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Workforce Attachment after Ischemic Stroke – The Importance of Time to Thrombolytic Therapy

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Objectives: The ability to remain in employment addresses an important consequence of stroke beyond the usual clinical parameters. However, data on the association between time to intravenous thrombolysis and workforce attachment in patients with acute ischemic stroke are sparse. *Materials and methods:* In this nationwide cohort study, stroke patients of working age (18-60 years) treated with thrombolysis (2011-2016) who were part of the workforce prior to admission and alive at discharge were identified using the Danish Stroke Registry. The association between time to thrombolysis and workforce attachment one year later was examined with multivariable logistic regression. *Results:* The study population comprised 1,329 patients (median age 51 years [25th-75th percentile 45-56], 67.3% men). The median National Institutes of Health Stroke Scale score at presentation was 4 (25th-75th percentile 2-8), and the median time from symptom-onset to initiation of thrombolysis was 140min (25th-75th percentile 104-196min). The proportion of patients who were part of the workforce at one-year follow-up was 64.6%, 64.3%, 64.9%, and 60.0% in patients receiving thrombolysis within 90min, between 91-180min, between 181-270min, and after 270min, respectively. In adjusted analysis, time to thrombolysis between 91-180min, 181-270min, and >270min was not significantly associated with workforce attachment compared with thrombolysis received ≤90min of symptom-onset (ORs 0.89 [95%CI 0.60-1.31], 0.93 [0.66-1.31], and 0.80 [0.43-1.52], respectively). *Conclusions:* In patients of working age admitted with stroke and treated with thrombolysis, two out of three were part of the workforce one year after discharge. There was no graded relationship between time to thrombolysis and the likelihood of workforce attachment.

Key Words: Stroke—Thrombolytic therapy—Workforce—Epidemiology

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Introduction

The efficacy and safety of intravenous thrombolytic therapy with intravenous recombinant tissue-type plasminogen activator for selected patients with acute ischemic stroke within the first 270 min after symptom-onset is well-established.[1–4] It is well-known that treatment delay alters the beneficial effect of thrombolytic therapy, and guidelines for the management of acute ischemic stroke consequently recommend that this treatment should be initiated as early as possible in eligible patients.[1–6] However, most studies have focused on traditional clinical outcomes such as mortality, degree of disability, and functional independence with little focus on cognitive outcomes, and they are based on patients who are no longer part of the workforce.[2–6] These traditional clinical outcome measures do not provide a complete assessment of the consequences of a stroke as younger patients may experience that the subtle impairments occurring in other domains, such as cognitive impairment, and depression often affect their ability to return to work, perhaps more so than in the elderly who are not in the workforce.[7–9] The ability to remain in employment addresses a consequence of stroke beyond the usual clinical parameters and is an important additional metric for downstream consequences of a stroke. From a socioeconomic perspective, the inability to return to work and the dependence on public benefits have substantial economic consequences for society. On a personal level, employment is important for financial independence and physical and mental health and may enhance recovery and life satisfaction by consolidating self-esteem, self-confidence, and social identity.[10–14] Whether the likelihood of returning to work diminishes with increasing treatment delay of thrombolytic therapy in patients with acute ischemic stroke has yet to be established. Such data may not only shed light on an unstudied consequence of ischemic stroke in a younger population treated with thrombolytic therapy and identify patients at high risk of workforce detachment, but also provide novel insights on the importance of time to initiation of thrombolytic treatment.

In this Danish cohort study, we examined workforce attachment in a large nationwide and contemporary cohort of patients of working age admitted with acute ischemic stroke according to time to intravenous thrombolysis. Further, we examined factors associated with workforce attachment.

Methods

The Danish healthcare and social welfare systems

The Danish healthcare system is tax-funded and provides free and equal access to healthcare care services for all citizens regardless of employment, financial and social status. Likewise, social welfare benefits and social services, also financed by taxes, are provided to citizens whenever indicated. These benefits include, but are not limited to, state educational grants, unemployment benefits, and disability pension. All citizens are offered a fully state-funded pension at the age of 65 or later depending on the date of birth.

Stroke management and the Danish stroke registry

Although intravenous thrombolysis with recombinant tissue-type plasminogen activator was approved for use in Europe in 2002, it first became a nationwide treatment in Denmark in 2008. In Denmark, thrombolysis is administered by neurologists at dedicated regional primary or comprehensive stroke centers with telemedicine treatment in associated stroke units, with subsequent referral within 24 hours to local stroke units for further clinical work-up and treatment by neurologists. All patients with acute stroke receiving treatment in Denmark are registered in the national stroke database, the Danish Stroke Registry, as part of a national quality improvement initiative.[15] The registry contains prospectively collected data on clinical and procedural characteristics including data on stroke symptoms and severity (as assessed by the National Institutes of Health Stroke Scale [NIHSS]), risk factors, and timing of arrival, scan, and treatment.[15] Reporting data to the Danish Stroke Registry is mandatory for all hospital departments treating patients with stroke, and a yearly evaluation of fulfillment of data entry of all stroke patients ensures a high compliance in all stroke units. The sensitivity and positive predictive value of acute stroke is > 90% in the Danish Stroke Registry.[16] In Denmark, vocational rehabilitation is offered to all patients with stroke, whenever indicated.

Data sources

In Denmark, all citizens are assigned a unique and permanent civil registration number which allows an accurate linkage of nationwide administrative and clinical registries at an individual level. The Danish Stroke Registry was linked to the following nationwide administrative registries: 1) The Danish registry on all public welfare benefits holds information on all Danish citizens who have received public welfare benefits at any time since 1991 and data are reported on a weekly basis; 2) The Danish National Patient Registry holds information on all hospital admissions and outpatient contacts according to the International Classification of Diseases (ICD-8 until 1994 and ICD-10 from 1994) and all surgical procedures

according to the NOMESCO Classification of Surgical Procedures;[17] 3) The Danish National Prescription Registry contains detailed information on dispensing date, strength, and quantity of all claimed drug prescriptions in Denmark;[18] 4) The Danish Civil Registration System holds information on birth date, sex, and vital status;[19] and 5) Statistics Denmark holds data on education, household income, and marital status.[20,21]

Study population

All Danish citizens who were admitted with ischemic stroke and treated with thrombolytic therapy between January 1, 2011 and December 31, 2016 were identified. Patients were excluded if they were not of working age (i.e. age between 18 and 60 years), died during admission, or were not part of the workforce 30 days prior to admission.

Study variables

Information on comorbidity was obtained using in-hospital and outpatient diagnosis codes any time prior to the discharge date (eTable 1 for ICD codes) with the following exceptions: diabetes and hypertension were identified using in-hospital and outpatient diagnosis codes any time prior to the discharge date and/or claimed drug prescriptions as described previously.[22,23] Pharmacotherapy was defined as claimed prescriptions within 180 days prior to admission (eTable 2 for Anatomical Therapeutic Chemical Classification System codes). The highest level of completed education was classified in accordance with the International Standard Classification of Education (i.e. basic school, high school, vocational education, short/medium length higher education, and long higher education or research). Average 5-year household income was calculated and graded in quartiles. Stroke severity, as assessed by the NIHSS score, at the time of thrombolytic therapy was classified into the following categories: Minor stroke (NIHSS 0-4), moderate stroke (NIHSS 5-15), and severe stroke (NIHSS 16-42). Time from symptom-onset to initiation of thrombolytic therapy was classified into the following clinically relevant categories: 0-90min, 91-180min, 181-270min, and more than 270 min.[2]

Workforce attachment

Patients were classified as part of the workforce if they were employed, unemployed but capable of working (i.e. not receiving paid sick leave or disability pension or not on early retirement), or received state educational grants, paid maternity leave, or other leave of absence. Employment status 30 days prior to admission was determined based on the five weeks leading up to this date, and only patients who were part of the workforce were included in the study. The five-week evaluation period was applied in order to reduce misclassification, i.e. to ensure that patients with short-term sick leave were not classified as detached from the workforce, as previously described.[24,25] Therefore, only patients with sick leave of at least three out of the five evaluated weeks were classified as detached from the workforce. No patients could by design reach the state pension age during follow-up.

Outcomes

Outcomes, i.e. part of the workforce, detached from the workforce, and death or emigration, were assessed every six months for a total of two years after stroke. By design, all patients had at least 2 years of potential follow-up. The primary outcome was workforce status estimated in the five-week period one year after discharge for stroke.

Statistical analyses

Baseline characteristics were reported as frequencies with percentages or medians with interquartile range. Differences in baseline characteristics according to time to thrombolytic therapy were tested with the Chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney test for continuous variables. A multivariable logistic regression model was used to examine the odds of workforce attachment according to time to thrombolytic therapy. Reported were odds ratios (OR) with 95% confidence intervals (CI), adjusted for age (categorical variable: ≤40 years, 41-50 years, 51-55 years, 56-60 years), sex, income, education, status on living alone, comorbidities (listed in Table 2), stroke severity (NIHSS, categorical variable: 0-4, 5-15, 16-42), time to thrombolytic therapy (categorical variable: 0-90 min, 91-180 min, 181-270 min, >270 min), and year of stroke. Patients who were not followed for one year due to emigration (0.4% of the study population) or death (0.8% of the study population) were set as detached from the workforce in the logistic regression analysis. Interactions between treatment delay, clinically relevant variables (including age, sex, and stroke severity), and outcomes were tested for and found insignificant. Factors associated with workforce attachment one year after stroke were identified using multivariable logistic regression, adjusted for the same variables at mentioned previously. All statistical analyses were performed with SAS statistical software (SAS 9.4, SAS Institute, Cary, NC, USA). The level of statistical significance was set at 5%. There were no missing data for any of the covariates or outcomes, except for NIHSS score at presentation (2.2% missing). These patients were excluded from the logistic regression models.

Sensitivity analyses

To test the robustness of our results, we conducted several sensitivity analyses. 1) We restricted the definition of workforce to patients in employment and not receiving any social benefits. Thus, we examined workforce attachment among patients, who were in employment 30 days

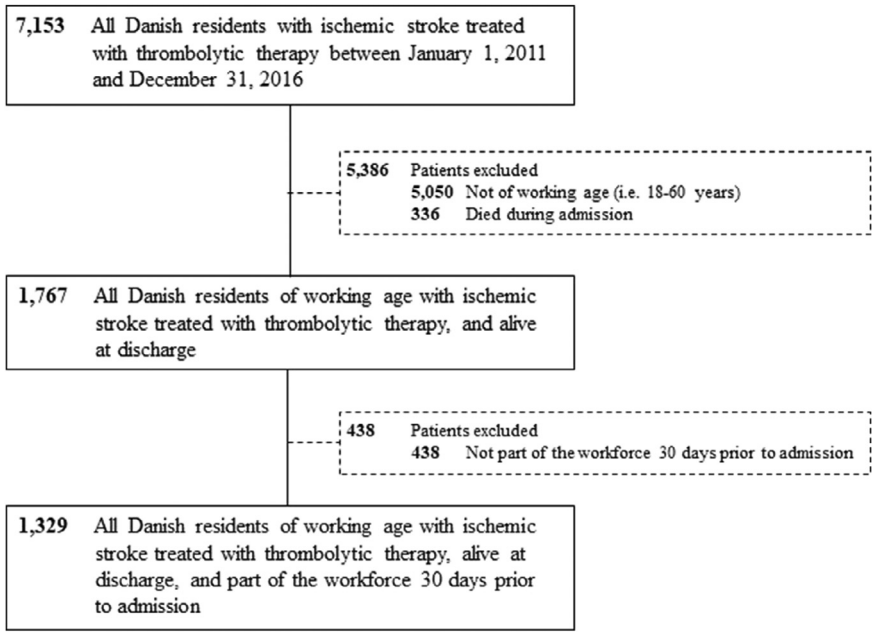

Fig. 1. *Flow chart of the study population selection process.*

prior to admission. 2) We varied the definition of detachment from the workforce to two and four out of five weeks, respectively. 3) We examined time to thrombolytic therapy in 15-minute intervals from symptom-onset.

Ethics

In Denmark registry-based studies that are conducted for the sole purpose of statistics and scientific research do not require ethical approval or informed consent by law. However, the study is approved by the data responsible institute (the Capital Region of Denmark [approval number: P-2019-523]) in accordance with the General Data Protection Regulation (GDPR) and the Danish Clinical Quality Program – National Clinical Registries (RKKP).

Results

From January 1, 2011 to December 31, 2016, 7,153 patients with acute ischemic stroke received thrombolytic therapy, of whom 1,767 patients were of working age between 18-60 years and were alive at discharge. Of these, 1,329 patients were part of the workforce 30 days prior to admission and comprised the study population (Figure 1, Table 1). The median age of the study population was 51 years (25^{th}-75^{th} percentile 45-56 years), and 67.3% were men. The median NIHSS score at presentation was 4 (25^{th}-75^{th} percentile 2-8), and the median time from symptom-onset to initiation of thrombolytic therapy was 140min (25^{th}-75^{th} percentile 104-196min). Baseline characteristics according to time to thrombolytic therapy are summarized in Table 2.

Workforce attachment

One year after discharge for stroke, 855 (64.3%) of the included patients were part of the workforce, 409 (30.7%) were on paid sick leave, 35 (2.6%) received disability pension, 11 (0.8%) were on early retirement, 14 (1.1%) had died, and 5 (0.4%) had emigrated. The proportion of patients who were part of the workforce at one-year follow-up was 64.6% in the ≤90min group, 64.3% in the 91-180min group, 64.9% in the 181-270min group, and 60.0% in the >270min group. The proportion of patients who died within the one-year follow-up was 0.9% in the ≤90min group, 1.3% in the 91-180min group, 0.9% in the 181-270min group, and 0.0% in the >270min group. In adjusted analysis, time to thrombolytic therapy between 91-180min, 181-270min, and >270min was not significantly associated with workforce attachment compared with thrombolytic therapy received ≤90min of symptom-onset (Figure 3). There was no interaction between time to thrombolytic therapy, stroke severity, and outcomes (P-value for interaction 0.30).

The proportions of patients who were part of the workforce every six months for a total of two years of follow-up after discharge for stroke according to time to thrombolytic therapy are shown in Figure 2. In all groups, the proportion of patients who were part of the workforce increased over time elapsed since stroke.

Factors associated with workforce attachment

Advanced age and increasing stroke severity were associated with lower odds of workforce attachment, whereas male sex was associated with higher odds of workforce attachment (Figure 3).

Table 1. *Employment status 30 days prior to stroke in patients of working age and alive at discharge*

	All patients N=1,239	0-90 min N=185	91-180 min N=659	181-270 min N=338	>270 min N=57
In the workforce, N (%)					
Employed	825 (66.6)	133 (71.9)	426 (64.6)	228 (67.5)	38 (66.7)
Study/maternity leave	32 (2.6)	4 (2.2)	18 (2.7)	6 (1.8)	4 (7.0)
Unemployed	116 (9.4)	10 (5.4)	70 (10.6)	32 (9.5)	4 (7.0)
Not in the workforce, N (%)					
Sick leave	49 (4.0)	6 (3.2)	31 (4.7)	11 (3.3)	1 (1.8)
Disability pension	206 (16.6)	31 (16.8)	110 (16.7)	56 (16.6)	9 (15.8)
Early retirement	11 (0.9)	1 (0.5)	4 (0.6)	5 (1.5)	1 (1.8)

Sensitivity analyses

To test the robustness of our findings, we performed several sensitivity analyses. We first examined workforce attachment (i.e. patients in actual employment and not receiving any social benefits) among those who were employed prior to stroke. In line with the main findings, time to thrombolytic therapy between 91-180min, 181-270min, and >270min was not significantly associated with workforce attachment compared with thrombolytic therapy received ≤90min of symptom-onset (adjusted ORs 0.97 [0.64-1.46], 0.93 [0.65-1.34], and 0.74 [0.38-1.47], respectively). Secondly, we varied our definition of detachment from the workforce from three to two or four out of five weeks, respectively. As in the main analysis, these analyses did not demonstrate an association between time to thrombolytic therapy and workforce attachment. Finally, we examined time to thrombolytic therapy in 15-minute intervals. Every 15-minute delay in thrombolytic treatment did not affect the likelihood of workforce attachment (OR 0.99 [0.96-1.02]).

Discussion

In this nationwide cohort study, we examined workforce attachment in all Danish patients who were part of the workforce and admitted with acute ischemic stroke according to time to thrombolysis. Our study yielded three major findings: First, around two out of three patients were part of the workforce one year after discharge. Second, there was no graded relationship between time to thrombolytic therapy and the likelihood of workforce attachment. Third, advanced age and increasing stroke severity were associated with lower odds of workforce attachment, whereas male sex was associated with higher odds of workforce attachment.

Workforce attachment

Among patients who were part of the workforce prior to stroke, we found that a significant proportion was detached from the workforce one year later. Specifically, less than two out of three patients were part of the workforce despite treatment with thrombolytic therapy. Compared with other studies in patients with stroke, we found a slightly higher proportion of patients who were part of the workforce after one year.[26] This difference is not surprising as treatment with thrombolytic therapy has been associated with favorable outcomes, including a greater likelihood of returning to work, compared with no thrombolytic therapy.[27] However, it is striking that the proportion of patients treated with thrombolytic therapy and part of the workforce was in line with patients alive 30 days after an out-of-hospital cardiac arrest of whom 56% were part of the workforce one year after their cardiac arrest.[24] In addition, a higher proportion of patients who were part of the workforce has been reported in other diseases with severe consequences on work capability, including heart failure, infective endocarditis, pneumococcal meningitis, and viral encephalitis.[25,28,29] Thus, our findings confirm that stroke, despite treatment with thrombolytic therapy, causes life-changing physical and mental disabilities and reduces a patient's capacity to maintain a normal life and live independently.

An interesting observation of this study was that the proportion of patients who were part of the workforce increased over time elapsed since stroke, irrespective of time to thrombolysis. This finding most likely reflects the time to recovery after stroke and underlines the importance of prolonged rehabilitation services. Further, from a clinical perspective, this information will add further to the information provided to the patients at discharge about long-term prospects and life expectancy.

Time to thrombolytic therapy

It is well-established that early thrombolytic therapy is associated with better outcomes in patients presenting with acute ischemic stroke.[2–6] In a registry study including 58,353 patients with stroke treated with thrombolytic therapy within 270 min of symptom onset, earlier thrombolytic treatment was associated with reduced in-hospital mortality and higher rates of discharge to home.[4] In addition, a recent meta-analysis of individual patient data from randomized trials including 6,756 patients found a graded relationship between increasing time to alteplase treatment and lower odds of achieving a good stroke outcome – defined as a modified Rankin scale of 0 or 1 – at 3-6

Table 2. *Baseline characteristics of the study population*

Characteristics	Time from symptom onset to thrombolytic therapy				P-value
	0-90 min N=147	91-180 min N=514	181-270 min N=266	>270 min N=46	
Demographics					
Age, median (25^{th}-75^{th} percentile)	51 (44-56)	50 (43-56)	51 (45-56)	51 (44-55)	0.59
Age, categorical					0.61
≤ 40 years	22 (15.0)	100 (19.5)	36 (13.5)	9 (19.6)	
41-50 years	51 (34.7)	161 (31.3)	91 (34.2)	14 (30.4)	
51-55 years	34 (22.1)	119 (23.2)	70 (26.3)	14 (30.4)	
56-60 years	40 (27.2)	134 (26.1)	69 (25.9)	9 (19.5)	
Male, N (%)	100 (68.0)	338 (65.8)	177 (66.5)	34 (73.9)	0.71
Income group, N (%)					0.33
Q1 (lowest)	34 (22.1)	133 (25.9)	64 (24.1)	12 (26.1)	
Q2	28 (19.1)	135 (26.3)	68 (25.6)	12 (26.1)	
Q3	37 (25.2)	121 (23.5)	71 (26.7)	15 (32.6)	
Q4 (highest)	48 (32.7)	125 (24.3)	63 (23.7)	7 (15.2)	
Education, N (%)					0.57
Basic school	33 (22.5)	130 (25.3)	62 (23.3)	11 (23.9)	
High school	6 (4.1)	26 (5.1)	5 (1.9)	< 3	
Vocational education	58 (39.5)	211 (41.1)	122 (45.9)	19 (41.3)	
Short/medium higher education	27 (18.4)	92 (17.9)	50 (18.8)	9 (19.6)	
Long/higher education	19 (12.9)	35 (6.8)	20 (7.5)	4 (8.7)	
Unknown	4 (2.7)	20 (3.9)	7 (2.6)	< 3	
Marital status, N (%)					
Living alone	49 (33.3)	152 (29.6)	76 (28.6)	11 (23.9)	0.61
Prior history, N (%)					
Ischemic stroke	3 (2.0)	12 (2.3)	< 3	< 3	0.42
Ischemic heart disease	8 (5.4)	42 (8.2)	19 (7.1)	< 3	0.37
Heart failure	8 (5.4)	12 (2.3)	5 (1.9)	< 3	0.12
Atrial fibrillation	15 (10.2)	28 (5.5)	14 (5.3)	7 (15.2)	0.01
Hypertension	19 (12.9)	52 (10.1)	25 (9.4)	7 (15.2)	0.49
Diabetes	6 (4.1)	10 (2.0)	10 (3.8)	< 3	0.29
Peripheral arterial disease	< 3	7 (1.4)	5 (1.9)	< 3	0.81
Malignancy	6 (4.1)	20 (3.9)	< 3	< 3	0.007
Chronic kidney disease	1 (0.7)	7 (1.4)	6 (2.3)	< 3	0.51
Chronic obstructive pulmonary disease	1 (0.7)	8 (1.6)	7 (2.6)	< 3	0.50
Liver disease	< 3	9 (1.8)	< 3	< 3	0.65
Pharmacotherapy, N (%)					
Antiplatelets	6 (4.1)	50 (9.7)	17 (6.4)	3 (6.5)	0.10
Oral anticoagulants	< 3	5 (1.0)	< 3	< 3	0.35
Lipid-lowering drugs	17 (11.6)	57 (11.1)	25 (9.4)	< 3	0.25
Antidepressants	**10 (4.3)**	**49 (6.9)**	**16 (4.6)**	**4 (6.7)**	
Antidepressants after discharge*	**42 (18.1)**	**140 (19.8)**	**62 (17.9)**	**10 (16.7)**	
NIHSS at presentation, median (25^{th}-75^{th} percentile)	5.5 (3-13)	5.0 (3-8)	3 (2-6.5)	5 (3-9)	< 0.001
NIHSS at presentation, N (%)					< 0.001
0-4, minor stroke	58 (39.5)	246 (47.9)	157 (59.0)	22 (47.8)	
5-15, moderate stroke	66 (44.9)	213 (41.4)	98 (36.8)	19 (41.3)	
16-42, severe stroke	20 (13.6)	49 (9.5)	9 (3.4)	5 (10.9)	
Missing	3 (2.0)	6 (1.2)	< 3	< 3	

*A redeemed prescription of antidepressants within 90 days after discharge.

months.[2] Although the modified Rankin scale is a commonly used scale for measuring the degree of disability or dependence after a stroke, this outcome measure does not provide a complete assessment of the consequences of such an event. The ability to remain in employment represents another important aspect of life in younger individuals with stroke and addresses a vital consequence and cost of stroke beyond the usual clinical parameters. However, data on the relationship between time to thrombolytic therapy and the ability to remain in employment are lacking.

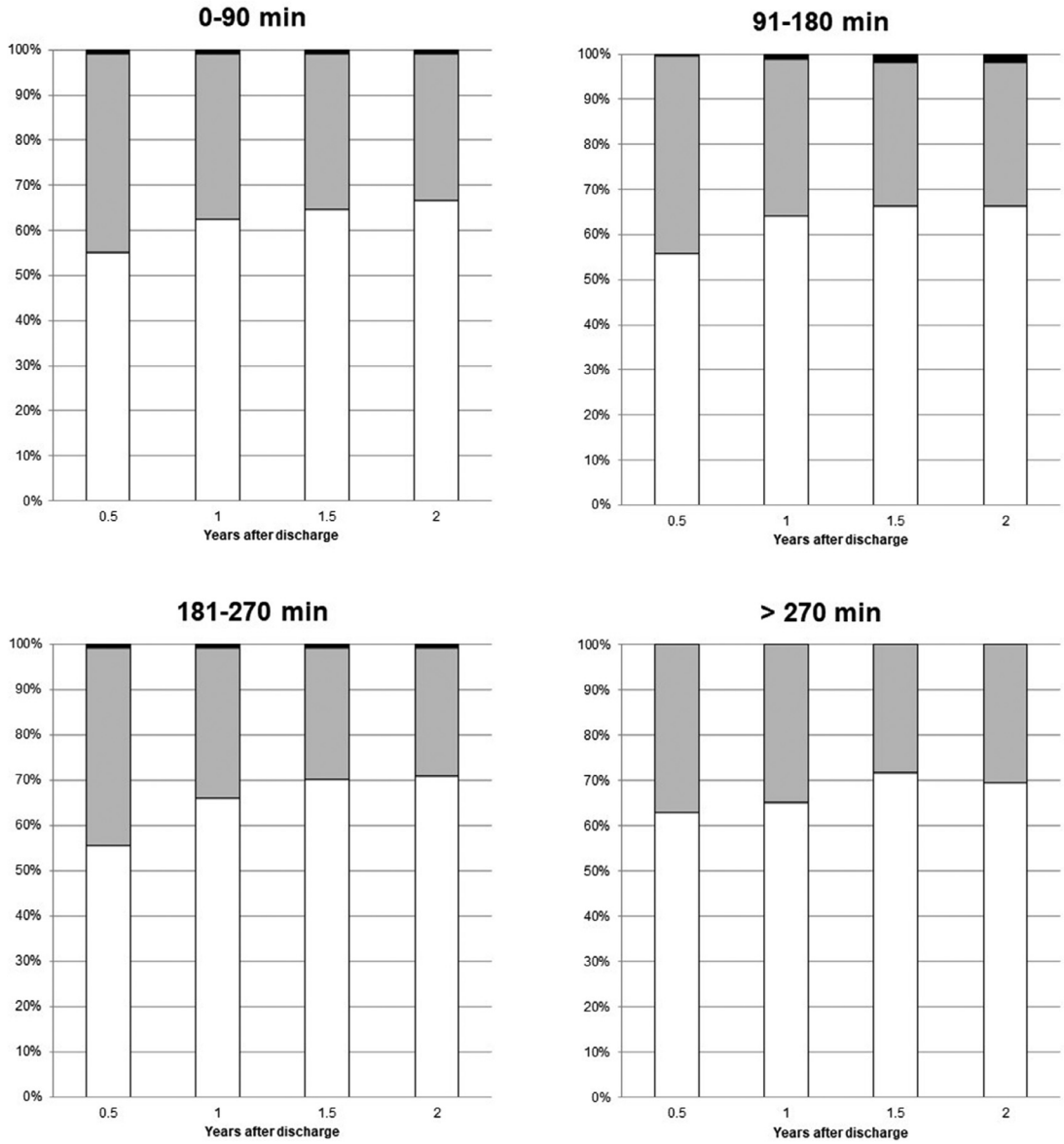

Fig. 2. *The proportion of patients who were part of the workforce every 6 months for a total of 2 years according to time to thrombolytic therapy. White, part of the workforce; gray, detached from the workforce; black, death.*

To our knowledge, this is the first study to examine the association between time to thrombolytic therapy and workforce attachment in a nationwide cohort of patients with ischemic stroke who were part of the workforce prior to the stroke event. We found that time to thrombolytic therapy between 91-180 min, 181-270 min, and >270 min was not associated with a significantly different likelihood of workforce attachment compared with thrombolytic therapy received within 90 min of symptom onset. Considering the current literature on the association between time to thrombolytic therapy and subsequent outcomes, this finding may seem controversial. However, it may be speculated that patients with advanced age to a greater degree have impaired cerebral collateral perfusion after stroke compared with younger patients.[30–33] The inclusion of patients of working age only in our study may therefore, in part, explain the lack of an inverse relationship between time to thrombolysis and subsequent workforce attachment. Another, and perhaps more plausible, explanation may be that a significant part of the study population only had minor strokes, thus diminishing the importance of time to thrombolysis. Nevertheless, it is reassuring that our data suggest that patients of working age treated with thrombolytic therapy up to 270 min achieve an outcome similar to those receiving early treatment. Thus, these findings support guidelines that recommend use of thrombolytic therapy up to 270 min after onset of stroke.[1] Finally, it is possible that the absence of a graded relationship between time to thrombolytic therapy and workforce attachment may be due to lack of power.

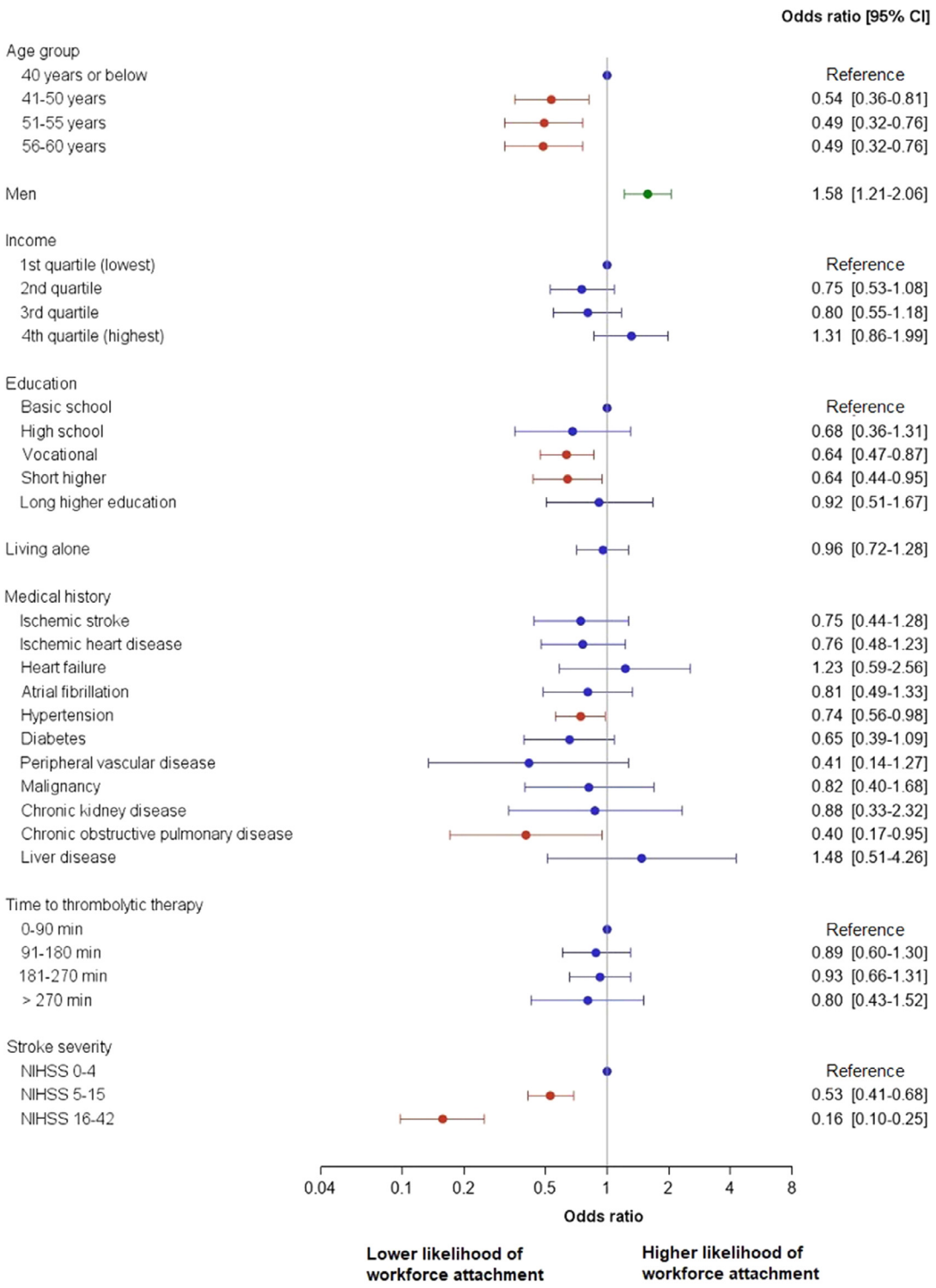

Fig. 3. *Factors associated with workforce attachment. An odds ratio >1 indicates a higher likelihood of workforce attachment, and an odds ratio <1 indicates a lower likelihood of workforce attachment. NIHSS, National Institutes of Health Stroke Scale.*

Factors associated with workforce attachment

Identifying patients at particularly high risk of detachment from the workforce has important implications for preventive efforts aimed at increasing the likelihood of returning to the workforce. In this study, there was a trend towards lower odds of returning to the workforce in the presence of significant comorbidities, such as chronic obstructive pulmonary disease, diabetes, and atrial fibrillation. These findings may encourage a multidisciplinary approach in the post-discharge management of patients with stroke treated with thrombolytic therapy

in order to increase the likelihood of returning to the workforce. This study also demonstrated that increasing stroke severity, as assessed by the NIHSS score, was associated with lower odds of workforce attachment. This finding is not surprising as patients presenting with more severe strokes to a greater degree develop permanent neurologic disabilities and impaired functional level and thus fail to meet the physical requirements of full-time employment.[34–38]

Consistent with other studies, advanced age was associated with lower odds of workforce attachment.[24,25,28] Possible explanations for this observation may include a greater burden of comorbidities, more severe cognitive and physical deficits, and prolonged recovery among older patients, and perhaps a greater determination to remain in employment among younger patients.[25,39–42] Another interesting observation of this study was that despite adjustment for age, stroke severity, and comorbidities, male sex was associated with a higher likelihood of workforce attachment and this is in accordance with other studies on work capability in patients with stroke and other diseases.[25,26,28,43,44] Although there is no clear explanation to this association, it may be speculated that differences in social roles and responsibilities as well as fewer opportunities in the workforce for women may explain the observed sex difference.[26,45–47] In order to prevent detachment from the workforce to the extent possible, a better understanding of the obstacles that prevent return to work after stroke is warranted.

Strengths and limitations

The main strength of this study is the completeness of data in a nationwide unselected cohort of patients with stroke treated with thrombolytic therapy followed in a real-world setting. Our study has several limitations which need to be acknowledged. The observational nature precludes the assessment of cause-effect relationships, and the possibility of residual confounding cannot be excluded despite adjustment for potential confounders. Data on important determinants of workforce attachment, including the degree of cognitive deficits at discharge and participation in rehabilitation programs, were not available. While it would have been interesting to examine if patients with e.g. physically demanding job had a lower likelihood of workforce attachment or were employed in a less physically demanding job during follow-up, data on job type prior to the stroke admission and during follow-up were not available. This study is based on the Danish healthcare and social systems which provide social services for all residents whenever indicated irrespective of socioeconomic or insurance status. This should be considered when translating our findings to countries with more restricted access to these services. By design, no patients could reach the state pension age during follow-up. However, the oldest patients had the opportunity to retire early and receive early retirement benefits if the criteria for such were met. Thus, it is possible that these patients, comprising 0.8% of the study population, were not part of the workforce due to lack of motivation and necessity rather than poor performance status. Patients who emigrated during follow-up were classified as detached from the workforce in the logistic regression model. This has most likely little to no impact on our results as only 0.4% of the study population emigrated.

Conclusions

In patients who were part of the workforce admitted with acute ischemic stroke and treated with thrombolytic therapy, less than two out of three patients were part of the workforce one year after discharge. There was no graded relationship between time to thrombolytic therapy and workforce attachment. Advanced age and increasing stroke severity were associated with lower odds of workforce attachment, whereas male sex was associated with higher odds of workforce attachment.

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Disclosures

None.

Data availability

Data for this study are derived from Statistics Denmark. By law, these data are not allowed to be shared. Therefore, data cannot not be made available to other researchers.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2021.106031.

References

1. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49:e46-e110.
2. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from randomised trials. Lancet 2014;384:1929-1935.

3. Whiteley WN, Emberson J, Lees KR, et al. Risk of intracerebral haemorrhage with alteplase after acute ischaemic stroke: a secondary analysis of an individual patient data meta-analysis. Lancet Neurol 2016;15:925-933.
4. Saver JL, Fonarow GC, Smith EE, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. JAMA - J Am Med Assoc 2013;309:2480-2488.
5. Goyal M, Almekhlafi M, DiW DIppel, et al. Rapid alteplase administration improves functional outcomes in patients with stroke due to large vessel occlusions: Meta-analysis of the noninterventional arm from the HERMES collaboration. Stroke 2019;50:645-651.
6. Lees KR, Emberson J, Blackwell L, et al. Effects of alteplase for acute stroke on the distribution of functional outcomes: a pooled analysis of 9 trials. Stroke 2016;47:2373-2379.
7. Schaapsmeerders P, Maaijwee NAM, Van Dijk EJ, et al. Long-term cognitive impairment after first-ever ischemic stroke in young adults. Stroke 2013;44:1621-1628.
8. Baum CM, Connor LT, Morrison T, et al. Reliability, validity, and clinical utility of the executive function performance test: a measure of executive function in a sample of people with stroke. Am J Occup Ther 2008;62:446-455.
9. Kapoor A, Scott C, Lanctot KL, et al. Symptoms of depression and cognitive impairment in young adults after stroke/transient ischemic attack. Psychiatry Res 2019;279:361-363.
10. Waddell G, Burton AK. Is work good for your health and wellbeing? Occup Health Rev 2006:30-31.
11. Brenner MH, Mooney A. Unemployment and health in the context of economic change. Soc Sci Med 1983;17:1125-1138.
12. Nordenmark M, Strandh M. Towards a sociological understanding of mental well-being among the unemployed: the role of economic and psychosocial factors. Sociology 1999;33:577-597.
13. Nordenmark M. Non-financial employment motivation and well-being in different labour market situations: A longitudinal study. Work Employ Soc 1999;13:601-620.
14. Black DC. Work, health and wellbeing. Saf Health Work 2012;3:241-242.
15. Johnsen S, Ingeman A, Holmager Hunborg H, et al. The Danish stroke registry. Clin Epidemiol 2016;8:697-702.
16. Wildenschild C, Mehnert F, Wernich Thomsen R, et al. Registration of acute stroke: validity in the Danish stroke registry and the Danish national registry of patients. Clin Epidemiol 2013;6:27-36.
17. Lynge E, Sandegaard JL, Rebolj M. The Danish national patient register. Scand J Public Health 2011;39:30-33.
18. Wallach Kildemoes H, Toft Sørensen H, Hallas J. The Danish national prescription registry. Scand J Public Health 2011;39:38-41.
19. Pedersen CB. The Danish civil registration system. Scand J Public Health 2011;39:22-25.
20. Jensen VM, Rasmussen AW. Danish education registers. Scand J Public Health 2011;39:91-94.
21. Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. Scand J Public Health 2011;39:103-105.
22. Schramm TK, Gislason GH, Køber L, et al. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. Circulation 2008;117:1945-1954.
23. Olesen JB, Lip GYH, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: Nationwide cohort study. Bmj 2011;342:320.
24. Kragholm K, Wissenberg M, Mortensen RN, et al. Return to work in out-of-hospital cardiac arrest survivors: a nationwide register-based follow-up study. Circulation 2015;131:1682-1690.
25. Rørth R, Wong C, Kragholm K, et al. Return to the workforce after first hospitalization for heart failure: a Danish nationwide cohort study. Circulation 2016;134:999-1009.
26. Edwards JD, Kapoor A, Linkewich E, et al. Return to work after young stroke: a systematic review. Int J Stroke 2018;13:243-256.
27. Budimkic MS, Pekmezovic T, Beslac-Bumbasirevic L, et al. Return to paid work after ischemic stroke in patients treated with intravenous thrombolysis. Neuroepidemiology 2016;46:114-117.
28. Butt JH, Kragholm K, Dalager-Pedersen M, et al. Return to the workforce following infective endocarditis—a nationwide cohort study. Am Heart J 2018;195:130-138.
29. Roed C, Sørensen HT, Rothman KJ, et al. Employment and disability pension after central nervous system infections in adults. Am J Epidemiol 2015;181:789-798.
30. Ma J, Ma Y, Shuaib A, et al. Impaired collateral flow in pial arterioles of aged rats during ischemic stroke. Transl Stroke Res 2020;11:243-253.
31. Faber JE, Zhang H, Lassance-Soares RM, et al. Aging causes collateral rarefaction and increased severity of ischemic injury in multiple tissues. Arterioscler Thromb Vasc Biol 2011;31:1748-1756.
32. Nannoni S, Sirimarco G, Cereda CW, et al. Determining factors of better leptomeningeal collaterals: a study of 857 consecutive acute ischemic stroke patients. J Neurol 2019;266:582-588.
33. Malik N, Hou Q, Vagal A, et al. Demographic and clinical predictors of leptomeningeal collaterals in stroke patients. J Stroke Cerebrovasc Dis 2014;23:2018-2022.
34. Fonarow GC, Saver JL, Smith EE, et al. Relationship of national institutes of health stroke scale to 30-day mortality in medicare beneficiaries with acute ischemic stroke. J Am Heart Assoc 2012;1:42-50.
35. Rost NS, Bottle A, Lee JM, et al. Stroke severity is a crucial predictor of outcome: An international prospective validation study. J Am Heart Assoc 2016;5:1-7.
36. Andersen KK, Andersen ZJ, Olsen TS. Predictors of early and late case-fatality in a nationwide danish study of 26 818 patients with first-ever ischemic stroke. Stroke 2011;42:2806-2812.
37. Hankey GJ, Spiesser J, Hakimi Z, et al. Rate, degree, and predictors of recovery from disability following ischemic stroke. Neurology 2007;68:1583-1587.
38. Adams HP, Davis PH, Leira EC, et al. Baseline NIH stroke scale score strongly predicts outcome after stroke: a report of the trial of Org 10172 in acute stroke treatment (TOAST). Neurology 1999;53:126-131.
39. Thomas SA, Browning CJ, Greenwood KM. Rehabilitation of older injured workers. Disabil Rehabil 1994;16:162-170.
40. Berecki-Gisolf J, Clay FJ, Collie A, et al. The impact of aging on work disability and return to work: Insights from workers' compensation claim records. J Occup Environ Med 2012;54:318-327.
41. MacKenzie EJ, Bosse MJ, Kellam JF, et al. Early predictors of long-term work disability after major limb trauma. J Trauma - Inj Infect Crit Care 2006;61:688-694.
42. Brown J, Katikireddi SV, Leyland AH, et al. Age, health and other factors associated with return to work for those

engaging with a welfare-to-work initiative: A cohort study of administrative data from the UK's Work Programme. BMJ Open 2018;8:e024938.
43. Butt JH, Rørth R, Kragholm K, et al. Return to the workforce following coronary artery bypass grafting: A Danish nationwide cohort study. Int J Cardiol 2018;251:15-21.
44. Palstam A, Westerlind E, Persson HC, et al. Work-related predictors for return to work after stroke. Acta Neurol Scand 2019;139:382-388.
45. Clarke PJ, Black SE, Badley EM, et al. Handicap in stroke survivors. Disabil Rehabil 1999;21:116-123.
46. Saeki S, Toyonaga T. Determinants of early return to work after first stroke in Japan. J Rehabil Med 2010;42:254-258.
47. Lederer V, Rivard M, Mechakra-Tahiri SD. Gender differences in personal and work-related determinants of return-to-work following long-term disability: A 5-year cohort study. J Occup Rehabil 2012;22:522-531.