number of medication, antiaggregants, antipsychotics, antidepressants, lipid-lowering agents, antihypertensives, atrial fibrillation, diabetes mellitus, hip fracture, ischemic heart disease, heart failure, renal failure, and liver failure (variables as shown in table 1).

Tests were 2 tailed with a value of $p < 0.05$ considered significant. The IBM Statistical Package for Social Sciences for Windows, Sciences Software version 23 (IBM Corp, Armonk, NY) and STATA version 14 (StataCorp, College Station, TX) were used.

Standard protocol approvals, registrations, and patient consents. This study complies with the Declaration of Helsinki and was approved by the regional ethics review board in Stockholm, Sweden (dnr 2015/743-31/4). Patients and relatives were informed of inclusion in the registries at the time of diagnosis and could decline participation or withdraw consent. Data were deidentified before analysis.

RESULTS

Characteristics of the study population. Of 8,111 patients with AIS, 1,356 patients had preexisting dementia and 6,755 patients did not have dementia registered. Because national Swedish stroke guidelines did not recommend IVT in patients >80 years of age until 2014 (except in particular cases after careful consideration),[19] we age-stratified the cohort (table 1).

In the dementia group, at the time of the registration in SveDem, median MMSE score was 21 (5), which is in line with previous SveDem studies.[12,20] Median time from dementia diagnosis to stroke was 546 days (705 days), and total days at risk were 894,439. Alzheimer dementia and mixed dementia were the most common dementia types (n = 628, 46.3%), and 311 patients (22.9%) had vascular dementia (results not presented).

Use of thrombolysis. Of all 8,111 patients, 733 (9.0%) received IVT, 94 (7.0%) patients with dementia and 639 (9.5%) patients without dementia. Patients with dementia were less often independent before stroke (52.8% vs 87.1%, $p < 0.001$). Patients who received IVT were more often independent than their

counterparts who did not receive IVT (90.5% ADL independence in IVT group vs 80.7% in non-IVT group, $p < 0.001$; results not presented).

Patients with dementia treated with IVT were older (median age 83 vs 81 years, $p = 0.016$) and received more medications (median 6 vs 4, $p < 0.001$) than IVT-treated controls. Apart from ischemic heart disease, there were no other important differences in comorbidities. Other characteristics are shown in table 2. There were no differences between the 2 thrombolysis

Table 1 Demographics, medications, and comorbidities before stroke in patients with AIS with and without dementia, stratified by age

	Patients ≤80 y of age (n = 2841)			Patients>80 y of age (n = 5270)		
	With dementia (n = 436)	Without dementia (n = 2,405)	p Value	With dementia (n = 920)	Without dementia (n = 4,350)	p Value[a]
Age at first stroke, median (IQR), y	77 (6)	76 (7)	0.190	86 (6)	86 (6)	0.871
Female sex, n (%)	197 (45.2)	1,124 (46.7)	0.550	567 (61.6)	2,714 (62.4)	0.666
Nursing home placement, n (%)	96 (22.3)	63 (2.6)	<0.001	327 (35.8)	441 (10.2)	<0.001
Lives alone (not in a nursing home), n (%)[a]	119 (27.7)	896 (37.5)	<0.001	327 (35.9)	2,485 (57.4)	<0.001
ADL independent, n (%)[a]	262 (62.7)	2,237 (93.7)	<0.001	412 (48.0)	3,548 (83.4)	<0.001
Smoking, n (%)[a]	29 (7.3)	320 (14.4)	0.001	25 (3.0)	194 (4.9)	0.018
Medications, n, median (IQR)	6 (5)	4 (5)	<0.001	6 (5)	5 (5)	<0.001
Antiaggregants, n (%)	181 (41.5)	732 (30.4)	<0.001	460 (50.0)	1,768 (40.6)	<0.001
Antipsychotics, n (%)	30 (6.9)	32 (1.3)	<0.001	71 (7.7)	62 (1.4)	<0.001
Antidepressants, n (%)	154 (35.3)	214 (8.9)	<0.001	272 (29.6)	509 (11.7)	<0.001
Antihypertensives, n (%)	272 (62.4)	1,460 (60.7)	0.509	620 (67.4)	3,080 (70.8)	0.040
Antidiabetics, n (%)	90 (20.6)	367 (15.3)	0.005	94 (10.2)	483 (11.1)	0.434
Statins, n (%)	107 (24.5)	543 (22.6)	0.369	139 (15.1)	797 (18.3)	0.021
AF, n (%)	108 (24.8)	449 (18.7)	0.003	345 (37.5)	1,425 (32.8)	0.006
Warfarin in patients with AF, n (%)	24 (22.2)	101 (22.5)	0.951	29 (8.4)	241 (16.9)	<0.001
Diabetes mellitus, n (%)	108 (24.8)	445 (18.5)	0.002	165 (17.9)	729 (16.8)	0.388
Hypertension, n (%)	222 (50.9)	1,079 (44.9)	0.020	552 (60.0)	2,402 (55.2)	0.008
Femur fracture, n (%)	41 (9.4)	90 (3.7)	<0.001	133 (14.5)	465 (10.7)	0.001
Any hemorrhage, n (%)	61 (14.0)	210 (8.7)	0.001	126 (13.7)	479 (11.0)	0.020
Ischemic heart disease, n (%)	105 (24.1)	230 (22.0)	0.346	267 (29.0)	1,312 (30.2)	0.493
Heart failure, n (%)	69 (15.8)	277 (11.5)	0.011	207 (22.5)	1,001 (23.0)	0.737
Renal disease, n (%)	43 (9.9)	157 (6.5)	0.012	86 (9.3)	448 (10.3)	0.385
Liver disease, n (%)	6 (1.4)	43 (1.8)	0.543	15 (1.6)	41 (0.9)	0.064
Stroke code, n (%)[b]	94 (22.1)	655 (27.7)	0.016	244 (27.1)	1,080 (25.3)	0.242
Arrival by ambulance, n (%)[b]	294 (82.1)	1,314 (68.3)	<0.001	710 (92.3)	2,992 (81.7)	<0.001
Unconscious at arrival, n (%)[b]	12 (2.8)	61 (2.6)	0.778	40 (4.4)	177 (4.1)	0.671
Unconscious or lethargic (RLS>1), n (%)[b]	78 (18.2)	221 (9.3)	<0.001	215 (23.8)	788 (18.3)	<0.001
Thrombolysis, n (%)[b]	29 (6.7)	282 (11.8)	0.002	65 (7.1)	357 (8.2)	0.255

Abbreviations: ADL = activities of daily living; AF = atrial fibrillation; AIS = acute ischemic stroke; IQR = interquartile range; IVT = intravenous thrombolysis; RLS = Reaction Level Scale.

Antiaggregants (acetylsalicylic acid and clopidogrel) = Anatomical Therapeutic Chemical (ATC) codes B01AC06 and B01AC04; antipsychotics = ATC code N05A; antidepressants = ATC code N06A; antihypertensives = ATC codes CO2-CO9D; drugs in diabetes mellitus = ATC code A10; statins = ATC code C10AA; and warfarin = ATC code B01AA03.

Number of medications refers to all prescribed medication; unconscious at arrival = RLS score of 4 to 8; unconscious or lethargic = RLS >1; symptom-to-needle time = time between the onset of stroke symptoms and initiation of thrombolysis; and IVT = IVT with recombinant tissue plasminogen activator. In variables for which number and percent are reported, *p* values were obtained by χ^2, whereas in variables for which median and IQR are reported, *p* values were obtained by Mann-Whitney test.

Arrival by ambulance: data are presented for years 2011 through 2014.

[a] The *p* values for differences between people with and without dementia.

[b] Variables with missing data, n (%): nursing home placement, 42 (0.5); lives alone (not in a nursing home), 51 (0.6); independent (in mobility, dressing, and toilet visits), 192 (2.4); smoking, 712 (8.8); stroke code, 144 (1.8); arrival by ambulance, 654 (8.9) (for years 2011–2014); unconscious at arrival and unconscious or lethargic, 95 (1.2); and thrombolysis, 37 (0.5).

Table 2 Demographics, medications, and comorbidities before stroke in patients with AIS treated with IVT

Demographics, medications, and comorbidities before stroke	Patients with dementia (n = 94)	Patients without dementia (n = 639)	*p* Value
Age at first stroke, median (IQR), y	83 (6)	81 (9)	0.016
Female sex, n (%)	54 (57.4)	353 (55.2)	0.688
Nursing home placement, n (%)	29 (30.9)	30 (4.7)	<0.001
Lives alone (not in a nursing home), n (%)[a]	24 (25.5)	226 (35.5)	0.058
ADL independent, n (%)[a]	60 (65.2)	597 (94.0)	<0.001
Smoking, n (%)[a]	8 (9.0)	43 (7.3)	0.577
Medications, median (IQR), n	6 (4)	4 (4)	0.001
Antiaggregants, n (%)	52 (55.3)	259 (40.5)	0.007
Antipsychotics, n (%)	3 (3.2)	8 (1.3)	0.157[b]
Antidepressants, n (%)	32 (34.0)	68 (10.6)	<0.001
Antihypertensives, n (%)	63 (67.0)	419 (65.6)	0.782
Antidiabetics, n (%)	13 (13.8)	74 (11.6)	0.529
Statins, n (%)	21 (22.3)	143 (22.4)	0.993
AF, n (%)	31 (33.0)	168 (26.3)	0.173
Warfarin in patients with AF, n (%)	1 (3.2)	17 (10.1)	0.318[b]
Diabetes mellitus, n (%)	15 (16.0)	98 (15.3)	0.876
Hypertension, n (%)	55 (58.5)	316 (49.5)	0.101
Femur fracture, n (%)	5 (5.3)	36 (5.6)	0.901
Any hemorrhage, n (%)	8 (8.5)	54 (8.5)	0.984
Ischemic heart disease, n (%)	36 (38.3)	175 (27.4)	0.029
Heart failure, n (%)	21 (22.3)	104 (16.3)	0.144
Renal disease, n (%)	4 (4.3)	47 (7.4)	0.27
Liver disease, n (%)	3 (3.2)	8 (1.3)	0.157[b]
Stroke code, n (%)[a]	92 (97.9)	615 (97.3)	0.75
Arrival by ambulance, n (%)[a]	86 (100)	547 (94.6)	0.028
Unconscious at arrival (RLS 4–8), n (%)[a]	1 (1.1)	9 (1.4)	1.0b
Unconscious or lethargic (RLS>1), n (%)[a]	20 (21.3)	107 (16.9)	0.291
Symptom-to-needle time, n (%)[a]			0.964[b]
≤3 h	70 (80.5)	471 (80.8)	
>3–≤4.5 h	15 (17.2)	100 (17.2)	
>4.5 h	2 (2.3)	12 (2.1)	
NIHSS points before IVT, mean ± SD[a]	12.0 ± 6.4	10.0 ± 6.4	0.009
NIHSS points after IVT, mean ± SD[a]	7.3 ± 6.1	6.3 ± 7.4	0.284
NIHSS change, mean ± SD[a]	−4.2 ± 4.1	−3.4 ± 6.0	0.305
sICH[a]	7 (7.4)	46 (7.3)	0.960
In-hospital death	12 (12.8)	85 (13.3)	0.886
mRS score at 3 mo[a]			
0–2	4 (4.9)	189 (33.2)	<0.001

Continued

groups in the geographic county of origin or urban and rural groups (results not presented).

Symptom-to-needle time did not differ between patients with and those without dementia (table 2). Patients with dementia had a higher NIHSS score before IVT (12 vs 10 points, $p = 0.009$). This difference in NIHSS score was no longer present in the evaluation after IVT treatment ($p = 0.284$); however, the proportion of missing data was 29.3%. There were no differences in sICH, in-hospital death, and death at the 3-month follow-up (table 2), but 56.1% of patients with dementia (compared to 18.8% of controls) presented with an mRS score of 5 or 6 at 3 months. Thrombectomy was performed in 3 (3.2%) patients with dementia and 37 (5.8%) patients without dementia receiving IVT ($p = 0.307$) (results not presented).

ORs for patients with dementia receiving IVT are presented in table 3. In the fully adjusted covariate model (model 2) and in the post hoc propensity score–adjusted model (model 3), dementia was associated with lower odds of receiving thrombolysis. However, when the analysis was repeated exclusively among patients who were ADL independent before stroke, the difference between patients with and without dementia was no longer significant for the whole cohort (OR 0.79, 95% CI 0.60–1.06), although differences persisted for patients ≤80 years of age (table 3).

Thrombolysis outcomes. In the fully adjusted model, there were no differences in OR for death at the 3-month follow-up between patients with and those without dementia who received IVT. Functional outcome at 3 months, assessed with mRS, was worse among patients with dementia. In the fully adjusted covariate model, the OR for a higher mRS score in dementia was 3.65 (95% CI 2.06–6.45). In patients with dementia, OR for new nursing home placement was tripled (table 4).

DISCUSSION

In this large, nationwide, longitudinal study, we observed the following key findings: (1) patients with dementia were less likely to receive IVT, but these differences disappeared in analyses focusing on previously independent patients, persisting only in patients ≤80 years of age; (2) the frequencies of sICH and in-hospital and 3-month mortality after IVT were similar in patients with dementia and controls; and (3) among patients who received IVT, dementia was associated with greater disability and new nursing home placement.

Before stroke, patients with preexisting dementia had more comorbidities and were more ADL dependent, which is in line with previous studies from SveDem.[21] The proportion of IVT-treated patients (9.5% for those without dementia and 7.0% for

Table 2 Continued

Demographics, medications, and comorbidities before stroke	Patients with dementia (n = 94)	Patients without dementia (n = 639)	p Value
3	20 (24.4)	155 (27.2)	0.592
4	12 (14.6)	66 (11.6)	0.425
5	28 (34.1)	53 (9.3)	<0.001
(Dead) 6	18 (22.0)	107 (18.8)	0.494
New nursing home placement, n (%)[a]	23 (35.9)	64 (13.6)	<0.001

Abbreviations: ADL = activities of daily living; AF = Atrial fibrillation; AIS = acute ischemic stroke; IQR = interquartile range; IVT = intravenous thrombolysis; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; RLS = Reaction Level Scale; sICH = symptomatic intracranial hemorrhage.
Symptom-to-needle time is time between the onset of stroke symptoms and initiation of thrombolysis. IVT is with recombinant tissue plasminogen activator.
In variables for which number and percent are reported, *p* values were obtained by χ^2. In variables for which median with IQR are reported, *p* values were obtained by the Mann-Whitney test. In variables for mean and SD are reported, *p* values were obtained by Student *t* test.
Arrival by ambulance: data are presented for years 2011 through 2014. New nursing home placement: for survivors of hospitalization (82 patients with dementia and 554 patients without dementia).
[a] Variables with missing data, n (%): lives alone (not in a nursing home), 2 (0.3); ADL independent (in mobility, dressing, and toilet visits), 6 (0.8); smoking, 56 (7.6); stroke code, 7 (1.0); arrival by ambulance, 29 (4.2) (for years 2011–2014); unconscious at arrival and unconscious or lethargic at arrival, 4 (0.5); symptom-to-needle time, 63 (8.6); NIHSS points before IVT, 60 (8.2); sICH, 9 (1.2); mRS at 3 months, 81 (11.1); and new nursing home placement, 103 (16.2).
[b] Fisher exact test.

patients with dementia) was slightly higher than other recent national averages (6.4% in New Zealand in 2016,[22] 6.1% in the United States[23]).

Patients treated with IVT (those with dementia and controls) were more independent than their counterparts who did not receive IVT. Moreover, ADL independence acted as a mediator for receiving IVT; hence, it probably represents an important decision factor for a physician contemplating IVT treatment, which is in line with the current guidelines.[3,19]

Worse functional prognosis after stroke in older patients[24] and in those with dementia[7,8] could lead to therapeutic nihilism and withholding of treatment. On the other hand, excessive enthusiasm for IVT could expose individuals to serious complications. Prior studies on IVT in AIS and dementia investigated death and sICH,[7–9] and to the best of our knowledge, only one study specifically addressed functional outcomes after IVT.[10] In that study, the proportion of independent patients with dementia in the initial cohort (28.9%) and in the cohort who received IVT (48.5%) was lower compared to ours (52.8% and 65.2%, respectively). This may be due to different definitions of independence or to the fact that dementia diagnosis in their study originated from clinical records (possibly including later dementia stages), whereas we included patients at the time of dementia diagnosis.[11] In SveDem, >60% of patients are diagnosed with dementia with an MMSE score of ≥20.[12] In our study, patients with dementia received the same standard of care regarding transport by ambulance and speedy initiation of IVT, but younger patients with dementia were less likely to have an activation of stroke code.

In line with previous studies,[25] patients with dementia and AIS who received IVT were more selected, which is supported by the lower IVT rate in this group compared to controls. It seems that the decision criteria in both patients with and without dementia were functional status and age, because the difference could not be attributed solely to greater comorbidities and resultant contraindications, for which we adjusted. However, there might still be some residual confounding for which we could not account. Current American guidelines for IVT in dementia are subject to individual judgment, and they suggest taking into account life expectancy, premorbid functional level, and clinically meaningful benefit.[3]

Table 3 Odds of receiving IVT for patients with dementia and patients without dementia (reference category)

Thrombolysis performed	Model 1	Model 2	Model 3
All patients (n = 8,074)	0.73 (0.58–0.91)	0.68 (0.54–0.86)	0.72 (0.57–0.91)
Those ≤80 y (n = 2,827)	0.55 (0.37–0.81)	0.51 (0.34–0.76)	0.53 (0.35–0.79)
Those >80 y (n = 5,247)	0.85 (0.65–1.12)	0.78 (0.59–1.03)	0.86 (0.65–1.14)
Only ADL independent (n = 6,445)	0.85 (0.64–1.12)	0.79 (0.60–1.06)	0.83 (0.62–1.09)
Those ≤80 y (n = 2,494)	0.63 (0.40–1.00)[a]	0.60 (0.38–0.97)	0.58 (0.36–0.94)
Those >80 y (n = 3,951)	1.03 (0.73–1.46)	0.94 (0.66–1.34)	1.02 (0.72–1.46)

Abbreviations: ADL = activities of daily living; IVT = intravenous thrombolysis.
Results are derived from logistic regression analysis for association between receiving thrombolysis and dementia status. Data are presented as odds ratio with 95% confidence interval. Model 1 is adjusted for age and sex. Model 2 is adjusted for age, sex, living alone, unconscious state at arrival, femur fracture, warfarin, interaction between heart failure and antiaggregants, and number of drugs without antithrombotics. Model 3 is adjusted for propensity scores of dementia.
[a] $p = 0.051$.

Table 4 Odds for mRS, death, and accommodation at 3 months after intravenous thrombolysis for patients with and without dementia (reference category)

Outcomes of thrombolysis	Model 1	Model 2	Model 3	Model 4
mRS score at 3 months	5.63 (3.41–9.30)	3.49 (2.02–6.01)	3.65 (2.06–6.45)	4.67 (2.81–7.75)
mRS score of 4 or 5	4.48 (2.56–7.84)	2.74 (1.48–5.05)	2.47 (1.21–5.05)	3.72 (2.10–6.59)
Death at 3 months	1.06 (0.60–1.90)	0.83 (0.44–1.53)	0.71 (0.36–1.8)	1.03 (0.58–1.84)
New nursing home placement	3.19 (1.78–5.72)	3.83 (1.98–7.42)	4.39 (2.07–9.31)	3.29 (1.79–6.07)

Abbreviation: mRS = modified Rankin Scale.
Results are presented as odds ratio with 95% confidence interval.
For mRS score at 3 months, results are derived from ordered logistic regression analysis. Model 1 was adjusted for age and sex, and the analysis was conducted on 527 patients. Model 2 was adjusted for age, sex, nursing home placement, antidepressants, and number of drugs minus antidepressants. Model 3 was adjusted as model 2 but also included NIH Stroke Scale score before thrombolysis (post hoc analysis).
For mRS score of 4 or 5 at 3 months, results are derived from multiple logistic regression analyses, reporting odds ratio of mRS score of 4 or 5 (vs 0 to 3) at 3 months, and are adjusted as above.
For death at 3 months, results are derived from multiple logistic regression analysis. Model 1 was adjusted for age and sex, while model 2 was adjusted for age, sex, nursing home placement, and number of medication. Analysis was conducted on all patients who received thrombolysis (n = 733). Model 3 included also NIH Stroke Scale score before thrombolysis (post hoc analysis).
For new nursing home placement, results are derived from multiple logistic regression analysis. Analysis was conducted on 529 patients. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, living alone (not in a nursing home), prior independence in activities of daily living, and number of medication. Model 3 included also NIH Stroke Scale score (post hoc analysis).
All results for model 4 were adjusted with propensity scores (post hoc analysis).

Some studies found that mortality after stroke in dementia is increased regardless of the use of IVT,[7,8] which could be partly explained by worse baseline status.[26] A recent SveDem study showed that stroke was a substantial cause of death in dementia.[27] The present study did not find differences in mortality in IVT-treated patients with dementia during hospitalization or at the 3-month follow-up, but functional outcomes were worse. The incidence of sICH was similar (7.4% vs 7.3%, $p = 0.960$).

We found no differences between the 2 groups in improvement in NIHSS score, but the proportion of missing data was high (≈30%). The initial difference in NIHSS could not be explained by the degree of consciousness, which was similar between groups, but might be due to greater stroke severity, confusional state, or poorer understanding of instructions in patients with both dementia and AIS.

IVT-treated patients with dementia had worse functioning at the 3-month follow-up. In a study from 2012,[10] dementia itself was not an independent predictor of a worse functional outcome. However, the groups were matched for prior residence and preadmission dependency, whereas we adjusted only for residence. Besides dementia, factors associated with poor outcome in our model were age, prior nursing home placement, and total number of medication. Consistent with a previous study based in the United States,[7] our IVT-treated patients with dementia had an unfavorable discharge destination compared to controls. In our study, dementia was independently associated with a new nursing home placement, a finding that differs from previous studies.[10] The odds for patients with dementia of being placed in a long-term facility were increased (OR 3.83, 95% CI 1.98–7.42).

A multicenter European study investigated the effects of preexisting dependency (often dementia) on outcomes and complications of IVT.[26] Dependent patients presented higher mortality rates; however, in our study, the incidence of poor outcome in survivors did not differ. Thus, previously dependent patients might still benefit from IVT.

This study has several limitations. First, baseline functioning in our cohort could be assessed only indirectly from degree of independence and living situation, while only an mRS estimation was available for outcome. Other methods of measuring functioning could be of interest, but the study could include only those assessed in Riksstroke. Second, the percentage of missing NIHSS after thrombolysis was ≈30%, limiting its usefulness. Third, nursing home residents with dementia and AIS are probably underrepresented in this study because they may be less often referred to hospitals. Causal inference is limited in cohort studies. IVT is an established treatment with a known risk-benefit profile. Our study shows that sICH and mortality outcomes were similar between patients with dementia and patients without dementia, although functional outcomes were worse. This may assuage some concerns when IVT is administered to this specific population. Those with dementia were eliminated from the control group by the exclusion of patients who were ever registered in SveDem, received a dementia or confusion diagnosis in the Swedish National Inpatient Register, or took antidementia drugs, but perfect case ascertainment is impossible. Riksstroke offers a >90% national coverage of ischemic stroke events, and the national

dementia registry, SveDem, provides superior accuracy in dementia diagnoses compared to claims data. However, in 2012, the estimated coverage of incident dementia cases in SveDem was 36%,[11] and the data on cognitive status (MMSE) were obtained at the time of dementia diagnosis, a median of 1.5 years before the stroke. SveDem may not be representative of the general dementia population, and dementia severity at the time of stroke is impossible to ascertain. SveDem diagnoses are not externally validated, but only ≈5% of patients change diagnoses at follow-up, suggesting that the initial diagnoses are robust.[12] Patients may refuse participation in SveDem or Riksstroke, and no information is collected on nonincluded patients. However, inclusion is the default, and refusal is generally low in our clinical experience. The absence of dementia among the control group was ascertained through SveDem and other registries, but further exclusion of dementia cases (by examining patients or their journals) was not attempted and is an important limitation of this study.

To the best of our knowledge, there have been no studies on this topic since the prolongation of the IVT treatment window to 4.5 hours in 2009, and we are the first to report symptom-to-needle time in this group of patients. The large nationwide cohort, detailed dementia and stroke characterization, and low proportion of missing (including for the 3-month follow-up) are strengths of our study.

The present study, investigating use of IVT and its outcomes in dementia, suggests that in selected patients IVT is safe, with rates of treatment complications similar to those in patients without dementia. Patients with dementia have worse functional outcomes after IVT, which might be explained by worse baseline functional status.

AUTHOR CONTRIBUTIONS

E. Zupanic: study concept, drafting the manuscript, statistical analysis and interpretation of data. M. von Euler: study concept, acquisition of data, and revising the manuscript for scientific content. I. Kåreholt: study concept, statistical analysis and interpretation of data, revising the manuscript. B. Contreras Escamez, Johan Fastbom, and Bo Norrving: interpretation of data and revising the manuscript. Dorota Religa: study concept, interpretation of data, and revising the manuscript. Milica G. Kramberger, Bengt Winblad, and Kristina Johnell: interpretation of data and revising the manuscript. Maria Eriksdotter: study concept and design, data acquisition, interpretation of data and revising the manuscript. Sara Garcia-Ptacek: study concept and design, data acquisition, statistical analysis and interpretation of data, and drafting and revising the manuscript.

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